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Incretin-Based Therapies for Type 2 Diabetes

Improving Comprehensive Patient Care

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Incretin-Based Therapies for Type 2 Diabetes

Improving Comprehensive Patient Care

FACULTY

EILEEN Egan, DNP, FNP-C, CDE

VIRTUAL PROFESSOR

Chief Nurse Practitioner, Winthrop Center for Comprehensive Diabetes Care
Winthrop Endocrine, Diabetes & Metabolism Faculty Practice
Mineola, New York
Adjunct Faculty
Department of Graduate Studies & Advanced Practice Nursing
Stony Brook University
Stony Brook, New York

JAVIER Morales, MD

Associate Clinical Professor of Medicine
North Shore-LIJ School of Medicine at Hofstra University
Principal Clinical Trials Investigator
Advanced Internal Medicine Group, PC
East Hills, New York

MARK W. Stolar, MD

Associate Professor of Clinical Medicine
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

LEARNING OBJECTIVES

- Describe the underlying mechanisms of T2DM, focusing on the pathophysiologic and potentially therapeutic roles of incretin hormone signaling
- Identify comprehensive treatment goals for T2DM that reflect the degree of hyperglycemia, relevant comorbidities, and other patient-specific factors
- Discuss the comprehensive clinical profiles of incretin-based therapies, including the potential benefits and risks of combining these agents with insulin
- Intensify antihyperglycemic regimens with incretin-based therapies to achieve individualized glycemic targets
- Educate patients with T2DM to motivate lifestyle modifications, reduce hypoglycemia risks, and enhance treatment adherence

FACULTY FINANCIAL DISCLOSURE STATEMENTS

The presenting faculty reported the following:

Eileen Egan, DNP, FNP-C, CDE, has nothing to disclose.

Javier Morales, MD, is a member of the Speakers Bureau for Abbott Laboratories, Eli Lilly and Company, and Novo Nordisk A/S. He is a member of the Medical Advisory Board for Abbott Laboratories, Boehringer Ingelheim, Janssen Pharmaceuticals, Inc., Eli Lilly and Company, Novo Nordisk A/S, and sanofi-aventis U.S. LLC.

Mark W. Stolar, MD, is a member of the Speakers Bureau for AstraZeneca plc and Takeda Pharmaceuticals U.S.A., Inc. He is a member of the Medical Advisory Board for AstraZeneca plc and sanofi-aventis U.S. LLC.

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10:30 – 11:45 AM

Incretin Based Therapies for Type 2 Diabetes Improving Comprehensive Patient Care

SPEAKER(S)

Javier Morales, MD
Mark W. Stolar, MD

Scientific Insights Into Incretin Signaling and T2DM

Key Points

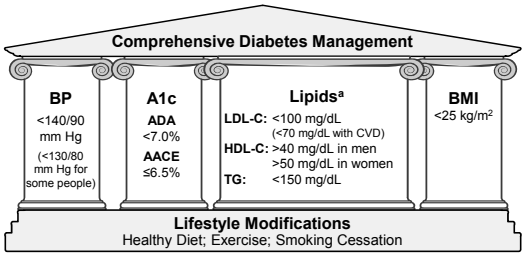
- **Incretin effect:** more insulin is secreted in response to orally delivered glucose compared with intravenously administered glucose[1]
- The gastrointestinal hormones GLP-1 and GIP stimulate insulin release in response to food intake[2]
- GLP-1 also reduces glucagon release following food intake, slows gastric emptying, and increases satiety[2]
- Reduced incretin effect is an early sign of T2DM development[3]
- GLP-1 and GIP are rapidly degraded by DPP-4[2]
  - Clinical research has focused on degradation-resistant GLP-1 RAs and inhibitors of DPP-4

DPP-4, dipeptidyl peptidase-4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2DM, type 2 diabetes mellitus.

1. Elrick H, et al. *J Clin Endocrinol Metab*. 1964;24:1076-1082; 2. Grunberger G. *J Diabetes*. 2013;5(3):241-253;
3. Holst JJ, et al. *Diabetes Care*. 2011;34 (suppl 2):S251-S257.

Reducing T2DM Complications

Multidimensional Treatment Goals



[a]2015 ADA/AHA guidelines: Treat patients 40-75 years old with T2DM and LDL-C levels between 70 and 189 mg/dL with moderate-intensity statin therapy (lower LDL-C by 30%-50%); use high-intensity therapy (lower LDL-C by ≥50%) if 10-year ASCVD risk is ≥7.5%).
A1c, glycated hemoglobin; AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides.

ADA. *Diabetes Care*. 2016;39(suppl 1):S1-S112; Garber AJ, et al. *Endocr Pract*. 2016;22(1):84-113;
Fox CS, et al. *Diabetes Care*. 2015;38(9):1777-1803.

ADA/EASD Position Statement

Setting Glycemic Goals in T2DM

More Stringent	Factors	Less Stringent
Highly motivated, adherent, excellent self-care capacities	Patient attitude and expected treatment efforts	Less motivated, nonadherent, poor self-care capacities
Low	Risks potentially associated with hypoglycemia, other adverse events	High
Newly diagnosed	Disease duration	Long-standing
Long	Life expectancy	Short
Absent	Important comorbidities	Severe
Absent	Established vascular complications	Severe
Readily available	Resources, support system	Limited

EASD, European Association for the Study of Diabetes.

Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-1379; Inzucchi SE, et al. *Diabetes Care*. 2015;38(1):140-149;
Ismail-Beigi F, et al. *Ann Intern Med*. 2011(6);154:554-559.

