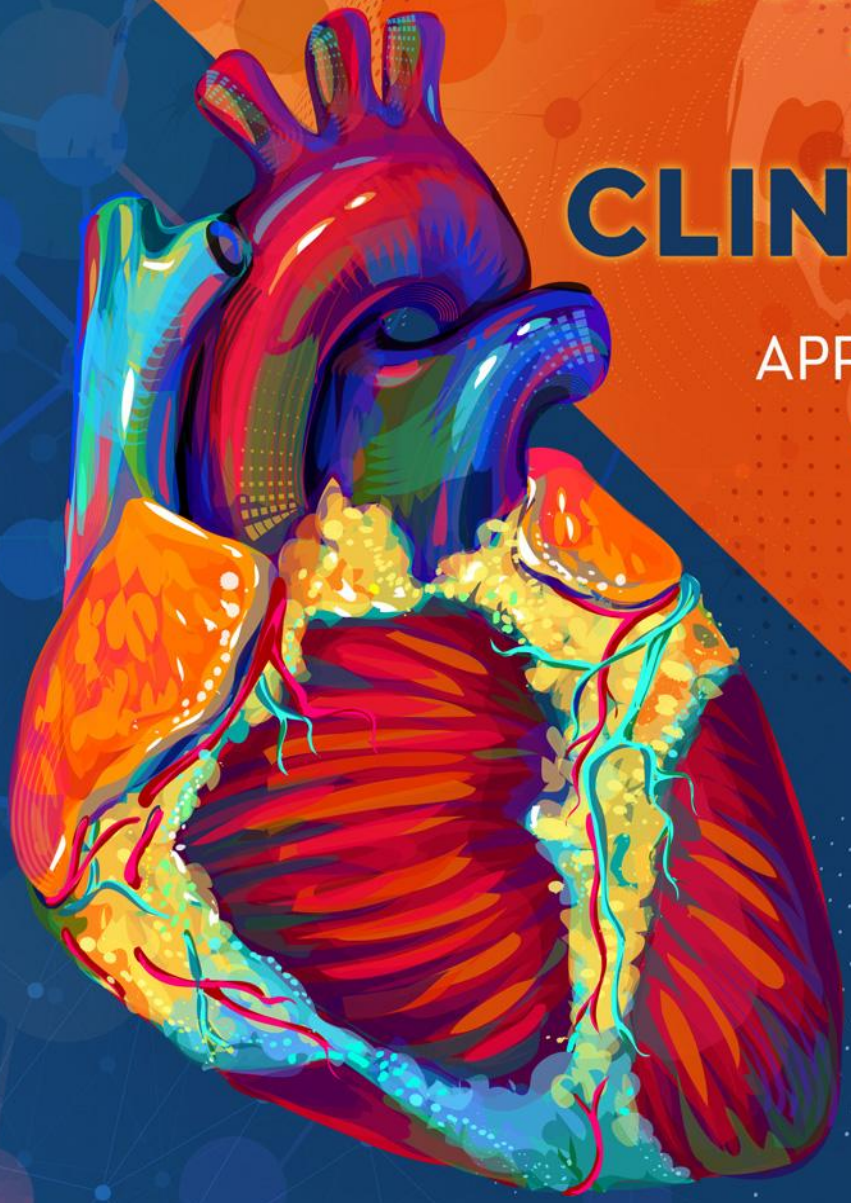

FROM CLINICAL TRIALS TO CLINICAL PRACTICE

APPLYING CARDIOVASCULAR OUTCOME TRIAL DATA TO REAL WORLD T2D MANAGEMENT

Presented by
Creative Educational Concepts, Inc.

Supported through an independent educational grant from AstraZeneca.

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Houston, Texas

Disclosures: None

Learning Objectives

1. Evaluate the interrelationship between diabetes, glycemic control, and cardiovascular disease events.
2. Examine evidence from cardiovascular outcome trials (CVOT) of glucose lowering therapies and elucidate the proposed pleiotropic CV effects of these therapies in patients with T2D.
3. Compare the data from real-world evidence studies of glucose lowering agents with the results of CVOTs, as well as potential implications for T2D management strategies in patients with and without established cardiovascular disease.
4. Explore opportunities for cardiologists, endocrinologists, primary care providers, and other members of the healthcare team to collaborate in order to improve T2D management and reduce CV risk.

Accreditation

- **Physicians:** 1.0 *AMA PRA Category 1 Credit(s)*™
- **Pharmacists:** 1.0 ACPE contact hour (.10 CEUs)
- **Nurses:** 1.0 contact hour
- **Physician Assistants:** 1.0 AAPA Category 1 CME credits

Faculty Information:

- You can find your faculty member's full bio and disclosure in your handout or online at www.ceconcepts.com/cvdmgr

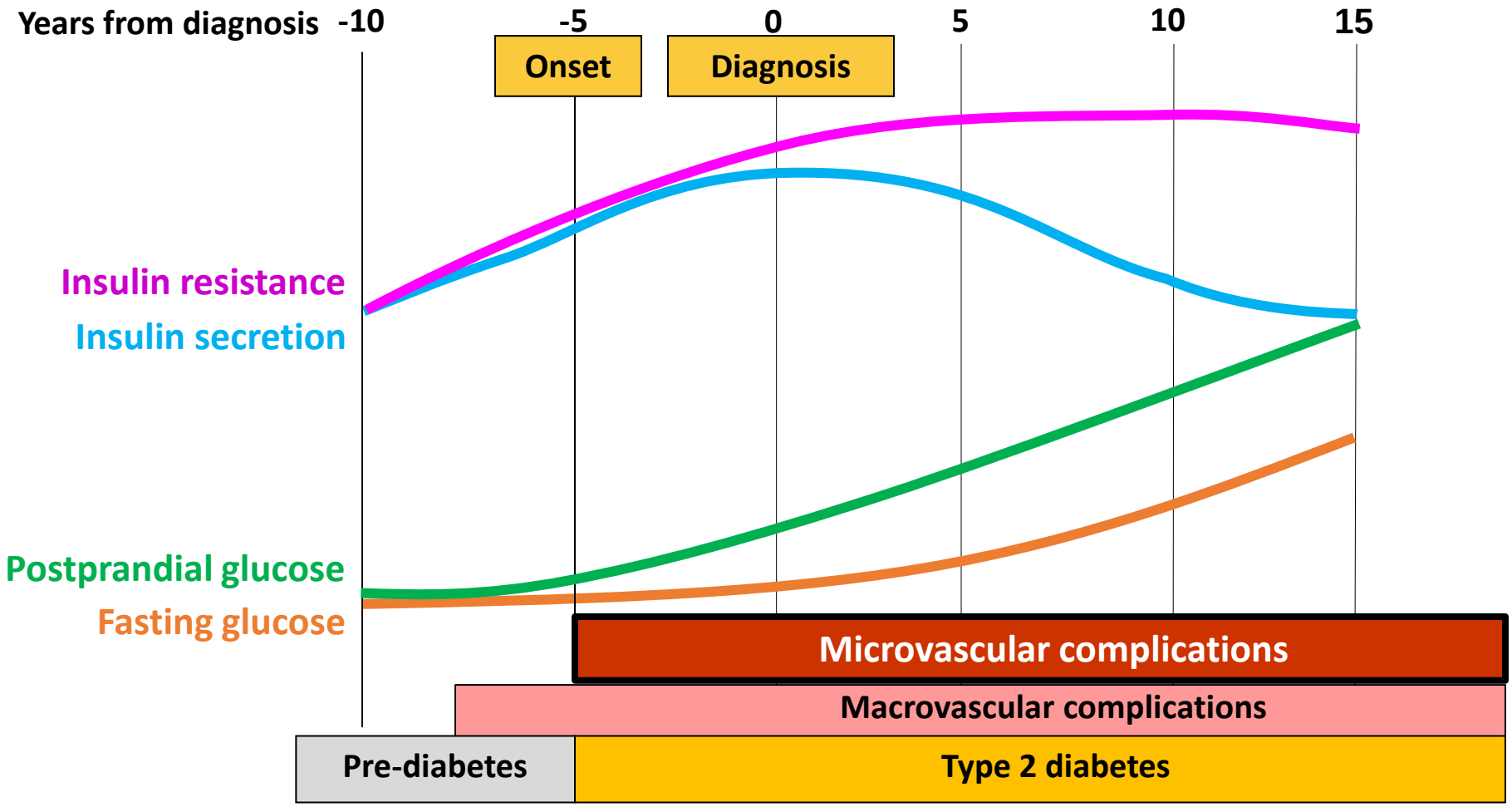
Presentation Slides and References:

- Available for download at www.ceconcepts.com/cvdmgr

Special Thanks!

- Supported through an independent educational grant from AstraZeneca
- Presented by Creative Educational Concepts, Inc. (CEC)

