Making the Link Between Diabetes and Cardiovascular Disease

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DISCLOSURES:

I have no relevant financial interest/arrangement or affiliation with any organizations related to commercial Products or services to be discussed at this program.

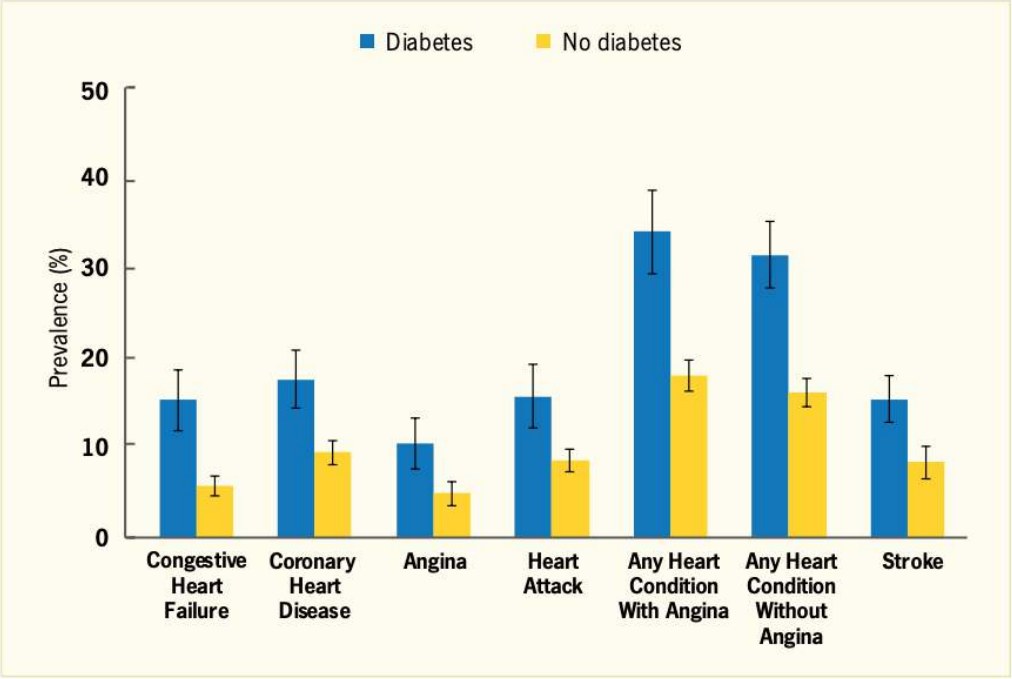
Learning Objectives

1. Describe how to integrate current guideline recommendations for diabetes therapies into clinical practice.
2. Identify co-morbid conditions that impact choice of therapy.
3. Summarize clinical trial data supporting the use of antidiabetic therapy in reducing cardiovascular risks and improving outcomes.
4. Explain a multidisciplinary, team-based approach to management of the patient with Type 2 Diabetes highlighting the role of the CV clinician.

Diabetes and CV Disease

- Atherosclerotic cardiovascular disease (ASCVD) = CAD, cerebrovascular disease, PAD from atherosclerotic origins
- Estimated cost of CV related spending per year associated with diabetes = $37.3 billion
- Co-existing CV risk factors: hypertension, hyperlipidemia, overweight/obesity, smoking, sedentary lifestyle, family history, ethnicity
- Co-existing complications: Heart failure (HFpEF, HFrEF), CKD, neuropathy

FIGURE 16.6. Cardiovascular Complications Among Adults Age ≥65 Years, by Diabetes Status, U.S., 2007–2010



Data are self-reported. Error bars represent 95% confidence intervals.

SOURCE: National Health and Nutrition Examination Surveys 2007–2010

→ Larger benefits if multiple CV risk factors are addressed simultaneously

Diabetes Care 2019. 42(S1):S103 -S123
Diabetes Care 2018;41:917–928 2.S
Diabetes in America, 3rd Edition (2017). Chapter 16. NIH

Glycemic Control and CV Disease

- Initial tighter glycemic control was associated with a "legacy" benefit later on (DCCT/EDIC, UKPDS), mostly for *microvascular* disease
- Less evidence for *macrovascular* disease
- Possibly more <u>benefit in secondary</u> prevention

Table 1—Early major trials evaluating the effects of intensive glycemic control of diabetes

Study	Diabetes type	CV composite		MI		CV mortality		All-cause mortality	
DCCT/EDIC (17,26,27)	Type 1	↔	↓	—	—	—	—	↔	↓
UKPDS	Type 2								
Main randomization (SU or insulin vs. conventional therapy) (18,28)		—	—	↔	↓	—	—	↔	↓
Additional randomization of overweight patients (metformin vs. SU vs. conventional therapy) (19,28)		—	—	↓*	↓*	—	—	↓*	↓*
ACCORD (20,30)	Type 2	↔	↔	↓	↔	↑	↑	↑	↔
ADVANCE (21)	Type 2	↔†		↔		↔		↔	
VADT (22,29)	Type 2	↔	↓	↔	↔	↔	↔	↔	↔

Left columns show initial results; right columns show long-term follow-up. ↔, Neutral effect; ↓, decrease; ↑, increase; —, not assessed/reported; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; SU, sulfonylurea. Adapted from Bergenstal et al. (97). *Metformin group only. †A decrease was reported in a combined CV/microvascular composite but was found to be mostly attributable to nephropathy.

JAMA 2015;313:45–53. N Engl J Med 2005;353:2643–2653.
N Engl J Med 2008;359:1577–1589. BMJ. 2000; 321(7258): 405–412.
Diabetes Care 2018;41:14–31

What is the Ideal A1c?

