Management of Type 2 Diabetes: An Update and Review of Non-Injectable Pharmacological Treatment

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Nothing to disclose

Objectives

- Describe the prevalence and burden of diabetes mellitus across the country, specifically among AI/AN communities.
- Review the standards of care for the management of patients with diabetes.
- Discuss the current non-injectable pharmacologic treatment of hyperglycemia and complications mitigation.

National Diabetes Statistics Report

Estimates of Diabetes and Its Burden in the United States

Among the US population overall, crude estimates for 2019 were:

Diabetes

- **Total:** 37.3 million people have diabetes (11.3% of the US population)
- **Diagnosed:** 28.7 million people, including 28.5 million adults
- **Undiagnosed:** 8.5 million people (23.0% of adults are undiagnosed)

Prediabetes

- **Total:** 96 million people aged 18 years or older have prediabetes (38.0% of the adult US population)
- **65 years or older:** 26.4 million people aged 65 years or older (48.8%) have prediabetes

Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed 4/22/23.

Diabetes Report Card 2021

The *Diabetes Report Card* provides current information on the status of diabetes and its complications in the United States. It has been published every 2 years since 2012 by the Centers for Disease Control and Prevention (CDC).

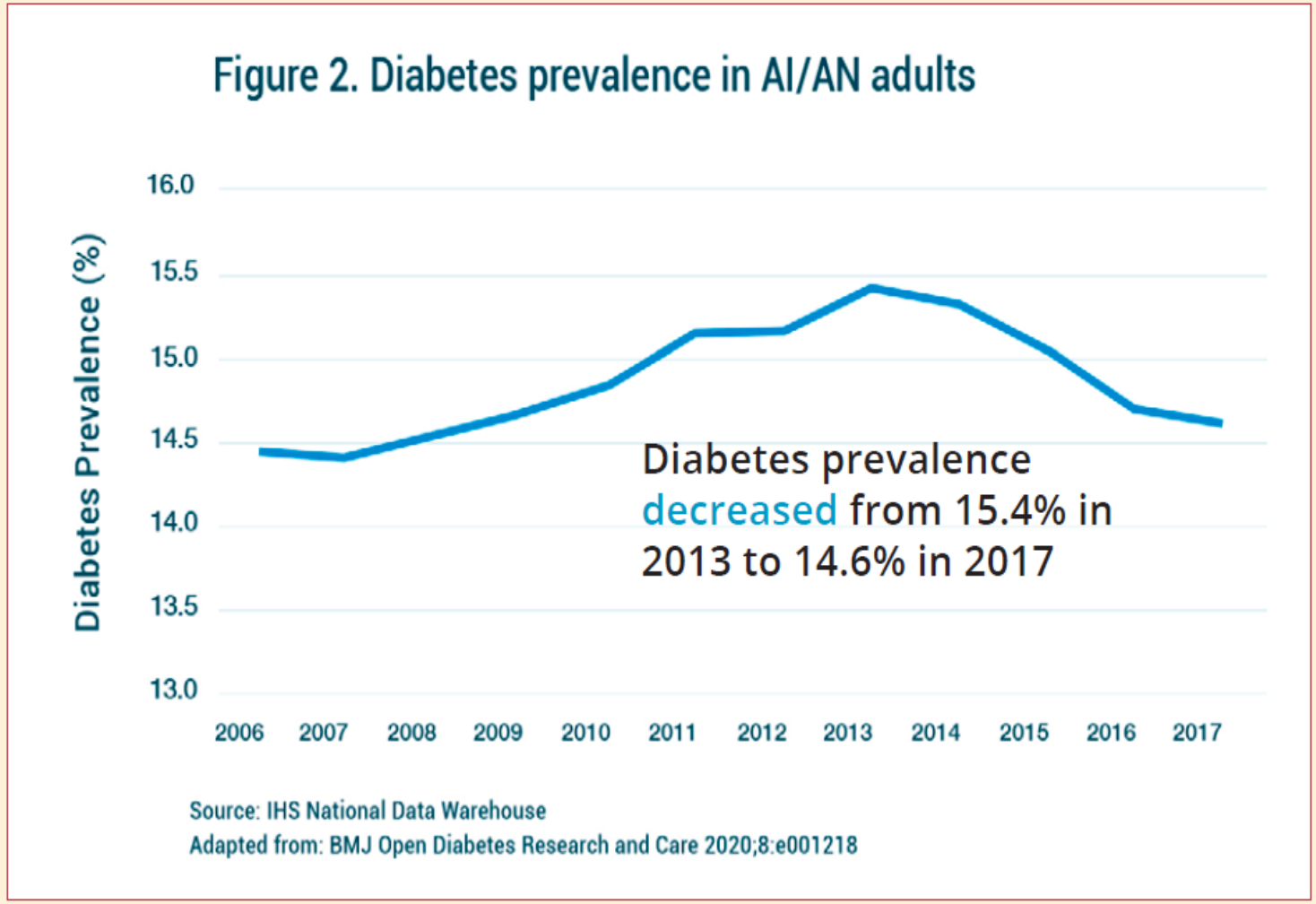
- After almost 2 decades of continual increases, the incidence of newly diagnosed cases of diabetes in the United States decreased from 9.3 per 1,000 adults in 2009 to 5.9 per 1,000 adults in 2019.[10]
- Prevalence of prediabetes among US adults remained steady from 2005–2008 to 2017–2020. However, notification of prediabetes status nearly tripled (from 6.5% to 17.4%).[10]
- American Indian or Alaska Native, non-Hispanic Black, Hispanic, and non-Hispanic Asian people are more likely to be diagnosed with diabetes than non-Hispanic White people (14.5%, 12.1%, 11.8%, 9.5%, and 7.4%, respectively).[10]
- During the COVID-19 pandemic, diabetes emerged as an underlying condition that increases the chance of severe illness. Nearly 4 in 10 adults who died from COVID-19 in the United States also had diabetes.[11]

Centers for Disease Control and Prevention. *Diabetes Report Card 2021*. US Dept of Health and Human Services; 2022.