ADA Recommendations

Managing Hyperglycemia in T2DM

Healthy Eating, Weight Control, Increased Physical Activity

Monotherapy — Metformin

Efficacy (↓A1c)	High
Hypoglycemia	Low risk
Weight	Neutral/Loss
Side Effects	GI/Lactic acidosis
Costs	Low

If individualized A1c target not reached after ~3 months, proceed to 2-drug combination

Dual Therapy[a] — Metformin

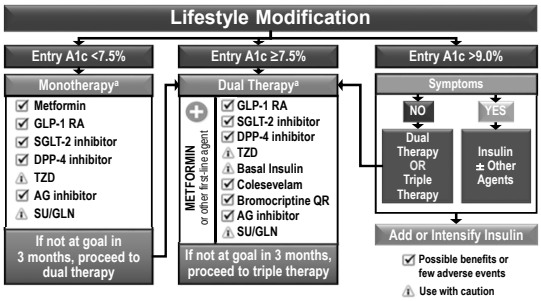
	+ SU	+ TZD	+ DPP-4 Inhibitor	+ SGLT-2 Inhibitor	+ GLP-1 RA	+ Insulin (Basal)
Efficacy (↓A1c)	High	High	Intermediate	Intermediate	High	Highest
Hypoglycemia	Moderate risk	Low risk	Low risk	Low risk	Low risk	High risk
Weight	Gain	Gain	Neutral	Loss	Loss	Gain
Major Side Effect(s)	Hypoglycemia	Edema, HF, Fx	Rare	GU, Dehydration	GI	Hypoglycemia
Costs	Low	High	High	High	High	Variable

[a]Consider starting at this stage when A1c ≥9%.
Fx, bone fracture; GI, gastrointestinal; GU, genitourinary; HF, heart failure; SGLT-2, sodium glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione.

ADA. *Diabetes Care*. 2015;38(suppl 1):S1-S94.

AACE/ACE Algorithm

Glycemic Control and Early Dual Therapy

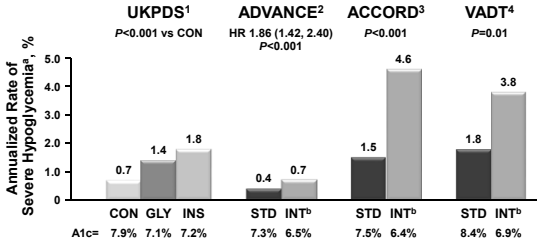


[a]Order of medications listed are a suggested hierarchy of usage.
ACE, American College of Endocrinology; AG, α-glucosidase; GLN, glinide; QR, quick release.

Garber AJ, et al. *Endocr Pract*. 2016;22(1):84-113.

Hurdles to Intensive Therapy

Rates of Severe Hypoglycemia

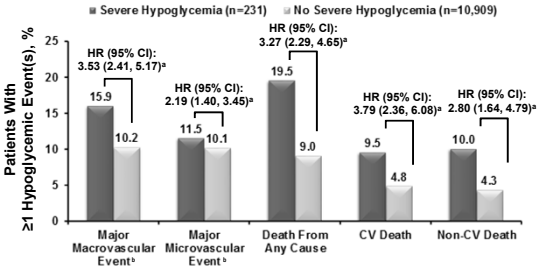


[a]Hypoglycemia requiring any assistance; [b]Intensive glycemic control was defined differently in these trials.
ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: PreterAx and DiamicroN MR Controlled Evaluation; CON, conventional therapy; GLY, glibenclamide; HR, hazard ratio; INS, insulin; INT, intensive therapy; STD, standard therapy; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

1. UKPDS Group. *Lancet*. 1998;352(9131):837-853; 2. Patel A, et al; [ADVANCE]. *N Engl J Med*. 2008;358(24):2560-2572;
3. Gerstein HC, et al; [ACCORD]. *N Engl J Med*. 2008;358(24):2545-2559; 4. Duckworth W, et al. *N Engl J Med*. 2009;360(2):129-139.

ADVANCE

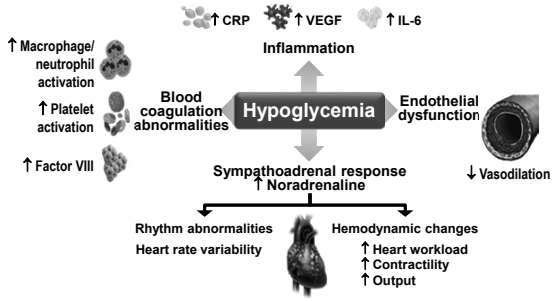
Severe Hypoglycemia vs Adverse Endpoints



[a]Adjusted for multiple baseline covariates; [b]Primary endpoints.
Major macrovascular event=CV death, nonfatal myocardial infarction, or nonfatal stroke.
Major microvascular event=new or worsening nephropathy or retinopathy.
CI, confidence interval.

Zoungas S, et al. *N Engl J Med*. 2010;363(15):1410-1418.

Pathophysiologic CV Consequences of Hypoglycemia

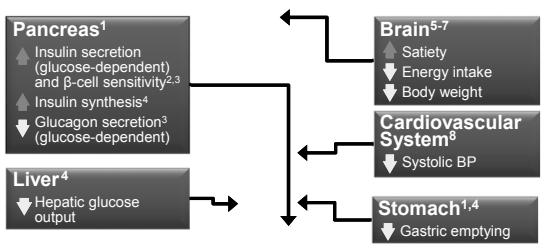


CRP, C-reactive protein; IL-6, interleukin-6; VEGF, vascular endothelial growth factor.

Desouza CV, et al. *Diabetes Care*. 2010;33(6):1389-1394.

