Non-Insulin Medications for Hyperglycemia Treatment in Type 2 Diabetes

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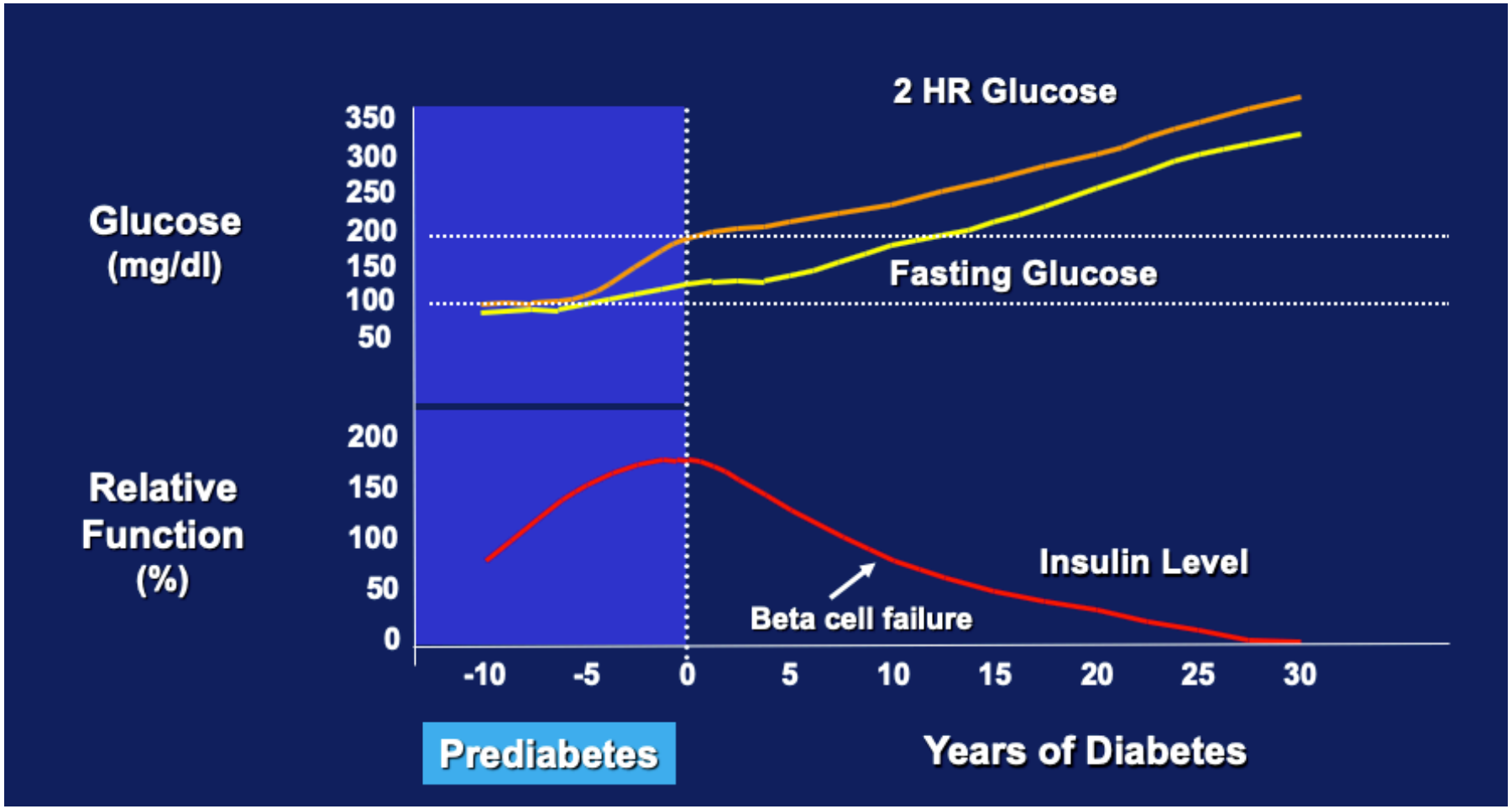
Nothing to Disclose

Objectives

- Discuss pathophysiologic approach to hyperglycemia treatment
- Review Diabetes Audit glycemia and treatment trends
- Assess medication treatment guidelines with emphasis on SGLT-2 inhibitors and GLP-1 Receptor Agonists

Progression of DM Type 2



Pathophysiologic Approach to the Treatment of Hyperglycemia in Type 2 Diabetes

Hyperglycemic Stress and Need for More Insulin

- Increased insulin resistance: obesity, other causes
- Increased gastric emptying, glucose absorption
- Increased glucagon secretion
  - Increased hepatic glucose output
- Increased renal tubular reabsorption

Beta-cell Failure

- Decreased insulin secretion to high glucose
- Decreased first-phase insulin response

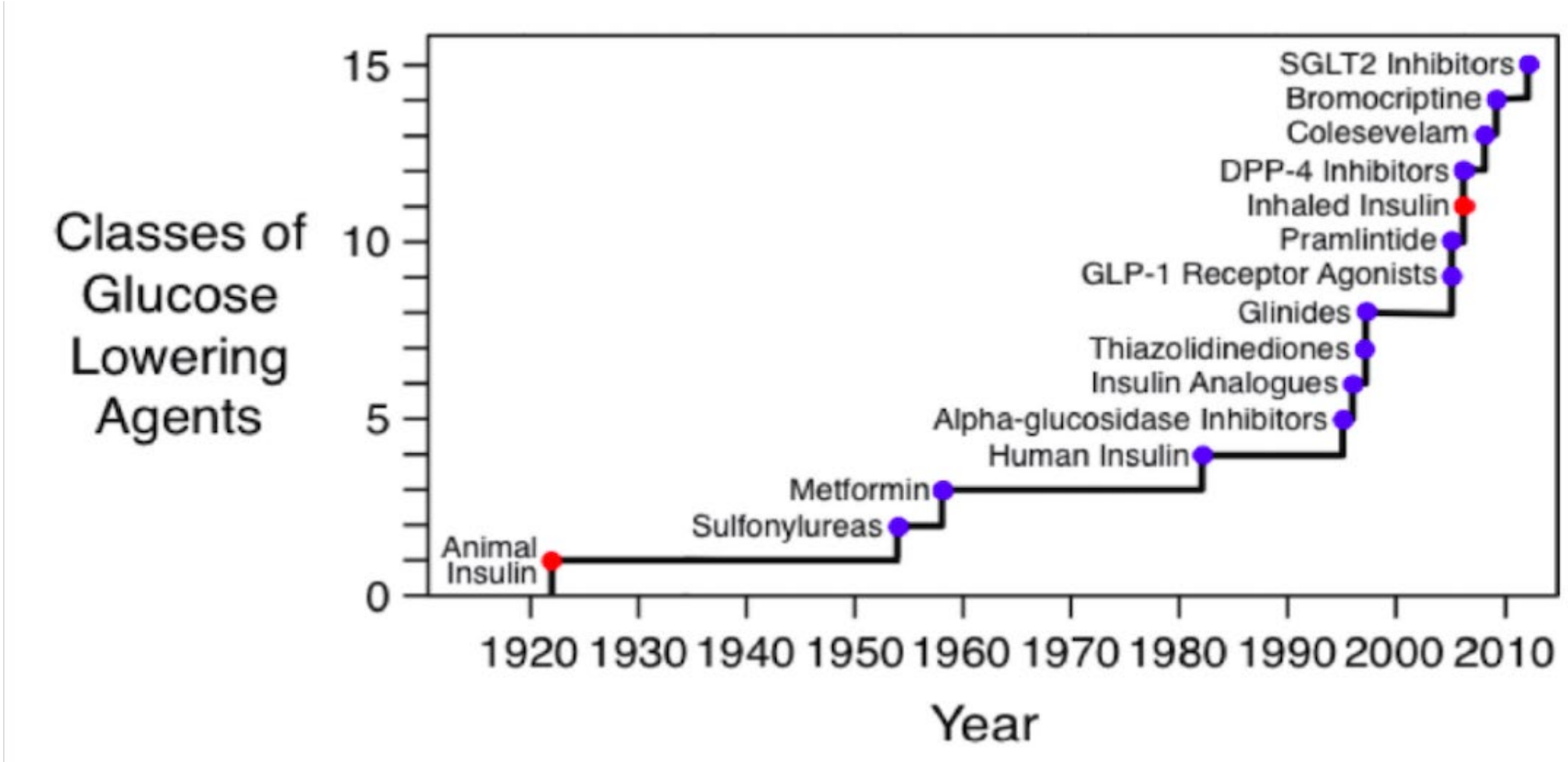
Agents for Reduction

- Weight loss, exercise, TZDs, dopamine agonist
- Decrease calorie, GLP-1 RA, a-GI, colesevelam
- DPP-4 Inhibitor; GLP-1 RA
  - Metformin
- SGLT-2 Inhibitor

