PREVENTION,DIAGNOSIS & DIABETES MANAGEMENT

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Endocrinology, Diabetes & Metabolism

No conflict of Interest to disclose

OBJECTIVES

1. Review current evidence from randomized controlled trials aimed to prevent diabetes in high risk individuals.

2. Review current guidelines for the diagnosis and management of diabetes.

✓ Both insulin resistance and pancreatic β-cell dysfunction are the key initiating physiologic events for development of T2D

✓ Genetic mutations and/or polymorphisms on a genomic scale

✓ Environmental factors
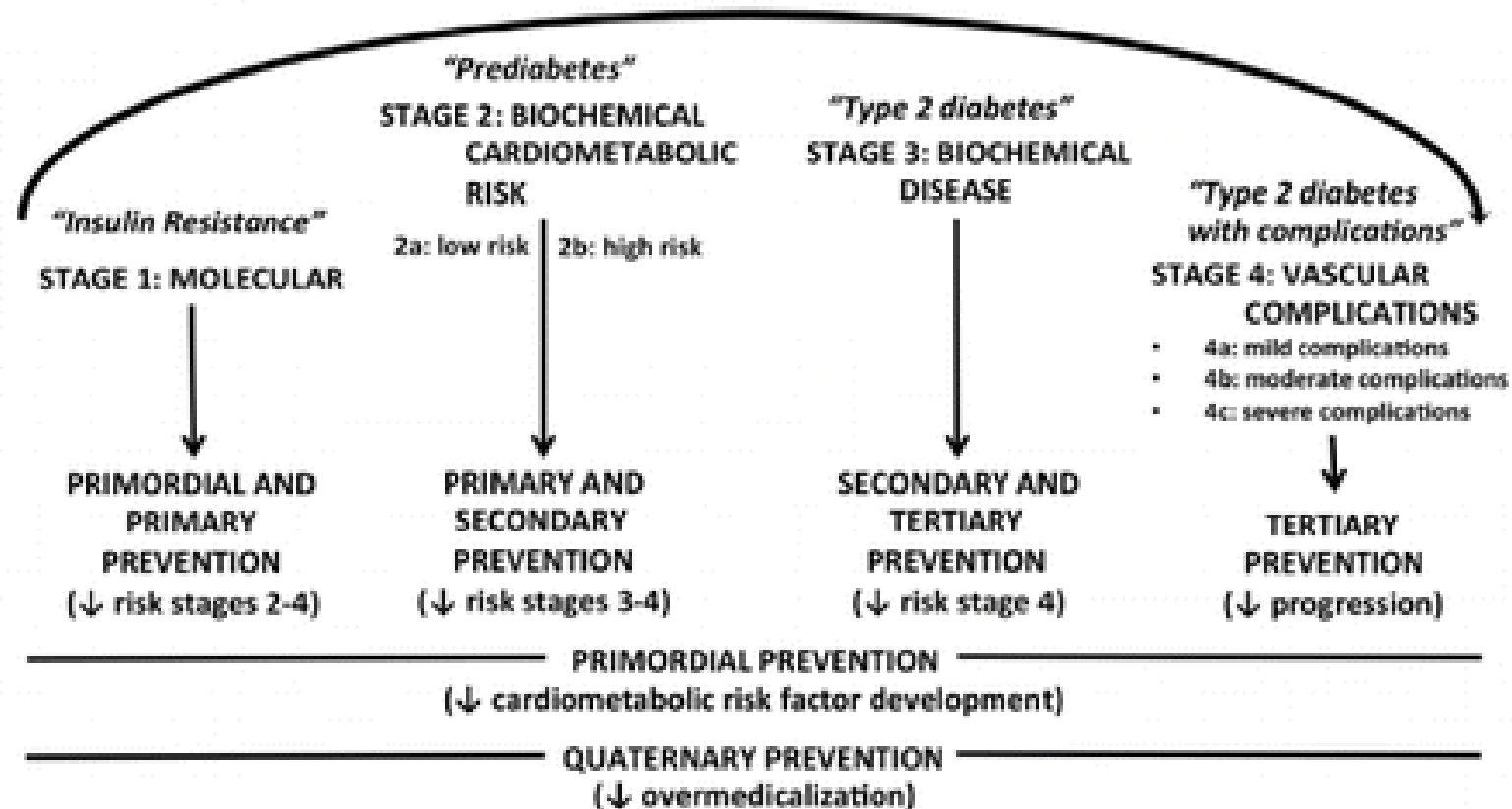
KEY MECHANISTIC DRIVERS

GENOME   EPIGENOME   ENVIRONMENT

COMPLEX INTERACTIONS

INSULIN RESISTANCE – PREDIABETES - T2D SPECTRUM

"Prediabetes"
STAGE 2: BIOCHEMICAL CARDIOMETABOLIC RISK

"Type 2 diabetes"
STAGE 3: BIOCHEMICAL DISEASE

"Insulin Resistance"

"Type 2 diabetes with complications"

STAGE 1: MOLECULAR

2a: low risk | 2b: high risk

STAGE 4: VASCULAR COMPLICATIONS
- 4a: mild complications
- 4b: moderate complications
- 4c: severe complications

PRIMORDIAL AND PRIMARY PREVENTION
(↓ risk stages 2-4)

PRIMARY AND SECONDARY PREVENTION
(↓ risk stages 3-4)

SECONDARY AND TERTIARY PREVENTION
(↓ risk stage 4)

TERTIARY PREVENTION
(↓ progression)

PRIMORDIAL PREVENTION
(↓ cardiometabolic risk factor development)

QUATERNARY PREVENTION
(↓ overmedicalization)

Diabetes

- ✓ 34.2 million people of all ages—or 10.5% of the US population with diabetes by 2018.

- ✓ Worldwide 463 million people had diabetes 2019.

- ✓ Prevalence of Diabetes in Puerto Rico 16.7% as per BRFSS 2019.

Prediabetes

- ✓ 88 million people aged 18 yrs or older have prediabetes (34.5% of the adult US population)

Centers for Disease Control and Prevention. National Diabetes Statistics Report. Atlanta: Centers for Disease Control and Prevention; 2017
National Diabetes Statistics Report 2020

Table 1a. Estimated crude prevalence of diagnosed diabetes, undiagnosed diabetes, and total diabetes among adults aged 18 years or older, United States, 2013–2016

Characteristic	Diagnosed diabetes Percentage (95% CI)	Undiagnosed diabetes Percentage (95% CI)	Total diabetes Percentage (95% CI)
Total	10.2 (9.3–11.2)	2.8 (2.4–3.3)	13.0 (12.0–14.1)
Age in years			
18–44	3.0 (2.6–3.6)	1.1 (0.7–1.8)	4.2 (3.4–5.0)
45–64	13.8 (12.2–15.6)	3.6 (2.8–4.8)	17.5 (15.7–19.4)
≥65	21.4 (18.7–24.2)	5.4 (4.1–7.1)	26.8 (23.7–30.1)
Sex			
Men	11.0 (9.7–12.4)	3.1 (2.3–4.2)	14.0 (12.3–15.5)
Women	9.5 (8.5–10.6)	2.5 (2.0–3.2)	12.0 (11.0–13.2)
Race/ethnicity			
White, non-Hispanic	9.4 (8.4–10.5)	2.5 (1.9–3.3)	11.9 (10.9–13.0)
Black, non-Hispanic	13.3 (11.9–14.9)	3.0 (2.0–4.5)	16.4 (14.7–18.2)
Asian, non-Hispanic	11.2 (9.5–13.3)	4.6 (2.8–7.2)	14.9 (12.0–18.2)
Hispanic	10.3 (8.1–13.1)	3.5 (2.5–4.8)	14.7 (12.5–17.3)

Notes: CI = confidence interval. Diagnosed diabetes was based on self-report. Undiagnosed diabetes was based on fasting plasma glucose and A1C levels among people self-reporting no diabetes. Numbers for subgroups may not add up to the total because of rounding. Age-adjusted estimates are presented in Appendix Table 1.

Data source: 2013–2016 National Health and Nutrition Examination Survey.

Figure 1. Trends in age-adjusted prevalence of diagnosed diabetes, undiagnosed diabetes, and total diabetes among adults aged 18 years or older, United States, 1999–2016.

Notes: Diagnosed diabetes was based on self-report. Undiagnosed diabetes was based on fasting plasma glucose and A1C levels among people self-reporting no diabetes.

Data source: 1999–2016 National Health and Nutrition Examination Surveys.
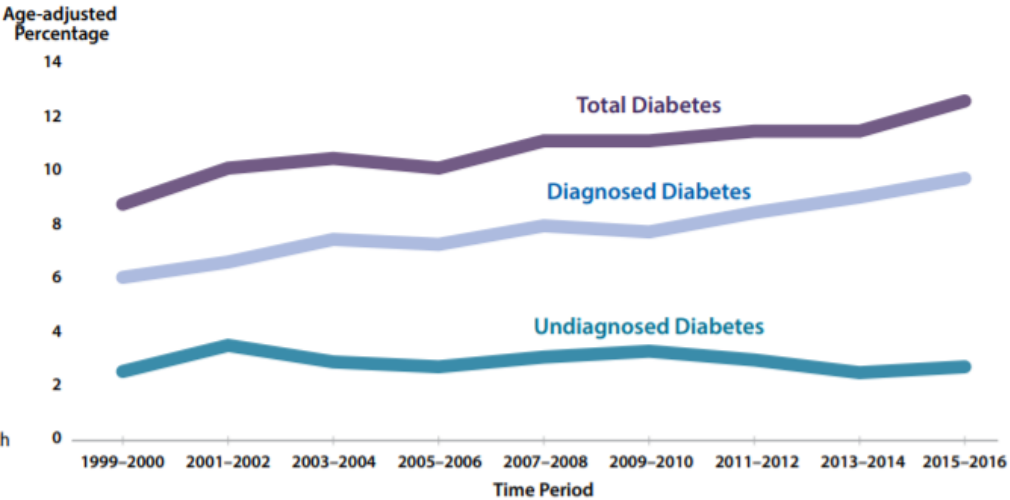
Natural history of type 2 diabetes
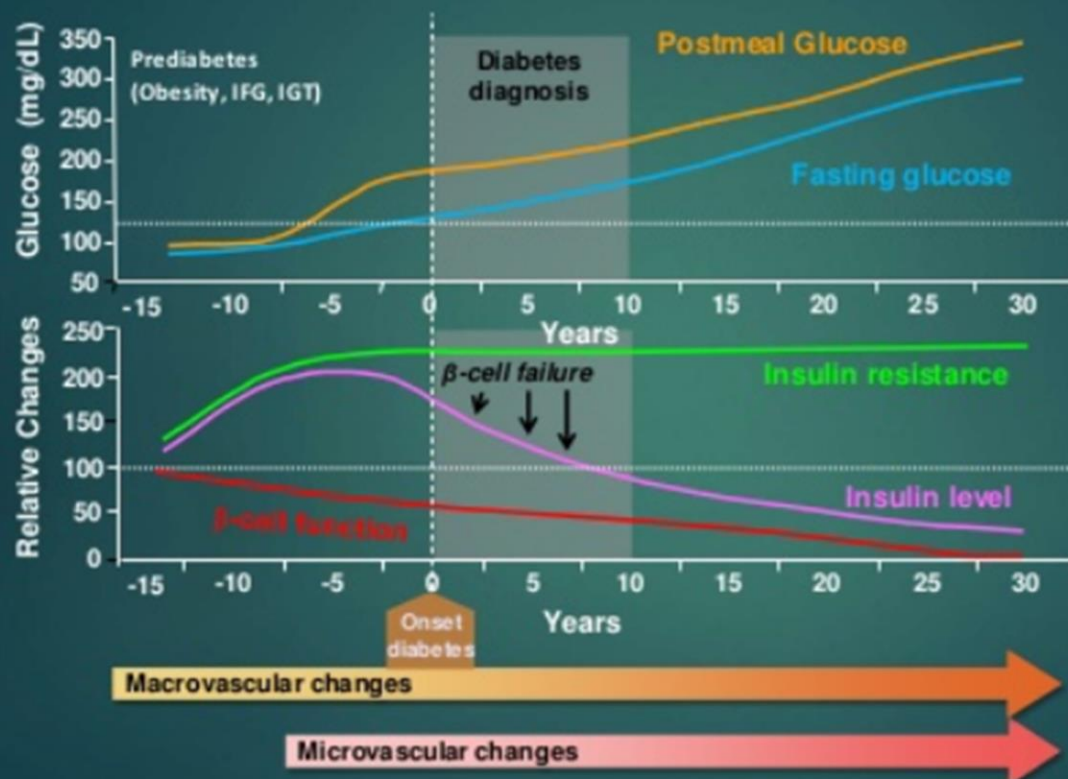
The total direct and indirect estimated costs of diagnosed diabetes in the United States in 2017 was $327 billion!

American Diabetes Association/European Association for the Study of Diabetes/American College of Physicians/Endocrine Society[6–9]

	Normal	Impaired fasting glucose
FPG	<100 mg/dL	100–125 mg/dL
	(5.6 mmol/L)	(5.6–6.9 mmol/L)
2-hour	<140 mg/dL	140–199 mg/dL
OGTT	(7.8 mmol/L)	(7.8–11.0 mmol/L)
HbA1c	<5.7%	5.7–6.4%
	(39 mmol/mol)	(39–46 mmol/mol)

American Association of Clinical Endocrinologists/American College of Endocrinology[7]

FPG	<100 mg/dL	100–125 mg/dL
	(5.6 mmol/L)	(5.6–6.9 mmol/L)
2-hour	<140 mg/dL	140–199 mg/dL
OGTT	(7.8 mmol/L)	(7.8–11.0 mmol/L)
HA1c	<5.5%	5.5–6.4%
	(37 mmol/mol)	(37–46 mmol/mol)

International Diabetes Federation[10]

FPG	<100 mg/dL	100–125 mg/dL
	(5.6 mmol/L)	(5.6–6.9 mmol/L)
2-hour	<140 mg/dL	140–199 mg/dL
OGTT	(7.8 mmol/L)	(7.8–11.0 mmol/L)
HbA1c		

Quattrocchi E, Goldberg T, Marzella N. Drugs in Context 2020

Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI $\geq$25 kg/m^2 or $\geq$23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension ($\geq$140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

2. Patients with prediabetes (A1C $\geq$5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.

3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.

4. For all other patients, testing should begin at age 45 years.

5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

CVD, cardiovascular disease; GDM, gestational diabetes mellitus.

Preventing or delaying the onset of diabetes

Preserving ß-cell function

Preventing or delaying microvascular and cardiovascular complications

Improving patient's quality of life

Reducing costs of diabetes care

CLINICAL TRIALS FOR DIABETES PREVENTION

THE DIABETES PREVENTION PROGRAM

✓ 3234 USA patients with prediabetes (mean age, 51yrs); BMI 34 kg/m2.

  (Placebo or lifestyle or metformin)

✓ 7% weight loss reduced the cumulative incidence of diabetes from 29% to 14% over 3 years compared with placebo .

✓The cumulative incidence of T2D was reduced by 58% in the lifestyle intervention group and 31% in metformin as compared to the control group.

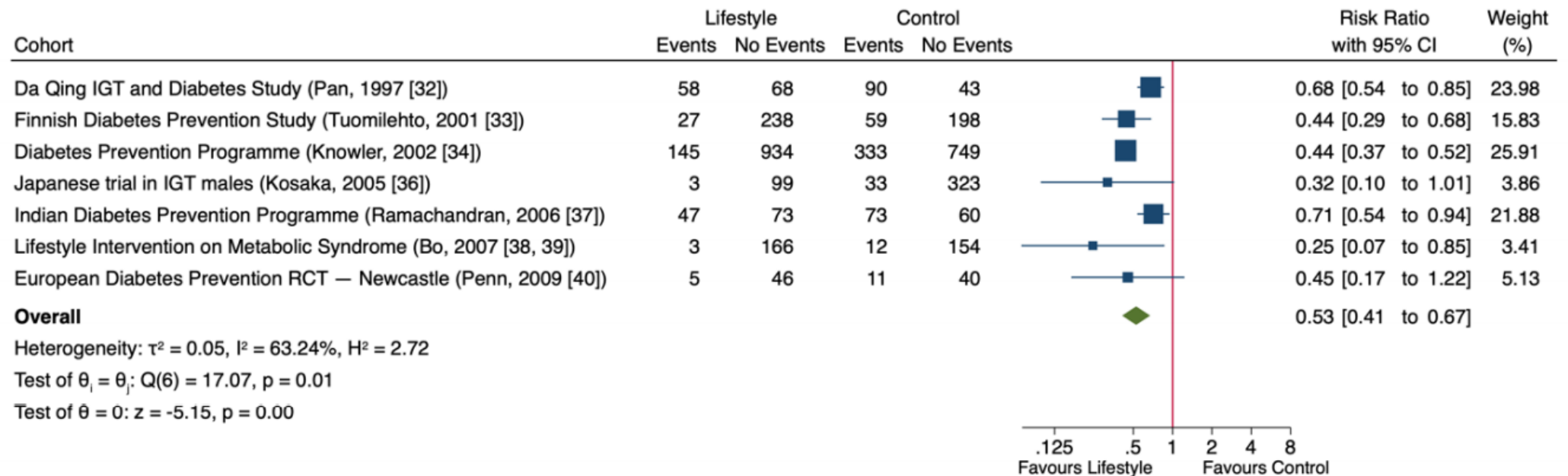✓16% reduction in diabetes risk for every kg reduction in weight.

THE FINNISH DIABETES PREVENTION STUDY (FDPS)

✓ 522 middle-aged overweight subjects with IGT ,randomized to either a usual care control group or an intensive lifestyle intervention group.

✓ 5% reduction in weight decreased the incidence of newly diagnosed DM2 from 23% to 11% over 3 years.

✓ The intervention involved a reduction in total and saturated fat intake to less than 30% and10% of energy consumed. High fiber intake and moderate exercise for 30 min/day

✓ Difference in weight reduction between the groups was 3.5 and 2.6 kg at 1 and 3 years. The risk reduction was 58% in the intervention group compared to the control group.

THE CHINESE DA QING STUDY

✓ 577 IGT individuals in 33 study clinics that were randomized to control, exercise, healthy diet, and healthy diet plus exercise clinics. F/U 6 yrs.

✓ Individuals were normal weight or overweight at baseline, and the reduction in total energy intake was 100–240 kcal depending on the intervention.

✓ Risk of diabetes ↓33% in the diet-only group, 47% in the exercise-only group and 38% in the diet-plus-exercise group as compared to the control group, without significant differences between the intervention groups.

Randomized controlled trials investigating the effect of lifestyle changes on type 2 diabetes risk.