Pushing the A1c too low…

- Hypoglycemia risk
- Medication side effects

Target	ADA	AACE/ACE
A1c (%)	<7%	≤6.5%
BP (mmHg)	<140/90	<130/80
Lipids (mg/dl)	Statin according to CVD risk	Extreme CVD risk: LDL <55 Low CVD risk: LDL <130
Weight	Sustained weight loss ≥7%	Weight loss until therapeutic targets are met

J Am Heart Assoc. 2019;8:e011295.
ADA Guidelines
AACE guidelines

Background for CV Outcome Trials (CVOT)

- Intensive glucose control may be associated with higher mortality (ACCORD) -- hypoglycemia
- Prior medication specific CV risk concerns:
  - Increased risk for CHF with pioglitazone and rosiglitazone
  - Increased CV events with peroxisome proliferator–activated receptor (PPAR) agonist muraglitazar
  - Prior meta-analysis in *Diabetes Care* showed increased risk of CV events and mortality with sulfonylureas

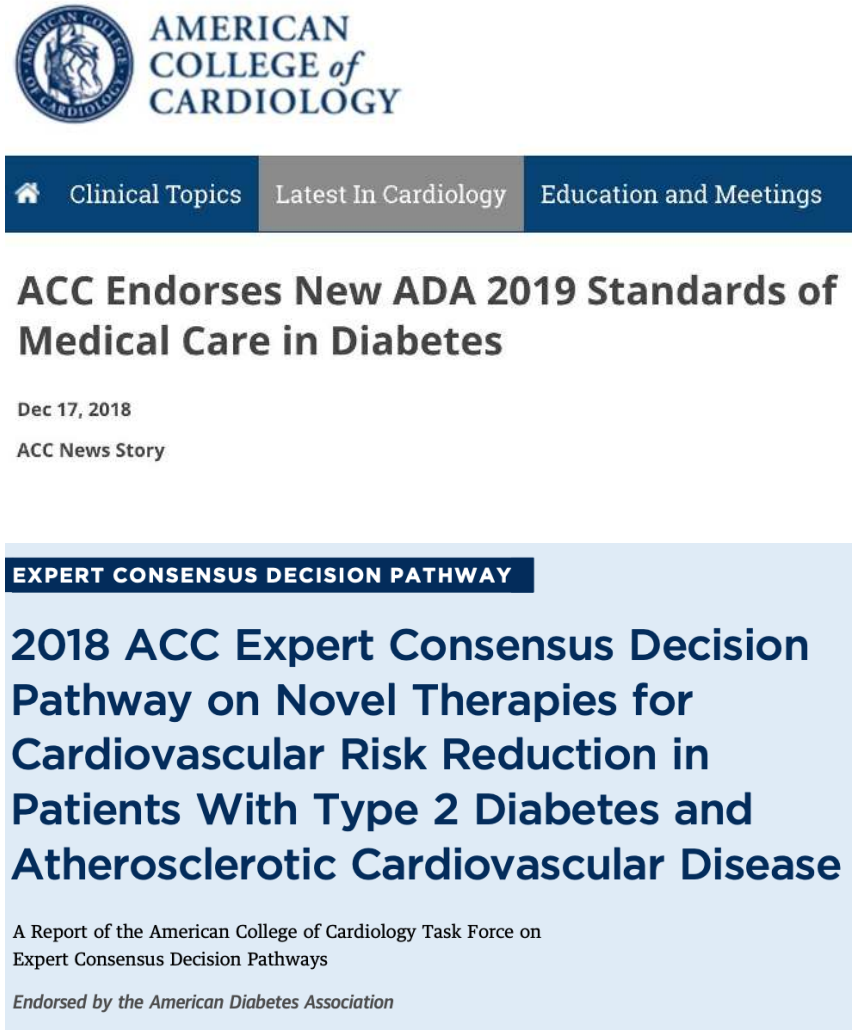
→ FDA requires post-marketing CV outcome studies to include high risk individuals

→ More focus on individualized A1c goals

→ Take an individualized approach

Lancet 375:2215–2222
N Engl J Med 358:2545–2559
Diabetes Care 2016; 39(5): 738-742
Diabtes Care 2017;40:706-714

American College of Cardiology (ACC)



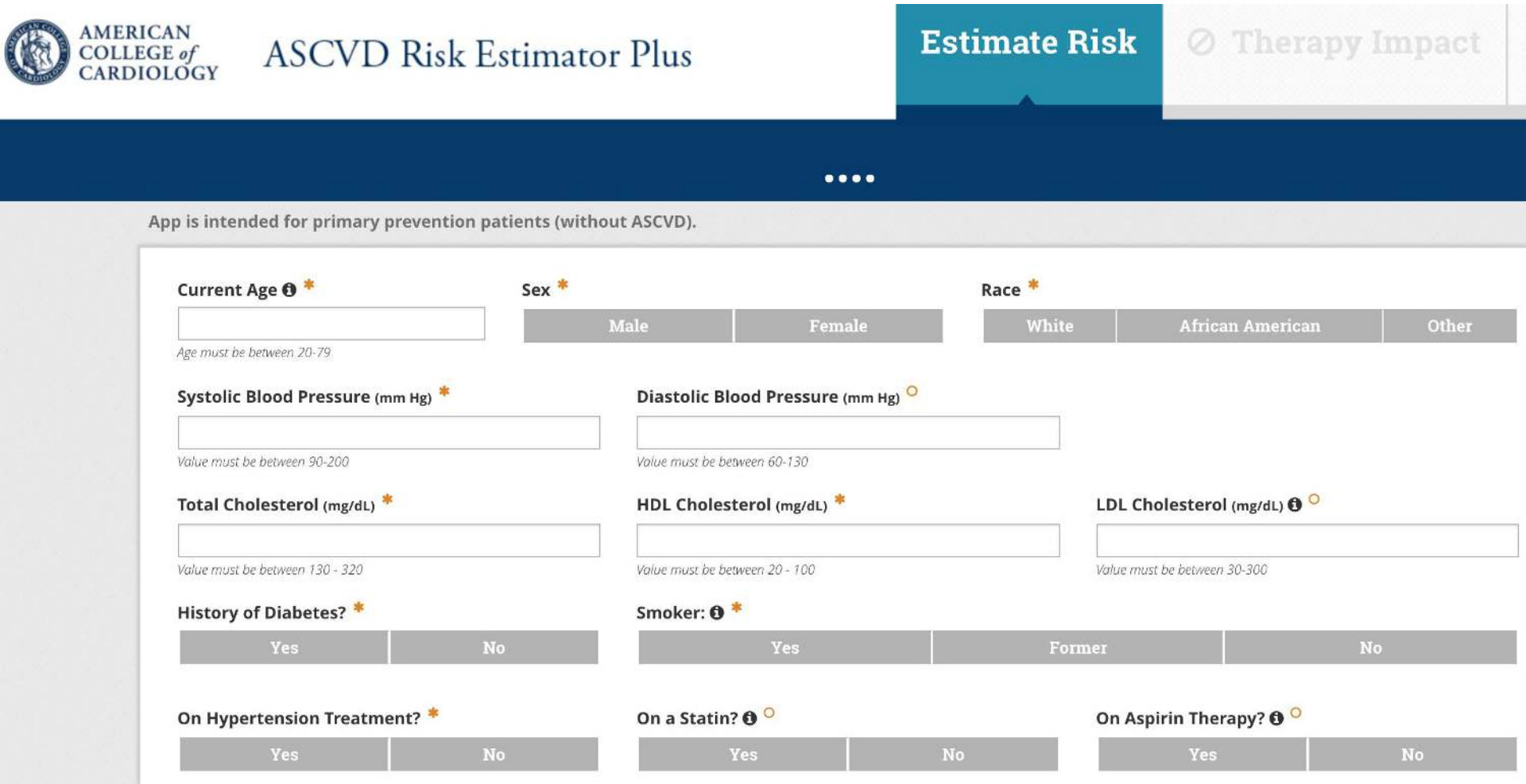
"The CV specialist is well-positioned to address 3 key areas in the management of patients with T2D:

1. Screening for T2D in their patients with or at high risk of CVD
2. Aggressively treating CV risk factors
3. Incorporating the data for newer antihyperglycemic agents into routine practice."