Changing the Course of Diabetes: Charting Remarkable Progress

Diabetes Prevalence

For the first time, diabetes prevalence in AI/AN adults has decreased – and has done so consistently for 4 years, dropping from 15.4 percent in 2013 to 14.6 percent in 2017 (Figure 2).[2] Neither the general United States (U.S.) population, nor any other U.S. racial/ethnic group has shown a decrease in prevalence.[3] Given that diabetes-related mortality has also decreased,[4] this improvement in prevalence appears to be driven by a reduction in new cases of diabetes in AI/AN adults.



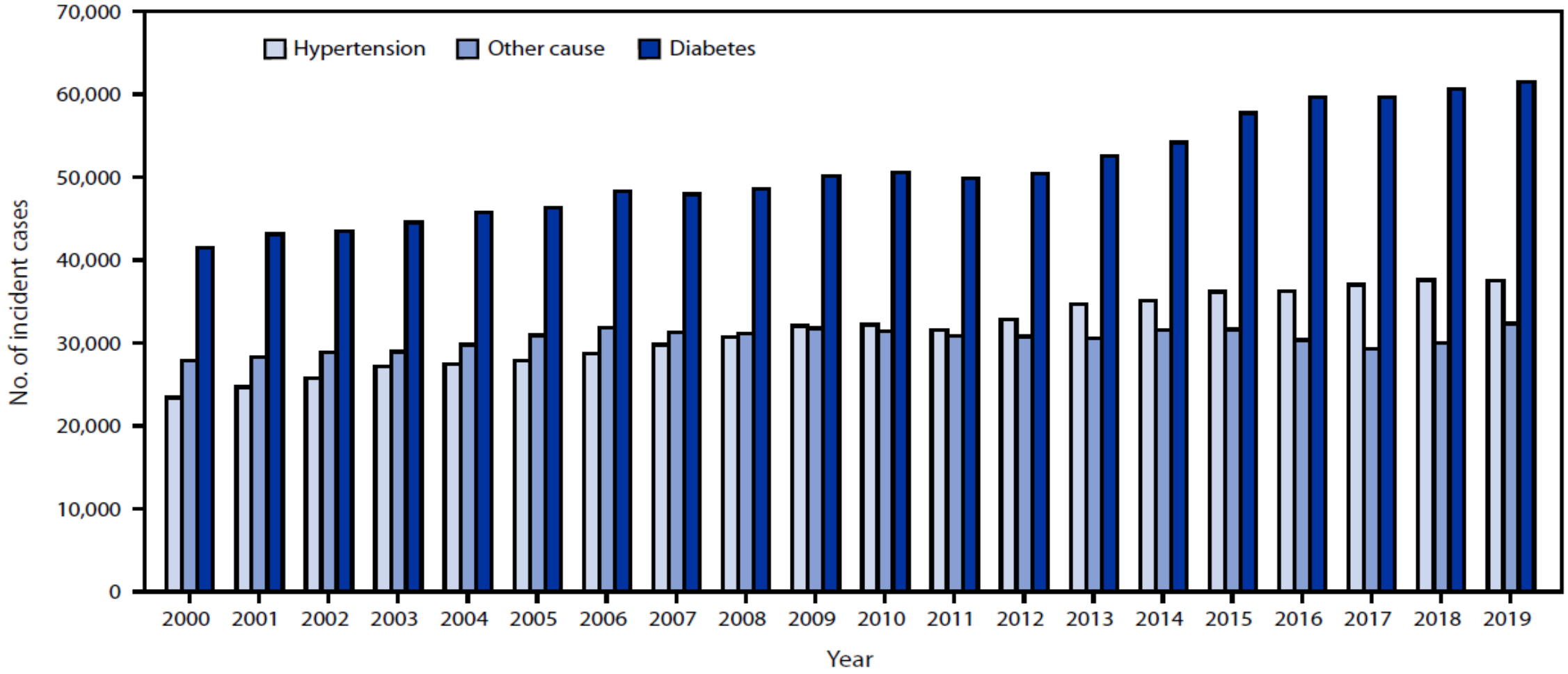
Complications Development and Co-Morbid Conditions

- 39.2 % with CKD, Stages 1-4 (CKD-EPI eGFR data), 2017-2020
  - 15.7% with moderate to severe CKD (Stage 3-4, eGFR 15-<60 ml/min)
  - Leading cause of ESRD with 62K developed ESRD in 2018; crude prevalence attributed to diabetes 38.8% (26.1% HTN, 14.9% glomerulonephritis.
- Diabetes is the leading cause of new cases of blindness among adults aged 18-64 years. 11.8% reported severe vision difficulty or blindness
- Emergency Room Visits (2018)
  - Diabetes as any listed diagnosis – 17.18 million (68.3/1000 adults), 35% admitted
  - Hyperglycemic crisis – 248 thousand (9.9/1000): DKA 223K, HHS 25K; 85.5% admitted
  - Hypoglycemia (BS<70 mg/dL)- 242 K (9.6/1000),23% admitted
- Hospitalizations (2018)
  - Diabetes as any listed diagnosis – 8.249 million (327/1000 adults)
  - Major CVD 1.871mil (74.4/1000); Ischemic Heart Disease 440K (17.5/1000), Stroke 334K (13.3/1000)
  - Lower-extremity amputation- 154K (6.1/1000)

Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed 4/22/23.