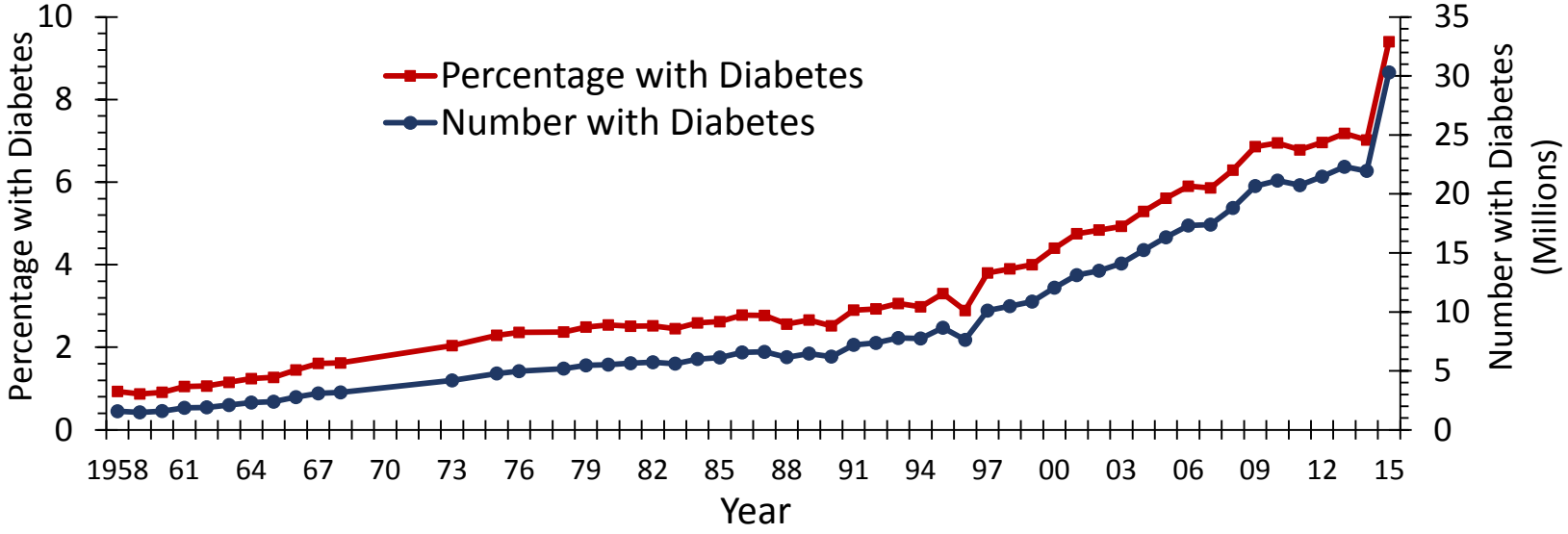
Natural History of Type 2 Diabetes



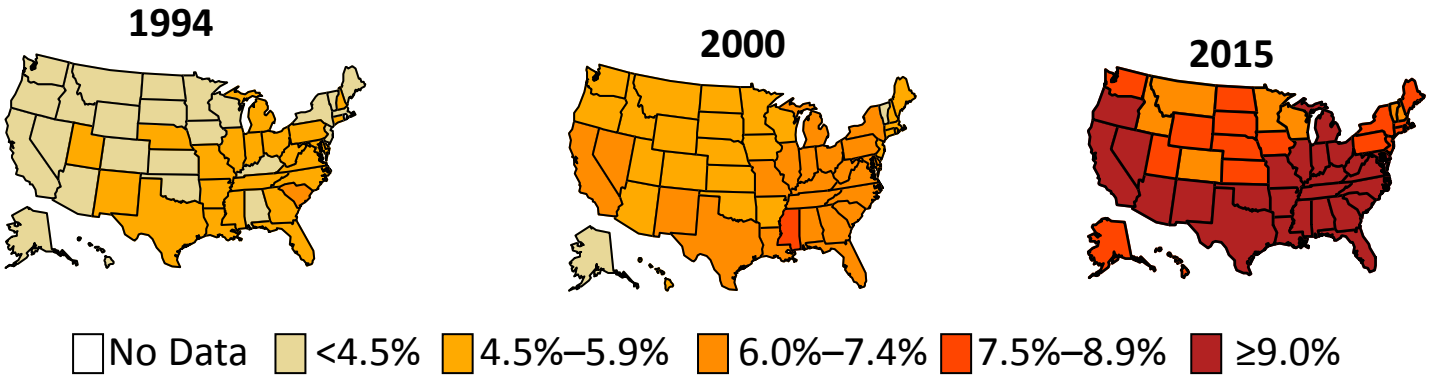
Adapted from Ramlo-Halsted BA, Edelman SV. *Prim Care.* 1999; Nathan DM. *N Engl J Med.* 2002.

Increasing Prevalence of T2D

Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958–2015

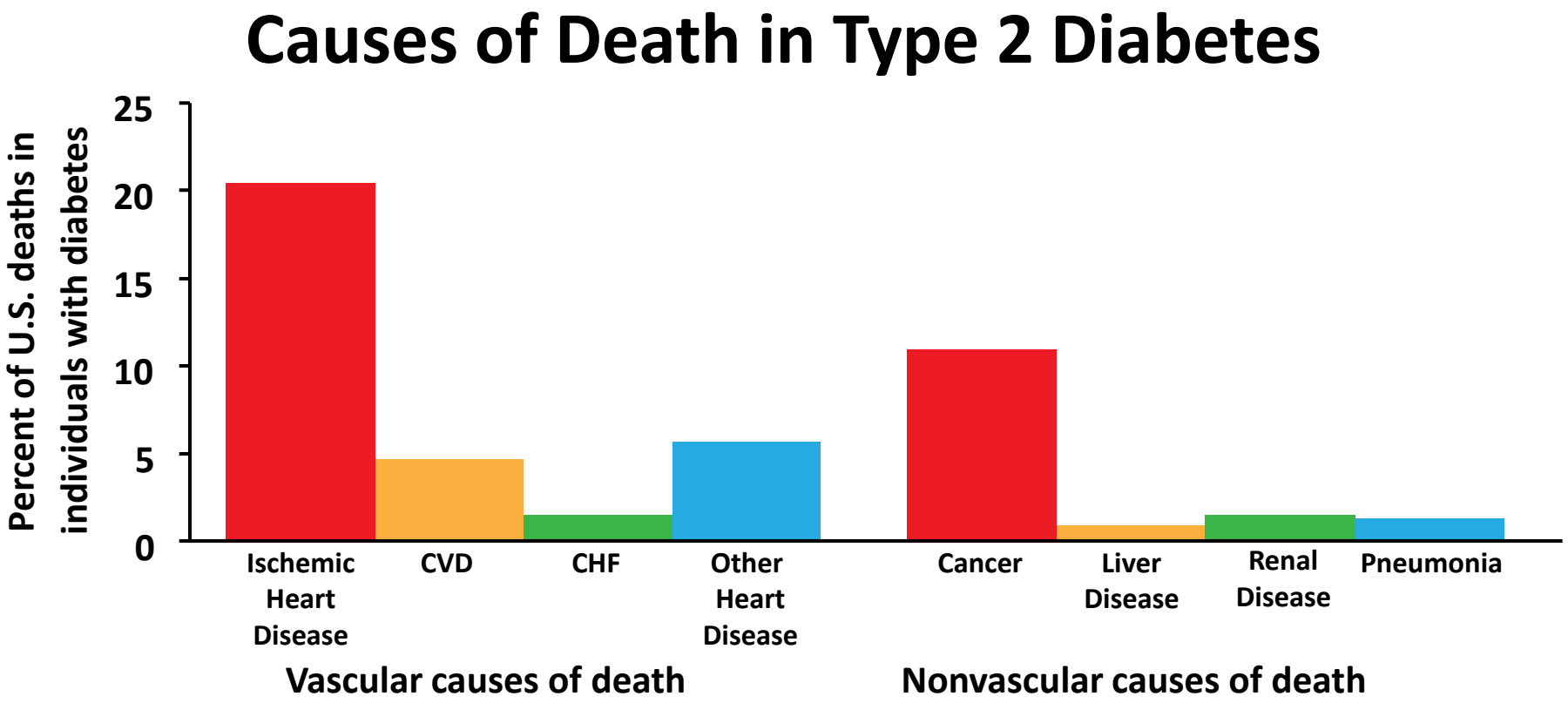


Age-adjusted Prevalence of Diagnosed Diabetes Among U.S. Adults



CDC's Division of Diabetes Translation. United States Diabetes Surveillance System. http://www.cdc.gov/diabetes/data. Accessed August 2018.

Diabetes and CV Risk



CHF, congestive heart failure; CVD, cardiovascular disease.

National Vital Statistics System 2008.

How do we address CV risk in patients with type 2 diabetes?

CV Risk Reduction

ADA Recommendations for CV risk reduction therapies:

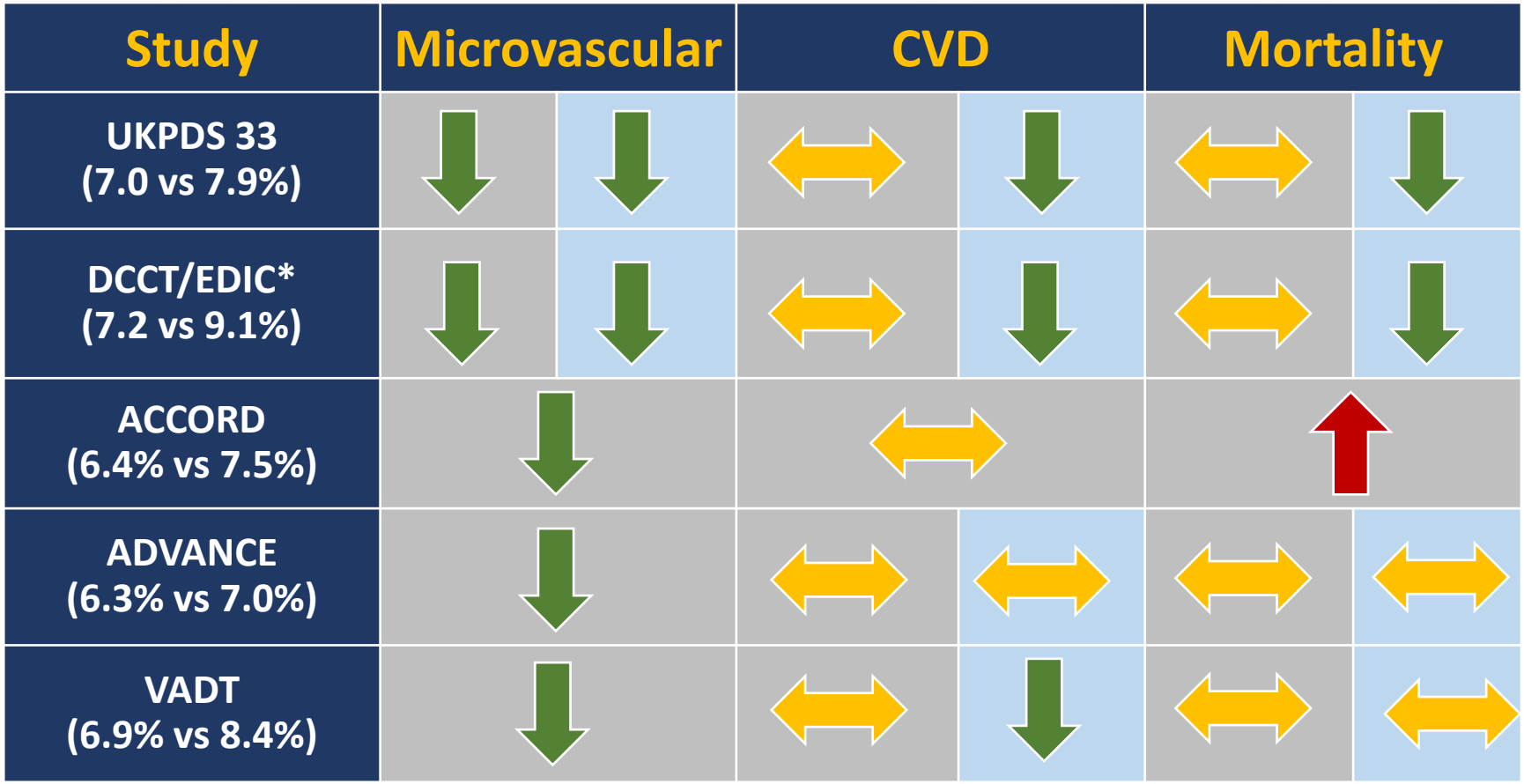
- Lifestyle modifications (weight loss, increase physical activity, etc.)
- Antiplatelet drugs
- BP management
- Lipid management
- Choice of antihyperglycemic agent
- Icosapent ethyl

ADA, American Diabetes Association.