"Specialists in CV medicine should be aware of the strong clinical evidence regarding new glucose-lowering therapies that lower CV risk"

Journal of the American College of Cardiology Nov 2018

ADA Guidelines - Assess CV Risk



Standards of Medical Care in Diabetes-2019
Diabetes Care 2019. 42(S1):S103 -S123
http://http://tools.acc.org/ASCVD-Risk-Estimator-Plus

10. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2019*

Diabetes Care 2019;42(Suppl. 1):S103–S123 | https://doi.org/10.2337/dc19S010

Treatment

(10.36) In patients with known atherosclerotic cardiovascular disease, consider **ACE inhibitor or angiotensin receptor blocker** therapy to reduce the risk of cardiovascular events.

(10.37) In patients with prior myocardial infarction, **b-blockers** should be continued for at least 2 years after the event.

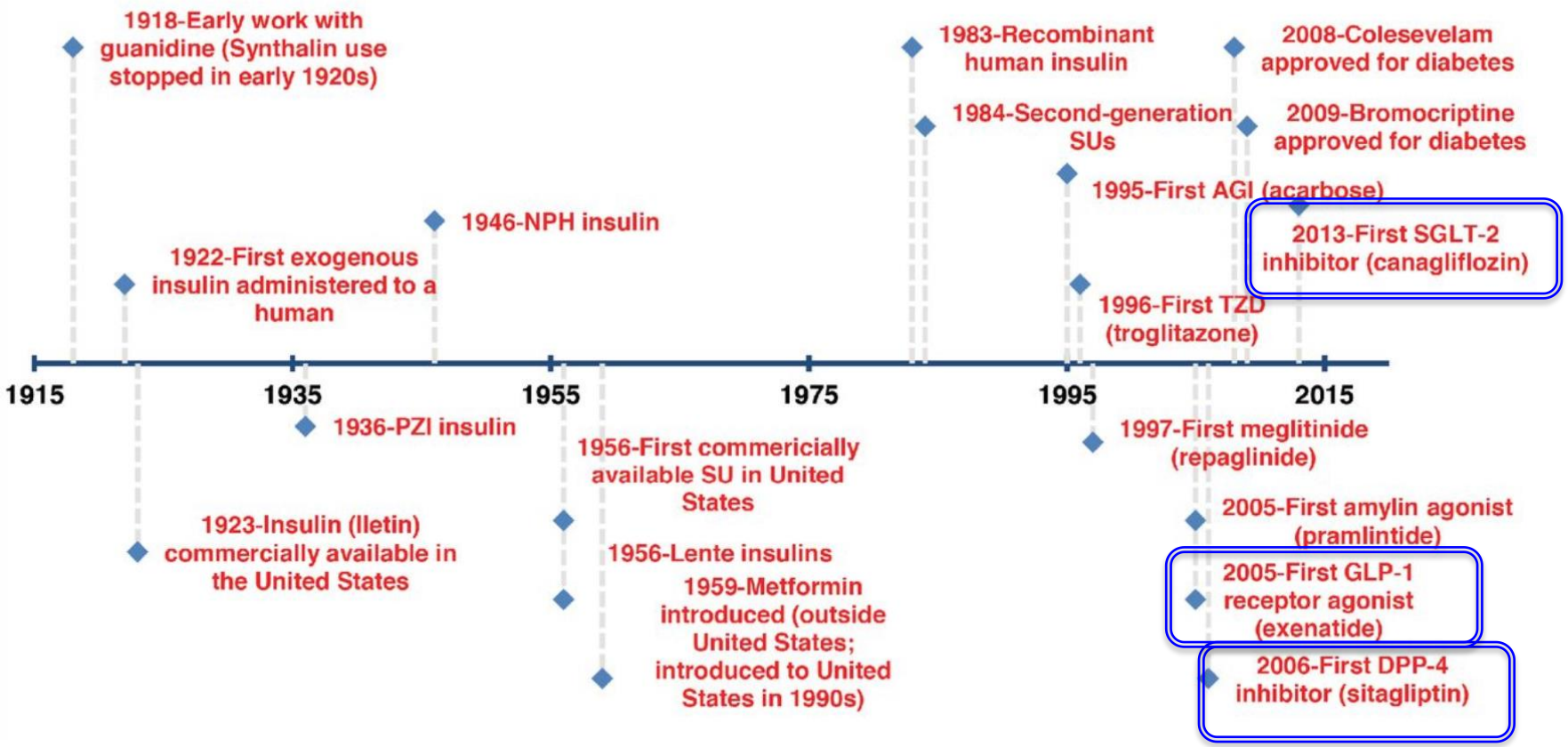
(10.38) In patients with type 2 diabetes with stable congestive heart failure, **metformin** may be used if estimated glomerular filtration rate remains >30 mL/min but should be avoided in unstable or hospitalized patients with congestive heart failure.

(10.39) Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, **sodium–glucose cotransporter 2 inhibitors** or **glucagon-like peptide 1 receptor agonists** with demonstrated cardiovascular disease benefit are recommended as part of the antihyperglycemic regimen.

(10.40) Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, **sodium–glucose cotransporter 2 inhibitors** are preferred.