Cohort	Lifestyle Events	Lifestyle No Events	Control Events	Control No Events		Risk Ratio with 95% CI	Weight (%)
Da Qing IGT and Diabetes Study (Pan, 1997 [32])	58	68	90	43		0.68 [0.54 to 0.85]	23.98
Finnish Diabetes Prevention Study (Tuomilehto, 2001 [33])	27	238	59	198		0.44 [0.29 to 0.68]	15.83
Diabetes Prevention Programme (Knowler, 2002 [34])	145	934	333	749		0.44 [0.37 to 0.52]	25.91
Japanese trial in IGT males (Kosaka, 2005 [36])	3	99	33	323		0.32 [0.10 to 1.01]	3.86
Indian Diabetes Prevention Programme (Ramachandran, 2006 [37])	47	73	73	60		0.71 [0.54 to 0.94]	21.88
Lifestyle Intervention on Metabolic Syndrome (Bo, 2007 [38, 39])	3	166	12	154		0.25 [0.07 to 0.85]	3.41
European Diabetes Prevention RCT — Newcastle (Penn, 2009 [40])	5	46	11	40		0.45 [0.17 to 1.22]	5.13
Overall						0.53 [0.41 to 0.67]	

Heterogeneity: $\tau^2 = 0.05$, $I^2 = 63.24\%$, $H^2 = 2.72$

Test of $\theta_i = \theta_j$: $Q(6) = 17.07$, $p = 0.01$

Test of $\theta = 0$: $z = -5.15$, $p = 0.00$

.125 .5 1 2 4 8
Favours Lifestyle   Favours Control

Random-effects REML model

SUSTAINED REDUCTION IN CONVERSION TO TYPE 2 DIABETES

Original Study	Risk Reduction	Comment	
FDPS, Lindström J et al. Diabetologia 2013 [47]	Hazard Ratio 0.61, adjusted to 0.59 as compared to control group 39%↓	Follow-up 13 years; follow-up data on the diet available	
China Da Qing Diabetes Prevention Study, Li G et al. Lancet 2008 [46]	In total, 43% reduction in the combined intervention clinics as compared to control clinic	Follow-up 20 years; no detailed dietary data	
Diabetes Prevention Program Group, Knowler WC et al. Lancet 2009 [49]	In total, 34% reduction in lifestyle intervention group and 18% reduction in metformin group as compared to placebo control group	Follow-up 10 year; no dietary data from the follow-up reported; long-term metformin use may modify the results	27% reduction in lifestyle intervention group at 15yrs

Table 5. Long-term post-intervention data on mortality, cardiovascular (CVD) mortality and microvascular complications in the former intervention groups compared to the control groups in three randomized controlled lifestyle intervention studies.
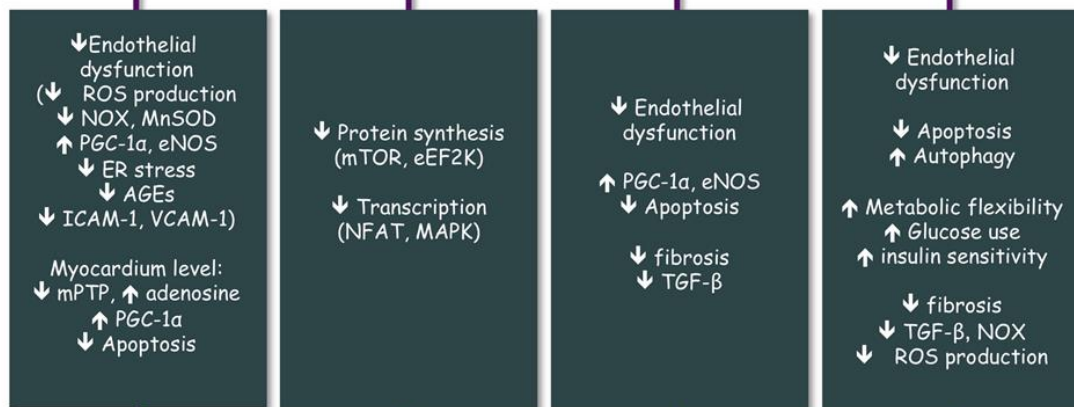
Original Study	Mortality	Cardiovascular Mortality	Reported Microvascular Complications
China Da Qing Diabetes Prevention Follow-up Study, Lancet Diabetes and Endocrinol, Gong Q et al., 2019 [54]	In total, 26% reduction in combined intervention clinics compared to original control group	In total, 33% reduction in combined intervention clinics compared to original control group	In total, 35% reduction in composite microvascular diseases and 40% reduction in any retinopathy in combined intervention clinics compared to original control group [54]
Diabetes Prevention Program Group, Lancet Diabetes and Endocrinol, Nathan DM et al., 2015 [55]	NA	NA	No group differences. Less microvascular complications in individuals who remained non-diabetic (RR 0.72, $p < 0.001$), less microvascular complications in intervention women (8.7% vs. control 11.0% or metformin groups, 11.2%, $p = 0.03$)
The Finnish Diabetes Prevention Follow-up Study PLoS One, Uusitupa M et al., 2009 [56] Nutrients, Aro A et al., 2019 [57]	NS between the original intervention and control groups	NS between the original intervention and control groups	Less early retinopathic changes in intervention (24% vs. 38%, adjusted odds ratio 0.52; 0.28–0.97, 95% CI, $p = 0.039$) than in control group; a subgroup analysis based on retinal photographs.

NA: Not available.

METFORMIN

✓DPP, metformin was as effective as lifestyle modification in participants with BMI ≥35 kg/m2 ,but not significantly better than placebo in patients ≥60 years of age.

✓For women with a history of GDM, metformin and intensive lifestyle modification led to an equivalent 50% reduction in diabetes risk , and both interventions remained highly effective during a 10-year follow-up period.

✓Follow-up (DPPOS), exploratory analyses demonstrated that participants with a higher fasting glucose(≥110 mg/dL) and women with a history GDM experienced higher risk reductions with metformin.

Metformin
via AMPK and other signaling pathways

↓ Endothelial dysfunction (↓ ROS production ↓ NOX, MnSOD ↑ PGC-1α, eNOS ↓ ER stress ↓ AGEs ↓ ICAM-1, VCAM-1) Myocardium level: ↓ mPTP, ↑ adenosine ↑ PGC-1α ↓ Apoptosis	↓ Protein synthesis (mTOR, eEF2K) ↓ Transcription (NFAT, MAPK)	↓ Endothelial dysfunction ↑ PGC-1α, eNOS ↓ Apoptosis ↓ fibrosis ↓ TGF-β	↓ Endothelial dysfunction ↓ Apoptosis ↑ Autophagy ↑ Metabolic flexibility ↑ Glucose use ↑ insulin sensitivity ↓ fibrosis ↓ TGF-β, NOX ↓ ROS production
Myocardial infarction	Cardiac hypertrophy	Heart failure	Diabetic cardiomyopathy

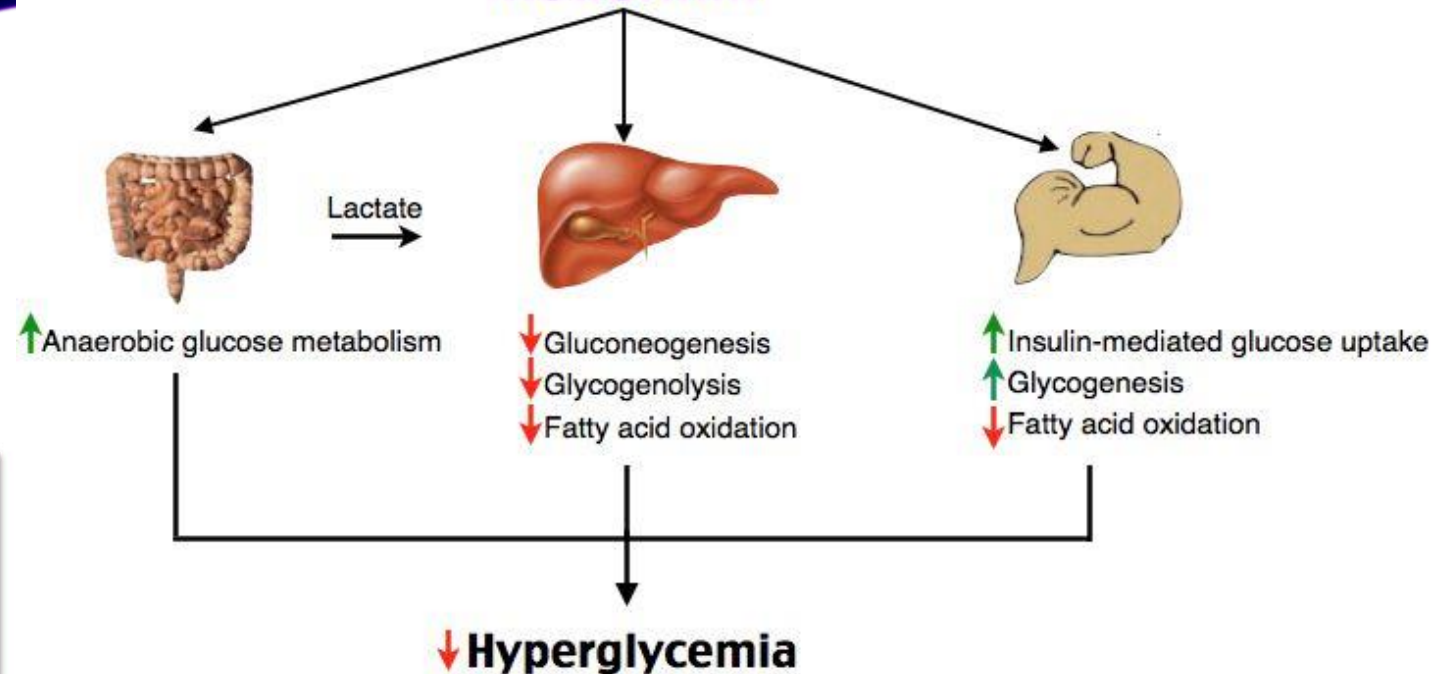### Myocardial complications linked to type 2 diabetes

Metformin

↑ Anaerobic glucose metabolism

Lactate →

↓ Gluconeogenesis
↓ Glycogenolysis
↓ Fatty acid oxidation

↑ Insulin-mediated glucose uptake
↑ Glycogenesis
↓ Fatty acid oxidation

↓ Hyperglycemia

Table 3. Prescribing Metformin by CKD Stage

eGFR Level mL/ 1.73m²	Action
≥ 60	No contraindication to metformin—monitor GFR yearly.
< 60 ≥ 45	Continue metformin—monitor GFR every 3-6 months.
< 45 ≥ 30	Prescribe metformin with caution. Use lower dose (eg, 50%, or half-maximal dose)—closely monitor GFR (every 3 months). Do not start new patients on metformin.
< 30	Do not use metformin.

eGFR, estimated glomerular filtration rate.
Lipska[24]

Pharmacologic Randomized Clinical Trials in Prevention of Type 2 Diabetes

William C. Knowler[1] · Jill P. Crandall[2]

Table 1 Randomized controlled trials of drugs used for preventing type 2 diabetes

Physio-logic Target	Study, place, and primary reference	Year*	Number randomized (sum of all intervention groups)	Drug class	Drug and comparator(s)	Primary follow-up time	Report of outcomes other than diabetes
Insulin secretion	Bedford, UK [4]	1992	241	Sulfonylurea	Tolbutamide, placebo (in 2 × 2 factorial design with diet intervention)	10 years	no
	Malmöhus, Sweden [5, 6]	1980	147	Sulfonylurea	Tolbutamide, placebo, no drug		mortality
	NAVIGATOR‡ [7]	2010	9306	Meglitinide	Nateglinide, placebo (in 2 × 2 factorial design with valsartan)	5 years	CVD#
Insulin action	Whitehall, UK [8]	1979	204	Biguanide	Phenformin, placebo	5 years	no
	Diabetes Prevention Program‡, USA [9]	2002	3234	Biguanide	Metformin, lifestyle, placebo	2.8 years	Further diabetes, microvascular complications
	Diabetes Prevention Program‡, USA [10]	2005	585	Thiazolidinedione	Troglitazone, metformin, lifestyle, placebo	0.9 years	no
	TRIPOD, USA [11]	2002	266	Thiazolidinedione	Troglitazone, placebo	30 months	no
	Indian Diabetes Prevention Program, India [12]	2006	531	Biguanide	Metformin, placebo, lifestyle, placebo	3 years	no
	DREAM‡, International [13]	2006	5269	Thiazolidinedione	Rosiglitazone, placebo (in 2 × 2 factorial design with ramipril)	3 years	CVD and renal
	CANOE, Canada [14]	2010	207	Biguanide + thiazolidinedione	Metformin + rosiglitazone, placebo	4 years	no
	Actos, USA [15]	2011	602	Thiazolidinedione	Pioglitazone, placebo	2.4 years	CVD
Weight loss§	3 orlistat trials pooled, international [16]	2000	675	Lipase inhibitor	Orlistat, placebo	2 years	no
	Xendos, international [17]	2004	3305	Lipase inhibitor	Orlistat, placebo	4 years	no
	SEQUEL, international [18]	2012	475	Appetite suppressants	Phentermine + topiramate, placebo	2 years	no
GLP-1 agonists	SCALE, international [19, 20]	2017	2254	GLP-1 agonist	Liraglutide, placebo	3 years	no
Alpha gluco-sidase inhibitors	STOP NIDDM, international [21, 22]	2002	1429	Alpha glucosidase inhibitor	Acarbose, placebo	3.3 years	CVD
	Voglibose trial in Japan [23]	2009	1780	Alpha glucosidase inhibitor	Voglibose, placebo	48 weeks	no
	Acarbose Cardiovascular Evaluation, China [24•]	2017	6522	Alpha glucosidase inhibitor	Acarbose, placebo	5 years	CVD
Renin-angiotensin system blockers	DREAM‡, international [25]	2006	5269	Angiotensin converting enzyme inhibitor	Ramipril, placebo (in 2 × 2 factorial design with rosiglitazone)	3 years	CVD and renal
	NAVIGATOR [26]	2010	9306	Angiotensin receptor blocker	Valsartan, placebo (in 2 × 2 factorial design with nateglinide)	5 years	CVD

The table gives only brief descriptions of the trials. Because results are presented with different measures and different time frames among the trials, they are not always directly comparable and are therefore not included in the table, but they are summarized in the text description of each trial

*Year of first publication of primary results

‡This trial appears in two places in the table because two different drugs were used

#CVD is cardiovascular disease

§Some drugs are listed in other categories but may also cause weight loss (e.g., metformin, liraglutide)

Agent	Study	Comparator arms	No. of participants	Baseline charact	Treatment duration	Persistence/ adherence to active therapy	Effect on diabetes onset
Glimepiride	NANSY [25]	Placebo or glimepiride	274	Men and women with IGT	3.71 years	Not reported	No significant effect on diabetes risk reduction
Pioglitazone	ACT NOW [73]	Placebo or pioglitazone	602	Men and women with IGT	Median follow-up 2.4 years	Adherence >80% with both placebo and pioglitazone assessed by pill count	Reduced diabetes risk (HR 0.28, $p < 0.005$)

72%↓

Pioglitazone Therapy in Patients With Stroke and Prediabetes: A Post Hoc Analysis of the IRIS Randomized Clinical Trial
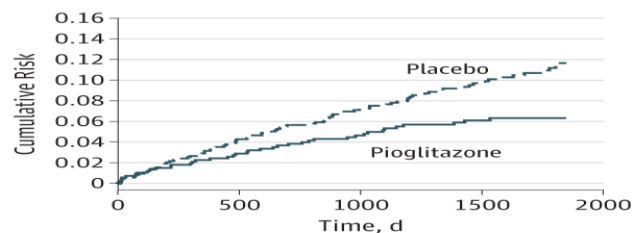
Activation of peroxisome proliferator activated receptor (PPAR) -α and gamma: modulation of gene expression

Improvement of insulin sensitivity , lipid and protein metabolism, vascular endothelial function, inflammation , fat distribution
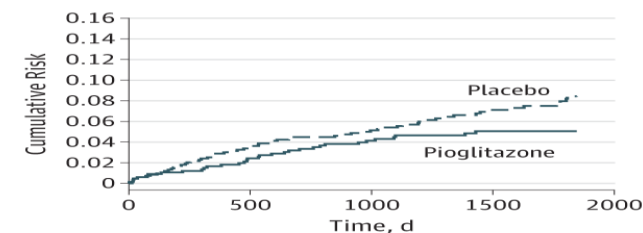
Hypothesis that pioglitazone reduces stroke and MI in nondiabetic patients with insulin resistance.
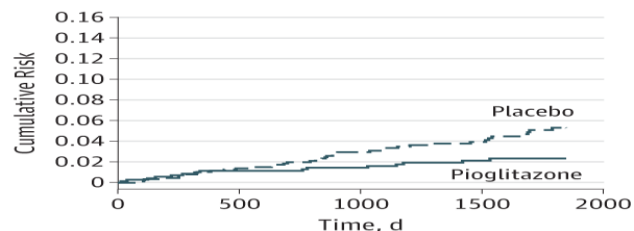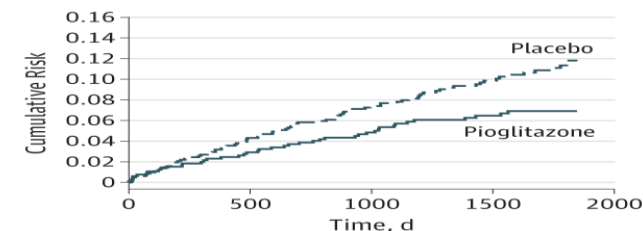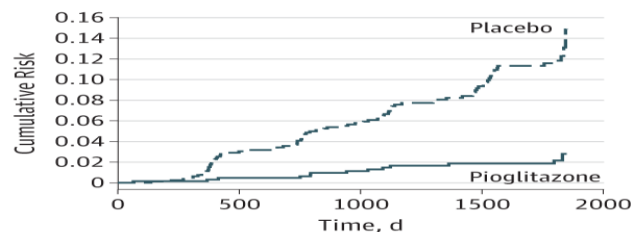
Proactive Trial

Primary Outcome Stroke and MI HR: 0.76;95% CI: 0.62-0.93;p=0.007 (24%↓)

Secondary Outcome-Progression to Diabetes Hazard Ratio 0.48;95%,CI 0.33-0.69;p<0.001(52%↓)

Agent	Study	Comparator arms	No. of participants	Baseline charact	Treatment duration	Persistence/ adherence to active therapy	Effect on diabetes onset
Acarbose	STOP-NIDDM [26]	Placebo or acarbose	714	Men and women with IGT	3.3 years	30% discontinuation rate acarbose group vs. 18% placebo group, mainly due to GI side effects	RRR 25% in new onset diabetes
Liraglutide	SCALE [43]	Placebo plus lifestyle or placebo plus liraglutide	3731	Men and women with BMI >30 kg/m^2	56 weeks	Discontinuation due to adverse events 9.9% liraglutide group vs. 3.8% placebo group	Reduced prevalence in pre-diabetes at 56 weeks in liraglutide arm (67.3% vs. 30.8%, $p < 0.001$)

Weight loss medications and diabetes prevention

Agent	Mechanism of Action	Study Outcomes	Cardioprotective Features
Phentermine/ Topiramate (Qsymia)	1. Phentermine 2. Topiramate	Guo et al. 3,040 participants The authors pooled data from three RCTs (CONQUER, SEQUEL, and EQUIP). The 1-year risk of incidence of diabetes in the treatment vs placebo groups was 0.67% vs 1.51% for those at low risk, 2.37% vs 4.67% for those at moderate risk, and 6.29% vs 10.43% for those at high risk	No studies have been conducted for cardioprotective features of. Teratogenic potentials and elevations in heart rate are possible concerns.