American Diabetes Association. *Diabetes Care*. 2019.

Impact of Intensive Glucose-Lowering Therapy in Diabetes Mellitus

Summary of Major RCTs



*In T1DM.

F/U, follow-up;
RCT, randomized controlled trial.

Courtesy of Silvio Inzucchi MD, Yale University. Duckworth W, et al. *N Engl J Med.* 2009; Gerstein HC, et al. *N Engl J Med.*2008; Hayward RA, et al. *N Engl J Med.* 2015; Holman RR. *N Engl J Med.* 2008; Nathan DM, et al. *N Engl J Med.* 1993; Nathan DM, et al. *N Engl J Med.* 2005; Orchard TJ, et al. *JAMA.* 2015; Patel A, et al. *N Engl J Med.* 2008; UKPDS Group. *Lancet.* 1998; Zoungas S, et al. *N Engl J Med.* 2014.

Present FDA Regulatory Guidance on Drugs for Type 2 Diabetes

FDA News Release
December 17, 2008

FDA Announces New Recommendations on Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes

The U.S. Food and Drug Administration recommended today that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack. The recommendation is part of a new guidance for industry that applies to all diabetes drugs currently under development.

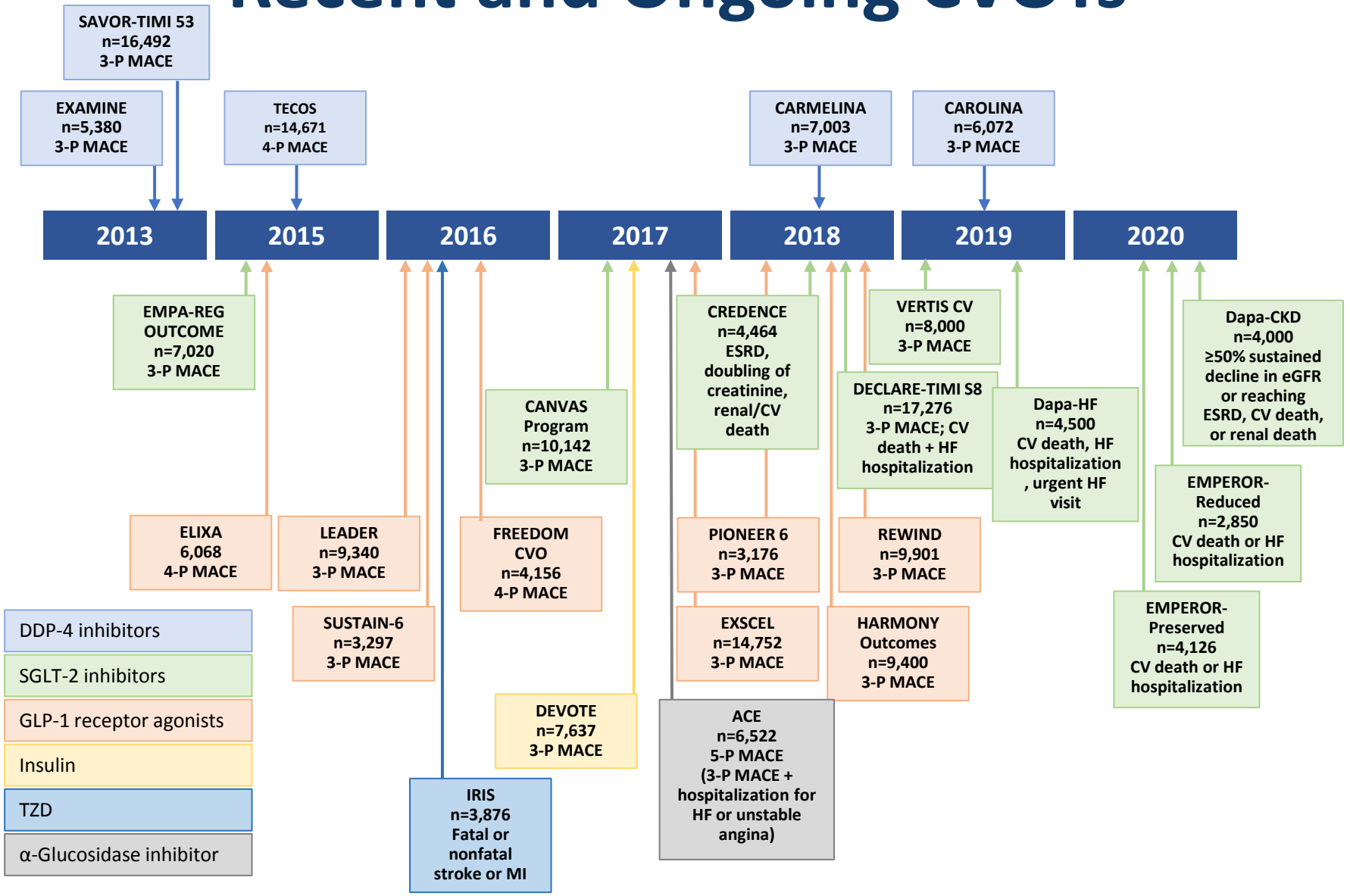
"We need to better understand the safety of new antidiabetic drugs. Therefore, companies should conduct a more thorough examination of their drugs' cardiovascular risks during the product's development stage," said Mary Parks, M.D., director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research (CDER), FDA. "FDA's guidance outlines the agency's recommendations for doing such an assessment."

"…sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk."

FDA, Food and Drug Administration.

FDA. News release. December 17, 2008. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116994.htm.

Recent and Ongoing CVOTs

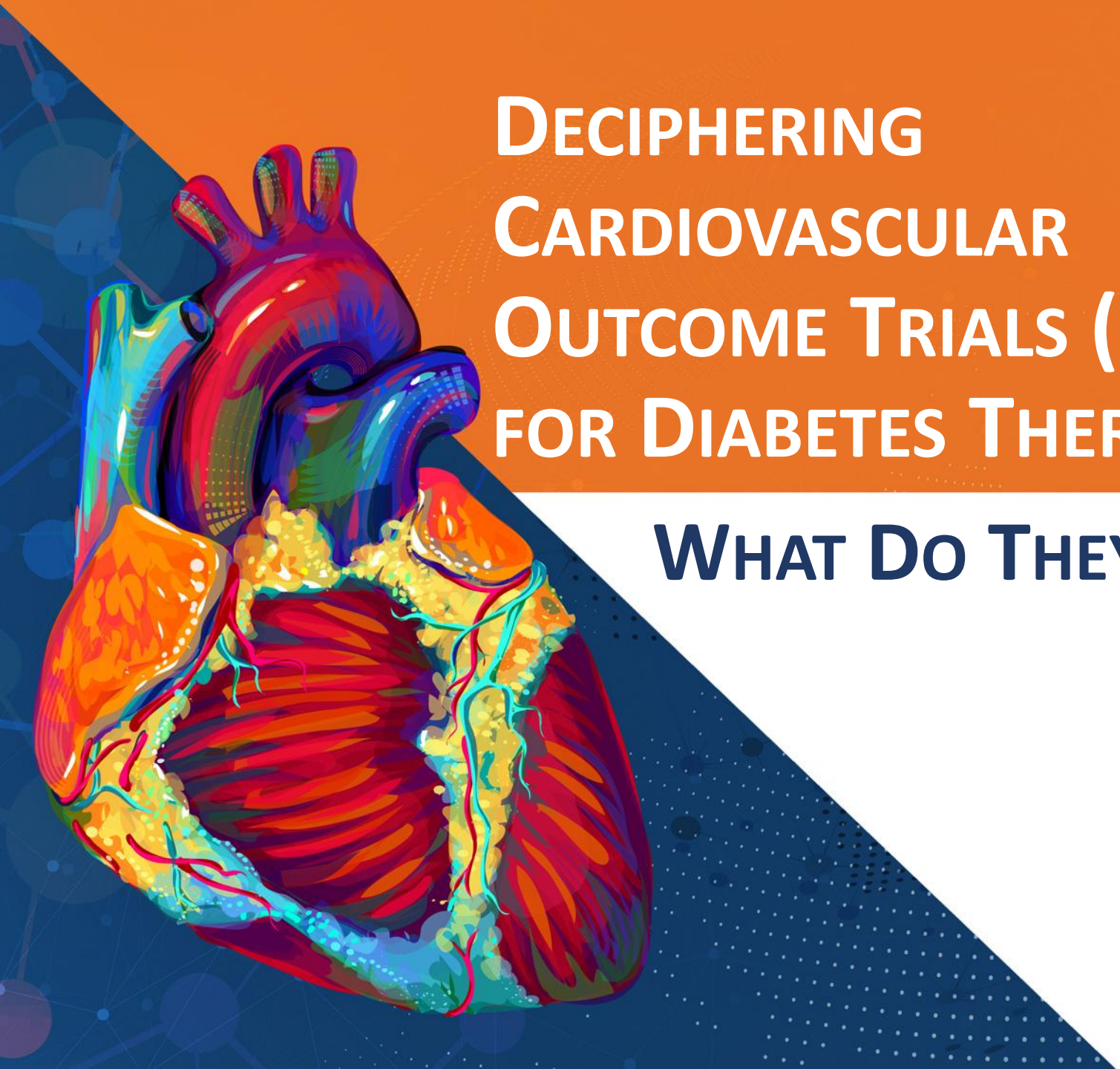


eGFR, estimated glomerular filtration rate;
ESRD, end-stage renal disease; HF, heart failure;
MACE, major adverse cardiovascular event; MI, myocardial infarction.