Standards of Medical Care in Diabetes-2019
Diabetes Care 2019. 42(S1):S103 -S123

Developments in Diabetes Medications



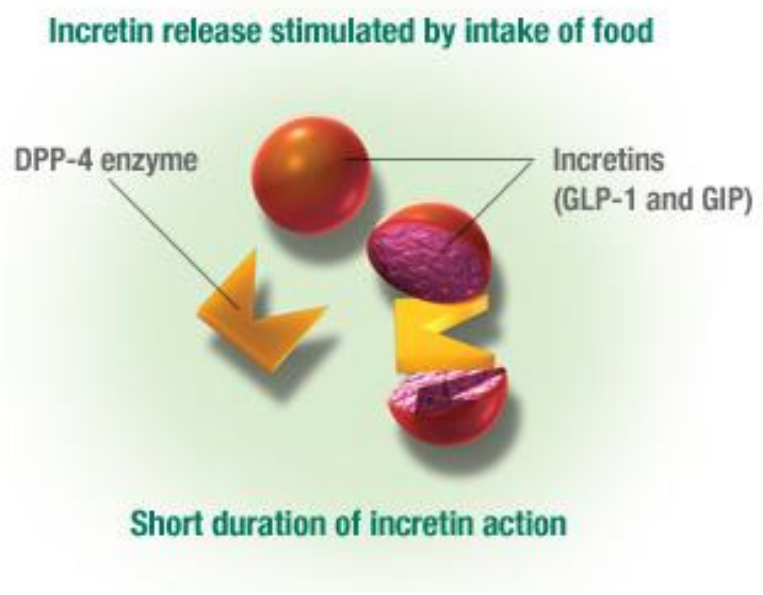
Diabetes Spectrum 2014 May; 27(2): 82-86.

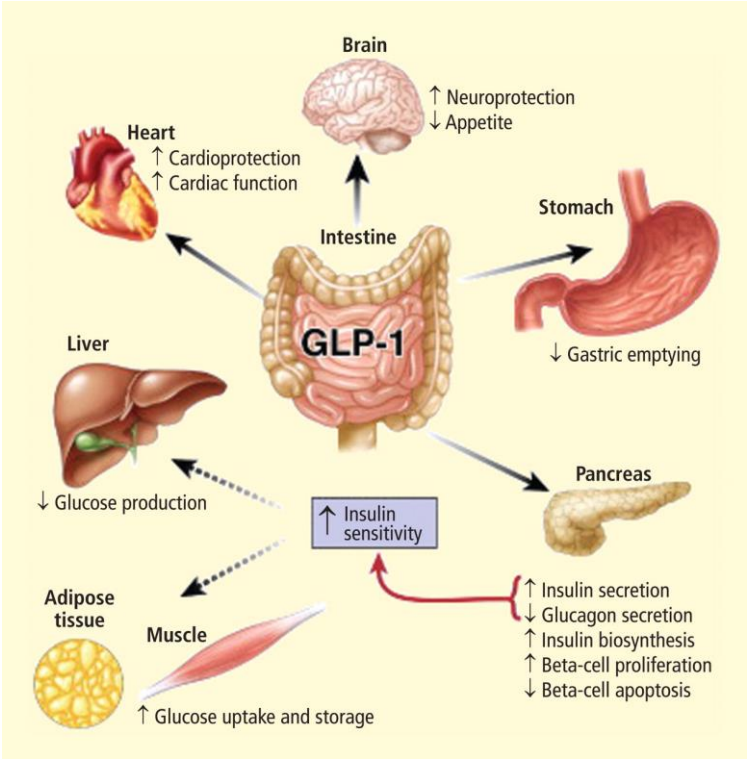
Newer Classes of Diabetes Medications

1. **DPP4 Inhibitors**
2. GLP1 agonists
3. SGLT2 inhibitors

Incretins

- Incretins = intestinal hormones released in response to meals that help regulate insulin release in a glucose dependent manner
- Incretin effect appears to be diminished in T2DM





DPP4 Inhibitors

- Delivery: oral
- Mechanism:
  - Decreases breakdown of GLP1 (DPP4 degrades GLP1)
  - Suppresses glucagon production
  - Enhances insulin production in glucose dependent manner
- Weight neutral
- Risk of hypoglycemia when used alone is low
- A1c reduction 0.5-0.9%
- All are approved for monotherapy

Available DPP4 Inhibitors in the United States

Drug	Brand Name
Sitagliptin	**Januvia**
Saxagliptin	**Onglyza**
Linagliptin	**Tradjenta**
Alogliptin	**Nesina**

DPP4 Inhibitor CVOT Summary

Drug	Trial	N	Population	Duration	Primary Outcome	CV effect
Saxagliptin	SAVOR TIMI 53	16,492	80% CVD; 20% high risk for CVD	24 months	3 point MACE	Slight but significant increased risk of heart failure hospitalization
Alogliptin	EXAMINE	5,380	MI or UA in 15-90 days	18 months	3 point MACE	Non significant trend towards hospitalization for heart failure
Sitagliptin	TECOS	14,671	CVD	36 months	4 point MACE	Neutral
Linagliptin	CARMELINA	6,980	CVD	~48 months	3 point MACE	Pending

3 point MACE = CV death, non fatal MI, non fatal stroke
4 point MACE = CV death, non fatal MI, non fatal stroke, hospitalization for UA

Scirica BM et al. N Engl J Med 2013;369:1317
White WB et al. N Engl J Med 2013;369:1327
Green JB et al. N Engl J Med 2015;373:232
Rosenstock J et al. Cardiovasc Diabetol 2018

Available DPP4 Inhibitors in the United States

Drug	Brand Name	Notes
Sitagliptin	**Januvia**	CV neutral
Saxagliptin	**Onglyza**	Statistically significant increased risk of hospitalization for heart failure
Linagliptin	**Tradjenta**	No adjustment for reduced GFR
Alogliptin	**Nesina**	Trend towards increased risk of hospitalization for heart failure

New Classes of Diabetes Medications

1. DPP4 Inhibitors
2. **GLP1 agonists**
3. SGLT2 inhibitors

GLP-1 Agonists

- Delivery:
  - Subcutaneous injection
  - Oral formulation in development
- Mechanism: raises GLP1 levels above natural levels
  - Stimulates glucose dependent insulin secretion from beta cells
  - Suppresses glucagon release from alpha cells
  - Slows gastric emptying → earlier satiety
  - Targets: receptors on islet cells, stomach, heart, hypothalamus
- A1c reduction 1-1.5%
- Associated with weight loss
- Low risk of hypoglycemia when used alone
- **Contraindications**: medullary thyroid cancer, pancreatitis

Available GLP1 Agonists in the United States

Drug	Brand name	Dosing schedule (subcutaneous)
Exenatide	Byetta	Twice daily
Exenatide extended release	Bydureon	Weekly
~~Albiglutide~~	~~Tanzeum~~	~~Weekly~~
Dulaglutide	Trulicity	Weekly
Liraglutide*	Victoza	Daily
Liraglutide	Saxenda	Daily
Lixisenatide*	Soliqua (combination)	Daily
Semaglutide	Ozempic	Weekly