Non glucose-lowering therapies and diabetes prevention

Agent	Study	Comparator arms	No. of participants	Baseline charact	Treatment duration	Persistence/ adherence to active therapy	Effect on diabetes onset
Orlistat	XENDOS [56]	Placebo or orlistat	3305	Men and women with BMI ≥ 30 kg/m^2	4 years	Compliance 93.3% orlistat vs. 92.8% placebo (NS)	RRR 37.3% in new onset diabetes (HR 0.63; 95% CI 0.46–0.86, $p = 0.003$)

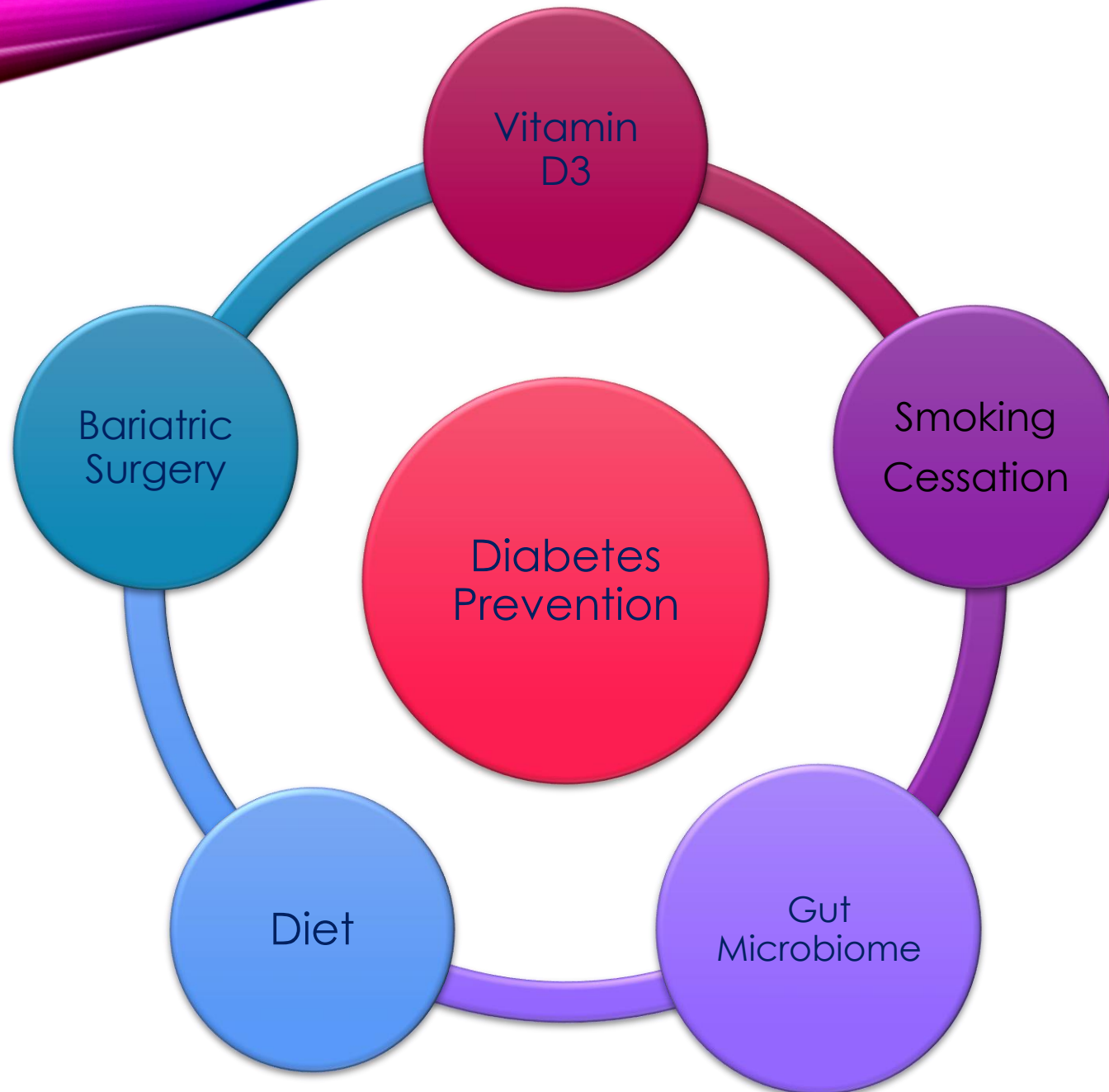# Antihypertensive medications on diabetes prevention

Agent	Study	Comparator arms	No. of participants	Baseline charact	Treatment duration	Persistence/ adherence to active therapy	Effect on diabetes onset
Valsartan	NAVIGATOR [60]	Placebo or valsartan or nateglinide or valsartan and nateglinide	9306	Men and women with IFG and one or more CVD risk factors	Median follow-up 5 years for diabetes	Persistence at study end 66.2% valsartan group vs. 66.7% placebo group ($p = 0.59$)	Significant reduction RRR 14% in new onset diabetes ($p < 0.001$)
Meta-analysis of RAS blockers	12 randomised controlled trials [61]	Placebo, diuretics, β-blockers or calcium channel blockers vs. RAS blockers	116,220 (72,333 without diabetes)	Men and women with hypertension or at least 1 other CVD risk factor	Mean follow-up 1–6.1 years	n/a	RRR 25% both agents RRR 27% ACE inhibitors RRR 23% ARBs

Statin therapy and diabetes prevention

Agent	Study	Comparator arms	No. of participants	Baseline charact	Treatment duration	Persistence/ adherence to active therapy	Effect on diabetes onset
Statins (pravastatin, rosuvastatin, atorvastatin, simvastatin, lovastatin)	Meta-analysis of 13 randomised controlled trials [62]	Placebo or statin comparison trials	91,140	Men and women assigned statin therapy for primary or secondary CVD	Mean follow-up 4 years	n/a	Increases risk of diabetes by 9% (OR 1.09; 95% CI 1.02–1.17)
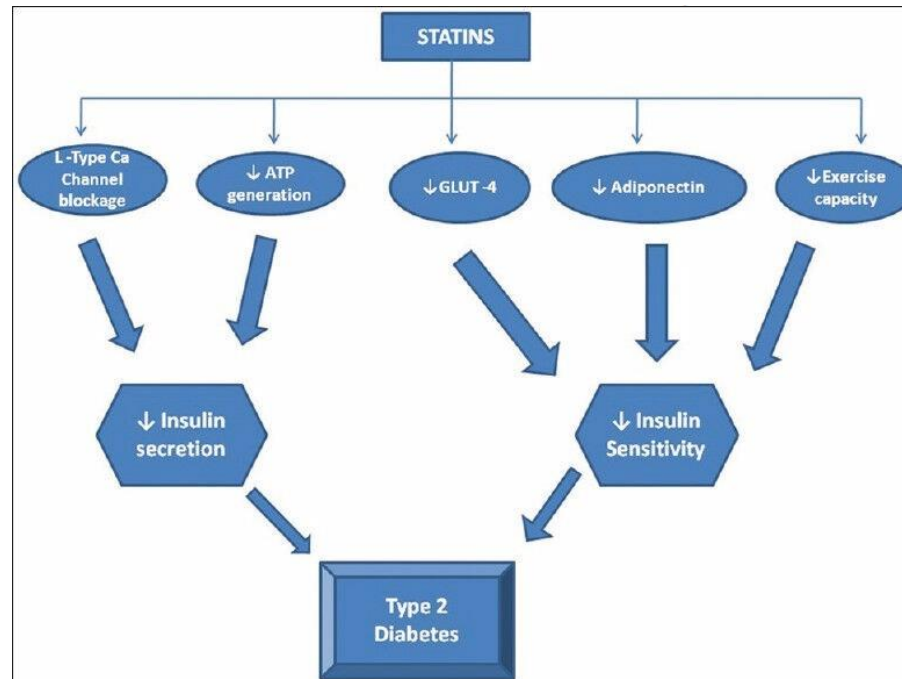
As per meta-analysis of patients taking statins; of 250 patients treated with statins 1 will develop DM Type 2 in 4 years 9 will have prevented a CV event.

PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)
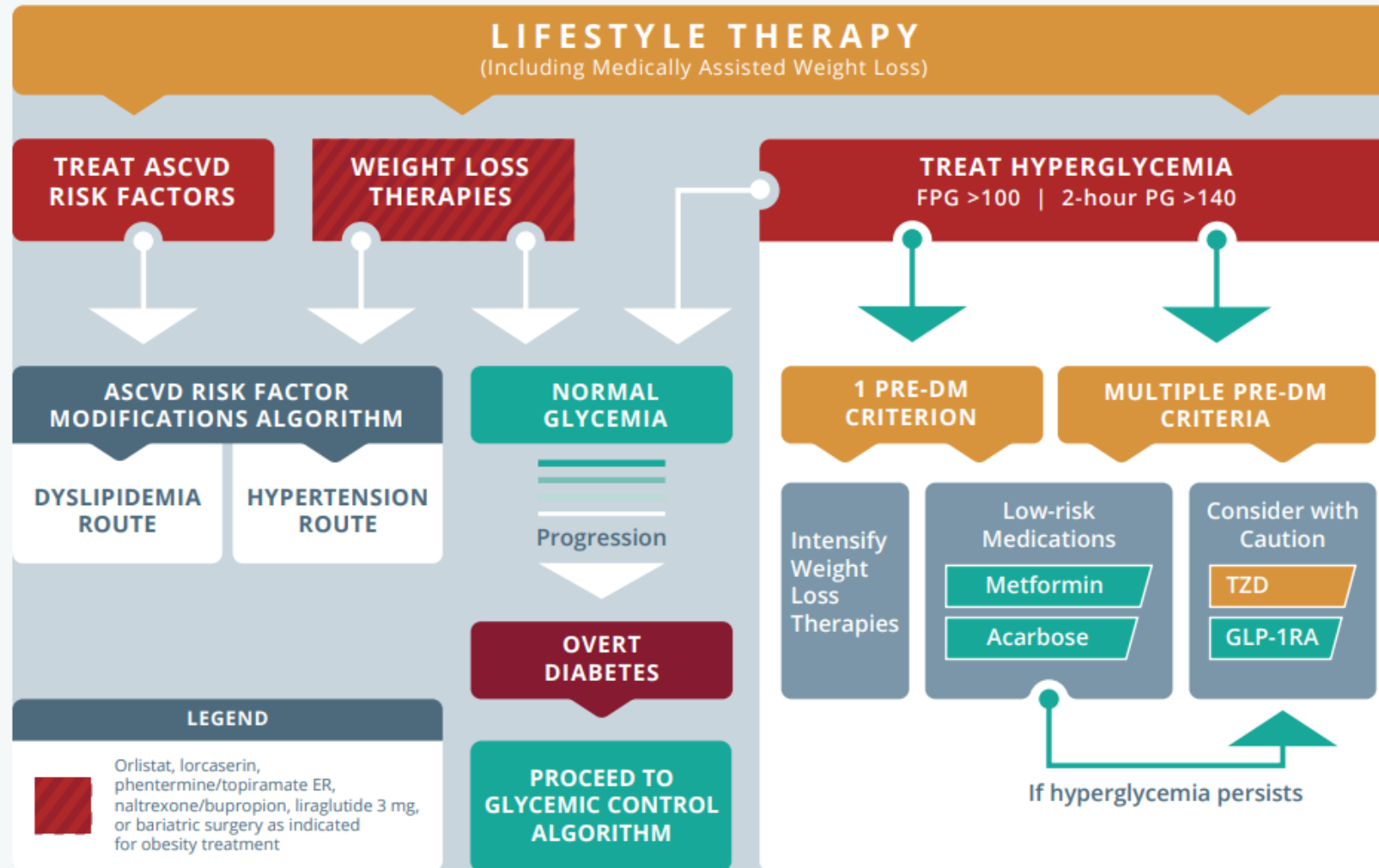
LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

TREAT ASCVD RISK FACTORS

WEIGHT LOSS THERAPIES

TREAT HYPERGLYCEMIA
FPG >100 | 2-hour PG >140

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

NORMAL GLYCEMIA

1 PRE-DM CRITERION

MULTIPLE PRE-DM CRITERIA

DYSLIPIDEMIA ROUTE

HYPERTENSION ROUTE

Progression

Intensify Weight Loss Therapies

Low-risk Medications
- Metformin
- Acarbose

Consider with Caution
- TZD
- GLP-1RA

LEGEND

Orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg, or bariatric surgery as indicated for obesity treatment

OVERT DIABETES

PROCEED TO GLYCEMIC CONTROL ALGORITHM

If hyperglycemia persists
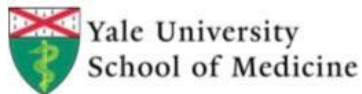
Background

- ✓ SGLT-2 inhibitors are glucose-lowering medications that work by inducing glucosuria. They also improve insulin actin and secretion and don't increase the risk of hypoglycemia.

- ✓ DAPA-HF was the first trial to show the effectiveness of an SGLT-2 inhibitor (Dapagliflozine) to improve clinical outcomes in patients with HF with reduced ejection fraction (HFrEF) with /without T2D.

- ✓ The trial was sought to determine wether dapagliflozin could reduce the incidenceof new onset T2D in patients without diabetes.

- ✓ Incident diabetes: hbA1C ≥6.5% on 2 consecutive study visits or a diagnosis of T2D by his PCP.

DAPA-HF Design

Enrollment   **Randomization**

Inclusion:
- NYHA class II-IV
- LVEF ≤40%
- NT-proBNP ≥600 pg/ml*

Exclusion:
- eGFR <30 ml/min/1.73 m²
- SBP <95 mmHg
- Type 1 diabetes

N=2371   Placebo

N=2373   Dapagliflozin 10 mg once daily

≥844 Primary outcomes
Composite of:
- CV death
- HF hospitalization
- Urgent HF visit

Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 etc.
Day −14	Day 0	Day 14	Day 60	Day 120	Every 120 days
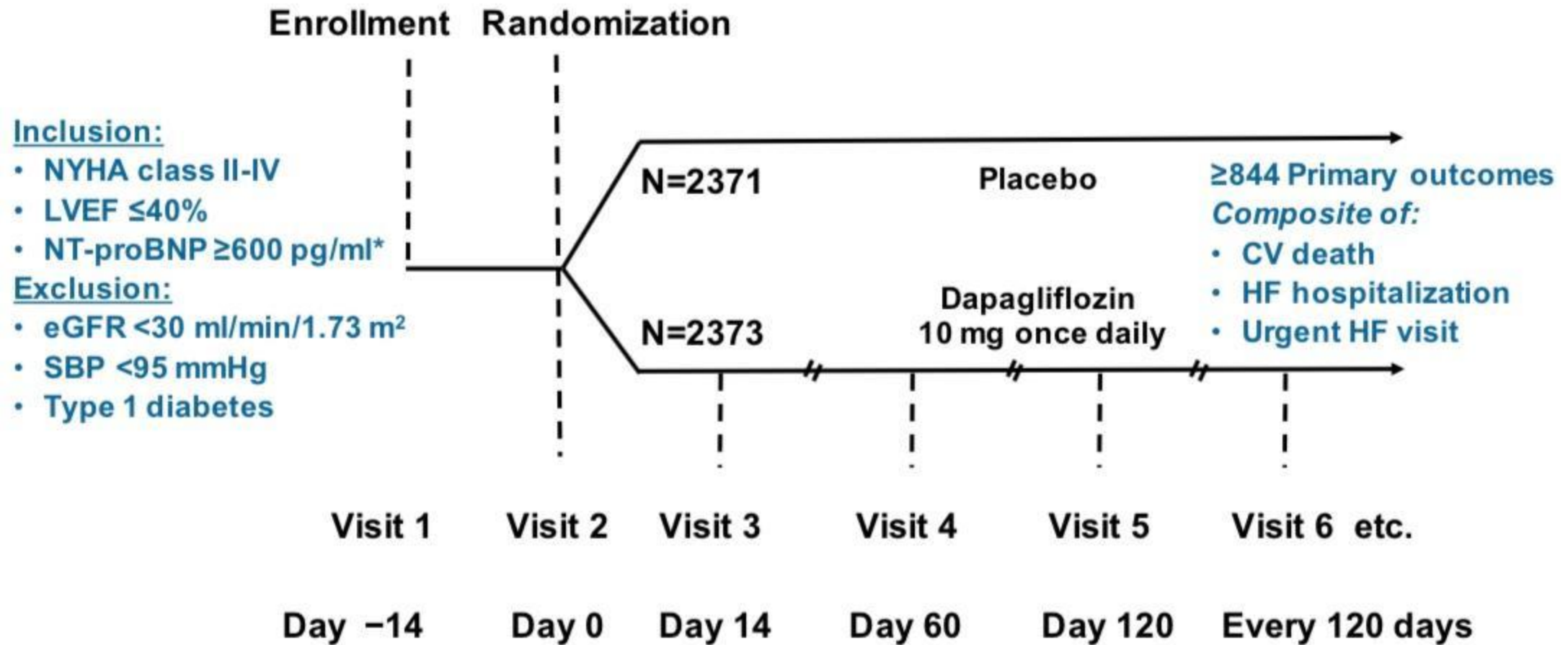
*≥400 pg/ml if HF hospitalization within ≤12 months; ≥900 pg/ml if atrial fibrillation/flutter

Dapagliflozin reduced worsening HF or CV death in patients with HFrEF

CV Death/HF hospitalization/Urgent HF visit

Similar benefit in patients with and without T2DM
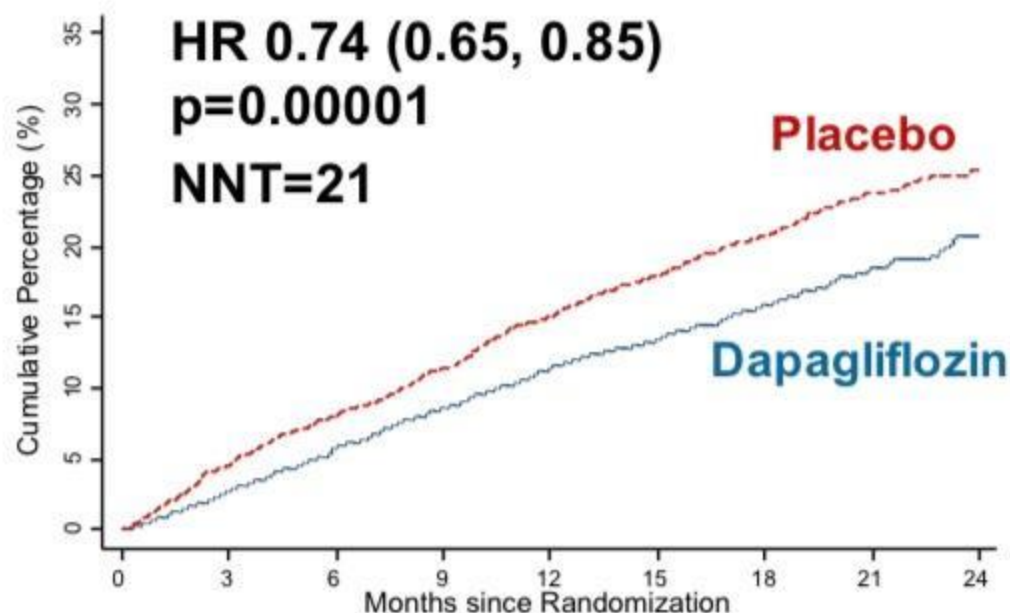
26% reduction in HHF

McMurray et al. *N Engl J Med* 2019;38:1995-2008
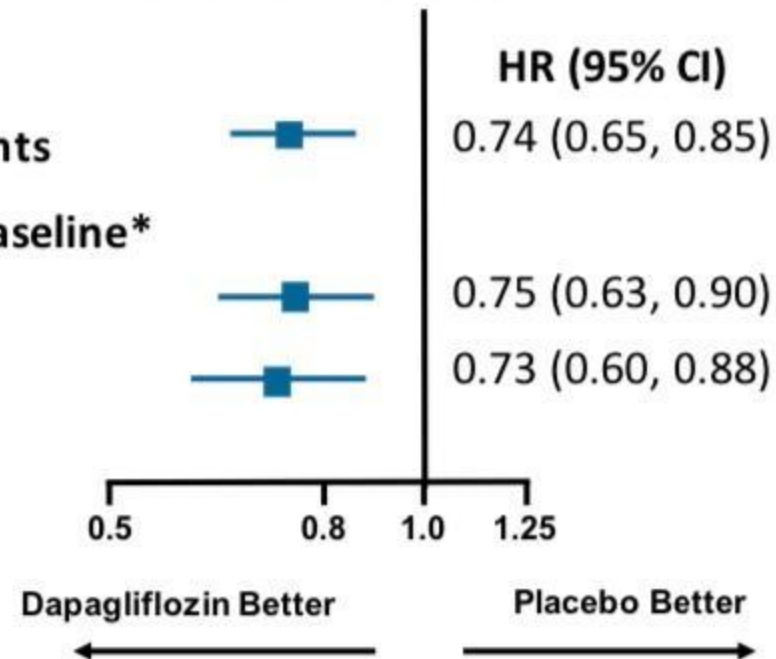
*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrolment and randomization visits.