Cefalu WT, et al. *Diabetes Care.* 2018.

Conclusions

- Diabetes is common and increasing, with significant associated CV morbidity and mortality
- Intensive glucose control has not resulted in improved CV outcomes
- Evolution of regulatory guidance has dramatically altered the trial landscape of drug development for type 2 diabetes therapies to assess CV outcomes



Deciphering Cardiovascular Outcome Trials (CVOTs) for Diabetes Therapies

What Do They Mean?

Cardiovascular Outcomes Trials (CVOTs)

- **Noninferiority**
  - Primary designed to assess CV safety
  - No increased CV risk vs placebo as part of standard of care
- **Superiority**
  - CV benefit of treatment demonstrated by significant reduction in CV outcomes

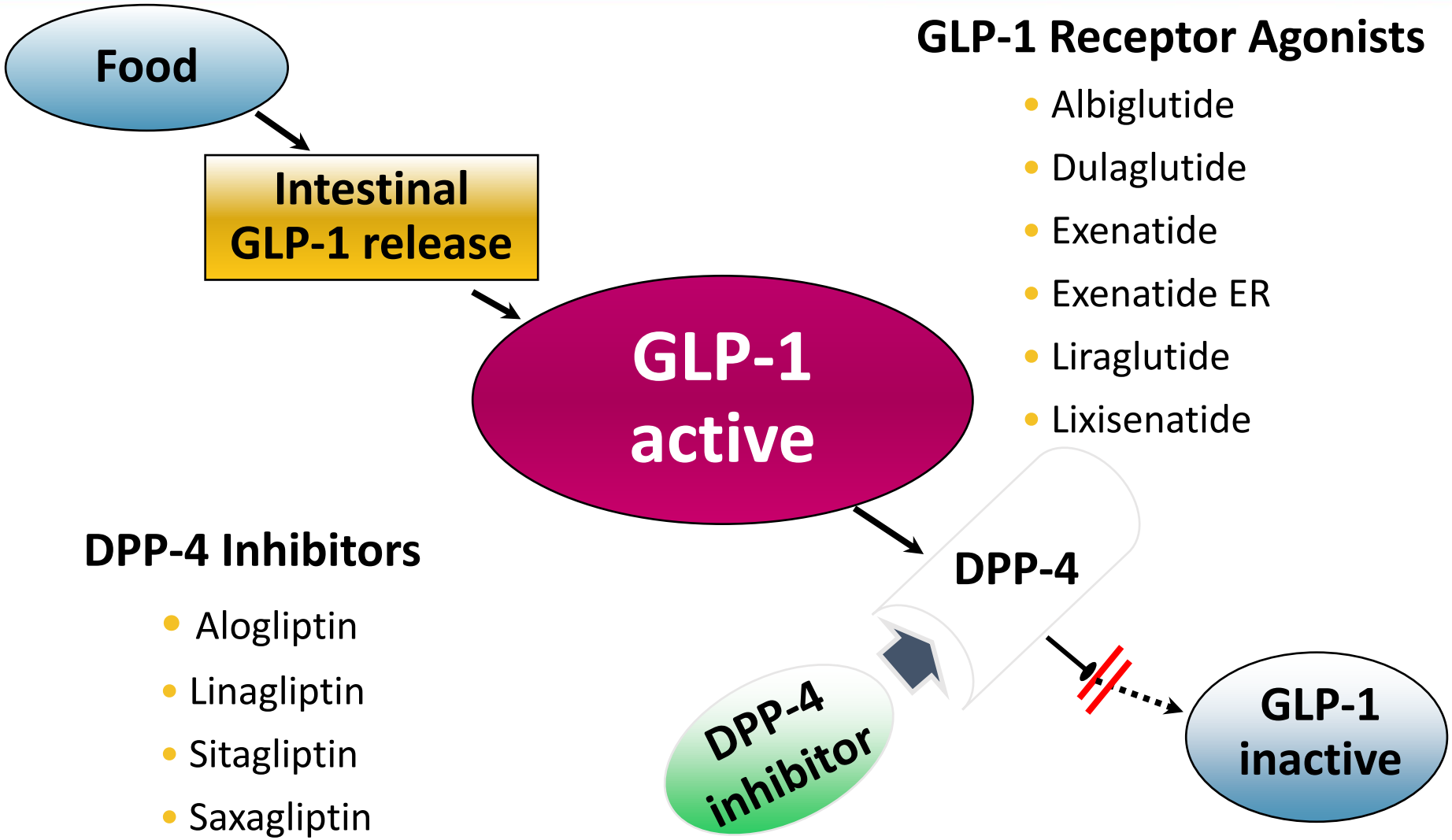
CVOTs

Since 2013, many CVOTs have been published on these newer classes of T2D agents:

- DPP-4 inhibitors
- GLP-1 RAs
- SGLT-2 inhibitors

T2D, type 2 diabetes.

Incretin Modulators



GLP-1 Receptor Agonists

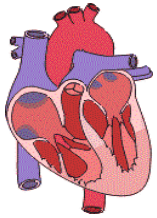
- Albiglutide
- Dulaglutide
- Exenatide
- Exenatide ER
- Liraglutide
- Lixisenatide

DPP-4 Inhibitors

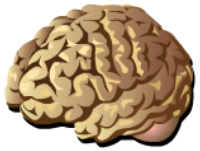
- Alogliptin
- Linagliptin
- Sitagliptin
- Saxagliptin

Rothenberg P, et al. *Diabetes.* 2000.
Drucker DJ, et al. *Expert Opin Invest Drugs.* 2003; Ahrén B. *Curr Diab Rep.* 2003.

Physiologic Actions of GLP-1

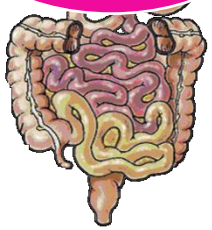


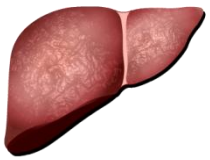
Heart
↑ Cardioprotection
↑ Cardiac output



Brain
↑ Neuroprotection
↓ Appetite

GLP-1

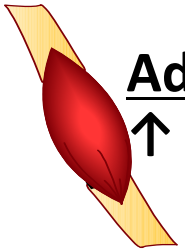




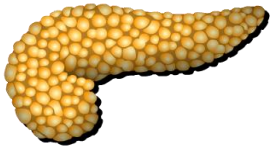
Liver
↓ Glucose production

Stomach
↓ Gastric emptying

↑ Insulin Sensitivity



Adipose tissue/Muscle
↑ Glucose disposal



Pancreas
↑ Insulin secretion
↓ Glucagon secretion
↑ Insulin biosynthesis
↑ β cell proliferation
↓ β cell apoptosis

Baggio LL, Drucker DJ. *Gastroenterology.* 2007.

DPP-4 Inhibitor CVOTs

DPP-4 Inhibitor CVOTs

Trial	Intervention v. placebo	N	Main Inclusion Criteria	Primary Endpoint	Median F/U, y	HR (95% CI)
SAVOR-TIMI 53	saxagliptin	16,492	CVD and/or multiple risk factors	3P-MACE	2.1	1.00 (0.89-1.12)
EXAMINE	alogliptin	5,380	ACS within 15 to 90 days	3P-MACE	1.5	0.96 (≤1.16)
TECOS	sitagliptin	14,671	CVD	3P-MACE + UA requiring hospitalization	3.0	0.98 (0.89-1.08)
CARMELINA	linagliptin	6,991	CVD + renal disease	3P-MACE	2.2	1.02 (0.89-1.17)

3P-MACE, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke;
ACS, acute coronary syndrome; UA, unstable angina.

Green JB, et al. *N Engl J Med*. 2015; Scirica BM, et al. *N Engl J Med*. 2013; White WB, et al. *N Engl J Med*. 2013; Rosenstock J, et al. JAMA 2019

DPP-4 Inhibitor CVOTs

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All were safe for composite endpoint (non-inferior to placebo)

3P-MACE, cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke;
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Green JB, et al. *N Engl J Med*. 2015; Scirica BM, et al. *N Engl J Med*. 2013; White WB, et al. *N Engl J Med*. 2013; Rosenstock J, et al. JAMA 2019

Hospitalization for Heart Failure
SAVOR-TIMI 53, EXAMINE, and TECOS

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	*P*-value
SAVOR-TIMI 53 (saxagliptin vs placebo)	**289/8,280 (3.5%)**	**228/8,212 (2.8%)**	**1.27**	**1.07, 1.51**	**0.007**
EXAMINE (alogliptin vs placebo)	**106/2,701 (3.9%)**	**89/2,679 (3.3%)**	**1.19**	**0.89, 1.59**	**0.235**
TECOS (sitagliptin vs placebo)	228/7,332 (3.1%)	229/7,339 (3.1%)	1.00	0.84, 1.20	1.000
SAVOR-TIMI 53 + EXAMINE + TECOS	623/18,313 (3.4%)	546/18,230 (3.0%)	1.14	0.97, 1.34	0.102
CARMELINA (linagliptin vs placebo)	209/3,494 (6.0%)	226/3,485 (6.5%)	0.90	0.74, 1.08	0.26

Green JB, et al. *N Engl J Med*. 2015; McGuire DK, et al. *JAMA Cardiol*. 2016; Scirica BM, et al. *N Engl J Med*. 2013; Zannad F, et al. *Lancet*. 2015; Rosenstock J, et al. JAMA 2019

Hospitalization for Heart Failure
SAVOR-TIMI 53, EXAMINE, and TECOS

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	*P*-value
SAVOR-TIMI 53 (saxagliptin vs placebo)					
EXAMINE (alogliptin vs placebo)					
TECOS (sitagliptin vs placebo)					
SAVOR-TIMI 53 + EXAM + TECOS					
CARMELINA (linagliptin vs placebo)					

FDA labeling changes to prescribing info for saxaglipitin, alogliptin

- Consider the risks and benefits prior to initiating treatment in patients at risk for heart failure.
- Monitor for heart failure signs/symptoms
- If occur, manage & consider discontinuation

More general changes to prescribing info for other DPP4 inhibitors

https://www.accessdata.fda.gov/scripts/cder/daf/

Green JB, et al. *N Engl J Med*. 2015; McGuire DK, et al. *JAMA Cardiol*. 2016; Scirica BM, et al. *N Engl J Med*. 2013; Zannad F, et al. *Lancet*. 2015; Rosenstock J, et al. JAMA 2019

Other DPP-4 Inhibitor CVOT

CAROLINA (linagliptin vs glimepiride)

- High CV risk or established CVD
- N=6,033
- Duration >6 years, completion Q1 2019
- Primary endpoint = 3P-MACE
- Unpublished data: non-inferior to glimepiride

www.clinicaltrials.gov; https://www.boehringer-ingelheim.us.