Burden of Diabetes: ESRD

FIGURE 1. Number of reported incident cases of end-stage kidney disease, by primary cause — United States, 2000–2019*



* Data from United States Renal Data System, 2021 Annual Data Report, Reference Tables. https://adr.usrds.org/2021/reference-tables

Rios Burrows N, Koyama A, Pavkov ME. *Reported Cases of End-Stage Kidney Disease – United States, 200-2019. MMWR* 2022;71:412-415

Burden of Diabetes: ESRD

TABLE. Number of reported incident and prevalent cases of end-stage kidney disease, by selected characteristics — United States, 2000 and 2019*

Characteristic	Incident cases			Prevalent cases		
	2000 No. (%)†	2019 No. (%)†	Percentage change	2000 No. (%)†	2019 No. (%)†	Percentage change
Total	92,660 (100.0)	131,422 (100.0)	41.8	358,247 (100.0)	783,594 (100.0)	118.7
Age group, yrs						
<45	14,194 (15.3)	16,230 (12.3)	14.3	87,769 (24.5)	118,208 (15.1)	34.7
45–64	32,370 (34.9)	48,874 (37.2)	51.0	144,703 (40.4)	331,220 (42.3)	128.9
65–74	23,494 (25.4)	35,744 (27.2)	52.1	71,825 (20.0)	199,005 (25.4)	177.1
≥75	22,602 (24.4)	30,574 (23.3)	35.3	53,950 (15.1)	135,161 (17.2)	150.5
Sex						
Men	49,500 (53.4)	76,631 (58.3)	54.8	195,216 (54.5)	456,821 (58.3)	134.0
Women	43,160 (46.6)	54,791 (41.7)	26.9	163,031 (45.5)	326,773 (41.7)	100.4
Race and Ethnicity						
White	51,156 (55.2)	67,919 (51.7)	32.8	180,636 (50.4)	349,596 (44.7)	93.5
Black	25,917 (28.0)	33,700 (25.6)	30.0	116,376 (32.5)	234,399 (29.9)	101.4
Hispanic	11,297 (12.2)	20,790 (15.8)	84.0	42,129 (11.8)	140,961 (18.0)	234.6
Asian	2,507 (2.7)	6,256 (4.8)	149.5	11,839 (3.3)	41,393 (5.3)	249.6
American Indian or Alaska Native	1,041 (1.1)	1,299 (1.0)	24.8	4,538 (1.3)	7,949 (1.0)	75.2
Native Hawaiian or other Pacific Islander	742 (0.8)	1,458 (1.1)	96.5	2,729 (0.8)	9,296 (1.2)	240.6
Primary cause						
Diabetes	41,458 (44.7)	61,522 (46.8)	48.4	129,699 (36.2)	307,385 (39.2)	137.0
Hypertension	23,384 (25.2)	37,539 (28.6)	60.5	83,553 (23.3)	209,437 (26.7)	150.7
Other cause	27,818 (30.0)	32,361 (24.6)	16.3	144,995 (40.5)	266,772 (34.0)	84.0

* Data from United States Renal Data System, 2021 Annual Data Report, Reference Tables. https://adr.usrds.org/2021/reference-tables
† Percentages might not sum to 100% because of rounding.

Rios Burrows N, Koyama A, Pavkov ME. *Reported Cases of End-Stage Kidney Disease – United States, 200-2019. MMWR* 2022;71:412-415

Burden of Diabetes: ESRD

- Incident and prevalent ESRD cases was slower in AI/AN than other populations from 2000-2019.
- “Population health and team-based approach to diabetes care including kidney disease testing and case management…supported by SDPI funding … may explain the lower percentage change”
- Goal of Advancing American Kidney Health Initiative of US HHS is to reduce incidence of ESRD by 25% by 2030.
- Need to address HTN and Diabetes management

Rios Burrows N, Koyama A, Pavkov ME. *Reported Cases of End-Stage Kidney Disease – United States, 200-2019. MMWR* 2022;71:412-415

Incidence of Microvascular Complications

Retinopathy

- Incidence of any diabetic retinopathy 69.6/1000 patient-years assessed through the JVN Tele-ophthalmology Program from 2015 to 2016-2019.
- Low DR incidence rate compares to other populations and similarly associated with duration of diabetes, higher A1C levels, and insulin therapy (w/wo oral meds)
- The low incidence rates support the ADA recommendation of biennial retinal examinations among patients with diabetes served by IHS.

Fonda SJ, Bursell SE, Lewis DG, Clary D, Shahon D, Cavallerano J. *Incidence and Progression of Diabetic Retinopathy in American Indian and Alaska Native Individuals Served by the Indian Health Service, 2015-2019. JAMA Ophthalmol*. 2023. doi:10.1001/jamaophthalmol.2023.0167

Incidence of Microvascular Complications

Nephropathy: CKD

- Incidence of DKD (new eGFR<60 or UACR >30 or UPCR > 150) from 2015-2016 was 81.6/1000 P-Y, 2017-2018 was 73.7/1000 P-Y and 2019-2020 was 64/1000 P-Y
- The incidence rates of DKD varied among ethnic groups in the cohort compared to White Americans; higher rates among NH/Pacific Islanders, African American, AI/AN, and Hispanic Americans; lower rate among Asian Americans.
- Higher Incidence rates associated with longer duration of diabetes, higher A1C levels, and HTN