Distribution of Patients by Glycemic Status: A Typical HFrEF Population

N=4744

History of diabetes (42%)

No diabetes (55%)

Undiagnosed diabetes (3%)

DAPAHF

45%

History of diabetes (n=1983)

- Provided by investigators

Undiagnosed diabetes (n=156)

- HbA1c ≥6.5% at Visits 1 and 2 in patients without diabetes history

55%

No diabetes (n=2605)

- HbA1c <6.5% at Visits 1 and 2

Petrie MC *et al. JAMA* 2020;323:1353-68
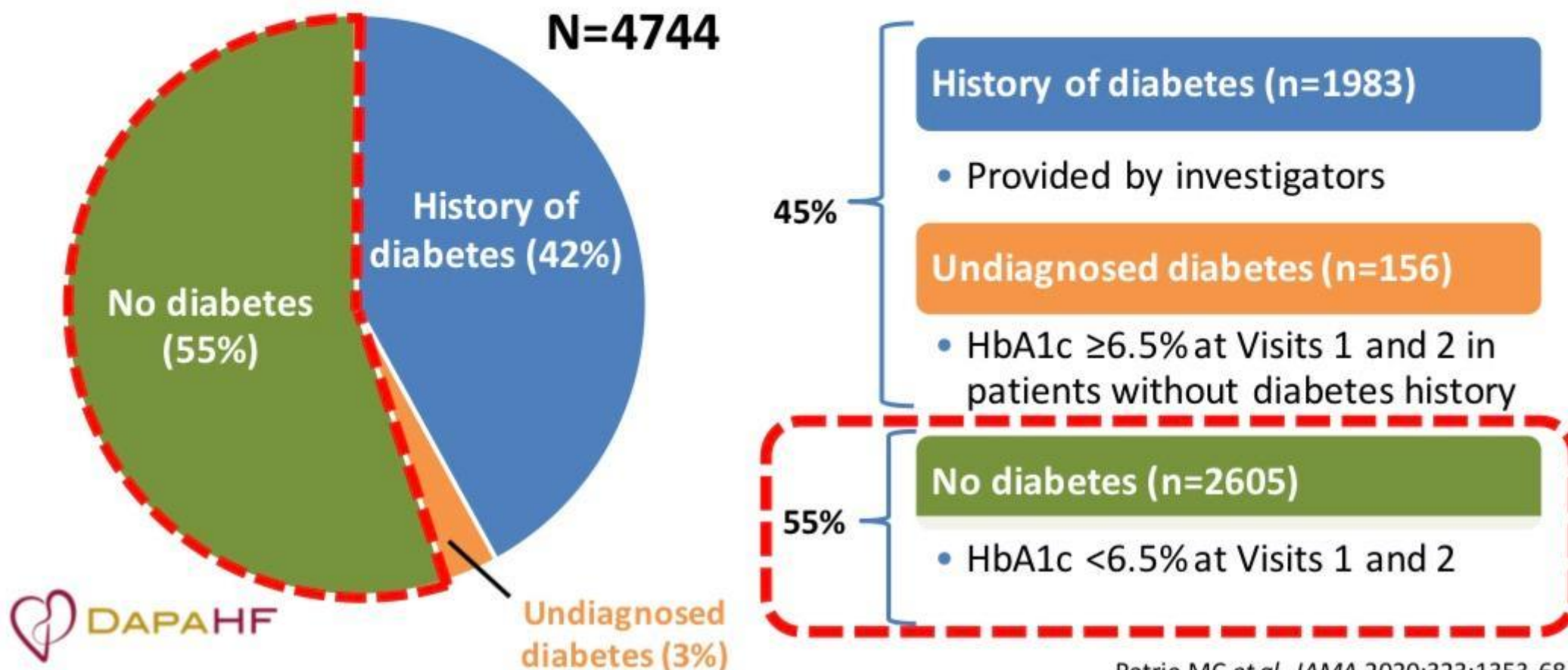
Results: HbA1c levels over time in dapa vs. placebo groups

Prediabetes
Placebo-adjusted △HbA1c @8 mo:
-0.04% (-0.07% to 0.00%), p=0.034

Normoglycemic
Placebo-adjusted △HbA1c @8 mo:
-0.05% (-0.10% to 0.00%), p=0.051

Adjusted Mean HbA1c (%)

Days From Randomisation

Placebo — Dapagliflozin
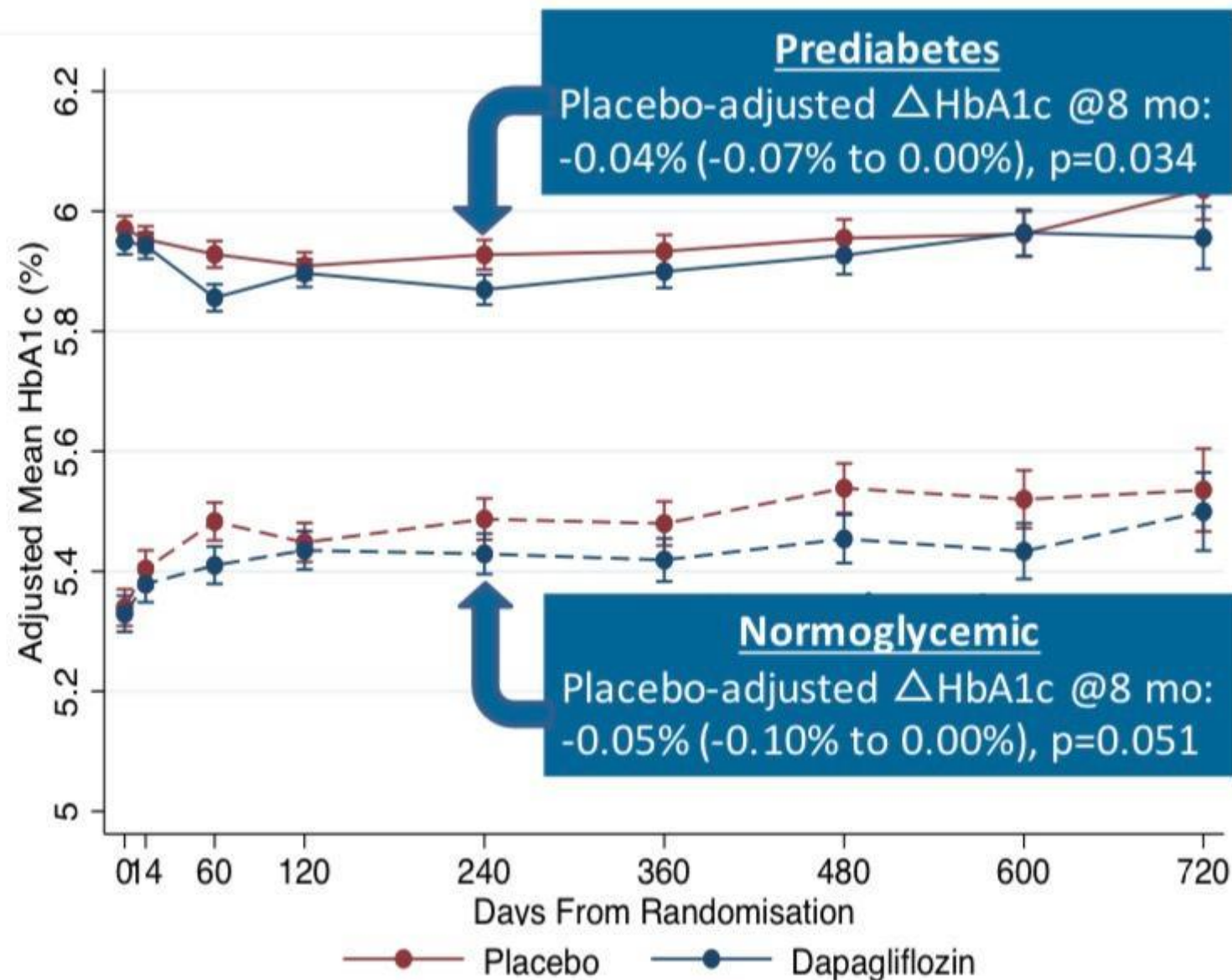
Results:
Incidence of new onset T2D in dapa vs. placebo groups

Placebo: 93/1307 (7.1%; 5.0/100 pt-yrs)

Dapa: 64/1298 (4.9%; 3.4/100 pt-yrs)

HR = 0.68 (95% CI, 0.50-0.94); p=0.019

32% ↓ in new onset DM2

Median follow-up:
18.2 months (IQR,14.2-21.5)

Cumulative Percentage (%)

Months since Randomization
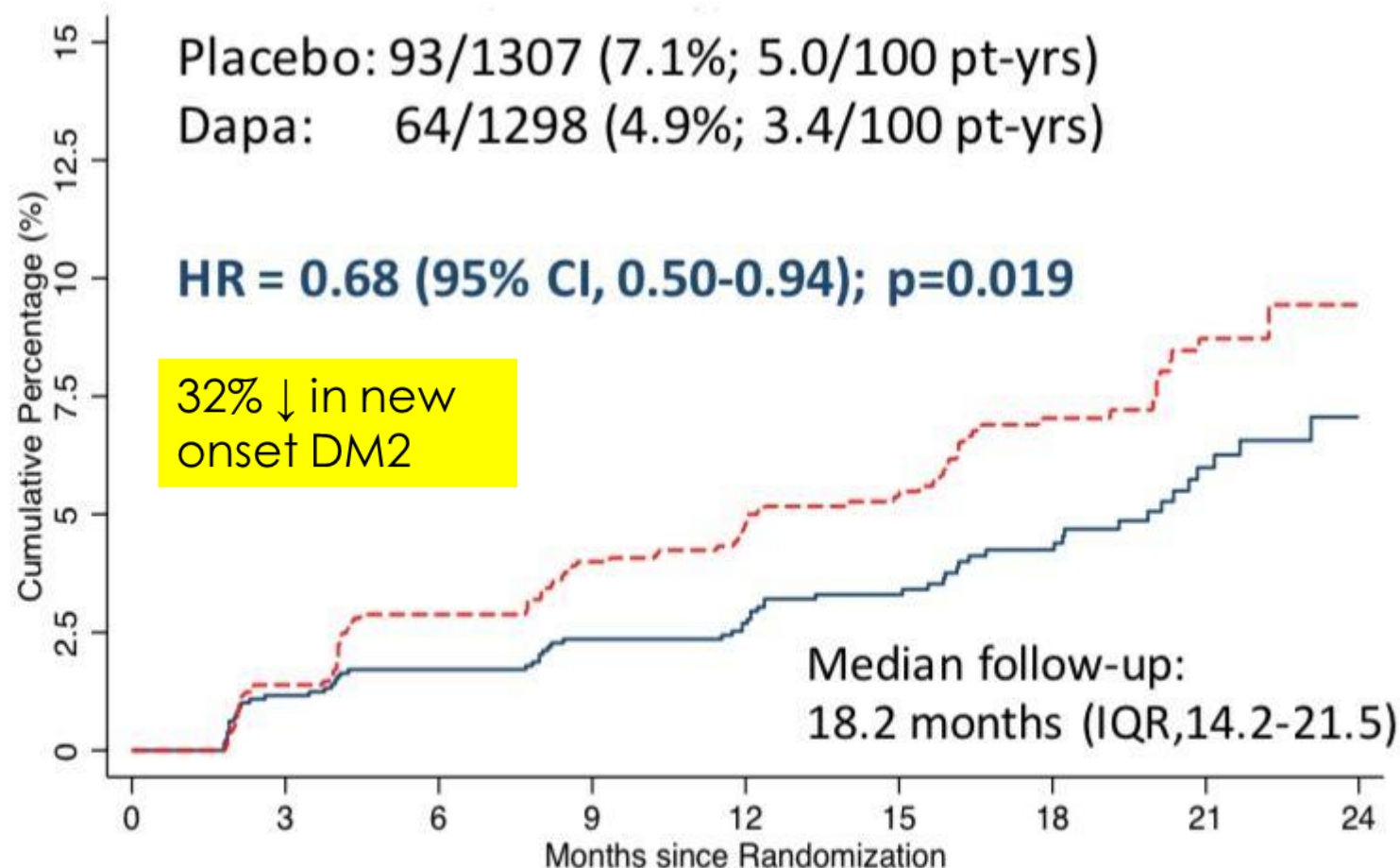
Number at Risk	0	3	6	9	12	15	18	21	24
Dapagliflozin	1298	1266	1233	1208	1147	895	666	366	123
Placebo	1307	1268	1225	1198	1127	874	642	358	125

Dapagliflozin ------- Placebo

Fine & Gray: HR 0.69 (0.50-0.95)
LR adjusted for baseline HbA1c: OR 0.72 (0.51, 1.02)

Limitations

- ✓ FPG or OGTT was not assessed

- ✓ Findings apply only to patients with HFrEF

- ✓ In this trial , due to strong effect of primary outcome, f/u 18 months

- ✓ Diabetes was not retested after drug withdrawal

We have have multiple studies that conclude that T2D is preventable by changing lifestyle and weight reduction.

The risk reduction of T2D is strongly related to the degree of long-term weight loss and adherence to lifestyle changes, and this preventive effect has been demonstrated to sustain for many years after active intervention.

A diet moderate in fat, low in saturated fat intake, rich in fiber, whole grains, and fruit and vegetables, as well as a Mediterranean-type diet(PREDIMED trial), may be recommended for theprevention of T2D in prediabetes.

There is still limited/insufficient evidence that the prevention of T2D by changing lifestyle may also prevent CVD or microvascular diseases.

DIABETES DIAGNOSIS

Table 1. Diagnostic criteria for diabetes.[69]

American Diabetes Association/European Association for the Study of Diabetes/American College of Physicians/Endocrine Society[6–9]

	Normal	Impaired fasting glucose	Diabetes
FPG	<100 mg/dL	100–125 mg/dL	≥126 mg/dL
	(5.6 mmol/L)	(5.6–6.9 mmol/L)	(7.0 mmol/L)
2-hour	<140 mg/dL	140–199 mg/dL	≥200 mg/dL
OGTT	(7.8 mmol/L)	(7.8–11.0 mmol/L)	(11.1 mmol/L)
HbA1c	<5.7%	5.7–6.4%	≥6.5%
	(39 mmol/mol)	(39–46 mmol/mol)	(48 mmol/mol)

American Association of Clinical Endocrinologists/American College of Endocrinology[7]

	Normal	Impaired fasting glucose	Diabetes
FPG	<100 mg/dL	100–125 mg/dL	≥126 mg/dL
	(5.6 mmol/L)	(5.6–6.9 mmol/L)	(7.0 mmol/L)
2-hour	<140 mg/dL	140–199 mg/dL	≥200 mg/dL
OGTT	(7.8 mmol/L)	(7.8–11.0 mmol/L)	(11.1 mmol/L)
HA1c	<5.5%	5.5–6.4%	≥6.5%
	(37 mmol/mol)	(37–46 mmol/mol)	(48 mmol/mol)

International Diabetes Federation[10]

	Normal	Impaired fasting glucose	Diabetes
FPG	<100 mg/dL	100–125 mg/dL	≥126 mg/dL
	(5.6 mmol/L)	(5.6–6.9 mmol/L)	(7.0 mmol/L)
2-hour	<140 mg/dL	140–199 mg/dL	≥200 mg/dL
OGTT	(7.8 mmol/L)	(7.8–11.0 mmol/L)	(11.1 mmol/L)
HbA1c			≥6.5%
			(48 mmol/mol)

Classic symptoms (polyuria, polydipsia, polyphagia, unexplained weight loss, weakness, blurred vision) and a random blood glucose ≥200 mg/dL (11.1 mmol/L).
Any test abnormality will require repeating the test. If two different tests demonstrate the diagnosis of diabetes additional testing is not needed.
FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; HbA1c, glycated hemoglobin.

Quattrocchi E, Goldberg T, Marzella N. Drugs in Context 2020

Diabetes Testing

✓ The A1C test should be performed using a method that is certified by the NGSP and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay.

✓ The A1C test, with a diagnostic threshold of ≥6.5% , diagnoses only 30% according to National Health and Nutrition Examination Survey.

✓ Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes .

Sources of error of A1C interpretation

International standardization of the A1C assay has decreased potential technical errors in interpreting A1C results.

A1C values are influenced by red cell survival.

Falsely high levels for iron, vitamin B12, or folate deficiency anemia.

Falsely low A1C values. In patients with hemolytic anemia, patients treated for iron, vitamin B12, or folate deficiency, and patients treated with erythropoietin.

Several studies have shown that A1C concentrations are higher in some ethnic groups (African American, Hispanic, Asian)

Risk Factors for Type 2 Diabetes

- Age >45 years
- First-degree relative with type 2 diabetes
- African American, Hispanic, Asian, Pacific Islander, or Native American race/ethnicity
- History of gestational diabetes or delivery of infant weighing ≥9 lb
- Polycystic ovary syndrome
- Overweight, especially abdominal obesity
- Cardiovascular disease, hypertension, dyslipidemia, or other features of metabolic syndrome

Type I Diabetes Diagnosis (5-10%)

Table 2.1—Staging of type 1 diabetes (8,9)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or $\geq$10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria

Autoimmune markers
Islet cell autoantibodies
Autoantibodies to GAD (GAD65), Insulin, the tyrosine phosphatases IA-2 and IA-2ß and zinc transporter 8 .

