HOSPITAL & INTERNAL MEDICINE FORUM

Individualizing Management of T2DM in the Hospital Setting to Reduce Macro and Microvascular Complications

INTEGRITY CONTINUING EDUCATION

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A DIVISION OF ULTIMATE MEDICAL ACADEMY

This CME activity is provided by Integrity Continuing Education.
This CE activity is jointly provided by Global Education Group and Integrity Continuing Education.

Learning Objectives

- Summarize correlations between macro and microvascular complications of uncontrolled T2DM and hospitalization
- Evaluate the risk/benefit profiles of novel T2DM therapies in achieving glycemic control and reducing vascular complications
- Employ evidence-based strategies to individualize treatment for diverse patients with T2DM to achieve glycemic control and reduce hospitalizations from vascular complications

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Introduction

Diabetes and Its Complications

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Burden of Diabetes in the US

- Estimated incidence in 2015
  - 30.3 million with diagnosed diabetes*
  - 7.2 million undiagnosed
  - 84.1 million with prediabetes
- Increasing prevalence with rising overweight and obesity rates
- Significant risk for complications, including CHD, stroke, HT, depression, pain, polypharmacy, and functional disability
- Leading cause of new cases of blindness (among adults) and end-stage renal failure

*Approximately 1.25 million children and adults have type 1 diabetes.

CHD, congenital heart disease; HT, hypertension.

Available at: https://www.cdc.gov/diabetes/pdfs/library/diabetesreportcard2017-508.pdf; Available at: http://www.diabetes.org/diabetes-basics/statistics/; Available at https://www.niddk.nih.gov/health-information/communication-programs/ndep/health-professionals/practice-transformation-physicians-health-care-teams/why-transform/current-burden-diabetes-us

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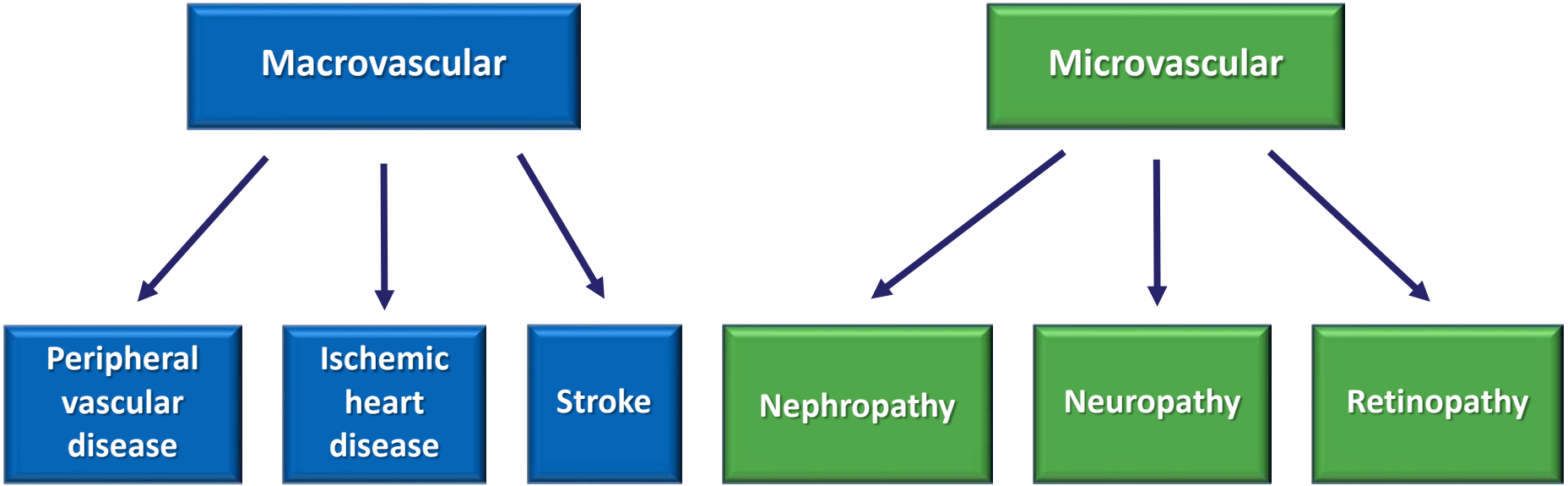
Vascular Complications of Diabetes



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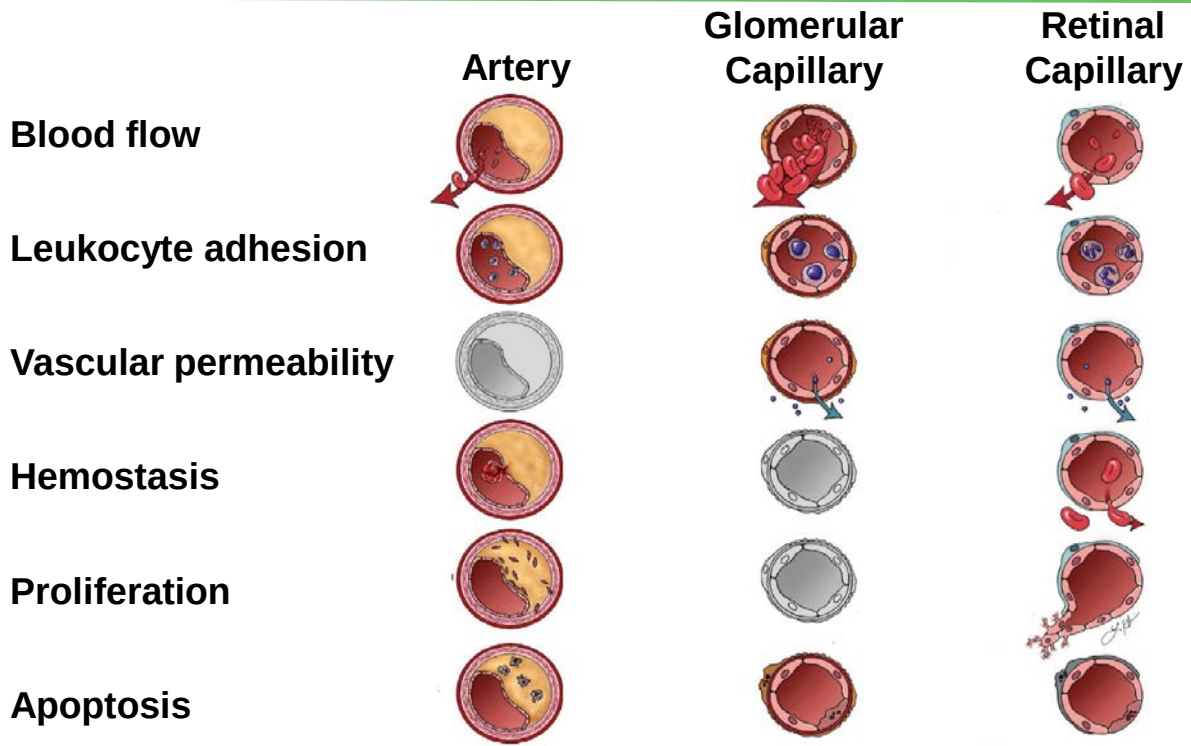
Abnormalities of Vascular Function in Diabetes



Rask-Madsen C et al. Cell Metab. 2013;17(1): 20-33.

