



FAMILY MEDICINE

DIABETES UPDATES LUNCHEON SYMPOSIUM

Integrating GLP-1 Inhibitors Into a Comprehensive Diabetes Care Management Regimen – The Incretin Experience

SYLLABUS

Monday, August 3, 2015
12:40 – 3:00 p.m. | Room 420B
COBO Center
Detroit, Michigan

Faculty Disclosures

WARREN A. JONES, M.D.¹

KWABENA ADUBOFOUR, M.D.¹

MORRIS L. BROWN, M.D.

Consulting / Speakers' Bureau:
Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk

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Speakers' Bureau: Astra Zeneca, Boehringer Ingelheim, Eli Lilly
Consultant/Speaker: Janssen

¹This speaker declares no relevant relationship with commercial entities.

New Models of Care in the Management of Type 2 Diabetes: Focus on Incretin Therapies

Introduction

We know that Diabetes has reached epidemic proportions, both worldwide and nationally. According to the American Diabetes Association, the prevalence of Diabetes in 2012, was 29.1 million Americans, or 9.3% of the population. 8.1 million of these Americans were undiagnosed.¹ The incidence of diabetes in 2012 was 1.7 million new diagnoses/year; in 2010 it was 1.9 million.²

Diabetes not only affects the quality of life of people with the disease, but also presents a tremendous economic burden on our health care system. Diabetes, including diagnosed and undiagnosed diabetes, pre diabetes, and gestational diabetes mellitus (GDM) and their complications, accounted for \$218 billion in direct and indirect costs in 2007 alone.³ Much of the economic burden of diabetes is related to its complications, including blindness, amputation, kidney failure, heart attack, and stroke.

Gaps/Needs Assessment

African American patients are more likely than white patients to have diabetes. The risk of diabetes is 77% higher among African Americans than among non-Hispanic white Americans.⁴ The rates of diagnosis of diabetes in non-Hispanic African Americans is 18.7% compared to 7.1% of non-Hispanic white Americans. That is 4.9 million African American adults with diagnosed or undiagnosed diabetes.⁵ In 2006, African-American men were 2.2 times more likely to start treatment for ESRD related to diabetes than non-Hispanic white men. In the same year, African Americans with diabetes were 1.5 times more likely to be hospitalized and 2.3 times more likely to die from diabetes than non-Hispanic whites.⁶ African Americans are almost 50% more likely to develop diabetic retinopathy than non-Hispanic whites.⁷

References:

1. <http://www.diabetes.org/diabetes-basics/statistics/#sthash.dsck9TDB.dpuf>
2. <http://www.diabetes.org/diabetes-basics/statistics/#sthash.FXE5LhiB.dpuf>
3. Dall TM, Zhang Y, Chen YJ, Quick WW, Yang WG, Fogli J: The economic burden of diabetes. *Health Aff* 29:297–303, 2010
4. Centers for Disease Control and Prevention: National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States. Atlanta, Ga., U.S. Department of Health and Human Services, 2011
5. National Diabetes Information Clearinghouse. National diabetes statistics, 2011 [article online]. Available from <http://www.diabetes.niddk.nih.gov/dm/pubs/statistics>. Accessed 7 March 2012
6. U.S. Department of Health and Human Services Office of Minority Health: Diabetes and African Americans [article online]. Available from <http://minorityhealth.hhs.gov/templates/content.aspx?lvl=2&lvlID=51&ID=3017>. Accessed 23 January 2012
7. American Diabetes Association: African Americans & complications [article online]. Available from <http://www.diabetes.org/living-with-diabetes/complications/african-americans-and-complications.html>. Accessed 7 March 2012

Intended Audience

This program is intended for primary care and family medicine physicians, endocrinologists, internists, nurse practitioners and other healthcare professionals interested in diabetes.

Objectives

Upon completion of this session, participants should be able to:

1. Summarize the efficacy, safety, and tolerability of GLP-1 agonists.
2. Identify patients who would benefit from GLP-1 agonist therapy and those for whom it may not be appropriate.
3. Describe in patient-appropriate terms how GLP-1 agonists can improve glycemic control.
4. Compare and contrast GLP-1 agonists, other incretin-based therapies, and traditional oral agents.
5. Develop evidence-based treatment plans to incorporate incretin therapies in combination with oral agents and insulin for optimal glycemic control

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Program Agenda

MONDAY, AUGUST 3, 2015

12:40 – 1:00	Registration and Luncheon
1:00 – 1:10 Moderator	Introduction and Program Overview/Pre-Test Warren A. Jones, M.D. Endowed Chair in Health Disparities Research Dillard University New Orleans, Louisiana Professor Emeritus of Family Medicine University of Mississippi School of Medicine Chair Emeritus, NMA Family Medicine Section Ridgeland, Mississippi
1:10 – 1:35	Characteristics and Functions of Endogenous Incretins: Review of Current ADA/AACE Diabetes Guidelines Morris L. Brown, M.D. Associate Clinical Professor of Family Medicine Wright State University Medical School Providence Medical Group Dayton, Ohio
1:35 – 1:40	Audience Interaction/Questions and Answers
1:40 – 2:05	Review of Clinical Evidence Supporting the Beneficial Effects of Incretins on Body Weight and the Cardiovascular System Kwabena Adubofour, M.D. Associate Clinical Professor Department of Internal Medicine University of California-Davis Medical Center Sacramento, California Medical Director East Main Clinic and Stockton Diabetes Intervention Center Stockton, California
2:05 – 2:10	Audience Interaction/Questions and Answers
2:10 – 2:35	Using Incretin-Based Treatments as Monotherapy and in Combination with Anti-Diabetes Medications James R. Gavin, III, M.D. Ph.D. Clinical Professor of Medicine Endocrinology Division Department of Internal Medicine Emory University School of Medicine Atlanta, Georgia
2:35 – 2:40	Audience Interaction/Questions and Answers
2:40 – 3:00	Panel Discussion/Post-Test/Audience Interaction with Faculty Kwabena Adubofour, M.D. Morris L. Brown, M.D. James Gavin, Jr., M.D., PhD Warren A. Jones, M.D.



Warren A. Jones, M.D.

Endowed Chair in Health Disparities Research
Dillard University
New Orleans, Louisiana
Professor Emeritus of Family Medicine
University of Mississippi School of Medicine
Chair Emeritus, NMA Family Medicine Section
Ridgeland, Mississippi

Moderator

Warren A. Jones, M.D., a family physician and retired Captain in the U.S. Navy, is the Endowed Chair of Health Disparities Research and Professor of Chemistry at Dillard University in New Orleans, LA. He was most recently the Director of Healthcare Quality and Disparities at Provider Resources, Inc. He was the founding Executive Director of the Mississippi Institute for Improvement of Geographic Minority Health at the University of Mississippi Medical Center where he is a Professor Emeritus of Family Medicine and has also been a Distinguished Professor of Health Policy, Professor of Family Medicine and a Professor of Anesthesiology. He is a previous Associate Vice Chancellor for Multicultural Affairs at the University of Mississippi and past Director of the Mississippi Area Health Education Centers (AHEC).

He was previously the Executive Director of the Division of Medicaid in the Office of the Governor of Mississippi, the state's health program for 25% Mississippi's total population. He currently serves on the congressionally Mandated Advisory Committee on Disability compensation for the Veterans Administration. He has also served on the congressionally mandated Council of Councils at the National Institutes of Health (NIH). He has also served as Chair Designee of the National Advisory Council to the NIH's National Institute on Minority Health and Health Disparities (NIMHD). He has served on the Emergency Medical Treatment and Labor Act (EMTALA) Technical Advisory Group (TAG) to the Secretary of Health and Human Services and on the National Commission for Prevention Priorities. He has completed his service on the Advisory Panel on Outreach and Education for the Centers for Medicare and Medicaid Services. He also has served on the Board of Trustees for his Alma Mater, Dillard University in New Orleans, LA. He currently serves as a Trustee at St. Andrews Episcopal School in Ridgeland, MS. He Chairs the Board of Directors for the American Health Information Management Association Foundation (AHIMA) and serves on the Board of the Diabetes Foundation of Mississippi.

Dr. Jones is a past President of the American Academy of Family Physicians, an 118,300-member primary care specialty society. He has also served Chair of the AAFP's Board of Directors and President-elect of the Academy. He is the Chair Emeritus of the Family Medicine Section of the National Medical Association (NMA). He has also Chair of the Maternal Child Council, Past Chair of the Family Medicine Section and Aerospace & Military Medicine Section of the NMA. He also served on the Minority Affairs Governing Council for the American Medical Association (AMA). He was most recently a Co-Lead for the Behavioral Health Subgroup of the Eunice Kennedy Shriver-National Institute of Child Health and Human Development Visioning Project.

Jones retired from the United States Navy and his position as the first African American Medical Director of the over 10 million member TRICARE Military Health Program, the military's health insurance program

in 2001. He previously served as Director of Medical and Clinical services for the Pacific region of TRICARE coordinating care for U.S. service members and their families from Alaska to Madagascar.

Jones has served on the *President's Select Panel* on Surviving and Living after Cancer, the Chiropractic Implementation Committee for the U.S. Secretary of Veterans Affairs and on the Secretary's *Chiropractic Advisory Committee*. In addition, Jones was a member of the *Expert Panel for the Medicaid Disease Management Initiative* for the Center for Health Care Strategies, the Robert Wood Johnson Foundation and the Kaiser Permanente Foundation,. He was a member of the Key Stakeholders Advisory Board to the Evidence Based Research Center for the Agency for Healthcare Research and Quality (AHRQ). He is currently a member of the Board of Directors of the Mississippi Diabetes Foundation and has previously served on the Board of the National Health Council and the National Advisory Council to *Rewarding Results*, an advisory panel to the Robert Wood Johnson Foundation and the California Health Foundation which led to the development of the Pay for Performance initiative in health care. He is also a member of the expert panel for the Innovations in *Prevention Awards*, sponsored by Health and Human Services Secretary, Tommy Thompson.