GLP-1 Signaling

Effects Related to Glucose Control



1. Holst JJ, et al. *Trends Mol Med*. 2008;14(4):161-168; 2. Flint A, et al. *Adv Ther*. 2011;28(3):213-226;
3. Degn K, et al. *Diabetes*. 2004;53(5):1187-1194; 4. Baggio LL, Drucker DJ. *Gastroenterology*. 2007;132(6):2131-2157;
5. Horowitz M, et al. *Diabetes Res Clin Pract*. 2012;97(2):258-266; 6. Vilsbøll T, et al. *BMJ*. 2012;344:d7771;
7. Niswender K, et al. *Diabetes Obes Metab*. 2013(1);15:42-54; 8. Fonseca V, et al. *Diabetes*. 2010;59(suppl 1):A79(296-OR).

Glucose Control and DPP-4 Inhibitors

Monotherapy and Metformin Combinations

Therapy vs Comparator	ΔA1c for Saxagliptin vs Comparator, %[1-3]	ΔA1c for Sitagliptin vs Comparator, %[4-6]	ΔA1c for Linagliptin vs Comparator, %[7-9]	ΔA1c for Alogliptin vs Comparator, %[10-12]
Monotherapy vs Placebo	-0.46 vs 0.19[a]	-0.48 vs 0.12[b]	-0.44 vs 0.25[a]	-0.59 vs -0.02[b]
Initial Combination With Metformin vs Metformin[2]	-2.50 vs -2.0[a]	-1.90 vs -1.13[b]	-1.7 vs -1.2[a]	-1.1 vs -1.6[c]
Add on to Metformin vs Metformin[3]	-0.69 vs 0.13[a]	-0.73 vs -0.22[b]	-0.49 vs 0.15[a]	-0.6 vs -0.1[b]

[a]P<0.0001 vs comparator; [b]P<0.001 vs comparator; [c]P<0.05 vs comparator.

1. Rosenstock J, et al. *Curr Med Res Opin*. 2009;25:2401-2411; 2. Jadzinsky M, et al. *Diabetes Obes Metab*. 2009;11:611-622; 3. DeFronzo RA, et al. *Diabetes Care*. 2009;32:1649-1655; 4. Raz I, et al. *Diabetologia*. 2006;49:2564-2571; 5. Goldstein BJ, et al. *Diabetes Care*. 2007;30:1979-1987; 6. Scott R, et al. *Diabetes Obes Metab*. 2008;10:959-969; 7. Del Prato S, et al. *Diabetes Obes Metab*. 2011;13:258-267; 8. Haak T, et al. *Diabetes Obes Metab*. 2012;14:565-574; 9. Taskinen MR, et al. *Diabetes Obes Metab*. 2011;13:65-74; 10. DeFronzo RA, et al. *Diabetes Care*. 2008;31:2315-2317; 11. Drugs@FDA (www.accessdata.fda.gov/drugsatfda_docs/label/2013/022271s000lbl.pdf); 12. Nauck MA, et al. *Int J Clin Pract*. 2009;63:46-55.

DPP-4 Inhibitors

Additional Safety Considerations

- Generally well tolerated
- Most common adverse effects
  - Nasopharyngitis
  - Headache
  - Nausea
  - Hypersensitivity
  - Skin reactions
- Dose reductions are required for alogliptin, saxagliptin, and sitagliptin in patients with moderate or severe renal impairment, or ESRD (CrCl ≤50 mL/min)

CrCl, creatinine clearance; ESRD, end-stage renal disease.

Grunberger G. *J Diabetes*. 2013;5(3):241-253.

DPP-4 Inhibitors
Recent FDA Warnings

- Joint pain
  - DPP-4 inhibitor class carries a warning about joint pain that can be severe and disabling
  - In rare identified cases, symptoms abate <1 month after drug is stopped
  - May relate to cytokines, chemokines, and matrix metalloproteinases
- Heart failure
  - For saxagliptin and alogliptin, consider benefits vs risks in patients at risk for heart failure, and consider discontinuing if heart failure develops
  - SAVOR: more patients hospitalized for heart failure in the saxagliptin group than in the placebo group (HR, 1.27; 95% CI: 1.07, 1.51)
    - Post hoc analysis showed that patients at highest risk of heart failure–related hospitalization had previous heart failure or chronic kidney disease[4]
  - EXAMINE: more patients hospitalized for heart failure in the alogliptin group (3.9%) than in the placebo group (3.3%)

Mascolo A, et al. *Drug Saf*. 2016;39(5):401-407; Scirica BM, et al. *Circulation*. 2014;130(18):1579-1588; White WB, et al. *N Engl J Med*. 2013;369(14):1327-1335; See Drugs@FDA: FDA Approved Drug Products; www.accessdata.fda.gov/Scripts/cder/drugsatfda/. Accessed September 5, 2016.

FDA-Approved GLP-1 RAs
Daily Formulations

	Medication	Dosage Forms	Adverse Events[a]	Dosing
Short Acting	Exenatide BID[1]	• 5 µg/dose in 1.2-mL prefilled pen • 10 µg/dose in 2.4-mL prefilled pen	Nausea, vomiting, dyspepsia	1. Start at 5 µg BID (1 h before morning and evening meals) 2. Increase to 10 µg BID at 1 month
Short Acting	Lixisenatide[2]	• 10 µg/dose in 3-mL green prefilled pen • 20 µg/dose in 3-mL burgundy prefilled pen	Nausea, vomiting, headache, diarrhea, dizziness	1. Start at 10 µg once daily for 14 days (1 h before morning meal) 2. Increase to 20 µg once daily on day 15
Long Acting	Liraglutide[3]	• Prefilled, multidose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg	Nausea, diarrhea, vomiting, constipation, headache	1. Initiate at 0.6 mg once daily, regardless of meals 2. After 1 week, increase to 1.2 mg once daily 3. If control is not at glycemic goal, dose can be increased to 1.8 mg