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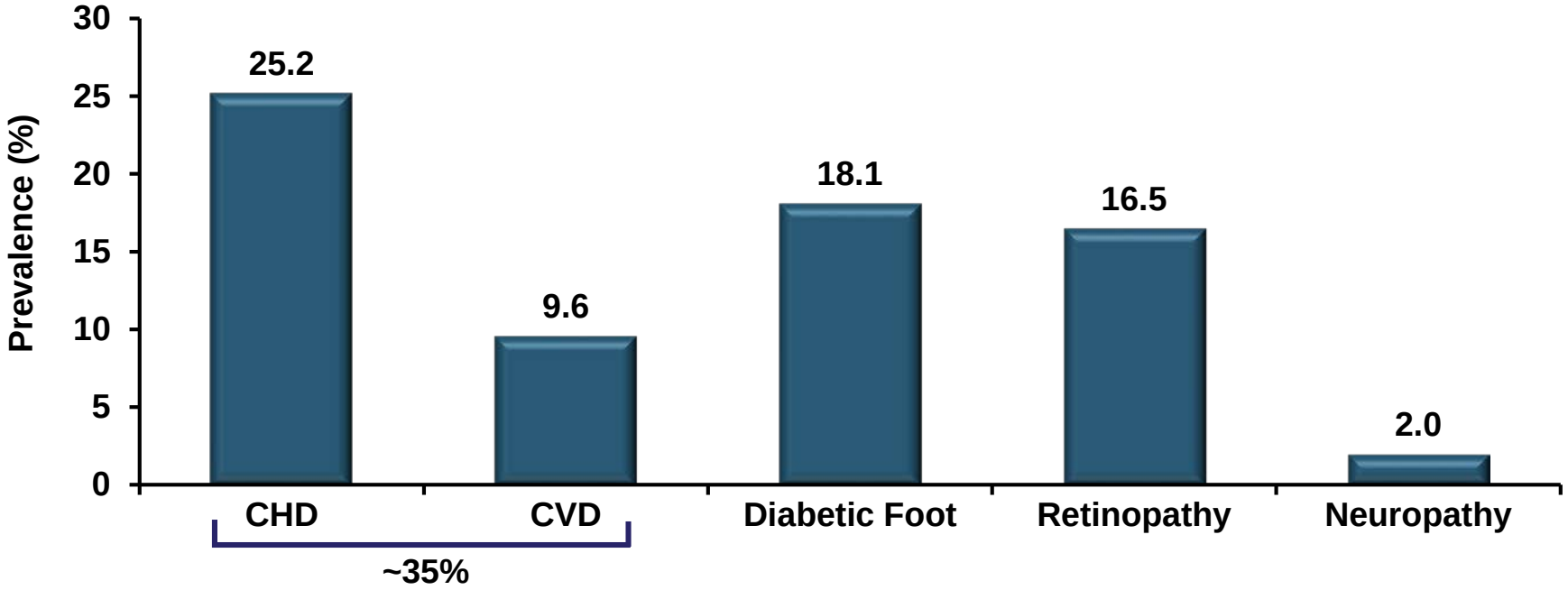
Prevalence of Vascular Complications Among Patients with Diabetes



Morgan CL et al. *Diabetic Med*. 2000;7:7.

Diabetes in the hospital setting

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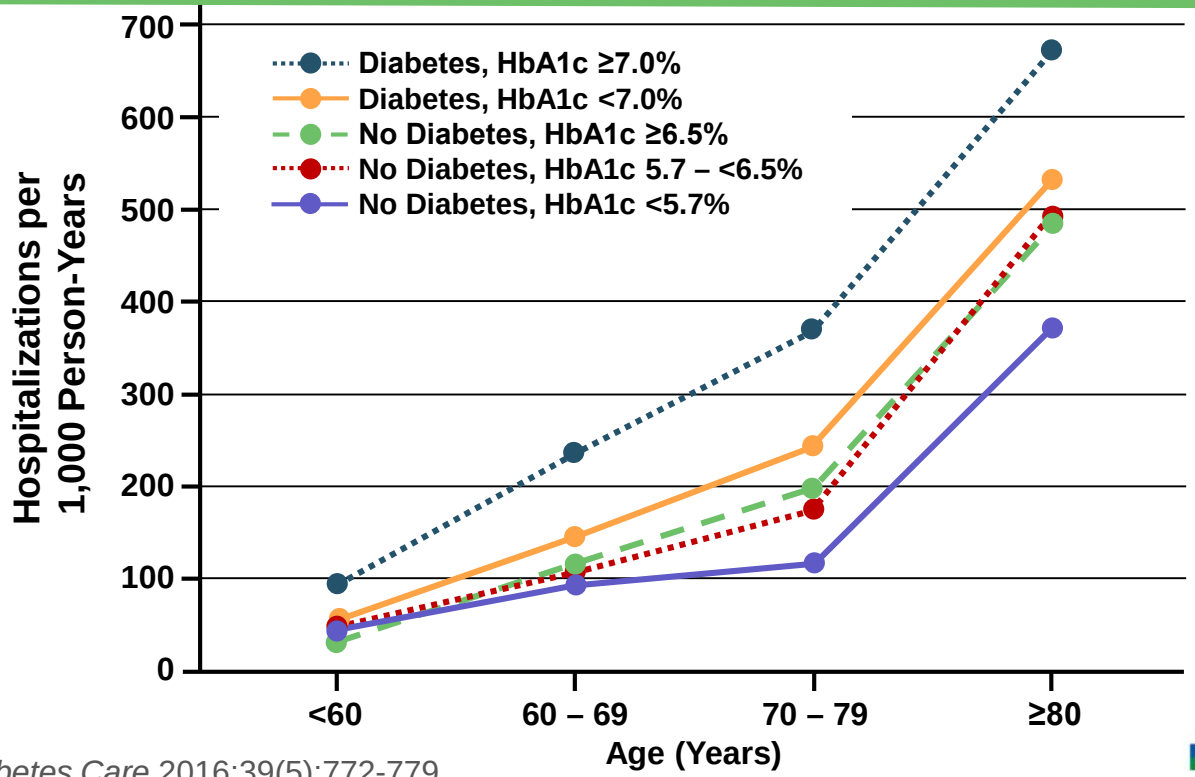
All-cause Hospitalizations Among Patients with Diabetes



Schneider AL et al. *Diabetes Care* 2016;39(5):772-779.

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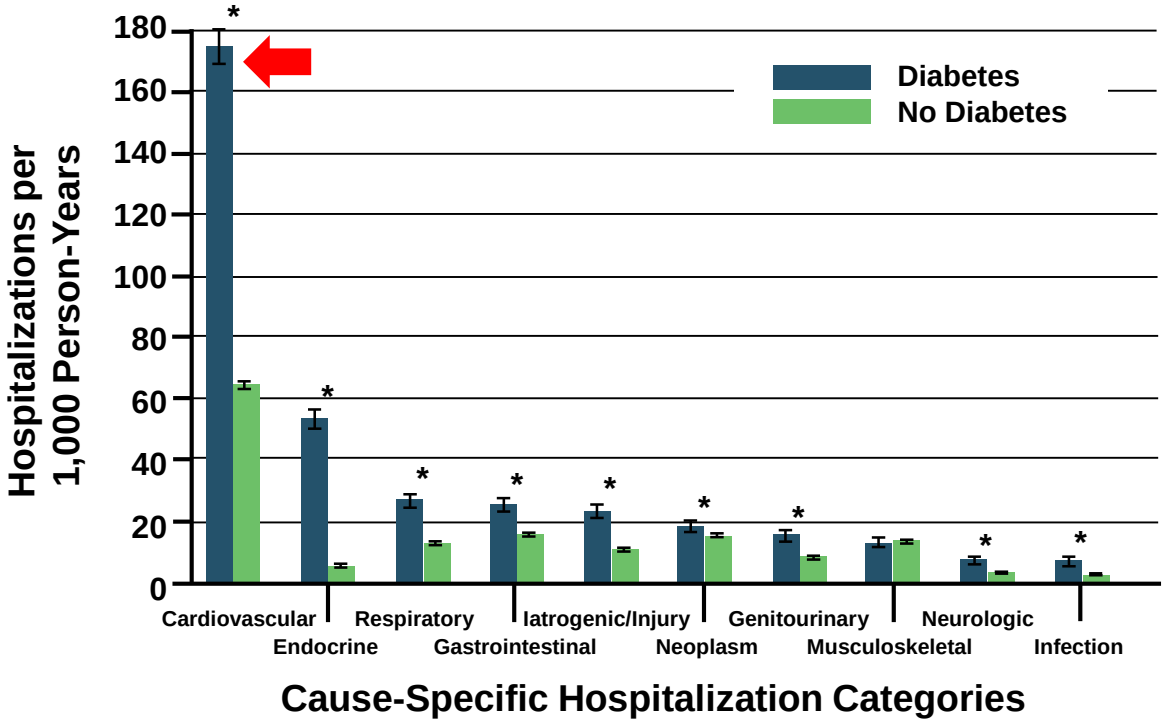
Cause-specific Hospitalizations Among Patients with Diabetes



Schneider AL et al. *Diabetes Care* 2016;39(5):772-779.

