HOSPITAL MEDICINE SUMMIT

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

INTEGRITY CONTINUING EDUCATION

PIM Postgraduate Institute for Medicine

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Faculty

Harold Bays, MD, FOMA, FTOS, FACC, FACE, FNLA
Medical Director/President
Louisville Metabolic and Atherosclerosis Research Center
Your Body Goal
Louisville, Kentucky

Faculty Disclosures

- Consultant: Aegerion, Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, ChromaDex, Esperion, Gemphire, Janssen, Johnson & Johnson, Kowa, Merck, Novartis, Prosciento, Regeneron, Sanofi
- Research: Acasti, Alere, Allergan, Amarin, Amgen, Arena, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, ChromaDex, Dr. Reddy, Eisai, Esperion, Ferrer/Chiltern, Gan and Lee, Gemphire, Gilead, GlaxoSmithKline, Home Access, iSpecimen, Ionis, Janssen, Johnson & Johnson, MedImmune, Merck, Necktar, Nichi-Iko, Novartis, NovoNordisk, Omthera, Pfizer, Regeneron, Sanofi, Selecta, Takeda, TIMI
- Speaker: Aegerion, Amarin, Amgen, Kowa, Regeneron, Sanofi

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

Diabetes and Its Complications

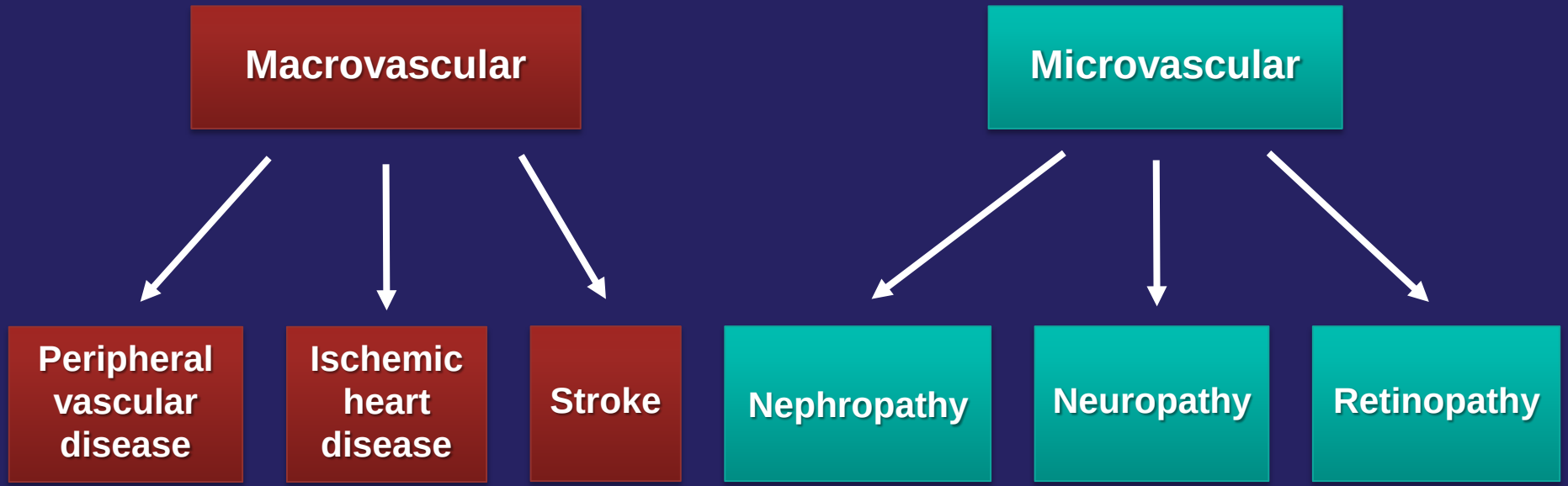
Introduction

Burden of Diabetes in the US

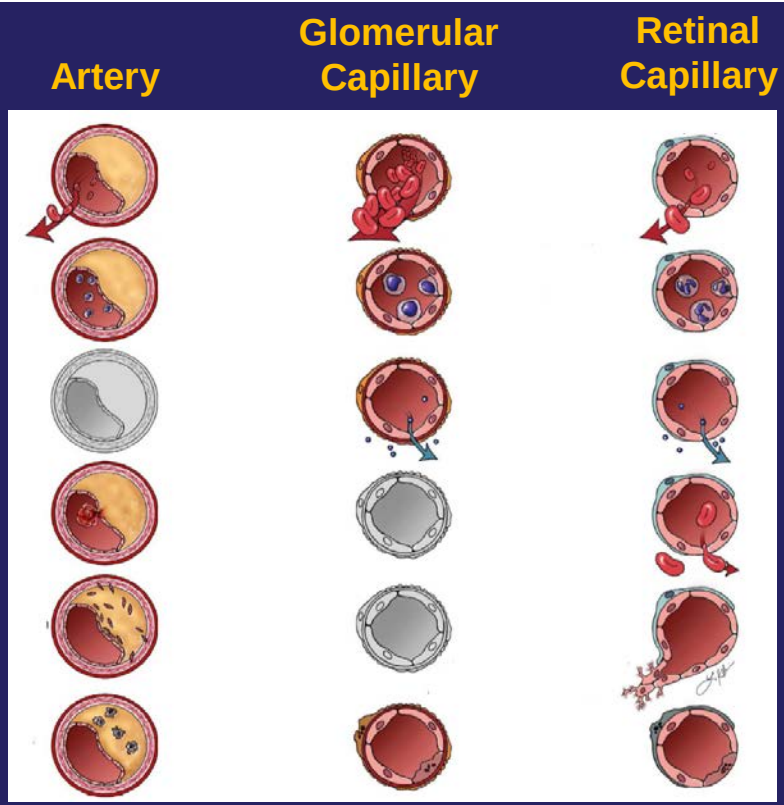
- Estimated incidence in 2015
  - **30.3 million** with diagnosed diabetes*
  - **7.2 million** undiagnosed
  - **84.1 million** with prediabetes
- Increasing prevalence with rising overweight and obesity rates
- Significant risk for complications, including CHD, stroke, HT, depression, pain, polypharmacy, 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