* Note: long acting insulin + GLP1 agonist combinations:
Glargine + lixisenatide = Soliqua (Lixilan)
Degludec + liraglutide = Xultophy (iDegLira)

GLP1 Agonist CVOT Summary

Drug	Trial	N	Duration	Primary Outcome	Result	Other
Liraglutide	LEADER	9,340	~3.8 years	3 point MACE	13% RR reduction for primary outcome	Has CV indication
Exenatide	EXSCEL	14,752	~7.5 years	3 point MACE	Non-inferior	
Lixisenatide	ELIXA	6,068	~2.1 years	4 point MACE	Non-inferior	
Semaglutide	SUSTAIN 6	3,297	~2.1 years	3 point MACE	26% RR reduction for primary outcome	More studies pending
Dulaglutide	REWIND	9,901	~6.5 years	3 point MACE	Pending	More primary prevention
Alibglutide	HARMONY	9,463	~3 years	3 point MACE	22% RR reduction in primary composite outcome, reduction in MI	Off market

Pfeffer MA et al. N Engl J Med 2015;373:2247
Holmann RR et al. N Engl J Med 2017;377:1228;
Mentz RJ et al. Am J Heart 2017;187:1
Marso SP et al. N Engl J Med 2016;375:311
Marso SP et al. N Engl J Med 2016; 375:1834
Fernandez,AF The Lancet 2018;392(10157): 1519-1529

CV Benefit Mechanisms

- In LEADER and SUSTAIN-6, differences in CV outcomes were apparent by 6 months – not a glycemic control effect
- No large published studies on GLP1 RAs for primary prevention (LYDIA trial in progress)
- Reduced blood pressure, weight loss, kidney protection
- Reduced LDL --> reduced atherogenesis
- Anti inflammatory (upreglated nitric oxide, suppressed NF-kB)
- GLP1 receptors in mice have been located on endocardium, cardiac myocytes, and microvascular endothelium
- In mice pretreated with liraglutide for 7 days prior to induction of MI, there was a significant increase in post-MI survival and improvement in cardiac output

N Engl J Med 2016; 375:311-322
NEJM 2015;373:2117-2128
N Engl J Med. 2016 Sep 15 Online first
Circulation 2004. 109 :962 –965
Diabetes 2004. 54(1):146-151

New Classes of Diabetes Medications

1. DPP4 Inhibitors
2. GLP1 agonists
3. **SGLT2 inhibitors**

SGLT2 Inhibitors

- Mechanism: Inhibitor of SGLT2 (sodium glucose co-transporter, responsible for 90% glucose reabsorption in the proximal tubule)
- Reduce A1c by ~0.5 to 0.7 %
- In 12-week trials, 2-3 kg weight loss
- Mild reductions in systolic *and* diastolic blood pressure
- Reduced uric acid levels
- Small increase in LDL-c and HDL, decrease in TG
- No hypoglycemia on its own but may increase hypoglycemia risk when on other glucose lowering drugs
- Contraindicated with GFR <30 ml/min/1.73 m^2
- Not approved for T1DM

BMJ Open. 2012;2(5)
Curr Med Res Opin. 2012;28(7):1173-8
Ann Med. 2012;44(4):375-93

Available SGLT2 Inhibitors in the United States

Generic Name	Brand Name	Dosing	Approval	SGLT2/SGLT1 Selectivity
Canagliflozin	Invokana	100 or 300 mg daily	2013	1:414
Dapagliflozin	Farxiga	5 mg or 10 mg daily	2014	1:1200
Empagliflozin	Jardiance	10 mg or 25 mg daily	2014	1:2500
Ertugliflozin	Steglatro	5 mg or 15 mg daily	2017	-

Observational CV Outcome Studies

TABLE 3 Selected Observational Studies of CV Benefits of SGLT2 Inhibitors

	CVD-REAL (31)	Patorno et al. (32)	EASEL (33)	CVD-REAL 2 (34)
Size	n = 309,056	n = 224,999	n = 25,258	n >400,000
Agent	Canagliflozin (53%), Dapagliflozin (42%), Empagliflozin (5%)	Canagliflozin	Canagliflozin (58%), Empagliflozin (26%), Dapagliflozin (16%)	Dapagliflozin (75%), Empagliflozin (9%), Ipragliflozin (8%), Canagliflozin (4%), Tofogliflozin (3%), Luseogliflozin (1%)
Mean duration of follow-up	<1 year	<1 year	1.6 years	>1 year
Baseline A1C	N/R	8.8-8.9	N/R	N/R
Proportion with established cardiovascular disease* at baseline	13%	16% to 18%	100%	27%
All-cause death, MI, stroke HR (95% CI)	N/R	N/R	0.67 (0.60-0.75)	N/R
Hospital admission for MI or stroke HR (95% CI)	N/R	0.89 (0.68-1.17)	N/R	N/R
CV death	N/R	N/R	N/R	N/R
MI	N/R	0.91 (0.64-1.29)	0.81 (0.64-1.03)	0.81 (0.74-0.88)
Stroke	N/R	0.81 (0.54-1.22)	0.85 (0.66-1.10)	0.68 (0.55-0.84)
All-cause death	0.49 (0.41-0.57)	0.66 (0.25-1.74)	0.57 (0.49-0.66)	0.51 (0.37-0.70)
HF hospitalization	0.61 (0.51-0.73)	0.70 (0.54-0.92)	0.57 (0.45-0.73)	0.64 (0.50-0.82)

*The specific definitions of established cardiovascular disease vary by study but generally include a history of myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary revascularization, heart failure, or peripheral artery disease.

A1C = hemoglobin A1C; CI = confidence interval; CV = cardiovascular; CVD-REAL = Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors; EASEL = Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World; HF = heart failure; HR = hazard ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; N/R = not reported; SGLT2 = sodium-glucose cotransporter-2.