Jones received his undergraduate degree in chemistry from Dillard University in New Orleans. He received his medical degree from Louisiana State University School of Medicine in 1978, and completed a family medicine residency at the Naval Hospital in Pensacola, Fla. Jones also earned a fellowship in Adolescent Medicine at the Naval Hospital in San Diego. Jones is a Fellow of the AAFP, an earned degree awarded to family physicians for distinguished service and continuing medical education.

Jones has extensive military and medical teaching experience, which includes serving as special assistant to the U.S. Navy Surgeon General and was Chair of the Department of Family Medicine at the Naval Hospital in Charleston, S.C. Jones has received numerous military honors including the Defense Superior Service Medal and the Navy Commendation Medal for superior performance. He received the Meritorious Service Medal three times. He was recently honored as the Outstanding Black Educator in Mississippi by the Board of the Institutions of Higher Learning. He is married to the former Gennie Lacy of Pickens, MS and has six children: Aaron, Keith, Winston, Deanna, Cassandra and Madison.



Morris L. Brown, M.D.

Associate Clinical Professor of Family Medicine
Wright State University Medical School
Providence Medical Group
Dayton, Ohio

Morris L. Brown, M.D., is a Family Practice physician who has practiced in the Dayton area for over 35 years. Dr. Brown earned his medical degree from Meharry Medical School in Nashville, Tennessee. Upon completing an internship at the Wright-Patterson Air Force Base in Ohio, he served as a Captain in the Medical Corps and Chief of Flight Medicine in the United States Air Force. Subsequently, he completed residency training in family practice at Miami Valley Hospital in Dayton, Ohio.

Dr. Brown is certified by the American Board of Family Practice. He currently serves on the Board of CareSource and The Physicians Charitable Foundation. He is the Medical Director for three area nursing and rehabilitations centers and one of the Medical Directors for Hospice of the Miami Valley. Dr. Brown served as President of the Gem City Medical, Dental and Pharmaceutical Association and as Treasurer of the Montgomery County Medical Society. Currently he serves as Associate Professor Wright State Medical School.

He continues to be an advocate for his patients and the community while serving as member of a pharmaceutical minority Advisory Board, local non- profit initiatives, seeing patients at his private practice Dayton Primary & Urgent Care, providing care at the 24 hours St E's Urgent Care and the weekly radio program on WDAO 'Health Living.

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Characteristics and Function of Endogenous Incretins: Review of Current ADA/AACE Diabetes Guideline

Morris Brown, M.D.
Associate Professor of Family Medicine
Wright State University Medical School
Providence Medical Group
Dayton, Ohio

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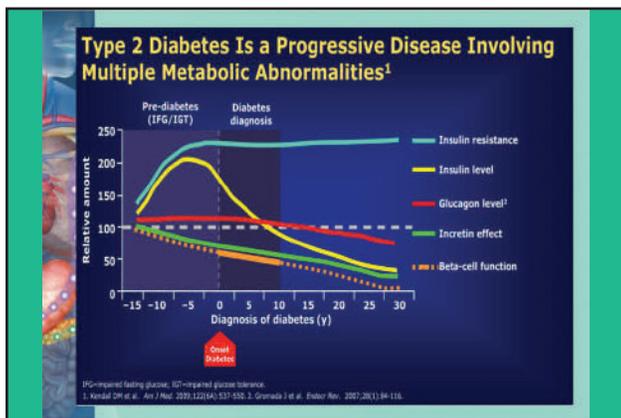
I have consulting, speaking affiliation with the following companies:

- Novo Nordisk
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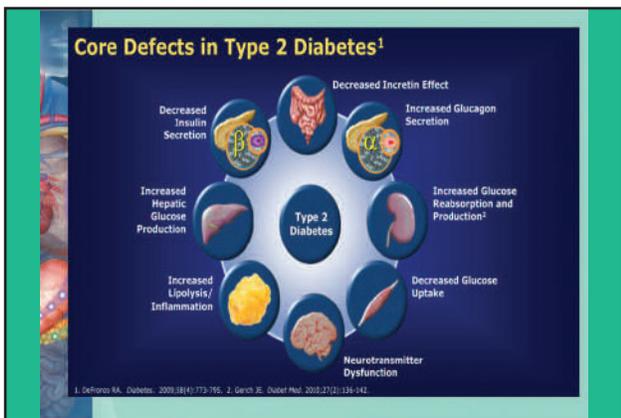
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Role of Native GLP-1 in Glucose Homeostasis

- Secreted by the gut in response to food intake¹
- Glucose regulation
 - Stimulates insulin secretion from beta cells in glucose-dependent manner¹
 - Suppresses glucagon secretion from alpha cells, which inhibits liver from releasing excess glucose²
- Gastrointestinal²
 - Slows gastric emptying
- CNS effects²
 - Feeling of satiety and fullness; energy intake

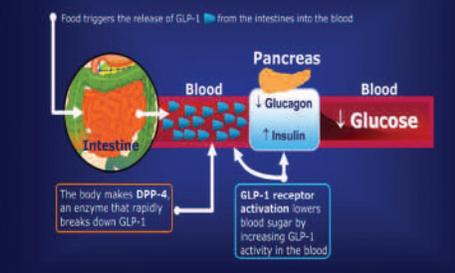


1. Holt D, Oakley C. Diabetologia. 2004;53(Suppl 2):S197-S204. 2. Boggs LJ, Drucker DJ. Gastroenterology. 2007;132(9):2131-2157.

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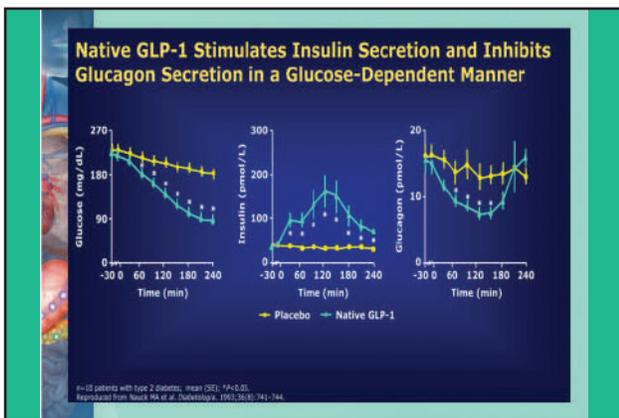
Glucagon-Like Peptide-1 (GLP-1): A Natural Hormone Released During Meals

Food triggers the release of GLP-1 from the intestines into the blood

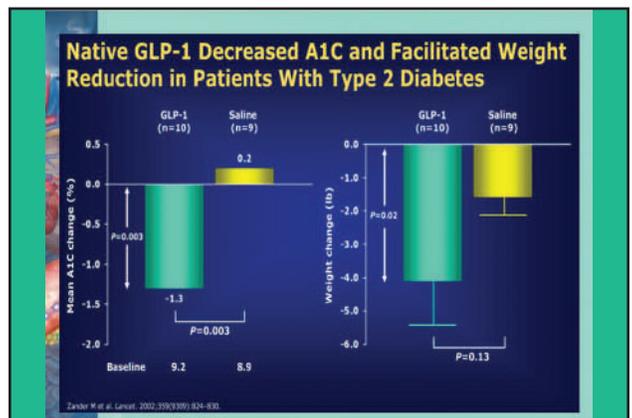


Aravoff SL, et al. Diabetic Spectrum. 2004;17(3):483-491.

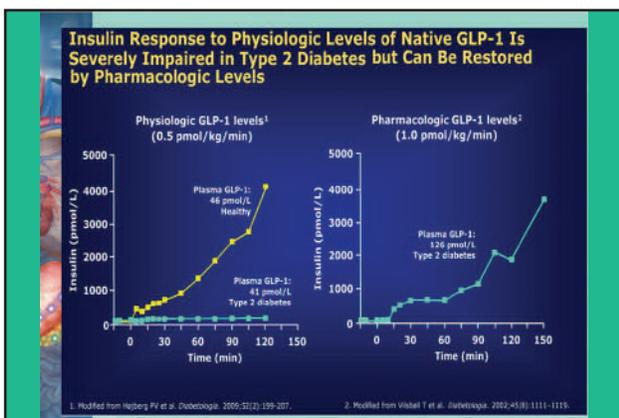
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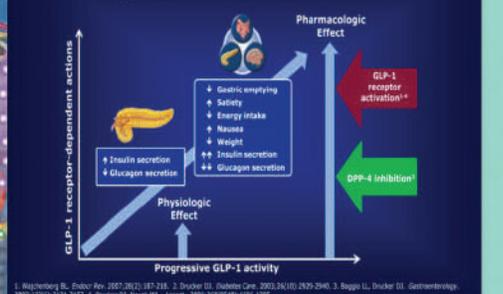


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Additional Physiologic Benefits Are Observed at Pharmacologic Levels of GLP-1



1. Weisberg SP. Endocr Rev. 2007;28(2):187-210. 2. Drucker DJ. Diabetologia. 2002;25(10):2929-2940. 3. Boggs LJ, Drucker DJ. Gastroenterology. 2007;132(9):2131-2157. 4. Drucker DJ, Nauck MA. Lancet. 2006;368(9548):1098-1105.

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Managing Disease Progression in Patients With Type 2 Diabetes

- Despite improvements in glycemic control, many patients are not at ADA A1C target goal <7.0%¹
- GLP-1 is an incretin (gut) hormone secreted in response to food intake²
- GLP-1 stimulates insulin secretion and suppresses glucagon secretion in a glucose-dependent manner³
- Insulin response to physiologic levels of native GLP-1 is severely impaired in type 2 diabetes but can be restored by pharmacologic levels^{4,5}
 - Insulin response is improved and glucagon suppression enhanced, resulting in improved glucose levels^{6,7}

1. Ford ES. J Diabetes. 2011;2(4):237-247. 2. Heist JJ, Orskov C. Diabetes. 2004;53(Suppl 2):S197-S204. 3. Baggio LL, Drucker DJ. Gastroenterology. 2007;132(5):2132-2157. 4. Minami T et al. Diabetologia. 2002;45(8):1111-1119. 5. Nagberg PV et al. Diabetologia. 2006;49(2):199-207. 6. Nauck WA et al. Diabetologia. 1993;36(8):741-746. 7. Zander M et al. Lancet. 2002;359(9300):824-830.

