Type 2 diabetes and cardiovascular disease

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Outline

- Scope of problem
- HTN, HLD, and aspirin
- A1c targets, effects of intensive therapy
- CVOTs for diabetes medications
- Summary

Cardiovascular disease in patients with diabetes

- Atherosclerotic cardiovascular disease (ASCVD) - coronary heart disease, cerebrovascular disease, or peripheral arterial disease is leading cause of morbidity and mortality for individuals with diabetes
- Those with diabetes have a higher prevalence of coronary heart disease and are more likely to have an MI than those without diabetes
- Heart failure hospitalization 2 fold higher in patients with diabetes than without
- Patients with diabetes have greater burden of atherogenic risk factors including HTN, obesity, lipid abnormalities

Risk calculator

- ADA recommends assessing 10-year risk of a first atherosclerotic cardiovascular disease event
- The American College of Cardiology/American Heart Association ASCVD risk calculator is a tool to estimate 10-year ASCVD risk (http://tools.acc.org/ASCVD-Risk-Estimator-Plus
- ****10-year risk for ASCVD is categorized as:**
  Low-risk (<5%)
  Borderline risk (5% to 7.4%)
  Intermediate risk (7.5% to 19.9%)
  High risk (≥20%)

Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD or 10-year ASCVD risk >20%	Recommended statin intensity* and combination treatment¶
<40 years	No	None[Δ]
	Yes	High ▪ In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)[◇]
≥40 years	No	Moderate[§]
	Yes	High ▪ In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

ASCVD: atherosclerotic cardiovascular disease; LDL: low-density lipoprotein; PCSK9: proprotein convertase subtilisin/kexin type 9.

* For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used.

¶ In addition to lifestyle therapy.

Δ Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD.

◇ Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin-based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

§ High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors.

Table 10.2 ADA 2019 Standards of Care

Table 10.3—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2–4 mg

*Once-daily dosing. XL, extended release.

Blood pressure targets (ADA)

- Patients with DM and HTN at higher CVD risk (existing atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >15%), BP target 130/80 may be appropriate
- DM and HTN with 10 year risk <15% target 140/90
- Lifestyle intervention- wt loss, DASH diet including reduced sodium and potassium intake, moderation of ETOH, increased physical activity

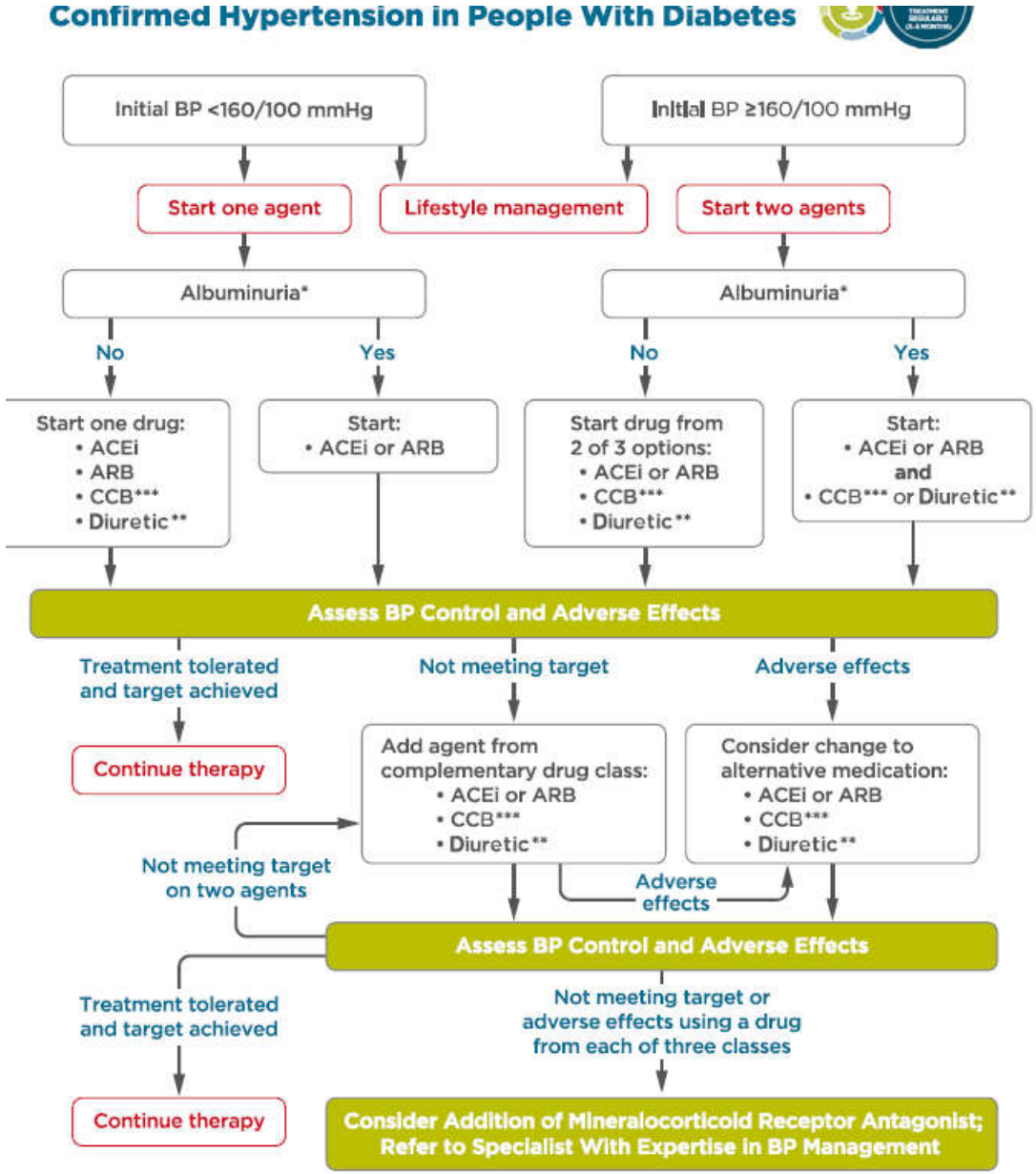


Figure 10.1—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for patients with urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for patients with urine albumin-to-creatinine ratio ≥300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine calcium channel blocker (CCB). BP, blood pressure. Adapted from de Boer et al. (17).