Agents for Stimulation/Replacement

- Sulfonylurea; glinide; insulin
- GLP-1 RA; DPP-4 Inhibitor

Pathophysiology and Treatment of Type 2 Diabetes: Perspectives on the Past, Present and Future



Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet. 2014; 383 (9922): 1068–1083. DOI: 10.1016/S0140-6736(13)62154-6

Questions

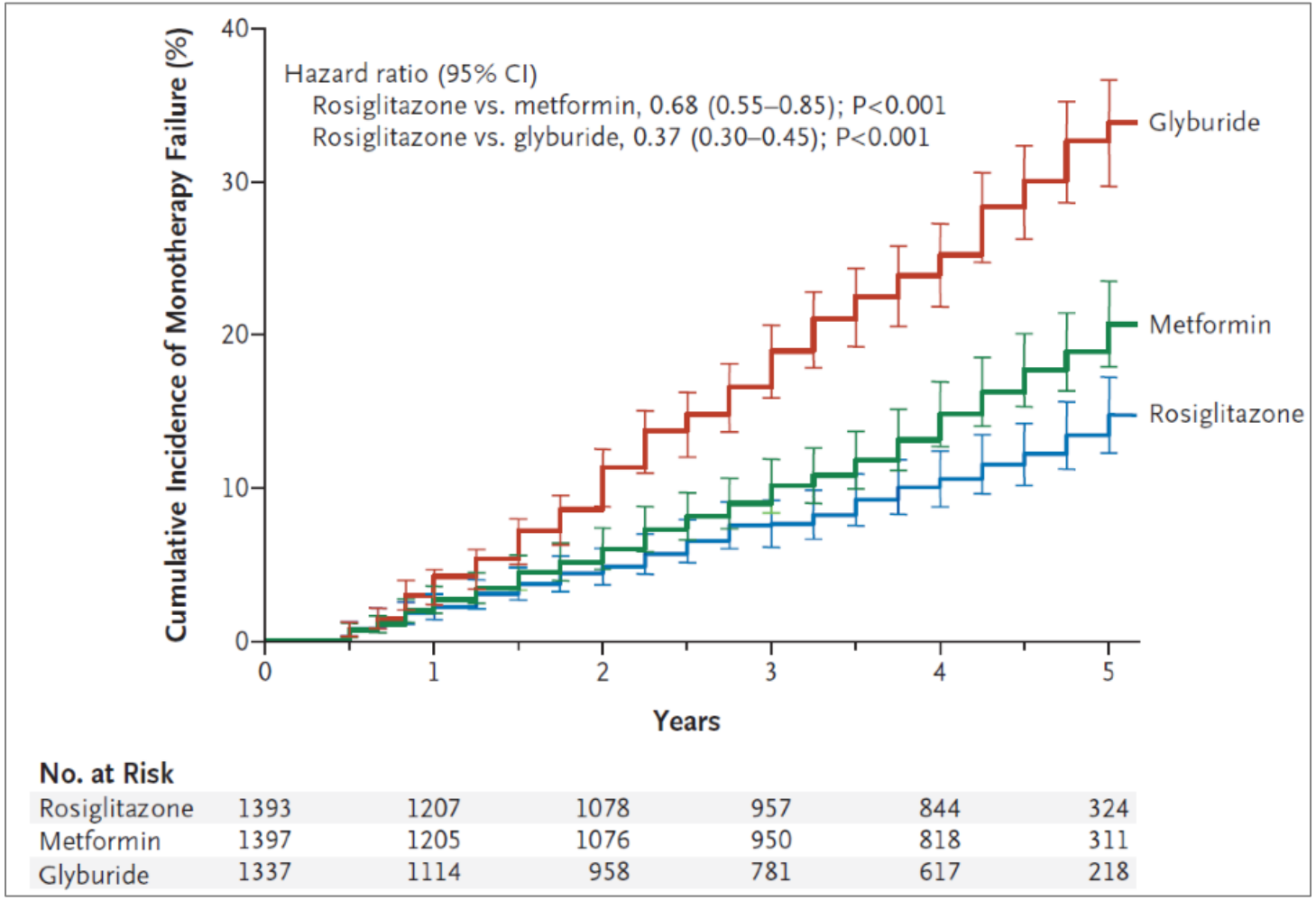
- Do non-insulin medications prevent and/or delay beta-cell failure?
  - Which medications?
  - What about combinations or more aggressive treatment?
- Do these agents decrease complications independent of hyperglycemia reduction?
  - Microvascular and macrovascular?
  - What are the mechanisms?

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

- What medications maintain long-term glycemic control in type 2 diabetes?
- 5-year, randomized, double-blind clinical trial involving 4,360 treatment-naïve, newly diagnosed type 2 DM subjects (96%–97% were < 2 years of Dx)
  - Randomized to metformin 1,000 mg BID (N = 1,454), glyburide 7.5 mg BID (N = 1,441), or rosiglitazone 4 mg BID (N = 1,456)
  - Mean age 56–57 years old; male 55%–59%; mean BMI 32; mean weight 91–92 kg
  - Average FPG 151 mg/dL, A1c 7.4%, HOMA B was used to measure beta-cell function (%)
  - Primary Outcome: Time to Fasting Plasma Glucose > 140 mg/dL
- Side Effects
  - Hypoglycemia and weight gain with glyburide
  - Edema and weight gain with rosiglitazone
  - Rates of CHF were similar between metformin and rosiglitazone
  - More GI side effects were seen with metformin

A Diabetes Outcomes Progression Trial (ADOPT) Study Group. N Engl J Med 2006; 355: 2427–43.

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy (1)