DPP-4 Inhibitor CVOTs Results to Date

- Saxagliptin, alogliptin, sitagliptin, linagliptin confer neither benefit nor harm for the composite outcome of cardiovascular death, MI, or stroke
- Saxagliptin and alogliptin - may increase risk of heart failure
- Sitagliptin, linagliptin – no change in risk of heart failure

Green JB, et al. *N Engl J Med*. 2015;
Scirica BM, et al. *N Engl J Med*. 2013; White WB, et al. *N Engl J Med*. 2013.

GLP-1RA CVOTs

Summary of CVOTs with GLP-1RAs

	Intervention v. placebo	N	CVD at baseline (%)	Primary Outcome	Median F/U (years)
ELIXA[1]	lixisenatide	6,068	100	4P-MACE	2.1
LEADER[2]	liraglutide	9,340	72	3P-MACE	3.8
SUSTAIN-6[3]	semaglutide	3,297	72	3P-MACE	2.1
EXSCEL[4]	exenatide ER	14,752	73	3P-MACE	3.2
HARMONY OUTCOMES[5]	albiglutide	9,463	100	3P-MACE	1.6

ER, extended release; CVD, cardiovascular disease; HHF, hospitalization for heart failure.

[1]Pfeffer MA, et al. *N Engl J Med.* 2015; [2]Marso SP, et al. *N Engl J Med*. 2016; [3]Marso SP, et al. *N Engl J Med*. 2016; [4]Holman RR, et al. *N Engl J Med*. 2017; [5]Hernandez AF, et al. *Lancet*. 2018.

Summary of CVOTs with GLP-1RAs

	Intervention v. placebo	N	CVD at baseline (%)	Primary Outcome	Median F/U (years)
ELIXA[1]	lixisenatide				
LEADER[2]	liraglutide				
SUSTAIN-6[3]	semaglutide				
EXSCEL[4]	exenatide ER				
HARMONY OUTCOMES[5]	albiglutide				

All were safe for composite endpoint (non-inferior to placebo)

ER, extended release; CVD, cardiovascular disease; HHF, hospitalization for heart failure.

[1]Pfeffer MA, et al. *N Engl J Med.* 2015; [2]Marso SP, et al. *N Engl J Med*. 2016; [3]Marso SP, et al. *N Engl J Med*. 2016; [4]Holman RR, et al. *N Engl J Med*. 2017; [5]Hernandez AF, et al. *Lancet*. 2018.

CVOTs with GLP-1RAs
Primary Endpoint & Individual Components

	Primary Composite MACE	CV mortality	All-cause mortality	HF hospitalizations
ELIXA[1]	1.02 (0.89-1.17) p=0.81	0.98 (0.78-1.22) p=0.85	0.94 (0.78-1.13) p =0.50	0.96 (0.75-1.23) p=0.75
LEADER[2]	0.87 (0.78-0.97) p=0.01	0.78 (0.66-0.93) p=0.007	0.85 (0.74-0.97) p=0.02	0.87 (0.73-1.05) P=0.14
SUSTAIN-6[3]	0.74 (0.58-0.95) P=0.02	0.98 (0.65-1.48) p=0.92	1.05 (0.74-1.50) p=0.79	1.11 (0.77-1.61) p=0.57
EXSCEL[4]	0.91 (0.83-1.00) p=0.06	0.88 (0.76-1.02) p=0.096	0.86 (0.77-0.97) p=0.016†	0.94 (0.78-1.13) p=0.94
HARMONY OUTCOMES[5]	0.78 (0.68-0.90) p=0.0006	0.93 (0.73-1.19) p = 0.58	.95 (0.79-1.16) p=0.64	Not reported

Hazard ration (95% CI). HARMONY OUTCOMES: fatal+nonfatal myocardial infarction 0.75 (0.61-0.90), p=0.003

ER, extended release; CVD, cardiovascular disease; HHF, hospitalization for heart failure.

†*Was not regarded as significant on the basis of the hierarchical statistical testing study design*

[1]Pfeffer MA, et al. *N Engl J Med.* 2015; [2]Marso SP, et al. *N Engl J Med*. 2016; [3]Marso SP, et al. *N Engl J Med*. 2016; [4]Holman RR, et al. *N Engl J Med*. 2017; [5]Hernandez AF, et al. *Lancet*. 2018.

CVOTs with GLP-1RAs Primary Endpoint & Individual Components

ELIXA[1]
LEADER[2]
SUSTAIN-6[3]
EXSCEL[4]
HARMONY OUTCOMES[5]

FDA labeling changes to prescribing info for liraglutide

- Added indication – reduce risk of major CV events in adults with T2D & established CVD

https://www.accessdata.fda.gov/scripts/cder/daf/

Hazard ration (95% CI
ER, extended release; CVD, cardiovascular disease; HHF, hospitalization for heart failure.
†*Was not regarded as significant on the basis of the hierarchical statistical testing study design*

[1]Pfeffer MA, et al. *N Engl J Med.* 2015; [2]Marso SP, et al. *N Engl J Med*. 2016; [3]Marso SP, et al. *N Engl J Med*. 2016; [4]Holman RR, et al. *N Engl J Med*. 2017; [5]Hernandez AF, et al. *Lancet*. 2018.

Potential Reasons for Heterogeneity in GLP-1RA Trial Results

- Patient populations
- Duration of follow up
- Peculiarities of trial design
- Potency and duration of GLP-1 RA antagonism
- Chemical structure of the molecules

Ongoing CVOTs of GLP-1RAs

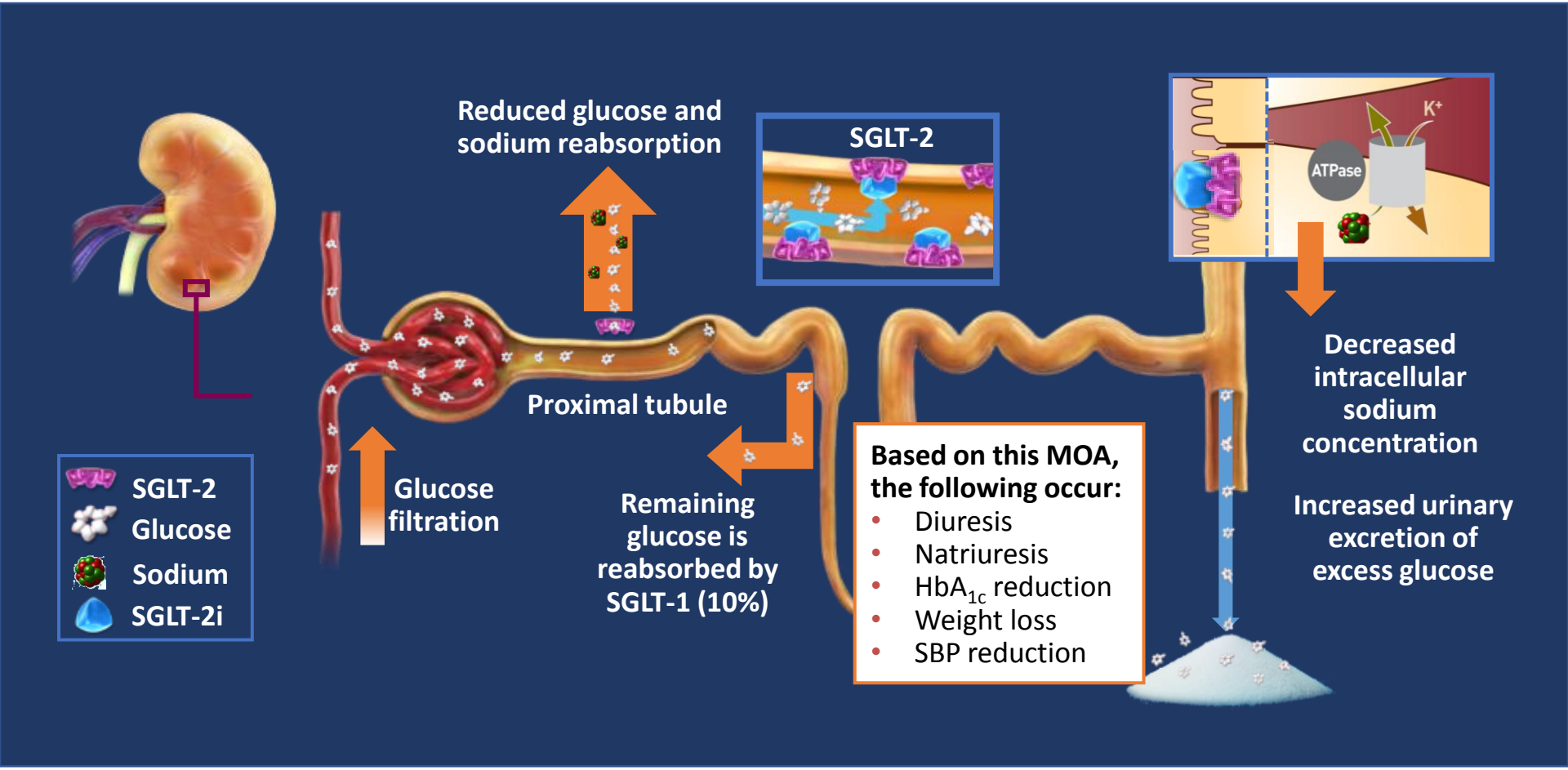
REWIND (dulaglutide)

- Unpublished data
  - N = 9,901
  - 31% with CVD
  - Follow-up: 5 years (median)
  - Preliminary report – superiority for 3-point MACE
- Full results will be reported at ADA Scientific Sessions 2019

https://www.healio.com/endocrinology/diabetes/news/online/%7B6a15d82b-f25b-4e5f-b14b-857ddc955fd8%7D/rewind-dulaglutide-reduces-cv-risk-in-type-2-diabetes-without-cvd

SGLT2 Inhibitor CVOTs

SGLT2 Inhibitors Block SGLT2 and Reduce Glucose and Na^+ Reabsorption



ATPase, adenosine triphosphatase; SBP, systolic blood pressure.

