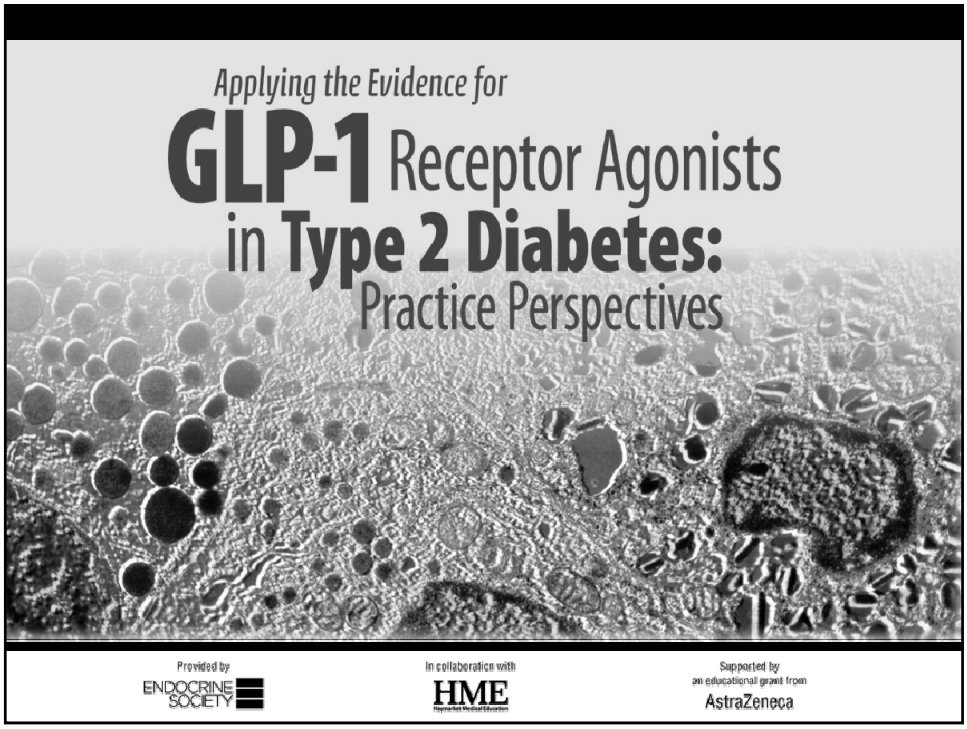

Agenda

- **Insights into the Physiologic Action of the GLP-1 RAs**
  Adrian Vella, MD
- **New Safety Data and Ongoing Cardiovascular Trials**
  Anne L. Peters, MD
- **Patient Preferences and Novel Regimens Incorporating GLP-1 RAs With Insulin**
  Sam Dagogo-Jack, MD, MBBS, FRCP

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Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Evaluate the most recent evidence when considering use of a GLP-1 RA as part of a T2DM treatment plan
- Review updated safety data for the GLP-1 RA drug class
- Discuss the nonglycemic effects of GLP-1 RAs, including their positive impact on weight and cardiovascular risk factors
- Describe the optimal use of GLP-1 RAs in the context of practice-based clinical scenarios

Disclosures

The following faculty reported relevant financial relationships:

- **Sam Dagogo-Jack, MD, MBBS, FRCP:** *Principal Investigator*, AstraZeneca, Boehringer Ingelheim, Novo Nordisk; *Consultant*: Merck & Co., Novo Nordisk
- **Silvio E. Inzucchi, MD:** *Scientific Board Member*, Boehringer Ingelheim, Eisai, Lexicon Pharmaceuticals, Inc.; *Speaker,* AstraZeneca; *Research Support,* Takeda
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- **Adrian Vella, MD:** *Consultant,* Genentech, Inc., Sanofi; *Research Funding,* BioKier, Novartis

The following SPC member who reviewed content for this activity reported relevant financial relationships:

- **Anton Luger, MD:** *Advisory Board Member, Investigator, and Speaker,* Novo Nordisk; *Advisory Board Member and Speaker,* AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Ipsen, Merck, Novartis, Pfizer, Reckitt Benckiser, Sharp & Dohme, Takeda; *Investigator*, Roche

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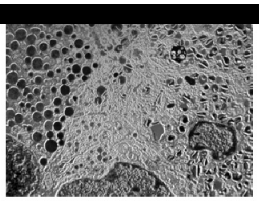

What's New With GLP-1 Receptor Agonists?

Adrian Vella, MD
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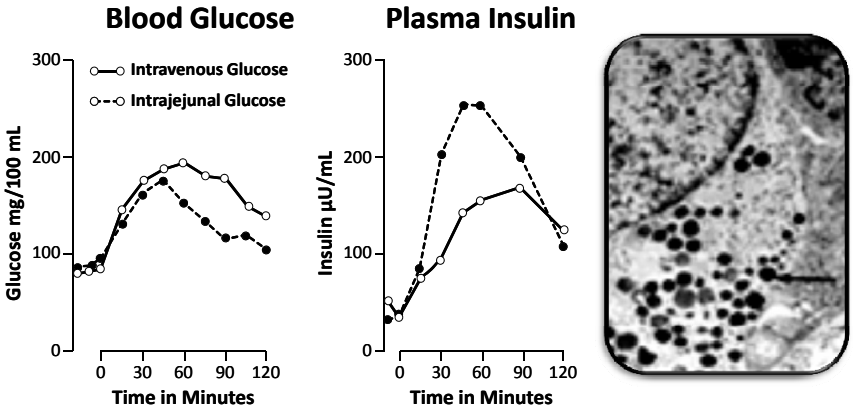
Physiology of GLP-1

- Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the gut in response to nutrients
  - Appears in the plasma within minutes of food ingestion; is rapidly degraded by dipeptidyl peptidase-4 (DPP-4)
  - Actions include:
    - Enhancement of insulin secretion
    - Suppression of glucagon secretion
    - Slowing of gastric emptying
    - Reduction in food intake

GLP-1 Corrects Several of the Metabolic Defects Seen in Patients With T2DM

	Defects in Type 2	Effects of GLP-1
Insulin secretion	↓	↑
Glucagon secretion	↑ or ↔	↓
Islet insulin content	↓	↑ (*in vitro*)
Food intake	Excessive	↓
Gastric emptying	↑ or ↔	↓
Glucose effectiveness	↓	—
Insulin action	↓	—

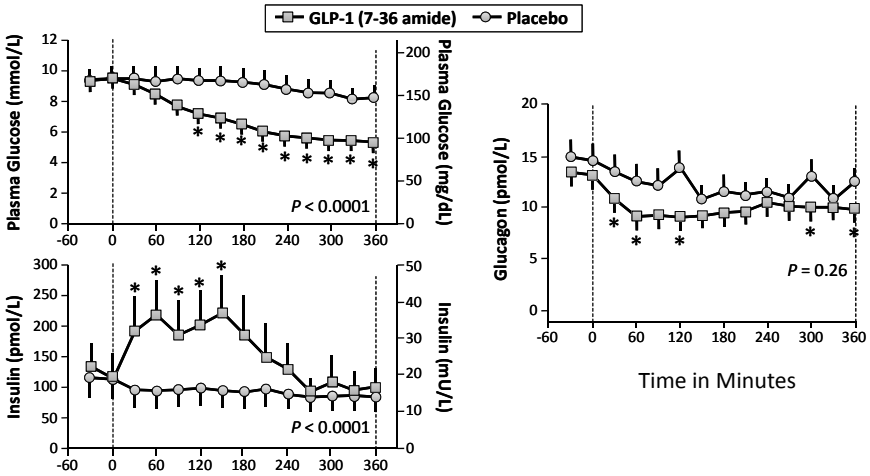
Route of Glucose Administration Affects Plasma Insulin Levels



Intrajejunal glucose infusion results in greater plasma insulin and lower blood glucose levels than intravenous glucose infusion, suggesting that the gut influences insulin secretion.

McIntyre N, et al. *Lancet*. 1964;2:20-21.

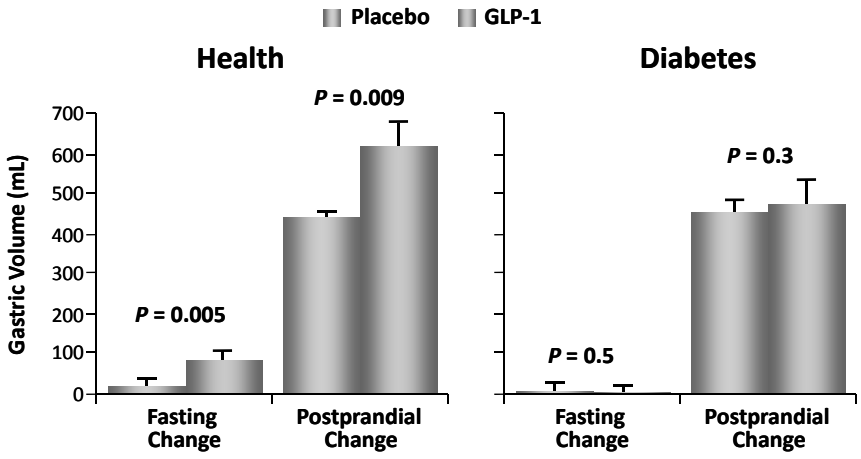
GLP-1 Affects Secretion of Pancreatic Hormones



Intravenous infusion of GLP-1 (7-36 amide) in patients with poorly-controlled T2DM results in normalization of fasting plasma glucose.

Nauck MA, et al. *Diabetologia.* 1993;36:741-744.

GLP-1 Increases Gastric Volume in Healthy Individuals But Not in Diabetic Patients With Vagal Neuropathy



Intravenous GLP-1 infusion did not increase gastric volume in diabetics with vagal neuropathy, suggesting GLP-1's effects on stomach volume are vagally mediated.

Delgado Aros S, et al. *Neurogastroenterol Motil*. 2003;15:435-443.

Measurement of Gastric Accommodation

Images of the stomach were acquired by single photon emission computed tomography (SPECT)

Delgado Aros S, et al. *Neurogastroenterol Motil*. 2003;15:435-443.