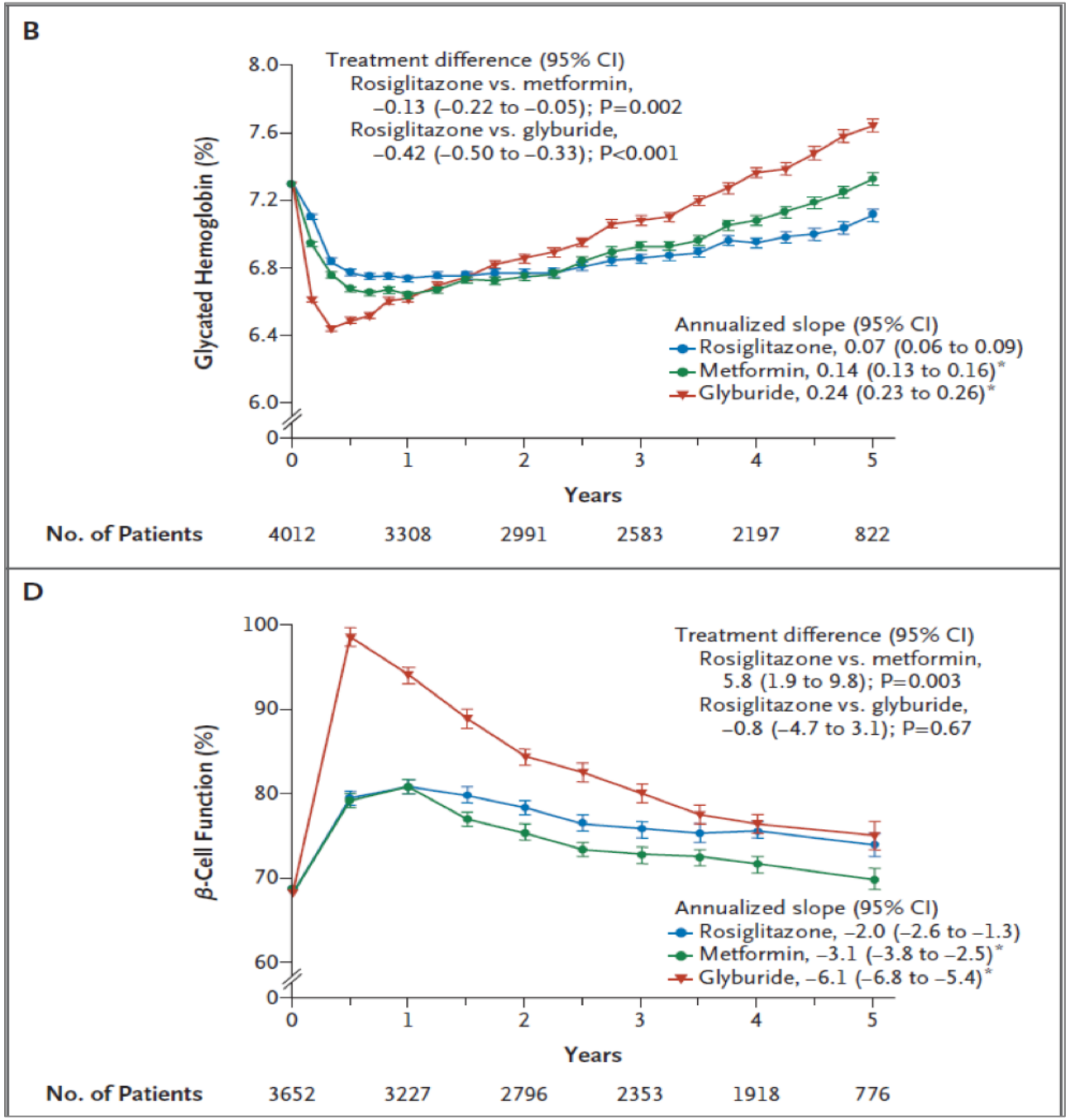
No. at Risk

Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

A Diabetes Outcomes Progression Trial (ADOPT) Study Group. N Engl J Med 2006; 355: 2427–43.

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy (2)

A Diabetes Outcomes Progression Trial (ADOPT) Study Group. N Engl J Med 2006; 355: 2427–43.



Management of Hyperglycemia in Type 2 Diabetes, 2018 Recommendations

- Metformin is the preferred initial glucose-lowering medication for most people with type 2 diabetes.
- The stepwise addition of glucose-lowering medication is generally preferred to initial combinations therapy.
- Access, treatment cost, and insurance coverage should all be considered when selecting glucose-lowering medications.
- Facilitating medication adherence should be specifically considered when selecting glucose-lowering medication.
- Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost.
- The selection of medications added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD and other comorbidities such as HF or CKD; the risk for specific adverse medication effects, particularly hypoglycemia and weight gain; as well as safety, tolerability and cost.

Davies MJ et al. Consensus Report by ADA and EASD. Diabetes Care 2018; 41:2669-2701.

Vildagliptin Efficacy in Combination with Metformin for Early Treatment of Type 2 Diabetes (VERIFY Study)

- Can early combination treatment versus stepwise approach lead to sustained good glycemic control in early type 2 diabetes?
- 5-year, multicenter, randomized, double-blind clinical trial in recently-diagnosed type 2 DM subjects (< two years diagnosis; N = 2,001 patients)
  - Eligibility: treatment-naïve subjects with A1c level between 6.5–7.5%
  - Design: Period 1: metformin (500–1,000 mg BID) versus metformin + vildagliptin* (50–500 mg or 50–1000 mg BID) or maximally tolerated doses. Period 2: vildagliptin added to metformin treatment failure group from Period 1.
  - Outcome: treatment failure A1c > 7.0% at two consecutive visits (13 weeks)
- Results and Summary
  - Less treatment failure over five years with dual therapy initiation than stepwise approach; a relative risk reduction of 49%.
  - Longer durability within treatment goal (A1c < 7%) with initial combination therapy.

VERIFY Study Group. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY). Lancet 2019; 394: 1519–1529.

*Vildagliptin is a DPP-4 Inhibitor similar to sitagliptin, saxagliptin, linagliptin, and alogliptin; available in Europe but not in the U.S.

Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE)

- 36-center, randomized, unmasked, parallel treatment group controlled clinical trial comparing the effectiveness of commonly used second medications in metformin-treated patients with type 2 diabetes.
- Eligibility: Patients with type 2; < 10 years of diagnosis (initial < 5 years), age 30 years and older (except AI/AN > 20 years), and A1c level 6.8%–8.5%
- Medications (background metformin dose 2000 mg daily)
  - Sulfonylurea (glimepiride), N = 1,254
  - Dipeptidyl Peptidase-4 Inhibitor (sitagliptin), N = 1,268
  - Glucagon-Like Peptide-1 Receptor Agonist (liraglutide), N = 1,262
  - Basal Insulin (glargine), N = 1,254
- Primary Outcome: Time to initial treatment failure, A1c > 7 %
- Baseline Characteristics
  - Mean age 57.2 years (41.6% > 60 years old); 63.6% males; 65.7% white, 19.8% black, 18.4% Hispanic
  - Duration of diabetes 4.2 years; mean BMI 34.3; % BP < 140/90, 75.3%; cigarette smoking 13.8%
  - History: family with DM 69.8%, MI/Stroke 6.5%, retinopathy 1.0%, neuropathy 21.5%, HTN 66.6%
  - Medications: BP medication 69.2%, statin 63.6%, ASA 45.3%, depression/anxiety 18.9%

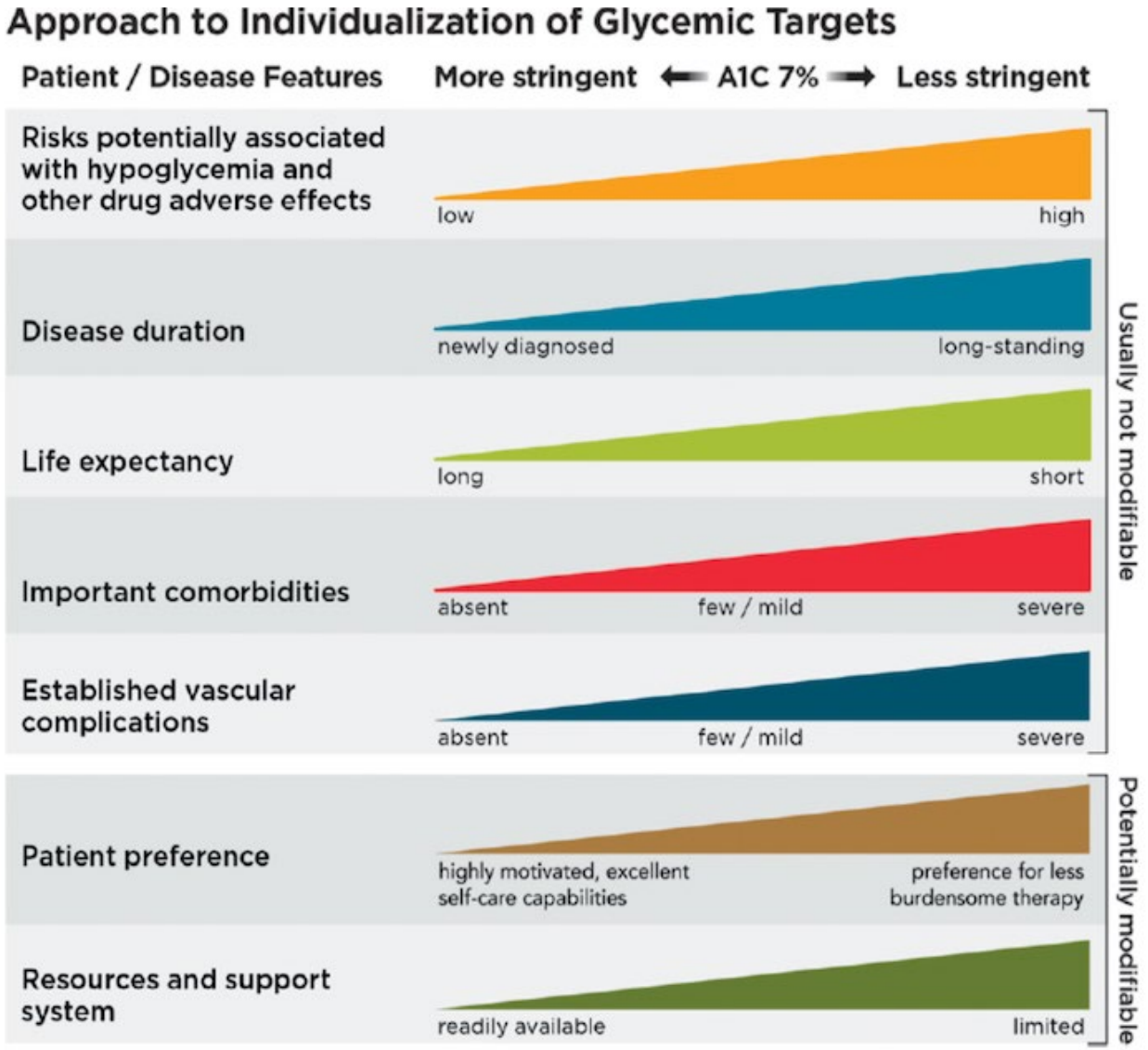
GRADE Research Group. Baseline Characteristics of Randomized Participants in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care 2019; 42: 2098–2107.