Vascular Complications of Diabetes

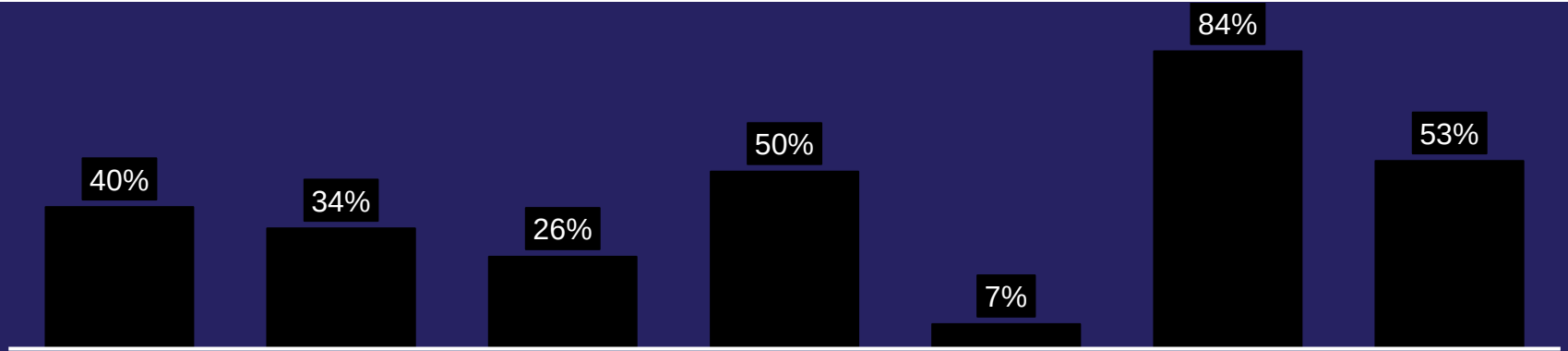


Abnormalities of Vascular Function in Diabetes



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

Prevalence of Vascular Complications in Diabetes



DM increases by 2-4 fold the risk of CAD (leading cause of morbidity and mortality in developed countries), stroke, PAD, and HF.

Zimmerman RS. Diabetes Mellitus: Management of Microvascular and Macrovascular Complications. Published: September 2016. Available at: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/endocrinology/diabetes-mellitus/#bib5.
Boccara F, Cohen A. *Heart*. 2004;90(12):1371-1373.

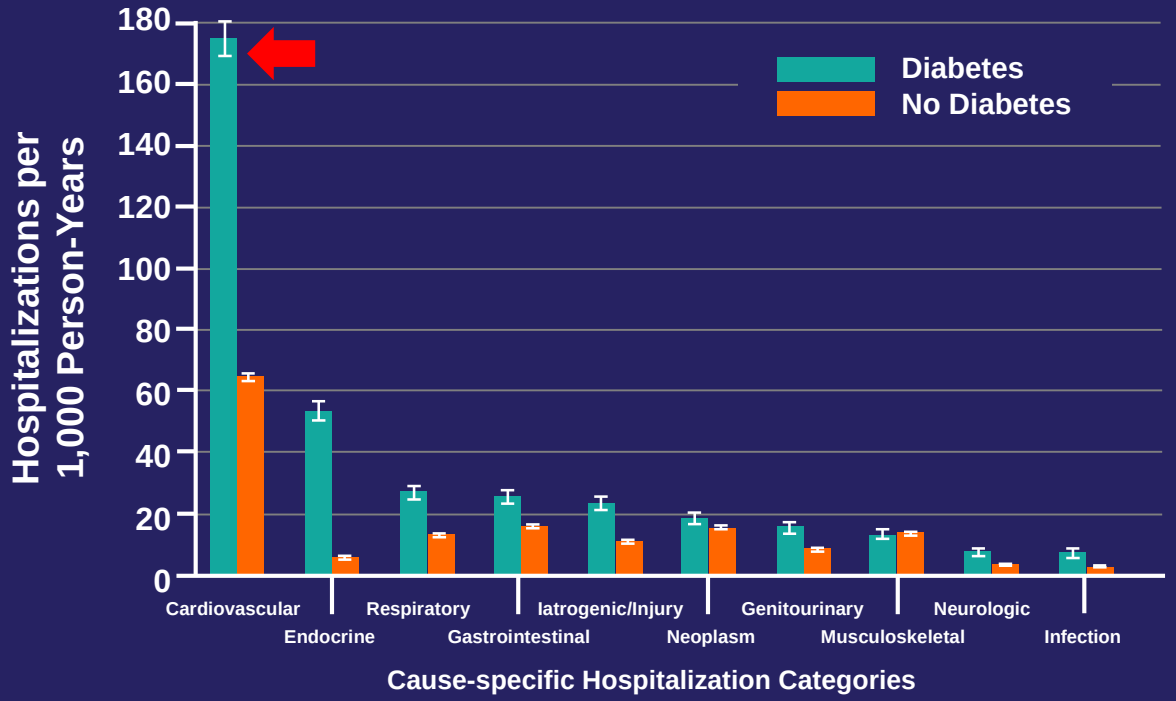
High Mortality Associated with Cardiovascular Complications in Diabetes

- Patients with diabetes are up to 4 times more likely have a stroke or die of heart disease
- Cardiovascular disease accounts for 50%-70% of all deaths in diabetes
- Heart disease is the leading cause of diabetes-related death in the US

Ahmed KA, et al. *Biomedical Research*. 2010;21(2):141-146.
Huang Dou, et al. *Biomed Res Int*. 2017;2017:7839101.

