Management of Blood Glucose with non-Insulin therapies in DM type 2

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april 23, 2016

Disclosures

- Dr Jorge De Jesús has received honorariums as speaker for the following pharmaceutical companies: Merck; Janssen; Sanofi -Aventis
- Dr Jorge De Jesús has no conflicts of interests with any entity for the information included in this presentation

Objectives

During this **30 minutes** presentation the audience will be able to :

- Recognize that DM 2 is a multifactorial disease
- DM is a progressive disease and eventually many patients will need insulin in their therapies
- Oral therapies included in the presentation:
- Metformin; DPP4 inhibitors; SGLT2 inhibitors
- Parenteral, non insulin therapies: GLP-1 RA
- Some non FDA approved therapies will be discussed

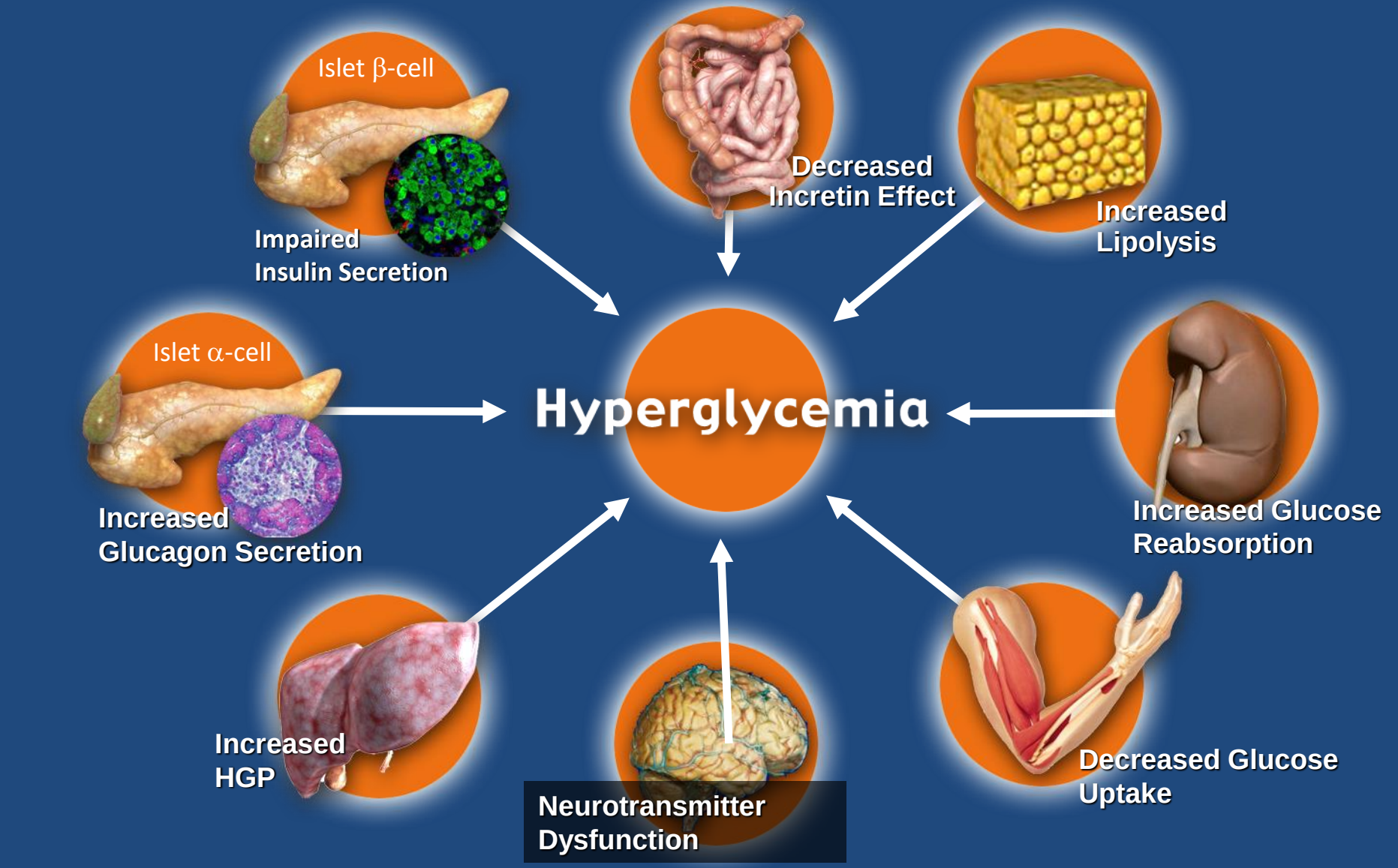
Pre- Test

- Treatment of Diabetes Mellitus should be centered in the patient and individualized.

- Due to the multifactorial nature of the disease combination therapy is needed early in the treatment of this condition
- Efforts should me made to prevent DM in high risk individuals.

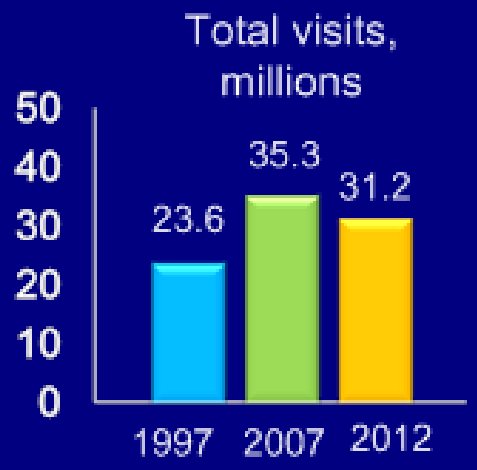
Diabetes type 2 is a polygenic and multifactorial disease

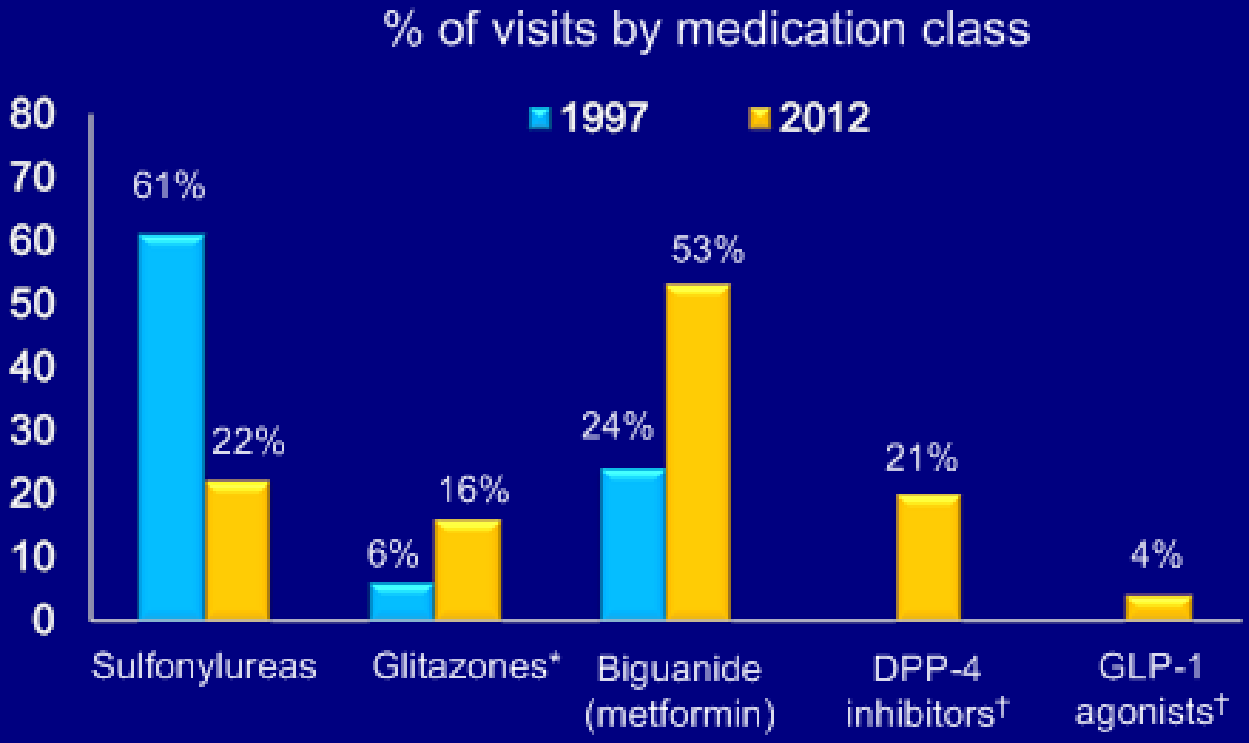
The Ominous Octet



US Trends in Type 2 Diabetes Treatment, 1997-2012: Medication Classes

Steady increase in type 2 diabetes treatment visits between 1997 and 2007, peaking at 35.3 million visits in 2007, and declining to 31.2 million visits in 2012



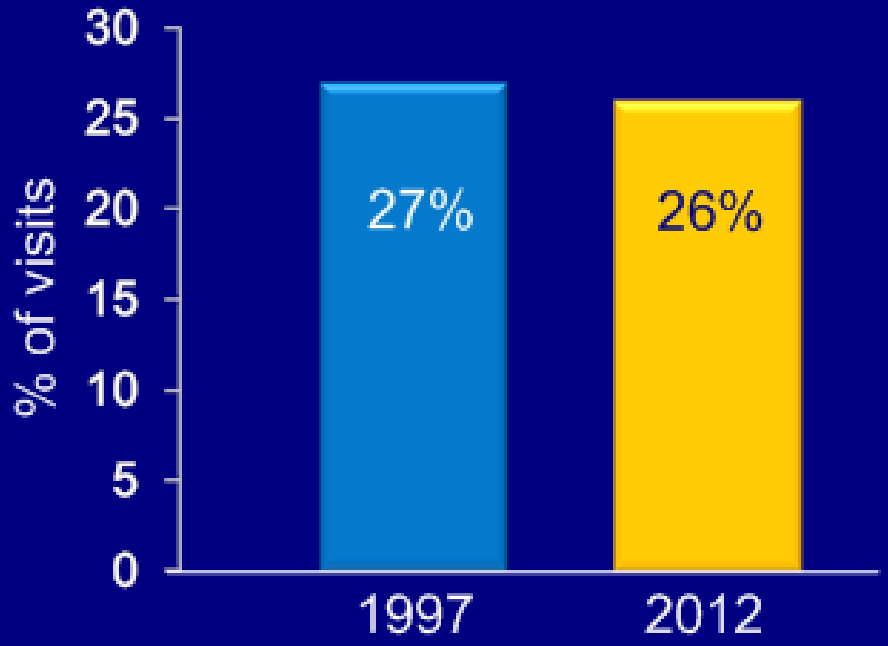


*~96% of visits involved pioglitazone products in 2012; †Not FDA approved in 1997
Percentages shown are % of treatment visits where medication classes were prescribed

Turner LW, et al. *Diabetes Care*. 2014;37:985-992.