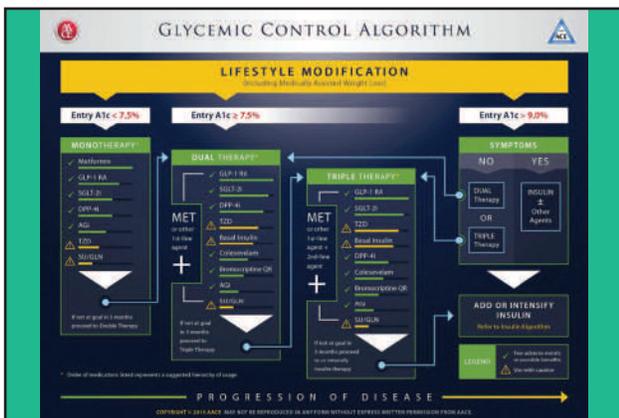
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Physiologic Impact of GLP-1 Activation and DPP-4 Inhibition

GLP-1 Activation	DPP-4 Inhibition
• Directly stimulate GLP-1 receptor ¹	• Indirectly stimulate GLP-1 receptor ¹
• Markedly increase GLP-1 activity ²	• Modestly increase endogenous GLP-1 & GIP levels ^{1,3}
• Markedly decrease glucagon secretion ^{1,3}	• Modestly decrease glucagon secretion ^{1,3}
• Increase insulin response ¹	• Increase insulin response ¹
• Delay gastric emptying ¹	• No effect on gastric emptying ¹
• Decrease appetite/energy intake ¹	• No effect on appetite/energy intake ¹

1. Drucker DJ. Lancet. 2006;368(9548):1496-1505. 2. Drucker DJ. Diabetes Care. 2003;26(10):2929-2940. 3. Heist JJ and Orskov CP. Diabetes. 1999;47(11):1463-1470.

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Key Principles for Hyperglycemia Management in Type 2 Diabetes

- Individualized treatment targets and strategies
 - No "one-size-fits-all" approach
 - Personalization necessary: Balance benefits of glycemic control with potential risks
- Emphasis on patient-centered care and shared decision-making
- Glucose control is the cornerstone of type 2 diabetes management
 - In context of comprehensive CVD risk factor reduction program*

*Includes smoking cessation, statins, blood pressure control, lipid management, and priority care.

Research: OR et al. Diabetes Care. 2012;35(1):140-148.



Kwabena Adubofour, M.D.

Associate Clinical Professor
Department of Internal Medicine
University of California-Davis Medical Center
Sacramento, California
Medical Director
East Main Clinic and Stockton Diabetes Intervention Center
Stockton, California

Kwabena Adubofour, M.D. is the Medical Director of East Main Clinic and Stockton Diabetes Intervention Center in Stockton, California. The clinic is active in the private practice of internal medicine and diabetes care.

He is the founder and current chair of the scientific and technical committee of the San Joaquin County Diabetes Society. The society seeks to improve the lives of individuals living with diabetes in San Joaquin County and holds an annual diabetes conference aimed at health care professionals involved in the day to day care of patients with diabetes.

Dr. Adubofour is also the current chair of Decision Medicine. Decision Medicine is a summer internship program of the San Joaquin County Medical Society and is designed to encourage high school students to pursue careers in the medical profession.

He has served as a preceptor at the level of Clinical Professor at the Division of General Internal Medicine, Department of Medicine, University of California Davis Medical Center in Sacramento.

Dr. Adubofour finished medical school at the University of Ghana Medical School in Accra, Ghana. He completed his residency in internal medicine at the Kaiser Permanente Medical Center in Oakland where he was also Chief resident in internal medicine.

Adubofour completed a fellowship in clinical pharmacology at the Division of Clinical Pharmacology, Stanford University Medical Center in Palo Alto.

Slide 1

REVIEW OF CLINICAL EVIDENCE SUPPORTING THE BENEFICIAL EFFECTS OF INCRETINS ON BODY WEIGHT AND THE CARDIOVASCULAR SYSTEM

KWABENA O.M. ADUBOFOUR, MD, FACP
MEDICAL DIRECTOR, EAST MAIN CLINIC AND STOCKTON DIABETES INTERVENTION CENTER

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Disclosures: Have previously served on speakers bureau and advisory boards for Novo-Nordisk, AstraZeneca

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DIABETES AND CARDIOVASCULAR DISEASE

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Diabetes and Cardiovascular Disease

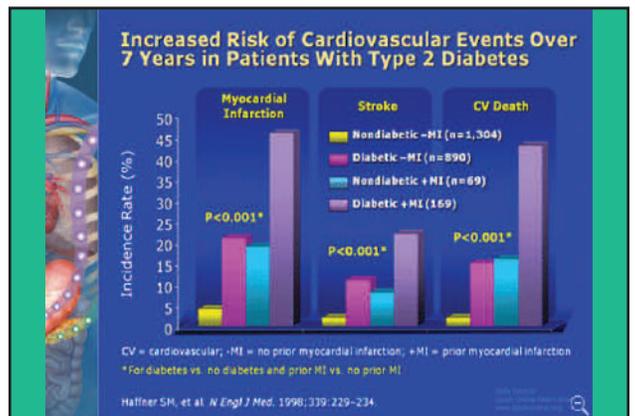
- Patients with T2D have a several fold increased risk of developing cardiovascular disease when compared to non-diabetic controls.
- Myocardial Infarction and stroke are responsible for 75% of all deaths in patients with diabetes.

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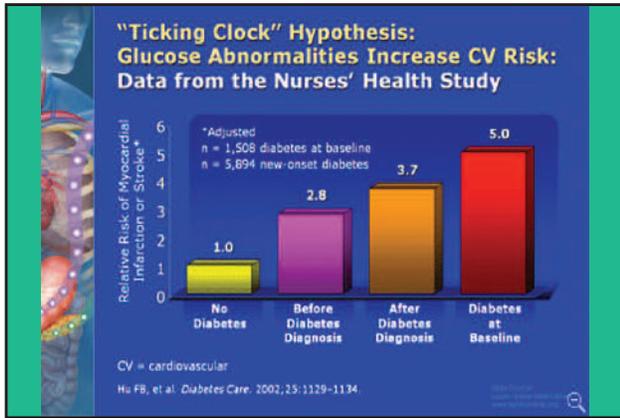
Diabetes and Cardiovascular Disease

- Patients with diabetes present with a 2-4X increased incidence of death from coronary artery disease.
- Patients with diabetes are considered for cardiovascular disease secondary prevention because their risk is similar to that reported in patients without diabetes who have already suffered a myocardial infarction.

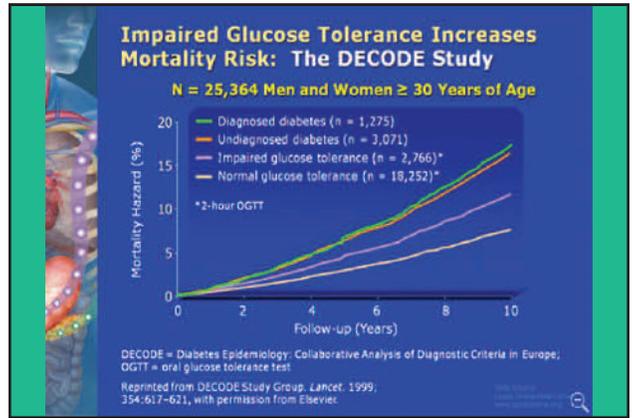
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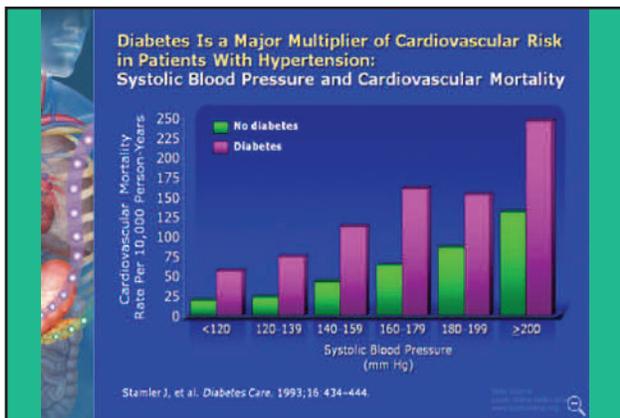
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Diabetes and Cardiovascular Disease

- Risk of coronary heart disease and myocardial infarction in patients with T2D is compounded by the coexistence of 3 or more additional risk factors:
- -insulin resistance
- -sustained hyperglycemia
- -dyslipidemia
- Obesity
- Hypertension
- Oxidative stress

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To add to the confusion.....

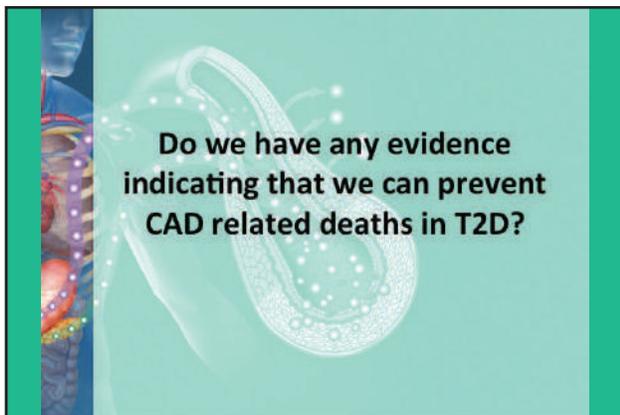
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Major Clinical Trials Show That Intensive Glucose Control Does Not Decrease Cardiovascular Events

- Action to Control Cardiovascular Risk in Diabetes (ACCORD)
- Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE)
- VA Diabetes Trial (VADT)

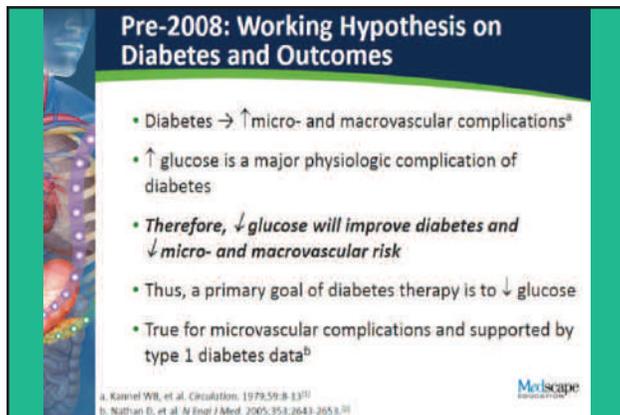
The Action to Control Cardiovascular Risk in Diabetes Study Group. *N Engl J Med*. 2008;358:2145-2159. | ADVANCE Collaborative Group. *N Engl J Med*. 2008;358:2560-2572. | Duckworth W, et al. *N Engl J Med*. 2008;360:129-139.