Journal of the American College of Cardiology Nov 2018

EMPA-REG: Empagliflozin

- 7,020 patients with T2DM
  - A1c 7-9%
  - Established CV disease
  - BMI <45
- Mean duration of treatment: 2.6 years; mean follow up: 3.1 years
- Empagliflozin group had significantly lower rates of:
  - Death from cardiovascular causes: 38% relative risk reduction
  - Hospitalization for heart failure: 35% relative risk reduction
  - Death from any cause: 32% relative risk reduction
- No significant between-group difference in nonfatal MI and nonfatal stroke

NEJM 2015;373:2117-2128

EMPA-REG: Empagliflozin

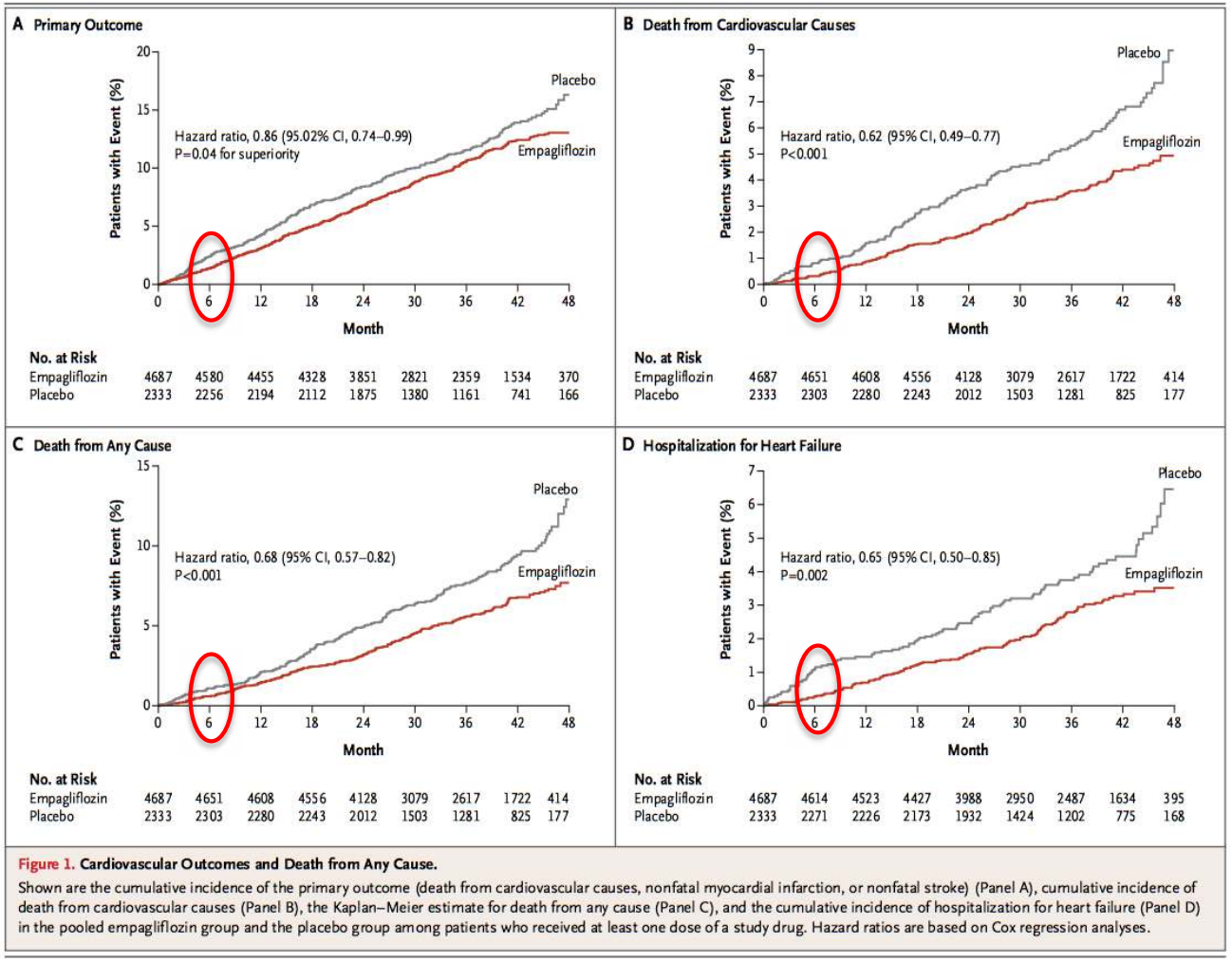


Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.

NEJM 2015;373:2117-2128

EMPA-REG: Renal Outcomes

Renal Outcome Measure	Empagliflozin: *no. with event/ no. analyzed (%)*	Empagliflozin: *rate/1000 patient-yr*	Placebo: *no. with event/ no. analyzed (%)*	Placebo: *rate/1000 patient-yr*	Hazard Ratio (95% CI)	P Value
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25

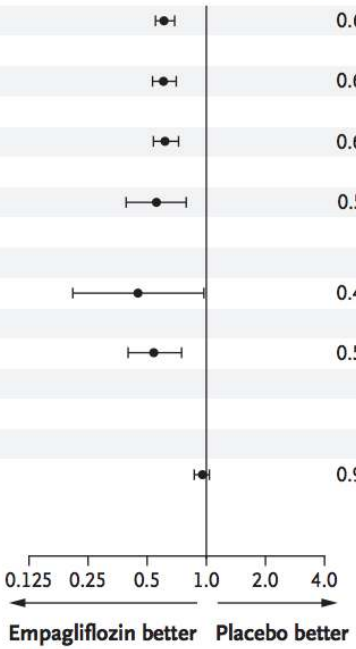


Figure 2. Risk Comparison for Seven Renal Outcomes.

All the analyses shown were performed with the use of Cox regression in patients who received at least one dose of either empagliflozin or placebo. All the analyses were prespecified except for the composite outcome of a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease. The abbreviation eGFR denotes estimated glomerular filtration rate.

EMPA REG Outcome investigators. NEJM 2016;375:323-34

SGLT2 Inhibitor CVOT Summary

Drug	Trial	N	Duration	Primary Outcome	Result	Other
Empagliflozin	EMPA-REG	7020	3.1 years	3 point MACE	- Significant reduction in MACE. - Significant reduction in incident/worsening nephropathy	Has CV indication
Canagliflozin	CANVAS (+CANVAS R)	10,142	~2.4 years	3 point MACE	- Significant reduction in MACE - All cause mortality and CV Death *not* significant - Significant reduction in progression of albuminuria.	Has CV indication
Dapagliflozin	DECLARE TIMI 58	17,160	~4 years	3 point MACE	- Non inferior for MACE. - Reduced CV death - Reduced hospitalization for heart failure.	
Ertugliflozin	VERTIS CV	8237	6.1 years	3 point MACE	*Pending*	

Zinman B et al. N Engl J Med 2015;373:2117
Neal B et al N Engl J Med 2017
Wiviott SD et al N Engl J Med 2018
Raz I et al. Diabetes Obes Metab 2018; 20:1102