US Trends in Type 2 Diabetes Treatment, 1997-2012: Insulin Use

Stable insulin use seen from 1997 to 2012



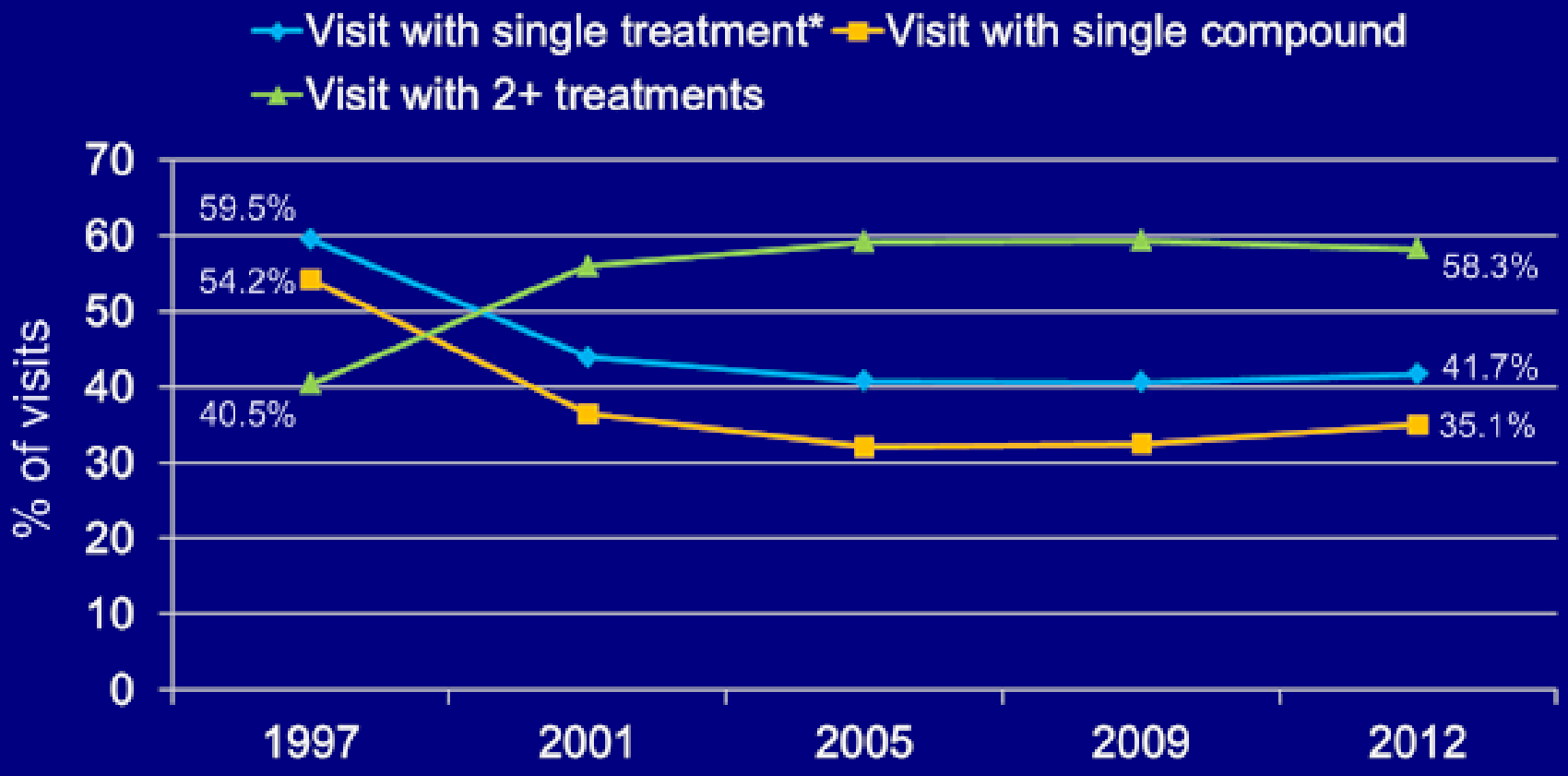
However, when visits examined by insulin type:

- Regular: 2% of visits since 1997
- NPH: 3% of visits since 1997
- Short-acting: doubled in use from 1997 to 2012
- Long-acting: <1% of visits in 1997 to ~18% in 2012

Percentages shown are % of treatment visits where medication classes were prescribed

Turner LW, et al. *Diabetes Care*. 2014;37:985-992.

US Trends in Type 2 Diabetes Treatment, 1997-2012: Number of Treatments



Percentages shown are % of treatment visits where medication classes were prescribed
*Including fixed-dose combination therapy

Turner LW, et al. *Diabetes Care*. 2014;37:985-992.

GOALS FOR GLYCEMIC CONTROL

INDIVIDUALIZE GOALS

A1C ≤ 6.5%

For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5%

For patients with concurrent serious illness and at risk for hypoglycemia

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

A1C < 8%

TDD 0.1–0.2 U/kg

A1C > 8%

TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** > 180 mg/dL: add 20% of TDD
  - **FBG** 140–180 mg/dL: add 10% of TDD
  - **FBG** 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - **BG** < 70 mg/dL: 10% – 20%
  - **BG** < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

***Glycemic Goal:**

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)

Add GLP-1 RA

Or SGLT-2I
Or DPP-4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals

- Start: 10% of basal dose or 5 units

Basal Bolus

- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg

- Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

PROFILES OF ANTIDIABETIC MEDICATIONS

3A=45-59; 3B=30-44

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL/ GU	Contra-indicated CKD Stage 3B,4,5	Exenatide Not Indicated CrCl < 30	Not Effective with eGFR < 45 / Genital Mycotic Infections	Dose Adjustment Necessary (Except Linagliptin)	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
ASCVD	Benefit		Possible Benefit			Neutral	?		Safe		
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits | Use with caution | Likelihood of adverse effects | ? Uncertain effect

TOP MEDICAL NEWS FROM ACROSS MEDSCAPE

FDA: Metformin Safe for Some Patients With Renal Problems

Changing its course in response to mounting evidence, the agency said the diabetes drug can be used safely in patients with mild and, in some cases, moderate kidney impairment.

News Alerts, April 08, 2016 | 13 comments

contraindicated GFR< 30 ml/min

DPP-4 Inhibitors: Benefits and Risks

Benefits[a]

- Lower HbA_{1c} by ~0.5% to 0.9%
- Low risk of hypoglycemia as monotherapy or when used with metformin
- Weight neutral

Risks and Adverse Events

- Hypoglycemia risk when given with SUs or insulin[a]
- Pancreatitis: new safety data available but patients should still be monitored for signs and symptoms[b,c]

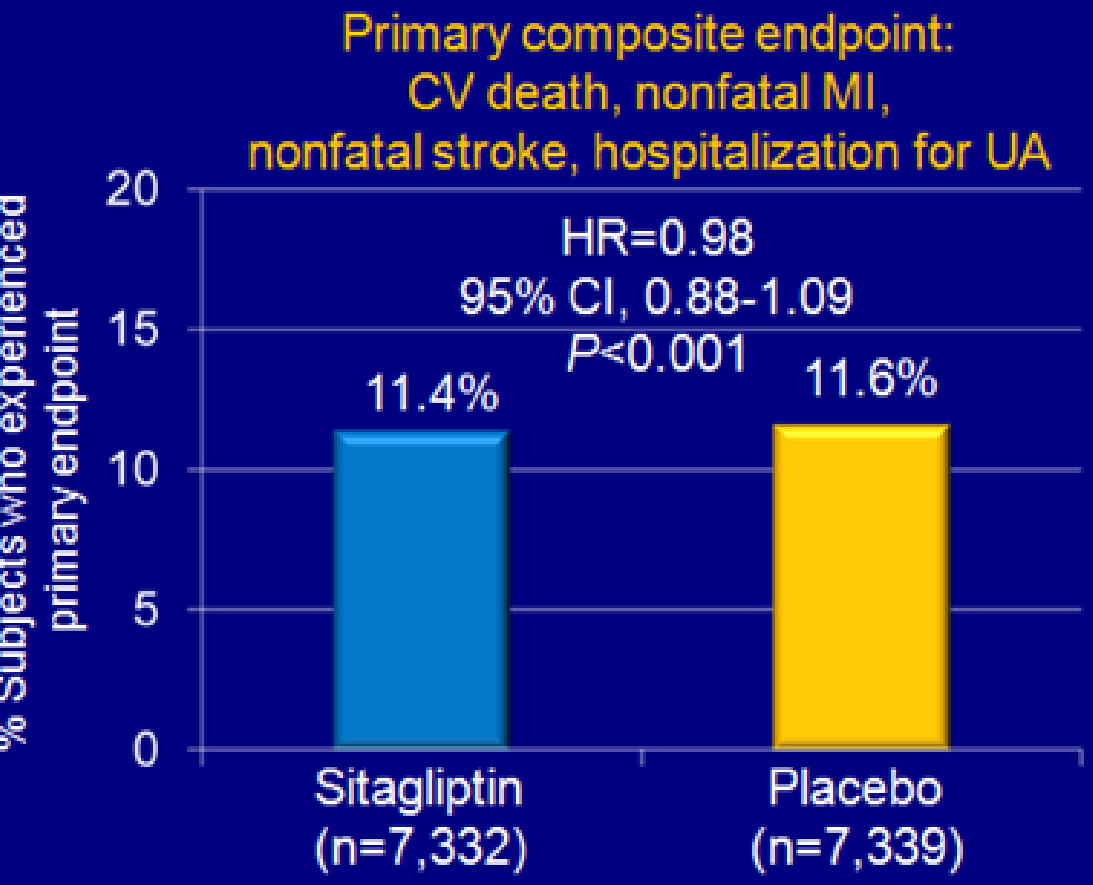
a. Garber AJ, et al. *Endocr Pract*. 2013;19(Suppl 1):1-48.[1]; b. Scirica BM, et al. *N Eng J Med*. 2013;369:1317-1326[8]; c. White WB, et al. *N Eng J Med*. 2013;369:1327-1335.[9]

DPP-4 Inhibitors: Large-Scale CV Safety Studies

Trial	DPP-4 Inhibitor	Study Findings Released/Expected
Post-hoc analyses	All	February 2013[a] June 2013[b]
SAVOR-TIMI	Saxagliptin	September 2013[c]
EXAMINE	Alogliptin	September 2013[d]
TECOS	Sitagliptin	2014[e]
CAROLINA	Linagliptin	2018[e]

a. Monami M, et al. *Adv Ther*. 2012;29:14-25[10]; b. Wu D, et al. *Diabetes Obes Metab*. 2013 June 26. [Epub ahead of print][11]; c. Scirica BM, et al. *N Eng J Med*. 2013;369:1317-1326[8]; d. White WB, et al. *N Eng J Med*. 2013;369:1327-1335[9]; e. Scheen AJ. *Postgrad Med*. 2013;125:7-20.[12]