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Do we have any evidence indicating that we can prevent CAD related deaths in T2D?

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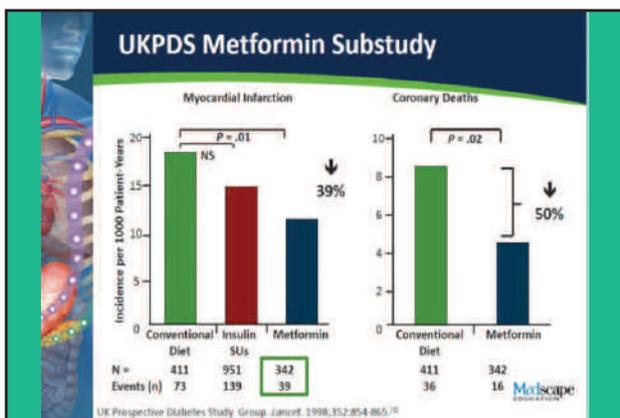


Pre-2008: Working Hypothesis on Diabetes and Outcomes

- Diabetes → ↑ micro- and macrovascular complications^a
- ↑ glucose is a major physiologic complication of diabetes
- *Therefore, ↓ glucose will improve diabetes and ↓ micro- and macrovascular risk*
- Thus, a primary goal of diabetes therapy is to ↓ glucose
- True for microvascular complications and supported by type 1 diabetes data^b

a. Kannel WB, et al. Circulation. 1979;59:8-13¹¹
b. Nathan D, et al. N Engl J Med. 2005;353:2643-2653.¹²

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UKPDS Metformin Substudy

Myocardial Infarction

Group	N	Events (n)	Incidence per 1000 Patient-Years
Conventional Diet	411	73	~18
Insulin SUUs	951	139	~15
Metformin	342	39	~11

NS (between Diet and Insulin), *P = .01* (between Diet and Metformin), **39%** reduction.

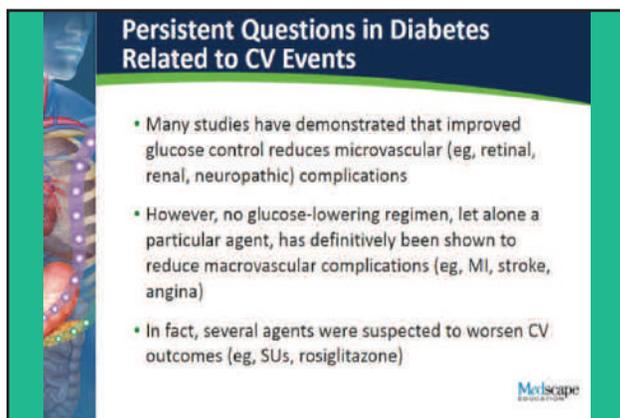
Coronary Deaths

Group	N	Events (n)	Incidence per 1000 Patient-Years
Conventional Diet	411	36	~9
Metformin	342	16	~5

P = .02, **50%** reduction.

UK Prospective Diabetes Study Group. Lancet. 1998;352:854-865.¹⁸

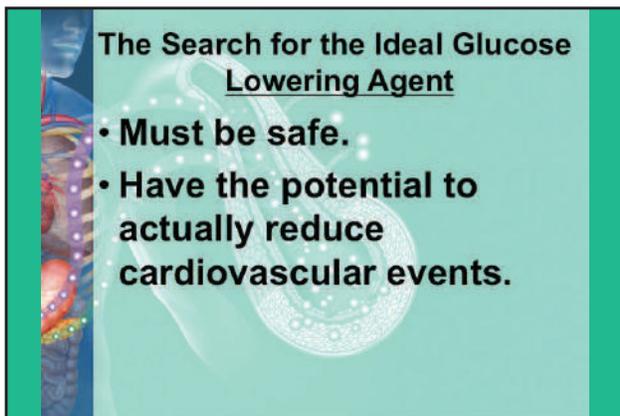
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Persistent Questions in Diabetes Related to CV Events

- Many studies have demonstrated that improved glucose control reduces microvascular (eg, retinal, renal, neuropathic) complications
- However, no glucose-lowering regimen, let alone a particular agent, has definitively been shown to reduce macrovascular complications (eg, MI, stroke, angina)
- In fact, several agents were suspected to worsen CV outcomes (eg, SUUs, rosiglitazone)

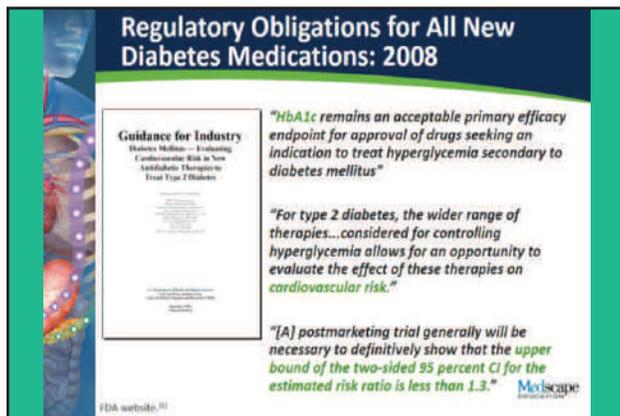
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The Search for the Ideal Glucose Lowering Agent

- **Must be safe.**
- **Have the potential to actually reduce cardiovascular events.**

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Regulatory Obligations for All New Diabetes Medications: 2008

Guidance for Industry
Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

"HbA1c remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication to treat hyperglycemia secondary to diabetes mellitus"

"For type 2 diabetes, the wider range of therapies...considered for controlling hyperglycemia allows for an opportunity to evaluate the effect of these therapies on cardiovascular risk."

"[A] postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent CI for the estimated risk ratio is less than 1.3."

FDA website.¹⁹

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INCRETINS: DPP-4 Inhibitors and GLP-1 Agonists and Cardiovascular Disease

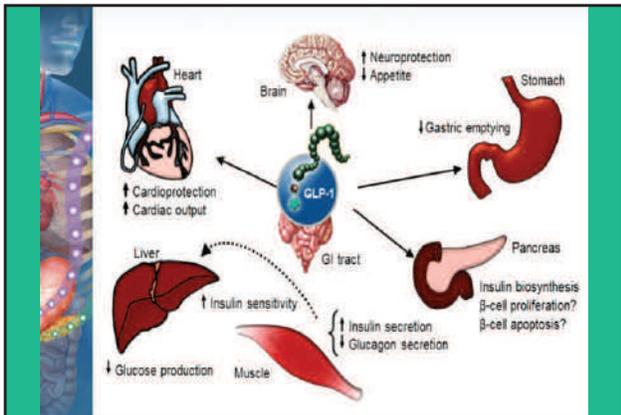
What is the evidence to date

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Glucagon-like peptide 1 (GLP-1)

- The observation that intrajejunal glucose promotes greater insulin release than intravenous glucose administration was reported 50 years ago by McIntyre et al.
- Perley and Kipnis estimated the intestinal component accounts for 50% - 70% of the total insulin secreted after an oral glucose load.
- The "incretin effect" was coined by Creuzfeld and Ebert in 1985 to designate this phenomenon.

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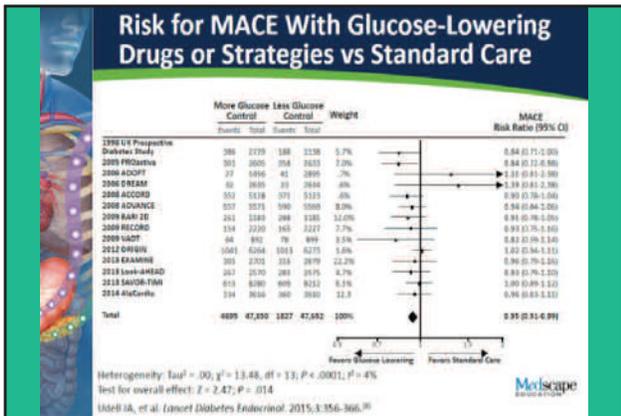
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Primary Objective

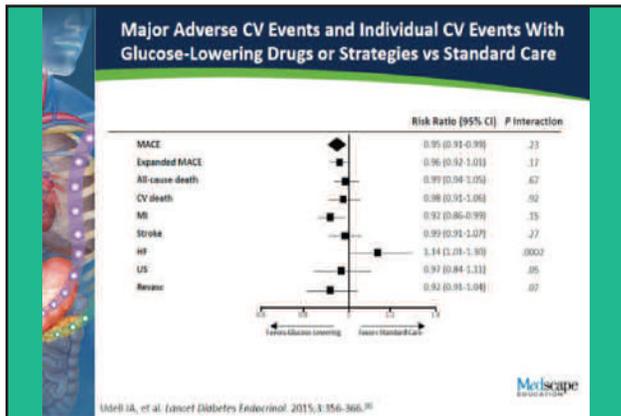
- To determine whether, when added to background therapy, DPP-4 inhibitors would be noninferior to placebo for the composite end point of CV death, nonfatal MI, or nonfatal ischemic stroke (upper 95% CI of HR < 1.3)
- And, if noninferiority were met, to determine whether DPP-4 inhibitors would be superior to placebo