Aspirin

- 75-162 mg/daily recommended for secondary prevention in those with DM and hx of CVD
- Can consider for primary prevention in patients with DM, after discussion of benefits vs risk of bleeding.
  - In patients with no previous CV events, its use is more controversial.
- For patients over the age of 70 years (with or without diabetes), the balance appears to have greater risk than benefit
- Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged <50 years with diabetes with no other major ASCVD risk factors

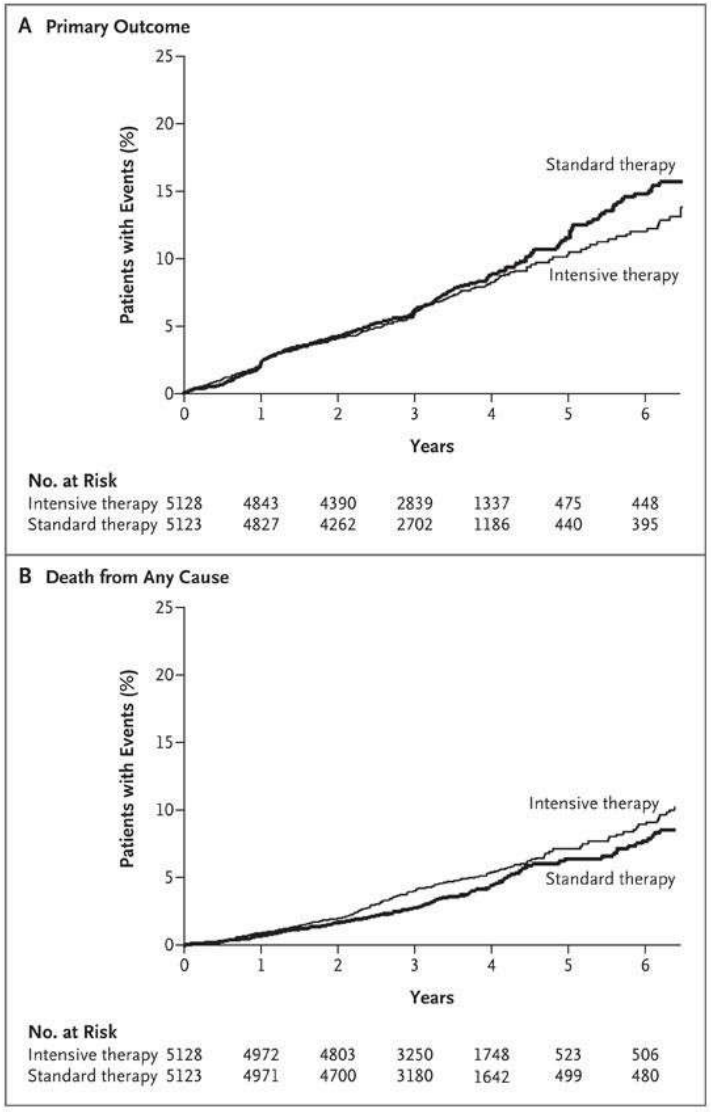
Effects of intensive glycemic control on CVD

- UKPDS- more intensive treatment in newly diagnosed patients may reduce long term rates of CVD; at 10 years of follow up, intensive group had significant reductions in MI and all cause mortality
- ACCORD, ADVANCE, VADT studied the effects of intensive glucose lowering in patients with longstanding DM2 and known CVD or high CV risk
  - ACCORD study showed increased mortality in intensive group
  - In higher risk patients, potential risks of intensive glycemic control may outweigh benefits