TECOS: No Increased CV Risk With Sitagliptin Vs Placebo in High-Risk Subjects With Type 2 Diabetes



About TECOS

Cardiovascular safety study of the DPP-4 inhibitor, sitagliptin

Randomized, double-blind, placebo-controlled, event-driven trial

N=14,671 subjects with type 2 diabetes and CVD

Randomization + usual care*:

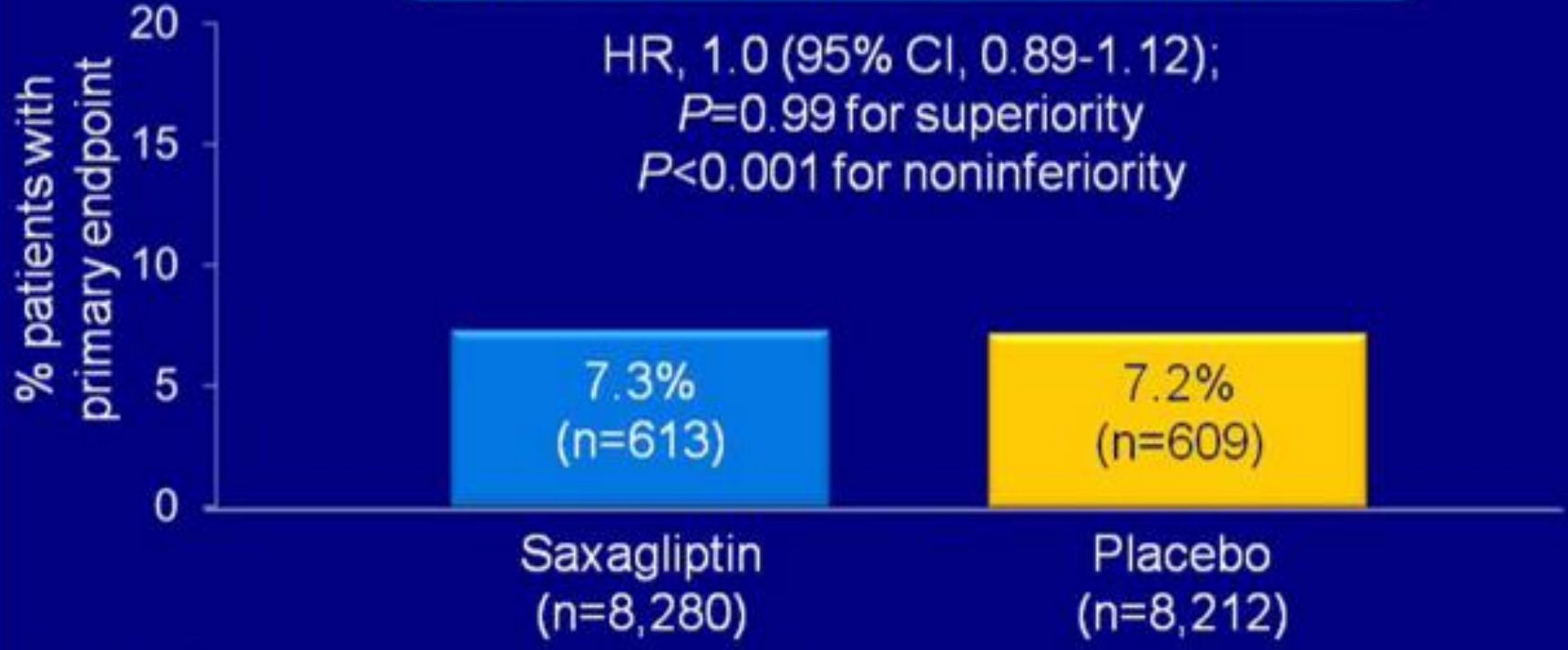
- Sitagliptin 100 mg/d†
- Placebo

TECOS=Trial Evaluating Cardiovascular Outcomes with Sitagliptin
HR=hazard ratio; UA=unstable angina
*Or 50 mg/d if baseline eGFR ≥30 and <50 ml/min/1.73 m^2; †Stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or insulin (with or without metformin)

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

SAVOR-TIMI 53: No Increase in CV Events with Saxagliptin in Patients With or At Risk for CVD

Primary endpoint: composite of CV death, nonfatal MI, or nonfatal ischemic stroke



Saxagliptin is not FDA approved for cardiovascular risk reduction.
SAVOR-TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; CV=cardiovascular; MI=myocardial infarction

Scirica BM et al; for the SAVOR-TIMI 53 Steering Committee and Investigators. *New Engl J Med*. 2013. DOI:10.1056/NEJMoa1307684.

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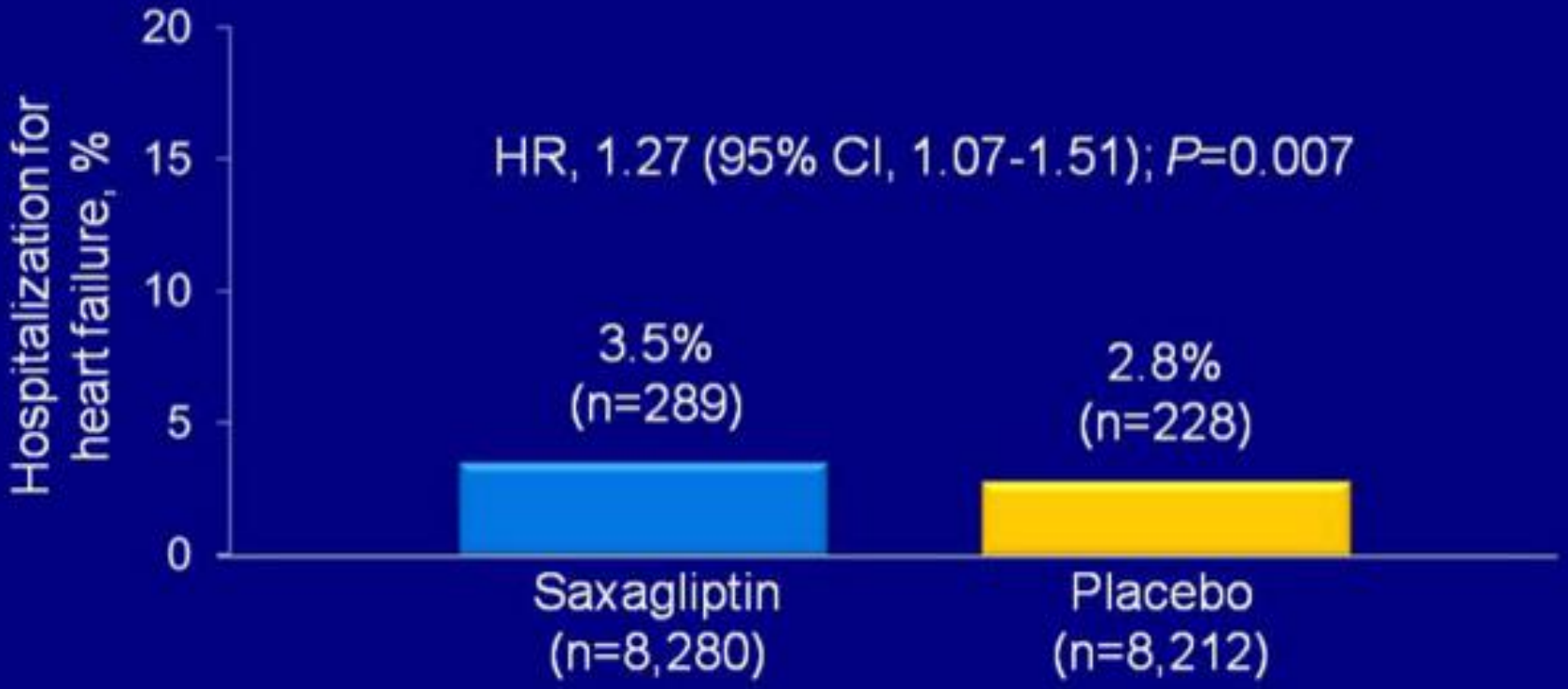
SAVOR-TIMI 53: Saxagliptin Increased Hospitalization for Heart Failure



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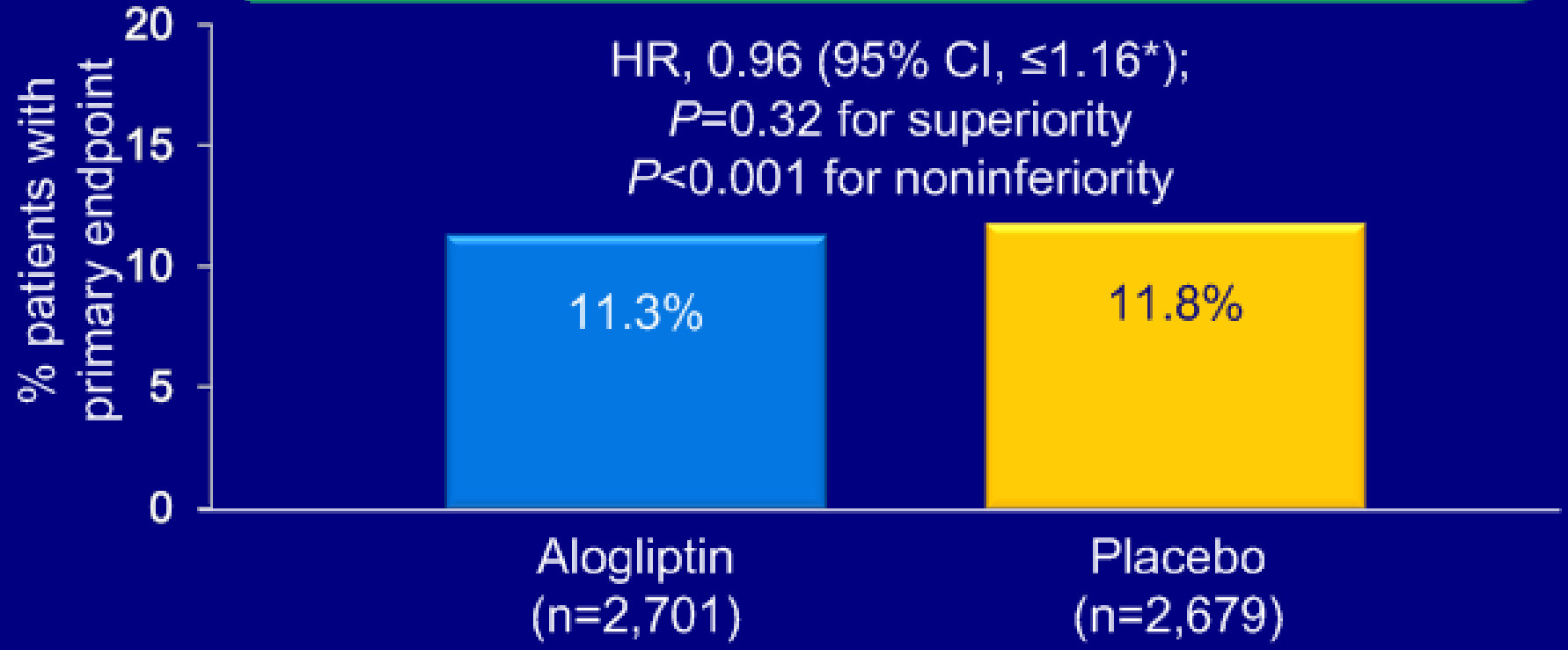
Scirica BM et al; for the SAVOR-TIMI 53 Steering Committee and Investigators. *New Engl J Med*. 2013. DOI:10.1056/NEJMoa1307684.