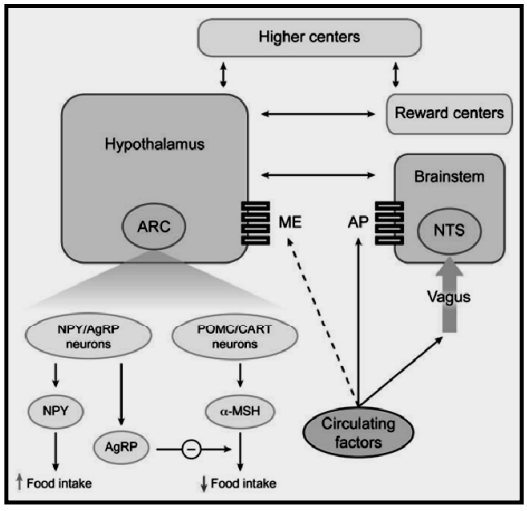
The CNS Integrates Appetite Signals

AP = area postrema

ME = median eminence

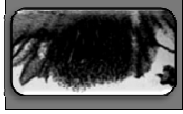
NTS = nucleus tractus solitarius

ARC = arcuate nucleus



Chaudhri OB, et al. *Annu Rev Physiol*. 2008;70:239-255.

Circumventricular Organs May Play a Role in Sensing GLP-1 and Other Hormones Controlling Energy Homeostasis

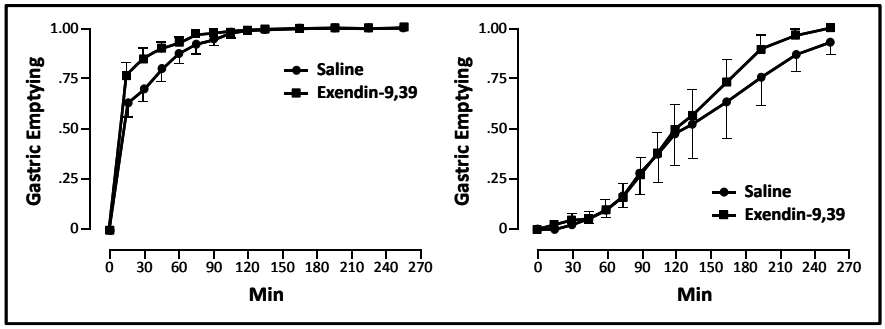
	Adiponectin	Amylin	Angiotensin	CCK	Ghrelin	GLP-1	Oxyntomodulin	Peptide YY	Vasopressin
	Adipo R1/R2	CTA-RAMP3	AT1A	CCK-1	GHSR	GLP-1R	GLP-1R	Y1/ Y2/Y5	V1
	R	R	R		R	R	R	R	
			P	P				P	
			Ph	Ph		Ph	Ph	Ph	Ph
	R	R	R		R	R	R	R	
		P	P						
		Ph	Ph			Ph	Ph	Ph	Ph

AP = area postrema; **NTS** = nucleus tractus solitarius; **SFO** = subfornical organ.

The circumventricular organs are a specialized group of CNS structures, which are not protected by the blood-brain barrier. They may play an important role in blood-brain communications and regulation of energy balance.

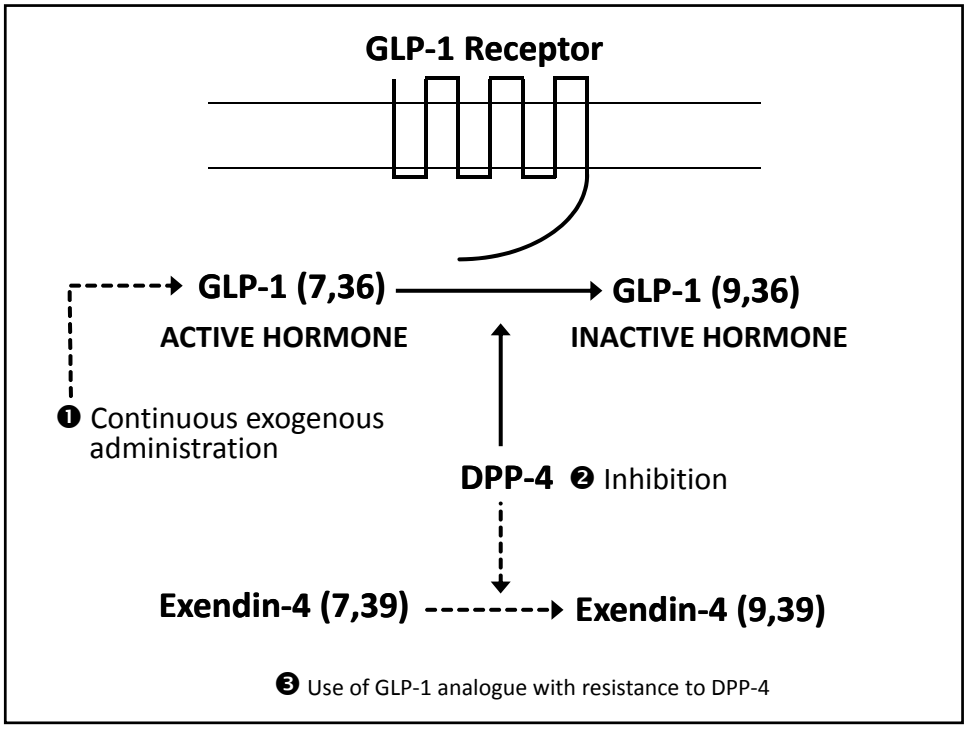
Hoyda TD, et al. *Int J Obes (Lond).* 2009;33 (suppl 1):S16-S21.

GLP-1 Regulates Food Intake and the Rate of Gastric Emptying



- Intravenous administration of exenatide decreases food intake. GLP-1 receptor blockade with exendin (9-39), a competitive antagonist of GLP-1, blocks this effect
- Exendin (9-39) significantly increases the rate of gastric emptying in the first 45 minutes after food ingestion In patients post-Roux-en-Y gastric bypass but not healthy controls

Van Bloemendaal, et al. *Diabetes.* 2014;63:4186-4196.
Shah M, et al. *Diabetes.* 2014;63:483-493.



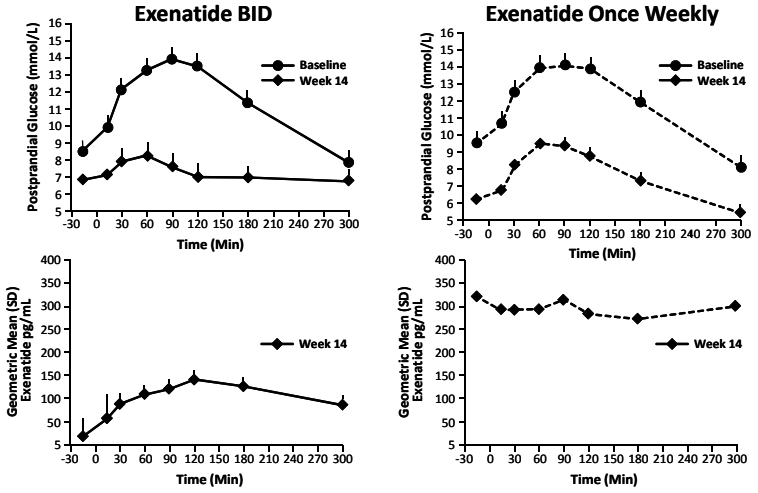
GLP-1 RAs: Approved and in Development

		Marketed Name	Company	Year Approved	Administration
Exenatide	Short-acting	Byetta	AstraZeneca	2005	BID
Exenatide	Long-acting	Bydureon	AstraZeneca	2012	QWK
Liraglutide	Long-acting	Victoza	Novo Nordisk	2010	QD
Lixisenatide	Short-acting	Lyxumia	Sanofi	EMA approval 2013 FDA submission pending	QD
Albiglutide	Long-acting	Tanzeum	GSK	2014	QWK
Dulaglutide	Long-acting	Trulicity	Eli Lilly	2014	QWK
IDegLira	Long-acting plus ultralong-acting basal insulin	Xultophy	Novo Nordisk	EMA approval 2014 FDA submission pending	QD
Semaglutide	Long-acting		Novo Nordisk	Phase III development	QWK
ITCA 650	Continuous subcutaneous delivery system for exenatide		Intarcia	Phase III development	Continuous
Taspoglutide	Long-acting		Roche	Development suspended	QWK

Pharmacokinetics of Short- vs Long-Acting GLP-1 RAs

- Short-acting GLP-1 RAs have strong effects on postprandial glucose, likely due to delays in gastric emptying
- Long-acting GLP-1 RAs produce more consistent activation of the GLP-1 receptor
- Long-acting GLP-1 RAs maintain some postprandial activity, but better control fasting plasma glucose levels leading to greater overall reductions in A1C

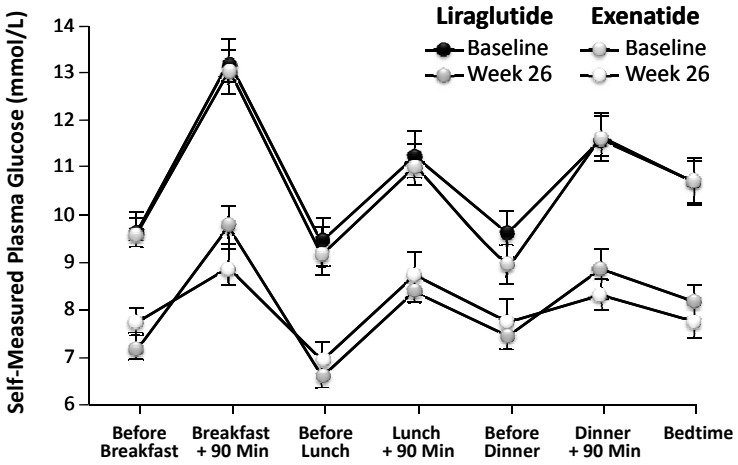
Pharmacokinetics of Short- vs Long-Acting GLP-1 RAs *(cont'd)*



Exenatide BID results in greater reductions in postprandial plasma glucose than exenatide QWK despite lower geometric mean plasma concentrations.

Fineman MS, et al. *Diabetes Obes Metab*. 2012;14:675-688.

Postprandial Pharmacokinetics of Short- vs Long-Acting GLP-1 RAs

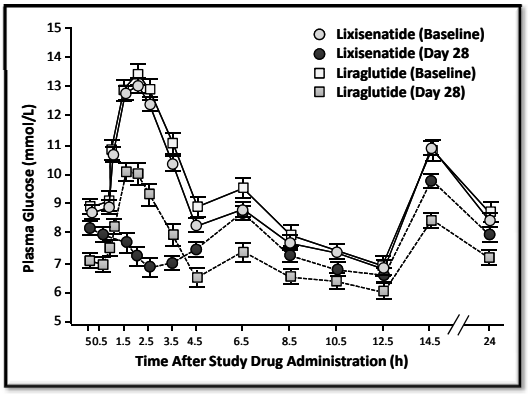


Exenatide BID reduced postprandial plasma glucose more than did liraglutide (self-measured with 7-point plasma glucose profiles) after breakfast and dinner.