ACCORD

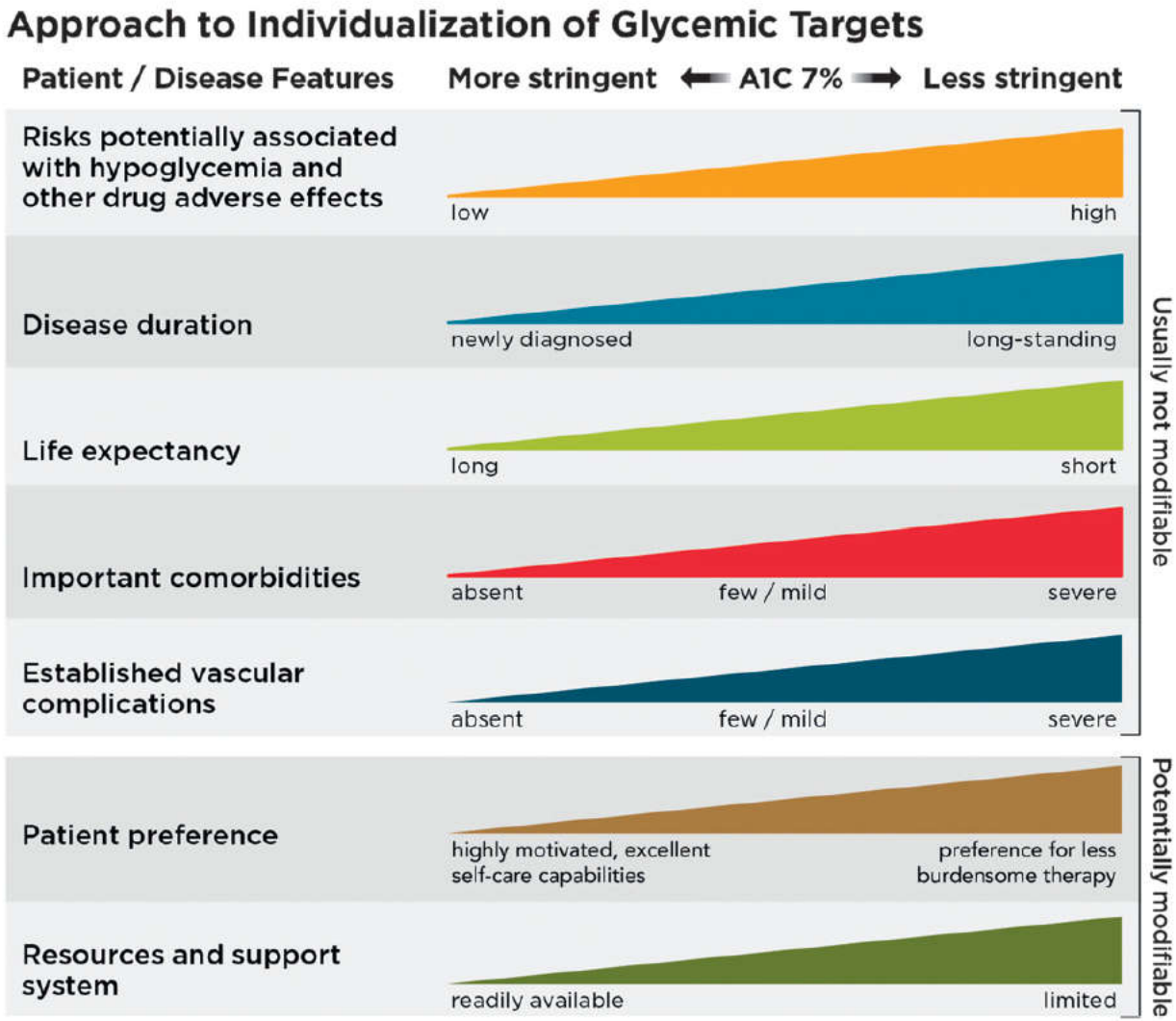
- Patients had type 2 diabetes and either established CVD or cardiovascular risk factors
- Compared intensive therapy (Targeting a1c <6%) vs standard therapy (7-7.9%)
- Primary outcome was composite of nonfatal MI, stroke, or death from CVD
- No significant difference in primary outcome
- Higher mortality in intensive therapy group (1.41% vs 1.14% per year, hazard ratio 1.22, P 0.04) lead to discontinuation after 3.5 years of follow up

The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med 2008;358:2545-2559.



The Action to Control Cardiovascular Risk in Diabetes Study Group. N Engl J Med 2008;358:2545-2559.

- ADA recommends modifying A1c goals based on disease duration, comorbidities
  - ADA recommend less stringent A1c goal such as <8% for patients with advanced macrovascular complications