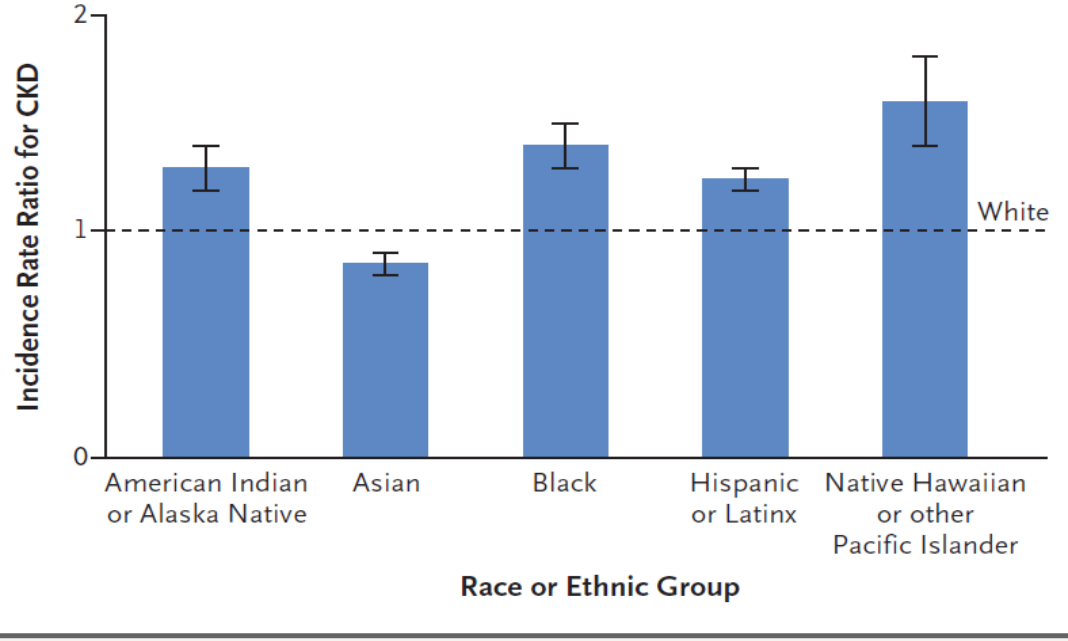


Figure 1. Incidence Rate Ratios for CKD among Patients with Diabetes. Shown are the incidence rate ratios for chronic kidney disease (CKD) among patients with diabetes, stratified according to race and ethnic group, between 2015 and 2020. The dashed line represents the incidence rate ratio among White patients (reference group). The analysis was adjusted for age and sex. I bars indicate 95% confidence intervals.

Tuttle KR, Jones CR, Daratha KB, et al. *Incidence of Chronic Kidney Disease among Adults with Diabetes, 2015-202. N Eng J Med.* 2022;387(15).

Comprehensive Assessment and Treatment

- **Patient-centered care**
  - **“providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patients values guide all clinical decisions”.**
- **Health literacy and numeracy**
- **Self-management resources and affordability**
- **Consideration of other comorbid conditions that impact self-care**
  - **Depression, cognitive impairment**
  - **Periodontal Disease**
  - **Sensory loss; hearing or vision or sensations**
  - **Arthritis; frailty**
  - **Liver disease and other gastrointestinal problems**

American Diabetes Association. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Care in Diabetes-2023*. *Diabetes Care* 2023;46(Suppl 1):S49-S67. https://doi.org/10.2337/dc23-S004.

Diabetes Self-Management Education and Support (DSMES)

- **Self-Management (self-care)**
  - **Practice healthy eating and physical activity**
  - **Use medication properly; knowing efficacy and adverse effects**
  - **Monitor and track changes**
  - **Learn to cope with stress and setbacks; problem solve**
  - **Teach self-advocacy; navigate health systems; assess SDOH**
  - **Achieve target goals**
- **Evaluation of self-management needs (professional services)**
  - **Four critical times- 1) at diagnosis, 2) annually and/or not meeting treatment goals, 3) when complicating factors develop, 4) when transitions in life and care occur.**
  - **Who, when, and where?**

American Diabetes Association. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: *Standards of Medical Care in Diabetes-2022. Diabetes Care* 2022;45(Suppl. 1):S60-S82. https://doi.org/10.2337/dc22-S005.

Medical Nutrition Therapy (MNT)

- Foundation of type 2 diabetes management: beyond hyperglycemia
- Ideally, provided by Registered Dietitian/Registered Dietitian Nutritionist
  - At the time of diagnosis and as needed
  - MNT shown to reduce A1C, 0.5 to 2.0 % similar to some medication effectiveness
  - Covers nutrition assessment, individualized interventions, and evaluation with ongoing followup to support long-term lifestyle changes
- MacroNutrients
  - Fats: minimize trans fat, choose mono or polyunsaturated fats (limit saturated fat to < 10% daily consumption)
  - Carbohydrates: eat variety of fruits and vegetables, choose high-fiber foods (25-30 gm per day); limit added sugars and avoid sugar-sweetened beverages
  - Proteins: choose low-fat animal and plant based proteins
  - Other: Sodium-2300 mg/day, alcohol, fluids- water and other low calorie beverages
- Physical Activity: At least, 150 minutes of moderate intensity activity per week.

NIDDK. Guiding Principles for the Care of People with or at Risk for Diabetes

Summary of glycemic recommendations for many nonpregnant adults with diabetes (Table 6.3)

A1C	<7.0% (53 mmol/mol)*#
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients.

#CGM may be used to assess glycemic target as noted in Recommendation 6.5b and Fig. 6.1. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations (as per Fig.6.2).

†Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

American Diabetes Association. 6. Glycemic Targets: *Standards of Care in Diabetes-2023. Diabetes Care* 2023;46(Suppl. 1):S97-S110. https://doi.org/10.2337/dc23-S0066.

Diabetes Type 2: Hyperglycemia Development

- The hyperglycemia in type 2 diabetes appears to result from a progressive loss of adequate β-cell insulin secretion, frequently on the background of insulin resistance.
  - β-cell secretory dysfunction is related to genetics, inflammation, or metabolic stress
  - Insulin resistance is related to obesity and/or visceral adiposity
  - Glucose toxicity (hyperglycemia begets hyperglycemia)
- Progressive dysglycemia occurs for many years starting with prediabetes
  - Interventions may delay or prevent diabetes development
  - Fasting and post-prandial hyperglycemia result from worsening β-cell failure

American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Care in Diabetes-2023*. *Diabetes Care* 2023;46 Suppl 1):S19-S40. https://doi.org/10.2337/dc23-S002.