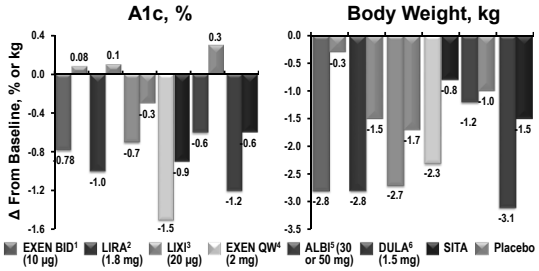
[a]Treatment-emergent adverse reactions with ≥5% incidence in clinical trials with drug as monotherapy (excluding hypoglycemia).
BID, twice daily.
1. See Drugs@FDA (www.accessdata.fda.gov/drugsatfda_docs/label/2015/021773s040lbl.pdf);
2. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208471Orig1s000lbl.pdf);
3. See Drugs@FDA (www.accessdata.fda.gov/drugsatfda_docs/label/2016/022341s025lbl.pdf).

FDA-Approved GLP-1 RAs
Weekly Formulations

	Medication	Dosage Forms	Adverse Events[a]	Dosing
Long Acting	Exenatide QW[1]	• Single-dose tray with 2-mg vial • Single-dose 2-mg prefilled pen	Nausea, diarrhea, injection-site nodule, constipation, headache, dyspepsia	1. Administer at 2.0 mg once weekly, regardless of meals
Long Acting	Albiglutide[2]	• 30-mg or 50-mg lyophilized powder in single-dose pen for reconstitution	URTI, diarrhea, nausea, injection-site reaction, cough, back pain, arthralgia, sinusitis, influenza	1. Administer at 30 mg once weekly, regardless of meals 2. If glycemic control not at goal, dose can be increased to 50 mg
Long Acting	Dulaglutide[3]	• 0.75-mg or 1.5-mg single-dose pen • Prefilled, single-dose syringe in 0.75-mg or 1.5-mg doses	Nausea, diarrhea, vomiting, abdominal pain, and decreased appetite	1. Initiate at 0.75 mg weekly, regardless of meals; dose can be increased to 1.5 mg 2. If dose is missed, missed dose must be taken within 3 days

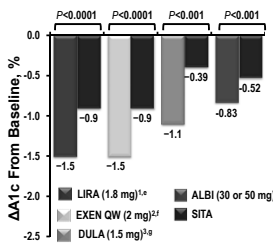
QW, once weekly; URTI, upper respiratory tract infection.
[a]Treatment-emergent adverse reactions with ≥5% incidence (excluding hypoglycemia) in clinical trials with drug as monotherapy.
1. See Drugs@FDA (www.accessdata.fda.gov/drugsatfda_docs/label/2015/022200s015s016s017s018lbl.pdf);
2. See Drugs@FDA (www.accessdata.fda.gov/drugsatfda_docs/label/2015/125431s009lbl.pdf);
3. Dulaglutide prescribing information. http://uspl.lilly.com/trulicity/trulicity.html#pi. Accessed September 2, 2016.

GLP-1 RAs Plus Metformin
Glucose Control and Weight Loss



All data are significant vs placebo ($P<0.01$ to $P<0.0001$), except for a nonsignificant Δ body weight for albiglutide vs placebo.
1. DeFronzo RA, et al. *Diabetes Care*. 2005;28(8):1092-1100; 2. Nauck M, et al. *Diabetes Care*. 2009;32(1):84-90;
3. Bolli GB, et al. *Diabet Med*. 2014;31(2):176-184; 4. Bergenstal RM, et al. *Lancet*. 2010;376(9739):431-439;
5. Ahren B, et al. *Diabetes Care*. 2014;37(8):2141-2148; 6. Nauck M, et al. *Diabetes Care*. 2014;37(8):2149-2158.

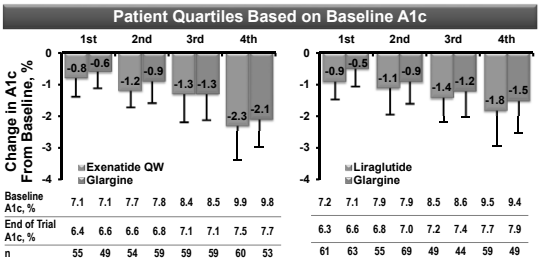
GLP-1 RAs vs DPP-4 Inhibitors
Added to Metformin



Agent	Δ Weight, kg		Hypoglycemia, % of patients	
	GLP-1 RA	DPP-4i	GLP-1 RA	DPP-4i
LIRA[3,e]	-3.4[a]	-1.0	5[d]	5
EXEN QW[2,f]	-2.3[b]	-0.8	1[d]	3
DULA[4,g]	-3.0[b]	-1.5	10[d]	5
ALBI[5,h]	-0.8[c]	-0.2	24[d,i]	16[i]

[a]$P<0.0001$ vs DPP-4 inhibitor; [b]$P<0.001$ vs DPP-4 inhibitor; [c]$P<0.05$ vs DPP-4 inhibitor; [d]No statistical analysis performed;
[e]LIRA: 26-week trial with liraglutide; baseline A1c, 8.5%; [f]EXEN QW: 26-week trial of exenatide once weekly; baseline A1c, 8.4%;
[g]DULA: 52-week trial; baseline A1c, 8.1%; [h]ALBI: 26-week trial of albiglutide; baseline A1c, 8.2%;
[i]Almost all patients experiencing hypoglycemia were also taking a sulfonylurea.
1. Pratley RE, et al. *Lancet*. 2010;375(9724):1447-1456; 2. Bergenstal RM, et al. *Lancet*. 2010;376(376):431-439;
3. Nauck M, et al. *Diabetes Care*. 2014;37(8):2149-2158; 4. Leiter LA, et al. *Diabetes Care*. 2014;37(10):2723-2730.