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

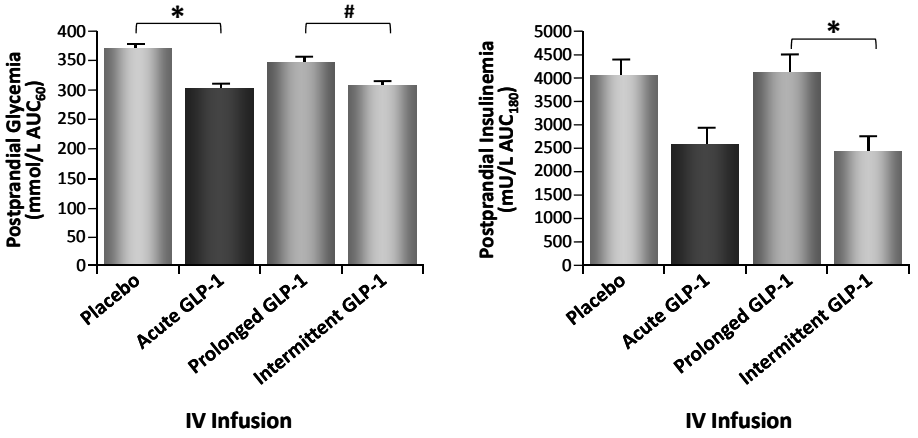
Pharmacokinetics of Short- vs Long-Acting GLP-1 RAs

- Lixisenatide produced greater reductions in postbreakfast glucose levels than liraglutide
- Fasting plasma glucose levels were lower in patients who received liraglutide
- **Remember:** the action of GLP-1RAs is 2-fold:
  (1) islet function
  (2) gastric emptying



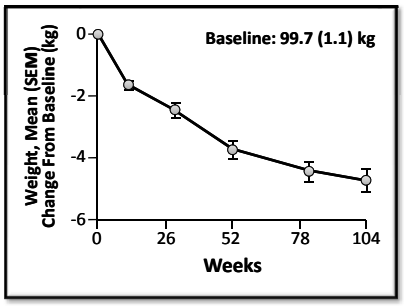
Kapitza C, et al. *Diabetes Obes Metab*. 2013;15:642-649.

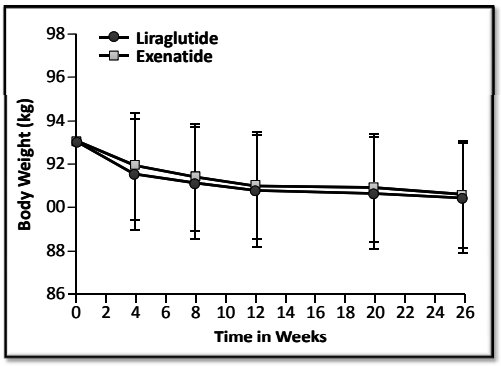
Intermittent GLP-1R Stimulation Slows Gastric Emptying



Umapathysivam MM, et al. *Diabetes*. 2014;63:785-790.

Both Short- and Long-Acting GLP-1 RAs Cause Weight Loss

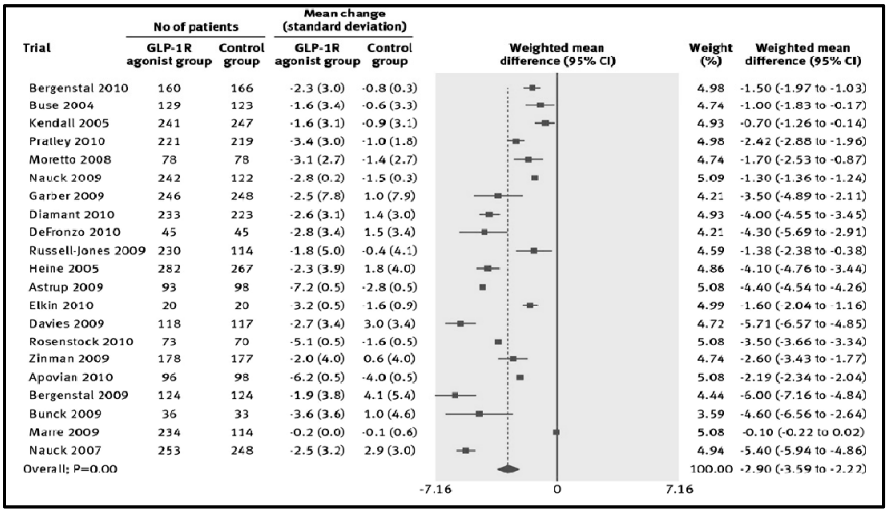




- 81% of patients lost weight with exenatide BID treatment (mean weight loss = 3.6 kg)
- Weight loss was similar with exenatide BID and liraglutide treatment

Buse JB, et al. *Clin Ther.* 2007;29:139-153.
Buse JB et al. *Lancet.* 2009;374:39-47.

GLP-1 RAs Are Associated With Weight Loss*



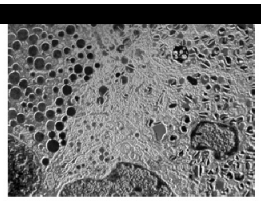
Trial	No of patients: GLP-1R agonist group	No of patients: Control group	Mean change (standard deviation): GLP-1R agonist group	Mean change (standard deviation): Control group	Weight (%)	Weighted mean difference (95% CI)
Bergenstal 2010	160	166	-2.3 (3.0)	-0.8 (0.3)	4.98	-1.50 (-1.97 to -1.03)
Buse 2004	129	123	-1.6 (3.4)	-0.6 (3.3)	4.74	-1.00 (-1.83 to -0.17)
Kendall 2005	241	247	-1.6 (3.1)	-0.9 (3.1)	4.93	-0.70 (-1.26 to -0.14)
Pratley 2010	221	219	-3.4 (3.0)	-1.0 (1.8)	4.98	-2.42 (-2.88 to -1.96)
Moretto 2008	78	78	-3.1 (2.7)	-1.4 (2.7)	4.74	-1.70 (-2.53 to -0.87)
Nauck 2009	242	122	-2.8 (0.2)	-1.5 (0.3)	5.09	-1.30 (-1.36 to -1.24)
Garber 2009	246	248	-2.5 (7.8)	1.0 (7.9)	4.21	-3.50 (-4.89 to -2.11)
Diamant 2010	233	223	-2.6 (3.1)	1.4 (3.0)	4.93	-4.00 (-4.55 to -3.45)
DeFronzo 2010	45	45	-2.8 (3.4)	1.5 (3.4)	4.21	-4.30 (-5.69 to -2.91)
Russell-Jones 2009	230	114	-1.8 (5.0)	-0.4 (4.1)	4.59	-1.38 (-2.38 to -0.38)
Heine 2005	282	267	-2.3 (3.9)	1.8 (4.0)	4.86	-4.10 (-4.76 to -3.44)
Astrup 2009	93	98	-7.2 (0.5)	-2.8 (0.5)	5.08	-4.40 (-4.54 to -4.26)
Elkin 2010	20	20	-3.2 (0.5)	1.6 (0.9)	4.99	-1.60 (-2.04 to -1.16)
Davies 2009	118	117	-2.7 (3.4)	3.0 (3.4)	4.72	-5.71 (-6.57 to -4.85)
Rosenstock 2010	73	70	-5.1 (0.5)	-1.6 (0.5)	5.08	-3.50 (-3.66 to -3.34)
Zinman 2009	178	177	-2.0 (4.0)	0.6 (4.0)	4.74	-2.60 (-3.43 to -1.77)
Apovian 2010	96	98	-6.2 (0.5)	-4.0 (0.5)	5.08	-2.19 (-2.34 to -2.04)
Bergenstal 2009	124	124	-1.9 (3.8)	4.1 (5.4)	4.44	-6.00 (-7.16 to -4.84)
Bunck 2009	36	33	-3.6 (3.6)	1.0 (4.6)	3.59	-4.60 (-6.56 to -2.64)
Marre 2009	234	114	-0.2 (0.0)	-0.1 (0.6)	5.08	-0.10 (-0.22 to 0.02)
Nauck 2007	253	248	-2.5 (3.2)	2.9 (3.0)	4.94	-5.40 (-5.94 to -4.86)
Overall; P=0.00					100.00	-2.90 (-3.59 to -2.22)

*Meta-analysis of change in body weight after at least 20 weeks of treatment

Vilsboll T, et al. *BMJ.* 2012;344:d7771.

Conclusions

- GLP-1 RAs have GI as well as islet effects
- Both actions interact to affect postprandial glycemia
- The relative contribution of these effects might change over time
- The duration of GLP-1 receptor stimulation might affect the contribution of these effects to the net effect on glycemia (and weight)



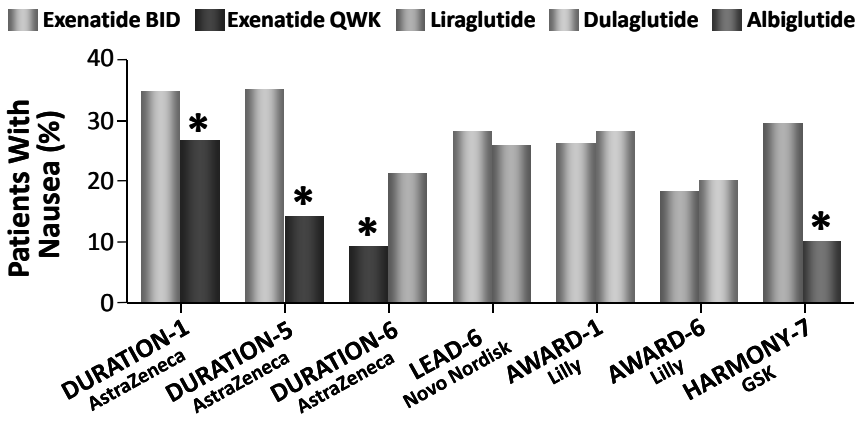
Addressing the Common Concerns Regarding the Use of GLP-1 RAs: Recent Safety Data and New Cardiovascular Trials

Anne L. Peters, MD
Director, USC Clinical Diabetes Program
Professor, Keck School of Medicine of USC
Los Angeles, CA