Oral Anti-Diabetes Medications

Medication	Mechanism	Efficacy (↓ A1C)	Other Benefits	Side effects; Caution	Comments
Metformin (biguanide)	Decrease Hepatic glucose production	1.0-2.0%	CVD; Dementia; Use in Youth	GI symptoms; eGFR>30 ml/min	B12 deficiency Lactic Acidosis
Sulfonylurea/Glinides (glipizide, glimepiride, glyburide, repaglinide, nateglinide)	Stimulate insulin secretion-SUR/K+ATPase	1.0-2.0%	Rapid effect; neutral/worsening CVD	Hypoglycemia; Weight Gain; Accelerates β-cell failure	cost
Thiazolidinediones (pioglitazone, rosiglitazone)	Reduce insulin resistance by activating PPARγ nuclear receptor	1.0-2.0%	CVD; NAFLD and NASH; No hypoglycemia	Weight gain; Edema; HF hospitalization	Slow activation and glycemic effects, 2-4 weeks

American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes-2023*. *Diabetes Care* 2023;46(Suppl 1):S140-S157. https://doi.org/10.2337/dc23-S009.

Oral Anti-Diabetes Medications

Medication	Mechanism	Efficacy (↓A1C)	Other Benefits	Side effects; Caution	Comments
DPP-4 Inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)	Increase GLP-1; insulin/decrease glucagon	0.5-1.0%	CVD neutral; Weight neutral	HF hospitalization – saxagliptin, alogliptin	All indications; renal dose adjustment
SGLT-2 Inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, bexagliflozin)	Inhibits Sodium Glucose Co-transporter 2; increase glycosuria	0.5-1.0%	CVD, CVD death; HF Hospitalization; Nephropathy; Weight loss; SBP	Need eGFR > 45 UTI & genital mycotic; acute kidney injury; DKA; Fournier's gangrene	Cost; Monitor renal function (stop if eGFR < 30)
GLP-1 RA (oral semaglutide)	Stimulates GLP-1 receptors; Increase insulin, decrease glucagon/appetite	1.0-2.0%	Weight loss; CVD trend lower	GI problems; Pancreatitis; MTC	Cost; nausea; vomiting

Other FDA-approved oral anti-diabetes medications include α-glucosidase inhibitors (acarbose, miglitol), bile acid sequestrant (colesevelam), and dopamine-2 agonist (bromocriptine).

American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes-2023*. *Diabetes Care* 2023;46(Suppl 1):S140-S157. https://doi.org/10.2337/dc23-S009.

USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*

+ASCVD†

Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.

+Indicators of high risk

While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)

+ASCVD/Indicators of High Risk

GLP-1 RA# with proven CVD benefit **EITHER/OR** SGLT2i§ with proven CVD benefit

If A1C above target

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
- TZD^

+HF

Current or prior symptoms of HF with documented HFrEF or HFpEF

+HF

SGLT2i§ with proven HF benefit in this population

+CKD

eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i§ with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

If additional cardiorenal risk reduction or glycemic lowering needed

Goal: Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycemic goals

Efficacy for glucose lowering

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD

Intermediate:
DPP-4i

Achievement and Maintenance of Weight Management Goals:

Set individualized weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1 RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If A1C above target

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g., diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF, and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and renal endpoints in individuals with T2D with established/high risk of CVD.

American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Care in Diabetes-2023*. *Diabetes Care* 2023;46(Suppl 1):S140-S157. https://doi.org/10.2337/dc23-S009.

Guidance for initiating oral anti-diabetes medication use

Assess glycemia and complications (emphasis on cardiorenal protection- CVD, HF, and CKD)

- At glycemic goal*
  - No CVD or HF and/or CKD – consider metformin
  - CVD or HF and/or CKD - prescribe SGLT-2 inhibitors
- Not at glycemic goal*
  - No CVD or HF and/or CKD – prescribe metformin
  - CVD or HF and/or CKD - prescribe SGLT-2 inhibitors

Reassess glycemia and complications, 3-6 month intervals

* A1C <7.0 % for most people with diabetes; consider more or less stringent consideration based on patient-centered approach.

Guidance for advancing oral anti-diabetes medication use

Reassess glycemia and complications (CVD, HF, and CKD)

- Not at glycemic goal*, consider
  - Metformin: start or optimize treatment
  - DPP-4 inhibitor: useful in older patients, mild side effects, HF
  - SGLT-2 inhibitor: low hypoglycemia risk, multiple side effects
  - Oral GLP-1 RA: weight loss, low hypoglycemia risk
  - TZDs: improves fatty liver, weight gain, edema, HF
  - Secretagogues (SU/glinides): hypoglycemia and weight gain
- Newly identified CVD, HF, and/or CKD
  - Prescribe SGLT-2 inhibitor (injectable GLP-1 RA is unable to use)