Lowering the Risk of Diabetes Complications

- **Foremost: Hyperglycemia management, A1C < 7 (individualize)**
- **Addressing other co-morbid conditions**
  - Blood pressure < 140/90
  - Statin therapy for high risk; targeting LDL cholesterol
  - RAS Inhibitor
  - Anti-platelet treatment
  - Smoking cessation
  - Lifestyle changes for weight loss
  - Recommended screenings and early treatment

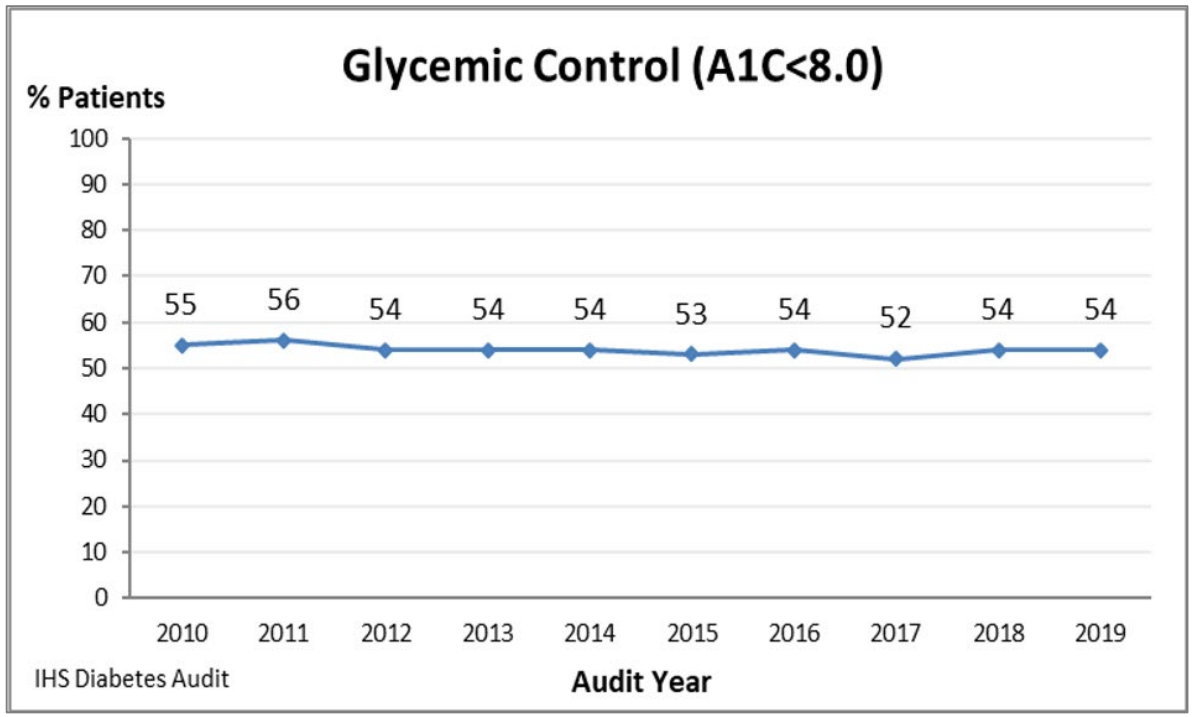
Approach to Individualization of Glycemic Targets

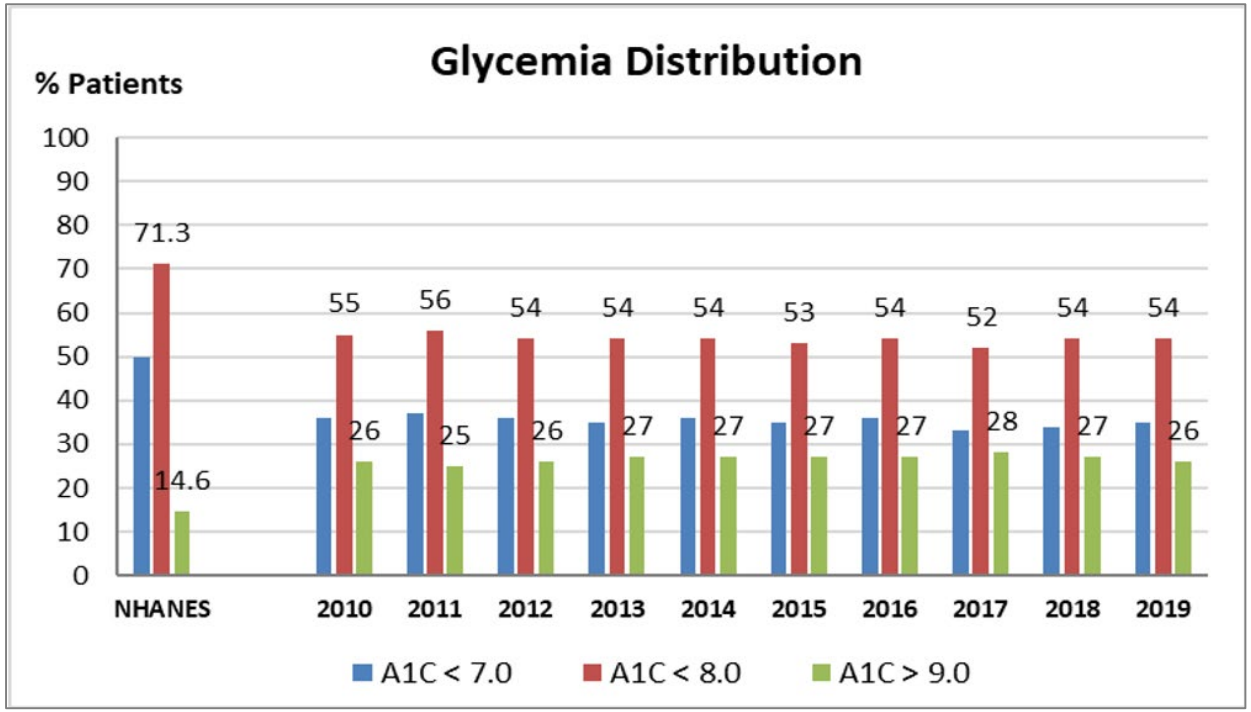
Glycemic Targets: Standards of Medical Care in Diabetes – 2020. Diabetes Care 2020; 43 (Suppl. 1): S66–S76