Medscape

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Implications

- Few antihyperglycemic agents have been evaluated as extensively as DPP-4 inhibitors in SAVOR-TIMI 53, EXAMINE, and TECOS
- The results point to likely but unproven benefit in microvascular disease without adverse macrovascular outcomes
- Together with other ongoing trials, these data provide a more rigorous and robust evidence base than is currently available to guide the future care of patients with diabetes



Medscape
EXCELLENCE IN EDUCATION

Slide 26

DPP-4 Inhibitors Were Associated With a Reduced Risk for MACE

More CV Events

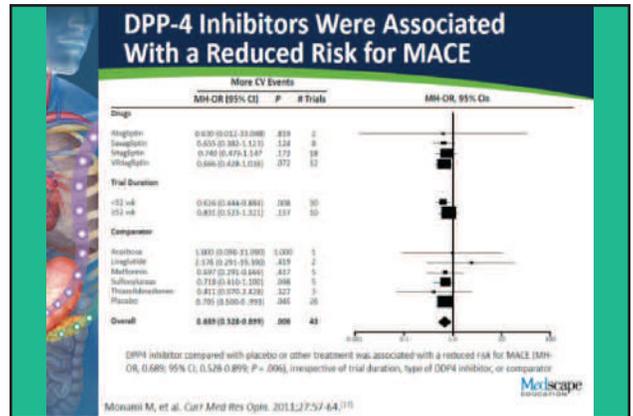
Drug	MH-OR (95% CI)	P	# Trials
Aglyptin	0.63 (0.102-3.088)	.839	2
Saxagliptin	0.65 (0.380-1.121)	.128	8
Linagliptin	0.74 (0.479-1.147)	.179	18
Vildagliptin	0.66 (0.468-0.936)	.072	12

Trial Duration	MH-OR (95% CI)	P	# Trials
<51 wks	0.626 (0.444-0.884)	.008	30
≥51 wks	0.85 (0.523-1.321)	.437	39

Comparator	MH-OR (95% CI)	P	# Trials
Acetohexa	1.00 (0.090-11.090)	1.000	1
Linagliptin	2.276 (0.291-19.960)	.419	2
Metformin	0.697 (0.291-0.844)	.017	5
Sulfonylureas	0.719 (0.410-1.291)	.008	5
Thiazolidinediones	0.612 (0.370-1.026)	.037	3
Placebo	0.791 (0.500-0.891)	.045	26

Overall: **0.68 (0.528-0.899)** .006 43

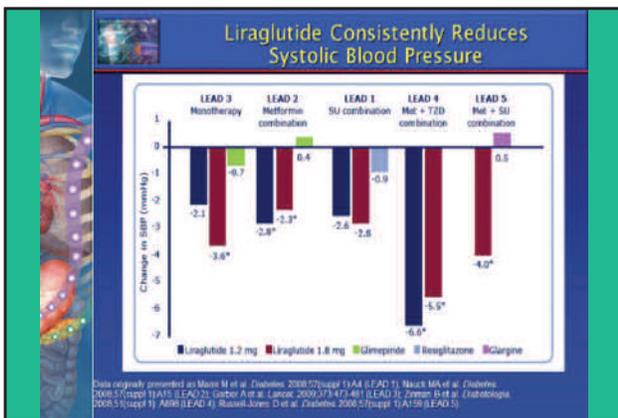
DPP4 inhibitor compared with placebo or other treatment was associated with a reduced risk for MACE (MH-OR, 0.68; 95% CI, 0.528-0.899; P = .006), irrespective of trial duration, type of DPP4 inhibitor, or comparator



Mitsumori M, et al. *Can J Med Res Opin*. 2013;12:757-64.115

Slide 27

Liraglutide Consistently Reduces Systolic Blood Pressure



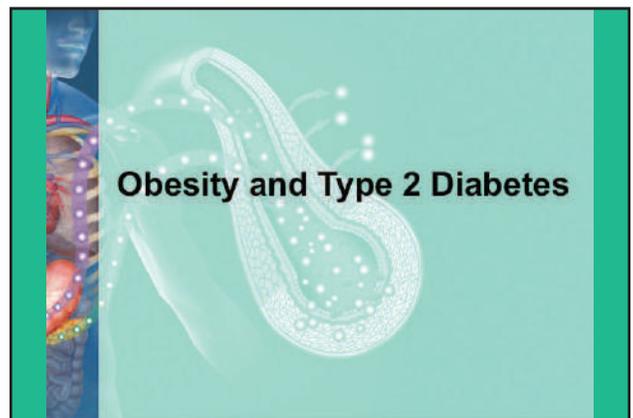
Lead	Treatment	Change in SBP (mmHg)
LEAD 3	Monotherapy	-2.1
LEAD 2	Metformin combination	-3.8*
LEAD 1	SU combination	-2.6
LEAD 4	Met + TZD combination	-6.6*
LEAD 5	Met + SU combination	-4.0*

Legend: Liraglutide 1.2 mg (dark blue), Liraglutide 1.8 mg (red), Glimepiride (green), Rosiglitazone (light blue), Cigargone (purple)

Data originally presented as Mann M et al. *Diabetes*. 2008;57(suppl 1):A4 (LEAD 1). Nauck MA et al. *Diabetes*. 2008;57(suppl 1):A45 (LEAD 2). Gember A et al. *Diabetes*. 2009;58(1):74 (LEAD 3). Zeman M et al. *Diabetologia*. 2008;51(suppl 1):A98 (LEAD 4). Rosenkranz S et al. *Diabetes*. 2008;57(suppl 1):A158 (LEAD 5).

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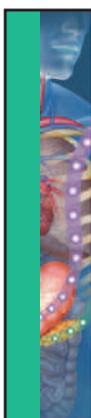
Obesity and Type 2 Diabetes



Slide 29

Obesity and Diabetes

- Moderate weight loss – 5% of body weight can improve glycemic control.
- Improvement in fasting blood glucose is directly related to the relative amount of weight lost.
- Marked weight loss – 30% of body weight –following gastric bypass surgery can normalize glycemic control in extremely obese patients with T2D



Slide 30

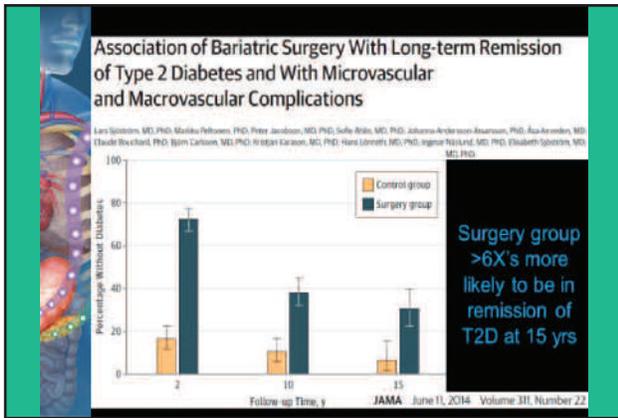
Weight Gain and Glycemic Control

- Weight gain seems to be inseparable from glycemic control with many antidiabetic treatments, including sulfonylureas, insulin, and thiazolidinediones, which have an estimated 2 kg weight gain for every 1% decrease in HbA1C



Blase J et al. *Clin Ther*. 2007;29:130-153

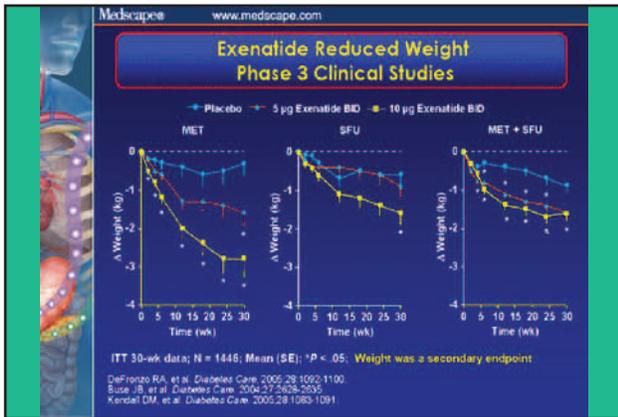
Slide 31



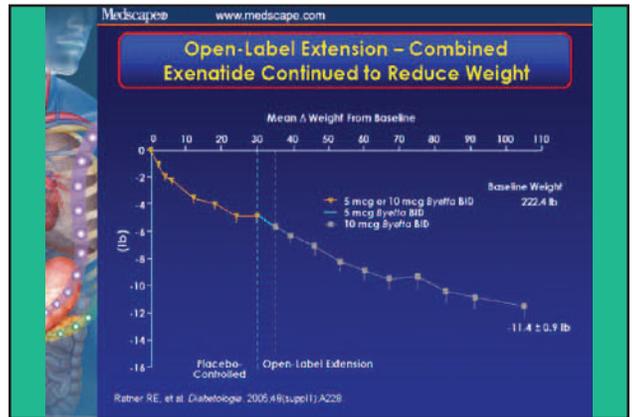
Slide 32



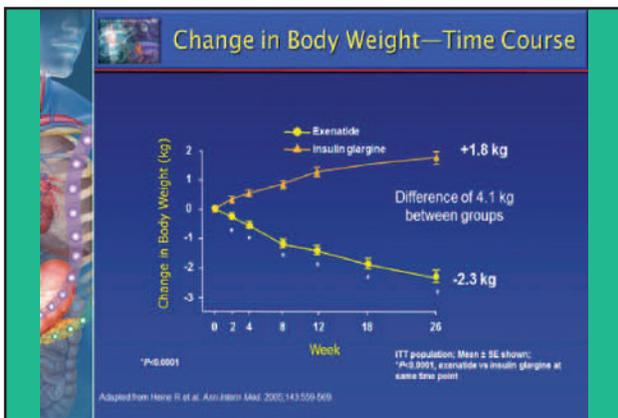
Slide 33



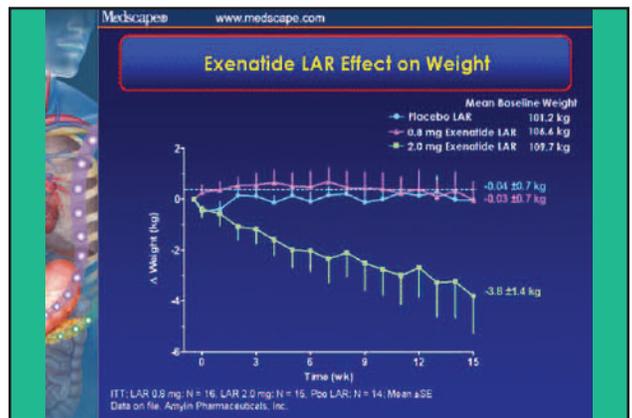
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Medscape www.medscape.com