Recommendations ADA for Type 1
2.4 Screening for type 1 diabetes risk with a panel of islet autoantibodies is currently recommended in the setting of a research trial or can be offered as an option for first-degree family members of a proband with type 1 diabetes. B

2.5 Persistence of autoantibodies is
a risk factor for clinical diabetes and may serve as an indication for intervention in the setting of
a clinical trial. B

- ✓ Onset of hyperglycemia usually at an early age(before 25).

- ✓ Characterized by impaired insulin secretion with minimal or no defects in insulin action.

- ✓ A diagnosis of MODY should be considered in individuals who have atypical diabetes and multiple family members with diabetes not characteristic of type1 or type 2 diabetes.

Table 1 MODY subtypes: gene mutations, pathophysiology, and clinical characteristics.

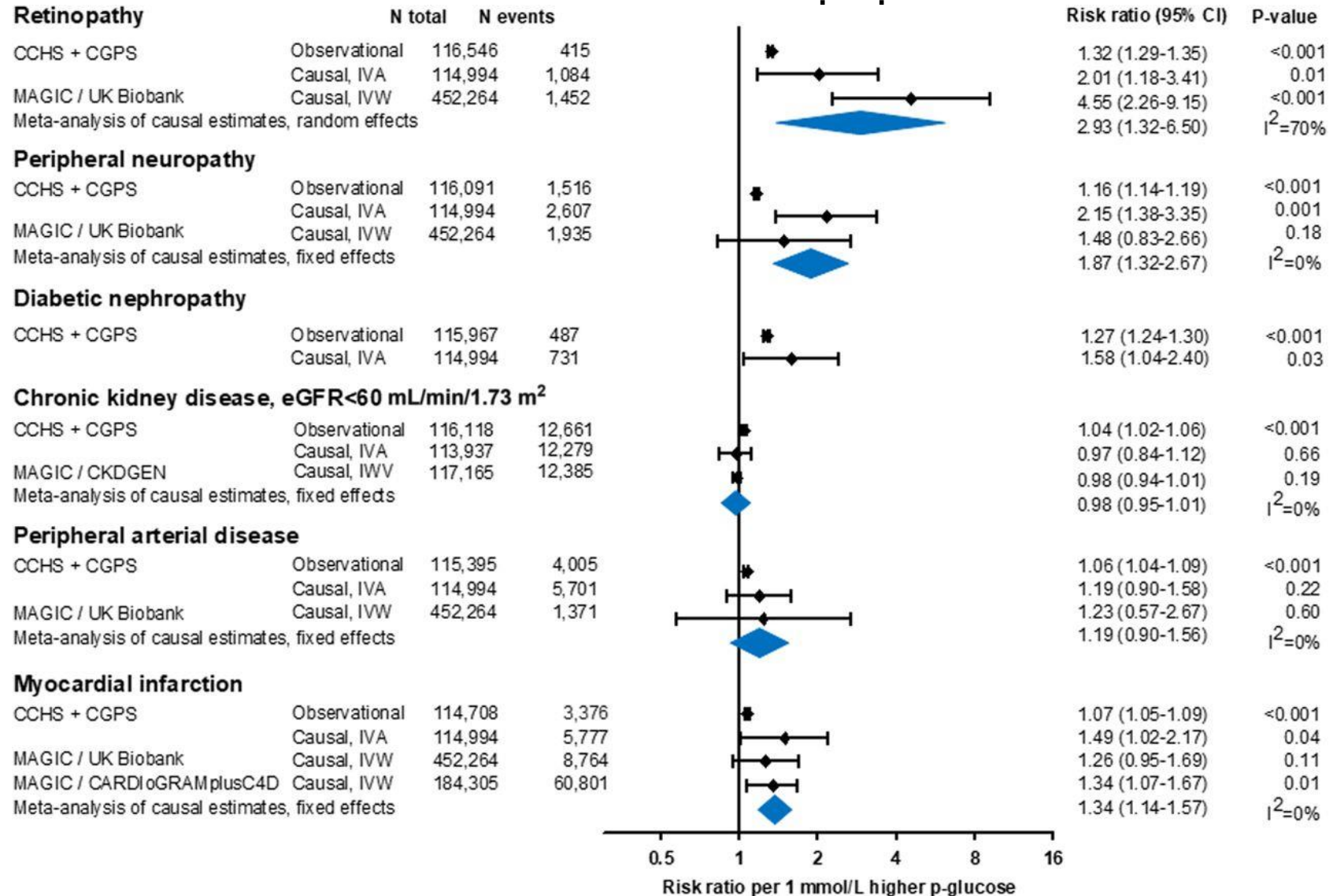| MODY	Gene	Pathophysiology	Clinical characteristics
1	HNF4A	Transcription factor; decreased insulin secretion	Rare (5%); neonatal hyperinsulinemia, low triglycerides, tendency for microvascular complications, sensitivity to sulfonylureas
2	GCK	Decreased glucose sensitivity due to phosphorylation defect; decreased glycogen storage	Common (30–50%); increased fasting glucose, increased likelihood of glucose <55 mg/dL on oral glucose tolerance test; mild diabetes that generally does not require anti-diabetes medication
3	HNF1A	Transcription factor; decreased insulin secretion, progressive β-cell damage	Common (30–50%), high penetrance; glycosuria, microvascular complications, sensitivity to sulfonylurea
4	PDX1/IPF1	Impaired pancreas development; homozygotes experience pancreas agenesis	Rare (1%); mean age at diagnosis 35 years, requires oral anti-diabetes treatment (and insulin)
5	HNF1B	Transcription factor; decreased insulin secretion	Rare (5%); extra pancreatic signs (renal cysts or dysplasia, genital abnormalities in females, azoospermia in males) with diabetes; variable phenotype; requires insulin treatment
6	NEUROD1	Abnormal development of β-cell functions	Very rare (<1%); adult-onset diabetes
7	KLF11	Tumor-suppressor gene; decreased glucose sensitivity of β-cells	Very rare (<1%); phenotype resembling type 2 diabetes
8	CEL	Decreased endocrine and exocrine pancreas functions (pathophysiology?)	Very rare (<1%); typically autosomal dominant diabetes
9	PAX4	Transcription factor affecting apoptosis and proliferation of β-cells	Very rare (<1%); possible ketoacidosis
10	INS	Heterozygous mutation of the insulin gene	Very rare (<1%); diabetes onset before 20 years of age; sulfonylurea or insulin treatment is generally required
11	BLK	Heterozygous mutation affecting insulin secretion	Very rare (<1%); increased penetrance with higher body mass indexes
12	ABCC8	ATP-sensitive potassium channels dysfunction	Very rare (<1%); clinical phenotype is similar to HNF1A/4A-MODY
13	KCNJ11	ATP-sensitive potassium channels dysfunction	Very rare (<1%); clinical phenotype is heterogenous

DIABETES MANAGEMENT

Pathophysiology of DM type 2

Risk of retinopathy, peripheral neuropathy, diabetic nephropathy, CKD (defined as eGFR <60 mL/min/1.73 m2), PAD, and MI per 1 mmol/L (18 mg/dL) higher observational and causal glucose

		N total	N events		Risk ratio (95% CI)	P-value
Retinopathy						
CCHS + CGPS	Observational	116,546	415		1.32 (1.29-1.35)	<0.001
	Causal, IVA	114,994	1,084		2.01 (1.18-3.41)	0.01
MAGIC / UK Biobank	Causal, IVW	452,264	1,452		4.55 (2.26-9.15)	<0.001
Meta-analysis of causal estimates, random effects					2.93 (1.32-6.50)	I^2=70%
Peripheral neuropathy						
CCHS + CGPS	Observational	116,091	1,516		1.16 (1.14-1.19)	<0.001
	Causal, IVA	114,994	2,607		2.15 (1.38-3.35)	0.001
MAGIC / UK Biobank	Causal, IVW	452,264	1,935		1.48 (0.83-2.66)	0.18
Meta-analysis of causal estimates, fixed effects					1.87 (1.32-2.67)	I^2=0%
Diabetic nephropathy						
CCHS + CGPS	Observational	115,967	487		1.27 (1.24-1.30)	<0.001
	Causal, IVA	114,994	731		1.58 (1.04-2.40)	0.03
Chronic kidney disease, eGFR<60 mL/min/1.73 m^2						
CCHS + CGPS	Observational	116,118	12,661		1.04 (1.02-1.06)	<0.001
	Causal, IVA	113,937	12,279		0.97 (0.84-1.12)	0.66
MAGIC / CKDGEN	Causal, IWV	117,165	12,385		0.98 (0.94-1.01)	0.19
Meta-analysis of causal estimates, fixed effects					0.98 (0.95-1.01)	I^2=0%
Peripheral arterial disease						
CCHS + CGPS	Observational	115,395	4,005		1.06 (1.04-1.09)	<0.001
	Causal, IVA	114,994	5,701		1.19 (0.90-1.58)	0.22
MAGIC / UK Biobank	Causal, IVW	452,264	1,371		1.23 (0.57-2.67)	0.60
Meta-analysis of causal estimates, fixed effects					1.19 (0.90-1.56)	I^2=0%
Myocardial infarction						
CCHS + CGPS	Observational	114,708	3,376		1.07 (1.05-1.09)	<0.001
	Causal, IVA	114,994	5,777		1.49 (1.02-2.17)	0.04
MAGIC / UK Biobank	Causal, IVW	452,264	8,764		1.26 (0.95-1.69)	0.11
MAGIC / CARDIoGRAMplusC4D	Causal, IVW	184,305	60,801		1.34 (1.07-1.67)	0.01
Meta-analysis of causal estimates, fixed effects					1.34 (1.14-1.57)	I^2=0%

Risk ratio per 1 mmol/L higher p-glucose

| Study	HbA1c[a]	Microvascular		CVD		Mortality	
		Initial Trial	Long-term Follow-up	Initial Trial	Long-term Follow-up	Initial Trial	Long-term Follow-up
UKPDS[2,3]	7.9 vs. 7.0	↓	↓	—	↓	—	↓
DCCT/EDIC[4,5]	9.1 vs. 7.0	↓	↓	—	↓	—	—
ACCORD[6,7]	7.5 vs. 6.4	?		—		↑	
ADVANCE[8]	7.3 vs. 6.5	↓		—		—	
VADT[9]	8.4 vs. 6.9	↓		—		—	

[a]Values presented are for conventional/standard therapy group vs. intensive therapy group at the end of initial trial

1. Bergenstal RM, et al. *Am J Med.* 2010;123(4):374.e 9 -18
2. UKPDS Group. *Lancet.* 1998;352(9131):854-65
3. Holman RR et al. *N Engl J Med.* 2008;359(15):1577-89
4. DCCT. *N Engl J Med* 1993;329(14):977-86
5. Nathan DM, et al. N Engl J Med. 2005;353(25):2643-53
6. ACCORD Study Group. *N Engl J Med.* 2008;358(24):2545-59
7. ACCORD Study Group. *N Engl J Med.* 2010;363(3):233-44
8. ADVANCE Collaborative Group. *N Engl J Med.* 2008;358(24):2560-72
9. Duckworth W et al *N Engl J Med.* 2009;360(2):129-39

MICROVASCULAR VS MACROVASCULAR COMPLICATIONS

✓ Traditional anti-hyperglycemic medications reduce BOTH blood sugar and microvascular complications

✓ There was NOT evidence to support that traditional anti-diabetes medications reduced macrovascular complications

✓ Episodes of hypoglycemia can actually INCREASE CV risk

Acharya, et al.JAAC.2018

Life expectancy is reduced by 12 years in patients with diabetes and previous CV disease*

60 years

End of life

No diabetes

Diabetes -6 years

Diabetes + CV disease -12 years
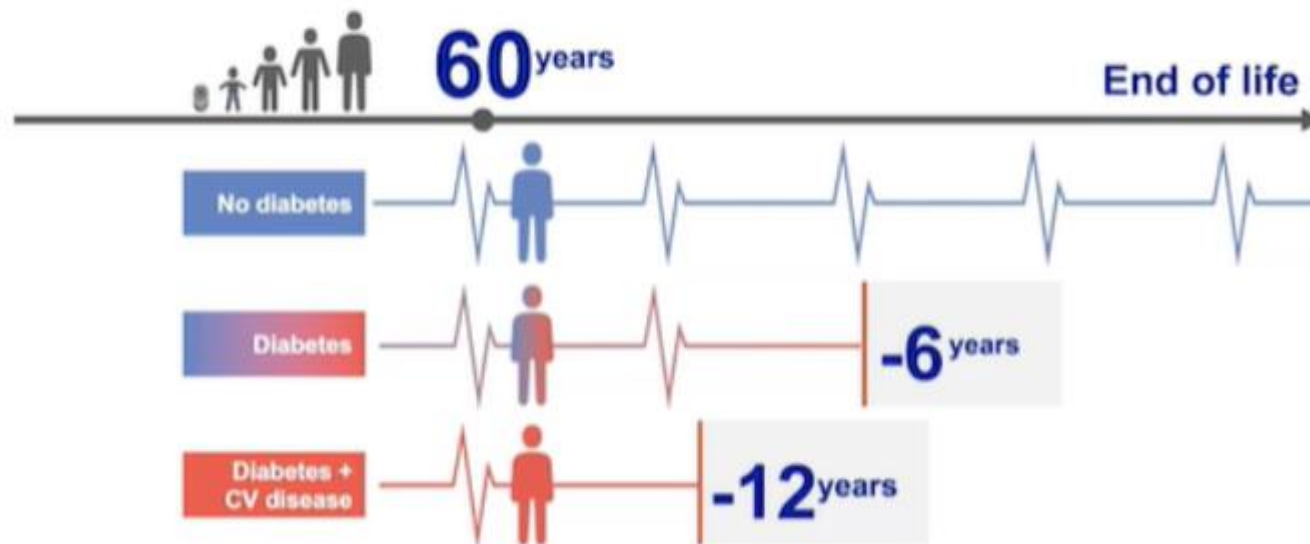
In this case, CV disease is represented by MI or stroke. *Male, 60 years of age with history of MI or stroke
The Emerging Risk Factors Collaboration. JAMA 2015;314:52

Reliable data are difficult to find, but the prevalence of CVD in the population with diabetes is ~18%

(Review of 57 epidemiologic studies with 4,549,481 with DM 2)

Myocardial infaction   10%
Stroke   7.6%

Einarson et al
Cardiovasc Diabetol 2018;17:8

Diabetes and risk factors for HF

✓ In the Framingham Heart Study, T2D increased the risk of HF incidence by two-fold in men and four-fold in women, after adjusting for other CV risk factors.

✓ With each 1% increase in HbA1c, the risk of HF increases by 8–32%.

✓ In recent trials, concomitant diabetes in patients with HF has shown an increased risk of death.

Diabetes 2010 Aug; 59(8): 2020-2026

Table 3. Prevention of CVD.[29,32]

Risk enhancers in patients with diabetes

- Long duration (≥10 years for T2D or ≥20 years for type 1 diabetes mellitus)

- Albuminuria ≥30 mcg albumin/mg creatinine

- eGFR <60 mL/min/1.73 m^2

- Retinopathy

- Neuropathy

- ABI <0.9

ABI, ankle–brachial index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; T2D, type 2 diabetes mellitus.

The ADA recommends evaluating cardiovascular risk factors in patients with T2D annually.

- ✓ obesity (BMI >30 adult, >95th% in children),
- ✓ Hypertension
- ✓ Hyperlipidemia,
- ✓ Smoking
- ✓ Chronic kidney disease
- ✓ Presence of albuminuria
- ✓ Family history of premature coronary disease

Rosiglitazone and CV Risk

- ✓ Approved in 2000 for DM2

- ✓ CV risk timeline (before 2013)

- ▪ 2007 : Rosiglitazone reported to show a statistically significant increase in risk of MI vs placebo