SGLT2 Inhibitors: Possible Mechanisms

- NOT dose dependent
- Likely not just glucose dependent
- Diuretic effect and natriuresis → reduced cardiac preload/afterload, reduced filling pressures
- Reduced systolic blood pressure (without increased heart rate): improved arterial stiffness, reduced sympathetic tone → reduced myocardial work, reduced filling pressures, preload/afterload reduction
- Weight loss → improved CV risk, improved blood pressure
- Reduced albuminuria / slowing of decline in GFR
- Modification of the intrarenal renin angiotensin axis
- Blockage of Na-H cotransporter → tissue protection, reduced kidney and myocardial injury
- Increased HDL
- Less use of agents that cause weight gain and fluid overload

Note: No SGLT2 inhibitors in the heart

FDA U.S. FOOD & DRUG ADMINISTRATION

Information on SGLT2 Inhibitors

- FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes
  8/29/2018
- FDA Drug Safety Communication: FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR)
  5/16/2017
- FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)
  6/14/2016
- FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate
  5-18-2016
- FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections
  12-4-2015
- FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density
  9-10-2015

Summary for New Diabetes Agents

Drug	Class	Delivery	CV Risk Reduction	Other
Empagliflozin	SGLT2 inhibitor	Oral	Beneficial	UTI, GU infections, DKA, AKI
Canagliflozin	SGLT2 inhibitor	Oral	Beneficial/Neutral	Amputations, fractures, UTI, DKA, AKI, GU infection
Dapagliflozin	SGLT2 inhibitor	Oral	Beneficial	UTI, GU infections, DKA, AKI
Ertugoflozin	SGLT2 inhibitor	Oral	-	-
Alogliptin	DPP4 inhibitor	Oral	Neutral/Negative	Hospitalization for heart failure (trend)
Sitagliptin	DPP4 inhibitor	Oral	Neutral	
Saxagliptin	DPP4 inhibitor	Oral	Neutral/Negative	Hospitalization for heart failure
Linagliptin	DPP4 inhibitor	Oral	Neutral	OK in CKD/ESRD
Liraglutide	GLP1 agonist	Daily, subQ	Beneficial	Pancreatitis, MTC
Lixisenatide	GLP1 agonist	Daily, subQ	Neutral	Pancreatitis
Semaglutide	GLP1 agonist	Weekly, subQ	Beneficial	Pancreatitis, MTC
Exenatide	GLP1 agonist	Weekly, subQ	Neutral	Pancreatitis

SLGT2 Inhibitors vs GLP1 Agonists

1. Which one do you choose?
2. Why not use both?
   - No head to head trials
   - No trials involving both classes for CV outcomes

TABLE 11 **Patient and Clinician Preferences and Priorities for Considering SGLT2 Inhibitors with Demonstrated CV Benefit Versus GLP-1RAs With Demonstrated CV Benefit**

Consider Using an SGLT2 Inhibitor First When Patient and Clinician Priorities Include:	Consider Using a GLP-1RA First When Patient and Clinician Priorities Include:
Reducing MACE and CV death	Reducing MACE and CV death
Preventing heart failure hospitalization	Substantial weight loss
Reducing blood pressure	Once weekly (subcutaneous) dosing
Orally administered therapies	Therapy when eGFR consistently <45 ml/min/1.73 m^2*
Consider alternative agents if: ■ Significant CKD* ■ History of prior amputation, severe peripheral arterial disease, neuropathy, or diabetic foot ulcers (avoid canagliflozin) ■ History of recurrent genital candidiasis ■ History of diabetic ketoacidosis ■ History of osteoporosis (avoid canagliflozin)	Consider alternative agents if: ■ Persistent nausea, even at low doses ■ History of pancreatitis ■ History of gastroparesis ■ History of MEN2 or medullary thyroid cancer ■ History of proliferative retinopathy (semaglutide)

*eGFR <45 ml/min/1.73 m^2 is currently a caution due to a decrease in glycemic efficacy (not due to safety), but SGLT2 inhibitors are currently being investigated for nephroprotection in these patients.

CKD = chronic kidney disease; CV = cardiovascular; DPP4 = dipeptidyl-peptidase 4; eGFR = estimated glomerular filtration rate; GLP-RAs = glucagon-like peptide-1 receptor agonists; MACE = major adverse cardiovascular event; MEN2 = multiple endocrine neoplasia type 2; SGLT2 = sodium-glucose cotransporter-2.

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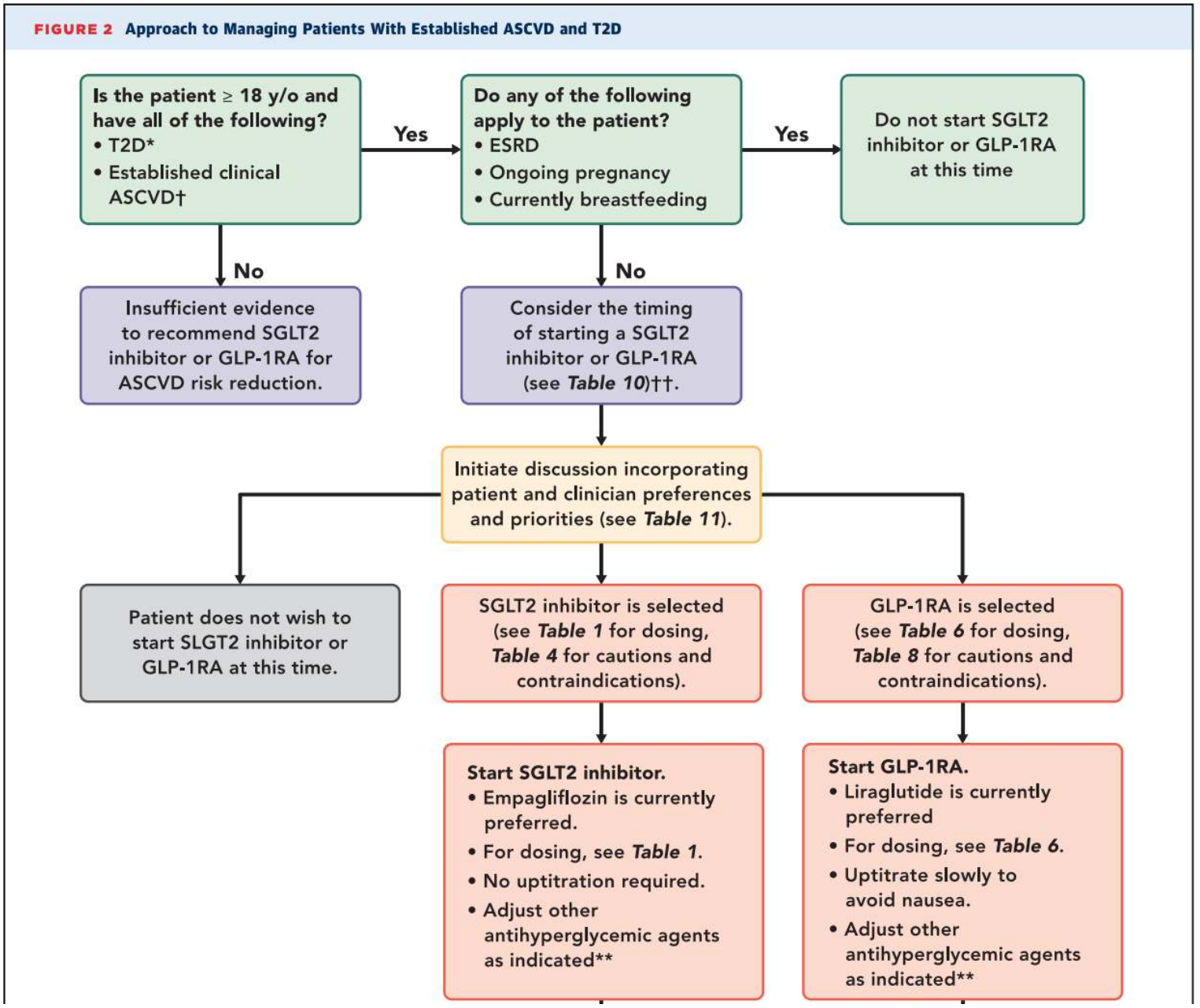
FIGURE 2 Approach to Managing Patients With Established ASCVD and T2D