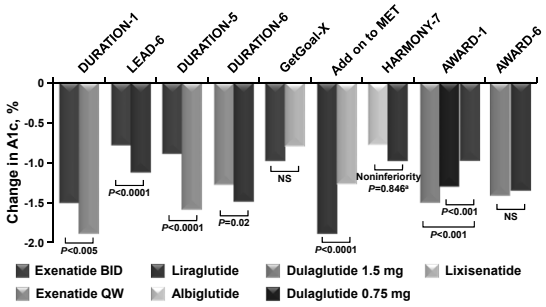
GLP-1 RAs vs Basal Insulin



	1st	2nd	3rd	4th	1st	2nd	3rd	4th
Baseline A1c, %	7.1	7.1	7.7	7.8	8.4	8.5	9.9	9.8
End of Trial A1c, %	6.4	6.6	6.6	6.8	7.1	7.1	7.5	7.7
n	55	49	54	59	59	59	60	53
Baseline A1c, %	7.2	7.1	7.9	7.9	8.5	8.6	9.5	9.4
End of Trial A1c, %	6.3	6.6	6.8	7.0	7.2	7.4	7.7	7.9
n	61	63	55	69	49	44	59	49

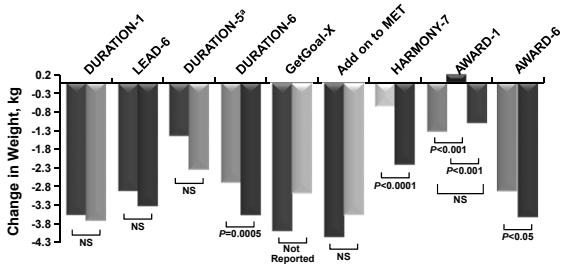
Post hoc analysis of DURATION-3 (exenatide QW) and LEAD-5 (liraglutide).
DURATION, Diabetes therapy Utilization: Researching changes in A1c, weight and other factors Through Intervention with exenatide ONce weekly; LEAD-5, Liraglutide Effect and Action in Diabetes.
Buse JB, et al. *Diabetes Obes Metab*. 2015;17(2):145-151; Diamant M, et al. *Lancet Diabetes Endocrinol*. 2014;2(6):464-473; Russell-Jones D, et al. *Diabetologia*. 2009;52(10):2046-2055.

GLP-1 RAs and ΔA1c
Head-to-Head Trials



[a]Did not meet predefined noninferiority margin.
AWARD, Assessment of Weekly AdministRAtion of LY2189265 in Diabetes; NS, not significant.
Nauck M, et al. *Diabetes Care*. 2016;39(9):1501-1509; Trujillo JM, et al. *Ther Adv Endocrinol Metab*. 2015;6(1):19-28.

GLP-1 RAs and ΔBody Weight
Head-to-Head Trials



Nauck M, et al. *Diabetes Care*. 2016;39(9):1501-1509; Trujillo JM, et al. *Ther Adv Endocrinol Metab*. 2015;6(1):19-28.

GLP-1 RAs and Blood Pressure
Meta-Analysis of Data From Obese and Overweight Individuals[a]

Parameter	Change vs Control	95% CI
Systolic blood pressure	–3.57 mm Hg	–5.49 to –1.66
Diastolic blood pressure	–1.38 mm Hg	–2.02 to –0.73

[a]Includes 11 or 12 trials examining overweight and obese individuals with or without T2DM; treatments included exenatide BID, exenatide QW, or liraglutide.
Vilsbøll T, et al. *BMJ*. 2012;344:d7771.

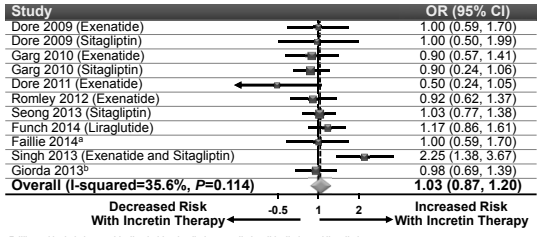
Safety With Incretin-Based Agents
Acute Pancreatitis

- **Precautions**
  - Cases have been reported
  - Consider treatments other than GLP-1 RAs in patients with history of pancreatitis
  - Unknown if pancreatitis history increases risk with DPP-4 inhibitors
- **Recommendations**
  - Ask about pancreatitis history
  - Educate patients about signs and symptoms of pancreatitis
  - Discontinue if pancreatitis symptoms occur
  - Report cases of pancreatitis to www.fda.gov/medwatch

See Drugs@FDA: FDA Approved Drug Products; www.accessdata.fda.gov/Scripts/cder/drugsatfda/. Accessed September 5, 2016.

Incretin Therapy and Acute Pancreatitis

Pancreatitis risk is 1.5-fold to 3-fold higher in all individuals with diabetes



[a]Faillie et al included exenatide, liraglutide, sitagliptin, saxagliptin, vildagliptin, and linagliptin;
[b]Giorda et al. included exenatide, liraglutide, sitagliptin, saxagliptin, and vildagliptin.
OR, odds ratio.
Wang T, et al. *Diabetes Obes Metab*. 2015;17(1):32-41; Yang L, et al. *Eur J Gastroenterol Hepatol*. 2013;25(2):225-231.

Safety of Incretin Therapy
2014 FDA and EMA Analysis

- FDA and EMA conducted parallel, independent safety assessments of incretin-based drugs following postmarketing reports of pancreatitis or pancreatic cancer in treated individuals

"Assertions of a causal association are not consistent with current data"

"Product information and labeling reflect current understanding of risk"

- Both agencies continue to investigate safety signals and data from ongoing trials

EMA, European Medicines Association.
Egan AG, et al. *N Engl J Med*. 2014;370(9):794-797.