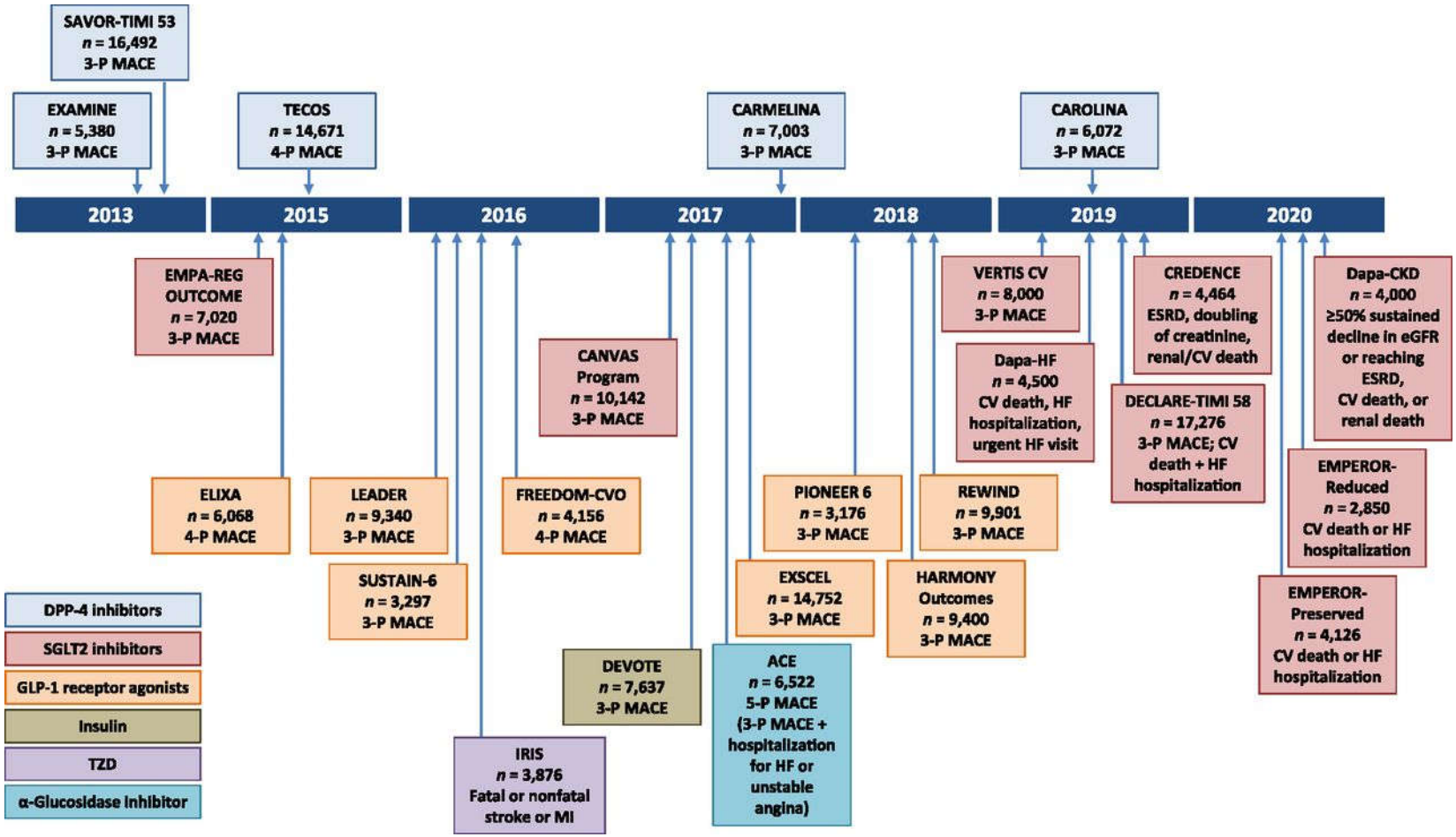


ADA 2019 Standards of Care

Cardiovascular outcome trials (CVOTs)

- Since 2008, the FDA requires cardiovascular safety trials for diabetes medications
- Primary endpoint in many trials is major adverse cardiac outcomes (MACE) including cardiovascular death, nonfatal MI and nonfatal stroke
- Several medications decrease cardiovascular morbidity and mortality in patients with DM2 and established CVD
  - Empagliflozin and liraglutide demonstrated reductions in cardiac death
- SGLT2 inhibitors are preferred in patients with heart failure (or high risk of heart failure)
- Less data for lower risk patients

Completed and ongoing CVOTs (6–14,39,44–58). 3-P, 3-point; 4-P, 4-point; 5-P, 5-point.

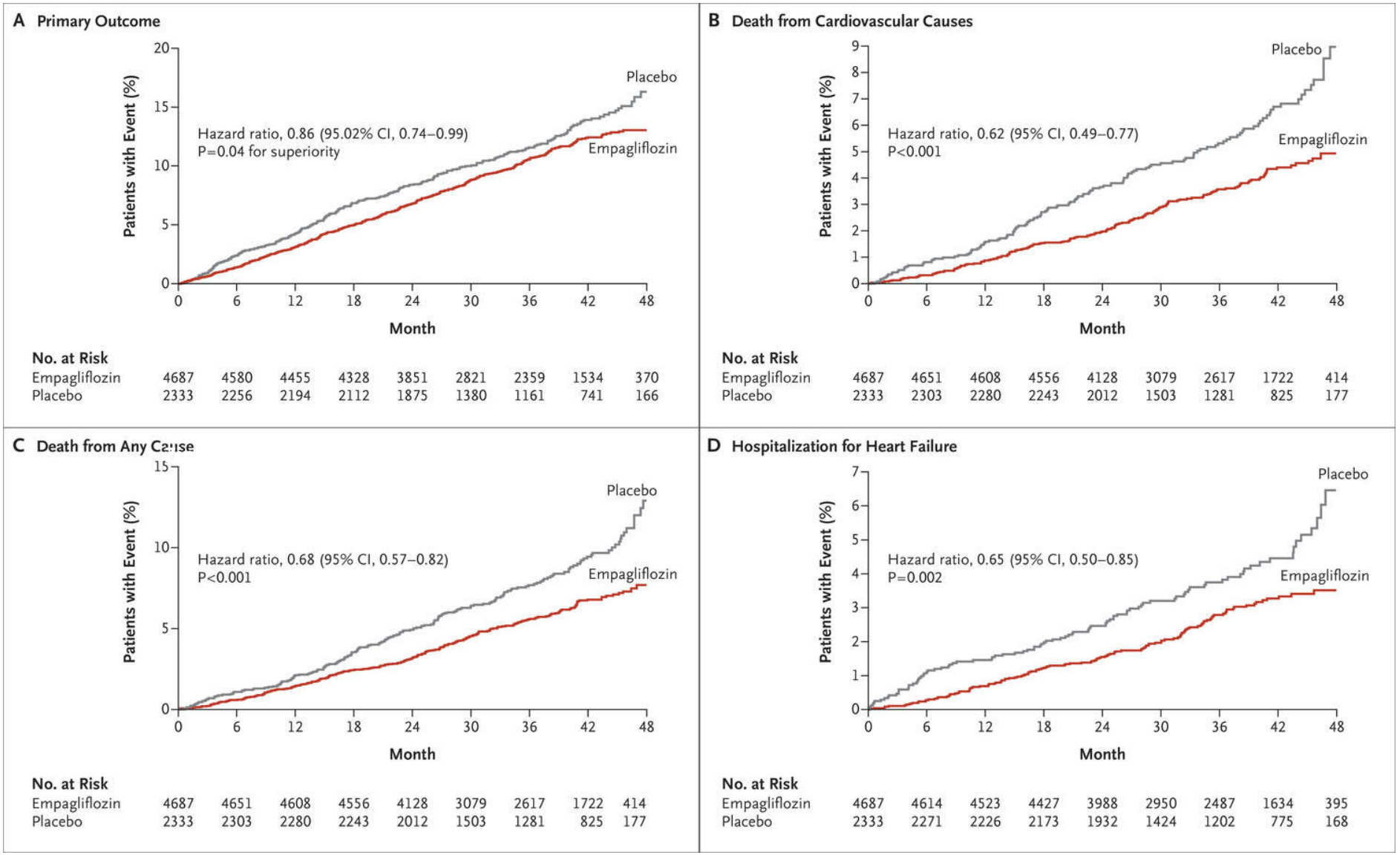


William T. Cefalu et al. Dia Care 2018;41:14-31

American Diabetes Association.