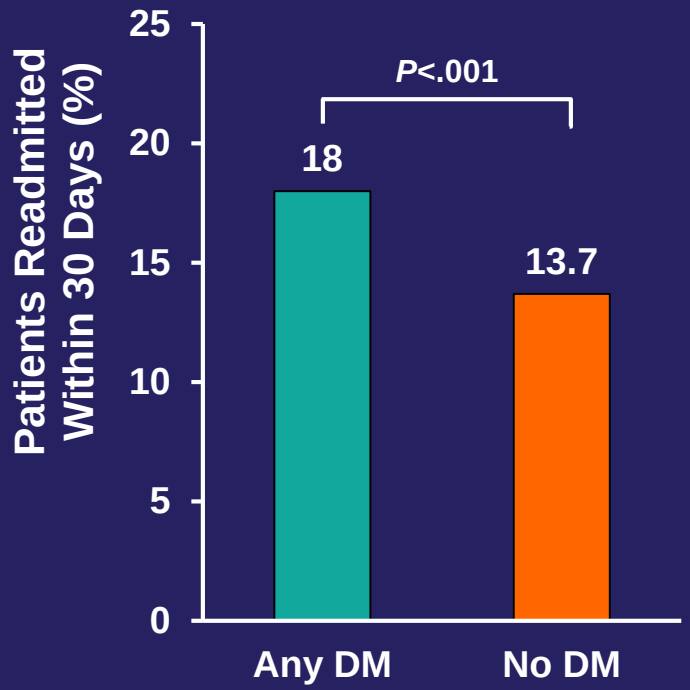
Diabetes in the Hospital Setting

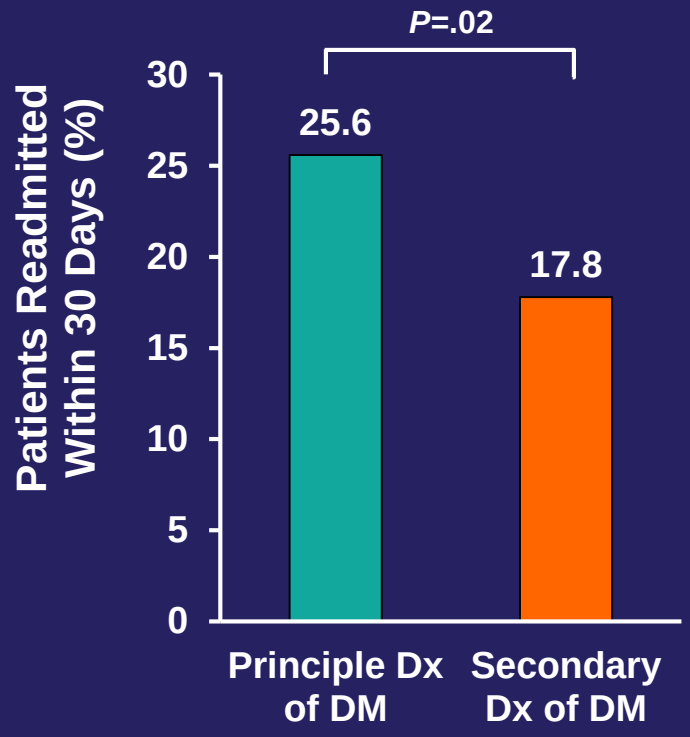
Cause-specific Hospitalizations Among Patients with Diabetes



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

30-day Readmissions Among Patients with Diabetes





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

Inpatient Management

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.

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

Moghissi ES, et al. AACE/ADA Consensus Statement. *Endocr Pract.* 2009;15(4):1-17.

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.

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.

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.

Pharmacologic Treatment of Hyperglycemia

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.

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

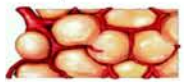
- **Metformin**
- *GK agonists*
- *Glucagon receptor antagonists*

Muscle

Decreased Glucose Uptake

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

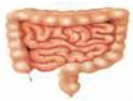
Adipose Tissue



Increased Lipolysis

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

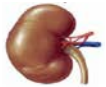
Gut



Decreased Incretin Effect

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

Kidney



Increased Glucose Reabsorption

- **SGLT2-I**

Brain

Neuro-transmitter Dysfunction

- *Bromocriptine*

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

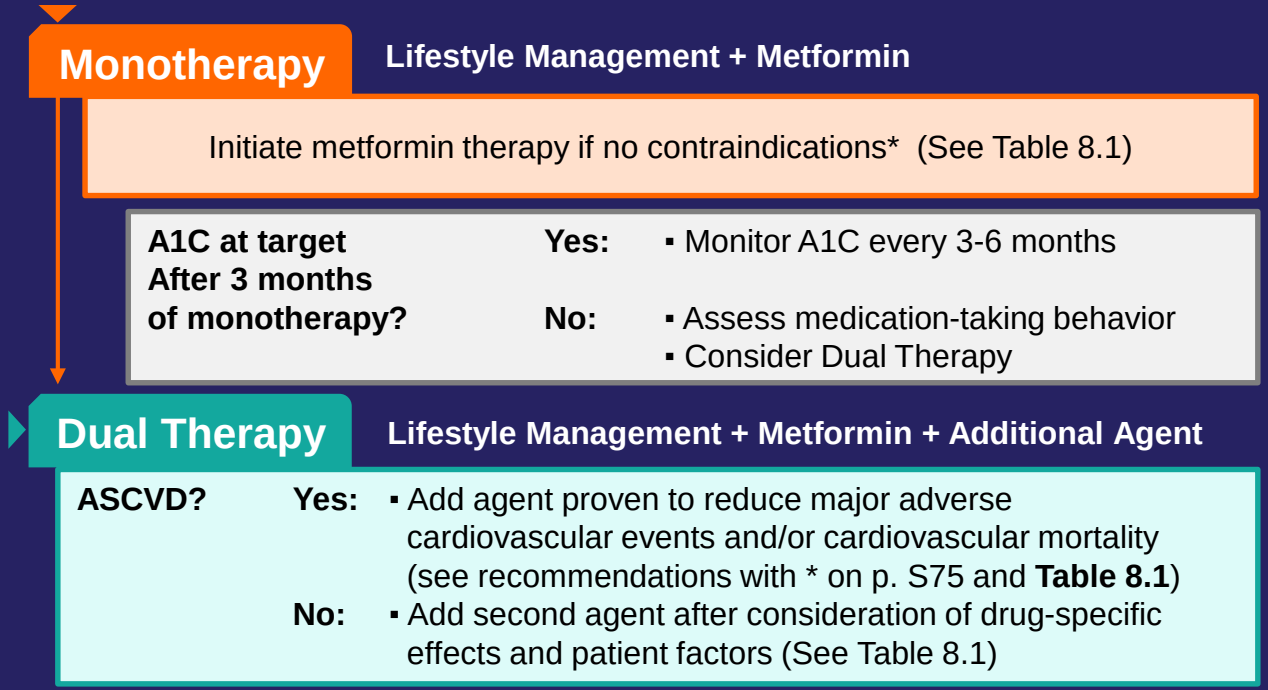
Approach to AHA Selection for Patients with T2DM

- **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
  - Consider drug-specific and patient factors, including efficacy, hypoglycemia, weight change, CV effects, cost, administration, and renal effects

GFR, glomerular filtration rate; MOAs, mechanism of actions.

Schernthaner-Reiter MH, et al. *Exp Rev Endocrinol Met.* 2016;11(3):281-296.
ADA Professional Practice Committee. Standards of Medical Care in Diabeites-2018. *Diabetes Care*. 2018;41(suppl 1):S77.