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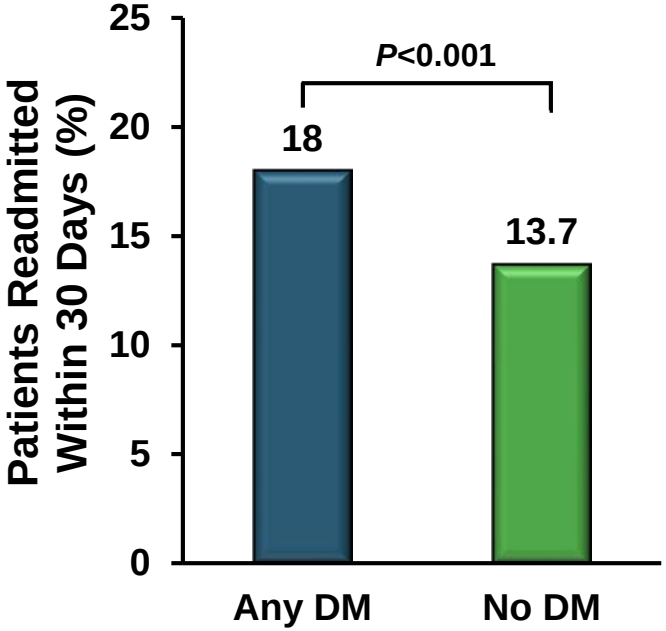
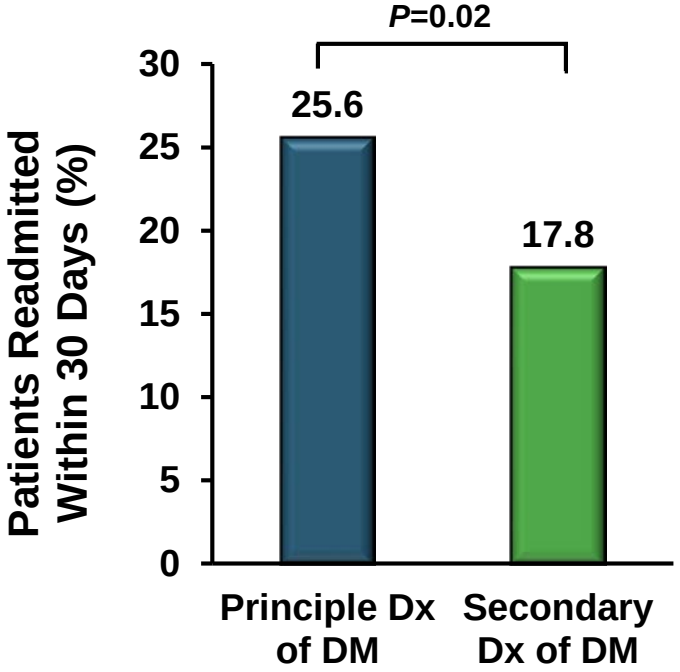
30-day Readmissions Among Patients with Diabetes





Ostling S et al. *Clin Diabetes Endocrinol*. 2017;22;3:3.

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Inpatient management

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Goals of Inpatient Diabetes Management

- Prevent hypoglycemia and hyperglycemia
- Restore glycemic stability
- Initiate long-term antidiabetic treatment/ optimize existing treatment
- Minimize the hospital stay
- Provide effective transitional care to prevent complications and readmission

ADA. *Diabetes Care*. 2016;39:S99-S104.

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ADA/AACE Recommended Glycemic Targets for ICU and Non-ICU Settings

ICU	Non-ICU
• Initiate insulin therapy for persistent hyperglycemia (glucose>180 mg/dl) • Treatment goal: For most patients, target a glucose level 140-180 mg/dl • More stringent goals (110-140 mg/dl) may be appropriate for selected patients, if achievable without significant risk for hypoglycemia	• No specific guidelines for insulin initiation • If treated with insulin: – Pre-meal glucose <140 mg/dl – Random glucose <180 mg/dl • More stringent targets may be appropriate for patients with previously tight glycemic control • Less stringent targets may be appropriate in patients with severe comorbidities

Available at: https://www.ncbi.nlm.nih.gov/books/NBK279093/?report=classic

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ADA Recommendations for In-hospital Diabetes Management

- A1C for all patients with diabetes or hyperglycemia*
- Insulin infusions using validated written/computerized protocols that allow for predefined adjustments based on glycemic fluctuations and insulin dose
- Basal or basal plus bolus insulin correction for noncritically ill patients with poor oral intake or NPO
- Insulin with basal, nutritional, and correction components for noncritically ill patients and good nutritional intake

*If not obtained within last 3 months.

NPO, nothing by mouth.

ADA. Diabetes Care 2017; 40(S1):S120-S127.

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ADA Recommendations for In-hospital Diabetes Management (cont'd)

- Sole use of sliding scale insulin is strongly discouraged
- Established hypoglycemia management protocol
- An individualized plan for hypoglycemia prevention and treatment
- Medical record of hypoglycemic episodes
- Review of treatment regimen (change as needed to prevent further hypoglycemia)
- A structured, individualized discharge plan

ADA. *Diabetes Care* 2017;40(S1):S120-S127.

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Factors Complicating Glucose Management in Hospitalized Patients

- Severity of illness
- Medications (eg, glucocorticoids)
- Inconsistent dietary intake
- Patient nutritional status
- Prevailing blood glucose concentration
- History and type of diabetes
- Pre-hospital diabetes treatment regimen

Lilley SH et al. *Am Fam Physician*. 1998;57(5):1079-1088; Hassan E. *Am J Health Syst Pharm*. 2007;64:S9-S14.

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Pharmacologic Treatment of Hyperglycemia

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Non-insulin Antihyperglycemic Agents (AHA)

Medication	Average A1C Reduction	Potential Adverse Effects and Impact on Weight
Alpha-glucosidase inhibitors	0.5% – 0.8%	Flatulence, diarrhea, abdominal bloating
Biguanides (metformin)	1.0% – 1.3%	Nausea, diarrhea, abdominal bloating; extended-release preparations have fewer GI adverse effects
DPP4 inhibitors	0.5% – 0.9%	Headache, pancreatitis (rare)
GLP-1 receptor agonists	0.8% – 2.0%	Nausea, vomiting, sense of fullness; weight loss of 2.2 - 8.8 lbs likely; pancreatitis (rare)
Meglitinides	0.5% – 1.0%	Hypoglycemia
SGLT2 inhibitors	0.5% – 0.9%	Increased urinary tract and genital infections, increased LDL; weight loss of 1.5 - 7.7 lbs is typical
Sulfonylureas	0.4% – 1.2%	Hypoglycemia, weight gain
Thiazolidinediones	0.5% – 1.4%	Weight gain, edema

DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter 2.

George CM et al. *Am Fam Physician*. 2015;92(1):27-34.

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Mechanisms of Action of Non-insulin AHAs

Pancreas

Impaired Insulin Secretion

- **Sulfonylureas**
- **Glinides**
- **DPP4-1**
- **GLP-1 agonists**
- *GK agonists*
- *GPRs, IL-receptor antagonists*

Increased Glucagon Secretion

- **DPP4-1**
- **GLP-1 agonists**
- *Glucagon receptor antagonist*

Liver

Increased Glucose Production

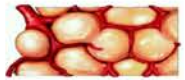
- **Metformin**
- *GK agonists*
- *Glucagon receptor antagonists*

Muscle

Decreased Glucose Uptake

- **TZDs**
- ***Metformin***
- *Dual/Pan PPARs*

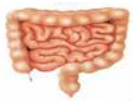
Adipose Tissue



Increased Lipolysis

- **TZDs**
- ***Metformin***
- *Dual/Pan PPARs*
- *11βHSD-I*

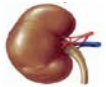
Gut



Decreased Incretin Effect

- **DPP4-I**
- **GLP-1 agonists**
- ***Bile acid sequestrants***

Kidney



Increased Glucose Reabsorption

- **SGLT2-I**

Brain

Neuro-transmitter Dysfunction

- *Bromocriptin*

Bianchi C et al. *Drugs*. 2017;77:247-264.

Approach to AHA Selection for Patients with T2DM

- **Metformin** remains recommended first-line therapy
  - Use is often limited by development of diabetic nephropathy and GFR decline
- **Dual or triple therapy** is typically required to achieve glycemic goals as disease progression occurs
  - Combining complementary MOAs can help achieve additional reduction in A1c
  - Newer classes that positively impact body weight, BP, and albuminuria may benefit patients with specific comorbidities or complications

GFR, glomerular filtration rate; MOAs, mechanism of actions; BP, blood pressure.

Schernthaner-Reiter MH et al. *Exp Rev Endocrinol Met.* 2016;11(3):281-296.