- ▪ 2008: Varios meta-analysis show increased CV risk for rosiglitazone

- ▪ 2010:EMA and FDA evaluate Safety

Overview of CVOT's of Glucose-Lowering Drugs
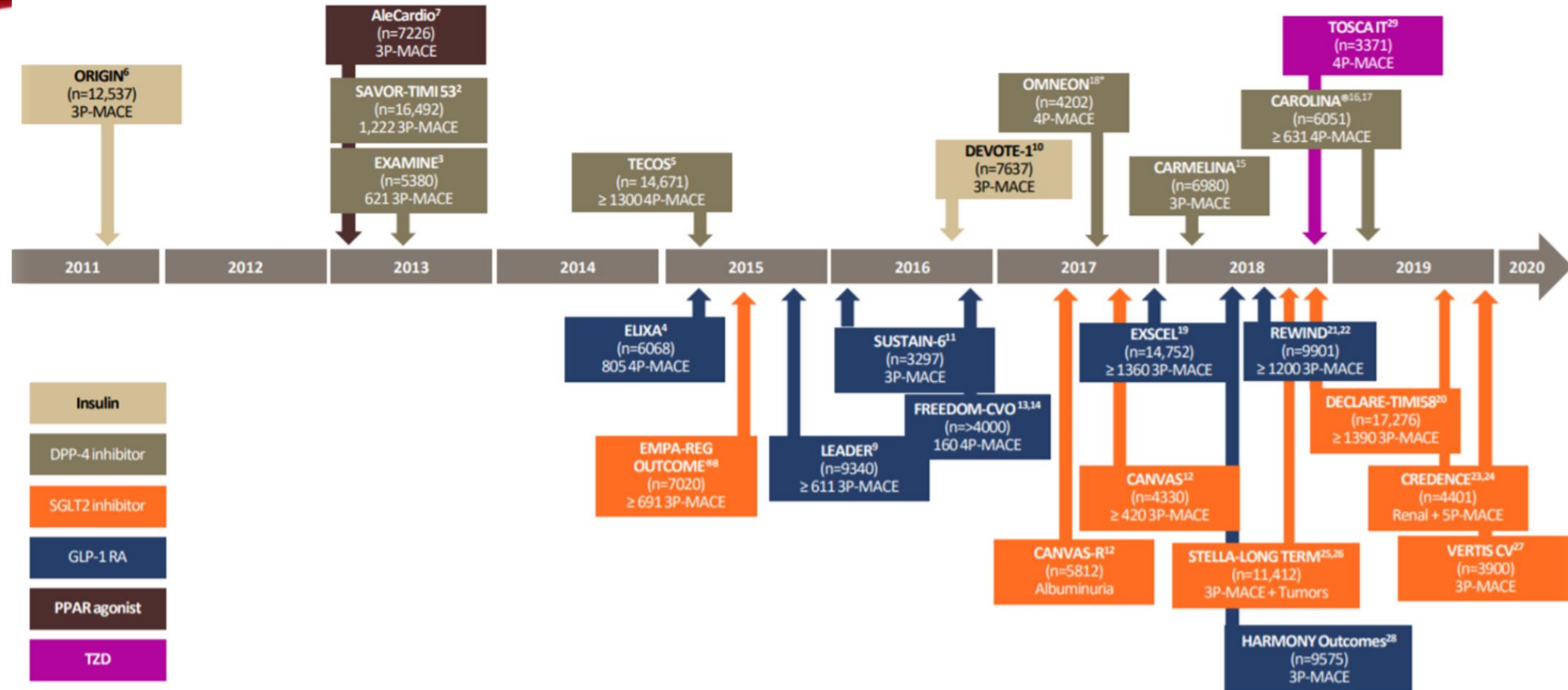
Timings represent estimated completion dates as per ClinicalTrials.gov
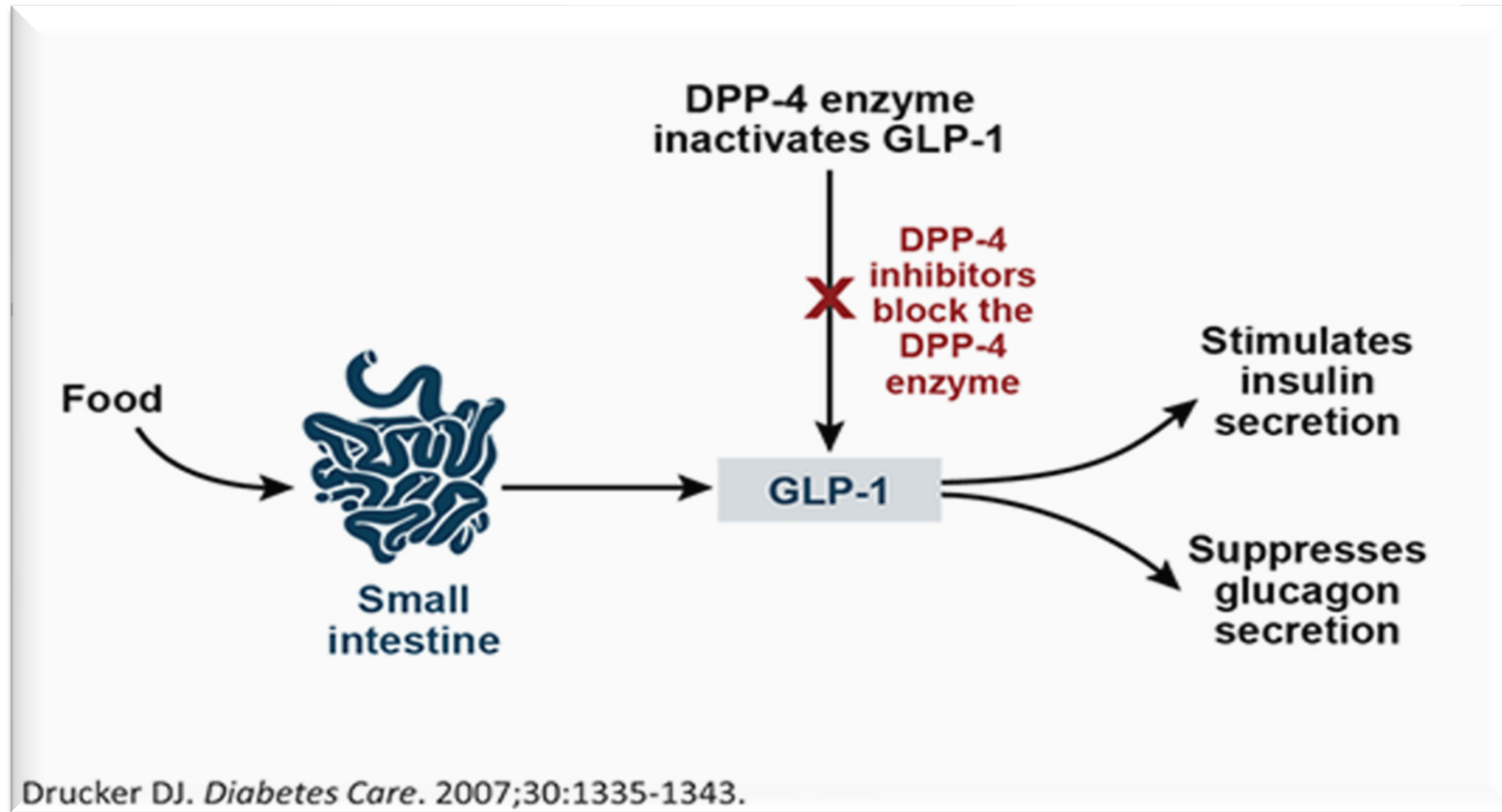
*The study was terminated for business reasons and not due to any safety or efficacy concerns related to omarigliptin

1. Data from Johansen OE. World J Diabetes 2015;6(9):1092-6. and study references

Glucose Lowering-Drugs Used In CVOT's

Drucker DJ. *Diabetes Care.* 2007;30:1335-1343.
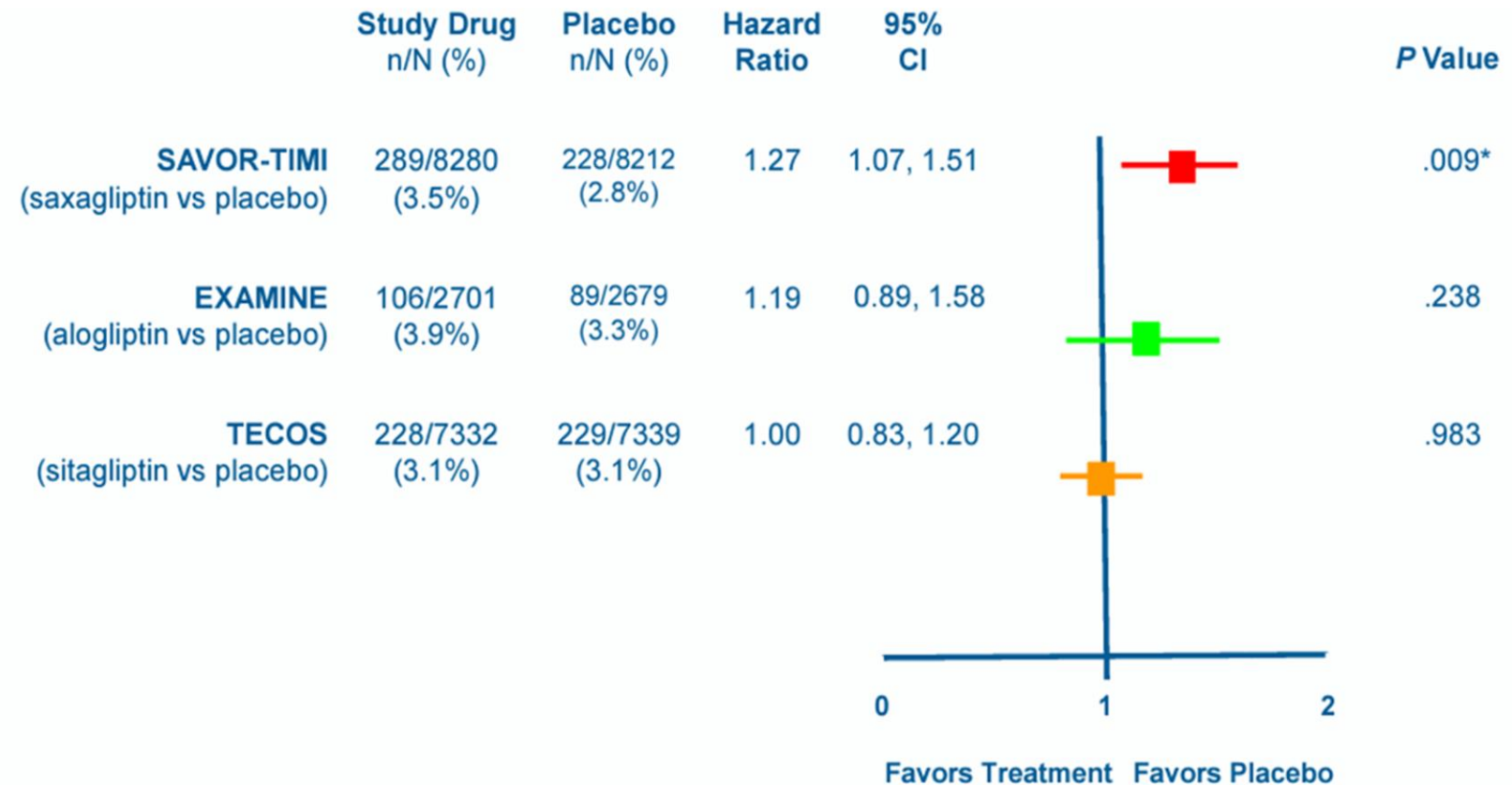
Cardiovascular Outcome Trials for DPP4 Inhibitors
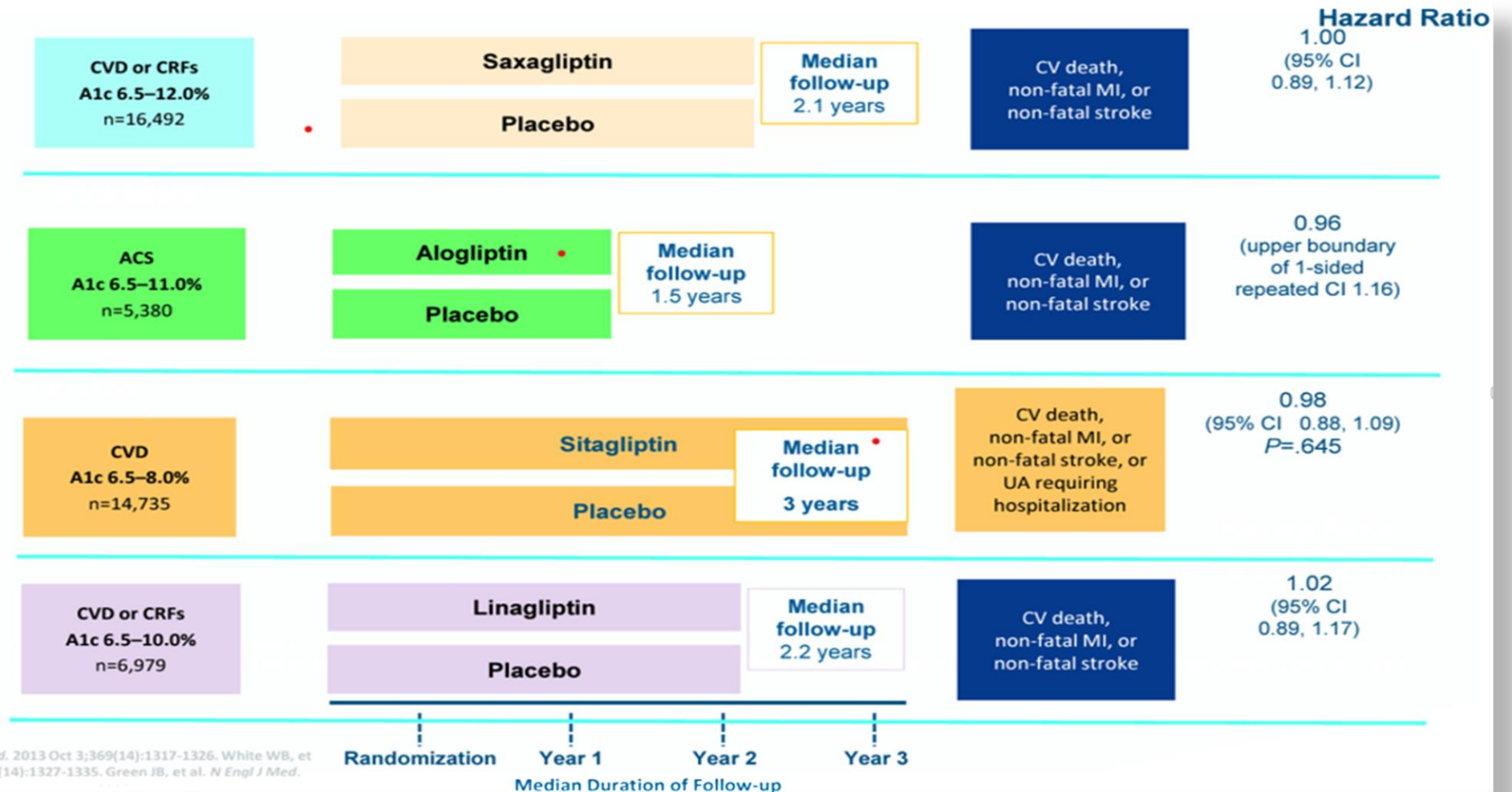
Scirica, BM, et al. *New Eng J Med.* 2013 Oct 3;369(14):1317-1326. White WB, et al. *N Engl J Med.* 2013 Oct 3;369(14):1327-1335. Green JB, et al. *N Engl J Med.*

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

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI		P Value
SAVOR-TIMI (saxagliptin vs placebo)	289/8280 (3.5%)	228/8212 (2.8%)	1.27	1.07, 1.51		.009*
EXAMINE (alogliptin vs placebo)	106/2701 (3.9%)	89/2679 (3.3%)	1.19	0.89, 1.58		.238
TECOS (sitagliptin vs placebo)	228/7332 (3.1%)	229/7339 (3.1%)	1.00	0.83, 1.20		.983

Favors Treatment   Favors Placebo

*Statistically significant increase in hospitalizations for heart failure associated with saxagliptin use in SAVOR-TIMI.
Scirica, BM, et al. *New Engl J Med*. 2013 Oct 3;369(14):1317-1326. White WB, et al. *N Engl J Med*. 2013 Oct 3;369(14):1327-1335.
Green JB, et al. *N Engl J Med*. 2015 Jul 16;373(3):232-242.

Current Recommendations of DPP4-inhibitors as per Renal Status

DPP-4 inhibitor	Excretion	Renal recommendation dosing (eGFR in ml/min/1.73m^2)	Renal impairment (RI)
Alogliptin	Renal	eGFR >50: 25mg OD eGFR 30–50: 12.5mg OD eGFR <30: 6.25mg OD	Pooled analysis showing no difference
Linagliptin	Biliary	5mg OD for all stages of renal impairment	-0.71% in severe RI (eGFR <30)
Saxagliptin	Renal	5mg OD Moderate–severe (eGFR <50): 2.5mg OD	-0.73%
Sitagliptin	Renal	eGFR >50: 100mg OD eGFR 30–50: 50mg OD eGFR <30: 25mg OD	-0.70%
Vildagliptin	Renal	eGFR >50: 50mg BD eGFR <50: 50mg OD	-0.40% in moderate RI (eGFR 30–50) and -0.70% in severe RI (eGFR <30)
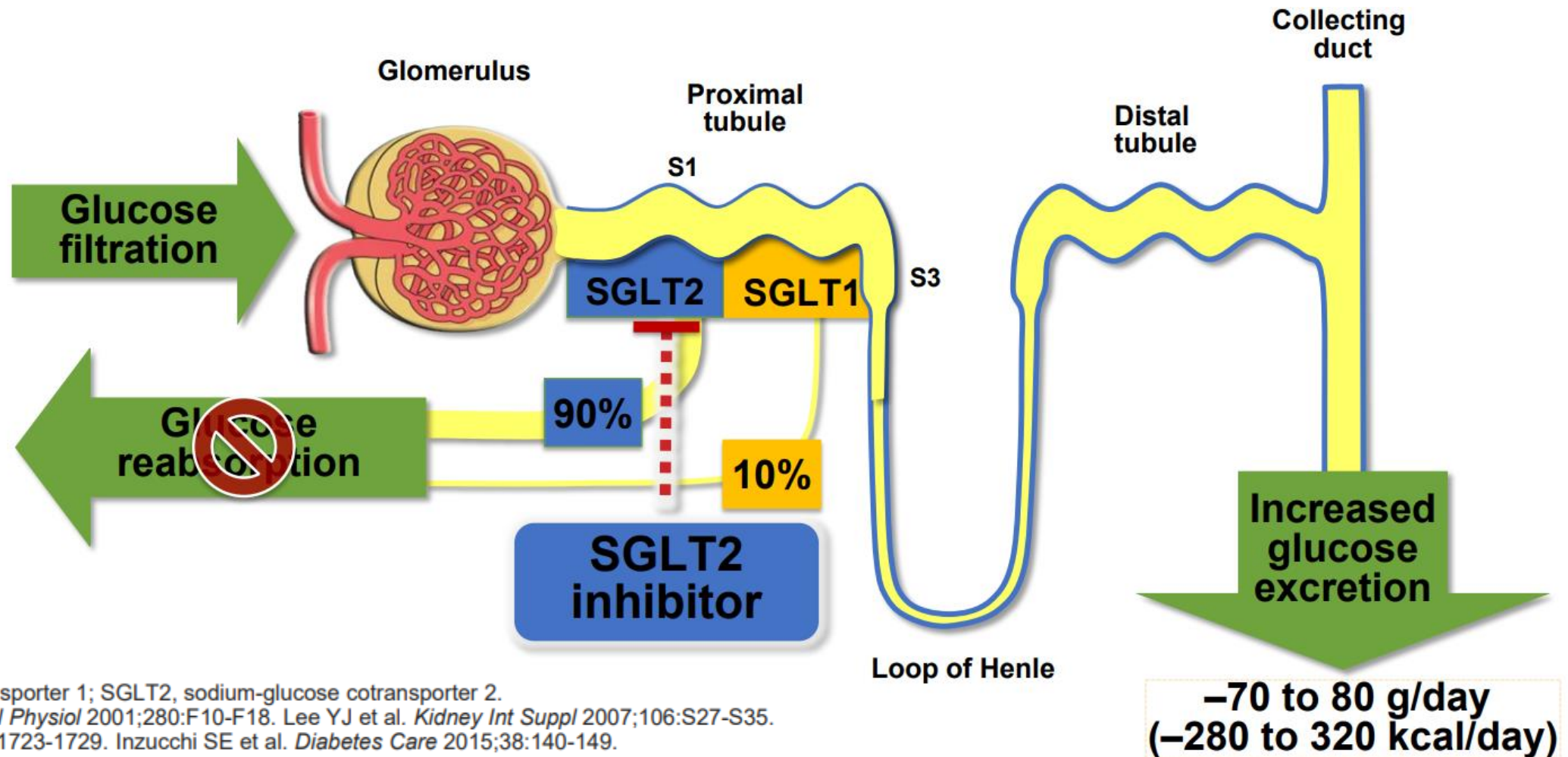
SGLT1, sodium-glucose cotransporter 1; SGLT2, sodium-glucose cotransporter 2.
Wright EM. *Am J Physiol Renal Physiol* 2001;280:F10-F18. Lee YJ et al. *Kidney Int Suppl* 2007;106:S27-S35.
Han S et al. *Diabetes* 2008;57:1723-1729. Inzucchi SE et al. *Diabetes Care* 2015;38:140-149.