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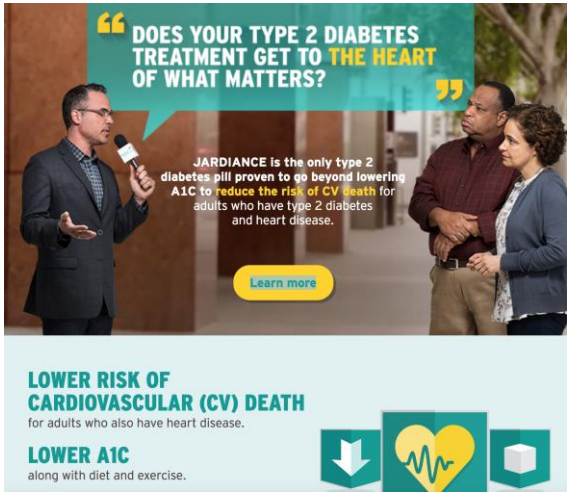
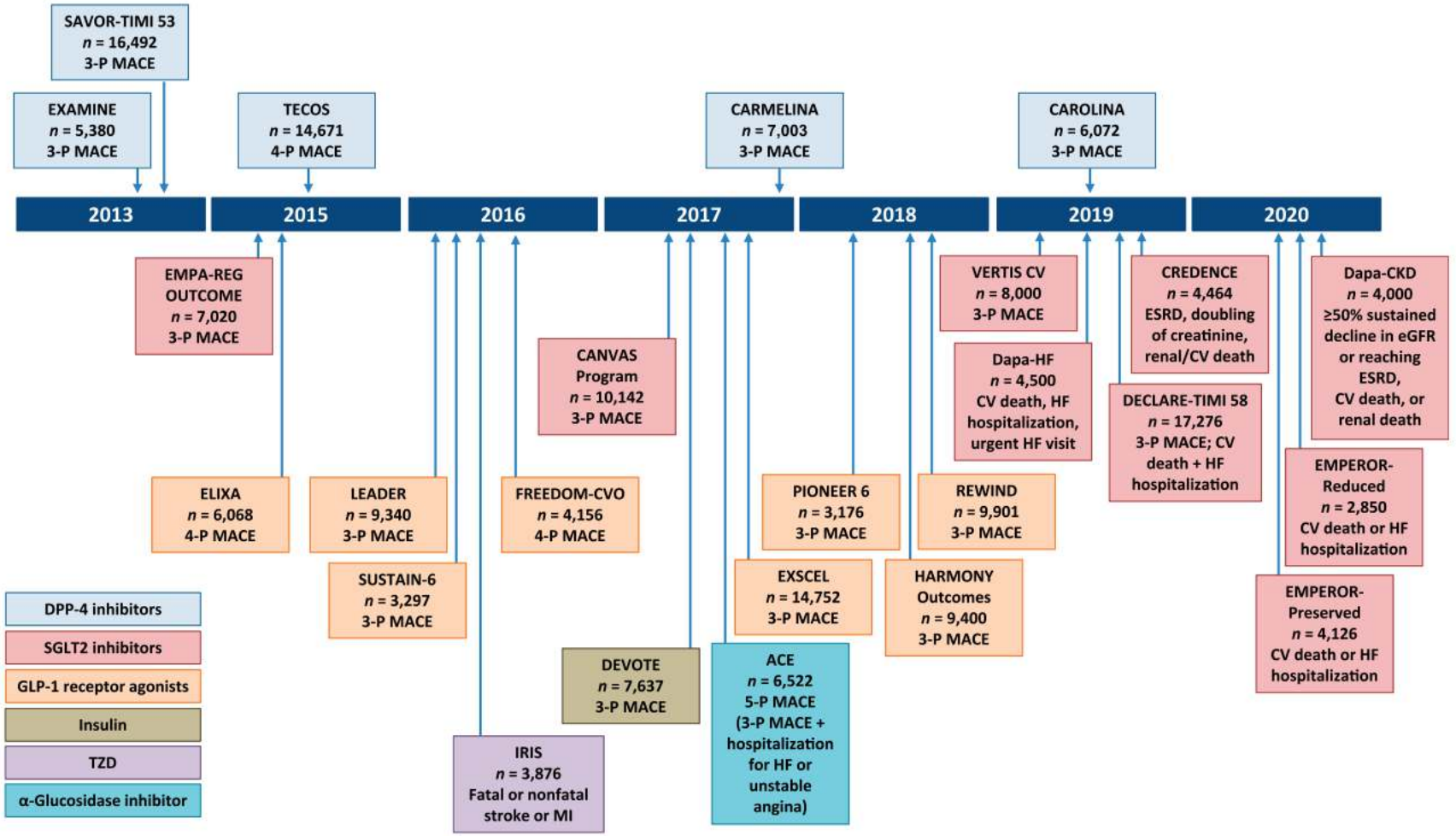
T2DM Medications with CV Indications



Completed and Ongoing CVOTs



→ FDA voted to continue CVOTs

Diabetes Care 2018;41:14–31

Questions?