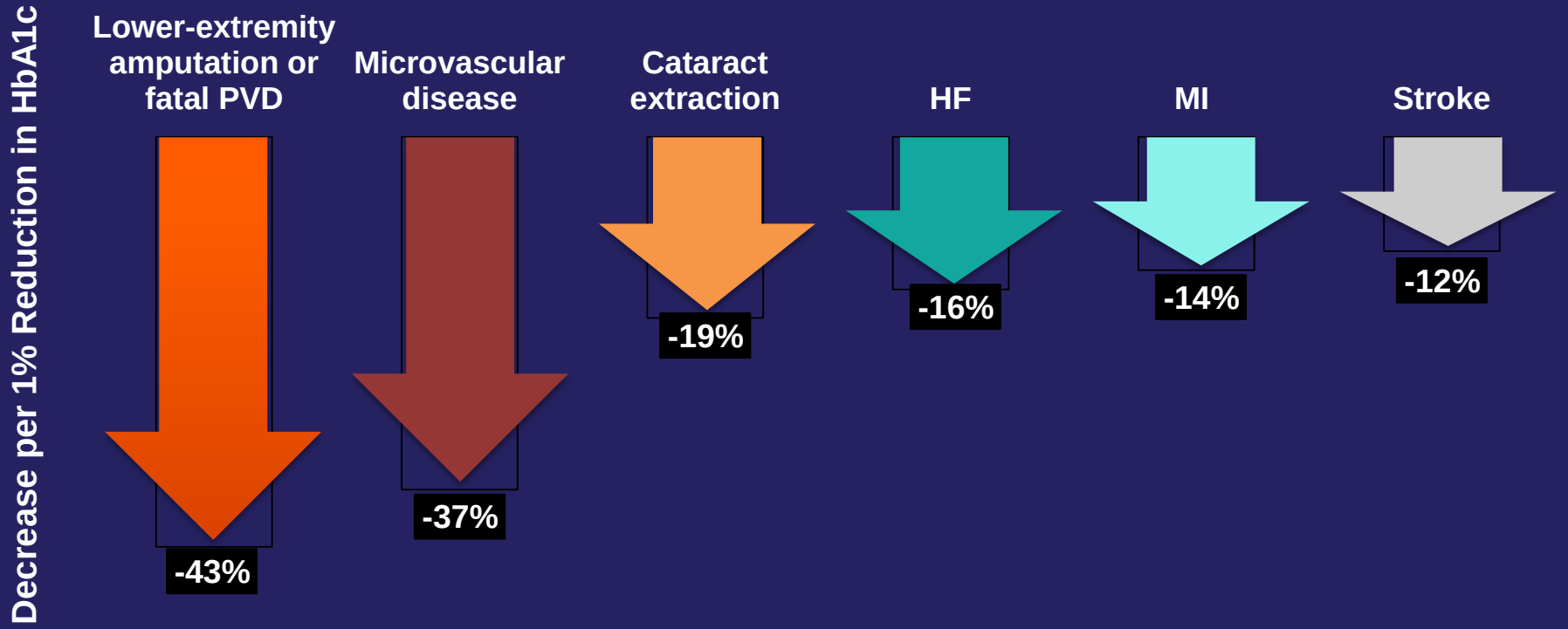
Antihyperglycemic Therapy in Adults with T2DM



ASCVD benefits = canagliflozin, empagliflozin, liraglutide, and possible metformin, pioglitazone.
CHF benefits = canagliflozin, empagliflozin; CHF risks – thiazolidinediones and possibly saxagliptin and alogliptin.
Diabetes Care. 2018;41(supplement):S1-S2.

Targeting Vascular Outcomes in T2DM

Long-term Glycemic Control Improves Vascular Outcomes: UKPDS



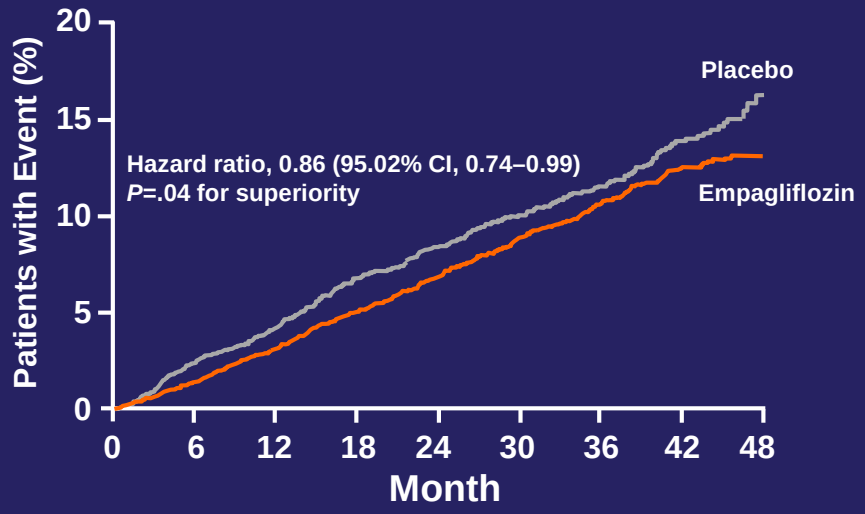
UKPDS, United Kingdom Prospective Diabetes Study.

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

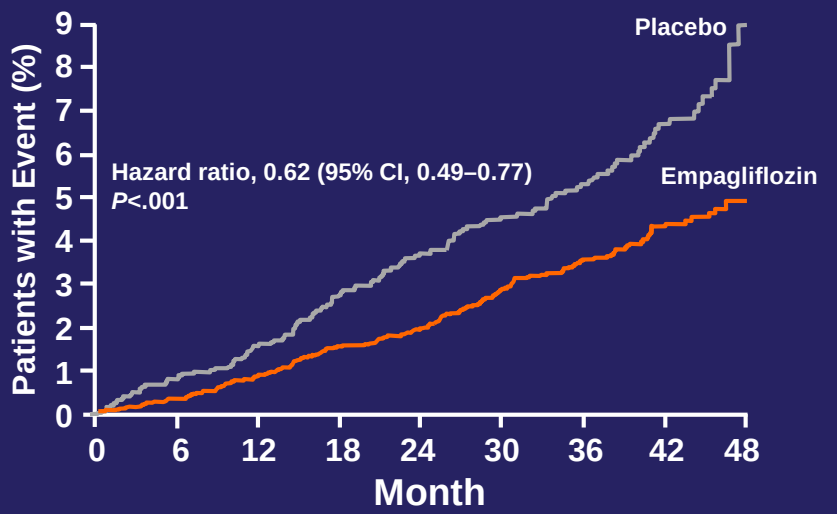
Addition of EMPA to Standard Care Improves CV Outcomes and Mortality