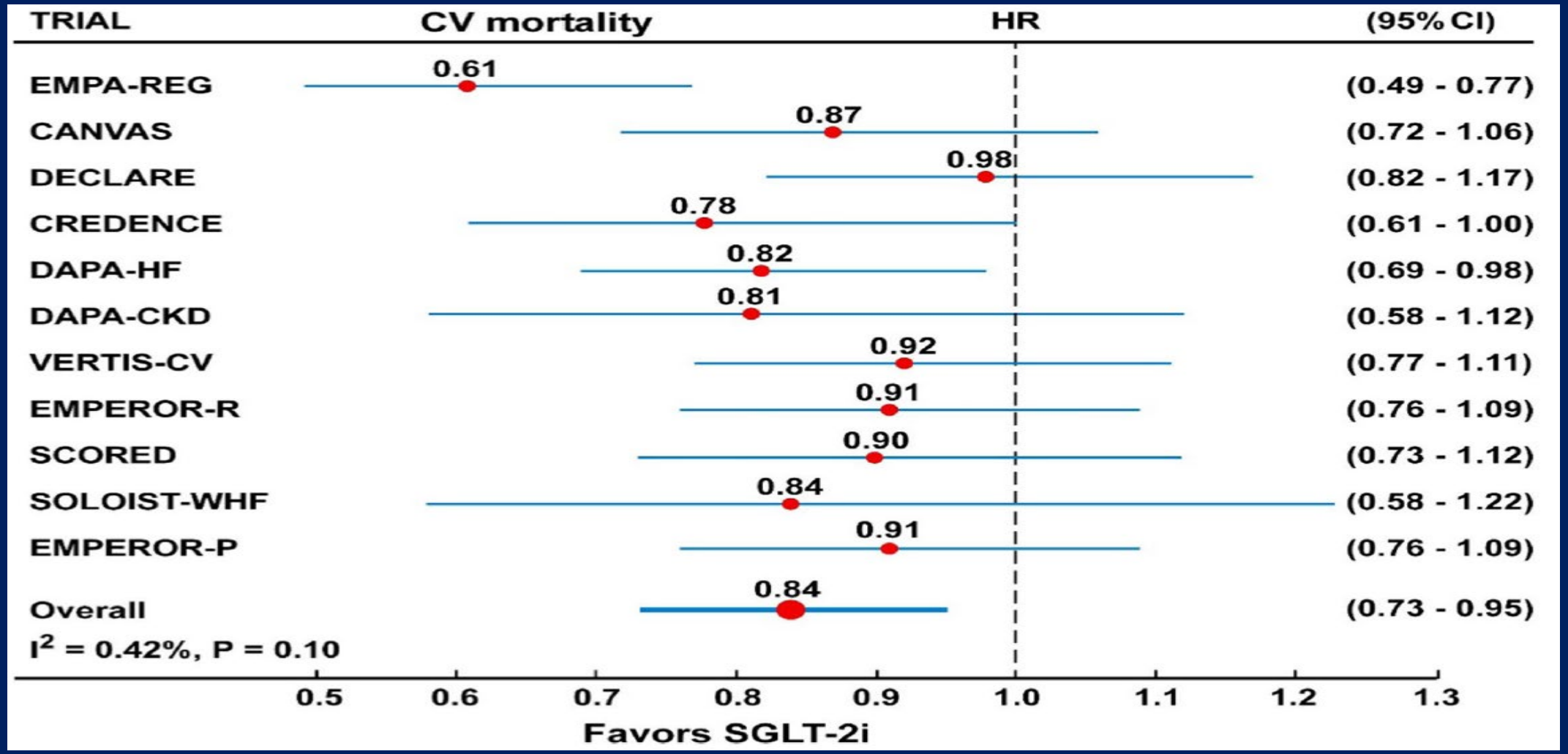
* A1C <7.0 % for most people with diabetes; consider more or less stringent consideration based on patient-centered approach.

SGLT-2 Inhibitors: CardioRenal Outcomes Trials

Medication (Study/# Pts)	Type of Patients	Duration	Outcome
Empagliflozin- (EMPA-REG 7,020)	Known CVD (99%)	3.1 yrs	MACE
Canagliflozin- (CANVAS 10,142)	Known CVD 71%	2.4 yrs	MACE
Dapagliflozin- (DECLARE 17,160)	Known CVD 40% CVD Risk Factors 60%	4.2 yrs	MACE
Ertugliflozin- (VERTIS CV 8,246)	Known CVD	3.0 yrs	MACE
Canagliflozin- (CREEDENCE 4,401)	Known CKD 100%; HF 17%	2.6 yrs	CKD
Dapagliflozin- (DAPA-CKD 4304)	Known CKD	2.4 yrs	CKD
Empagliflozin- (EMPEROR- R 3,730; EMPEROR- P 5,988)	Known HFreducedEF Known HFpreservedEF (40% w DM)	1.5 yrs 2.2 yrs	HHF, CV Death
Dapagliflozin- (DAPA-HF 4,744)	Known HFrEF Known HFpEF (40% w DM)	1.5 yr	HF, CV Death
Sotogliflozin- (SCORED 10,584)	Known CKD	1.5 yrs	HHF, CV Death
Sotogliflozin- (SOLOIST-WHF 1,222)	Known HF	0.75 yrs	HHF, CV Death

MACE: CVD death, Nonfatal MI, Nonfatal stroke; **HHF:** Hospitalization for Heart Failure and CVD Death; **CKD:** doubling creatinine, renal replacement, progressing or incident albuminuria, sustained eGFR decrease >40 % to < 60 ml/min