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Targeting Vascular Outcomes in T2DM

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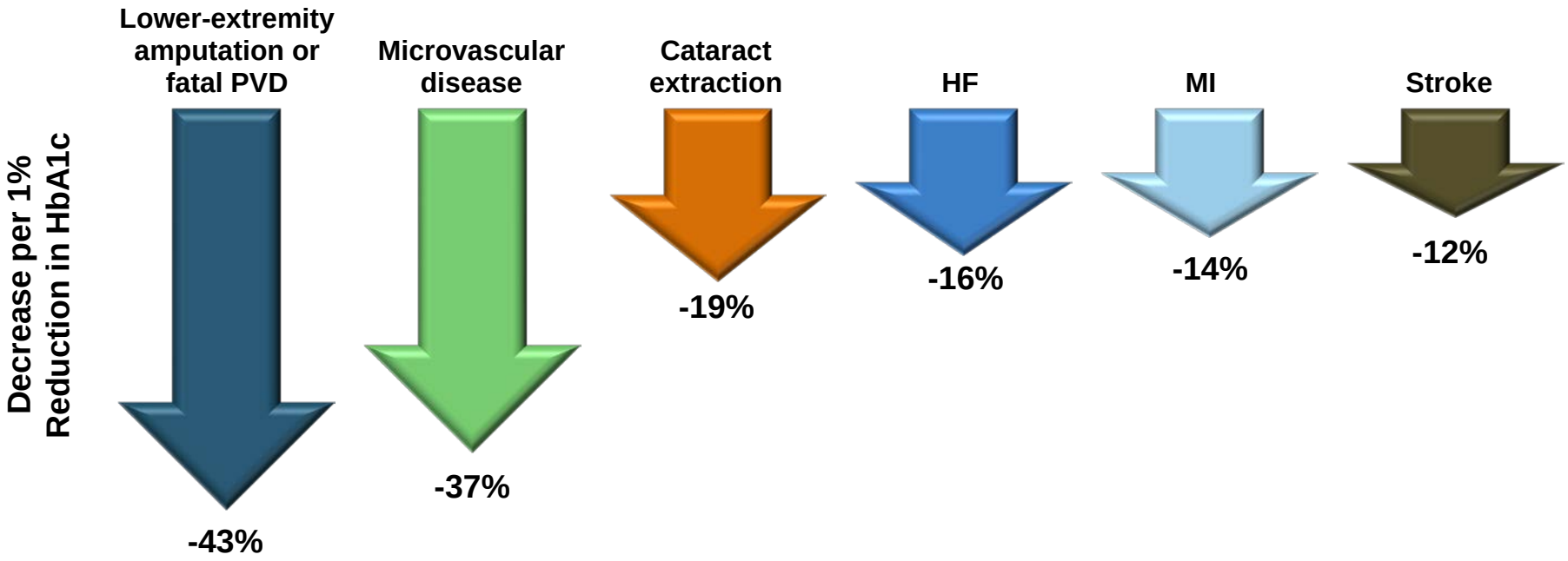
Long-term Glycemic Control Improves Vascular Outcomes: UKPDS



UKPDS, United Kingdom Prospective Diabetes Study.

Stratton IM et al. *BMJ.* 2000;321:405-12.

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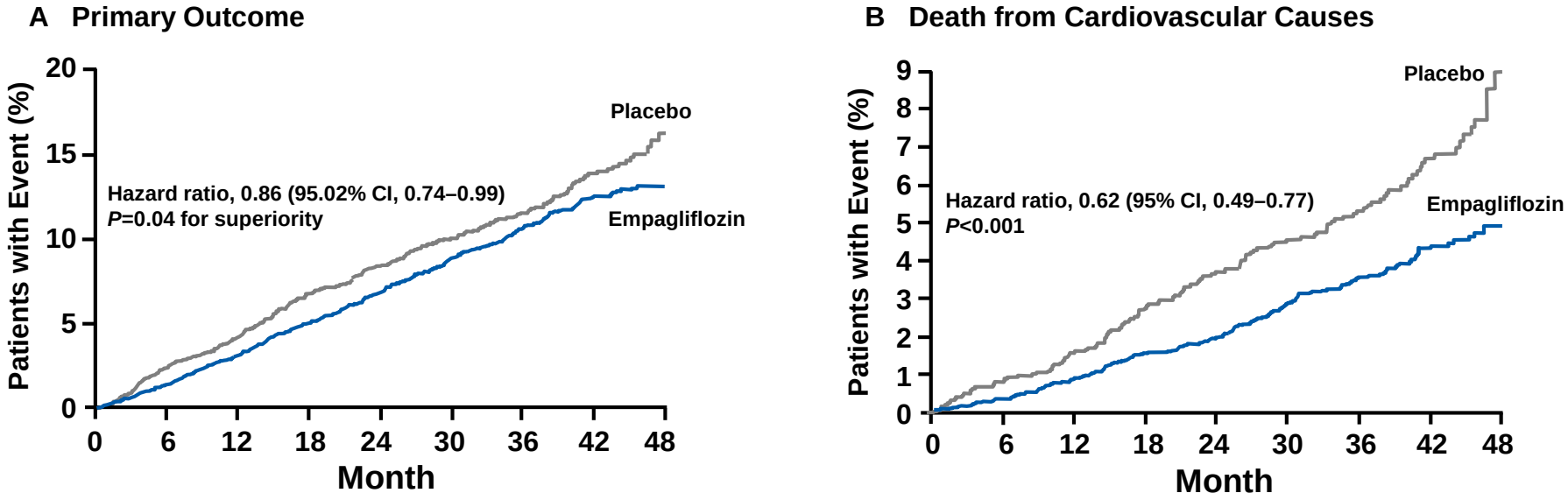
Addition of EMPA to Standard Care Improves CV Outcomes and Mortality

EMPA-REG Study

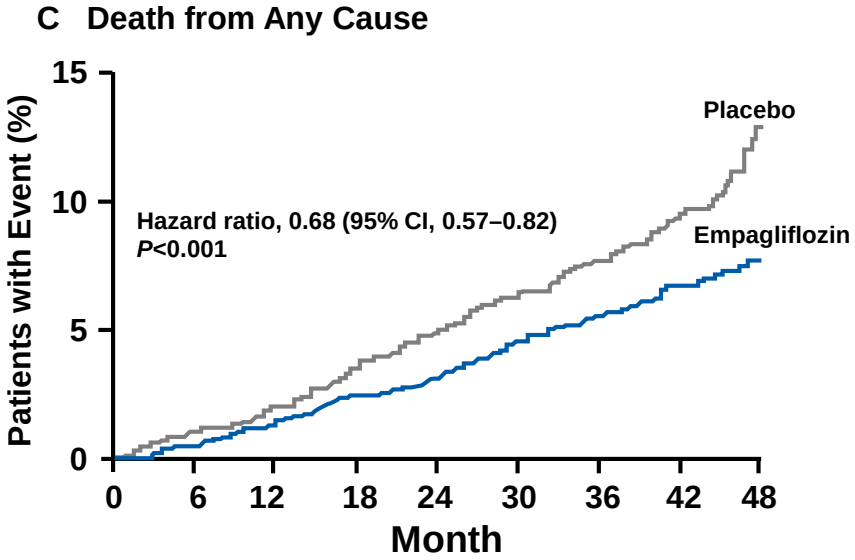


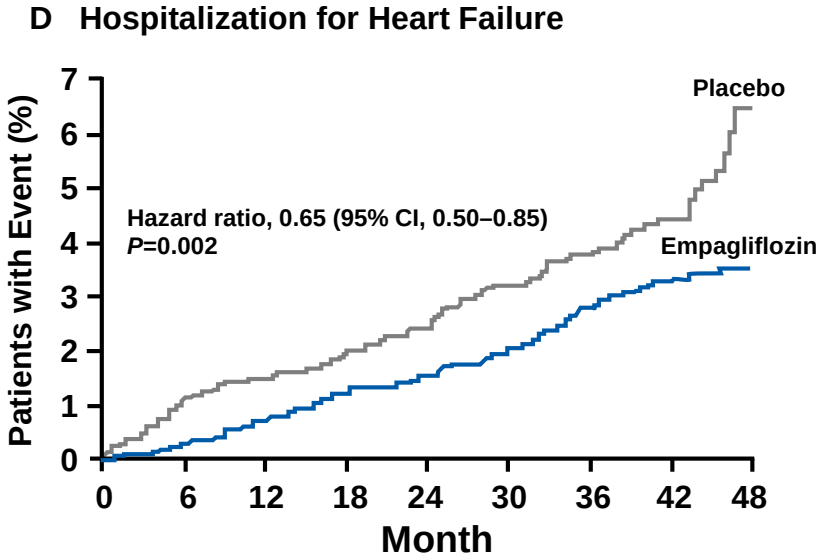
EMPA, empagliflozin.

Zinman et al. *N Engl J Med.* 2015;373:2117-28.