Butler J, et al. *Euro J Heart Fail*. 2017;
Marsenic O. *Am J Kidney Dis*. 2009;
Mudaliar S, et al. *Diabetes Care*. 2016.

Summary of CVOTs with SGLT2 Inhibitors

	Intervention v. placebo	N	CVD at baseline (%)	Primary Outcome	Median F/U (years)
EMPA-REG OUTCOME	empagliflozin	7,020	>99%	3P-MACE	3.1
CANVAS PROGRAM	canagliflozin	10,142	66%	3P-MACE	2.4
DECLARE-TIMI 58	dapagliflozin	17,160	41%	3P-MACE	4.2

Neal B, et al. *N Engl J Med*. 2017; Zinman B, et al. *N Engl J Med*. 2015; Langkilde AM, et al. *N Engl J Med*. 2018.

Summary of CVOTs with SGLT2 Inhibitors

	Intervention v. placebo	N	CVD at baseline (%)	Primary Outcome	Median F/U (years)
EMPA-REG OUTCOME	empagliflozin	All were safe for composite endpoint (non-inferior to placebo)			
CANVAS PROGRAM	canagliflozin				
DECLARE-TIMI 58	dapagliflozin				

Neal B, et al. *N Engl J Med*. 2017; Zinman B, et al. *N Engl J Med*. 2015; Langkilde AM, et al. *N Engl J Med*. 2018.

Summary of CVOTs with SGLT2 Inhibitors
Primary Endpoint & Individual Components

	Primary Composite MACE	CV Mortality	All-cause Mortality	HF Hospitalizations
EMPA-REG OUTCOME	***P*=0.04 for superiority**	**0.62 (0.49-0.77) *p*<0.001**	**0.68 (0.57-0.82) *p*<0.001**	**0.65 (0.50-0.85) *p*=0.0017**
CANVAS PROGRAM	***P*=0.02 for superiority**	0.87 (0.72-1.06)	0.87 (0.74–1.01) *p*=.24	**0.67 (0.52–0.87)**
DECLARE-TIMI 58	p=0.17 for superiority	0.98 (0.82-1.17)	0.93 (0.82-1.04)	**0.73 (0.61-0.88)**

DECLARE-TIMI 58 additional primary efficacy outcome:CV death or HF hospitalization 0.83 (0.73-0.95), p=0.005

Neal B, et al. *N Engl J Med*. 2017; Zinman B, et al. *N Engl J Med*. 2015; Langkilde AM, et al. *N Engl J Med*. 2018.

Summary of CVOTs with SGLT2 Inhibitors
Primary Endpoint & Individual Components

EMPA-REG OUTCOME

CANVAS PROGR

DECLARE-TIMI

FDA labeling changes to prescribing info for

<u>empagliflozin</u>

- Added indication – reduce risk of CV death in adults with T2D & established CVD

<u>canagliflozin</u>

- Added indication – reduce risk of major CV events in adults with T2D & established CVD

<u>dapagliflozin</u>

- Changed labeling – no dosing adjustment needed with eGFR <u>≥</u>45 mL/min/1.73 m^2

https://www.accessdata.fda.gov/scripts/cder/daf/

DECLARE-TIMI 58 additional primary efficacy outcome:CV death or HF hospitalization 0.83 (0.73-0.95), p=0.005

Neal B, et al. *N Engl J Med*. 2017; Zinman B, et al. *N Engl J Med*. 2015; Langkilde AM, et al. *N Engl J Med*. 2018.

EMPA-REG OUTCOME
Adverse Events

	Placebo (N=2,333)		Empagliflozin 10 mg (N=2,345)		Empagliflozin 25 mg (N=2,342)	
	N (%)	Rate	N (%)	Rate	N (%)	Rate
Events consistent with UTI	423 (18.1%)	8.21	426 (18.2%)	8.02	416 (17.8%)	7.75
Male	158 (9.4%)	3.96	180 (10.9%)	4.49	170 (10.1%)	4.09
Female	265 (40.6%)	22.81	246 (35.5%)	18.83	246 (37.3%)	20.38
Events consistent with genital infection	42 (1.8%)	0.73	**153 (6.5%)**	**2.66**	**148 (6.3%)**	**2.55**
Male	25 (1.5%)	0.60	89 (5.4%)	2.16	77 (4.6%)	1.78
Female	17 (2.6%)	1.09	64 (9.2%)	3.93	71 (10.8%)	4.81
Events consistent with volume depletion	115 (4.9%)	2.04	115 (4.9%)	1.97	124 (5.3%)	2.11
Diabetic ketoacidosis	1 (<0.1%)	0.02	3 (0.1%)	0.05	1(<0.1%)	0.02
Acute renal failure	155 (6.6%)	2.77	121(5.2%)	2.07	125 (5.3%)	2.12
Bone fractures	91(3.9%)	1.61	92(3.9%)	1.57	87(3.7%)	1.46
Lower-limb amputation	43 (1.8%)	0.65	88 (1.9%)*			0.65

Participants treated with ≥1 dose of study drug
Rate=per 100 patient-years
*Empagliflozin pooled

UTI, urinary tract infection.

Inzucchi SE, et al. *Diabetes Care.* 2017; Zinman B, et al. *N Engl J Med*. 2015.

CANVAS
Adverse Events

Event	Placebo (N=4,347)	Canagliflozin (N=5,795)	*P*[†]
	Event rate per 1,000 patient years		
Mycotic genital infection in women	17.5	**68.8**	**<0.001**
Infection of male genitalia[‡]	10.8	**34.9**	**<0.001**
Urinary tract infection	37.0	40.0	0.38
Osmotic diuresis	13.3	**34.5**	**<0.001**
Volume depletion	18.5	**26.0**	**0.009**
Acute kidney injury	4.1	3.0	0.33
Hyperkalemia	4.4	6.9	0.10
Amputation	3.4	**6.3**	**<0.001**
Fracture (adjudicated)[§]			
All	11.9	**15.4**	**0.02**
Low-trauma	9.2	11.6	0.06
Diabetic ketoacidosis (adjudicated)	0.3	0.6	0.14

[†] *P* values were estimated from Cox regression models.
[‡] Infection of male genitalia included balanitis, phimosis, and events leading to circumcision.
[§] Low-trauma fracture was the prespecified primary fracture outcome, and all fracture was a secondary outcome.

Neal B, et al. *N Engl J Med*. 2017.

DECLARE-TIMI 58
Adverse Events

	Placebo (N=8,569)	Dapagliflozin (N=8,574)		
	N (%)	N (%)	HR (95% CI)	p-value
UTI	133 (1.6)	127 (1.5)	0.93 (0.73–1.18)	0.54
Genital infection	9 (0.1)	**76 (0.9)**	**8.36 (4.19–16.68)**	**<0.001**
Symptoms consistent with volume depletion	207 (2.4)	213 (2.5)	1.00 (0.83–1.21)	0.99
Diabetic ketoacidosis	12 (0.1)	**27 (0.3)**	**2.18 (1.10–4.30)**	**0.02**
Acute kidney injury	**175 (2.0)**	125 (1.5)	**0.69 (0.55–0.87)**	**0.002**
Bone fractures	440 (5.1)	457 (5.3)	1.04 (0.91–1.18)	0.59
Amputation	113 (1.3)	123 (1.4)	1.09 (0.84–1.40)	0.53
Major hypoglycemic event	83 (1.0)	58 (0.7)	0.68 (0.49-0.95)	0.02
Bladder cancer	45 (0.5)	26 (0.3)	0.57 (0.35–0.93)	0.02

HR, hazard ratio; UTI, urinary tract infection.

Langkilde AM, et al. *N Engl J Med*. 2018.

Ongoing CVOT SGLT-2 Inhibitors

VERTIS-CV

- Ertugliflozin vs placebo
- Established CVD (2^0 prevention)
- N=8,237
- Results anticipated late 2019
- Primary endpoint: 3P-MACE