Empagliflozin

- EMPA-REG OUTCOME- patients had established cardiovascular disease and type 2 diabetes
- Primary outcome (composite of death from cardiovascular causes, nonfatal MI or stroke) occurred in 10.5% in treatment group vs 12.1% in placebo group (hazard ratio 0.86)
  - Treatment reduced composite outcome by 14%
- Significantly lower rates of death from cardiovascular cause in treatment group, 3.7% vs 5.9% in placebo; HR 0.62, 38% relative risk reduction
  - FDA added indication to reduce risk of cardiovascular death in patients with type 2 DM and established CVD
- 35% reduction in hospitalization for heart failure compared with placebo; benefit consistent in patients with and without prior hx of heart failure



Zinman B et al. N Engl J Med 2015;373:2117-2128.

Canagliflozin

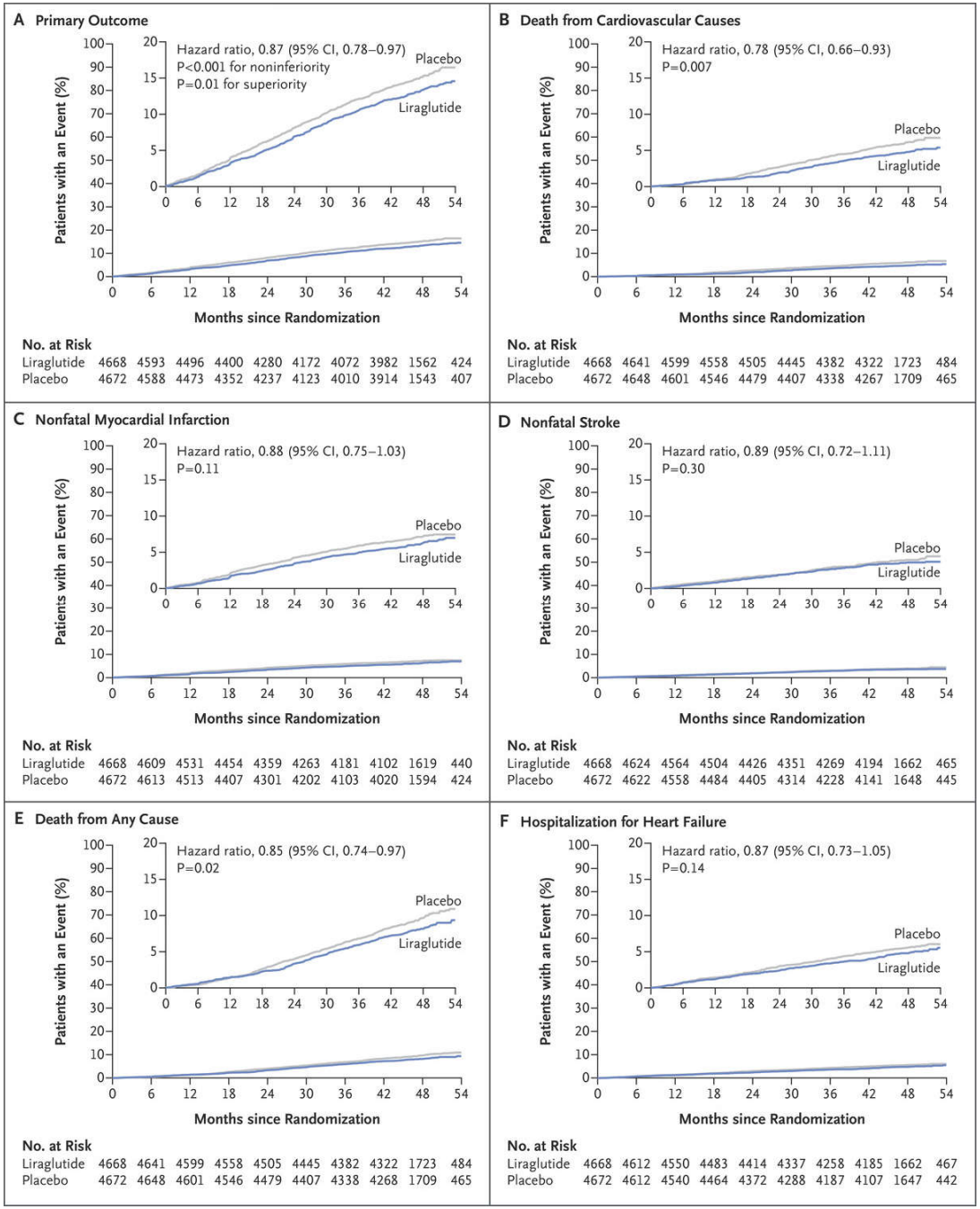
- CANVAS- 2/3 of pts had established CVD
- Treatment significantly reduced composite outcome of CV death, MI, or stroke- 26.9 vs 31.5%, HR 0.86
- there was not a statistically significant difference in cardiovascular death (HR 0.87 [95% CI 0.72–1.06]).
- 33% reduction in hospitalization for heart failure with canagliflozin versus placebo
- There was increased risk of lower-limb amputation with canaglifozin
- Indications in prescribing information:
  - to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease (1)
  - to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria

Dapagliflozin

- No significant differences in primary outcome with treatment vs placebo
- Significant reduction in hospitalization for heart failure
- Reduces all cause mortality and worsening heart failure in patients with or without diabetes

GLP-1: Liraglutide

- LEADER- pts with DM2 at high risk for CVD or with established CVD (in 80%)
- Primary composite outcome (MI, stroke, or CV death) occurred in 13% in treatment group, 14.9% in placebo group (HR 0.87)
- Deaths from cardiovascular causes significantly reduced in liraglutide group vs placebo (4.7% vs 6%), HR 0.78
- FDA approved to reduce risk of adverse cardiovascular events, including MI, stroke, and cardiovascular death in pts with DM2 and established CVD