Addition of EMPA to Standard Care Improves CV Outcomes and Mortality

EMPA-REG Study



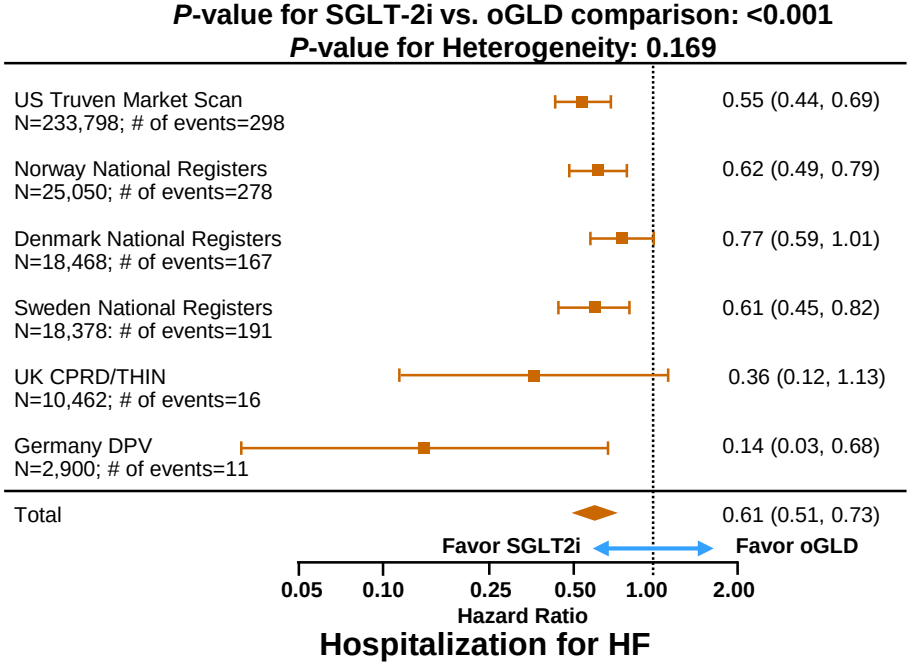


EMPA, empagliflozin.

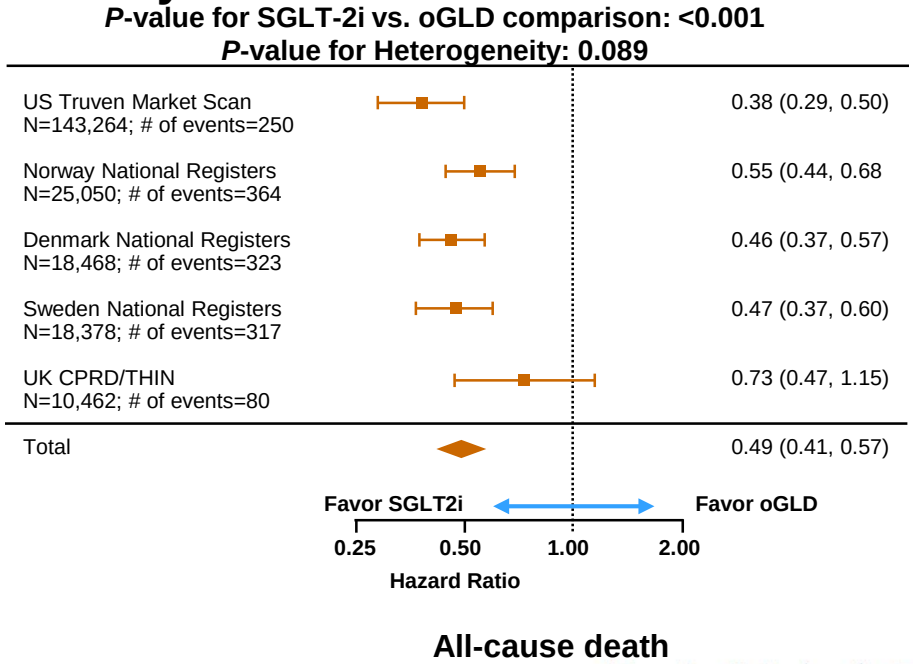
Zinman et al. *N Engl J Med.* 2015;373:2117-28.

SGLT2 Inhibition Lowers the Risk of HF and Death

CVD-REAL Study



Hospitalization for HF

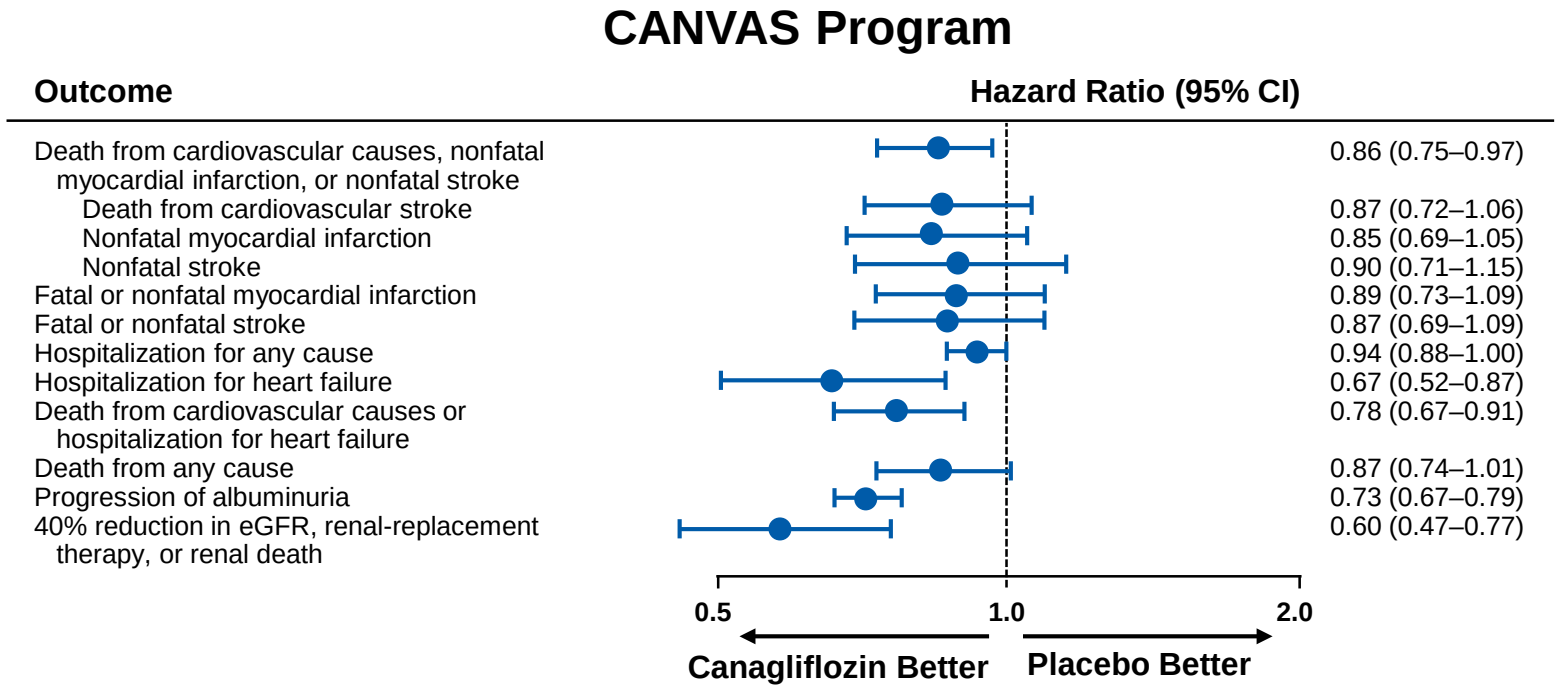


All-cause death

CVD, cardiovascular disease.

Kosiborod M et al. *Circulation*. 2017;136(3):249-259.

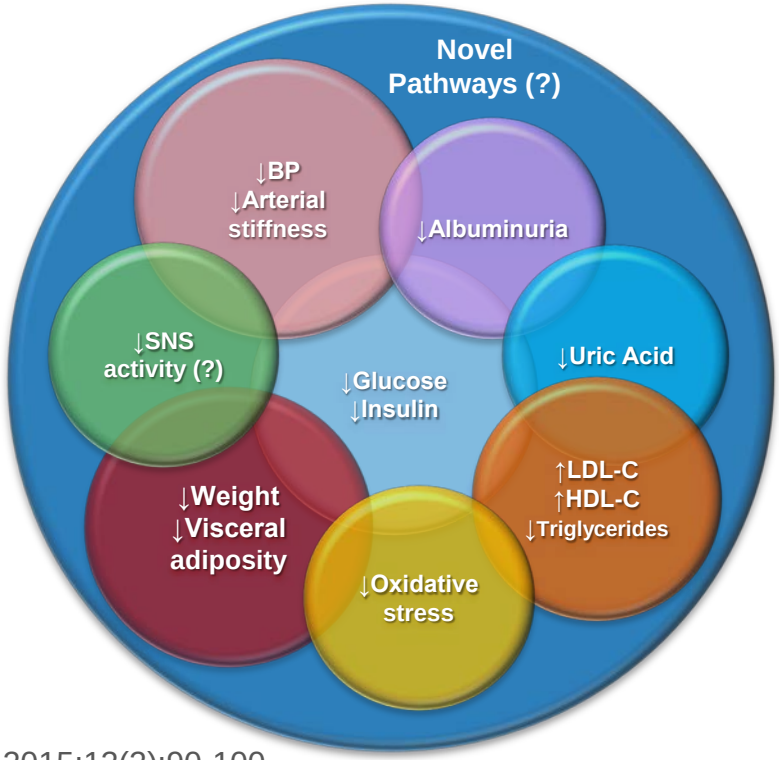
Treatment with CANA Improves CV, Renal, and Mortality Outcomes



CANA, canagliflozin.