The Pleiotropic Effects of Sodium–Glucose Cotransporter-2 Inhibitors: Beyond the Glycemic Benefit

Dhiren K. Patel · Jodi Strong
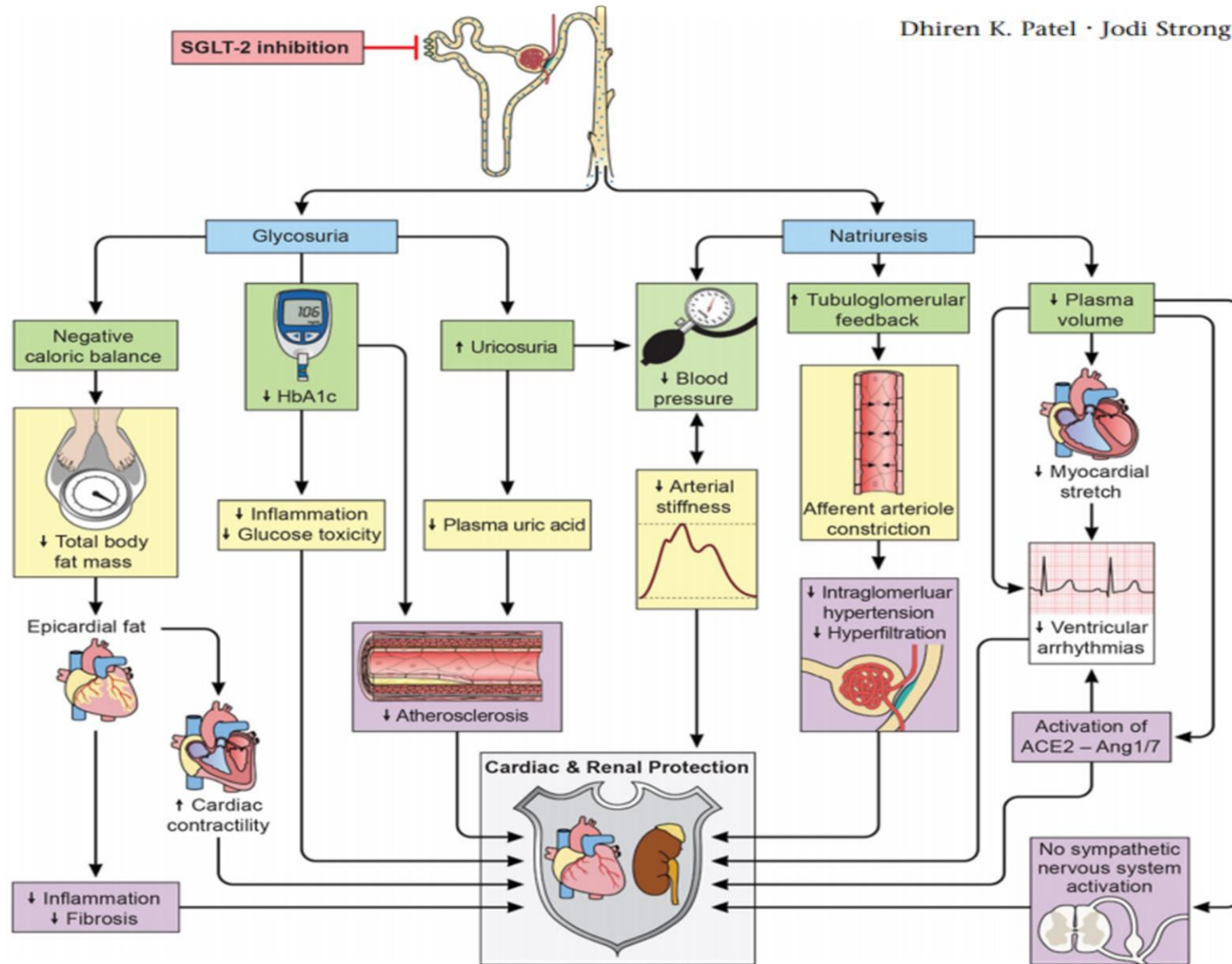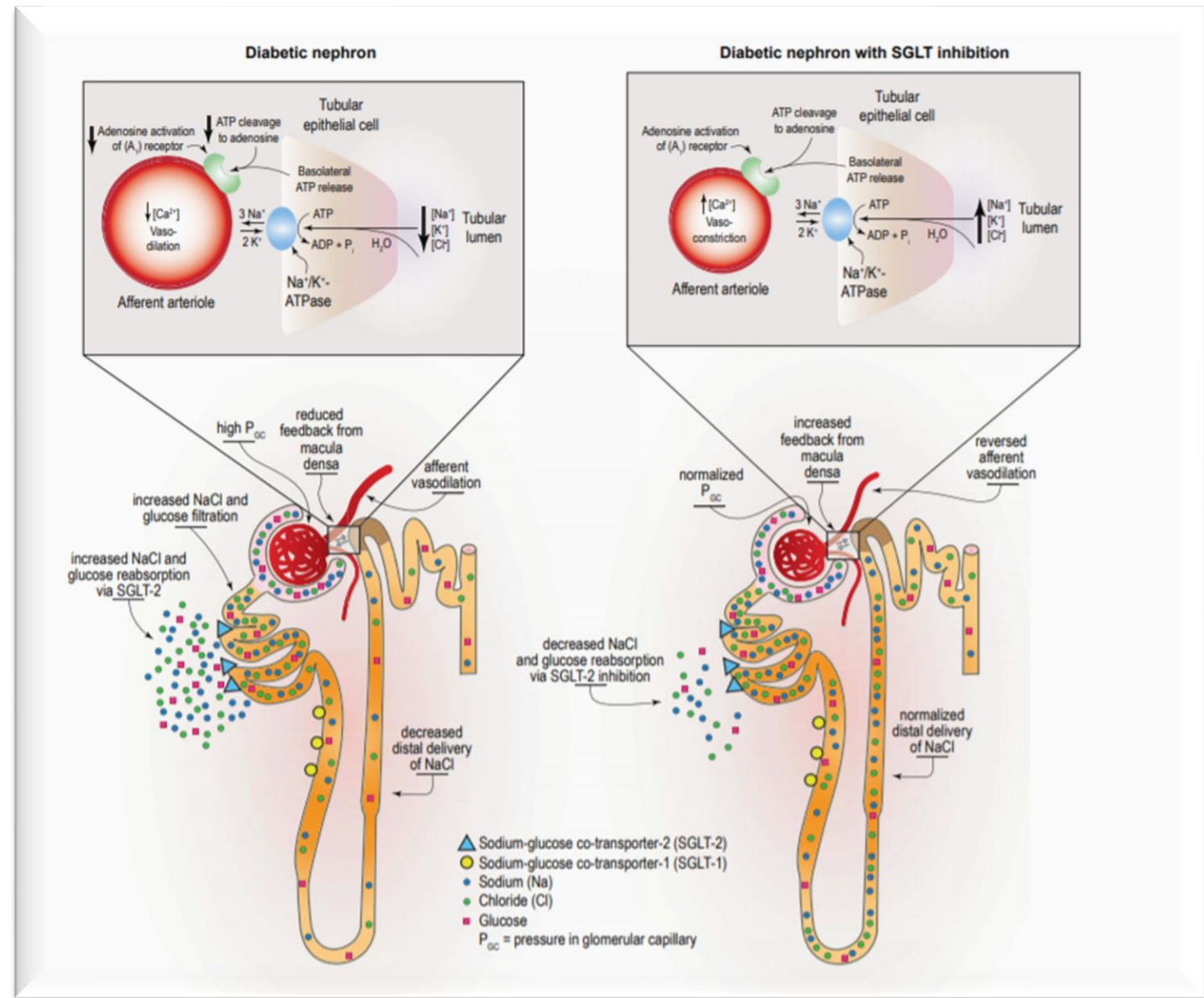
SGLT2 Inhibitors Lower Renal Threshold for Glucose Excretion
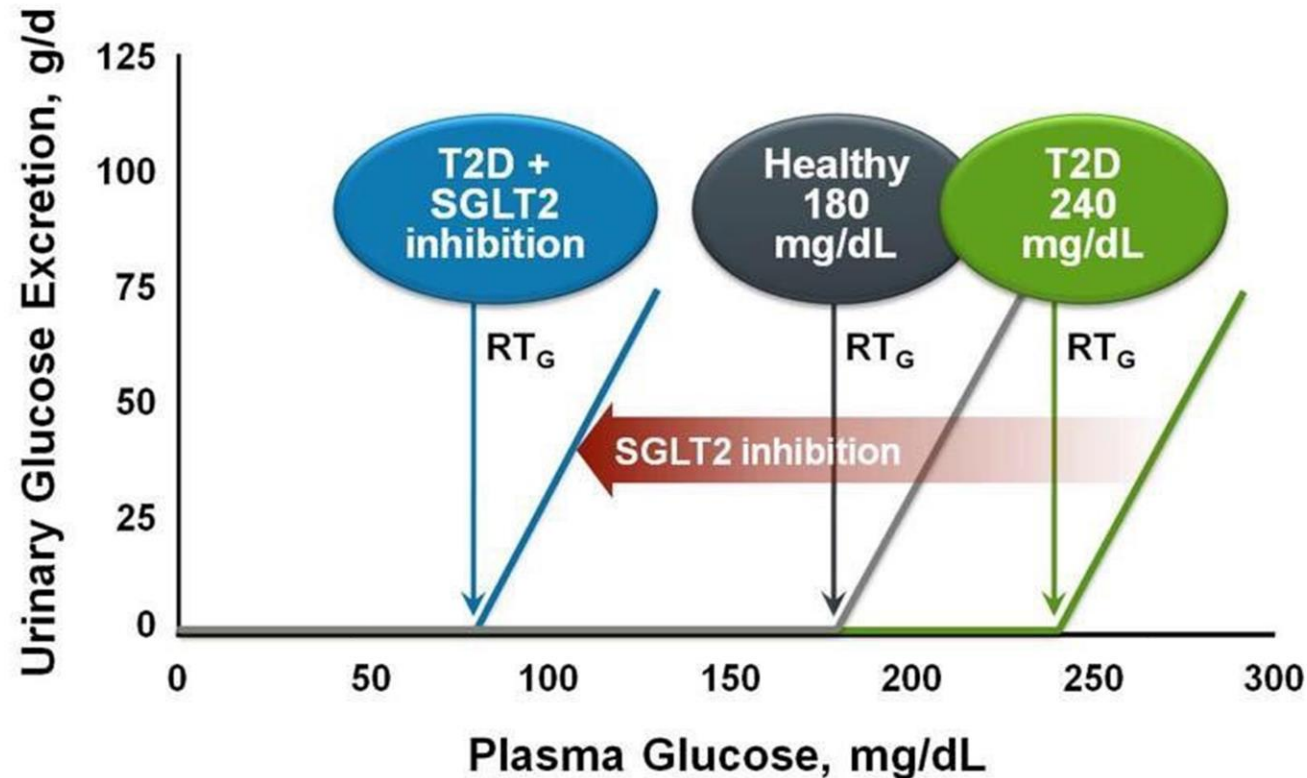
Abdul-Ghani MA, et al. *Endocr Pract*. 2008;14:782-790[8]; Nair S, Wilding JF. *J Clin Endocrinol Metab*. 2010;95:34-42.[5]

Current Recommendations for use of SGLT-2 inhibitors as per Renal Status

Agent	FDA Indications	Dosing	Other considerations
Canagliflozin	T2DM T2DM + CV disease	100 – 300mg daily	Renally dosed (Cl'ed GFR < 30) Not recommended with hepatic impairment 300 mg dose GFR ≥60 100mg dose ≥30
Dapagliflozin	T2DM T2DM + CV disease T2DM + HF Heart failure	5 – 10mg daily	Cl'ed if GFR < 30 (T2DM) Insufficient data for renal impairment in the setting of HF May increase serum creatinine GFR≥30
Empagliflozin	T2DM T2DM + CV disease	10 – 25mg daily	Do not initiate with GFR < 45 Cl'ed in ESRD May increase LDL-C GFR≥45
Ertugliflozin	T2DM	5 – 15mg daily	Do not initiate/DC with GFR < 60 Cl'ed if GFR <30 May increase LDL-C GFR≥60

Timelines of SGLT2 inhibitor CV outcome trials designed to fulfill 2008 regulatory guidance

2010	2012	2014	2016	2018	2020	2022

EMPA-REG OUTCOME
Empagliflozin

CANVAS Program
Canagliflozin

DECLARE TIMI-58
Dapagliflozin

VERTIS CV
Ertugliflozin

Baseline characteristics of patient populations by trial

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]	CREDENCE[4]	VERTIS CV
SGLT2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
N	7020	10,142	17,160	4401	8246
Duration of follow-up, median, years	3.1	2.4	4.2	2.6	3.0
Age, mean ± SD, years	63.1 ± 8.6	63.3 ± 8.3	63.9 ± 6.8	63.0 ± 9.2	64.4 ± 8.1
Female, %	28.5	35.8	37.4	33.9	30.0
HbA1c, mean ± SD, %	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2	8.3 ± 1.3	8.2 ± 1.0
Diabetes duration, mean ± SD, years	NA	13.5 ± 7.8	11.8 ± 7.8	15.8 ± 8.6	13.0 ± 8.3
Established CV disease, %	100	65.6	40.6	50.4	100
History of HF, %	10.1	14.4	10.0	14.8	23.7
Reduced kidney function (eGFR <60 mL/min/1.73 m^2), %	25.9	20.1	7.4	59.8	21.9

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; NA, not available; SD, standard deviation.
1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657. 3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.
4. Perkovic V et al. *N Engl J Med* 2019; 380:2295-306.

Class effects of SGLT2 inhibitors on cardiorenal outcomes

Aaron Y. Kluger[1,2]* [iD], Kristen M. Tecson[1,2,3], Andy Y. Lee[4,5], Edgar V. Lerma[6], Janani Rangaswami[7,8], Norman E. Lepor[9,10], Michael E. Cobble[11] and Peter A. McCullough[1,3,4,5]
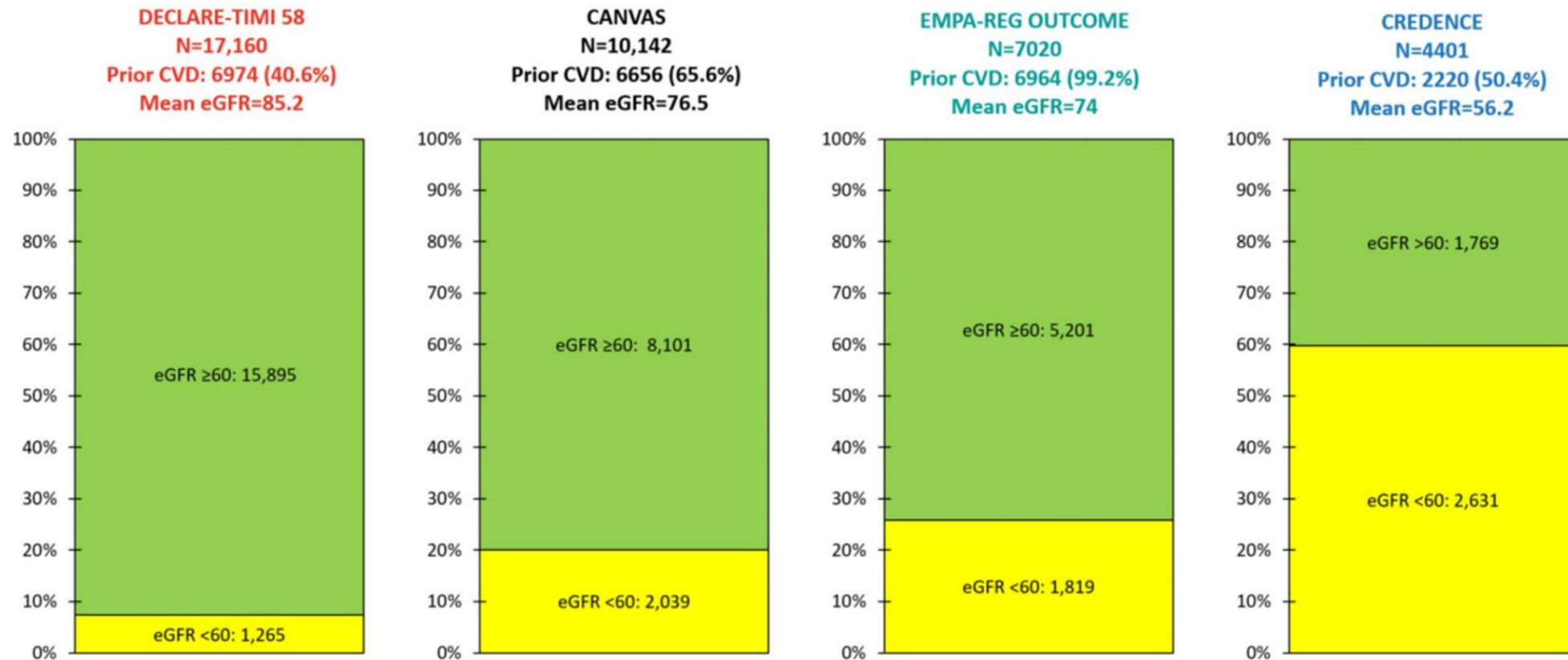
Fig. 1 Baseline estimated glomerular filtration rates (eGFRs) and prior cardiovascular disease (CVD) rates in the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58), CANagliflozin CardioVascular Assessment Study (CANVAS) Program, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA–REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trials. Prior CVD displayed as incidence (percentage)

CV death endpoint in SGLT2 inhibitor CV outcomes trials

EMPA-REG OUTCOME[1]

HR, 0.62
(95% CI, 0.49, 0.77)
P<0.001

Placebo
Empagliflozin

CANVAS Program[2]

HR, 0.87
(95% CI, 0.72, 1.06)

Placebo
Canagliflozin

DECLARE-TIMI 58[3]

Dapagliflozin N=8582		Placebo N=8578		HR (95% CI)
n (%)	Rate/1000 patient-years	n (%)	Rate/1000 patient-years	
245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82, 1.17)