GLP-1 RAs: Common Safety Concerns

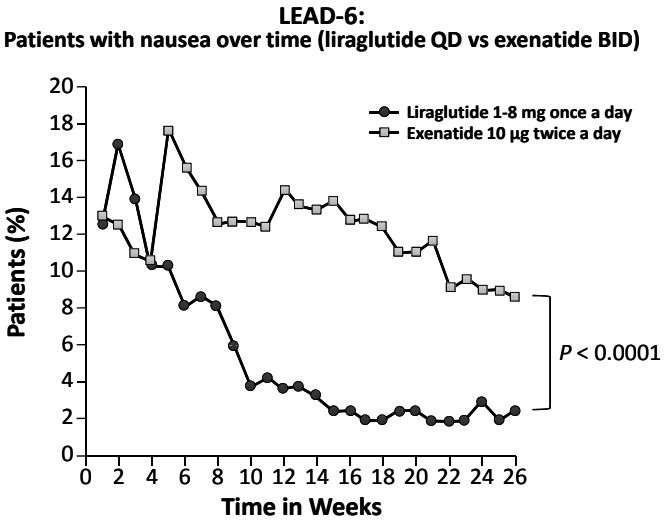
- Tolerability
  - Gastrointestinal (GI) side effects (eg, nausea)
  - Injection-site reactions
- Safety
  - Hypoglycemia
  - Cardiovascular (CV) outcomes
  - Medullary thyroid carcinoma (MTC)
  - Acute pancreatitis

Total Proportion of Patients Experiencing Nausea Varies by Therapy



Buse JB, et al. *Lancet.* 2009;374:39-47.
Drucker DJ, et al. *Lancet*. 2008;372:1240-1250.
Blevins T, et al. *J Clin Endocrinol Metab.* 2011;96:1301-1310.
Wysham C, et al. *Diabetes Care*. 2014;37:2159-2167.
Buse JB, et al. *Lancet*. 2013;381:117-124.
Dungan KM, et al. *Lancet*. 2014;384:1349-1357.
Pratley RE, et al. *Lancet Diabetes Endocrinol*. 2014;2:289-297.

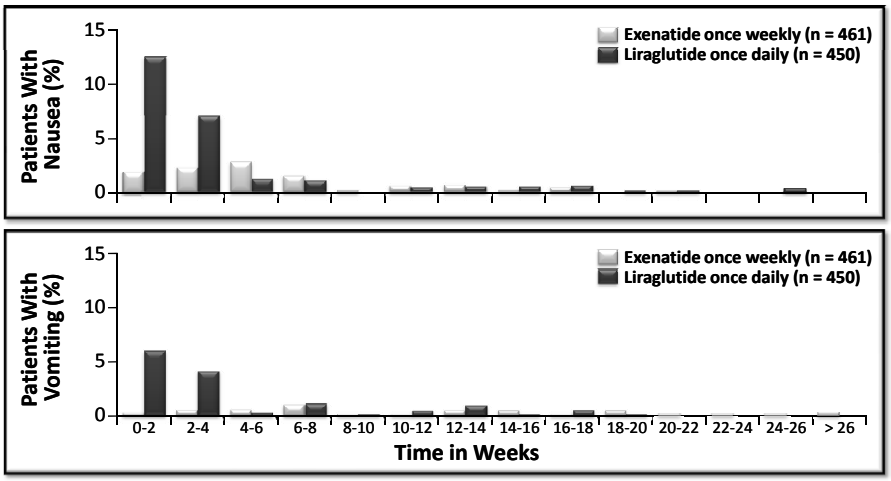
Nausea Is Transient and Decreases More Rapidly in Patients Taking Long-Acting GLP-1 RAs



Buse JB, et al. *Lancet.* 2009;374:39-47.
Buse JB, et al. *Lancet.* 2013;381:117-124.

Nausea Is Transient and Decreases More Rapidly in Patients Taking Long-Acting GLP-1 RAs *(cont'd)*

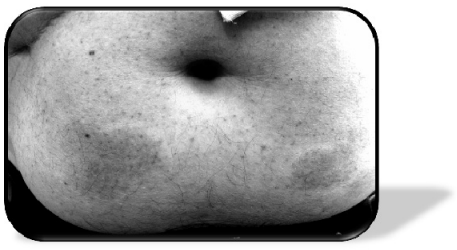
DURATION-6:
Patients with nausea and vomiting over time (exenatide QWK vs liraglutide QD)



Buse JB, et al. *Lancet.* 2009;374:39-47.
Buse JB, et al. *Lancet.* 2013;381:117-124.

Injection-Site Reactions

	Exenatide QWK	Exenatide BID	Liraglutide
Needle size	23 gauge (0.64 mm)	29-32 gauge (0.24-0.34 mm)	29-32 gauge (0.24-0.34 mm)
Injection site reactions	~10-15% of patients	<2%	<2%



Meier JJ. *Nat Rev Endocrinol*. 2012;8:728-742.

GLP-1 RAs and Hypoglycemia

Warnings and Precautions

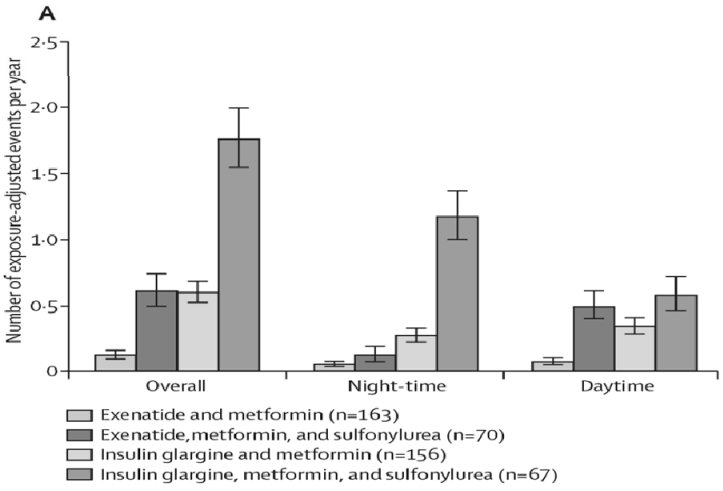
- Consider lowering the dose of the insulin secretagogue or insulin to reduce the risk of hypoglycemia

Percentage of patients with at least 1 episode of hypoglycemia

	Nonsulfonylurea Background		Sulfonylurea Background	
	Exenatide QWK N = 93	Exenatide BID N = 93	Exenatide QWK N = 55	Exenatide BID N = 54
Major	0	0	0	0
Minor	0	1 (1.1)	8 (14.5)	8 (15.4)

Drucker DJ, et al. *Lancet*. 2008;372:1240-1250.

Hypoglycemia Rates With GLP-1 RAs Combined With Insulin/Metformin



Diamant M, et al. *Lancet Diabetes Endocrinol*. 2014;2:464-473.

Contrasting Action of Native GLP-1, GLP-1R Agonists, DPP-4 Inhibitors, and GLP-1 (9-36) on the Cardiovascular System and Cardiovascular Risk Factors

	GLP-1R Agonists	GLP-1	DPP-4 Inhibitors	GLP-1 (9-36)
LV function	Increased	Increased	Increased	Increased
Heart rate	Increased	Increased	No effect	No effect
Coronary flow	No effect	Increased	No effect	Increased
Infarct size	Decreased	Decreased	Decreased	Decreased
Body weight	Decreased	Decreased	No effect	No effect
Blood pressure	Decreased	Decreased	No effect/ decreased	ND

DPP-4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 (GLP-1) receptor; LV, left ventricular; ND, not determined.

Ussher JR, et al. *Circ Res*. 2014;114:1788-1803.

Incretin Mimetics Do Not Increase Risk of Congestive Heart Failure

Current Exposure	Case Subjects (n = 1118)	Control Subjects (n = 17,626)	Crude OR (95% CI)	Adjusted OR (95% CI)
≥ 2 oral antidiabetic drugs, n (%)	267 (23.9)	4198 (23.8)	1.00 (Reference)	1.00 (Reference)
Incretin-based drugs, n (%)	64 (5.7)	923 (5.2)	0.98 (0.73-1.33)	0.85 (0.62-1.16)
DPP-4 inhibitors	54 (4.8)	808 (4.6)	0.96 (0.70-1.32)	0.88 (0.63-1.22)
GLP-1 analogs	10 (0.9)	115 (0.7)	1.18 (0.59-2.39)	0.67 (0.32-1.42)
Duration of incretin-based drug use, n (%)				
1-83 days	25 (2.2)	310 (1.8)	1.18 (0.74-1.89)	1.01 (0.62-1.63)
84-265 days	18 (1.6)	299 (1.7)	0.86 (0.51-1.44)	0.79 (0.46-1.36)
> 265 days	21 (1.9)	314 (1.8)	0.92 (0.56-1.50)	0.75 (0.45-1.25)

P trend = 0.39

Yu OH, et al. *Diabetes Care*. 2015;38:277-284.

Ongoing/Recent Cardiovascular Outcomes Trials

Trial (Sponsor)	Study Drug	Primary Outcome	Patients (n)	Timeline
ELIXA (Sanofi)	Lixisenatide 20 mg QD	MACE	~ 6000	Jun 2010 – Dec 2014
LEADER (Novo Nordisk)	Liraglutide 1.8 mg QD	MACE	~ 9000	Aug 2010 – Oct 2015
SUSTAIN 6 (Novo Nordisk)	Semaglutide 0.5 or 1.0 mg QWK	MACE	~ 3000	Feb 2013 – Jan 2016
EXSCEL (AstraZeneca)	Exenatide 2.0 mg QWK	MACE	~ 14,000	Jun 2010 – Dec 2017
REWIND (Eli Lilly)	Dulaglutide 1.5 mg QWK	MACE	~ 95,00	Jul 2011 – Apr 2019

MACE, major adverse cardiovascular events.

ClinicalTrials.gov: NCT01147250, NCT01179048, NCT01720446, NCT01144338, NCT01394952.