EMPA-REG Study

Primary Outcome



Death from Cardiovascular Causes



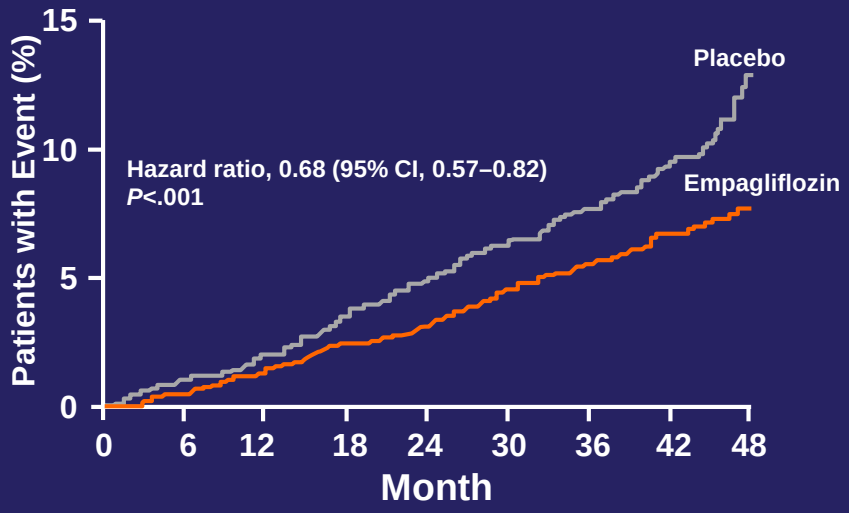
EMPA, empagliflozin.

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

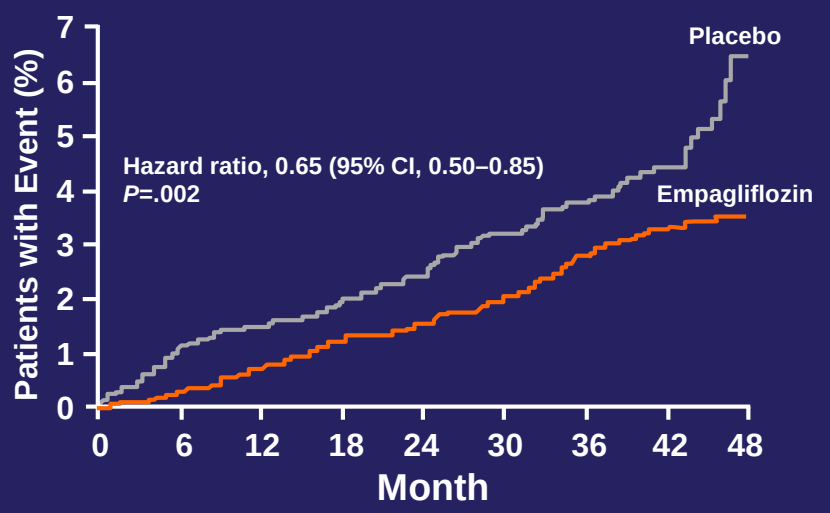
Addition of EMPA to Standard Care Improves CV Outcomes and Mortality

EMPA-REG Study

Death from Any Cause



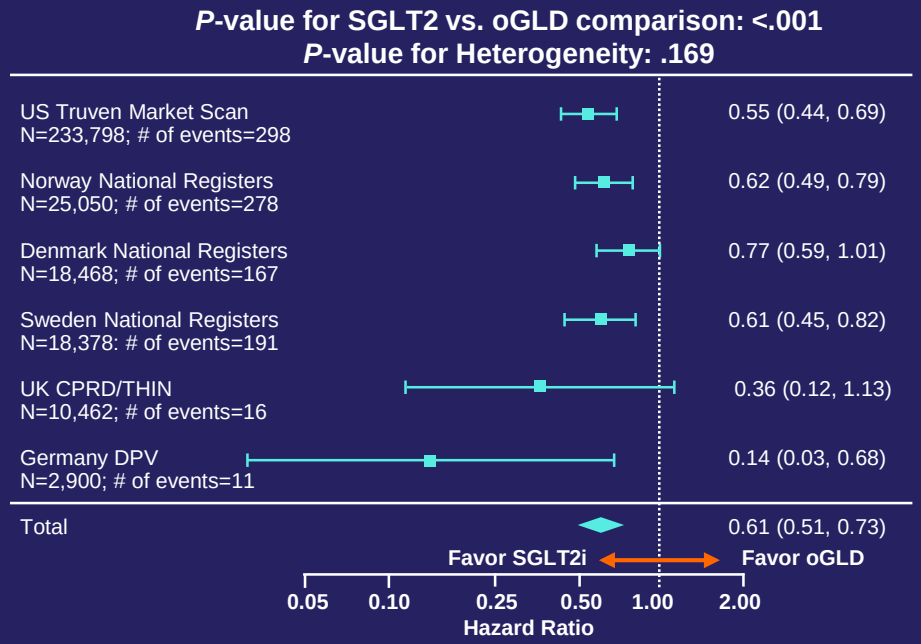
Hospitalization for Heart Failure



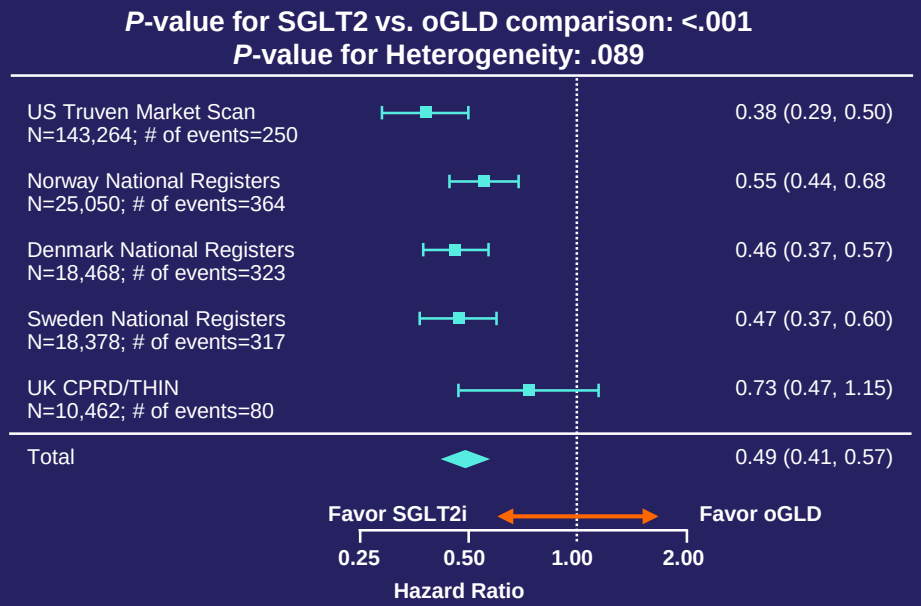
Zinman et al. *N Engl J Med.* 2015;373:2117-28.