Diabetes Audit Trend Report: 2010–2019

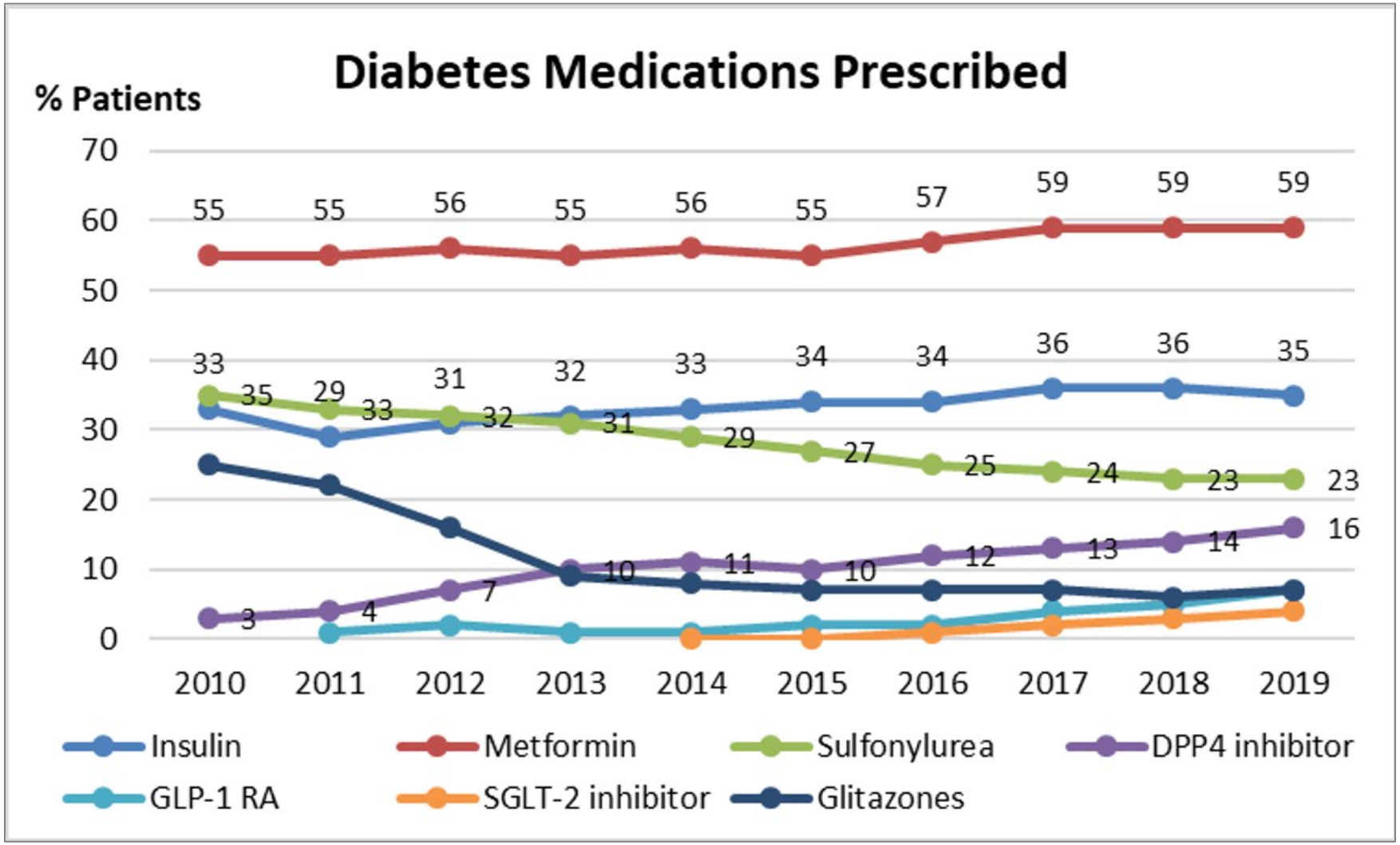
Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2020





Diabetes Audit Trend Report: 2010–2019

What glucose-lowering medications are patients using?



Anti-Diabetes Medications: IHS — Most Frequently Used

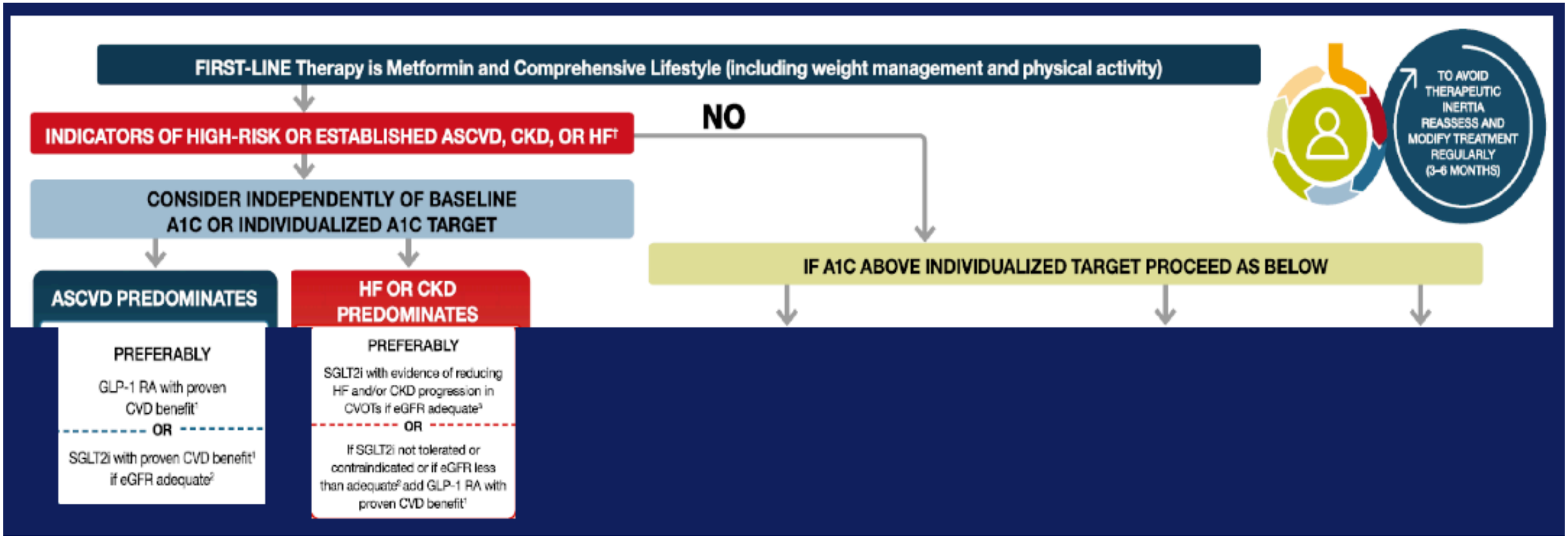
Medication	Mechanism	Efficacy (Decreased A1c)	Other Benefits	Side effects; Caution	Comments
Metformin (biguanide)	Decrease Hepatic glucose production	1.0–2.0% Decrease	CVD; Dementia; Cost	GI symptoms; Need eGFR > 30 ml/min	B12 deficiency Lactic Acidosis
Sulfonylurea/Glinides (glipizide, glyburide, glimepiride, repaglinide, nateglinide)	Stimulate insulin secretion- SUR/K+ATPase	1.0–2.0% Decrease	CVD neutral/worsening; Cost	Hypoglycemia; Weight Gain	Accelerates beta-cell failure?
DPP-4 Inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)	Inhibit degradation of GLP-1; increase insulin/decrease glucagon	0.5–1.0% Decrease	CVD neutral; Weight neutral	Pharyngitis, pemphigous; HF hospitalization – saxagliptin, alogliptin	All indications; renal dose adjustment (not linagliptin)
Insulin (Regular, NPH; analogues- rapid and basal, concentrated)	Insulin receptor activation	Unlimited decrease (> 2.5%)	Inpatient, surgical, and pregnancy use; Weight gain	Hypoglycemia; Weight Gain	Many options

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes – 2020. Diabetes Care 2020; 43 (Suppl. 1): S99–S110

Question

- Do non-insulin medications decrease complications, independent of hyperglycemia reduction?
  - Microvascular and macrovascular?
  - What are the mechanisms?