Risk of Thyroid Cancer

Contraindications

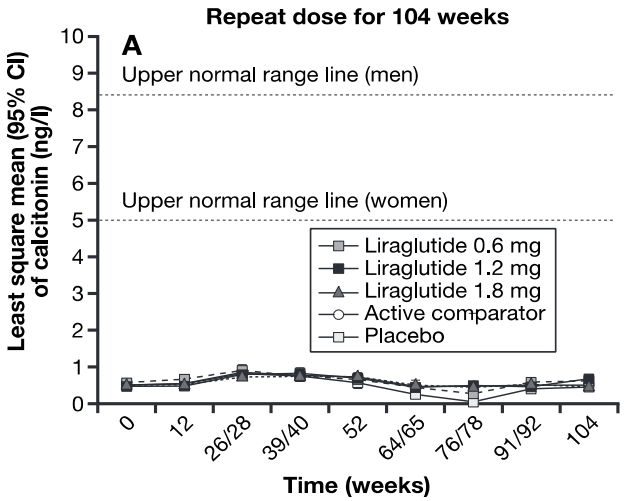
- Patients with a personal or family history of MTC
- Patients with multiple endocrine neoplasia syndrome (MEN 2)

Warnings and Precautions

- Counsel patients regarding the risk of MTC and symptoms of thyroid tumors

- Thyroid C-cell tumors have been observed in rodents exposed to GLP-1 RAs at clinically relevant doses
- It is unknown whether GLP-1 RAs cause thyroid C-cell tumors, including MTC, in humans
- It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the potential risk of MTC, and such monitoring may increase the risk of unnecessary procedures, due to low test specificity for serum calcitonin and a high background incidence of thyroid disease
- Patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation

Risk of Thyroid Cancer



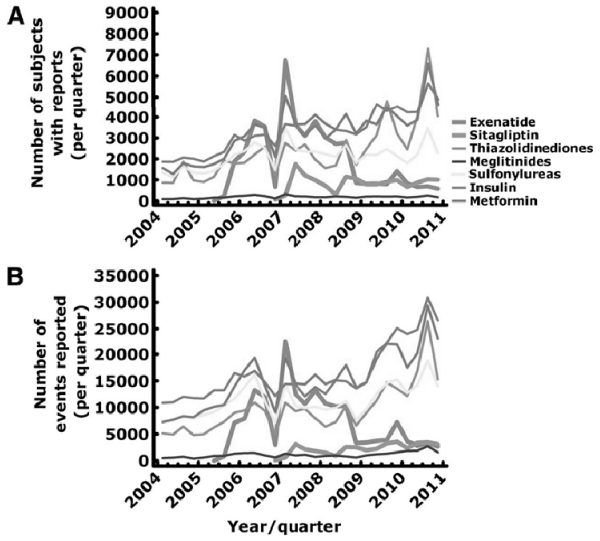
Gallo M. *J Endocrinol Invest*. 2013;36:140-145.

Cases of Acute Pancreatitis Have Been Reported But Relationship to GLP-1 RAs Is Unclear

- Several analyses of health care claims data demonstrated no increased risk of pancreatitis with GLP-1 RA use
- Controversial analysis of FDA Adverse Events Reporting Database showed increased risk of pancreatitis with GLP-1 RA use

Warnings and Precautions
❖ Discontinue promptly if pancreatitis is suspected
❖ Do not restart if pancreatitis is confirmed
❖ Consider other antidiabetic therapies in patients with a history of pancreatitis

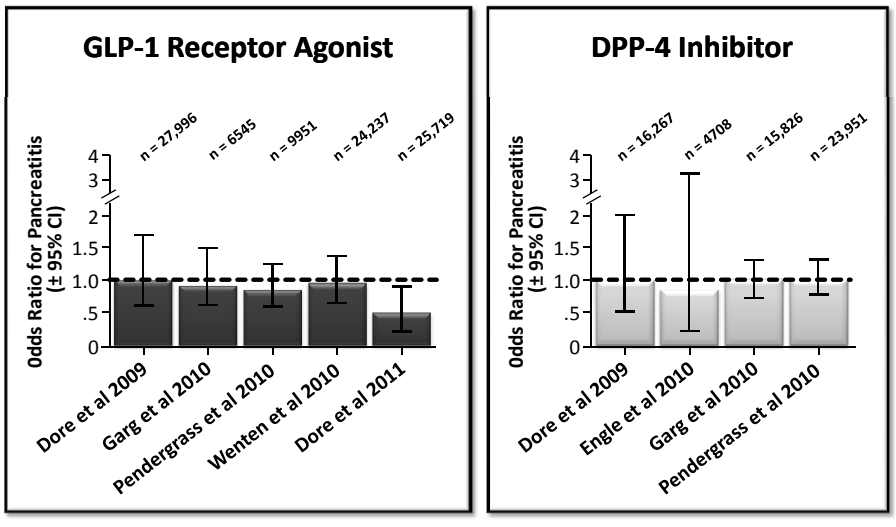
Number of subjects with reports (A) and number of adverse events (B) reported to the FDA Adverse Event Reporting System between 2004 and 2010 for different glucose-lowering medications including exenatide (green lines) and sitagliptin (blue lines).



Michael A. Nauck, and Nele Friedrich Dia Care 2013;36:S245-S252.

American Diabetes Association.

Large Database Studies Suggest No Increase in Risk of Pancreatitis



Nauck MA, et al. *Diabetes Care.* 2013 ;36(suppl 2):S245-S252.

GLP-1 RA Pancreatitis Data 2014

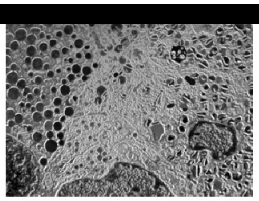
Country/Ref	Type of Database	N	Findings
Italy, *Lancet Diab Endo*. 2:111-115, 2014	Administrative database from Piedmont	282,429 pts T2DM; 1003 cases pancreatitis vs 4012 controls	Use of incretins not associated with increased risk of pancreatitis
Indiana, *Pharmacoepidemiology & Drug Safety*. 23:234-9, 2014	Large observational database	1.2 million pts, 7992 on sita (245 cases) and 3552 on exenatide (96 cases)	No relationship between use of GLP-1 based therapies and pancreatitis
United Kingdom, *Diabetologia*. 57:1320-4, 2014	Population based cohort study	20,748 new incretin users vs 51,712 users of SU's	Rates panc: 1.45 per 1,000 pts/yr incretins vs 1.47 for SU's. Adjusted HR = 1.0
International, *BMJ*. 348:g2780, 2014	Pooled Phase III trial data	GLP-1 38 cases/17,775 PYO's vs 9/5,863 PYO's	Non-significant trend to pancreatitis. Pooled event rates 2.1 and 1.5 per 1,000 PYOs (OR 1.39, CI 0.67, 2.88)

Conclusions

- GI symptoms such as nausea are the most common adverse event seen with GLP-1 RAs
  - Nausea tends to be transient, varies according to therapy, and decreases more rapidly with long-acting formulations
- Risk of hypoglycemia is low
  - Increases when used in combination with insulin secretagogues or insulin
- It is currently unknown whether GLP-1 RAs cause thyroid C-cell tumors, including MTC, in humans
  - Counsel patients regarding the risk of MTC and symptoms of thyroid tumors

Conclusions (*cont'd*)

- Controversial analysis of FDA Adverse Events Reporting Database showed increased risk of pancreatitis with GLP-1 RA use
  - However, multiple analyses of health care claims data demonstrated no increased risk
- Retrospective analysis shows no increased risk for major adverse CV events with GLP1-RAs
  - In response to an FDA requirement, several long-term trials examining CV outcomes with GLP-1 RAs have been established



Patient Preferences and Novel Regimens Incorporating GLP-1 RAs and Insulin

Sam Dagogo-Jack, MD, FRCP
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Patient
DOI 10.1007/s40271-014-0057-0

SYSTEMATIC REVIEW

The Patient Perspective of Diabetes Care: A Systematic Review of Stated Preference Research

Lill-Brith von Arx · Trine Kjær

© Springer International Publishing Switzerland 2014

Abstract

Background The importance of understanding the perspective of patients towards their own care is increasingly recognized, both in clinical practice and in pharmaceutical drug development. Stated preference methods to assess the preference of patients towards different aspects of diabetes treatment have now been applied for over a decade.

Objective Our goal was to examine how stated preference methods are applied in diabetes care, and to evaluate the value of this information in developing the patient perspective in clinical and policy decisions.

Methods A systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The information sources were MEDLINE, EMBASE, Biosis, Current Contents, Web of Science, CINAHL, PsycINFO, and EconLit.

Results Three contingent valuation studies and 11 discrete choice experiments were retrieved. The majority of studies were conducted from 2009 onwards, but some date back to 1998. The reasons provided for applying the stated preference methods were to help differentiate between products, or to enable inclusion of the patient's perspective in treatment decisions. The main aspects of treatment examined were related to glucose control, adverse events, and drug administration. The majority of patients preferred glucose control over avoiding minor hypoglycemic events. Patient willingness to pay was above $US100/month for glucose control, avoiding immediate health hazards such as nausea, and oral or inhaled drug administration. Preference towards drug administration was highly associated with previous experience with injectable diabetes medicine.

Conclusions The ability of a drug to lower glucose levels plays a decisive role in the choice between alternative treatments. Future research should strive to develop questionnaire designs relevant for the decision context of the study. That is, if the aim is to foster shared decision making, in clinical practice or drug development, this should guide the study design. Furthermore, concise reporting of all study dimensions—from the qualitative prework to the analysis stage—is warranted.

Key Points for Decision Makers

Recent applications of stated preference methods may inform economic evaluations of medicine adopting a user perspective.

Glucose control is important to patients, and in most cases a higher priority than avoiding minor hypoglycemic events.

Drug administration and the reduction of insulin injections motivate patient preference for inexperienced insulin users.

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Published online: 02 April 2014

1 Introduction

Diabetes care involves a number of therapeutic challenges affecting health outcomes. For insulin users, one example is the adjustment of insulin therapy to control glucose

Patient's Perspective

- **Efficacy:** Preference for glucose control over avoiding minor hypoglycemic events
- **Route:** Preference towards drug administration highly associated with previous experience with injectable diabetes medicine
- **Adverse events:** "Avoiding a 3-kg weight gain is important but not superior to avoiding hypoglycemic events"
- **Cost:** Patient willingness to pay (WTP): US $28 - $205/mo

Conclusions

- The ability of a drug to lower glucose levels plays a decisive role in the choice between alternative treatments
- Future research should develop questionnaire designs to foster shared decision making in clinical practice or drug development

von Arx LB, et al. *Patient*. 2014;7:283-300. Gelhorn HL, et al. *Diabetes Obes Metab*. 2013;15:802-809.

WTP for Pharmaceutical Diabetes Treatment

Efficacy

- **WTP among studies of all insulin users**
  - $28/mo for having a 2hrPG of 9.4 mmol/L
  - $36/mo for having optimal BG 2-6 days/wk
- **WTP in studies with ~ 50% insulin users**
  - $146/mo for optimal FPG
  - $205/mo for a 1% HbA1c reduction

von Arx LB, et al. *Patient*. 2014;7:283-300; Guimaraes C, et al. *Diabetes Technol Ther.* 2009;11:567-573. Lloyd A, et al. *Clin Ther*. 2011;33:1258-1267. Jendle J, et al. *Curr Med Res Opin*. 2010;26:917-923.