SGLT2 Inhibition Lowers the Risk of HF and Death

CVD-REAL Study



Hospitalization for HF



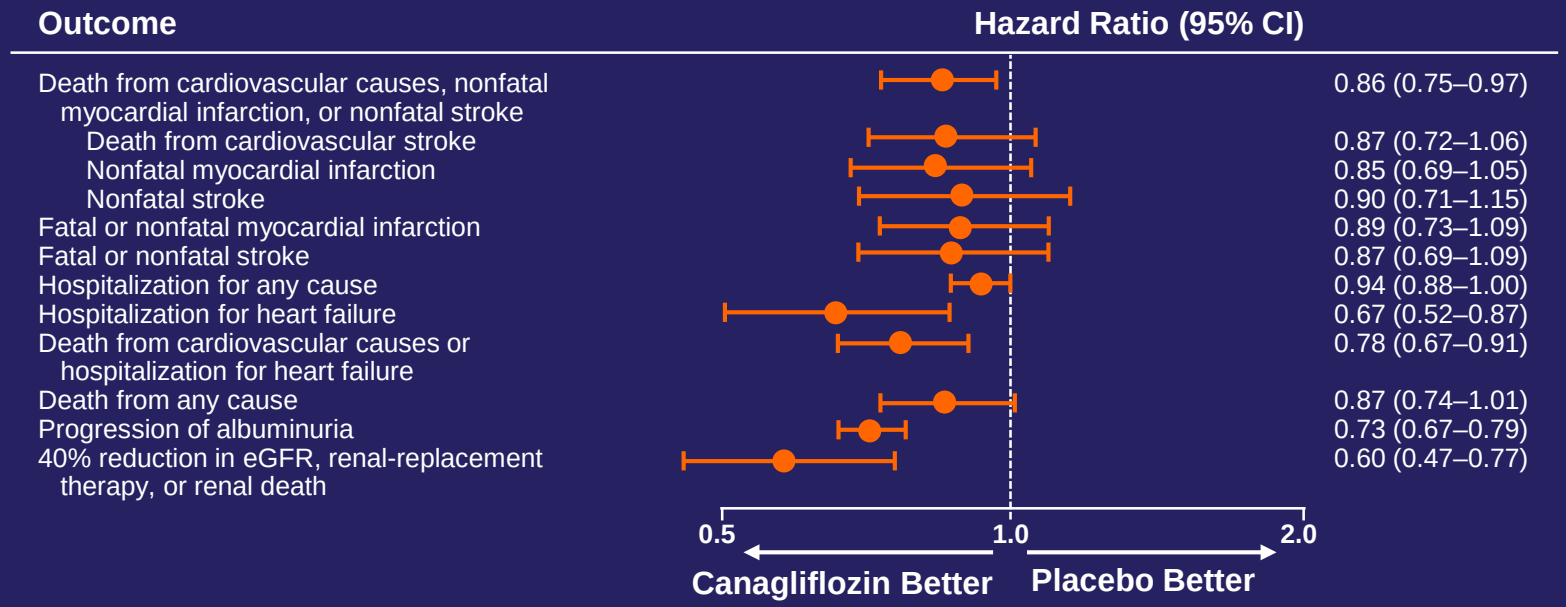
All-cause death

CVD, cardiovascular disease.

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

Treatment with CANA Improves CV, Renal, and Mortality Outcomes

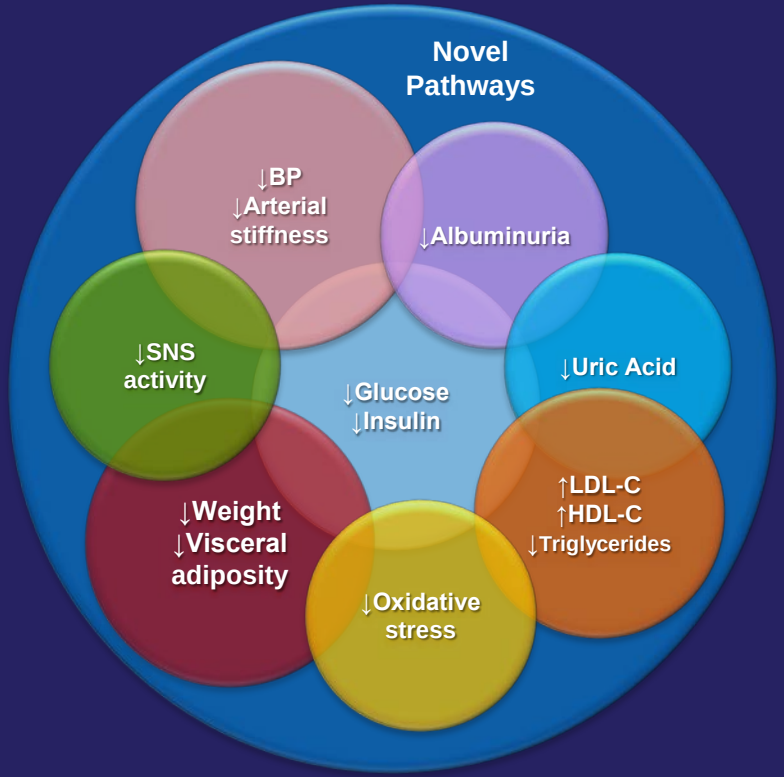
CANVAS Program



CANA, canagliflozin.

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

Potential Pathways Associated with CV Effects of SGLT2 Inhibitors



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

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; bmpm, beats per minute.

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

DPP-4 Inhibitors and CV Risk

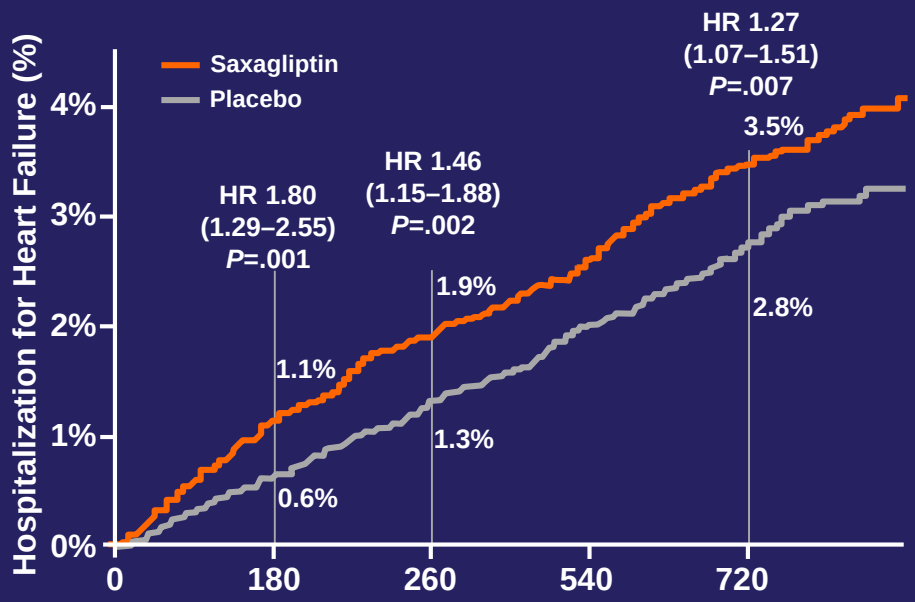
Clinical Trial Findings	AHA Investigated
Neutral for CV risk factors	• Saxagliptin • Alogliptin • Sitagliptin
Increased risk for HF-related hospitalization	• Saxagliptin (significant) • Alogliptin (nonsignificant trend)