ADA Standards of Medical Care in Diabetes – 2020



Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes–2020. Diabetes Care 2020; 43 (Suppl. 1): S99–S110

Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) and Sodium Glucose CoTransporter-2 (SGLT-2) Inhibitor Medications

Medication	Mechanism	Efficacy (Decreased A1c)	Other Benefits	Side effects; Caution	Comments
GLP-1 RA (exenatide, liraglutide, semaglutide*, dulaglutide, lixisenatide)	Stimulate GLP-1 receptors; Increase insulin/decrease glucagon, delay gastric emptying, decrease appetite	Decreased 1.0–2.0%	Decreased CVD (liraglutide, semaglutide, dulaglutide) CKD Weight loss	GI problems; Injection site issues; Pancreatitis; Medullary Thyroid CA; Renal assessment for exenatide, lixisenatide	Cost; Injectable; Nausea/vomiting major side effect
SGLT-2 Inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin^)	Inhibit Sodium Glucose Co-transporter 2; increase glycosuria	Decreased 0.5–1.0%	Decreased CVD, CVD Mortality, HF Hospitalization, CKD, SBP Weight loss	Need eGFR > 45 ml/min UTI & genital mycotic; amputation (cana); bone fracture (cana); acute kidney injury; DKA; Fournier's gangrene	Cost; Monitor renal function

*(semaglutide, oral and injectable formulations are FDA approved; ^ertugliflozin without CVD outcomes studies)

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes–2020. Diabetes Care 2020; 43 (Suppl. 1): S99-S110

CVD Intervention Trials: GLP-1 RA Medications

Medication (Study, N)	Type of Patients	Mean Duration	MACE Hazard Ratio	Secondary Outcomes (HR)	NNT
Liraglutide (daily) (LEADER 9340)	Known CVD 81%	3.8 years	0.87 (p=0.01) 13% vs. 14.9%	CV Mortality (0.85) 4.7% vs 6.0%	MACE = 53 Death = 71
Semaglutide (weekly) (SUSTAIN 3297)	Known CVD 83%	2.1 years	0.74 (p=0.02) 6.6% vs. 8.9%	CV Mortality (0.98) 2.7% vs 2.8%	MACE= 43
Exenatide Weekly (EXSCEL 14,752)	Known CVD 70%	3.2 years	0.91 (p=0.061) 11.4% vs. 12.2%	CV Mortality (0.86) 4.6% vs 5.2%	~100 Death=~150
Lixisenatide (daily) (ELIXA 6068)	Acute Coronary Syndrome Hx	2.1 years	1.02 13.4% vs. 13.2%	Mortality (0.96) lower Albuminuria	NA
Dulaglutide (weekly) (REWIND 9,901)	Known CVD 31.5%	5.4 years	0.88 (p=0.02) 12.0% vs. 13.4%)	CV Mortality (0.90)	MACE = 60 CVD Hx 18
Oral Semaglutide (daily) (PIONEER 3183)	Known CVD 85%	1.4 years	0.79 (p=0.01) 3.8% vs. 4.8%	CV Mortality (0.49) 0.9% vs. 1.9%	MACE = 100

MACE: CVD death, Nonfatal MI, Nonfatal stroke

CVD Intervention Trials: SGLT-2 Inhibitor

Medication (Study, N)	**Type of Patients**	**Mean Duration**	**MACE Hazard Ratio**	**Secondary Outcomes (HR)**	**NNT**
Empagliflozin (EMPA-REG 7020)	Known CVD 99%	3.1 years	0.86 (p=0.04) 10.5% vs. 12.1%	CV Death 0.62 3.7% vs. 5.9% HF 0.65, 2.7% vs. 4.1%	MACE = 59 CV Death = 45 HF = 71
Canagliflozin (CANVAS 4,330; CANVAS-R 5,812)	Known CVD 71%	3.6 years (CANVAS)	0.86 (p=<0.02) 9.5% vs. 10.5%	HF 0.67 1.5% vs 3.0%	MACE = 80–100
Dapagliflozin (DECLARE 17,160)	Known CVD 40% CVD Risk Factors 60%	4.2 years	0.93 (p=0.17) 8.8% vs 9.4%	HF 0.73 (p=0.005) 2.5% vs 3.3%	MACE= NA HF= 111

MACE: CVD death, Nonfatal MI, Nonfatal stroke

Association of Heart Failure with Anti-Diabetes Medications

- Worsening and/or cause of heart failure hospitalization
  - **Pioglitazone** and risk of CVD events in patients with type 2 DM. JAMA 2007; 298: 1180–88.
  - Effect of **Rosiglitazone** on the frequency of diabetes inpatients with IGT or IFG: a randomized controlled trial. Lancet 2006; 368: 1096–1105.
  - SAVOR TIMI-53; **saxagliptin** and CVD outcomes in patients with DM. N Engl J Med 2013; 369: 1317–26.
  - EXAMINE; heart failure and mortality outcomes with **alogliptin** in patients with type 2 DM. Lancet 2015; 385: 2067–76.
- No effect on cardiac heart failure (CHF)
  - **Sitagliptin** TECOS Study N Engl J Med 2015; 373: 232–242. DOI: 10.1056/NEJMoa1501352.
  - **Linagliptin** CARMELINA. JAMA 2019; 321: 69–79.
- Improvement of CHF and CHF mortality
  - **Empagliflozin** reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in EMPA-REG OUTCOME Trial. Circulation 2019; 139: 1384–95. DOI: 10.1161/CIRCULATIONAHA.118.037778.
  - **Canagliflozin** and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS); N Engl J Med 2017; 377: 644–657. DOI: 10.1056/NEJMoa1611925
  - **Dapagliflozin** and Cardiovascular Outcomes in Type 2 Diabetes (DECLARE). N Engl J Med 2019; 380: 347–57. DOI: 10.1056/NEJMoa1812389.

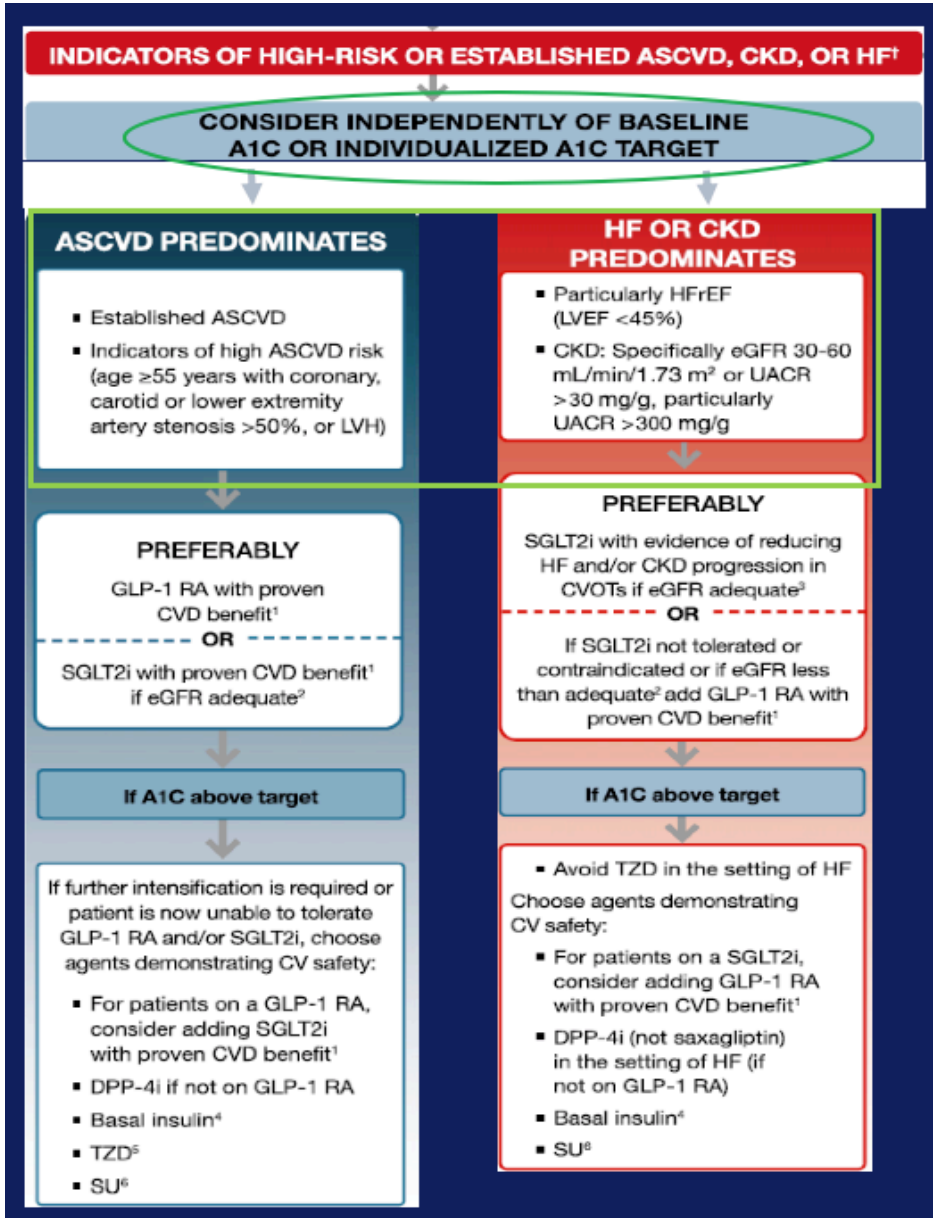
CKD Outcomes: SGLT-2 Inhibitor and GLP-1 RA Medications