EXAMINE: No Increase in CV Events with Alogliptin
Primary Endpoint

Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke

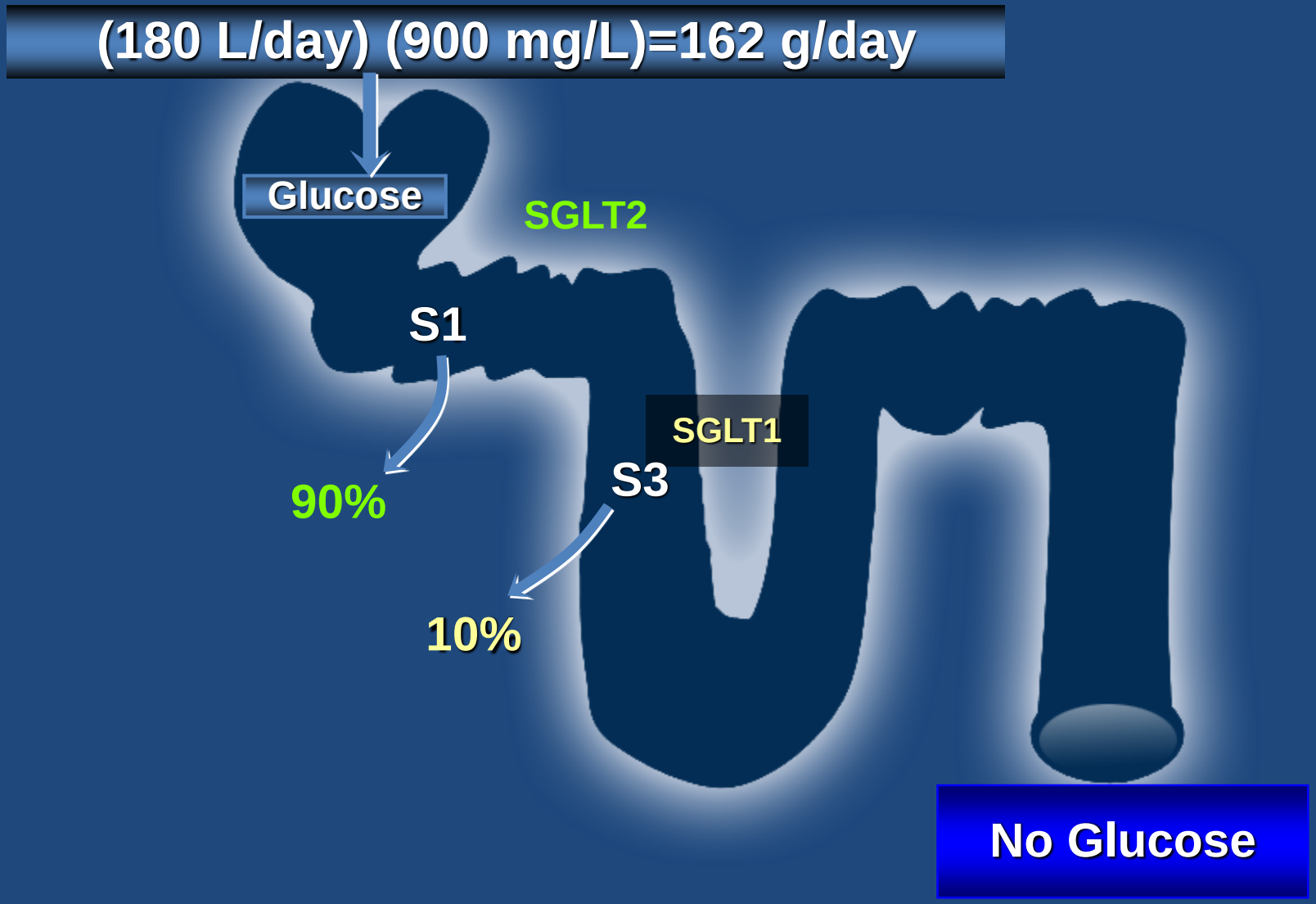


*Upper boundary of one-sided repeated CI
Median follow-up: 18 months
Alogliptin is not FDA approved for cardiovascular risk reduction.
EXAMINE=Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care
CV=cardiovascular; MI=myocardial infarction

FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin


Severe
Joint Pain
from
Diabetes Meds

Renal Handling of Glucose



Rationale for SGLT2 Inhibitors

- Inhibit glucose reabsorption in the renal proximal tubule
- Resultant glucosuria leads to a decline in plasma glucose and reversal of glucotoxicity
- This therapy is simple and nonspecific
- Even patients with refractory type 2 diabetes are likely to respond

SGLT-2 Inhibitors: Benefits

- Lower HbA_{1c} by ~0.4% to 0.9%[a]
- Reduce weight by ~3 to 4 kg[a-c]
- Reduce systolic BP by ~5 to 6 mm Hg[d,e]
- Low risk of hypoglycemia[d,e]
- No increased cardiovascular risk; studies ongoing[f-h]

a. Garber AJ, et al. *Endocr Pract.* 2013;19(Suppl 1):1-48.[1]; b. Abdul-Ghani MA, et al. *Endocr Rev.* 2011;32:515-531[16]; c.Tahrani AA, Barnett AH. *Diabetes Ther.* 2010;1:45-56[17]; d. Stenlöf K, et al. *Diabetes Obes Metab.* 2013;15:372-382[20]; e. Whaley JM. *Diabetes Metab Syndr Obes.* 2012;5:135-148[21]; e. US FDA Briefing Document NDA 204042, 2013[22]; g. US FDA Briefing Document NDA 202293, 2011[23]; h. Foote C, et al, *Diabetes Vasc Dis Research.* 2012;9:117-123.[24]

SGLT-2 Inhibitors: Risks & Adverse Effects

- Main adverse effects
  - Genitourinary tract infections, mainly genital
  - Increased LDL-C with canagliflozin
- Safety concerns
  - Volume depletion/orthostatic hypertension
- Less HbA_{1c} reduction in patients with stage 3 CKD; not recommended for those with stage 4-5 CKD
- Cardiovascular safety studies show no increased cardiovascular risk

a. US FDA Briefing Document NDA 202293, 2011[23]; b. US FDA Briefing Document NDA 204042, 2013.[22]

SGLT2 and DKA

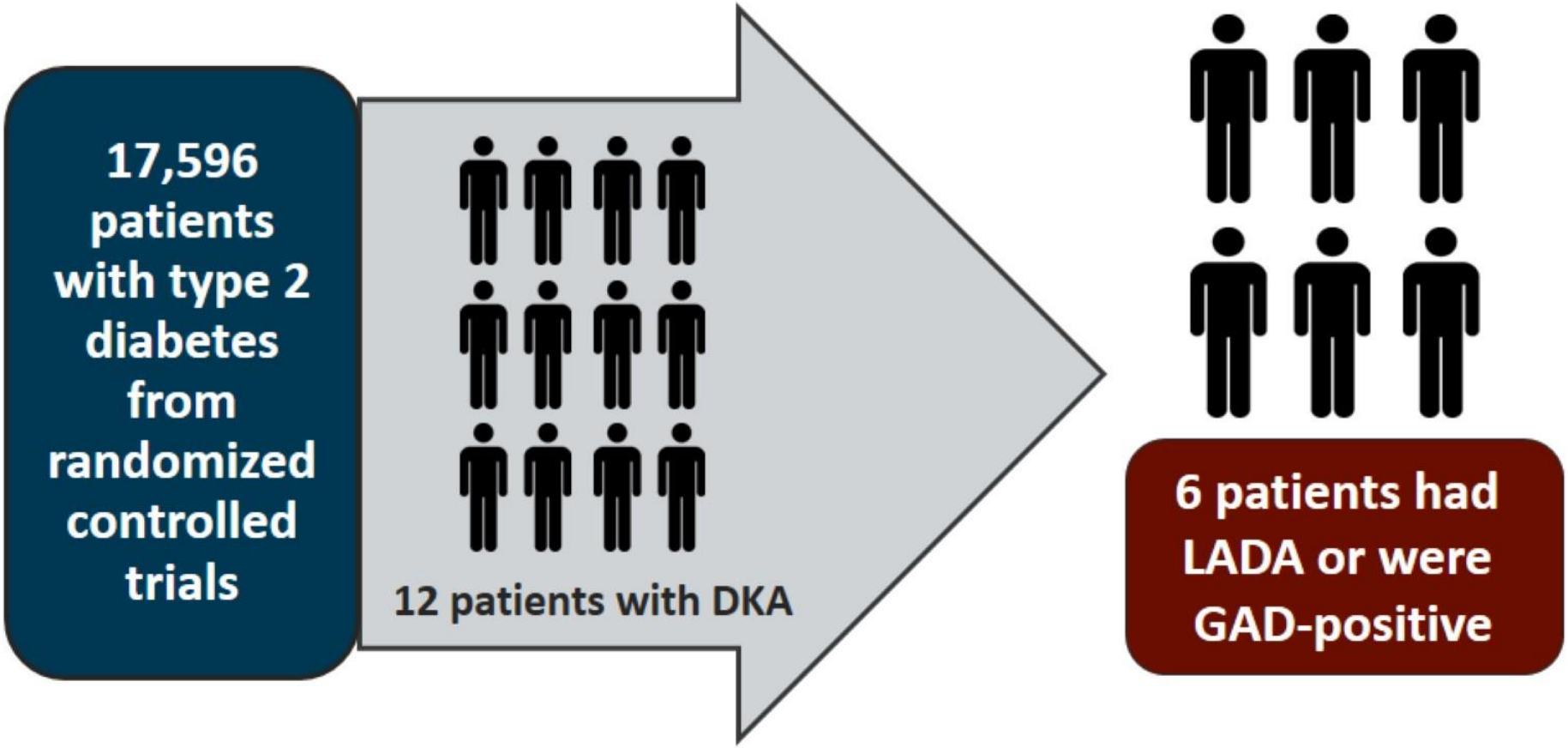
AACE/ACE Scientific and Clinical Review: Association of SGLT2 Inhibitors and DKA

October 24-25, 2015 | Grand Hyatt Dallas Fort Worth Airport

Conclusion Summary

Following recent reports of cases of diabetic ketoacidosis (DKA) in patients treated with sodium glucose cotransporter 2 (SGLT2) inhibitors, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) convened a public conference in which experts from Europe and the United States evaluated each case and case series. Upon review of the available material, together with a thorough discussion of the impact of SGLT2 inhibitors on human metabolism, the experts concluded that the prevalence of DKA is infrequent and the risk-benefit ratio overwhelmingly favors continued use of SGLT2 inhibitors with no changes in current recommendations.