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

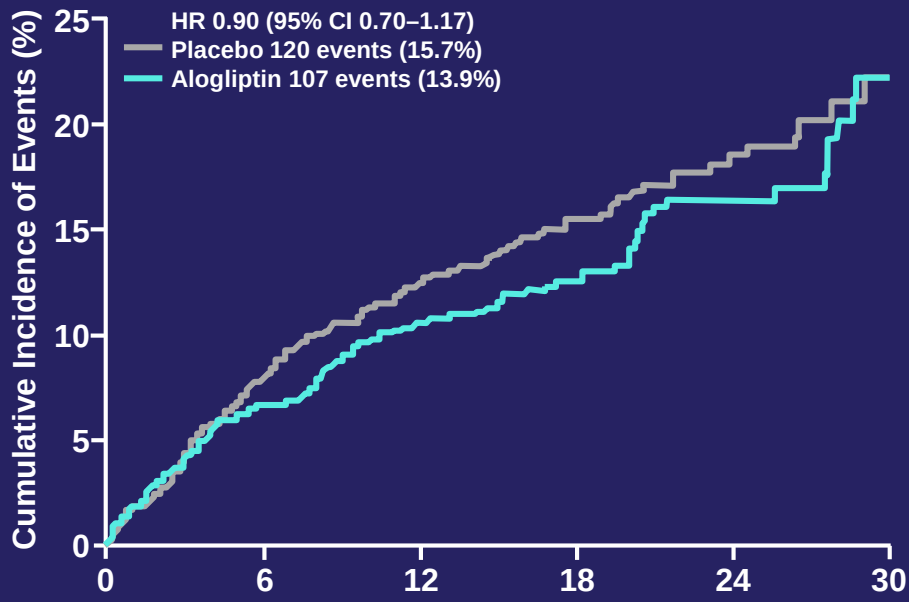
Nauck MA, et al. *Circulation*. 2017;136:849-870.

DPP-4 Inhibitors and HF Outcomes

EXAMINE



SAVOR-TIMI 53

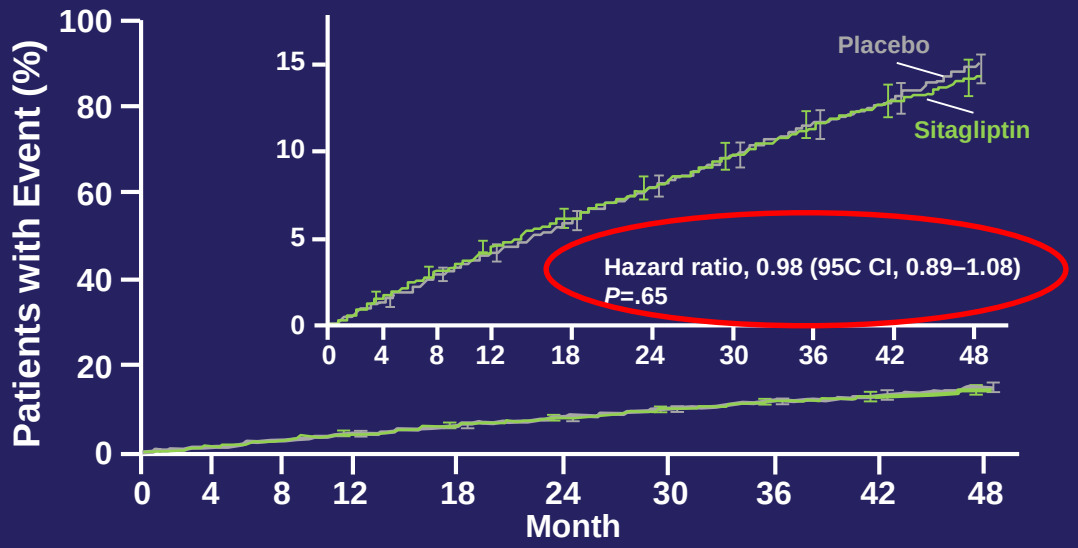


Scirica BM, et al. *Circulation*. 2014;130(18):1579-88; Zannad et al. *Lancet*. 2015;385(9982):2067-76.

Impact of Sitagliptin Therapy on CV Outcomes

TECOS Study

Primary Cardiovascular Outcome



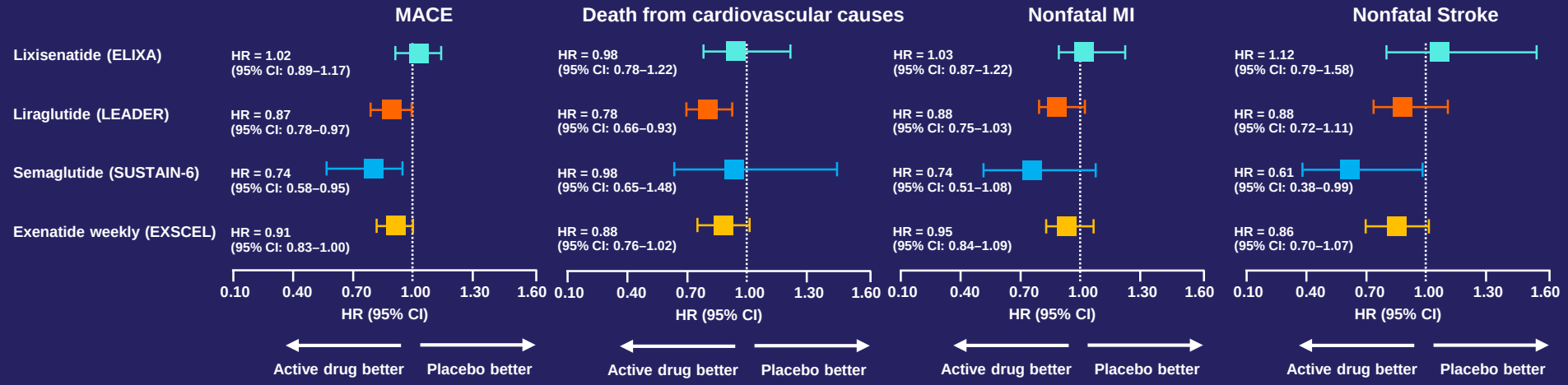
Sitagliptin added on to usual care was **NOT** associated with increased risk for:

- 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]

Risk Reduction in Four Completed Trials Showing CV Benefit

	Leader (10)	SUSTAIN-6 (11)	EMPA-REG Outcome (13,60)	CANVAS Program (14)
Subjects (n)	9,340	3,297	7,020	10,142
Mean age (years)	64.3	64.6	63.1	63.3
Diabetes duration (years)	12.8	13.9	57% >10	13.5
Mean baseline A1C (%)	8.7	8.7	8.1	8.2
Mean placebo-corrected A1C difference (%)	-0.4	-0.7 (0.5 mg dose) -1.0 1.0 mg dose)	-0.24 (10 mg dose) -0.36 (25 mg dose)	-0.58
Median follow-up duration (years)	3.8	2.1	3.1	2.4
3-point MACE RRR (%)	13	26	14	14
3-point MACE ARR (%)	1.9	2.3	1.6	—[†]
CV death RRR (%)	22	2	38	4[§]; 13[‖]
Nonfatal MI RRR (%)	12	26	13	15
Nonfatal stroke RRR (%)	11	39	+24	10
All-cause mortality RRR (%)	15	+5	32	13[§]; 10[‖]
HF hospitalization RRR (%)	13	+11	35	33
Worsening nephropathy RRR (%)	22	36	39	40

RRR, relative risk reduction.

Cefalu WT, et al. *Diabetes Care*. 2018;41:14-31.

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

Injectable Non-Insulin Agents Used to Treat Diabetes

Drug Class	Examples
GLP-1 Agonists (incretin mimetics)	Liraglutide, exenatide, exenatide ER, dulaglutide, albiglutide
Amylin Analogs	Pramlintide

Food and Drug Administration. https://www.fda.gov/forpatients/illness/diabetes/ucm408682.htm. Accessed October 11, 2017.

Insulin Therapy Used to Treat Diabetes[1]

Drug Class	Examples
Basal Insulin	Glargine (Lantus®, Basaglar®), degludec (Tresiba®), detemir (Levemir®), glargine U-300 (Toujeo®)
Rapid-acting Insulin Analogs	Aspart (NovoLog®), degludec + aspart (Ryzodeg®), lispro (Humalog®), glulisine (Apidra®), lispro U-200 (Humalog® U-200)
Premixed Insulin	70:30, 75:25, 50:50 (Humulin®, Novolin®)
Regular Insulin	U-500 (Humulin® R)
Inhaled Insulin	Afrezza®

Food and Drug Administration. https://www.fda.gov/forpatients/illness/diabetes/ucm408682.htm. Accessed October 11, 2017.

Insulin Delivery Devices Used to Treat Diabetes[1] (

Company	Examples
Medtronic[1-4]	MiniMed® 530G, 630G, 670G; Paradigm® Real-Time Revel™
Tandem[5,6]	t:slim X2™, t:flex®
Insulet[7]	Omnipod®
Accu-chek®[8]	Combo, Spirit

1. MiniMed 530G System. http://bit.ly/2Gl9sHN. Accessed February 16, 2018.
2. MiniMed 630G Insulin Pump System. http://bit.ly/2HjkKO1. Accessed February 16, 2018.
3. MiniMed 670G Insulin Pump System. http://bit.ly/2Ewt1MZ. Accessed February 16, 2018.
4. MiniMed Paradigm Real-Time Revel System. http://bit.ly/2sATyHd. Accessed February 16, 2018.
5. Tandem t:slim X2 Insulin Pump. http://bit.ly/2C4j9fF. Accessed February 16, 2018.
6. Tandem t:flex Insulin Pump. http://bit.ly/2EOdg7p. Accessed February 16, 2018.
7. Insulet Corporation. Omnipod Insulin Management System. http://bit.ly/2BAaQr9. Accessed February 16, 2018.
8. Accu-Chek. Insulin Pumps. http://bit.ly/2EIDpEH. Accessed February 16, 2018.

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

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.

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.

Case Evaluations

Case Evaluation: Patient Description

A 50-year-old woman is admitted to the intensive care unit with significant chest pain, dizziness, nausea, and vomiting. Based upon an electrocardiogram and cardiac enzyme test results, she is diagnosed as having a MI.

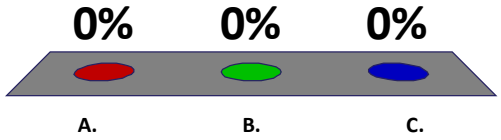
Case Evaluation: Discussion Question

At what point do you recommend testing the patient's blood glucose levels?

A. On admission

B. Once the patient has been stabilized

C. Throughout hospitalization every 24 to 48 hours



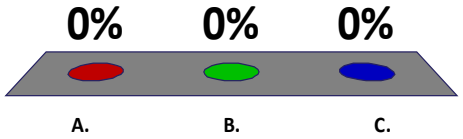
Case Evaluation: Discussion Question

The patient's glucose level is 205 mg/dl. Which of the following would you recommend?

A. Treat her hyperglycemia only if she has a history of diabetes

B. Manage the MI first, then treat her hyperglycemia

C. Treat her hyperglycemia aggressively along with the MI



Case Evaluation: Patient Description

A 68-year-old man is admitted to the hospital following an acute ischemic stroke. He is obese and has a 10-year history of CVD and T2DM. His current treatment regimen consists of dual combination therapy with a DPP-4 inhibitor and metformin. At the time of admission, his blood glucose level is 270 mg/dl.

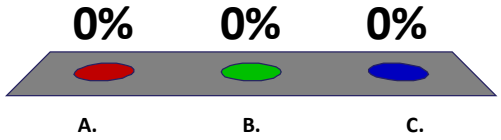
Case Evaluation: Discussion Question

Which of the following would you recommend to address the patient's hyperglycemia during his hospital stay?

A. Sliding-scale insulin therapy after discontinuation of the outpatient diabetes regimen

B. Subcutaneous insulin treatment with a basal-bolus regimen

C. Continuous intravenous insulin infusion



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

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

Questions and Answers

Thank You!