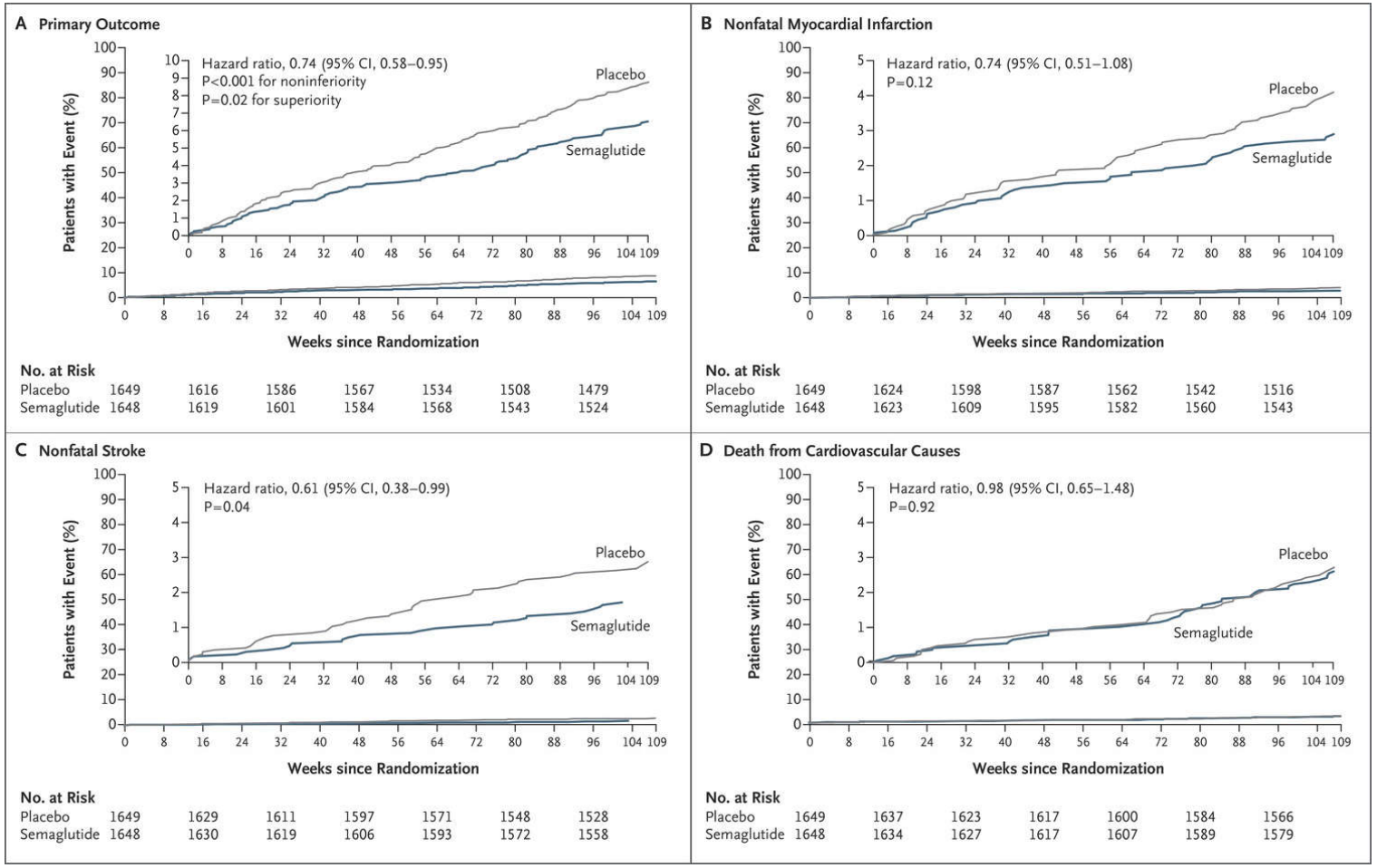


Marso SP et al. N Engl J Med 2016;375:311-322.

Semaglutide

- Once weekly GLP-1
- Sustain-6 trial- Primary outcome (composite of death from CVD, nonfatal MI or stroke) occurred in 6.6% in treatment group vs 8.9% in placebo, HR 0.74
  - Risk of cardiovascular death similar
- More treatment discontinuation due to adverse effects (GI)
- More diabetic retinopathy complications

Semaglutide



Marso SP et al. N Engl J Med 2016;375:1834-1844.

Dulaglutide

- Primary endpoint occurred in fewer patients in the dulaglutide group (12 versus 13.4 percent, HR 0.88
- Among individual components of composite outcome, occurrence of nonfatal stroke significantly lower in treatment group