DKA: *Canagliflozin Clinical Program*

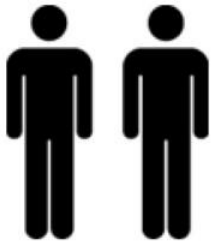


Erondu N, et al. *Diabetes Care*. 2015;38:1680-1686.

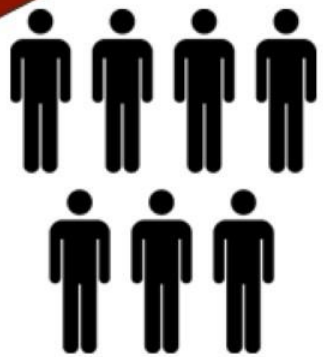
Euglycemic DKA: *Case Studies*

13 episodes of euglycemic DKA

9 patients from clinical practices across the United States on SGLT2 inhibitors



2 had type 2 diabetes; DKA occurred post-surgical procedure

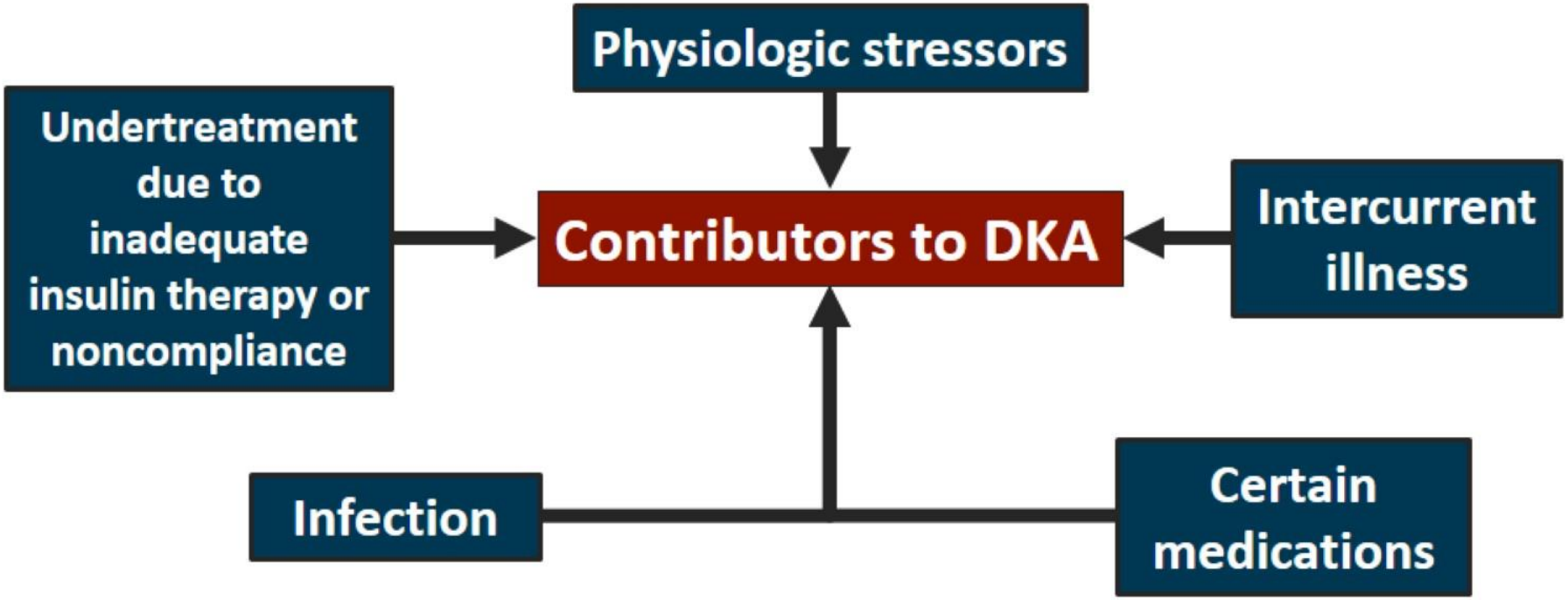


7 had type 1 diabetes

Peters AL, et al. *Diabetes Care*. 2015;38:1687-1693.

Euglycemic DKA

Predictable and Detectable



Rosenstock J, et al. *Diabetes Care*. 2015;38:1638-1642.

SGLT2 Inhibitor-Induced Euglycemic DKA

- Misdiagnosis? Type 2 diabetes vs latent autoimmune diabetes (LADA)
- Patients with type 2 diabetes can be susceptible to DKA under stressful conditions
- SGLT2-induced glycosuria lowers plasma glucose levels, predisposing to increased ketogenesis

Rosenstock J, et al. *Diabetes Care*. 2015;38:1638-1642.

DKA Prevention

- Euglycemic DKA is detectable, and therefore, preventable
- Patients can test their blood ketone at home
- Ketouria and ketonemia can be monitored
- Clinicians and patients need to be educated on the unique presentation of euglycemic DKA

Rosenstock J, et al. *Diabetes Care*. 2015;38:1638-1642.

2015 AACE/ACE Expert Recommendations: DKA

- Unclear if DKA occurs more often in patients with type 2 diabetes than prior to the use of SGLT2 inhibitors
- DKA mostly occurs in situations of insulin deficiency
- At this time, no changes in prescribing guidance have been mandated for SGLT2 inhibitors

AACE/ACE 2015.

2015 AACE/ACE Expert Recommendations: DKA (cont)

- Patients and healthcare professionals need to be aware of the signs of DKA and promptly seek treatment to properly manage the acidosis, if present
- Urinary ketones and low bicarbonate may be inaccurate measures of DKA
- Beta hydroxybutyrate and arterial pH recommended for diagnostic confirmation

AACE/ACE.

Invokana and Invokamet (canagliflozin): Drug Safety Communication - New Information on Bone Fracture Risk and Decreased Bone Mineral Density

Class effect??

Canagliflozin: Changes to Adverse Reactions Section: *Risk for Bone Fractures*

"The occurrence of bone fractures was evaluated in a pool of 9 clinical trials with a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator, canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively. Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (eg, fall from no more than standing height), and affect the upper extremities."

Invokana® PI 2015.

EMPA-REG OUTCOME TRIAL

Bone Fractures

Adverse Effect	Placebo (n = 2333)		Empagliflozin 10 mg (n = 2345)		Empagliflozin 25 mg (n = 2342)	
	N (%)	Rate*	N (%)	Rate*	N (%)	Rate*
Bone fractures	91 (3.9)	1.6	92 (3.9)	1.6	87 (3.7)	1.5

*Rate = per 100 patient-years. Patients treated with ≥ 1 dose of study drug.

Zinman B, et al. *N Engl J Med*. 2015;Sep 17 [Epub ahead of print].

Clinical Relevance

Use of SGLT2 Inhibitors in Older Individuals

- In patients at high risk for falls, consider discontinuing the diuretic if starting an SGLT2 inhibitor
- Consider lowering the recommended dose of the SGLT2 inhibitor in high-risk patients (off-label)
- Physical therapy for balance and strength training can be helpful

Canagliflozin
Change in BMD

- Postmarketing study evaluated changes in BMD over 2 years in 714 older adults (mean age, 64 y)

- Placebo-corrected decreases in BMD at the total hip (0.9% and 1.2% with 100 mg and 300 mg canagliflozin, respectively) and lower spine (0.3% and 0.7% with 100 mg and 300 mg canagliflozin, respectively)

- Placebo-adjusted BMD declines of 0.1% seen at the femoral neck for both canagliflozin doses, and of 0.4% at the distal forearm for patients taking the 300-mg canagliflozin dose

Invokana® PI 2015.

Risk Factors for Recurrent Falls

Major Risk Factors for Recurrent Falls
Age
Female gender
History of previous falls
Mobility impairment
Low level of activity
Arthritis
Cognitive impairment
Fall-risk-increasing drugs

de Jong MR, et al. *Ther Adv Drug Saf*. 2013;4:147-154.

EMPA-REG OUTCOME TRIAL

DKA

Adverse Effect	Placebo (n = 2333)		Empagliflozin 10 mg (n = 2345)		Empagliflozin 25 mg (n = 2342)	
	N (%)	Rate*	N (%)	Rate*	N (%)	Rate*
DKA	1 (< 0.1)	0.02	3 (0.1)	0.05	1 (<0.1)	0.02

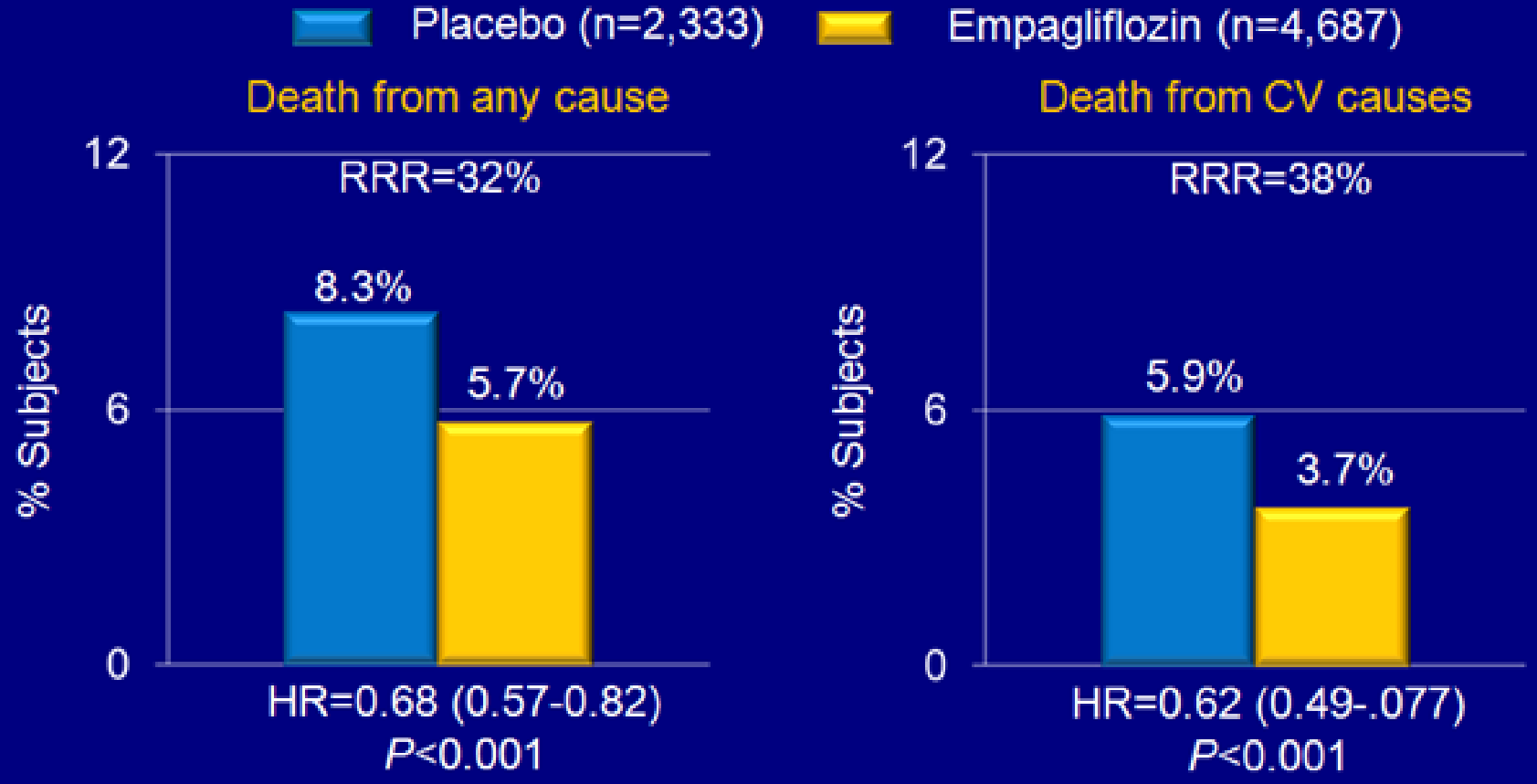
*Rate = per 100 patient-years. Patients treated with ≥ 1 dose of study drug.