Gastrointestinal Adverse Reactions With GLP-1 RAs

Results From Pooled Placebo-Controlled Trials

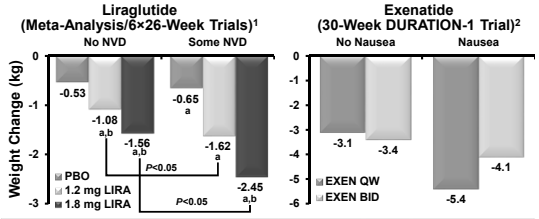
Medication[1,2]	Nausea, % of Patients	Vomiting, % of Patients	Diarrhea, % of Patients
Albiglutide	11%	4%	13%
Dulaglutide[a]	12%, 21%	6%, 13%	9%, 13%
Exenatide BID[b]	44%	13%	13%
Exenatide QW[c]	24%	11%	20%
Liraglutide[d]	18%, 20%	6%, 9%	10%, 12%
Lixisenatide	25%	10%	8%

- **Potential approaches to reduce risks for nausea and vomiting[1,3]**
  - Educate on meal size, eating pace, and dose timing relative to meals
  - Use incremental dose titration, particularly with shorter-acting agents

[a]Two numbers in each column reflect 0.75 mg and 1.5 mg doses, respectively; [b]Data from add on to metformin +/- sulfonylurea trial; [c]Data from add on to metformin trial; [d]Two numbers in each column reflect 1.2 mg and 1.8 mg doses, respectively.
1. See Drugs@FDA: FDA Approved Drug Products; www.accessdata.fda.gov/Scripts/cder/drugsatfda/. Accessed September 5, 2016;
2. Dulaglutide prescribing information. http://uspl.lilly.com/trulicity/trulicity.html#pi. Accessed September 2, 2016;
3. Ellero C, et al. *Diabet Med*. 2010;27(10):1168-1173.

Weight Loss With GLP-1 RAs

Not Driven by Gastrointestinal Adverse Events



In 82-week exenatide completer cohort, weight loss was 1) similar across degrees of nausea, 2) progressive despite stable nausea incidence, and 3) unlikely to be driven by nausea.[3]

NVD, nausea, vomiting, diarrhea; PBO, placebo.
[a]P<0.05 vs baseline; [b]P<0.05 vs placebo.
1. Russell-Jones D, et al. 70th ADA Scientific Sessions. 2010;1886-P; 2. Drucker DJ, et al. *Lancet*. 2008;372(9645):1240-1250;
3. Blonde L, et al. *Diabetes Obes Metab*. 2006;8(4):436-447.

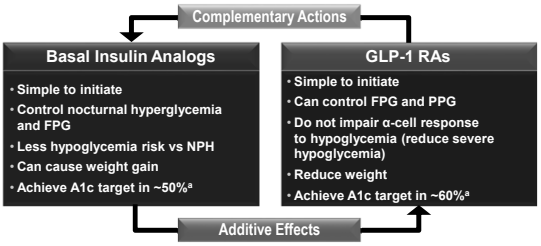
GLP-1 RAs

Additional Safety Considerations

- Use with caution in patients with renal impairment or renal transplantation, especially when initiating or escalating doses[1-3]
  - Hypovolemia due to nausea/vomiting may worsen renal function
  - Do not use exenatide formulations in patients with severe renal impairment (CrCl <30 mL/min) or ESRD
- All long-acting GLP-1 RAs should not be used in patients with MEN2 or personal/family history of MTC[1,2]
  - Counsel regarding MTC risk and symptoms of thyroid tumors
  - Report MTC to state cancer registry, regardless of treatment http://www.naaccr.org/Membership/MembershipDirectory.aspx

MEN2, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma.
1. See Drugs@FDA: FDA Approved Drug Products; www.accessdata.fda.gov/Scripts/cder/drugsatfda/. Accessed September 5, 2016;
2. Dulaglutide prescribing information. http://uspl.lilly.com/trulicity/trulicity.html#pi. Accessed September 2, 2016;
3. Idorn T, et al. *Diabetes Care*. 2016;39(2):206-213.

Combining GLP-1 RAs and Basal Insulin Analogs

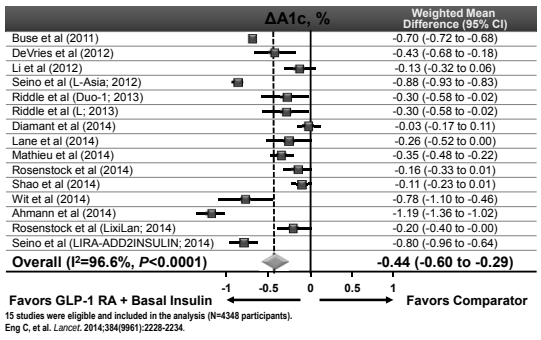


Insulin degludec/liraglutide and insulin glargine/lixisenatide fixed combinations have received recommendations for approval from an FDA advisory panel

[a]Percentage achieving <7% across baseline A1c quartiles for liraglutide and exenatide QW vs insulin glargine.
FPG, fasting plasma glucose; NPH, neutral protamine Hagedorn; PPG, postprandial glucose.
Buse JB, et al. *Diabetes Obes Metab*. 2015;17(2):145-151; Holst JJ, Vilsbøll T. *Diabetes Obes Metab*. 2013;15(1):3-14;
Vora J, et al. *Diabetes Metab*. 2013;39(1):6-15.