Medication (Study, N)	**Type of Patients**	**Mean Duration**	**CKD Hazard Ratio**	**Secondary Outcomes (HR)**	**NNT**
Empagliflozin (EMPA-REG 7020)	75% eGFR >60, 60% w UACR<30, High-Risk CVD (99%)	3.1 years	0.61 12.7% vs. 18.8%	Doubling Cr (0.66) CVD death (0.71); HF (0.61)	CKD = 16 (CVD = 90)
Canagliflozin (CREEDENCE 4,401)	CKD 2-3, eGFR ≥ 60 (1/3), 30- <45 (1/3), 45 -< 60 (1/3) UACR >300, 50% w CVD	2.6 years	0.70 (ESRD-0.68) 11.1% vs. 15.5%	CVD (0.80) 8.1% vs 11.5% HF (0.61), 4.0% vs. 6.4%	CKD = 23 (CVD = 30) (HF = 42)
Dapagliflozin (DECLARE 8,162)	95% eGFR > 60, UACR < 30 (71%), 40% CVD, 60% Risk	4.2 years	0.54, 4.3% vs 5.6% eGFR, 1.4% vs. 2.5%	ESRD/Death (0.41) 0.1% vs. 0.3%	CKD = 77
Liraglutide (LEADER 9340)	Known CVD 81%	3.8 years	0.78 5.7% vs. 7.2%	CVD 0.87 13% vs. 14.9%	CKD = 71
Dulaglutide (REWIND 9,901)	Known CVD 31.5%	5.4 years	Improved CKD 0.85	CV Mortality (0.90)	

CKD: doubling creatinine, renal replacement, progressing or incident albuminuria, sustained eGFR decrease > 40% to < 60 ml/min

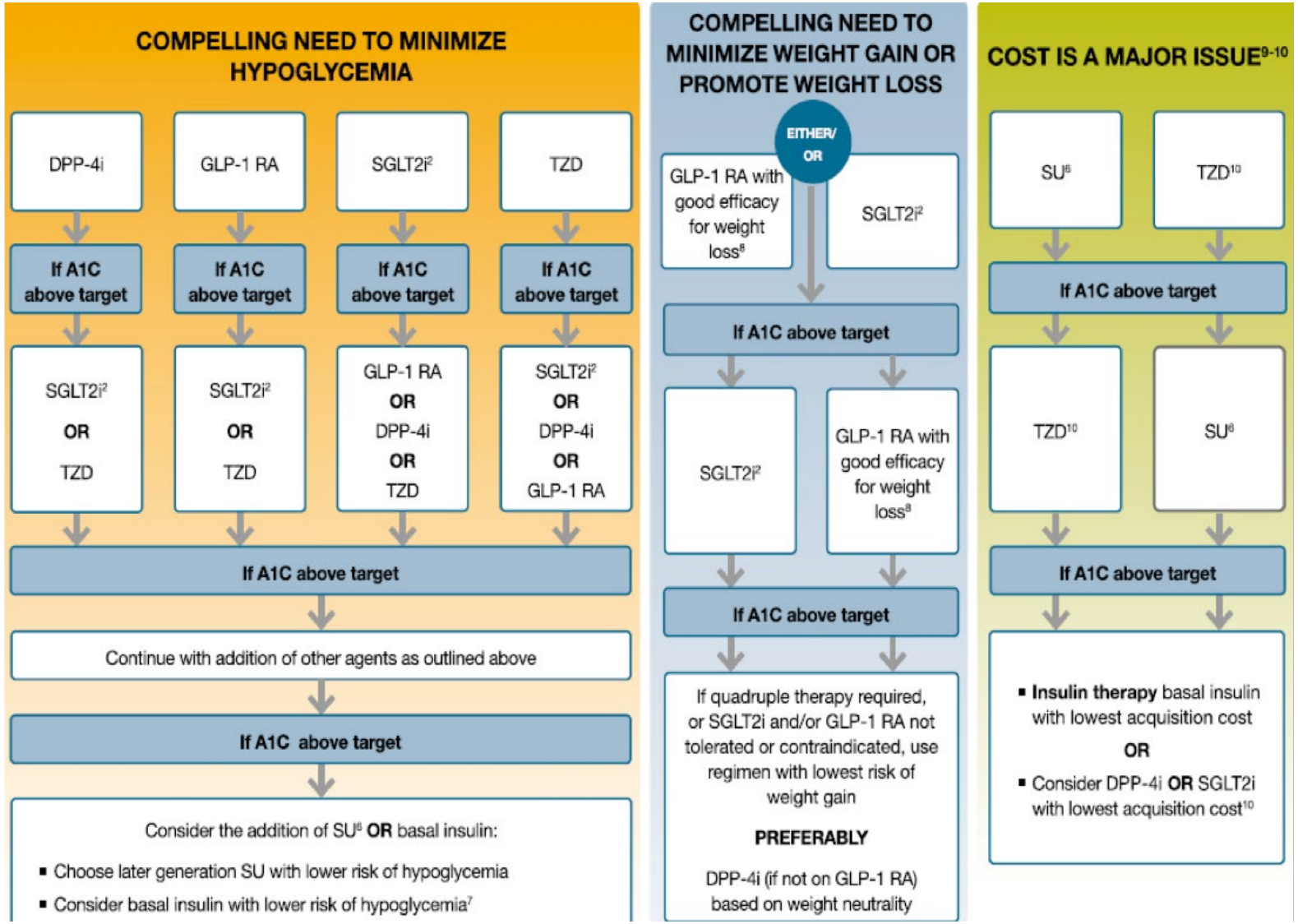
ADA Standards of Medical Care in Diabetes–2020

Pharmacologic Approaches to Glycemic Treatment*: Standards of Medical Care in Diabetes–2020*. Diabetes Care 2020; 43 (Suppl. 1): S99–S110



ADA Standards of Medical Care in Diabetes–2020 (2)

Pharmacologic Approaches to Glycemic Treatment. *Standards of Medical Care in Diabetes–2020*. Diabetes Care 2020; 43 (Suppl. 1): S99–S110



Clinical Experience (Dr. Arakaki) with GLP-1 RAs and SGLT-2 Inhibitors: Summary

- GLP-1 RA, liraglutide is effective in obese AI/AN patients with type 2 diabetes and high A1c level (mean 9.87%; BMI 41; N=98)
  - 68% decreased A1c level; 84% decreased weight
  - A1c level reduced on average 0.73%; weight loss average of 14 lbs.
  - Treatment response independent of initial BMI
  - Mean duration of treatment 369 days; well tolerated
  - GI side effects are common; 1 case of pancreatitis over 3 years
- SGLT-2 inhibitor, empagliflozin offered mixed results but the database of patients treated is small (N=17)
  - Slightly increased average A1c level; no effect on BP
  - Average weight loss of 10 lbs.
  - Mean duration of treatment 242 days; well tolerated
  - UTI/balanitis side effects noted

Indian Health Service
National Pharmacy & Therapeutics Committee
2019 NPTC Fall Meeting (UPDATE)
November 2019