Cohort 1: Exenatide for 82 Weeks

Parameter	Baseline (±SE)	Mean Change from Baseline (±SE)	95% Confidence Interval (CI)
Total cholesterol (TC) (mg/dL)	185.92 (2.41)	-2.52 (1.99)	-6.43 to +1.39
HDL (mg/dL)	37.97 (0.56)	+4.46 (0.41)	+3.64 to +5.27
LDL (mg/dL)	115.07 (2.19)	-1.41 (1.82)	-4.99 to +2.16
Apo B (mg/dL)	91.59 (1.54)	-1.30 (1.26)	-3.79 to +1.19
Triglycerides (TG) (mg/dL)	239.17 (11.14)	-36.94 (9.66)	-55.96 to -17.91
Systolic blood pressure (mm Hg)	126.59 (0.64)	-1.48 (1.01)	-3.46 to +0.51
Diastolic blood pressure (mm Hg)	78.66 (0.48)	-3.24 (0.58)	-4.37 to -2.10

Ratner, et al. *Diab Ob Met*. 2008;8:419

Slide 38

The screenshot shows a Medscape article page. The main heading is "GLP-1 Receptor Agonists vs. DPP-4 Inhibitors for Type 2 Diabetes". There are several sub-headings and a sidebar with a "You're either out or you're In" advertisement. The article text is partially visible but mostly obscured by the sidebar.

Slide 39

- ### Potential Roles of GLP-1 Mimetics
- ▶ Once-weekly injection of exenatide-LAR in overweight patients with T2DM who require initial therapy or combination with other oral agents
 - ▶ Potential treatment for overweight nondiabetic patients
 - ▶ Potential treatment of overweight, insulin-treated patients with T2DM

Slide 40

- ### Why DPP-4 Inhibitors?
- ▶ Excellent in patients with mild hyperglycemia requiring insulin secretagogue
 - ▶ No contraindication in heart failure and no risk of edema or lactic acidosis
 - ▶ Can be used in renal insufficiency without risk of hypoglycemia or lactic acidosis
 - ▶ No weight gain
 - ▶ Immediate activity without causing hypoglycemia

Slide 41

- ### Goals for Diabetes Management
- A1C ≤6.5% AACE/ACE/ACP; <7% ADA
 - Blood pressure <130/80 mm Hg
 - Dyslipidemia
 - LDL <100 mg/dL
 - HDL — men >40 mg/dL; women >50 mg/dL
 - Triglycerides <150 mg/dL
 - Prothrombotic state
 - ASA therapy (75–162 mg/day) in adult patients with diabetes and macrovascular disease or for primary prevention in patients ≥40 years with diabetes or who have ≥1 other cardiovascular risk factors
 - Cigarette smoking — cessation
- American Diabetes Association. *Diabetes Care*. 2006;Jan;29 Suppl 1:S4-S42; *Endocr Pract*. 2002;8(suppl 1):40-88.



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James R. Gavin III, MD, PhD is clinical professor of medicine at Emory University School of Medicine in Atlanta, Georgia, and Clinical Professor of Medicine at the Indiana University School of Medicine, Indianapolis, Indiana. He currently serves as Chief Executive Officer and Chief Medical Officer of Healing Our Village, Inc. Prior to this, he served as president and chief executive officer of Microlslet, Inc., San Diego, California, from January 2006 to July, 2007, and was president of the Morehouse School of Medicine in Atlanta from 2002-2005. He served as senior scientific officer at the Howard Hughes Medical Institute (HHMI) from 1991 to 2002 and as director of the HHMI–National Institutes of Health Research Scholars Program from 2000 to 2002. Before joining the senior staff of HHMI, Dr Gavin was a professor and chief of the Diabetes Section, acting chief of the Section on Endocrinology, Metabolism, and Hypertension, and William K. Warren Professor for Diabetes Studies at the University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma. He previously served as an associate professor of medicine at Washington University School of Medicine in St. Louis, Missouri. Dr Gavin served as a lieutenant commander in the US Public Health Service from 1971 to 1973 and continues to serve as a reserve officer.

Dr Gavin belongs to a number of organizations, including the Institute of Medicine of the National Academies of Sciences, the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), the American Society of Clinical Investigation (ASCI), the American Association of Physicians (AAP), the National Medical Association (NMA), the Sigma Pi Phi Leadership Fraternity, and the Downtown Atlanta Rotary Club. He is a past president of the ADA and was voted Clinician of the Year in Diabetes by the ADA in 1991. He has served on many advisory boards and on the editorial boards of the American Journal of Physiology and the American Journal of Medical Sciences. He is on the board of trustees for Emory University, Livingstone College, and Trustee Emeritus for the Robert Wood Johnson Foundation. In addition, he is immediate past national program director of the Harold Amos Faculty Development Program of the Robert Wood Johnson Foundation. Dr Gavin is also past chairman of the National Diabetes Education Program (NDEP) and a past member of the Board of Scientific Councilors for the Intramural Research Program of NIDDK at the NIH. He also serves as chairman of the Data Safety Monitoring Board for the VA Cooperative Diabetes Study (VADT). He is co-chair of the Advisory Committee to the Associate Director of Intramural Research of the NIDDK, and serves as Chairman of the Board for the Partnership for a Healthier America.

Dr Gavin has published more than 230 articles and abstracts in such publications as Science, Journal of Applied Physiology, Diabetes, and the American Journal of Physiology. He is coauthor of two books: Healing Our Village: A Self-Care Guide for Diabetes Control (written with L. Coleman) and Dr. Gavin's Health Guide for African Americans (written with S. Landrum). Among the many honors Dr Gavin has received are the Daniel Hale Williams Award, the E.E. Just Award, the Herbert Nickens Award, the Daniel Savage Memorial Award, the Emory University Medal for Distinguished Achievement, the Banting Medal for Distinguished Service from the ADA, the Distinguished Alumni Award from the Duke University School of Medicine, the F.C. Greenwood Award from the RCMI of NCRR at NIH and the Internist of the Year Award from the National Medical Association. He was named a "Living Legend in Diabetes" by the American Association of Diabetes Educators (AADE) in 2009, and was named one of the "175 Emory History Makers" on the occasion of the celebration of the University's 175th Anniversary. He was designated an inaugural Senior Fellow of the W. Montague Cobb Research Institute of the NMA.

Dr Gavin graduated from Livingstone College in Salisbury, North Carolina, with a degree in chemistry. He earned his PhD in biochemistry from Emory University and his MD degree from Duke University School of Medicine, Durham, North Carolina. He and his wife, Dr. Annie Gavin, are the parents of three adult sons.

Slide 1

USING INCRETIN-BASED TREATMENTS AS MONOTHERAPY AND IN COMBINATION WITH ANTI-DIABETES MEDICATIONS

James R Gavin III, MD, PhD
 Clinical Professor of Medicine
 Emory University School of Medicine
 CEO and Chief Medical Officer
 Healing Our Village, Inc.
 Atlanta, Georgia

Slide 2

Disclosures for Dr. James R. Gavin III

- Serves as consultant for Abbott Diabetes Care, Intarcia Pharmaceuticals, Janssen Pharmaceuticals, Astra Zeneca, Novo Nordisk Pharmaceuticals
- Serves on speaker bureaus for Janssen, BI-Lilly, Astra Zeneca
- Clinical Research support for Janssen Pharmaceuticals and Pfizer, Inc.
- Serves as Director and shareholder for Baxalta Biopharmaceuticals

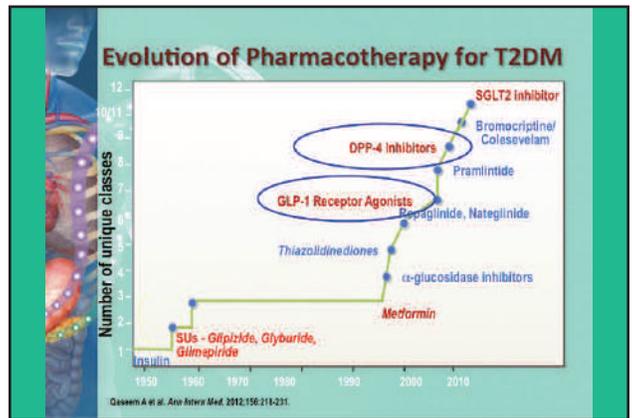
Slide 3

Learning Objectives

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

- Compare the actions of incretin therapies and contrast characteristics of available glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in the context of matching individual agents with specific patient needs and preferences
- Evaluate the individualized application of incretins in the context of common T2DM disease management scenarios
- Appraise recent evidence regarding the use of GLP-1 RAs across T2DM disease progression, especially in terms of their impact on disease management when used in combination with other oral agents

Slide 4



Slide 5

GLP-1 Receptor Agonists and Their Use With Other Anti-Diabetes Agents

- Comparing currently available GLP-1 receptor agonists
 - Glycemic control
 - Other treatment priorities (ie, weight, hypoglycemia, patient-related factors)
 - Safety and tolerability
- Using GLP-1 receptor agonists in combination with oral antihyperglycemic agents
 - GLP-1 receptor agonists added to metformin
 - Using GLP-1 receptor agonists with newer agents (ie, SGLT2 inhibitors)