Neal B et al. *N Engl J Med*. 2017;377:644-57.

Potential Pathways Associated with CV Effects of SGLT-2 Inhibitors



Inzucchi et al. *Diabetes Vasc Dis Res.* 2015;12(2):90-100.

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Impact of Incretin-based Therapies on CV Risk Factors

Risk factor	GLP1RA	DPP-4I
A1c	• Reduced	• Reduced
Body weight	• Reduced	• Potential minor reduction (<1 kg)
BP	• SBP lower (2-3 mmHg) in patients with HT • DBP less consistently affected	• No uniform lowering effect
HR	• 2–3 bpm rise	• No major effects reported
Lipids	• Lower triglycerides • Increased HDL cholesterol • Small reduction in LDL cholesterol	• No major effects on fasting lipoprotein patterns

LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, spontaneous bacterial peritonitis; DBP, diastolic blood pressure; bmp, beats per minute.

Nauck M. *Circulation*. 2017;136:849–870.

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DPP-4 Inhibitors and CV Risk

Clinical Trial Findings	AHA Investigated
Neutral for CV risk factors	• Saxagliptin • Alogliptin • Sitagliptin
Increased risk for HF-related hospitalization	• Saxagliptin (significant) • Alogliptin (nonsignificant trend)

In the absence of clear benefits regarding overall CV risk, further mechanistic clarification and caution is recommended for individuals at risk for CHF

Nauck MA et al. *Circulation*. 2017;136:849-870.

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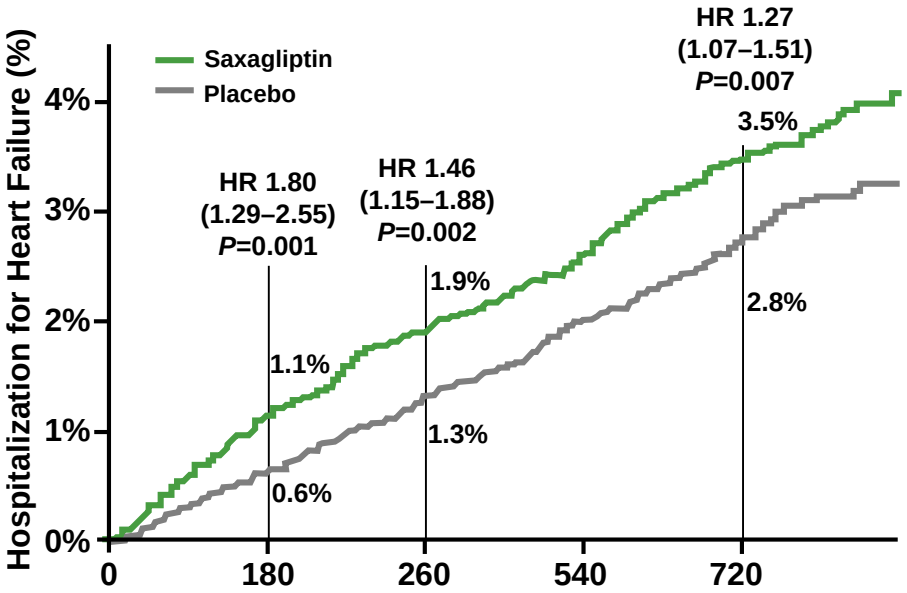
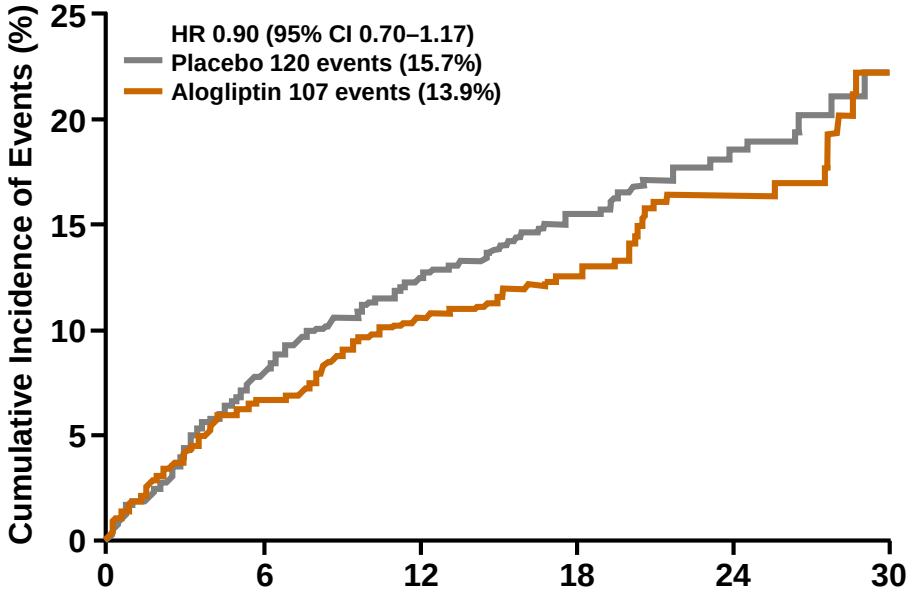
DPP-4 Inhibitors and HF Outcomes

EXAMINE



SAVOR-TIMI 53



Scirica BM et al. *Circulation*. 2014;130(18):1579-88; Zannad et al. *Lancet*. 2015;385(9982):2067-76.

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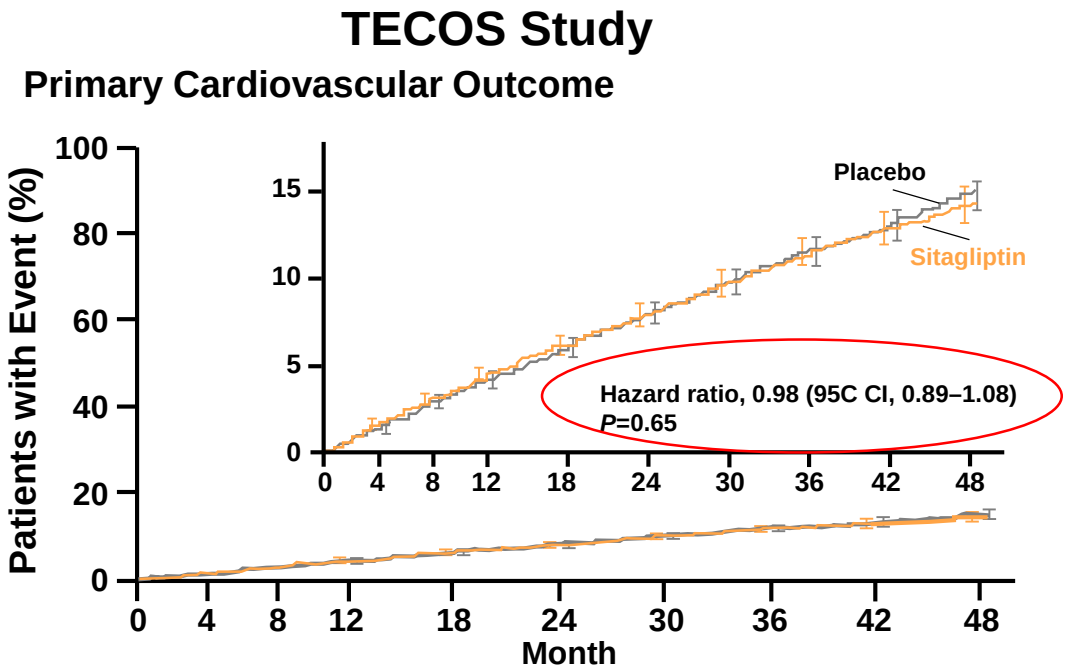
Impact of Sitagliptin Therapy on CV Outcomes



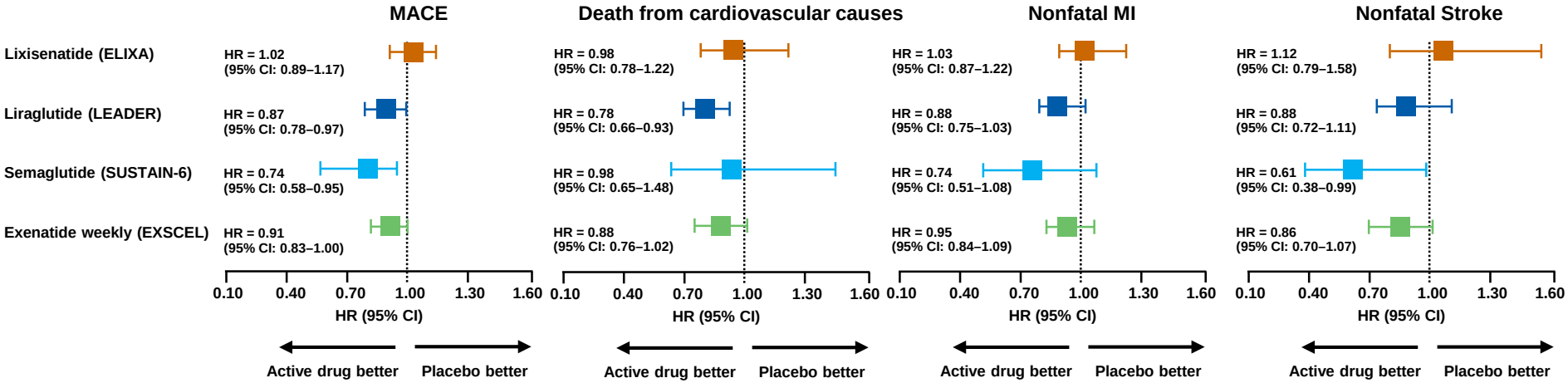
Sitagliptin added on to usual care was **NOT** associated with increased risk for:

- MACE
- HF-related hospitalization
- Other AEs

MACE, major adverse cardiac events; AEs, adverse events.