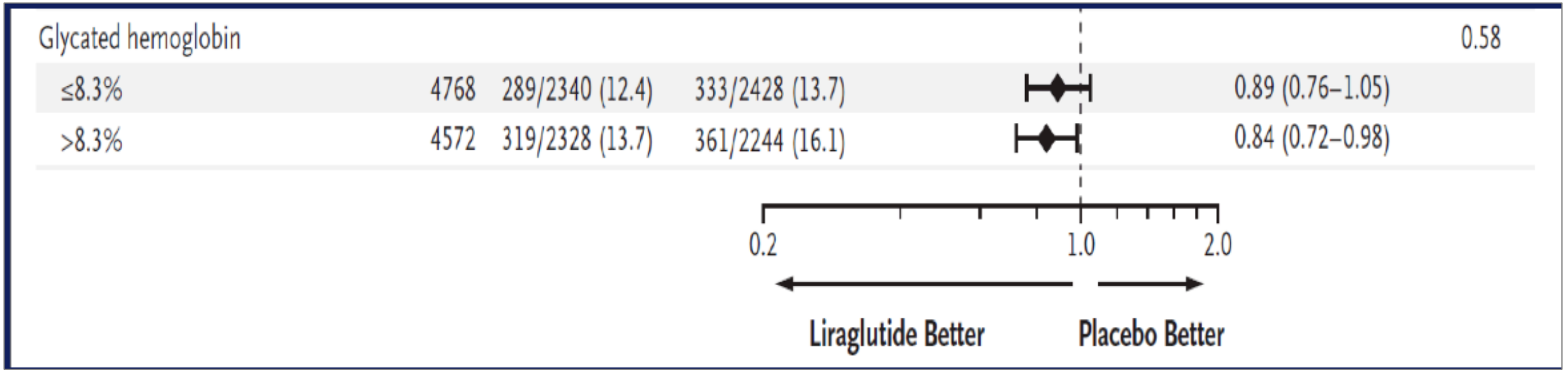
- A drug class review of the **Sodium-Glucose CoTransporter-2 inhibitors (SGLT2s)** was performed. Clinical practice guidelines from the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE), the ACC, and the National Institute for Health and Care Excellence (NICE) were shared in supporting the role and use of SGLT2s. Cardiovascular outcomes trial (CVOT) findings for each medication were reviewed in detail which offered valuable insight. Internal IHS data of pharmacoepidemiologic and drug utilization trends and cost utility were used to add perspective to the review. Ultimately, the NPTC voted to add empagliflozin to the NCF.
- A drug class review of the **Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs)** was also provided. Medical literature reviewed in the evaluation included findings from CVOTs, various published meta-analyses, and practical guidance from the American Diabetes Association, AACE/ACE, NICE and European Society of Cardiology. Agency-specific medication procurement, utilization and pharmacoepidemiologic data were also reviewed. Following the comprehensive analysis, the NPTC voted to **add either subcutaneous dulaglutide, liraglutide or semaglutide to the NCF** (listed alphabetically only, no preference).
- https://www.ihs.gov/sites/nptc/themes/responsive2017/display_objects/documents/updates/NPTC-Update-NOVEMBER-2019.pdf

- No national “Use Criteria” for SGLT-2 inhibitors or GLP-1 Receptor Agonists. However, local pharmacies may elect to establish their own “use criteria.”
- Agency-wide distribution of NPTC Formulary Briefs are available on NPTC website for reference:
  - https://www.ihs.gov/NPTC/

Thank you for your attention.
Questions or comments?

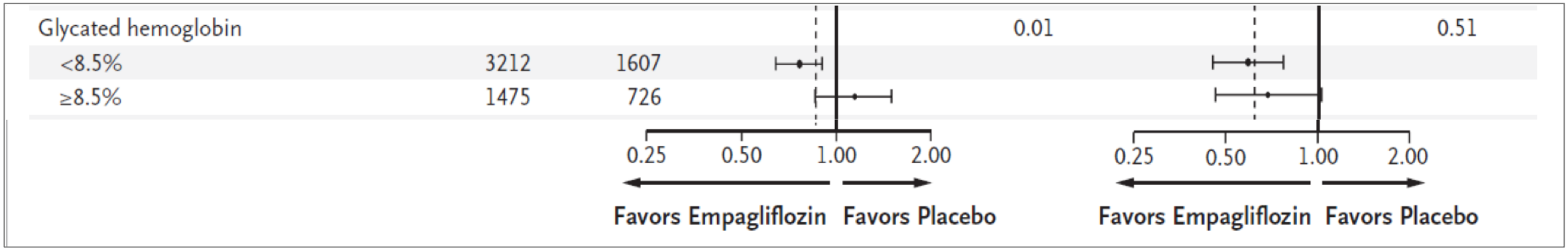
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

N Engl J Med 2016; 375:311-322 DOI: 10.1056/NEJMoa1603827



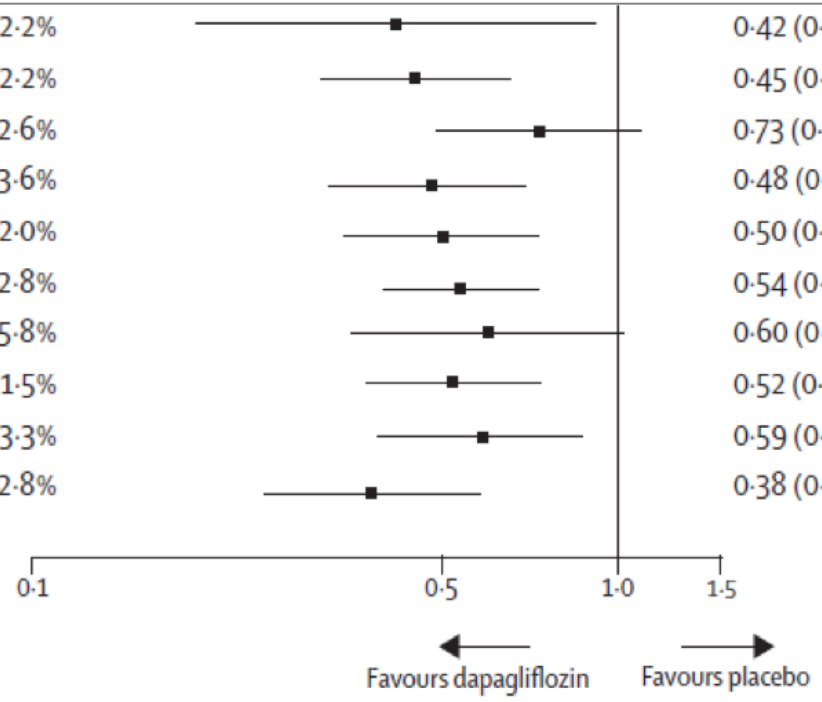
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.

N Engl J Med. 2015 Nov 26; 373 (22): 2117–28. DOI: 10.1056/NEJMoa1504720



Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE–TIMI 58 randomised trial

Hba_{1c} <7%	9/773 (1·2%)	1·0%	21/774 (2·7%)	2·2%	0·42 (0·19–0·91)	0·028	0·26
Hba_{1c} 7 to <8%	38/3317 (1·1%)	1·2%	83/3309 (2·5%)	2·2%	0·45 (0·31–0·66)	<0·0001	
Hba_{1c} 8 to <9%	41/2193 (1·9%)	1·9%	59/2327 (2·5%)	2·6%	0·73 (0·49–1·09)	0·12	
Hba_{1c} ≥9%	39/2297 (1·7%)	1·7%	75/2164 (3·5%)	3·6%	0·48 (0·32–0·70)	0·0002	
eGFR ≥90 mL/min per 1·73m²	41/4137 (1·0%)	1·0%	79/4025 (2·0%)	2·0%	0·50 (0·34–0·73)	0·0003	0·87
eGFR 60 to <90 mL/min per 1·73m²	65/3838 (1·7%)	1·6%	121/3894 (3·1%)	2·8%	0·54 (0·40–0·73)	<0·0001	
eGFR <60 mL/min per 1·73m²	21/606 (3·5%)	3·8%	38/659 (5·8%)	5·8%	0·60 (0·35–1·02)	0·059	
UACR <30 mg/g	50/5819 (0·9%)	0·9%	95/5825 (1·6%)	1·5%	0·52 (0·37–0·74)	0·0002	0·30
UACR 30–300 mg/g	39/2017 (1·9%)	2·0%	66/2013 (3·3%)	3·3%	0·59 (0·39–0·87)	0·0082	
UACR >300 mg/g	31/594 (5·2%)	4·8%	75/575 (13·0%)	12·8%	0·38 (0·25–0·58)	<0·0001	



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