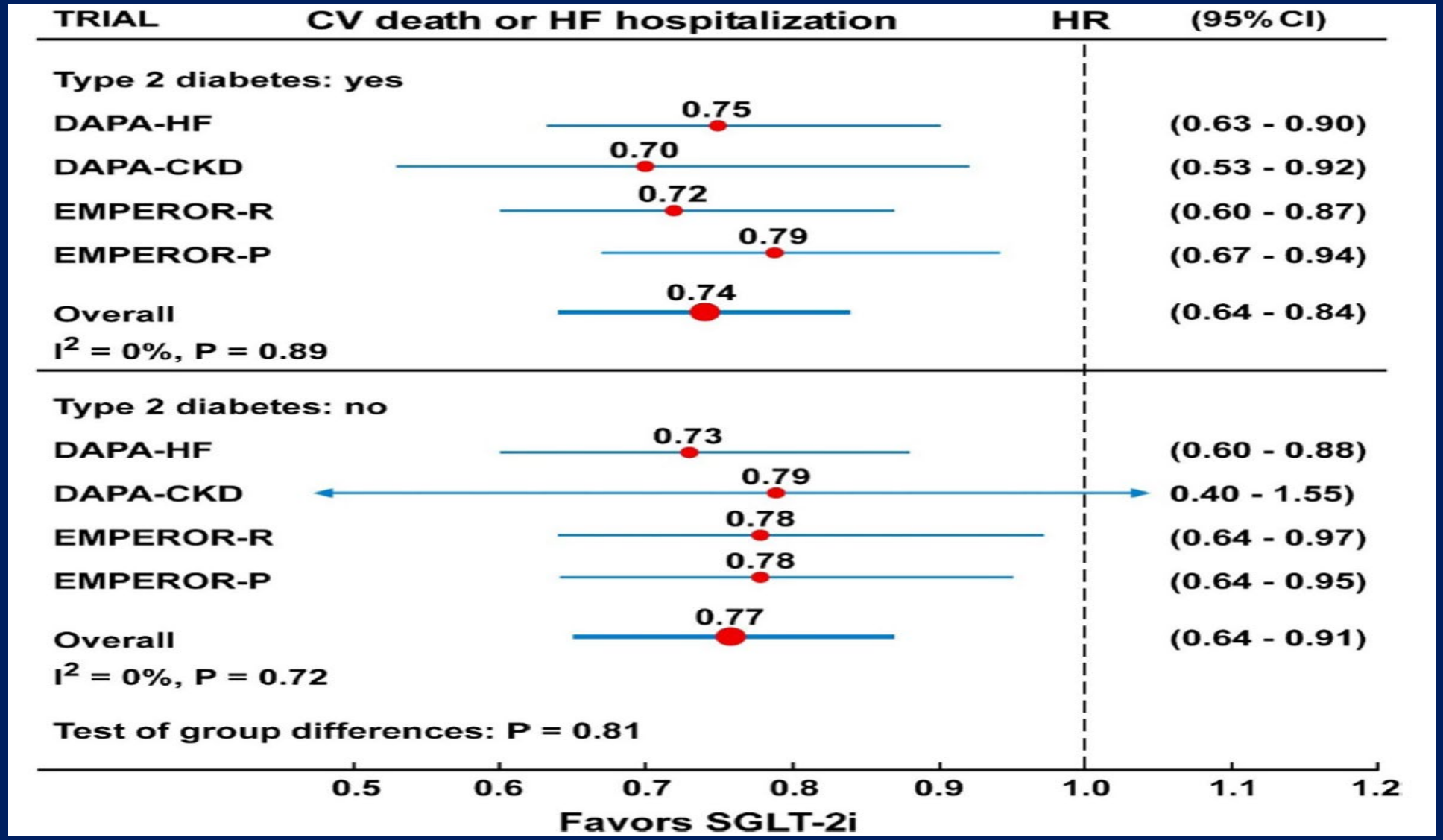
SGLT-2 Inhibitors: Cardiovascular Outcomes Trials



MACE: CVD death, Nonfatal MI, Nonfatal stroke

Giugliano D, Longo M, Scappaticcio L, et al. *SGLT-2 inhibitors and cardiorenal outcomes in patients with or without type 2 diabetes: a meta-analysis of 11 CVOTs. Cardiovascular Diabetology*. 2021;20:236. https://doi.org/10.1186/s12933-021-01430-3.

SGLT-2 Inhibitors: HHF/CV Mortality Outcomes Trials



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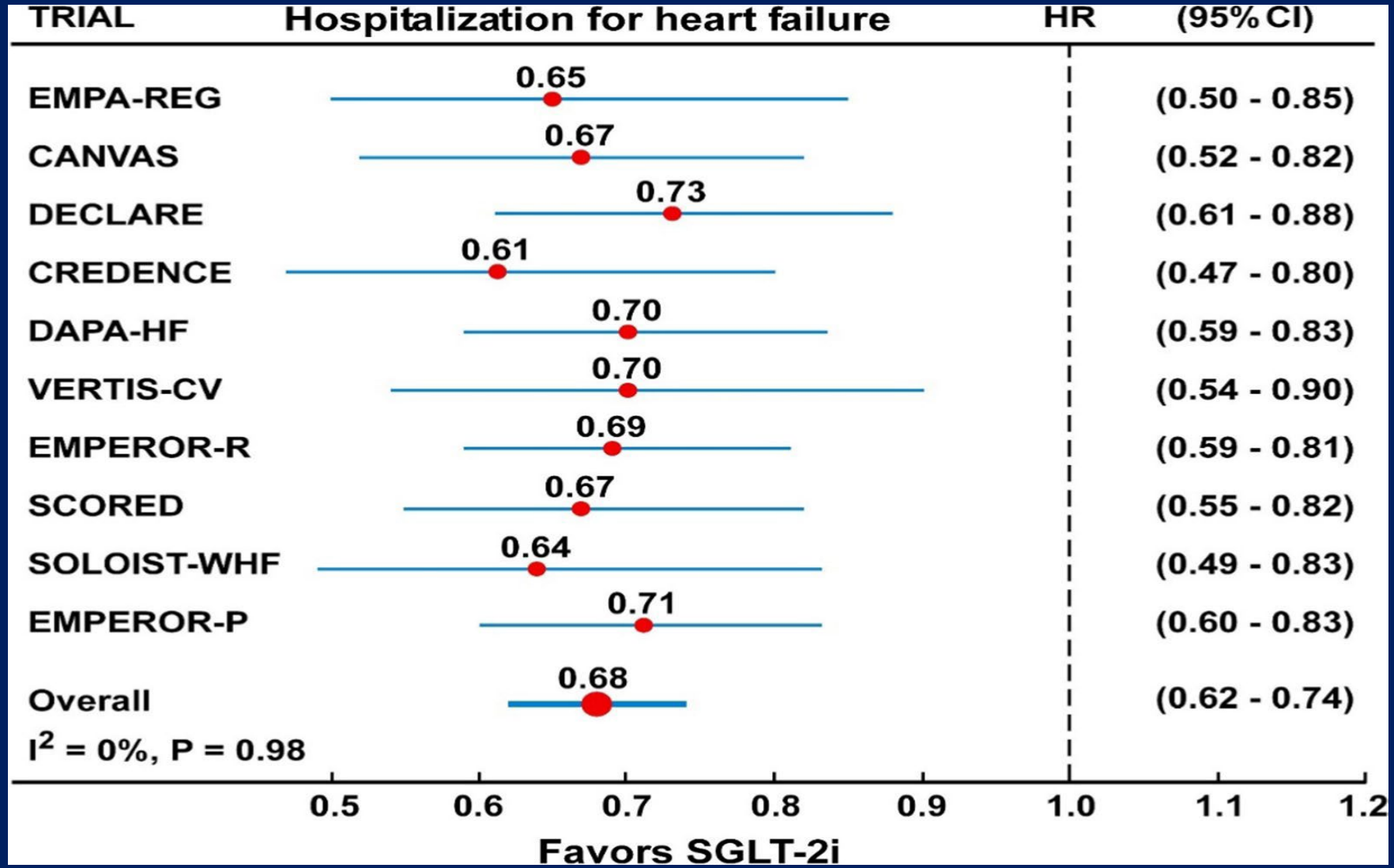
SGLT-2 Inhibitors: HHF Outcomes Trials