Comparison of all-cause mortality reduction

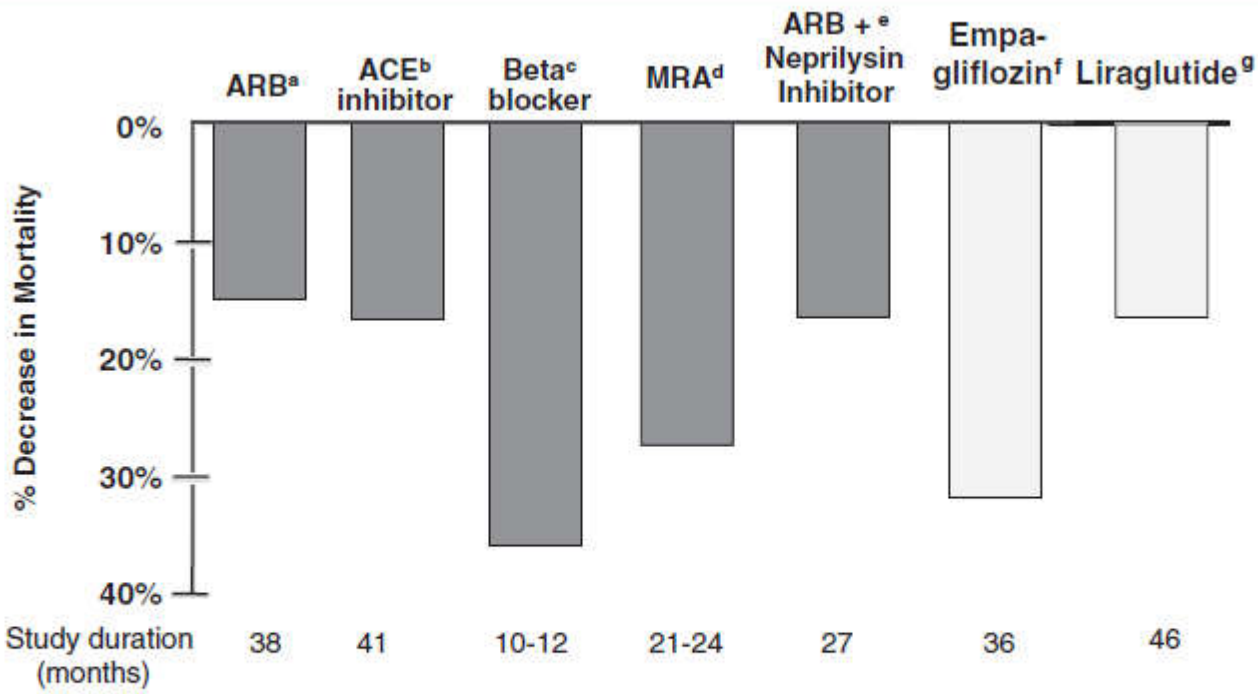


Figure 5 Comparison of all-cause mortality reduction observed in heart failure trials with the EMPA-REG OUTCOME and LEADER cardiovascular outcome trials in patients with diabetes. [a]SOLVD Treatment[69], [b]CHARM Alternative[70], [c]COPERNICUS[71] and MERIT-HF[72], [d]RALES[73] and EMPHASIS-HF[74], [e]PARADIGM[75], [f]EMPA-REG OUTCOME[65], [g]LEADER.[51]

Fitchett et al. Eur J Heart Fail. 2017 Jan;19(1):43-53

Metformin

- Decreased cardiovascular events in certain populations
  - UKPDS study- reduced risk of macrovascular complications in metformin group
  - In trial of patients with coronary heart disease, fewer cardiovascular events or death in metformin group vs SFU group
- In patients with DM2 and stable CHF, can be used if GFR remains >30 ml/min; avoid in pts with unstable CHF

Sulfonylureas

- There does not appear to be increased risk of cardiovascular events with second generation SFU (glimepiride, glipizide), but studies suggest higher rates of cardiac events with SFU than metformin (metformin has protective effect)
- In patients who have had an MI, treatment w/ SFU may be associated with poorer outcomes

Insulin

- Insulin does not seem to prevent or increase cardiovascular events

TZD

- Pioglitazone potential MACE benefit, BUT Increased risk of heart failure, weight gain, fluid retention, fractures

DPP-4 inhibitors

- No cardiovascular benefits in trials of DPP-4 inhibitors, possible increased risk of heart failure w/ saxagliptin

Table 2 Impact of glucose-lowering drugs on major adverse cardiac event outcome, and heart failure hospitalization

	MACE outcome	HF Outcome	Use in HF
Insulin	↔	↔	✓
Metformin	↔	↔	✓
SU	?↔	?↔	✓
TZD	Rosiglitazone ↔ Pioglitazone ↓	↑	✖
GLP-1 A	Lixisenatide ↔ Liraglutide ↓	↔	✓
DPP4-I	↔	Saxagliptin ↑	Caution
		Alogliptin ↑ns	Caution
		Sitagliptin ↔	✓
SGLT2-I	↓	↓	✓

↔ Unchanged, ↓ Decreased, ↑ Increased.
DPP4-I, dipeptidyl peptidase 4 inhibitor; GLP-1 A, glucagon-like peptide 1 agonist; HF, heart failure; MACE, major adverse cardiac event; SGLT2-I, sodium–glucose co-transporter 2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