Zinman B, et al. *N Engl J Med*. 2015 Sep 17. [Epub ahead of print].

Lower All-Cause & CV Mortality With Empagliflozin Vs Placebo in High-Risk Patients

EASD 2015

EMPA-REG OUTCOME



39 patients would need to be treated over 3 years to prevent 1 death

CV=cardiovascular; MI=myocardial infarction; RRR=relative risk reduction

Zinman B, et al; for the EMPA-REG OUTCOME Investigators. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa1504720.

New Long acting basal Insulins

Many patients with type 2 diabetes continue to have poor control and would benefit from insulin therapy . However, resistance to the introduction of insulin therapy can be high on both the part of the healthcare provider and the patient .

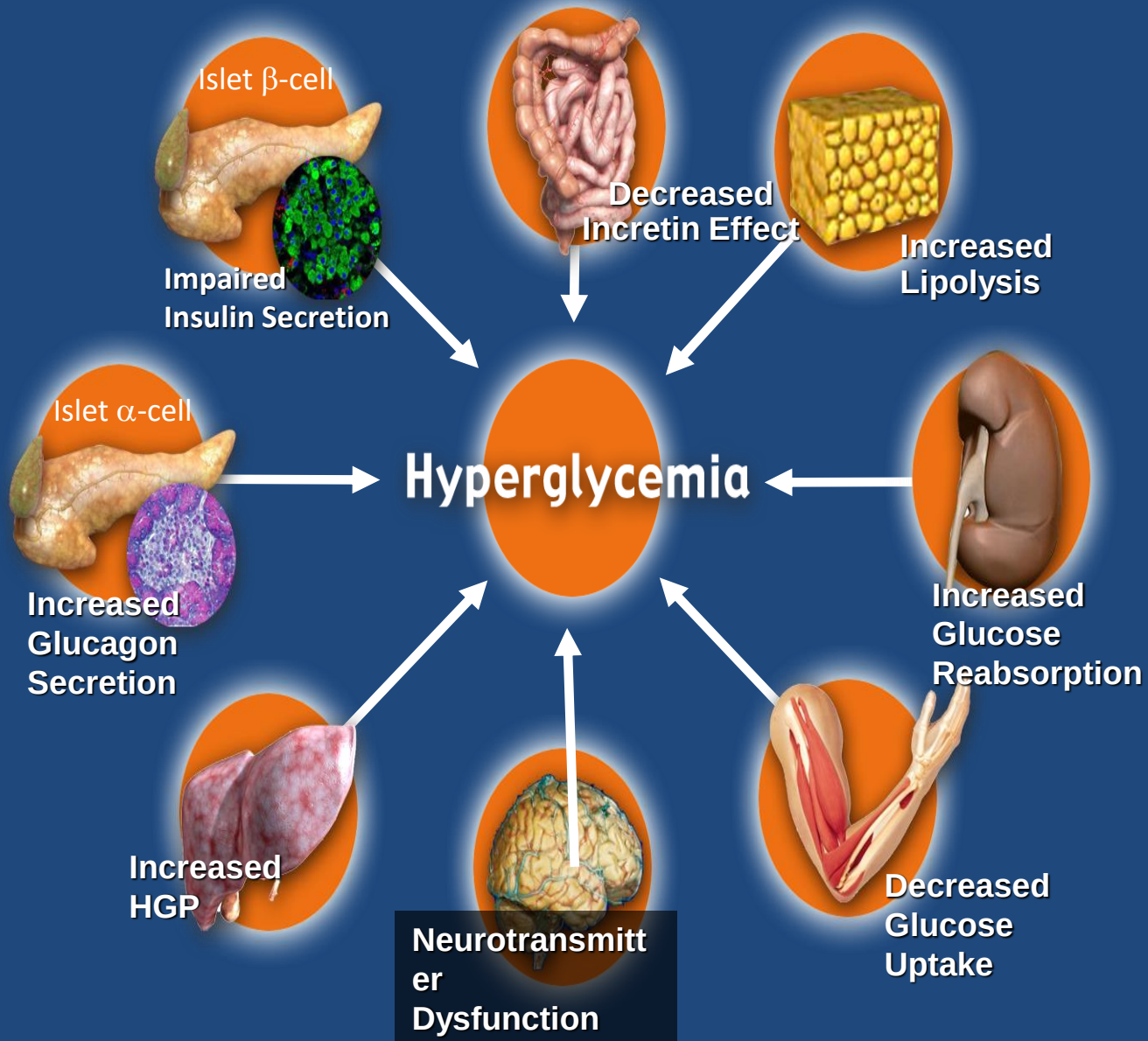
A number of new, long acting basal insulins are in development that provide good metabolic control , with **lower a risk of hypoglycemia** , than the currently available insulins.

Providing **greater flexibility** in dosing time from day to day.

These attributes may address some of the current barriers to **insulin initiation and intensification** that currently limit the effectiveness of diabetes care.

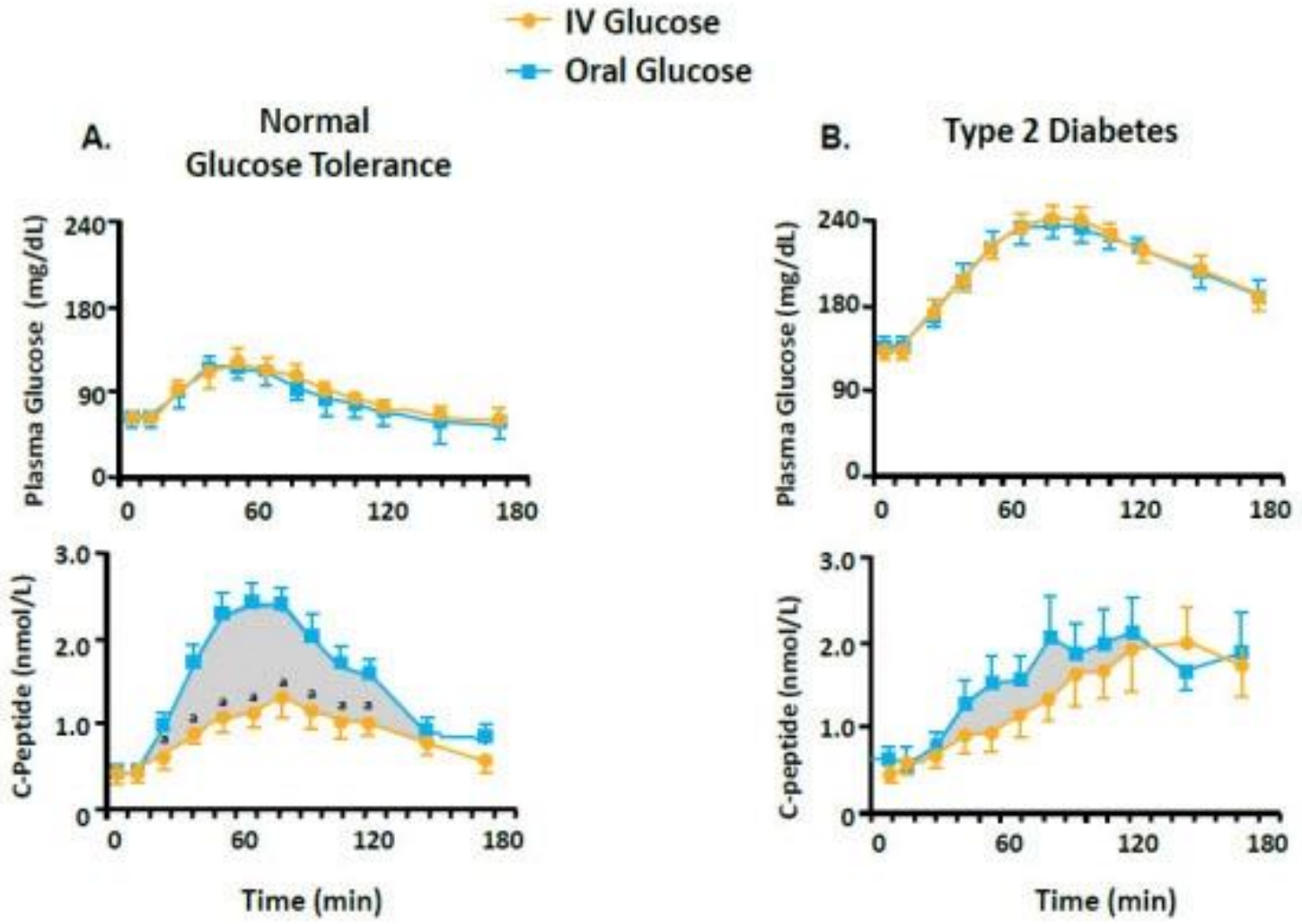
Diabetes type 2 is a polygenic and multifactorial disease

The Ominous Octet



THE HISTORY OF INCRETINS

- In 1902, **Bayliss and Starling** proposed that intestinal mucosa contains a hormone, which stimulates the exocrine secretion of the pancreas ("**Secretin**"). However, oral administration of extracts of intestinal mucosa failed to help several patients with type 1 diabetes.
- In 1932 **La Barre** proposed the **name 'incretin'** for a hormone extracted from the upper gut mucosa, which caused hypoglycaemia and proposed a possible therapeutic role in diabetes.
- In **1939–1940**, based on their studies, **Leow et al. concluded the existence of incretins was "questionable**." No further research in this area was performed for about thirty years until 1970. However, as molecular biology advanced this **hypothesis was re-vi**sited with the subsequent development of a therapeutic strategy that would revolutionise the treatment of type 2 diabetes.