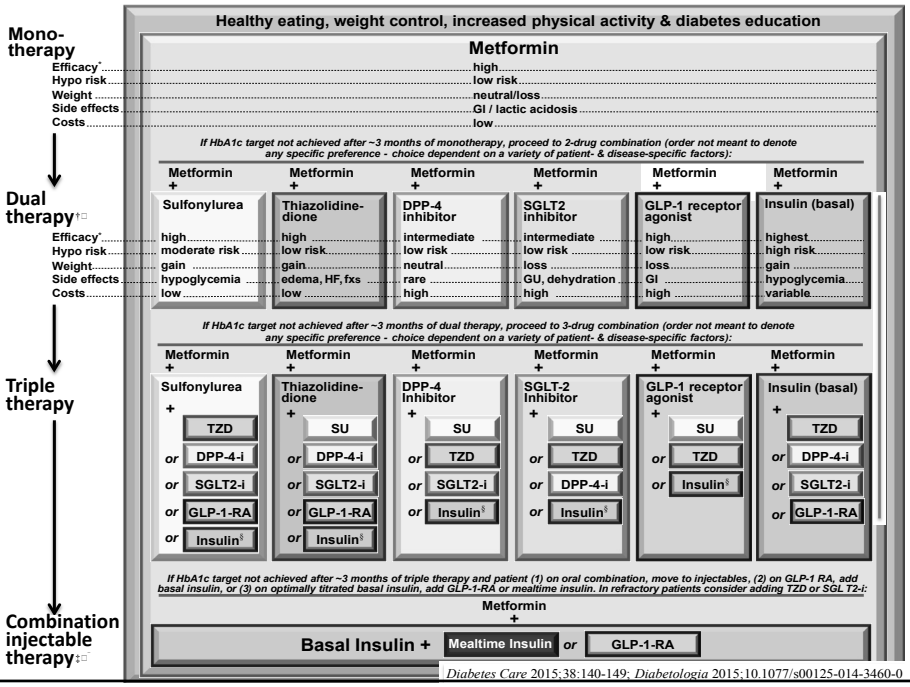
Patient WTP for Pharmaceutical Diabetes Treatment

Adverse events and mode of treatment

- **WTP for adverse events**
  - Highest ($124 - $220/mo) for avoiding nausea
  - $45 - $94/mo for avoiding hypoglycemia
  - $72 - $94/mo for avoiding night-time events
  - WTP reported for weight control: $58 - $76/mo
- **WTP for mode of treatment**
  - $86 for meal-independent injections (prandial experience $117/none $65)
  - Inhaled administration: $62 - $215/mo
  - Oral drug administration $50 - $108/mo

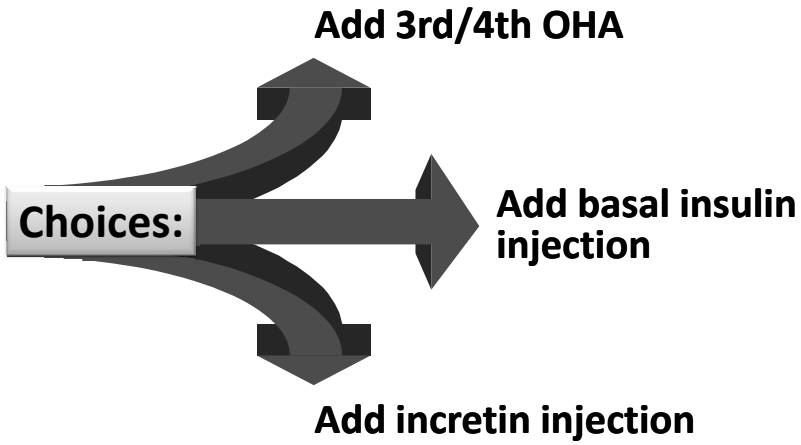
von Arx LB, et al. *Patient*. 2014;7:283-300; Guimaraes C, et al. *Diabetes Technol Ther.* 2009;11:567-573. Lloyd A, et al. *Clin Ther*. 2011;33:1258-1267. Jendle J, et al. *Curr Med Res Opin*. 2010;26:917-923.

ADA-EASD Position Statement: 2015 Update



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0

What Do You Do When 2 or More Oral Agents Fail to Control T2DM?



Annals of Internal Medicine
Established in 1927 by the American College of Physicians

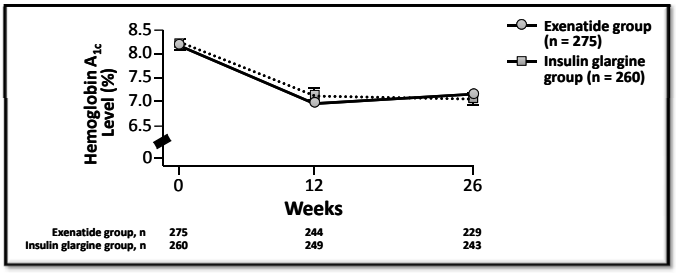
Exenatide vs Insulin Glargine in Patients With Suboptimally Controlled Type 2 Diabetes: A Randomized Trial

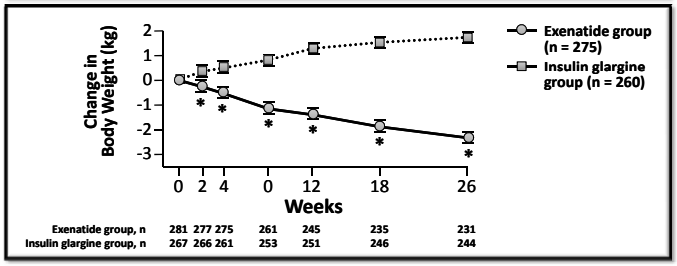
Robert J. Heine, MD, PhD; Luc F. Van Gaal, MD; Don Johns, PhD; Michael J. Mihm, PhD; Mario H. Widel, MS; and Robert G. Brodows, MD, for the GWAA Study Group

- 82 sites
- 13 countries
- 551 patients
- Background SU + metformin

Heine RJ, et al. *Ann Intern Med*. 2005;143:559-569.

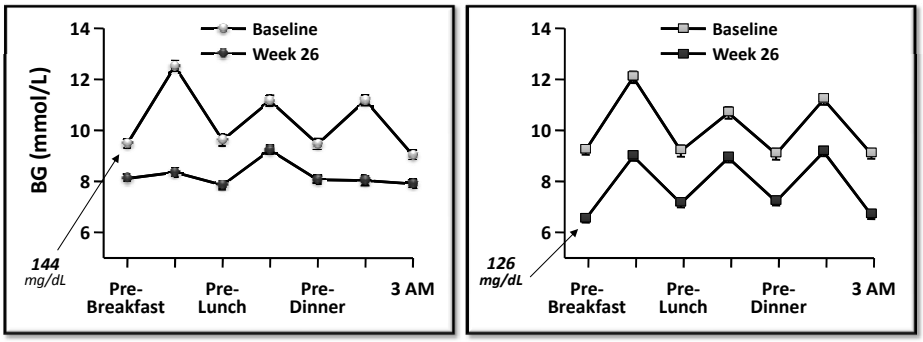
Exenatide BID vs Glargine: Effects on HbA1c and Weight





Heine RJ, et al. *Ann Intern Med*. 2005;143:559-569.

Exenatide vs Glargine Added to Oral Agents



MDG (mg/dL)
Exenatide: 146 ± 2
Glargine: 144 ± 2
HbA1c: -1.11%

ITT population; mean ± SE.

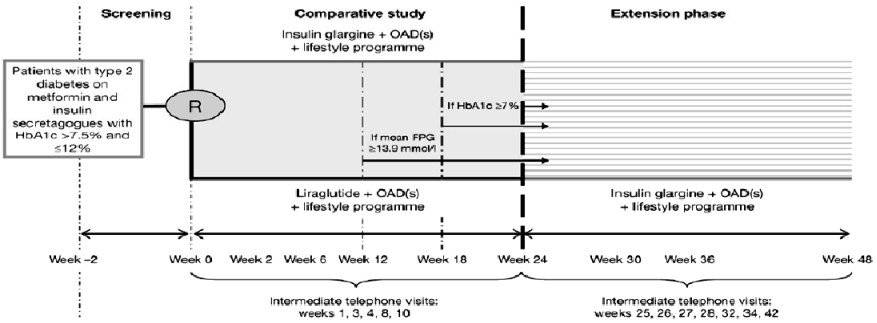
Heine RJ, et al. *Ann Intern Med*. 2005;143:559-569.

original article

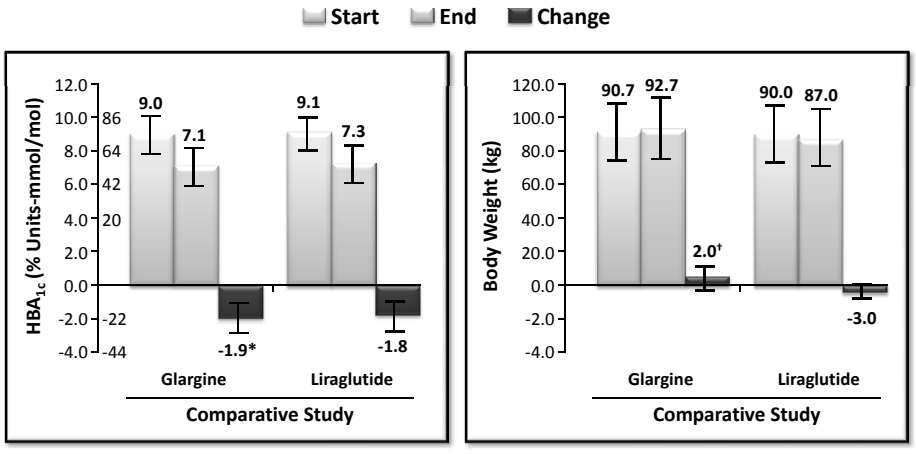
Diabetes, Obesity and Metabolism 17: 170–178, 2015.

Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes

D. D'Alessio[1], H.-U. Häring[2], B. Charbonnel[3], P. de Pablos-Velasco[4], C. Candelas[5], M.-P. Dain[6], M. Vincent[6], V. Pilorget[7] & H. Yki-Järvinen[8] on behalf of the EAGLE Investigators



HbA1c and Body Weight During the Comparative Study



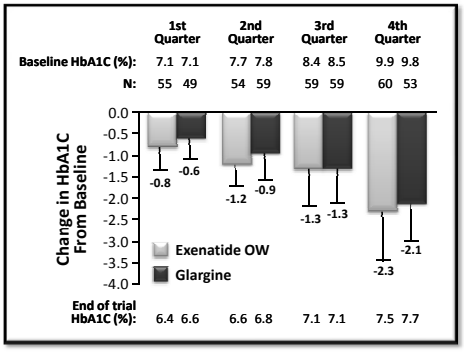
*P = 0.019; †P < 0.001 compared with liraglutide.

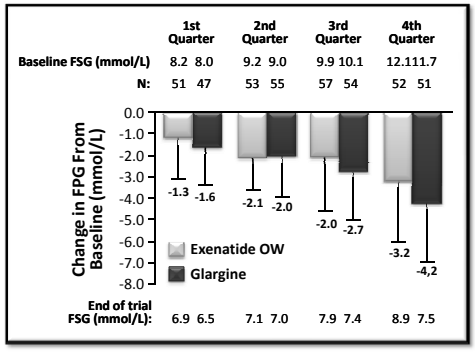
D'Alessio D, et al. *Diabetes Obes Metab.* 2015;17:170-178.

Change in HbA1c and FSG After 26 Wks Across Baseline HbA1c Quartiles

DURATION

Diabetes therapy Utilization: Researching changes in A1c, weight, and other factors Through Intervention with exenatide ONce-Weekly



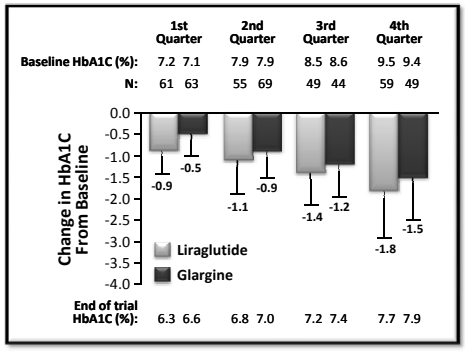


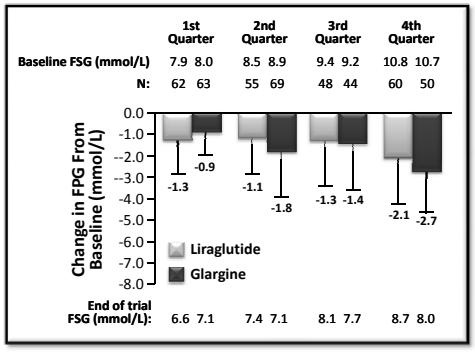
Buse JB, et al. *Diabetes Obes Metab.* 2015;17:145-151.

Change in HbA1c and FSG after 26 Wks Across Baseline HbA1c Quartiles (*cont'd*)

LEAD

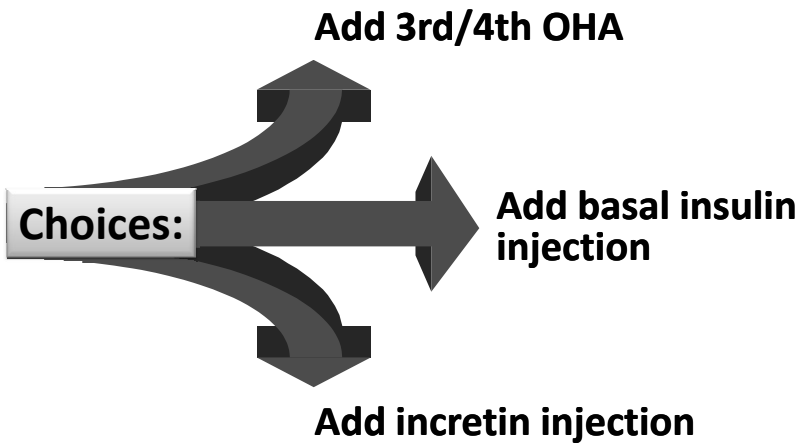
Liraglutide Effect and Action in Diabetes



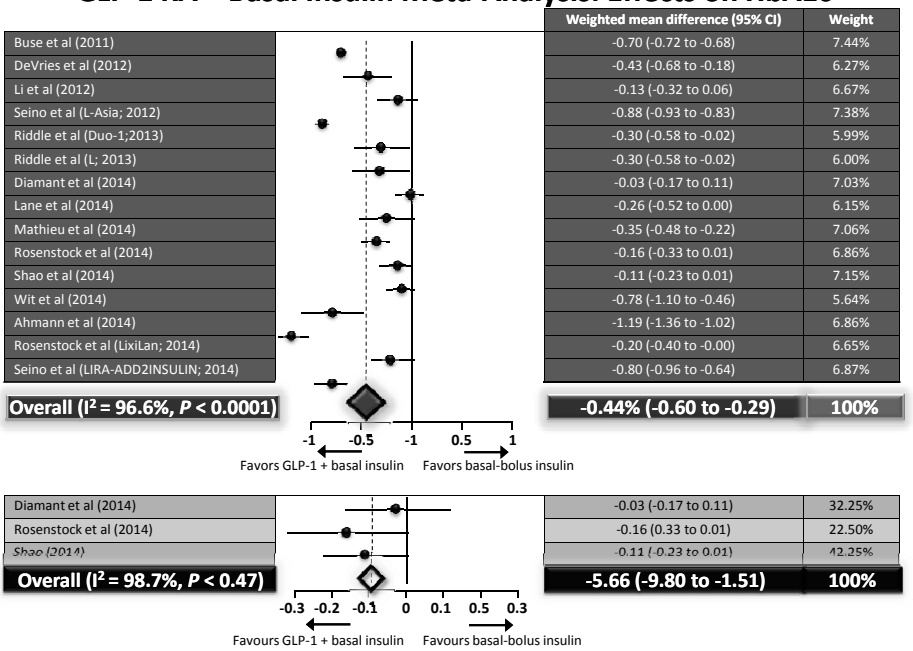


Buse JB, et al. *Diabetes Obes Metab.* 2015;17:145-151.

What Do You Do When 2 or More Oral Agents Fail to Control T2DM?



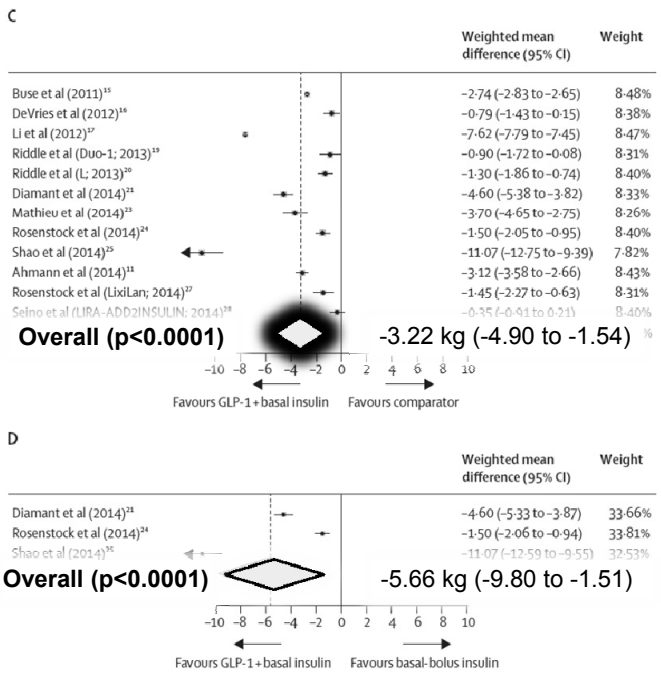
GLP-1 RA + Basal Insulin Meta-Analysis: Effects on HbA1c



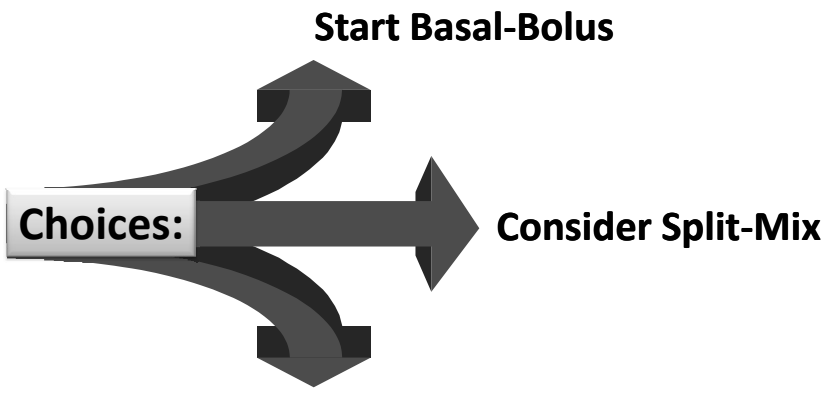
Eng C, et al. *Lancet*. 2014; 384:2228-2234.

GLP-1 RA + Basal Insulin Meta-Analysis: Effects on Body Weight

Eng C, et al. *Lancet*. 2014; 384:2228-2234.



What Do You Do When Basal Insulin Added to OHA Fails?



Comparison of Adding Liraglutide vs a Single Daily Dose of Insulin Aspart to Insulin Degludec in Subjects With T2DM

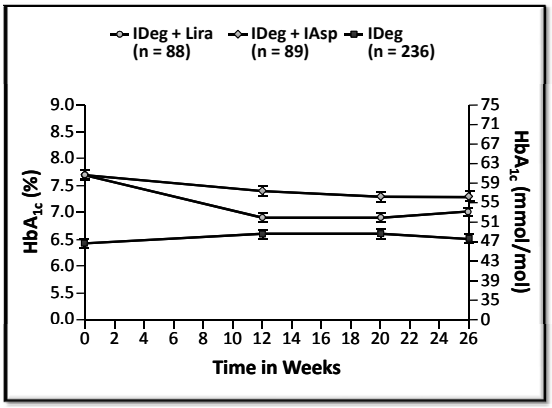
Subjects completing a 104-week trial on insulin degludec (IDeg) OD + metformin with HbA1c ≥ 7.0% were randomized to:

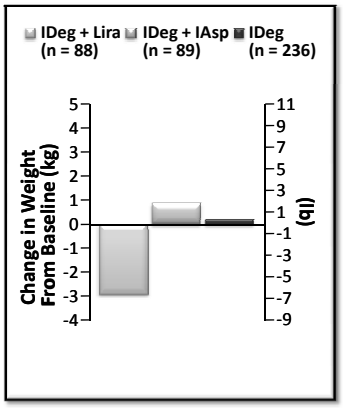
- IDeg + Lira (n = 88, mean HbA1c: 7.7%) or
- IDeg + IAsp (n = 89, mean HbA1c: 7.7%)
- Metformin continued in both groups
- Assessed after 26 weeks

Subjects completing 104 weeks with HbA1C < 7.0% continued IDeg + metformin in a third, nonrandomized arm (n = 236)

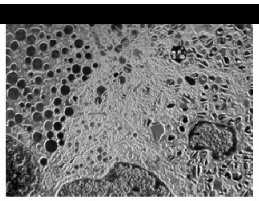
Mathieu C, et al. *Diabetes Obes Metab*. 2014;16:636-644.