Green JB et al. *N Engl J Med.* 2015;373:232-42.

Overview of the Impact of GLP-1R Agonists on CV Outcomes



Lim S et al. *Trends Endocrinol Metab.* 2018 [Epub ahead of print]

Recently Approved Incretin-based Therapies and SGLT2 Inhibitors

Therapy		Approval Date
Single agent	Ertugliflozin	December 2017
	Semaglutide	December 2017
Fixed-dose combination	Ertugliflozin and sitagliptin	December 2017
	Dapagliflozin and saxagliptin	February 2017
	Empagliflozin and linagliptin	January 2015

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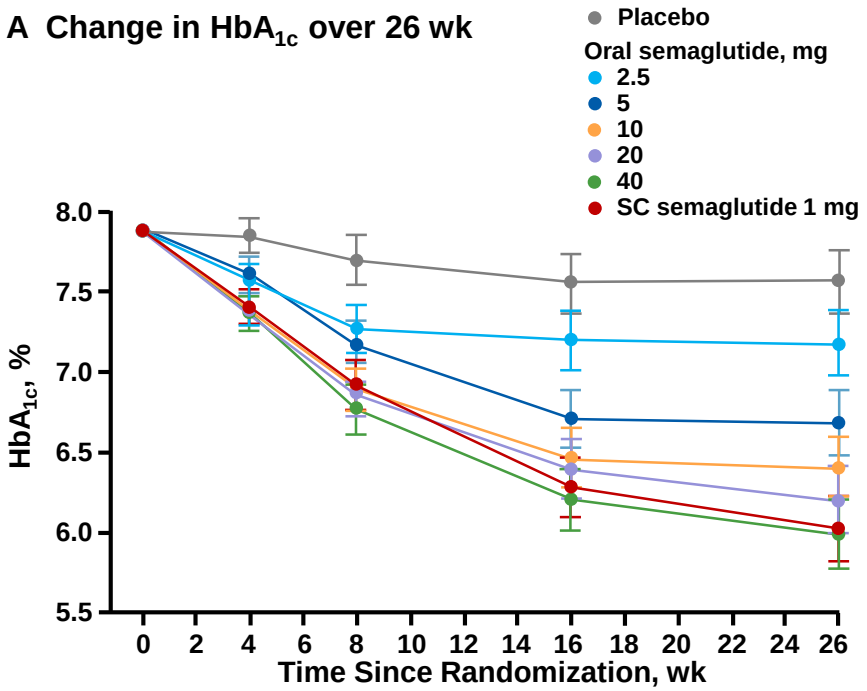
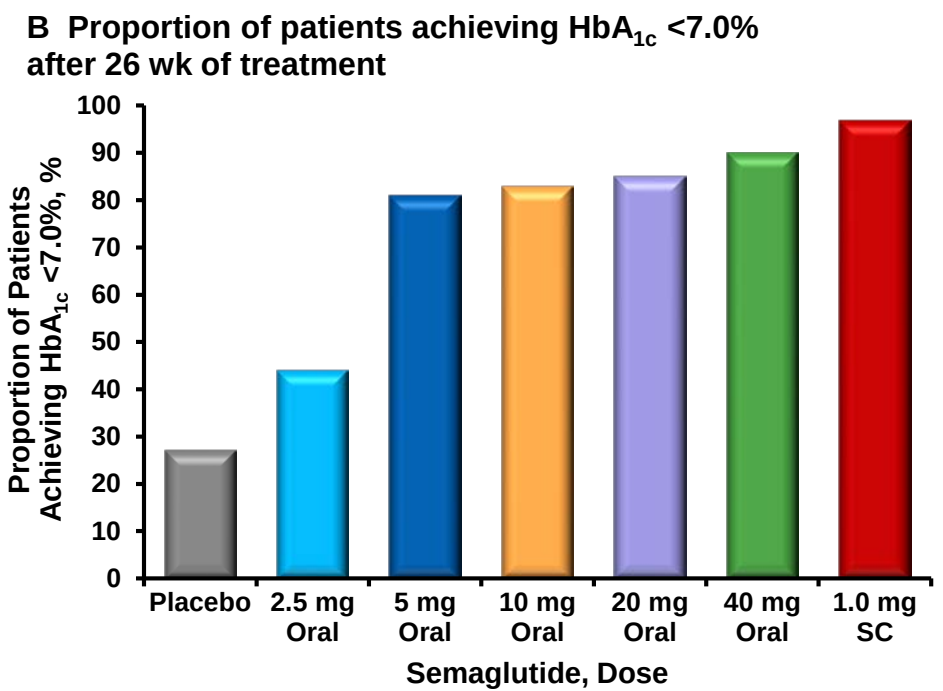
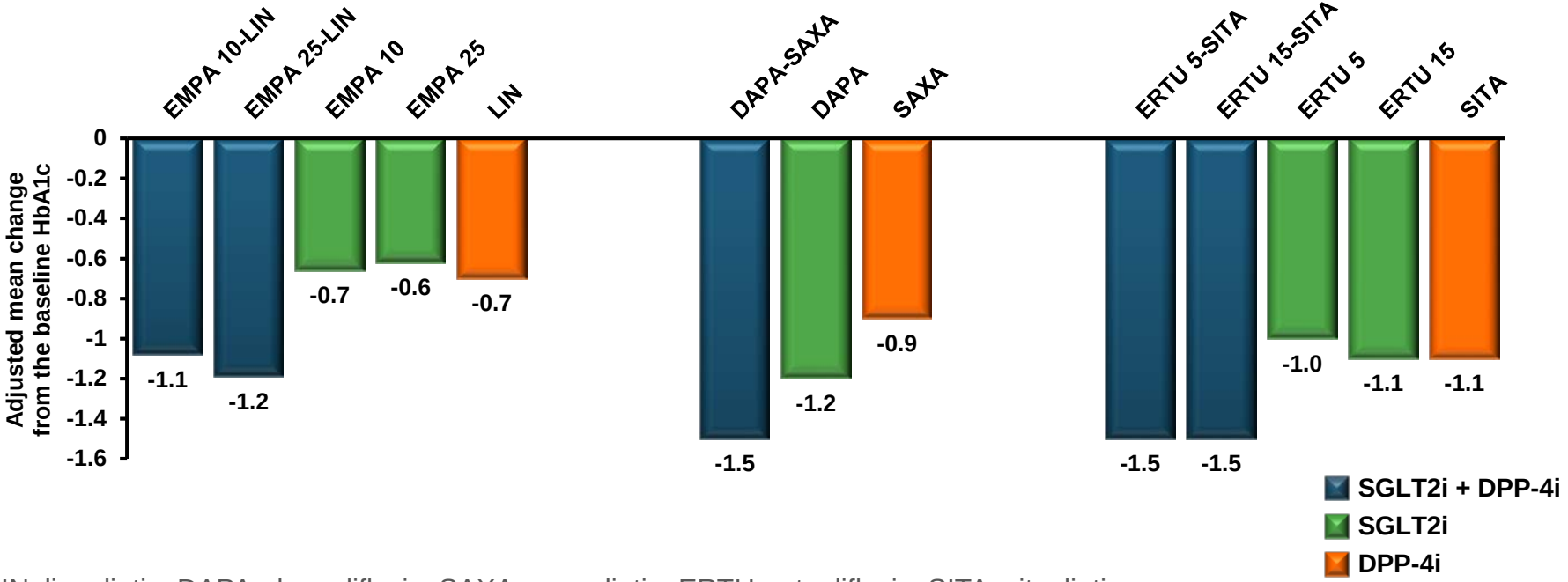
Efficacy of Oral Semaglutide in Patients with T2DM





Davies M et al. *JAMA*. 2017;318(15):1460-1470.