Slide 6

Anti-Diabetes Therapy: 2015 ADA Standards

Healthy eating, weight control, increased physical activity & diabetes education

Monotherapy
 Metformin

Dual Therapy
 Metformin + Sulfonylurea
 Metformin + DPP-4 Inhibitor
 Metformin + SGLT2 Inhibitor
 Metformin + GLP-1 Receptor Agonist
 Metformin + Insulin

Triple Therapy
 Metformin + Sulfonylurea + DPP-4 Inhibitor
 Metformin + Sulfonylurea + SGLT2 Inhibitor
 Metformin + Sulfonylurea + GLP-1 Receptor Agonist
 Metformin + SGLT2 Inhibitor + GLP-1 Receptor Agonist

Continuation (injectable therapy)
 Basal insulin + Metformin or GLP-1 RA

GLP = glucagon-like peptide; DPP4 = Dipeptidyl peptidase-4
 American Diabetes Association. *Diabetes Care.* 2015;38:54. doi:10.2337/dia15-0003

Slide 7

Strategies for Enhancing Incretin (GLP-1) Action

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

- Inhibit the actions of DPP-4
- FDA approved: sitagliptin, saxagliptin, linagliptin, alogliptin

GLP-1 Receptor Agonists

- Resistant to DPP-4 inactivation
- Activators of the GLP-1 receptor
- FDA approved: exenatide, liraglutide, exenatide extended-release

Drucker DJ, et al. Diabetes Care 2010;33(2):429-433

Slide 8

Incretins for Improved Glucose Control

DPP-4 Inhibitors	Incretin Mimetics
Significant A _{1c} reduction	Significant A _{1c} reduction
Weight neutral	Significant and sustained wt loss
Oral administration	Injection
Almost no GI side effects	Higher rate in GI side effects
Low rate of hypoglycemia	Low rate of hypoglycemia
Multiple targets (GLP-1 & GIP)	Single target (GLP-1)
Cardiovascular benefits	Cardiovascular benefits

Alvarez R, et al. Diabetes Care 2005;28:1936-1940; Gohokuz E. Minerva Endocrinol 2006;31(2):133-147; Gauseby JP, et al. Diabetes Metab 2005;31:233-242; Poun T, et al. Diabetes Technol Ther 2005;7(3):467-477; data on file, Novartis.

Slide 9

Profiles of Antidiabetic Medications

	MET	DPP-4i	GLP-1 RA	TZD	AGI	COLNVI	BCR-06	SU	GLM	INULIN	SGLT-2	PRAMI
WFOFO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
WEIGHT	High gain	Neutral	Loss	Loss	Neutral	Neutral	Neutral	Loss	Loss	Loss	Loss	Loss
RENAL/GU	Lowest risk (SGLT-2)	Low risk (DPP-4i)	Low risk (GLP-1 RA)	Low risk (TZD)	Low risk (AGI)	Low risk (COLNVI)	Low risk (BCR-06)	Low risk (SU)	Low risk (GLM)	Low risk (INULIN)	Low risk (SGLT-2)	Low risk (PRAMI)
GI	Moderate	Neutral	Moderate	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
BCR-06	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

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Slide 10

Individualizing Glycemic Control in T2DM

Most Intensive 6.0% Less Intensive 7.0% Least Intensive 8.0%

Psychosocial/economic considerations

Highly motivated, adherent, knowledgeable, excellent self-care capacities, and comprehensive support systems Less motivated, nonadherent, limited insight, poor self-care capacities, and weak support systems

Hypoglycemia risk: Low, Moderate, High

Patient age, y: 40, 45, 50, 55, 60, 70, 75

Disease duration, y: 5, 10, 15, 20

Other comorbid conditions: None, Few or mild, Multiple or severe

Established vascular complications: None, Cardiovascular disease, Early microvascular, Advanced microvascular

Individualizing glycemic targets according to risk of/ from complications is the current standard of care in T2DM

Considerations based on UKPDS, ACCORD, ADVANCE, and VADT. Inzucchi S, et al. Ann Intern Med 2011;154:554-560; Inzucchi S, et al. Diabetes Care 2015;38:140-148.

Slide 11

Individualizing T2DM Therapy With Currently Available GLP-1 Receptor Agonists

- Current treatment guidelines emphasize individualized care and prioritize the use of GLP-1 RAs when avoidance of hypoglycemia or weight gain are important management goals for T2DM
- GLP-1 RAs may be used in patients with T2DM as:
 - An adjunct to diet and exercise^{1,2}
 - Monotherapy when metformin (MET) is contraindicated or not tolerated^{3,4}
 - Part of dual or triple therapy^{1,5}

FDA-Approved Agent	Administration ^{1,2}
Exenatide BID (EXN BID)	Subcutaneous injection, twice daily
Liraglutide (LIRA)	Subcutaneous injection, once daily
Exenatide QW (EXN QW)	Subcutaneous injection, once weekly
Albiglutide (ALBI)	
Dulaglutide (DULA)	

1. US FDA. <http://www.accessdata.fda.gov/scripts/cder/Drugs/IFA/>; 2. Dulaglutide prescribing information. <http://api.illy.com/api/multicity-uspi.pdf>; 3. Inzucchi SE, et al. Diabetes Care. 2015;38:140-148; 4. American Diabetes Association. Diabetes Care. 2015;38(suppl 1):S1-S33; 5. Gaster AJ, et al. Endocr Pract. 2013;19(suppl 2):1-48.

Slide 12

COMPARING CURRENTLY AVAILABLE GLP-1 RECEPTOR AGONISTS

Slide 19

Renal Safety of GLP-1 Receptor Agonists Compared With Other Oral Antihyperglycemic Agents^{1,2}

Agent	Renal Safety
GLP-1 RA ³	Exenatide BID or QW: should not use in severe renal impairment (RI ⁴ or ESRD); use with caution in moderate RI or renal transplant ⁵ Liraglutide: no dose adjustment recommended; use with caution in RI Alogliptide and dulaglutide: no dose adjustment; use with caution, monitor renal function in RI and severe gastrointestinal adverse effects
MET ⁶	Contraindicated in CKD stages IIIb, IV, V
SU/GLinides ⁷	Use with caution in RI; lower starting doses are recommended
TZDs ⁸	No dose adjustment recommended
DPP-4 inhibitors ⁹	Dose adjustment may be necessary (except linagliptin)
SGLT2 inhibitors ¹⁰	Canagliflozin: dose limitation if eGFR ¹¹ 45 to < 60; do not use if eGFR ¹¹ < 45 Dapagliflozin: do not use if eGFR ¹¹ < 60 Empagliflozin: do not use if eGFR ¹¹ < 45

Direct nephrotoxicity has not been demonstrated with GLP-1 RAs. Altered renal function has been reported with GLP-1 RAs. Some events have occurred in conjunction with existing/starting or agents affecting renal function and/or volume status.

¹ US FDA. <http://www.accessdata.fda.gov/scripts/cder/Drugs/FDA/>
² Dulaglutide prescribing information. <http://vip.kry.com/usa/duh-usip.pdf>
³ Garber AJ, et al. *Endocr Pract*. 2015;19(suppl 2):1-48
⁴ Metformin clearance < 30 mL/min
⁵ Canagliflozin: clearance 30 to 50 mL/min
⁶ eGFR in mL/min/1.73 m²

Slide 20

Risk of Pancreatitis With GLP-1 Receptor Agonists

- FDA/EMA statement regarding potential pancreatitis risk with GLP-1 receptor agonists¹
 - "...assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer... are inconsistent with the current data..."
 - "...current knowledge is adequately reflected in the product information and labeling..."
- Findings from a recent study in Denmark suggest that incretin therapies (both GLP-1 RAs and DPP-4 inhibitors) are not associated with increased acute pancreatitis risk²

Discontinue promptly if pancreatitis symptoms occur

Consider other agents if patient has a history of pancreatitis

If acute pancreatitis is confirmed, do not restart GLP-1 RA

Report cases of pancreatitis to www.fda.gov/medwatch³

¹ Egge-Aas, et al. *N Engl J Med*. 2014;370:794-797. ² Thomsen RW, et al. *Diabetes Care*. 2015; Jan 20. [Epub ahead of print]. ³ US FDA. <http://www.accessdata.fda.gov/scripts/cder/Drugs/FDA/>
⁴ Dulaglutide prescribing information. <http://vip.kry.com/usa/duh-usip.pdf>
⁵ Dulaglutide prescribing information. <http://vip.kry.com/usa/duh-usip.pdf>

Slide 21

Risk of Thyroid C-Cell Tumors With GLP-1 Receptor Agonists

- AACE/ACE Statement on Diabetes and Cancer indicates that current evidence does not support an increased risk of MTC with GLP-1 RA use¹
 - ALBI, DULU, EXN QW, and LIRA are contraindicated in patients with MEN2 or a personal or family history of MTC
- With the exception of EXN BID, all GLP-1 RAs have approved REMS²

Clinical Recommendations^{2,3}

Counsel patients regarding MTC risk and symptoms of thyroid tumors

Value of routine calcitonin and/or ultrasound monitoring is uncertain and may lead to unnecessary procedures

Patients with thyroid nodules or elevated serum calcitonin levels identified for other reasons should be sent to an endocrinologist

To monitor potential associations, report all cases of MTC, regardless of regimen: <http://www.fda.gov/medwatch>

¹ More REMS information can be found at http://www.accessdata.fda.gov/drugsatfda_docs/appl/etd/2011/021779s011.pdf. ² US FDA. <http://www.accessdata.fda.gov/scripts/cder/Drugs/FDA/>
³ Dulaglutide prescribing information. <http://vip.kry.com/usa/duh-usip.pdf>

Slide 22

USING GLP-1 RAs IN COMBINATION WITH ORAL ANTIHYPERGLYCEMIC AGENTS

Slide 23

GLP-1 RAs Offer Complementary Actions to Common Oral Antihyperglycemic Agents

- Increased insulin secretion/sensitivity and decreased hepatic glucose production are common actions associated with many oral antihyperglycemic agents (MET, SU, glinides, TZDs)

Oral glucose load leads to secretion of incretin hormones, resulting in enhanced pancreatic insulin secretion (impaired in patients with TZDM)

GLP-1 RAs mediate glucose-dependent changes

- Increase insulin
- Decrease glucagon
- Slow gastric emptying
- Increase satiety

GLP-1 activity is higher with GLP-1 RAs (= 9 × baseline) vs DPP-4 inhibitors (= 2 × baseline)

- Data regarding use of GLP-1 RAs and SGLT2 inhibitors in combination is limited at this time¹
- GLP-1 RAs should not be used in combination with DPP-4 inhibitors^{2,4}

¹ Inzucchi SE, et al. *Diabetes Care*. 2015;38:1467-1471. ² Garber AJ, et al. *Endocr Pract*. 2013;19(suppl 2):1-48.
³ Bagro L, Drucker D. *Gastroenterology*. 2007;132(2):2137-2137.
⁴ DeFronzo RA, et al. *Curr Med Res Opin*. 2008;24:2843-2852.