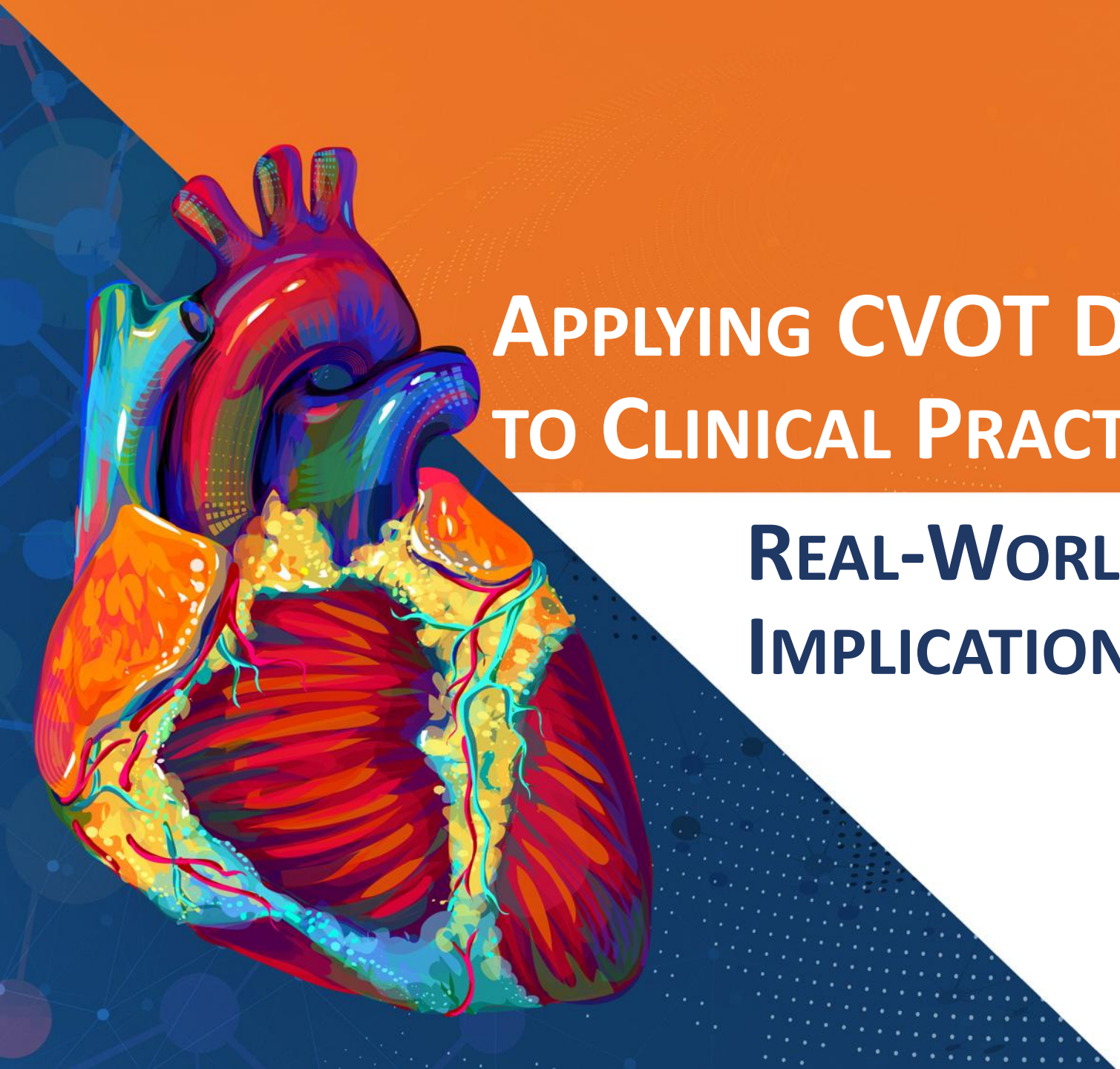
AHA, American Heart Association.

www.clinicaltrials.gov

Meta-Analysis of GLP-1RA & SGLT2i CVOTs

- Included
  - ELIXA, LEADER, SUSTAIN-6, EXCEL (N=42,9290)
  - EMPA-REG, CANVAS PROGRAM, DECLARE-TIMI 58 (N=34,322)
- **3-point MACE:**
  - **GLP-1RA -** HR 0.88 (95% CI 0.84–0.94, p=0.001)
  - **SGLT2i -** HR 0.89 (95% CI 0.83–0.96, p=0.001)
  - Benefit only in patients with ASCVD, HR 0.86; 95% CI, 0.80–0.93, p=0.002)
- **HF hospitalization:**
  - **SGLT2i -** HR 0.69 (95% CI, 0.61–0.79; p< 0.001
- **Progression of renal disease:**
  - **GLP-1RA -** HR 0.82 (95% CI 0.75–0.89; p < 0.001)
  - **SGLT2i -** HR 0.62 (95% CI 0.58–0.67; p < 0.001)
    - Reduced risk of worsening eGFR, end-stage kidney disease, renal death (HR 0.55 (95% CI 0.48-0.64, p<0.001)

Zelniker, et al. *Lancet.*2019



Applying CVOT Data to Clinical Practice

Real-World Implications

How Does Data from Randomized Clinical Trials Compare with Real-World Clinical Practice?

The CVD-REAL Studies

(Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)

CVD-REAL Study (US and Europe)
Inclusion/Exclusion Criteria

Inclusion Criteria

- New users receiving SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) or other glucose-lowering drugs
  - Established T2DM on or prior to the index date
  - ≥18 years old
  - >1 year* historical data available prior to the index date

Exclusion Criteria

- Patients with type 1 diabetes
- Patients with gestational diabetes

*In Germany, >6 months

Kosiborod M, et al. *Circulation*. 2017.

CVD-REAL Study

Baseline Characteristics—Full Propensity Matched Cohort

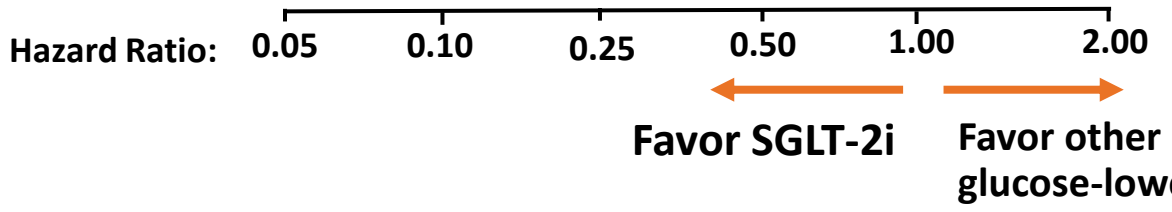
	SGLT-2 Inhibitor (N=154,528)	Other Glucose-lowering Drug (N=154,528)
Age (years), mean (SD)	56.9 (10.0)	57.0 (10.6)
Women	68,420 (44.3)	68,772 (44.5)
Established cardiovascular disease†	20,044 (13.0)	20,302 (13.1)
Acute myocardial infarction	3,793 (2.5)	3,882 (2.5)
Unstable angina	2,529 (1.6)	2,568 (1.7)
Heart failure	4,714 (3.1)	4,759 (3.1)
Atrial fibrillation	5,632 (3.6)	5,698 (3.7)
Stroke	6,337 (4.1)	6,394 (4.1)
Peripheral arterial disease	5,239 (3.4)	5,229 (3.4)
Frailty (yes)‡	11,982 (7.8)	12,731 (8.2)
Microvascular disease	42,217 (27.3)	42,215 (27.3)
Chronic kidney disease	3,920 (2.5)	4,171 (2.7)

Data are n (%) unless otherwise stated.
†Myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization or occlusive peripheral artery disease.
‡in UK CPRD/THIN, frailty defined as ≥1 hospitalization within 1 year prior to or on index date.
In other databases defined as ≥1 hospital stay of ≥3 days within 1 year prior to the index date.

Kosiborod M, et al. *Circulation*. 2017.

Hospitalization for Heart Failure
CVD-REAL Primary Analysis

Database	N	# of Events	HR (95% CI)
United States	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2,900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)



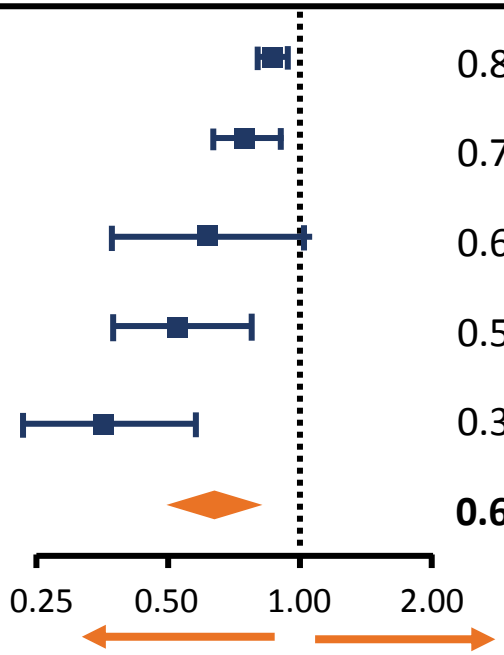
***P*-value for SGLT-2 inhibitor vs other glucose-lowering drug <.001**

Heterogeneity *P*-value=.169

Kosiborod M, et al. *Circulation*. 2017.

Hospitalization for Heart Failure
CVD-REAL 2

Database	N	Events, n	HR (95% CI)
Korea	336,644	5149	0.87 (0.82-0.92)
Japan	67,780	565	0.75 (0.63-0.89)
Singapore	2726	67	0.62 (0.38-1.02)
Israel	19,472	128	0.53 (0.37-0.75)
Canada	16,064	88	0.36 (0.24-0.56)
Total			**0.64 (0.50-0.82)**