IV Glucose
Oral Glucose
A.
Normal
Glucose Tolerance
B.
Type 2 Diabetes
Plasma Glucose (mg/dL)
240
180
90
0
0
60
120
180
C-Peptide (nmol/L)
3.0
2.0
1.0
0
Time (min)
C-peptide (nmol/L)

$P \leq .05$

The Potential for GLP-1 Agonists and Other Gut Hormones

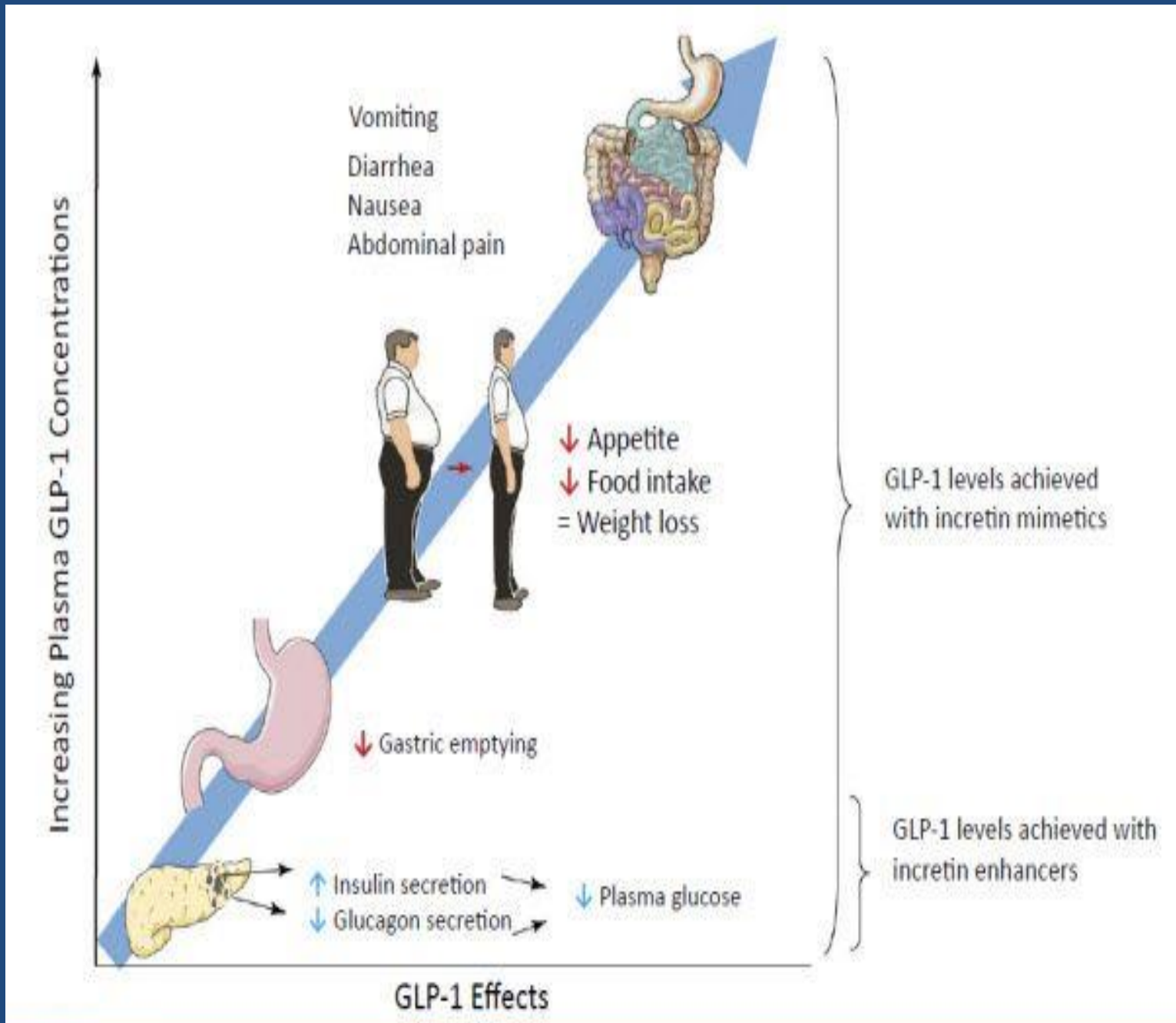
- Limitations of native or mimetic GLP-1 as therapy
  - Rapidly degraded by DPP-4 in minutes
  - Requires continuous subcutaneous injection
- Alternative approaches
  - Modification of molecule to prolong time of action

Exenatide; Liraglutide

  - Agents to limit DPP-4 activity

DPP-4 Inhibitors: Sitagliptin, Vildagliptin , Saxagliptin, denagliptin

Kieffer TJ, Habener JF. *Endocr Rev.* 1999;20:876-913.


Increasing Plasma GLP-1 Concentrations
Vomiting
Diarrhea
Nausea
Abdominal pain
↓ Appetite
↓ Food intake
= Weight loss
↓ Gastric emptying
↑ Insulin secretion
↓ Glucagon secretion
↓ Plasma glucose
GLP-1 levels achieved with incretin mimetics
GLP-1 levels achieved with incretin enhancers
GLP-1 Effects

Differentiation of GLP-1-RAs

Criteria	Characteristic
Source[a]	Human-based OR exendin-4-based
Dose frequency[a]	Twice-daily OR once-daily OR once-weekly
Pharmacokinetics[a]	Short-acting OR long-acting
Receptor agonism[b]	Transitory OR continuous
Main glycemic target[a,b]	Prandial OR fasting

a. Meier JJ. *Nat Rev Endocrinol*. 2012;8:728-742[1]; b. Fineman et al. *Diabetes Obes Metab*. 2012;14:675-688.[2]

Short-Acting vs Long-Acting GLP-1 RAs: Pharmacokinetic Differences

Increasing protraction

Category	Agent	Half-life	T_{max}
Short-acting GLP-1 RAs	**Exenatide bid**[a]	2.4 hours	2 h
	Lixisenatide[a]	2.7-4.3 hours	1.25-2.25 hours
Long-acting GLP-1 RAs	**Liraglutide**[a]	13 hours	8-12 hours
	Dulaglutide[b]	90 hours	24-48 hours
	Albiglutide[a]	5 days	3-5 days
	Semaglutide[a]	~7 days	1-1.5 days
	Exenatide qw[g]	7-14 days	6-7 weeks

a. www.ema.europa.eu/ema/; b. Barrington P, et al. *Diabetes Obes Metab.* 2011;13:434-438; c. Fineman M, et al. *Clin Pharmacokinet.* 2011;50:65-74.

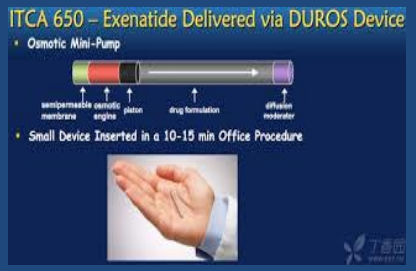
Glp-1 receptor agonists

Short acting

- Exenatide (twice a day)
- Liraglutide (once daily)
- Lixisenatide* (once daily)

Long acting (one a week)

- Exenatide QW (Bydureon)
- Albiglutide (Tanzeum)
- Dilaglutide (Trulicity)
- *Semaglutide
- *ITCA 650 pump (exenatide continuous)



*not yet approved by FDA

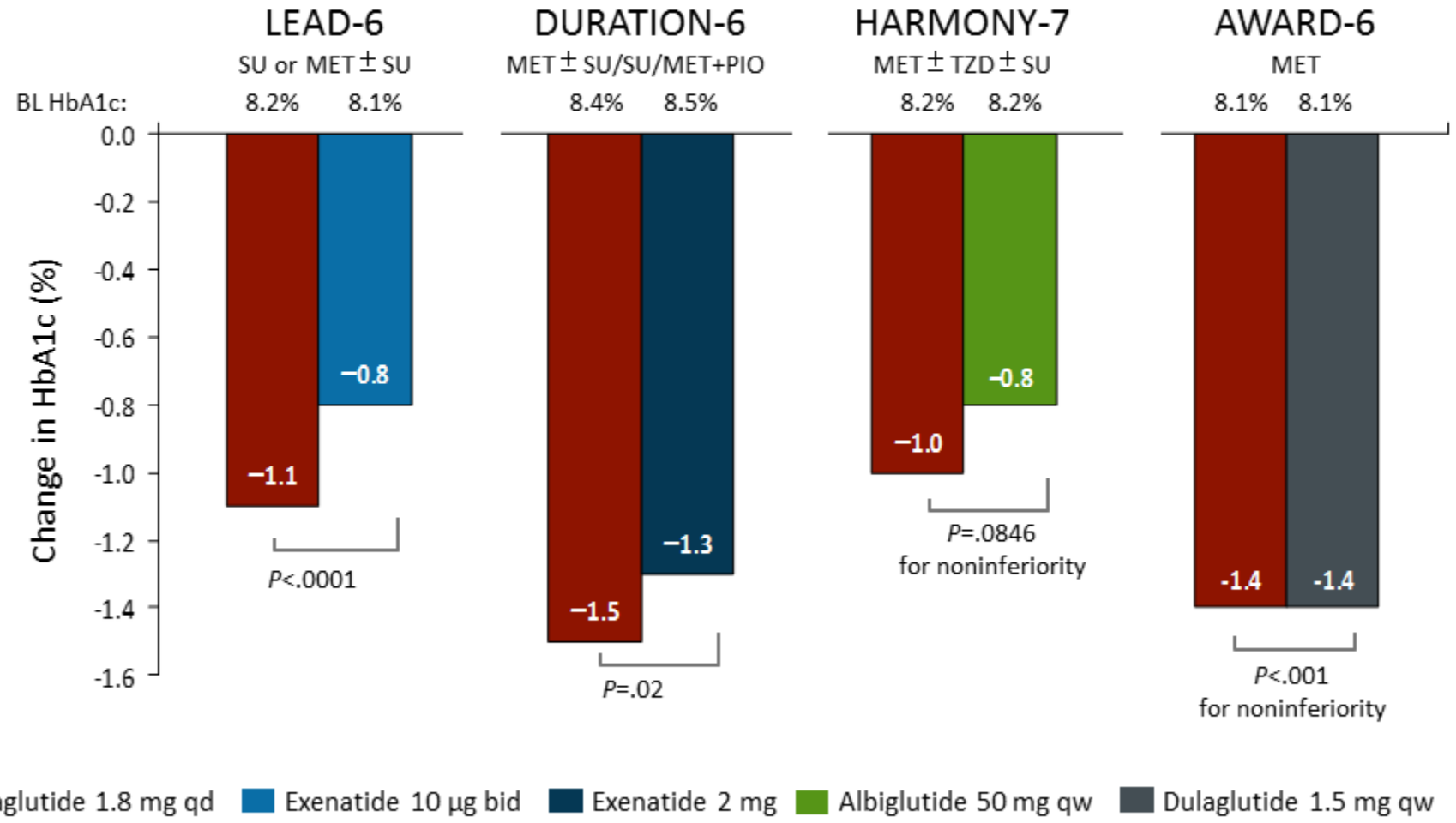
Potential of Once-Weekly GLP-1 Receptor Agonists: Exenatide QW

- HbA_{1c} lowering = -1.6%
- Fewer gastrointestinal adverse effects than shorter-acting GLP-1 RAs
  - Incidence varies among once-weekly GLP-1 RAs
- Average weight loss = -4.3 kg
- Durability of response

Exenatide once-weekly
Albiglutide once-weekly
Dulaglutide*

Henry R, et al. ADA 2014. Poster 964-P.[12]

Glycemic Control With GLP-1 RAs: Head-to-Head Studies



Buse JB, et al. *Lancet.* 2009;374:39-47 (LEAD-6); Buse JB, et al. *Lancet.* 2013;381:117-124 (DURATION-6); ClinicalTrials.gov (NCT01029886) (DURATION-6); Pratley RE, et al. *Lancet Diabetes Endocrinol.* 2014;2:289-297 (HARMONY-7); Dungan KM, et al. *Lancet.* 2014;384:1349-1357 (AWARD-6).