Slide 24

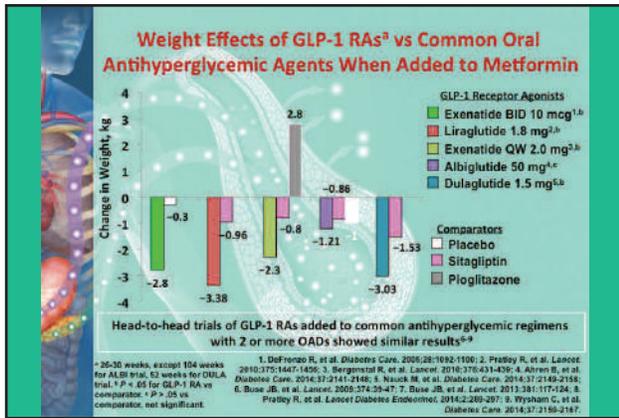
Glycemic Efficacy of GLP-1 RAs^{a,b} vs Common Oral Antihyperglycemic Agents When Added to Metformin

Agent	Change in A1C (%)
GLP-1 Receptor Agonists	
Exenatide BID 10 mcg ¹	0.1
Liraglutide 1.8 mg ²	-0.8
Exenatide QW 2.0 mg ³	-0.9
Alogliptide 50 mg ⁴	-0.9
Dulaglutide 1.5 mg ⁵	-0.9
Comparators	
Placebo	-0.27
Sitagliptin	-0.28
Pioglitazone	-0.39

Head-to-head trials of GLP-1 RAs added to common antihyperglycemic regimens with 2 or more OADs showed similar results⁶⁻⁹

¹ DeFronzo R, et al. *Diabetes Care*. 2005;28:1062-1160. ² Pratley R, et al. *Lancet*. 2010;375:1447-1456. ³ Bergenfelz R, et al. *Lancet*. 2010;376:431-439. ⁴ Arora D, et al. *Diabetes Care*. 2014;37:2141-2148. ⁵ Nauck M, et al. *Diabetes Care*. 2014;37:2149-2158. ⁶ Buse JB, et al. *Lancet*. 2008;374:238-47. ⁷ Buse JB, et al. *Lancet*. 2012;381:117-124. ⁸ Pratley R, et al. *Lancet Diabetes Endocrinol*. 2014;2:259-267. ⁹ Silyansky C, et al. *Diabetes Care*. 2014;37:2155-2167.

Slide 25



Slide 26

Increased Risk of Hypoglycemia With GLP-1 RA Use in Combination With SUs

Hypoglycemia; Patients Reporting ≥ 1 Event, %		
	Without SU	With SU
Exenatide BID ^{1,2}	1-11	15-42
Liraglutide ^{1,3,4}	1-6	12-33
Albiglutide QW ⁵	2-3	13-17
Exenatide QW ^{2,3}	0-4	15
Dulaglutide QW ⁶	-	39-40

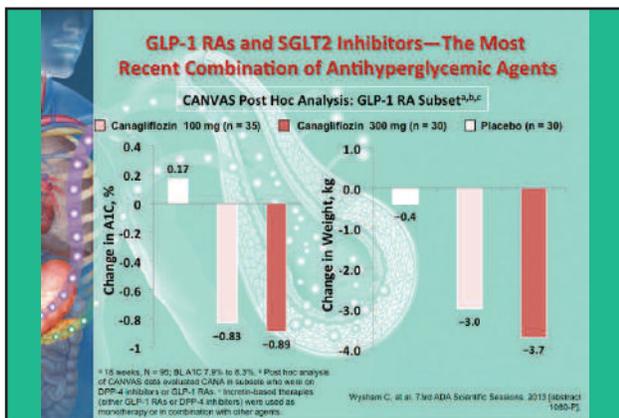
Possible increased hypoglycemia risk when used with SU

Consider a lower dose of SU to decrease hypoglycemia risk^{6,6}

Educate or review hypoglycemia recognition and treatment

1. Buse JB, et al. *Lancet*. 2009;374:39-47. 2. Drucker DJ, et al. *Lancet*. 2008;372:1340-1350. 3. Buse JB, et al. *Lancet*. 2013;381:117-124. 4. DeVries JH, et al. *Diabetes Care*. 2012;35:1446-1454. 5. US FDA. <http://www.accessdata.fda.gov/drugsatfda/drugs/nda/021235/1446/1454.pdf>. 6. Dulaglutide prescribing information. <http://pi.hjy.com/us/duh/duh.pdf>.

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Mechanisms of Action: Insulin Compared With GLP-1 Receptor Agonists

Class of Agent	Mechanism(s) of Action	Administration
Insulin ^{1,2}	<ul style="list-style-type: none"> ↓ Hepatic glucose production ↑ Glucose disposal ↑ Glucose uptake in muscle 	Subcutaneous injection
GLP-1 Receptor Agonists ^{1,3,4}	<ul style="list-style-type: none"> ↑ Insulin secretion ↓ Hepatic glucose production ↓ Gastric emptying/glucose absorption ↑ Satiety 	Subcutaneous injection

1. Inzucchi SE, et al. *Diabetes Care*. 2010;33:140-148. 2. Aronoff SL, et al. *Diabetes Spectrum*. 2004;17:183-190. 3. Drucker D, et al. *Diabetes Care*. 2010;33:428-432. 4. Rodbard H, et al. *Endocr Pract*. 2003;15:540-558.

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Considerations for Advancing Therapy to Include GLP-1 Receptor Agonists or Insulin

GLP-1 Receptor Agonists	Insulin
Advantages <ul style="list-style-type: none"> Robust A1C change Low hypoglycemia risk Weight loss/avoidance of weight gain Multiple dosing options with available agents 	Advantages <ul style="list-style-type: none"> Theoretically unlimited efficacy Universal effectiveness
Limitations <ul style="list-style-type: none"> Training required for injection GI adverse effects Contraindicated/not recommended in some populations¹ 	Limitations <ul style="list-style-type: none"> Training required for injection SMIG (dose adjustment, hypoglycemia avoidance) Hypoglycemia Weight gain

1. Patients with MEN2 or with a personal or family history of MEN2 (ALB, BADA, ENX, CWR, LRA); patients with a history of pancreatitis (all patients with severe RV, ESRD, EDN, BDN, ENX, QW).

1. Garber AJ, et al. *Endocr Pract*. 2013;19(suppl 2):1-48. 2. Inzucchi SE, et al. *Diabetes Care*. 2010;33:140-148. 3. US <http://www.accessdata.fda.gov/drugsatfda/drugs/nda/021235/1446/1454.pdf>. 4. Dulaglutide prescribing information. <http://pi.hjy.com/us/duh/duh.pdf>.

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Glycemic Efficacy of GLP-1 RAs Compared With Basal Insulin When Intensifying Oral Therapy

Background Therapy	Change in A1C, % GLP-1 RA	Change in A1C, % Basal Insulin
MET + SU ^{1,2}	-1.1	-1.1
	Exenatide BID ³	Glargine
MET + SU ^{2,3}	-0.7	-0.8
	Albiglutide ⁴	Glargine
MET + GLIM ^{3,4}	-1.3	-1.1
	Liraglutide ⁵	Glargine
MET ± SU ^{4,6,7}	-1.3	-0.9
	Exenatide QW ⁸	Detemir
MET + GLIM ^{4,8}	-1.1	-0.6
	Dulaglutide ⁹	Glargine

15 weeks, BLA1C 8.2% to 8.6%. 20 weeks, BLA1C 8.3% to 8.6%. 52 weeks, BLA1C 8.3%, 82% on MET + SU background. 52 weeks, BLA1C 8.1%. Noninferior vs insulin. P < .05 vs insulin.

1. Heino R, et al. *Ann Intern Med*. 2005;143:659-669. 2. Pralby R, et al. *ADA 73rd Scientific Sessions*. 2013 (abstract 144-125). 3. Russell-Jones D, et al. *Diabetologia*. 2008;51:2046-2055. 4. Davies M, et al. *Diabetes Care*. 2013;36:1368-1376. 5. Giorgino F, et al. *Diabetes*. 2014;63(suppl 1):M47.

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Clinical Pearls: GLP-1 Receptor Agonists and Their Use With Other Anti-Diabetes Agents

- Compared with other classes of antihyperglycemic therapy, therapeutic intensification with GLP-1 RAs offers:
 - More robust A1C lowering than DPP-4 approach to incretin therapy
 - Lower rates of hypoglycemia, except when used in combination with sulfonylureas
 - Favorable weight effects
- GLP-1 RAs complement the actions of many oral antihyperglycemic agents, *except for DPP-4 inhibitors*
- GLP-1 RAs offer considerable flexibility with regard to matching agents to an individual patient's needs and preferences
- Consider patient risk factors
 - History of thyroid tumors
 - History of pancreatitis
- Educate patients about potential risks and/or adverse effects associated with GLP-1 RAs
 - Nausea and other gastrointestinal effects