***P*-value for SGLT-2i vs other glucose-lowering drugs: *P*=.001**

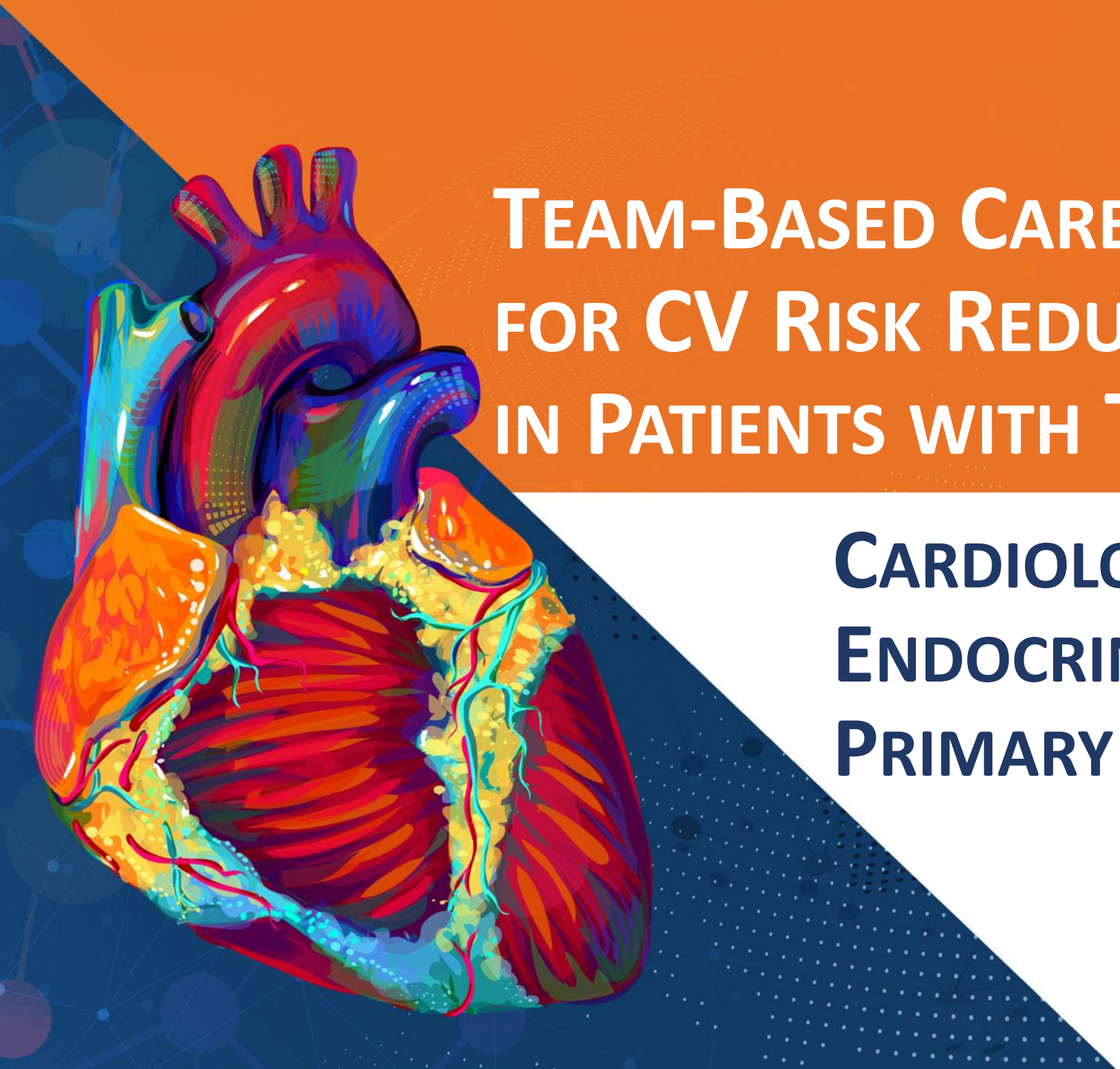
Heterogeneity *P*-value: *P*<.001

Kosiborod, et al. *J Am Coll Cardiol*.2018.

Clinical Implications of CVD-REAL Studies

- No significant heterogeneity across countries, despite geographic variations in use of SGLT-2i
  - The observed cardiovascular benefits are likely class related
- Broad population of patients with type 2 diabetes in general practice, the overwhelming majority (87%) of whom did not have known cardiovascular disease
  - Benefits may extend to those at the lower end of the risk spectrum

Kosiborod M, et al. *Circulation*. 2017;
Kosiborod M, et al. *J Am Coll Cardiol*. 2018



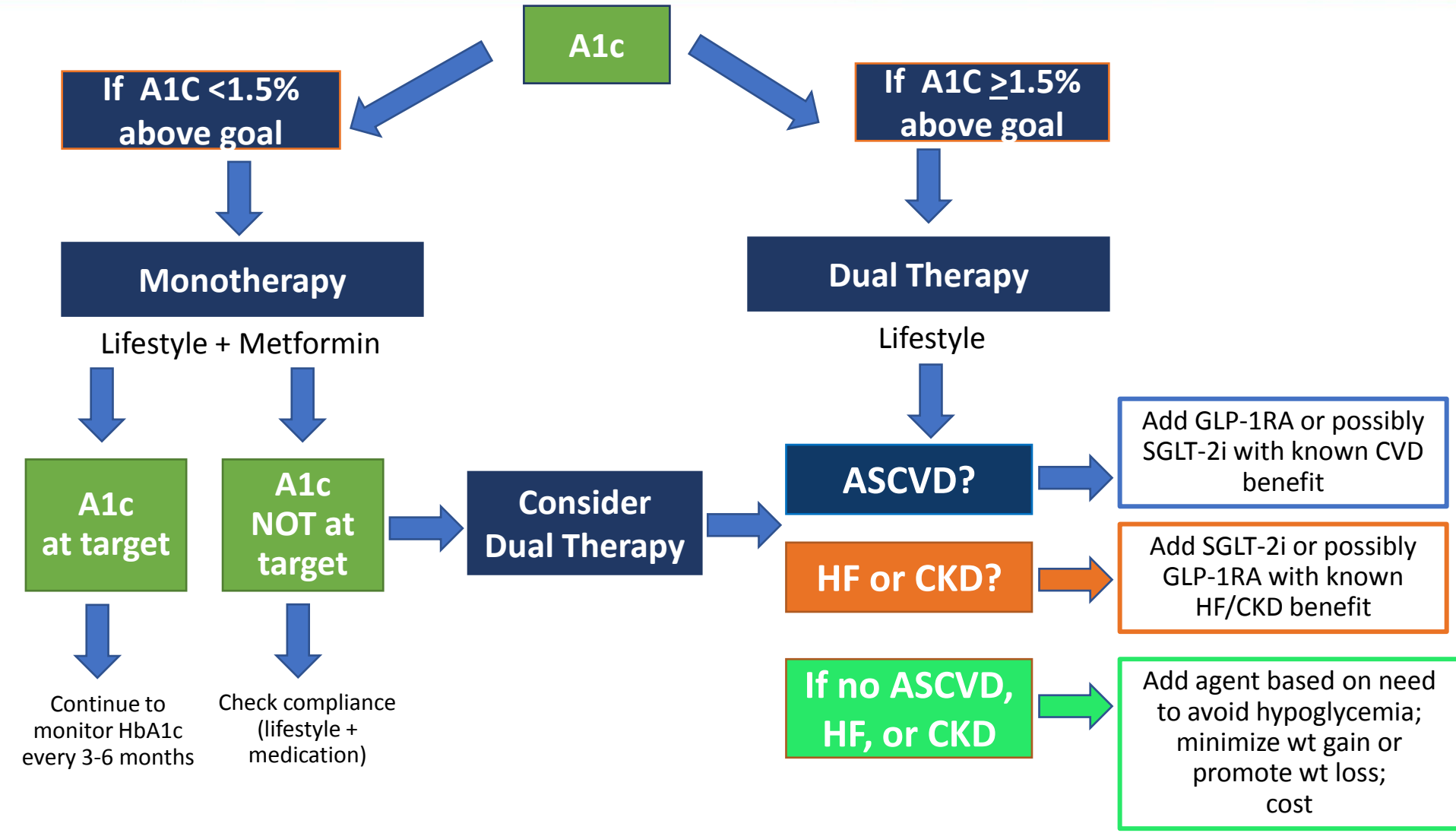
Team-Based Care for CV Risk Reduction in Patients with T2D

Cardiology
Endocrinology
Primary Care

Management of type 2 diabetes

- Achieve & maintain normal glycemic goals
- At diagnosis:
  - Lifestyle interventions AND metformin
  - **If A1C ≥ 1.5% above goal - use dual therapy**
    - **Pick 2nd agent based on patient characteristics**
      - **ASCVD**
      - **Heart failure or CKD**
      - Hypoglycemia risk, impact on weight, cost, side effects, patient preferences)
  - If A1C ≥ 10%, BS ≥ 300 mg/dL, or markedly symptomatic - initiate insulin

Current ADA 2019 Guidelines



ASCVD, atherosclerotic cardiovascular disease; HF, heart failure; CKD, chronic kidney disease

American Diabetes Association. *Diabetes Care*. 2019.

Take Home Points

- Fundamental paradigm shift in T2D management
- CVD remains the main cause of death and disability in T2D
- Several classes of glucose-lowering therapies improve CV outcomes—seen in RCTs and real-world studies
- These emerging data should shift focus of T2D therapies from A_{1c} alone to comprehensive CV risk reduction

Case Studies

Case Study 1

A 55-year-old male presents for follow-up in the clinic.

- Positive medical history: T2D, HTN, lower extremity PAD
- Patient states adherence to
  - Aspirin, cilostazol, lisinopril/HCTZ, metformin, rosuvastatin
  - Lifestyle modifications
- Examination and labs find
  - Blood pressure 146/92 mm/Hg; pulse rate 68/minute; body mass index 28.7 kg/m^2
  - Kidney/liver function is normal
  - HbA_{1c} 8.6%
  - Lipids: TC 162mg/dL; LDL 70 mg/dL; TG 300 mg/dL; and HDL 32 mg/dL
- He is willing to take additional oral medication to lower CV risk

HCTZ, hydrochlorothiazide; HDL, high-density lipoprotein; HTN, hypertension;
LDL, low-density lipoprotein; PAD, peripheral artery disease; TC, total cholesterol; TG, triglycerides.

Which is the best addition to the patient's current regimen to reduce his blood glucose and CV risk?

A. SGLT-2 inhibitor (i.e., empagliflozin)
B. GLP-1 RA (i.e., liraglutide)
C. DDP-4 inhibitor (i.e., sitagliptin)
D. Sulfonylurea (i.e., glipizide)

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SGLT-2 Inhibitor Considerations

Potential Adverse Side Effects:

- Mycotic genital infections – counsel patients about urinary hygiene
- Dehydration – consider stopping or reducing background diuretics
- Hypotension – use caution in patients with low blood pressure or on antihypertensive medication (ie, increase monitoring of BP and may need to modify antihypertensive regimen)
- Euglycemic ketoacidosis – cases of diabetic ketoacidosis have arisen in patients who reduce oral intake while continuing their SGLT2i. Consider SGLT2i to be "sick day medications"
- Fractures, amputations (canagliflozin)

Patel KV, et al. *Cleve Clin J Med.* 2017.

Case Study 2

A 63-year-old female presents for follow-up in the clinic.

- Positive medical history: T2D, HTN, CAD, CKD (stage 3), osteoporosis, diabetic retinopathy, microalbuminuria, and frequent UTIs
- States adherence to
  - Alendronate, aspirin, atorvastatin, chlorthalidone, insulin glargine, lisinopril, metformin, sulfamethoxazole/trimethoprim (3x week)
  - Lifestyle modifications
- Examination and labs find
  - Blood pressure 130/80 mm/Hg; pulse rate 68/minute; and body mass index 31.1 kg/m^2
  - eGFR 50 mL/min/1.73 m^2; liver function is normal; and HbA_{1c} 8.6%
- She is willing to take additional medication to lower CV risk.

CKD, chronic kidney disease.

Which is the safest addition to the patient's current regimen to lower her blood glucose and CV risk?

A. SGLT-2 inhibitor (i.e., canagliflozin)

B. GLP-1 RA (i.e., liraglutide)

C. TZD (i.e., pioglitazone)

D. DDP-4 inhibitor (i.e., sitagliptin)

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