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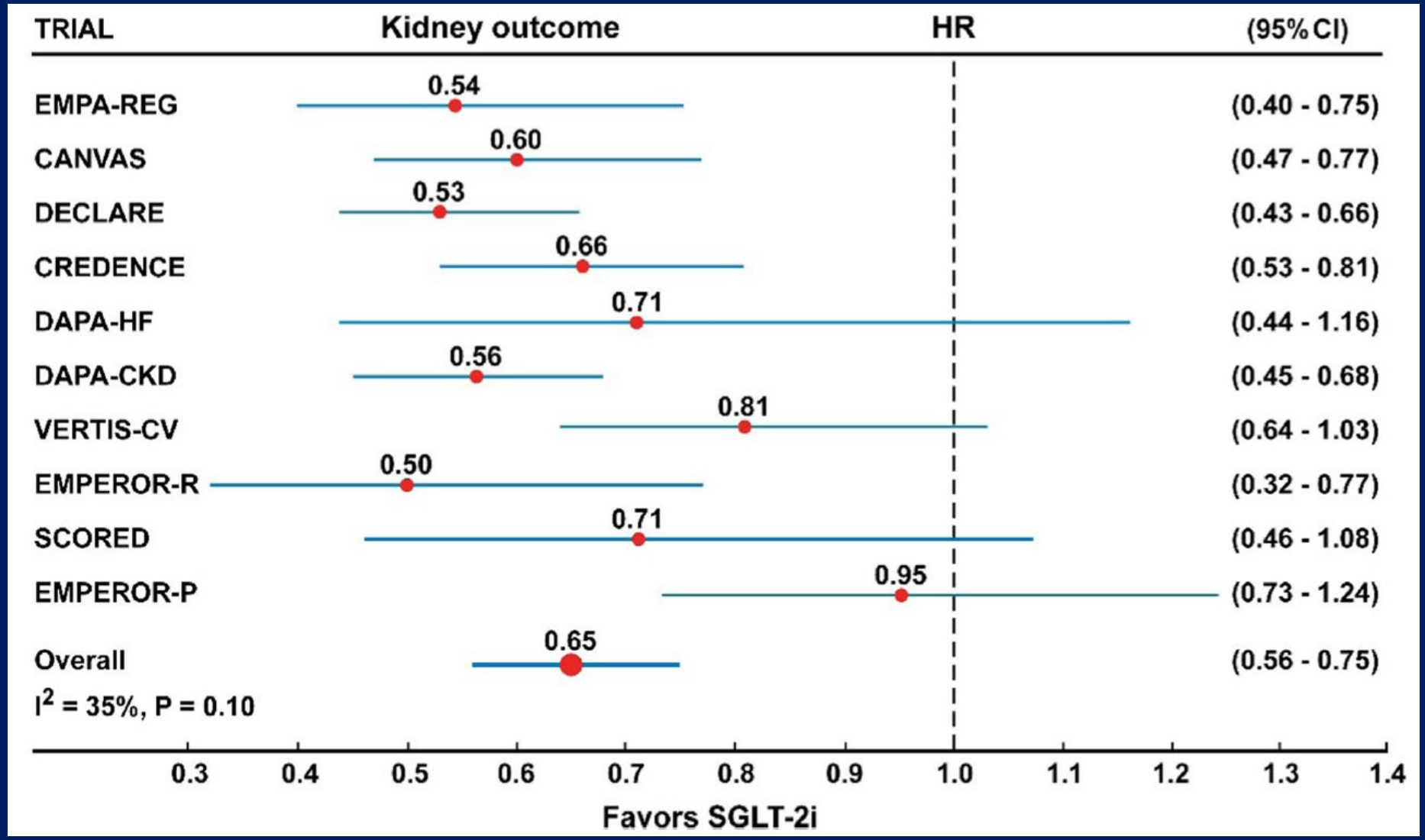
SGLT-2 Inhibitors: CKD Outcomes Trials



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SGLT-2 Inhibitors: CVD and Renal Outcomes Summary

- SGLT-2 inhibitors provide robust reduction in Heart Failure in people with and without diabetes (RRR 32%)
  - A class effect- absence of heterogeneity among studies
  - Reduced risk of HHF is > 25% among all studies
  - Narrow confidence interval (27% - 39% CI)
- Provide strong evidence for reduction in renal outcomes (RRR 35%)
  - CVOT showed heterogeneity of outcomes
  - Greater effects seen in patients with HFrEF; a potential secondary effect
- Mild reduction in CV death and MACE (RRR 16%)

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Thank you for your attention

Any Questions? Comments?