Potential Clinical Advantages of GLP-1 Receptor Agonists

- Weight reduction
- Low to no risk for hypoglycemia when used as monotherapy

Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379.[4]

Physiologic Effects of GLP-1 Receptor Agonists

- Increased GLP-1 activity
  - Decreased glucagon production[a]
  - Increased insulin synthesis and secretion[a]
- Glycemic control
  - Decreased HbA_{1c}[b,c]
  - Decreased FPG[a-c]
  - Decreased PPG[a]
- Weight effects
  - Decreased gastric emptying[a]
  - Decreased caloric intake[a]
  - Weight loss[a-c]

a. DeFronzo RA, et al. *Curr Med Res Opin*. 2008;24:2943-2952[5]; b. Pratley R, et al. *Lancet*. 2010;375:1447-1456[6]; c. Russell-Jones D, et al. *Diabetes Care*. 2012;35:252-258.[7]

Potential for GLP-1 RAs as First-Line Therapy

- Metformin will likely remain first-line therapy
- Increasing clinical research into clinical effects of GLP-1 RAs but no current evidence that these agents improve insulin sensitivity
- Can we identify early responders to treatment?
- Cost of GLP-1 RAs currently high; may be a barrier for some

Cernea S, et al. *Diabetes Care*. 2011;34(suppl 2):S264-S271.[8]

Choosing Between Agents With Low Rates of Hypoglycemia

Antihyperglycemic Agent	Effect on Weight
GLP-1 RAs	
DPP-4 inhibitors	
SGLT-2 inhibitors	

Potential Clinical Disadvantages of GLP-1 Receptor Agonists

- Compliance
- Injectable
- Gastrointestinal adverse effects
- Training requirements
- High cost

Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379.[4]

ADA/EASD Position Statement: Managing Hyperglycemia in Type 2 Diabetes

Pharmacologic Treatment Options for Type 2 Diabetes (2 of 4)

Lifestyle interventions—diet, exercise, and education—are the foundation of any type 2 diabetes treatment program

Class/Agent(s)	Cost	Advantages	Disadvantages
Dopamine-2 agonists* • Bromocriptine (quick release)	High	No hypoglycemia ?↓ CVD events	Modest A1C efficacy Dizziness/syncope Nausea Fatigue Rhinitis
DPP-4 inhibitors • Linagliptin • Saxagliptin • Sitagliptin • Alogliptin • Vildagliptin†	High	No hypoglycemia Well tolerated	Urticaria/angioedema ?Acute pancreatitis ? Heart failure hospitalization
GLP-1 receptor agonists • Exenatide (regular, XR) • Liraglutide • Albiglutide • Dulaglutide • Lixisenatide	High	No hypoglycemia Weight reduction ↓ PPG excursions ↓ Some CVD risk factors	GI side effects (nausea, vomiting, diarrhea) ?Acute pancreatitis C-cell hyperplasia/medullary thyroid tumors† ↑ Heart rate Injectable Training requirements

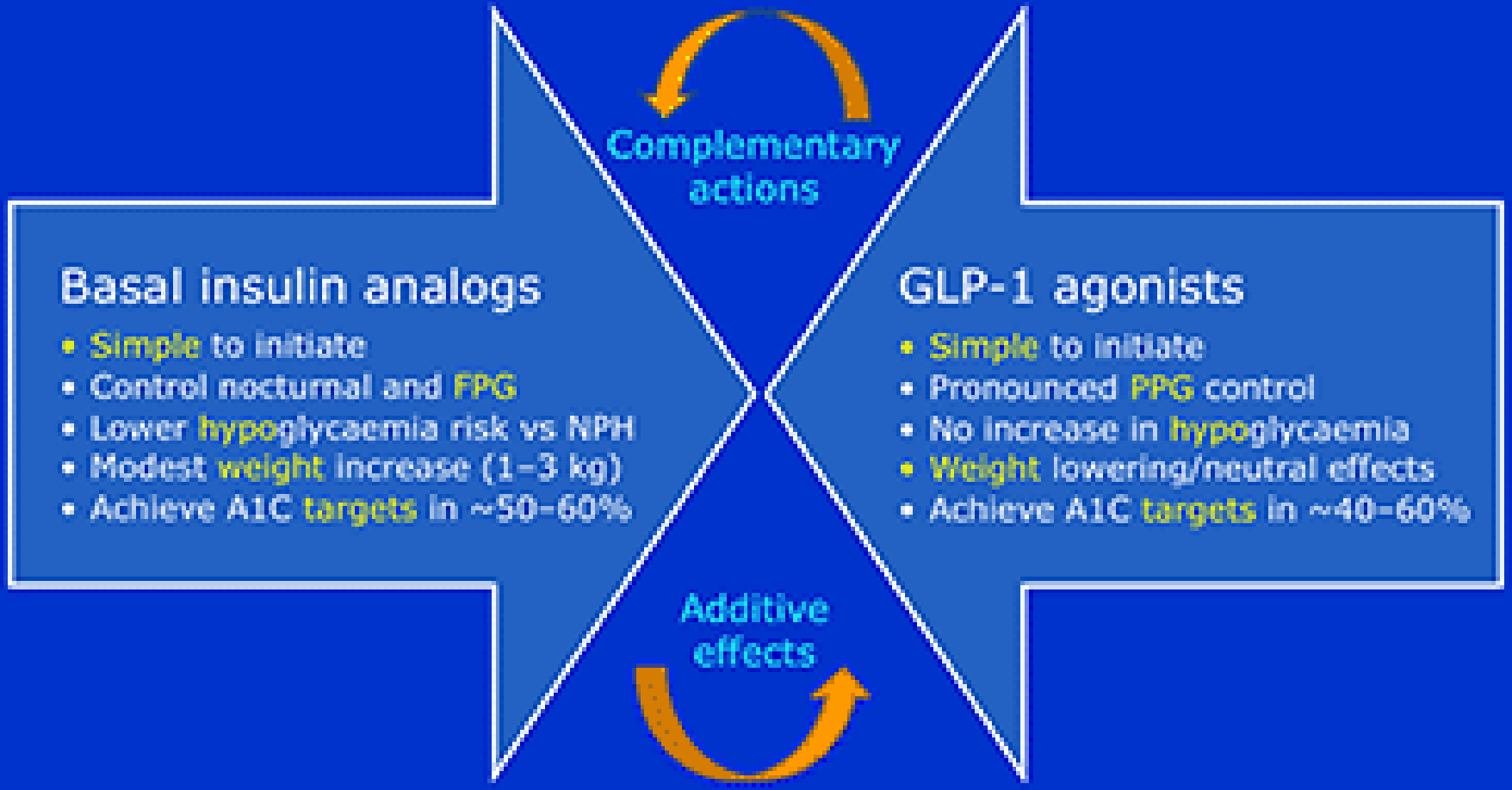
*Limited use in US; †In animals; ‡Not FDA approved in US

Inzucchi SE et al. *Diabetes Care*. 2015;38(1):140-149.

GLP-1 receptor agonists
—Exenatide (regular, XR)
—Liraglutide
—Albiglutide
—Dulaglutide
—Lixisenatide†

Cost	*Advantages*	*Disadvantages*
High	No hypoglycemia Weight reduction Decreases PPG excursions Decreases some CVD risk factors	GI side effects May cause acute pancreatitis C-cell hyperplasia/ medullary thyroid tumors in animals Increases heart rate Injectable Training requirements

Combination of Basal Insulin with a GLP-1 Agonist Has a Scientific Logic



IDegLira* vs Glargine

Comparison of Efficacy and Safety in DUAL V

Degludec and liraglutide

	IDegLira* (N = 278)	Glargine (N = 279)	*P* Value
Mean HbA_{1c} at randomization, %	8.4	8.2	-
Mean HbA_{1c} at wk 26, %	6.6	7.1	< .001
HbA_{1c} change at wk 26, %	-1.8	-1.1	< .001
HbA_{1c} < 7% at wk 26, %	71.6	47.0	< .001
Body weight at baseline, kg	88.3	87.3	-
Body weight at wk 26, kg	86.9	89.1	< .001
Body weight change at wk 26, kg	-1.4	+1.8	< .001
Hypoglycemia rate, events/patient year of exposure			
Confirmed	2.23	5.05	< .001
Nocturnal	0.22	1.23	< .001

*The US FDA has not approved this medication for use.

Buse JB, et al. ADA 2015. Abstract 166-OR.[11]

LixiLan* vs Glargine

Proof-of-Concept Study in Patients With T2D Inadequately Controlled on Metformin

Lixenatide GLP-1 RA

	LixiLan (N = 161)	Glargine (N = 162)
Mean HbA_{1c}, %	8.1	8.0
Mean HbA_{1c} at week 24, %	6.3	6.5
Change in HbA_{1c} at week 24, %	-1.8	-1.5
Proportion achieving HbA_{1c} < 7.0%, %	84.4	78.3
Body weight at baseline, kg	90.3	91.7
Body weight at week 24, kg	89.1	92.1
Change in body weight at week 24, kg	-1.2	+0.4
Proportion with documented hypoglycemia (≤ 70 mg/dL), %	22	23

*The US FDA has not approved this medication for use.

Rosenstock J, et al. ADA 2014. Abstract 332-OR.[14]
Venkat MV, et al. *J Diabetes.* 2014;6:491-495.[15]

Safety – Patient Education

- "Both [the FDA and EMA] agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data."[a]
- Educate patients; monitor for signs and symptoms of pancreatitis; ask about medical history of pancreatitis.[a,b]
- Discontinue the GLP-1 receptor agonist if pancreatitis symptoms occur.[a,b]

a. Egan AG, et al. *N Engl J Med*. 2014;370:794-797.[17]
b. EMA website.[18]