GLP-1 RAs Plus Basal Insulin

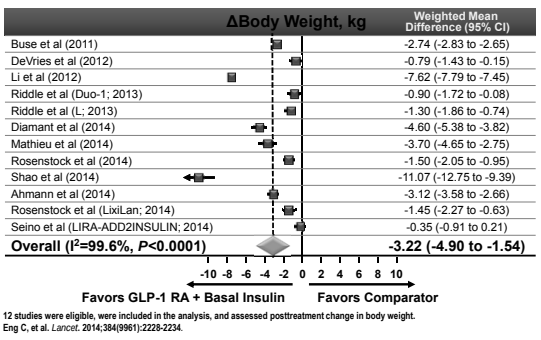
Meta-analysis for ΔA1c



15 studies were eligible and included in the analysis (N=4348 participants).
Eng C, et al. *Lancet*. 2014;384(9961):2228-2234.

GLP-1 RAs Plus Basal Insulin

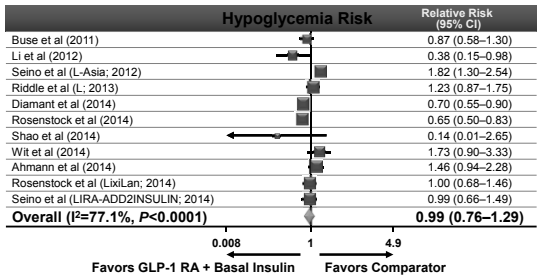
Meta-analysis for ΔBody Weight



12 studies were eligible, were included in the analysis, and assessed posttreatment change in body weight.
Eng C, et al. *Lancet*. 2014;384(9961):2228-2234.

GLP-1 RAs Plus Basal Insulin

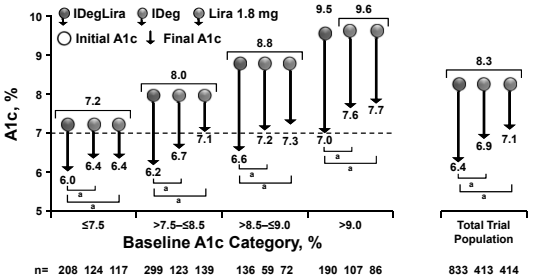
Meta-analysis for Hypoglycemia



11 studies were eligible, were included in the analysis, and assessed relative risk of hypoglycemia.
Eng C, et al. *Lancet*. 2014;384(9961):2228-2234.

GLP-1 RA/Basal Insulin Fixed-Ratio Combination

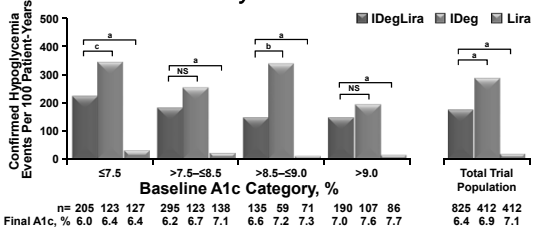
Glycemic Control in DUAL I



[a]P<0.01.
N=1660 insulin-naive adults with T2DM (mean A1c, 8.3%; mean BMI, 31.2 kg/m²) uncontrolled on oral agents assigned to IDegLira, insulin degludec, or liraglutide 1.8 mg daily (DUAL I Extension).
Gough SC, et al. *Lancet Diabetes Endocrinol*. 2014;2(11):885-893; Rodbard HW, et al. *Diabetes Obes Metab*. 2016;18(1):40-48.

GLP-1 RA/Basal Insulin Fixed-Ratio Combination

Safety in DUAL I



Fewer patients in the IDegLira group than in the liraglutide group reported GI adverse events (nausea, 8.8% vs 19.7%)

[a]P<0.0001; [b]P=0.001; [c]P<0.05.
N=1660 insulin-naive adults with T2DM (A1c, 8.3%; BMI, 31.2 kg/m²) uncontrolled on oral agents assigned to IDegLira, insulin degludec, or liraglutide 1.8 mg daily (DUAL I Extension).
Gough SC, et al. *Lancet Diabetes Endocrinol*. 2014;2(11):885-893; Rodbard HW, et al. *Diabetes Obes Metab*. 2016;18(1):40-48.

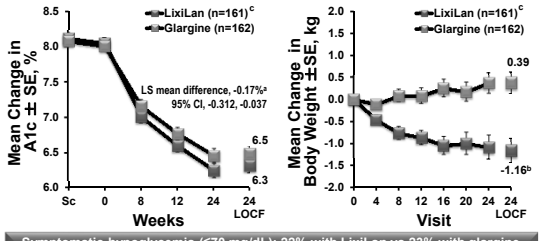
Additional Published IDegLira Studies

Study Name (Drug)	Study Population	Background Therapy	Comparator	ΔA1c
DUAL II[1] (IDegLira)	Inadequate control with MET + basal insulin ± SU	MET	Degludec (max dose, 50 U)	IDegLira, -1.9% Degludec, -0.9% *P*<0.0001
DUAL III[2] (IDegLira)	Inadequate control with GLP-1 RAs + OADs	Pretrial OADs	Continued GLP-1 RA	IDegLira, -1.3% Placebo, -0.3% *P*<0.001
DUAL IV[3] (IDegLira)	Inadequate control with SU ± MET	SU ± MET	Placebo	IDegLira, -1.5% Placebo, -0.5% *P*<0.001
DUAL V[4] (IDegLira)	Inadequate control with MET + insulin glargine 20-50 U	MET	Up-titration of glargine	IDegLira, -1.81% Glargine, -1.13% *P*<0.001

OADs, oral antidiabetes drugs (MET±PIO±SU); PIO, pioglitazone.
1. Buse JB, et al. *Diabetes Care*. 2014;37(11):2926-2933; 2. Linjawi S, et al. *Diabetes*. 2015;64(suppl 1):A255.abstract 1002-P;
3. Rodbard HW, et al. *Diabetes*. 2015;64(suppl 1):A255-A256. abstract 1003-P; 4. Lingvay I, et al. *JAMA*. 2016;315(9):898-907.