Comparison of Adding Liraglutide vs a Single Daily Dose of Insulin Aspart to Insulin Degludec in Subjects With T2DM





Mathieu C, et al. *Diabetes Obes Metab*. 2014;16:636-644.

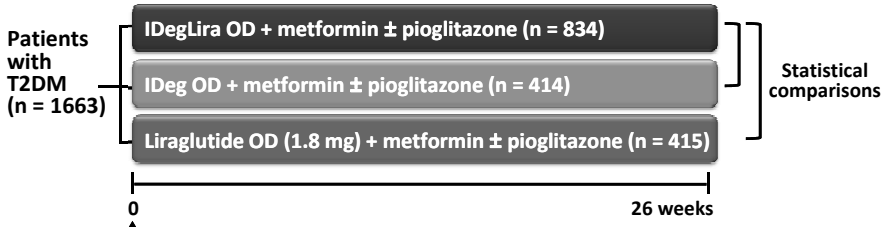


Efficacy and Safety of a Fixed-Ratio Combination of Insulin Degludec and Liraglutide Compared to Each of Its Components Given Alone: Results of a Phase 3, Randomised, 26-Week, Treat-to-Target Trial in Insulin-Naïve Patients With Type 2 Diabetes.

(Clinicaltrials.gov identifier: NCT01336023)

Gough SC, et al. *Lancet Diabetes Endocrinol*. 2014;2:885-893.

Trial Design



Inclusion criteria
- T2DM
- Insulin naïve, treated with metformin ± pioglitazone
- HbA_{1c} 7.0%-10.0%
- BMI ≤40 kg/m^2
- Age ≥ 18 years*

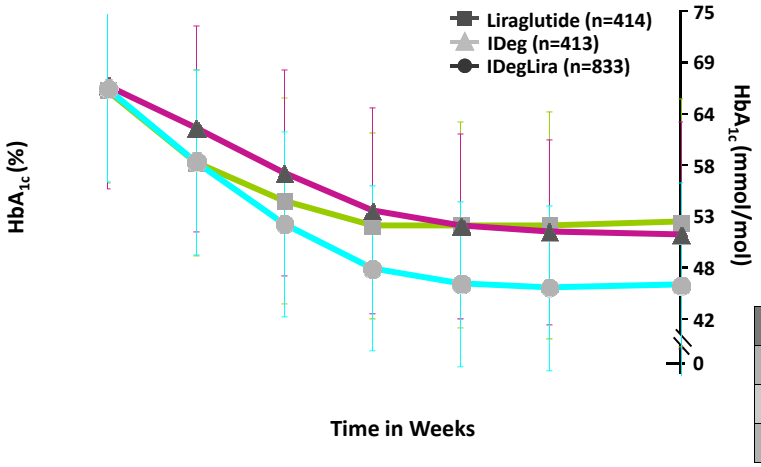
	Start dose	Max. dose
IDeg	10 units	Not specified
Lira	0.6 mg	1.8 mg
IDegLira	10 dose steps (10 units IDeg/ 0.36 mg Lira)	50 dose steps (50 units IDeg/ 1.8 mg Lira)

*Singapore, age ≥ 21 years.

BMI, body mass index; lira, liraglutide; OD, once daily.

Gough SC, et al. *Lancet Diabetes Endocrinol.* 2014;2:885-893.

HbA_{1c} Over Time

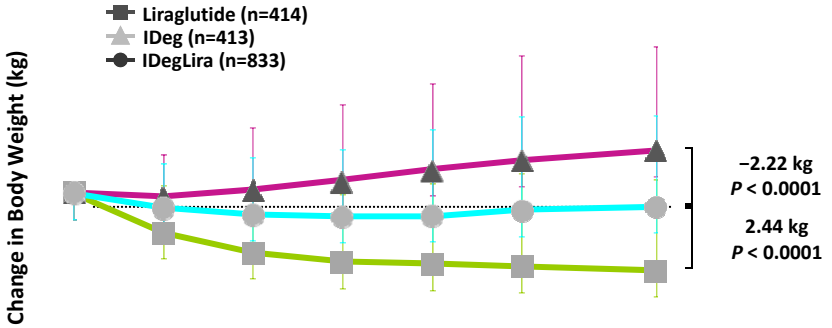


ΔHbA_{1c}	EOT
-1.28%	7.0%
-1.44%	6.9%
-1.91%*	6.4%

*$P < 0.0001$ vs IDeg and vs liraglutide

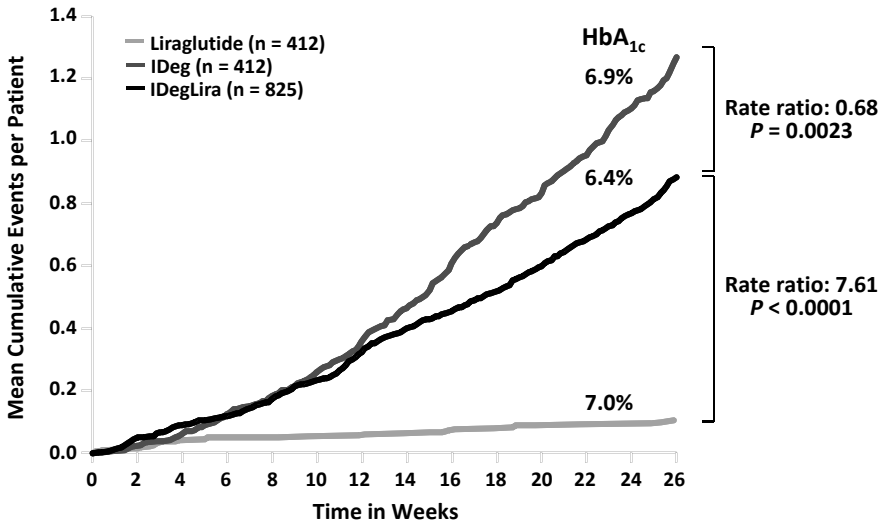
Gough SC, et al. *Lancet Diabetes Endocrinol.* 2014;2:885-893.d

Change in Body Weight Over Time



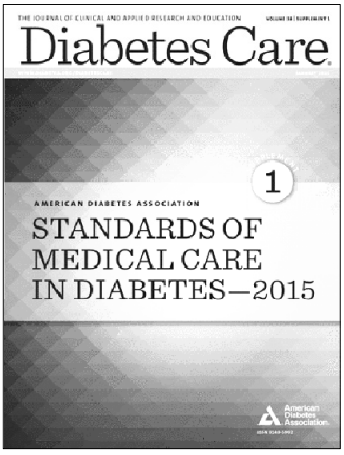
Gough SC, et al. *Lancet Diabetes Endocrinol.* 2014;2:885-893.d

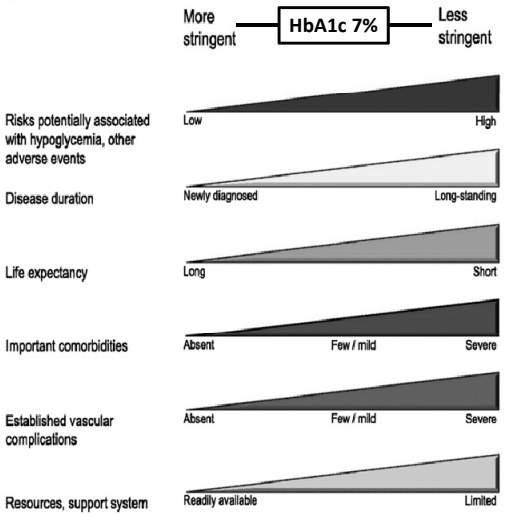
Confirmed Hypoglycemia



Gough SC, et al. *Lancet Diabetes Endocrinol.* 2014;2:885-893.d

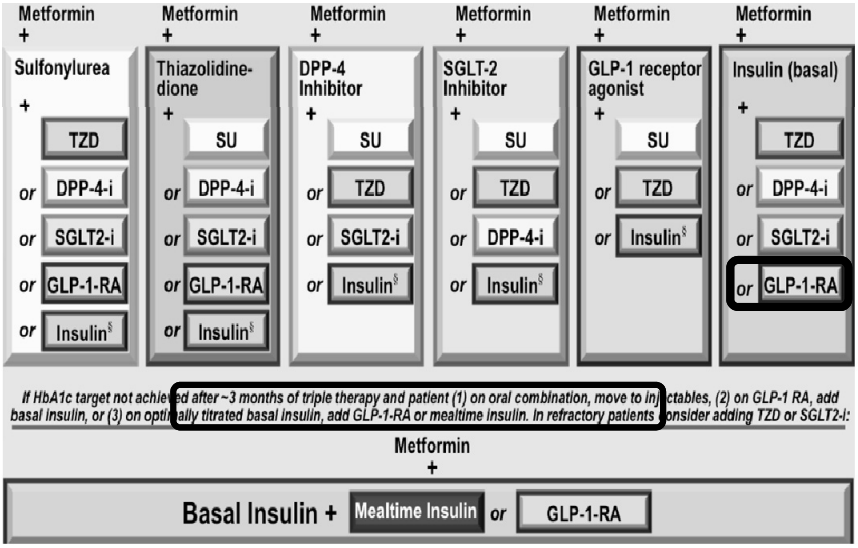
Approach to Management of Hyperglycemia





ADA. *Diabetes Care.* 2015;38(suppl 1) Adapted from Ismail-Beigi et al. *Ann Intern Med*. 2011;154:554-555.

Approach to Management of Hyperglycemia



ADA. *Diabetes Care.* 2015;38(suppl 1); Adapted from Ismail-Beigi et al. *Ann Intern Me*d. 2011;154:554-555.

What Do You Do When 2 or More Oral Agents Fail to Control T2DM?