Changes from Baseline A1C with Combined SGLT2 and DPP-4 Inhibition



LIN, linagliptin; DAPA, dapagliflozin; SAXA, saxagliptin; ERTU, ertugliflozin; SITA, sitagliptin.

DeFronzo RA et al. *Diabetes Care.* 2015;38:384-393; Rosenstock et al. *Diabetes Care.* 2015;38:376-383; *Diabetes Obes Metab*. 2018;1-10.

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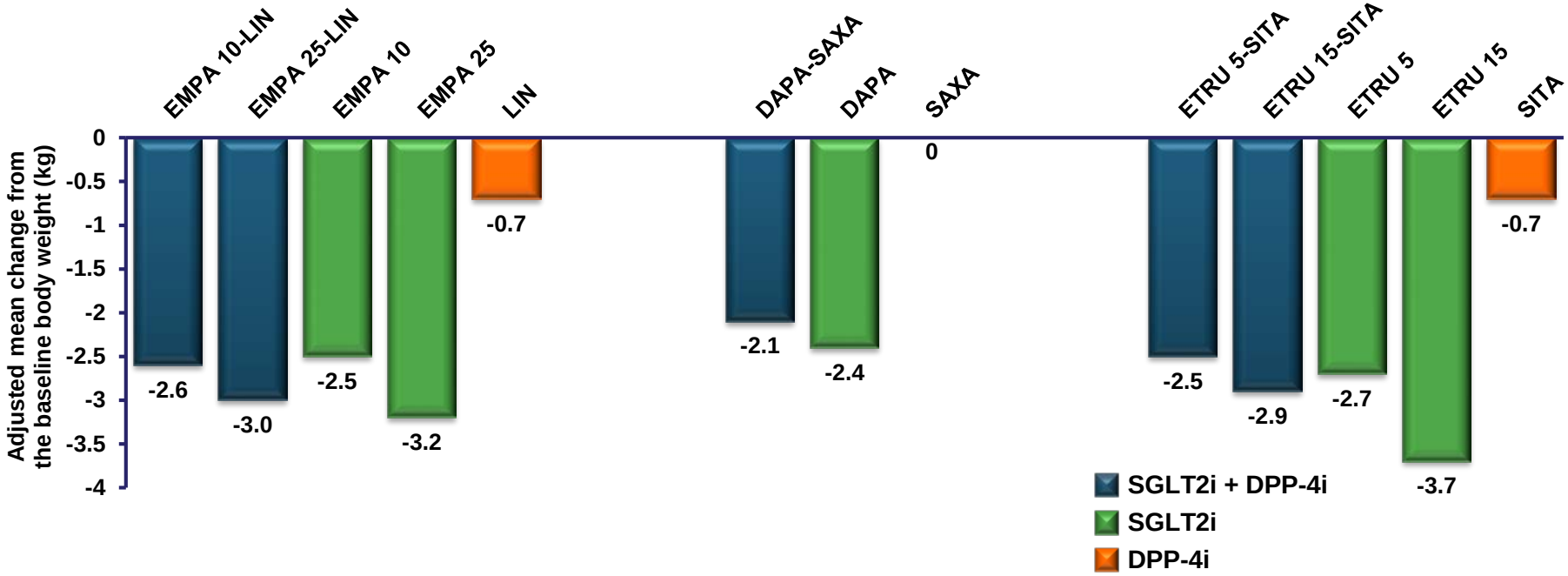
Changes from Baseline Weight with Combined SGLT2 and DPP-4 Inhibition



DeFronzo RA et al. *Diabetes Care.* 2015;38:384-393; Rosenstock et al. *Diabetes Care.* 2015;38:376-383; *Diabetes Obes Metab*. 2018;1-10.

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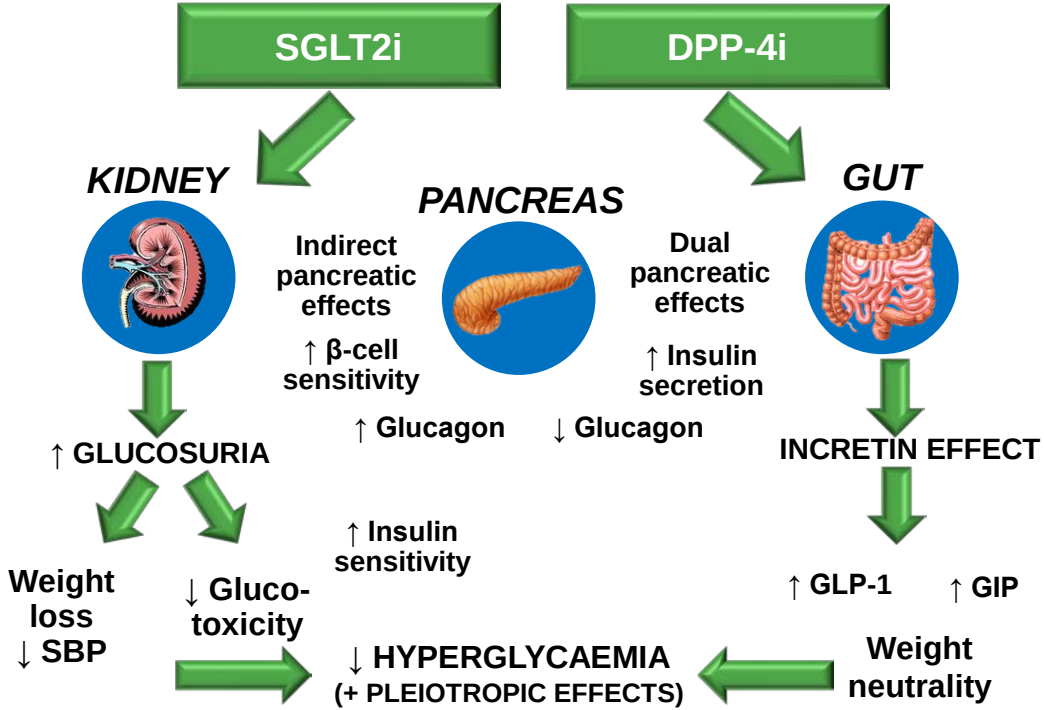
Complementary Glucose-lowering Actions of DPP-4 Inhibitors and SGLT2 Inhibitors



Scheen AJ et al. *Exp Op Drug Met Toxicol.* 2016;12;1407-1417.

Potential Advantages of Fixed-dose SGLT2 and DPP-4 Inhibitor Combination Therapies

- Simplify treatment
- Reduce tablet burden
- Increase medication adherence
- May be particularly beneficial for patients for whom reduction of body weight, BP, and CV risk are important

Transitional Care

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Discharge Planning

- Ensure stable blood glucose levels
- Measure A1C before discharge (if not measured during the previous months)
- Simplify treatment regimen for hyperglycemia (if possible)
- Schedule follow-up care within several weeks
- Communicate with outpatient providers regarding follow-up care

ADA. *Diabetes Care.* 2017;40(Suppl. 1):S120-S127.

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Patient Education, Instruction, and Referral

- **Educate patients/caregivers**
  - Self-monitoring of blood glucose and follow-up to address post-discharge changes (diet, exercise, and physiological stress)
  - Diabetes and self-care
  - Blood glucose targets
  - Signs and symptoms that require HCP consultation
- **Provide specific instruction**
  - Proper medication use
  - Self-monitoring of blood glucose
  - Hypoglycemia and hyperglycemia prevention
- **Refer to a diabetes educator**

ADA. *Diabetes Care.* 2017;40(Suppl. 1):S120-S127.

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Summary

- T2DM is a chronic, progressive disease closely associated with a range of macro and microvascular complications, which frequently lead to hospitalization.
- Hospital-based clinicians play a crucial role in ensuring optimal glycemic management during the hospital stay as well as providing guidance on antihyperglycemic therapy following discharge.
- Optimal glycemic management requires treatment that takes into account a wide range of patient characteristics, including a high risk for vascular complications and the presence of comorbidities.
- Many antihyperglycemic therapies with good efficacy and safety profiles have been developed, including incretin-based therapies and SGLT2 inhibitors, which have shown beneficial effects on both cv risk factors and vascular outcomes.

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Clinical Pearls

- Patients with diabetes are at increased risk of vascular complications and hospitalizations for CV related events compared to patients without diabetes
- Diabetes and hypertension are among the 9 modifiable risk factors that account for >90% of the risk of initial acute MI
- For most hospitalized patients with diabetes, target a glucose level of 140-180 mg/dl
- Newer treatments for diabetes, including SGLT2 and GLP-1 indicators, have been shown to reduce micro and macrovascular events
- More intensive glucose control has been associated with a 20% reduction in kidney disease
- Prior to discharge of a patient with diabetes, ADA guidelines recommend measurement of hbA1c level

THANK YOU!

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