Fixed-Ratio LixiLan vs Glargine

Add-on to Metformin in T2DM

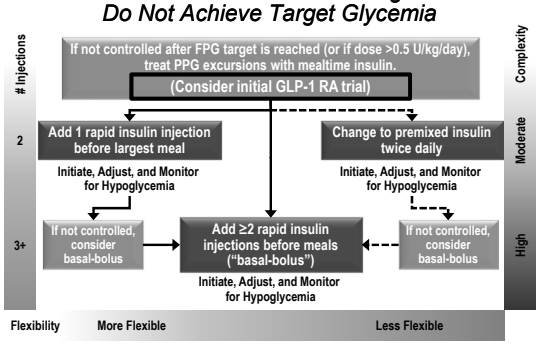


Symptomatic hypoglycemia (≤70 mg/dL): 22% with LixiLan vs 23% with glargine
Incidence of nausea/vomiting was 7.5%/2.5% with LixiLan

[a]P=0.013; [b]P<0.0001 vs glargine; [c]LixiLan formulation: insulin glargine 2 U/lixisenatide 1 µg.
LOCF, last observation carried forward; LS, least squares.
Rosenstock J, et al. Benefits of a Fixed-ratio Formulation of Once-Daily Insulin Glargine/Lixisenatide (LixiLan) vs. Glargine in Type 2 Diabetes (T2DM) Inadequately Controlled on Metformin. Presented at the 74th Scientific Sessions of the ADA; June 13-17, 2014: San Francisco, CA. Abstract 332-OR.

ADA/EASD Position Statement

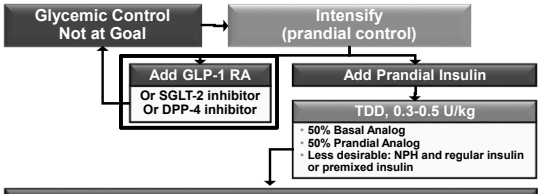
When Basal Insulin ± Oral Agents Do Not Achieve Target Glycemia



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

Improving Prandial Hyperglycemia

AACE Recommendations



Insulin Titration Every 2-3 Days to Reach Glycemic Goal

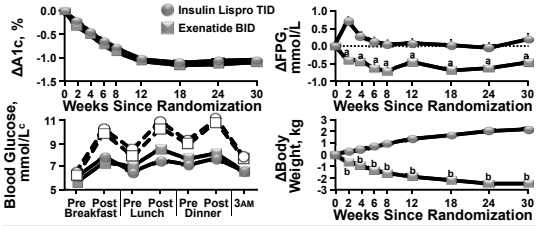
- Increase prandial dose by 10% for any meal if the 2-h postprandial or next premeal glucose is >180 mg/dL
- Premixed: Increase TDD by 10% if fasting/premeal blood glucose >180 mg/dL
- If fasting AM hypoglycemia, reduce basal insulin
- If nighttime hypoglycemia, reduce basal and/or presupper or pre-evening snack short/rapid-acting insulin
- If between-meal daytime hypoglycemia, reduce previous premeal short/rapid-acting insulin

TDD, total daily dose.

Garber AJ, et al. *Endocr Pract*. 2015;21(4):438-447.

GLP-1 RA or Bolus Insulin

With Optimized Basal Insulin for T2DM



Compared with lispro, exenatide caused more GI issues (47% vs 13%), but fewer nonnocturnal hypoglycemic episodes (15% vs 34%)

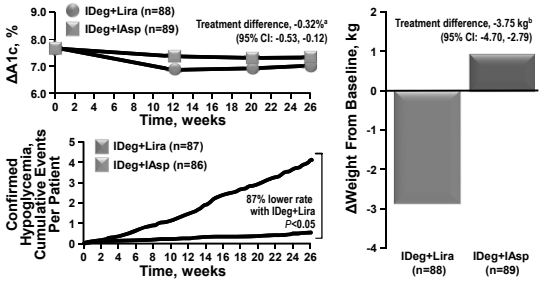
[a]P<0.01 for exenatide BID vs insulin lispro TID; [b]P<0.001 for exenatide BID vs insulin lispro TID; [c]Open symbols and dashed lines are at randomization, whereas closed symbols and solids lines are at 30 weeks.

N=627 patients with insufficient A1c control after 12 weeks of basal insulin optimization (mean background dosing was insulin glargine 61 units/day and metformin 2000 mg/day).

Diamant M, et al. *Diabetes Care*. 2014;37(10):2763-2773.

Liraglutide vs Bolus Insulin Once Daily

In Patients Treated With Insulin Degludec



[a]P<0.005; [b]P<0.0001.

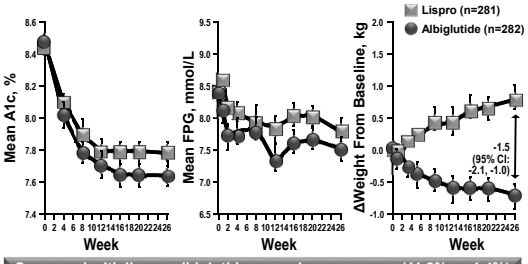
IAsp, insulin aspart.

N=177 patients with T2DM and A1c ≥7.0% despite completing a 104-week trial on insulin degludec + MET.

Mathieu C, et al. *Diabetes Obes Metab*. 2014;16(7):636-644.

Albiglutide Once Weekly vs Thrice-Daily Insulin Lispro

With Basal Insulin for T2DM



Compared with lispro, albiglutide caused more nausea (11.2% vs 1.4%) and vomiting (6.7% vs 1.4%), but less hypoglycemia (15.8% vs 29.9%)

N=563 patients with T2DM treated with insulin glargine with metformin and/or pioglitazone.

Rosenstock J, et al. *Diabetes Care*. 2014;37(10):2317-2325.