Fitchett et al. Eur J Heart Fail. 2017 Jan;19(1):43-53

Cardiovascular Outcome Trials: Reported Studies to Date

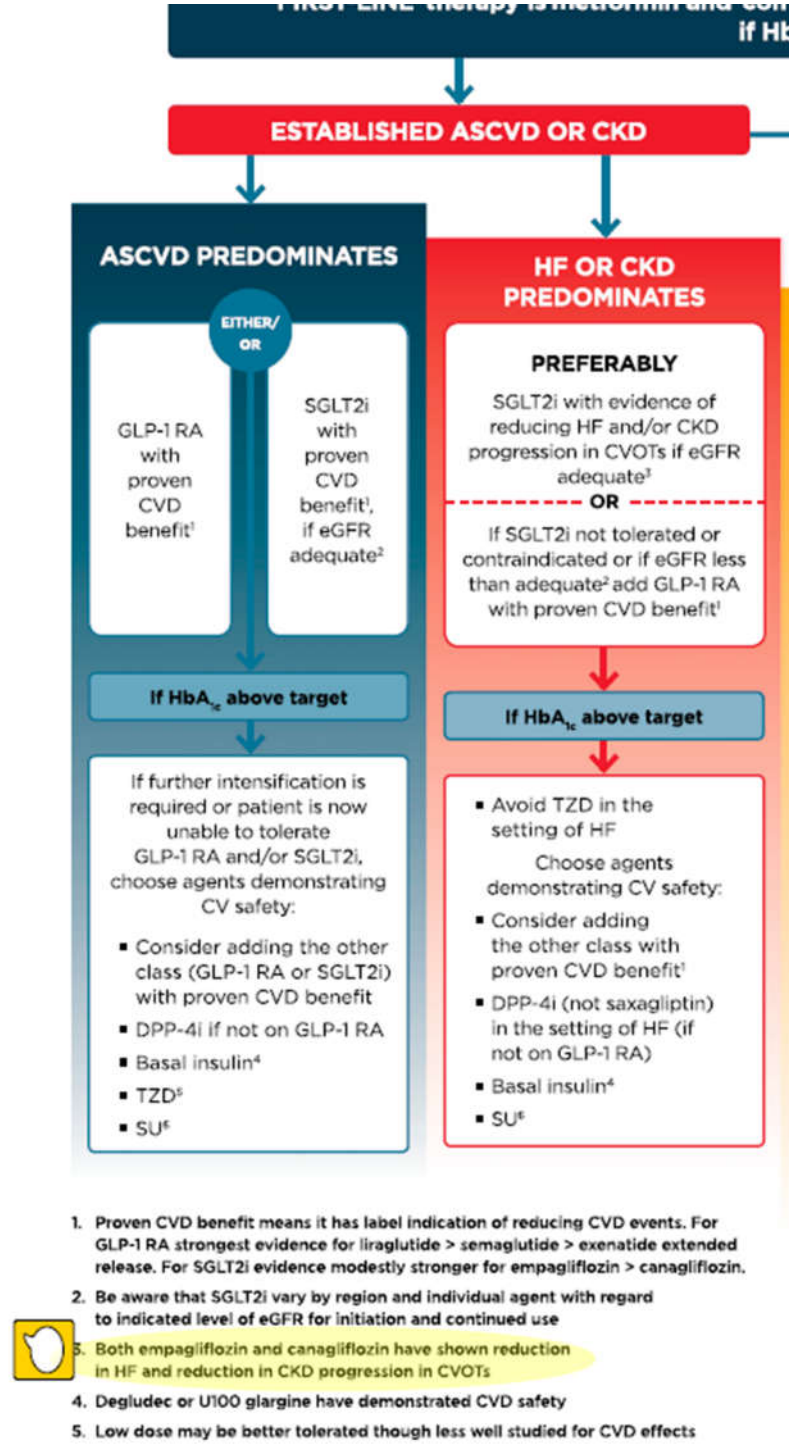
	Cardiovascular events	Mortality
SAVOR-TIMI 53 (DPP4i - saxagliptin)[2]	↔	↔
EXAMINE (DPP4i - alogliptin)[3]	↔	↔
TECOS (DPP4i - sitagliptin)[4]	↔	↔
ELIXA (GLP-1 RA - lixisenatide)[5]	↔	↔
LEADER (GLP-1RA – liraglutide)[7]	↓	↓
EXSCEL (GLP-1RA – exenatide QW)	↔	↔
SUSTAIN-6 (GLP-1RA – semaglutide)	↓	↔
EMPA-REG OUTCOME (SGLT2i –empagliflozin)[6]	↓	↓
CANVAS (SGLT-2i – canagliflozin)	↓	↔

1. Bergenstal RM et al. *Am J Med* 2010;123:374.e18; ; 2. Scirica BM et al. *N Engl J Med* 2013;369:1317-26; 3. White WB et al. *N Engl J Med* 2013;369:1327-35.
4.Green JB et al. *N Engl J Med* 2015;373:232-42 5. Pfeffer MA et al. *N Engl J Med* 2015;373:2247-57; ; 6. Zinman B et al. *N Engl J Med* 2015;373:2117-28;
7. Marso SP et al. *N Engl J Med* 2016; epub ahead of print.

https://professional.diabetes.org/sites/professional.diabetes.org/files/media/wysham_cardiovascular_outcome_trials_of_diabetes_medications_0.pdf

	GLP-1			SGLT2		DPP-4		
MNIADs	Liraglutide	Semaglutide	Lixisenatide	Empagliflozin	Canagliflozin[a]	Saxagliptin	Alogliptin	Sitagliptin[b]
CVOT	LEADER	SUSTAIN 6	ELIXA	EMPA-REG	CANVAS	SAVOR	EXAMINE	TECOS
Composite MACE	0.87*	0.74*	1.02	0.86*	0.86*	1.00	0.96	0.98
CV death	0.78*	0.98	0.98	0.62*	0.87	1.03	0.79	1.03
Non-fatal MI	0.88	0.74	1.03^	0.87	0.85	1.95	1.08	0.95^
Non-fatal stroke	0.89	0.61*	1.12^	1.24	0.90	1.11	0.91	0.97^
Hospitalization for HF	0.87	1.11	0.96	0.65*	0.67	1.27*	1.07	1.00
All-cause mortality	0.85*	1.05	0.94	0.68*	0.87	1.11	0.88	1.01

https://professional.diabetes.org/sites/professional.diabetes.org/files/media/wysham_cardiovascular_outcome_trials_of_diabetes_medications_0.pdf



ADA 2019 Figure 9.1

Jardiance- prescribing information

- The recommended dose of JARDIANCE is 10 mg once daily, taken in the morning, with or without food
- Dose may be increased to 25 mg once daily
- Assess renal function before initiating JARDIANCE. Do not initiate JARDIANCE if eGFR is below 45 mL/min/1.73 m2
- Discontinue JARDIANCE if eGFR falls persistently below 45 mL/min/1.73 m2

Victoza- prescribing information

- Inject VICTOZA® subcutaneously once-daily at any time of day, independently of meals, in the abdomen, thigh or upper arm
- • Adult Dosage: Initiate at 0.6 mg daily for one week then increase to 1.2 mg daily. If additional glycemic control is required, increase the dose to 1.8 mg daily after one week of treatment with the 1.2 mg daily dose

Summary

- Lower A1c is not necessarily better in high risk patients
- In patients with DM2 and established CVD, incorporate an agent with strong evidence for cardiac risk reduction
  - Several SGLT2 inhibitors and GLP-1 agonists may reduce CVD events
  - EMPA-REG OUTCOME and LEADER (liraglutide) trials showed decreased mortality
  - SGLT2 inhibitors have shown benefit in heart failure