Favors Dapagliflozin   Favors Placebo

VERTIS CV

HR, 0.92
(95.8% CI, 0.77–1.11)
P=0.39

Placebo
Ertugliflozin
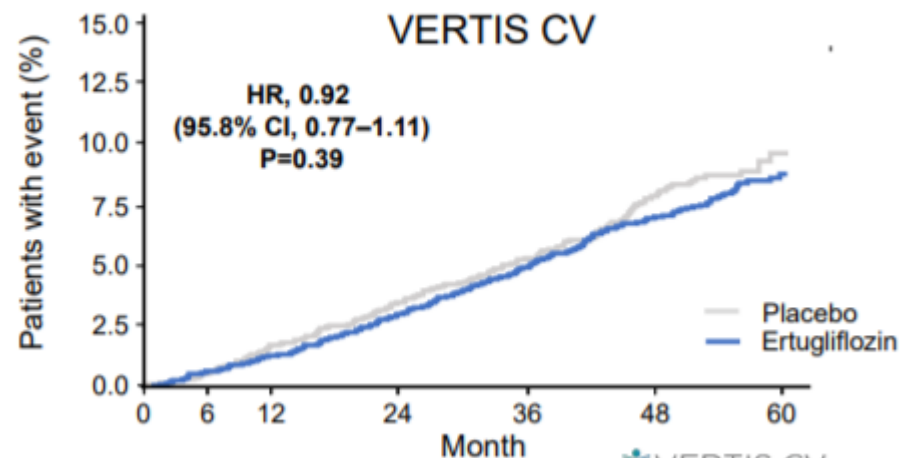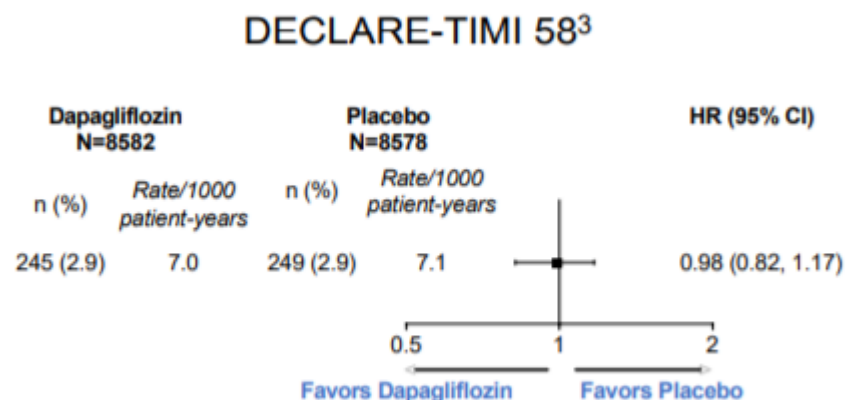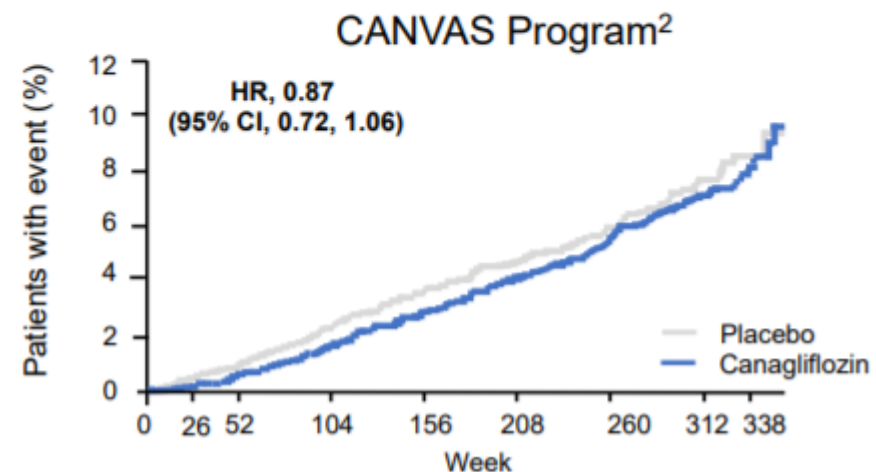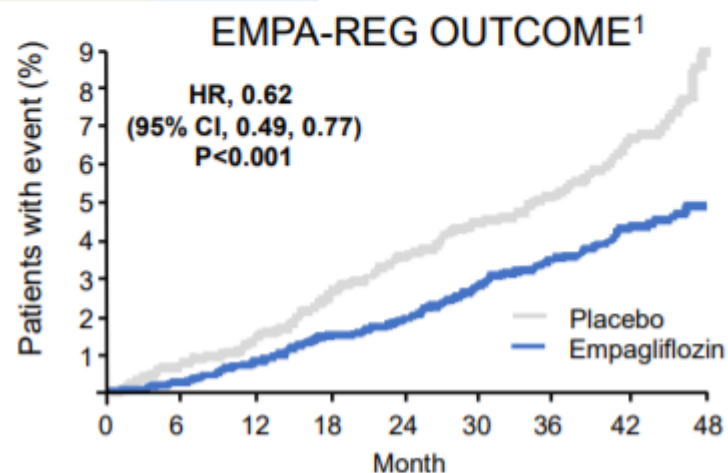
CI confidence interval; CV, cardiovascular; HR, hazard ratio
1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128; 2. Neal B et al. *N Engl J Med* 2017;377:644-657;
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

VERTIS CV

Time to first MACE – subgroup analysis by ASCVD

MACE		Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years		Hazard ratio (95% CI)
ASCVD	EMPA-REG OUTCOME	37.4	43.9		0.86 (0.74-0.99)
	CANVAS Program	34.1	41.3		0.82 (0.72-0.95)
	DECLARE-TIMI 58	36.8	41.0		0.90 (0.79-1.02)
	CREDENCE	55.6	65.0		0.85 (0.69-1.06)
	VERTIS CV	40.0	40.3		0.99 (0.88-1.12)
	Pooled estimate				**0.89 (0.84-0.95)**
	(Q statistic P = 0.34; I^2 = 11.8%)				
No ASCVD	CANVAS Program	15.8	15.5		0.98 (0.74-1.30)
	DECLARE-TIMI 58	13.4	13.3		1.01 (0.86-1.20)
	CREDENCE	22.0	32.7		0.68 (0.49-0.94)
	Pooled estimate				**0.94 (0.83-1.07)**
	(Q statistic P = 0.10; I^2 = 56.5%)				

0.25   0.5   1.0   2.0

Favors Treatment ← → Favors Placebo

P interaction = 0.63

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval;
MACE, major adverse cardiovascular events.

VERTIS CV   70

HHF outcomes in SGLT2 inhibitor CV outcomes trials
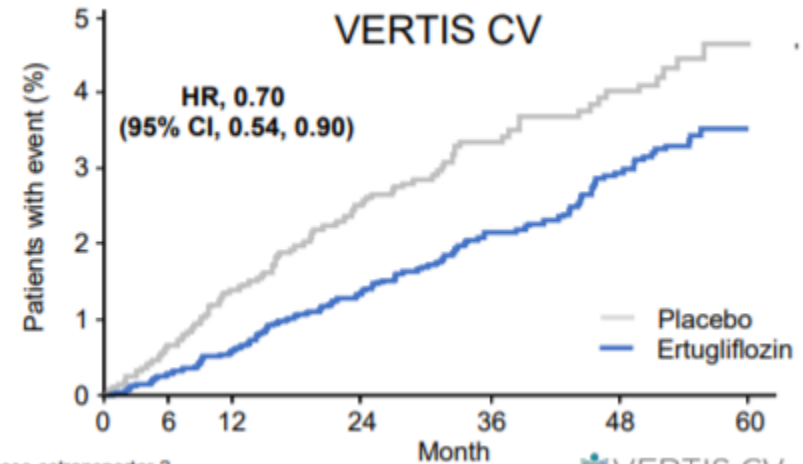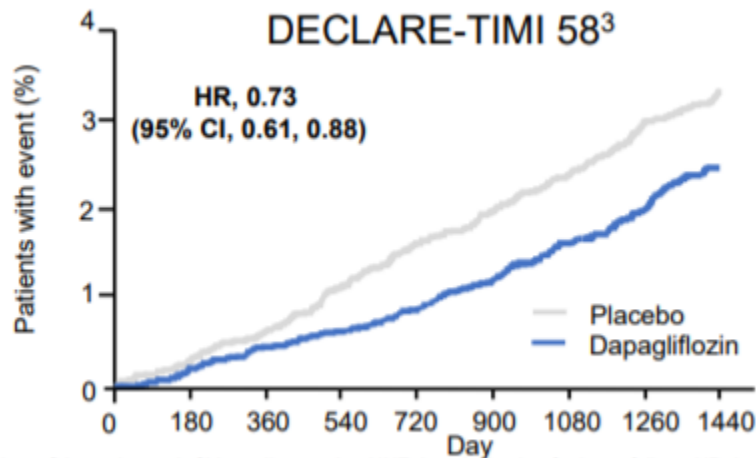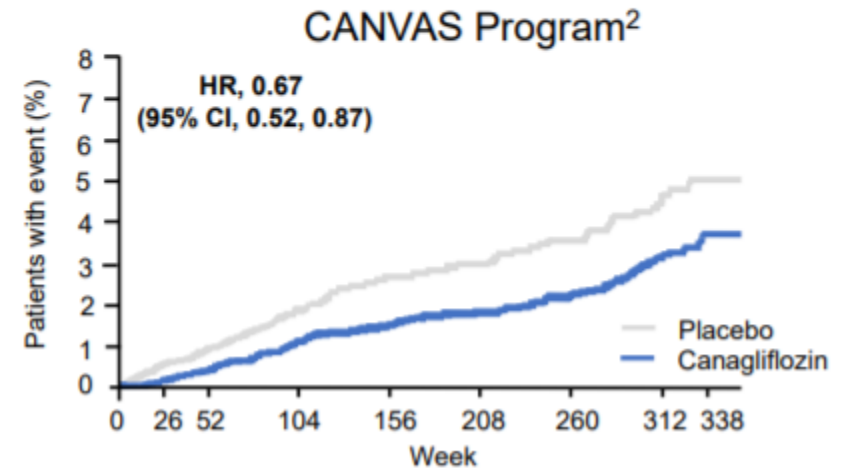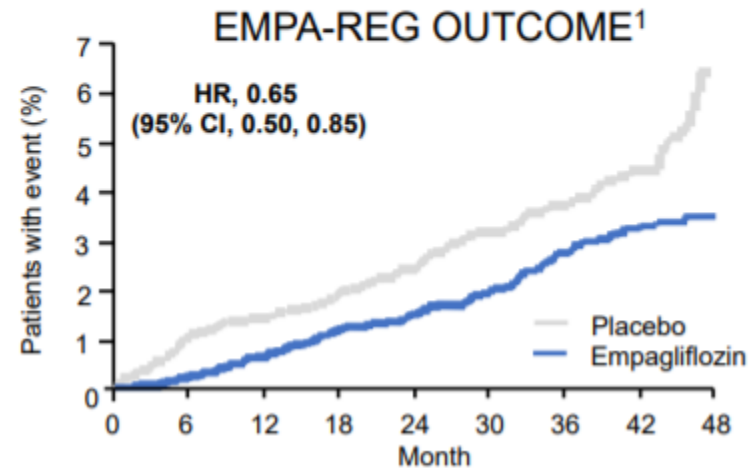
CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657.
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357 (figure provided by D.K. McGuire, with permission).

CV outcomes

	MACE HR (95% CI)	CV Death HR (95% CI)	HHF HR (95% CI)

EMPA-REG OUTCOME

CANVAS

DECLARE

VERTIS CV

MACE:
- MACE efficacy across class generally modest
  - EMPA-REG OUTCOME significant on MACE due to effect on CV death and no effect on MI or stroke
  - CANVAS significant on MACE due to contribution from MI, CV death, and stroke
  - DECLARE and VERTIS CV only found trend on MACE

CV Death:
- Only EMPA-REG OUTCOME found significant reduction, driving heterogeneity in the beneficial effect for the class

HHF:
- Consistent effects across class are substantial
- Benefits are independent of baseline ASCVD, prior HF, and across spectrum of baseline eGFR

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128; 2. Neal B et al. *N Engl J Med* 2017;377:644-657;
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

VERTIS CV   85

Renal outcomes

Renal-related Composite Outcomes

Study	Composite Outcome	HR (95% CI)
EMPA-REG OUTCOME[1]	Doubling of the serum creatinine level accompanied by an eGFR ≤ 45 mL/min/1.73m^2, initiation of renal-replacement therapy, or death from renal disease	**0.54 (0.40, 0.75)**
CANVAS Program[2]	Sustained 40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.60 (0.47, 0.77)**
DECLARE-TIMI 58[3]	Sustained ≥40% decrease in eGFR to <60 mL/min/1.73 m^2, end-stage renal disease, or death from renal causes	**0.53 (0.43, 0.66)**
VERTIS CV	Renal death, dialysis/transplant, or doubling of serum creatinine from baseline	**0.81 (0.63, 1.04)**

FDA granted SGLT2i's additional CV Indications

In adults with T2DM + established CVD...

- ✓ Empagliflozin ↓ risk of CV death
- ✓ Canagliflozin ↓ risk of MACE
- ✓ Canagliflozin ↓ risk of ESKD
- ✓ Dapagliflozin ↓ risk of HHF

GIT
↓Gastric emptying
↑Acid secretion
↓GI motility

Brain
↓Apetite
↑Satiety
↑Energy expenditure

Heart
↓Blood pressure
↑Heart rate
↑Myocardial contractility
↑Cardioprotection

GLP-1
or
GLP-1R AGONISTS

Pancreas
↑Insulin secretion
↓Glucagon secretion
↑Insulin biosynthesis
↑ß-cell survival
↑ß-cell proliferation

↑Insulin sensitivity

Kidney
↑Natriuresis

Liver
↓Hepatic glucose production

Adipose tissue
↑Lyposis
↑FFA synthesis
↑Glucose uptake

Muscle
↑Glycogen synthesis
↑Glucose oxidation

Pleitropic effects of GLP-1 or GLP-1R agonists (Adapted from references [24]).

Cardiovascular Diabetology volume 13, Article number: 142 (2014

Liraglutide Supresses Cytokine Reduction in Isolated Human PBMCs in 8 weeks
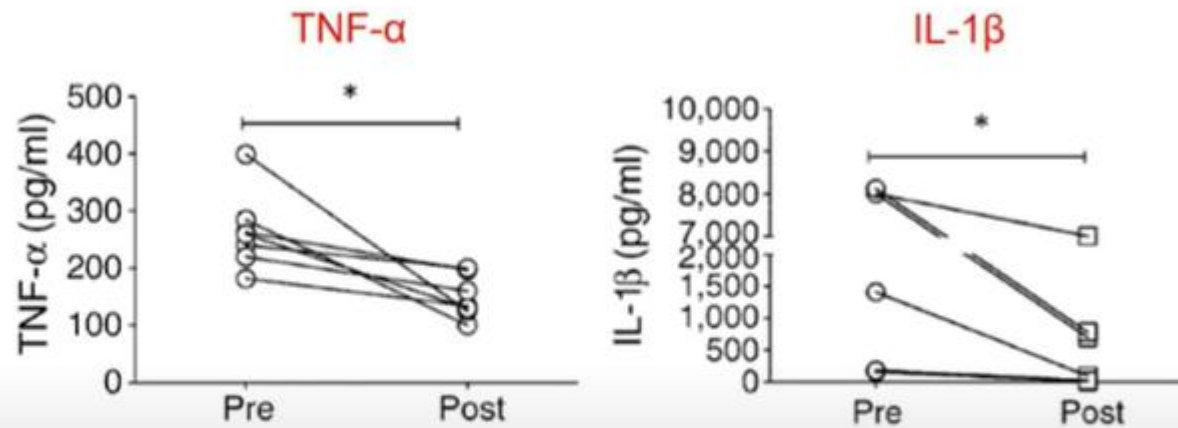
Hogan et al. Diabetologia 2014

Semaglutide Reduces Systemic Inflammation as measured by CRP

PIONEER 1[1]
Mean baseline C-reactive protein 2.80 mg/L

PIONEER 2[2]
Mean baseline C-reactive protein 2.68 mg/L

C-reactive protein – ratio to baseline

Time since randomisation (weeks)

Oral semaglutide 3 mg | Oral semaglutide 7 mg | Oral semaglutide 14 mg | Placebo | Empagliflozin 25 mg

CRP, C-reactive protein.
1. Aroda V, et al. *Diabetes Care* 2019;42:1724-32; 2. Rodbard HW, et al. *Diabetes Care* 2019;42(12):2272-2281.

Dosing Characteristics Of GLP-1RA

Table 1 GLP-1 receptor agonists with completed cardiovascular outcomes trials to date

GLP-1 RA	Administration	Half-life	Starting dose	Maximum dose	Renal function*
Lixisenatide (Adlyxin)	Daily	3 hours	10 mcg	20 mcg	Not recommended eGFR <15
Liraglutide (Victoza)	Daily	13 hours	0.6 mg	1.8 mg	No dosage adjustment
Semaglutide (Ozempic)	Weekly	1 week	0.25 mg	1.0 mg	No dosage adjustment
Exenatide QW (Bydureon)	Weekly	2 weeks	2.0 mg	2.0 mg	Not recommended eGFR <45
Albiglutide† (Eperzan)	Weekly	5 days	30 mg	50 mg	Not recommended eGFR <15
Dulaglutide (Trulicity)	Weekly	5 days	0.75 mg	1.5 mg	No dosage adjustment
Oral semaglutide (Rybelsus)	Daily	1 week	3 mg	14 mg	No dosage adjustment

*Drug manufacturer dosage adjustments for renal impairment.
†Not currently being marketed.
eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; QW, every week; GLP-1 RA, glucagon-like peptide 1 receptor agonist.

Sheahan KH, et al. Postgrad Med J 2020;96:156–161.

Table 2 Summary of baseline characteristics and primary composite cardiovascular outcomes of the completed CVOTs for GLP-1 RA

GLP-1 RA: Study name	No. of patients	Median follow-up (years)	% with CV disease*	% of statin use	Baseline age	Baseline HgA1c	Baseline BMI	Primary composite CV outcome HR (95% CI)	P value
Lixisenatide: ELIXA	6068	2.1	100%	93%	60.3	7.7%	30.1	1.02 (0.89 to 1.17)	0.81
Liraglutide: LEADER	9340	3.8	81%	72%	64.3	8.7%	32.5	0.87 (0.78 to 0.97)	0.01
Semaglutide: SUSTAIN-6	3297	2.1	60%	73%	64.6	8.7%	32.8	0.74 (0.58 to 0.95)	0.02
Exenatide QW: EXSCEL	14752	3.2	73.1%	74%	62.0	8.0%	31.8	0.91 (0.83 to 1.00)	0.06
Albiglutide: Harmony	9463	1.6	100%	84%	64.1	8.7%	32.3	0.78 (0.68 to 0.90)	0.0006
Dulaglutide: REWIND	9901	5.4	31.5%	66%	66.2	7.2%	32.3	0.88 (0.79 to 0.99)	0.026
Oral semaglutide: PIONEER 6	3183	1.3	84.7%	85%	66.0	8.2%	32.3	0.79 (0.57 to 1.11)	0.17

*Remaining participants with cardiovascular risk factors.
BMI, body mass index; CV, cardiovascular; HgA1c, glycated haemoglobin.

Sheahan KH, et al. Postgrad Med J 2020;96:

Cardiovascular Benefits of GLP-1RA
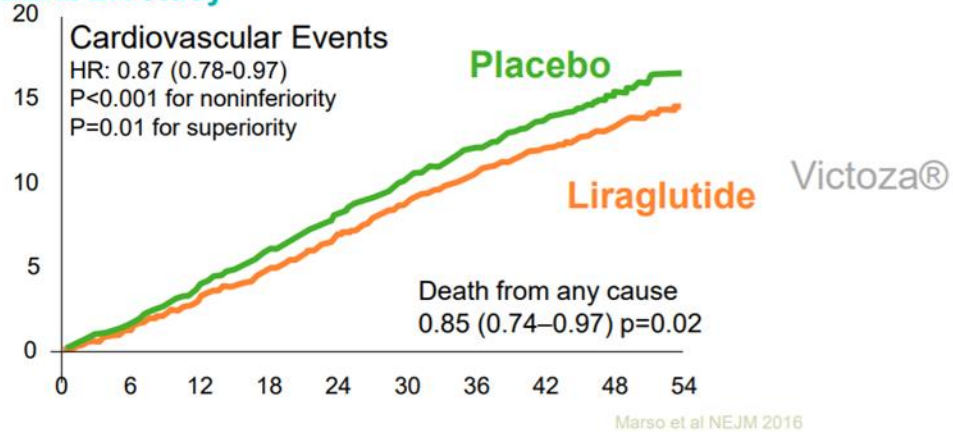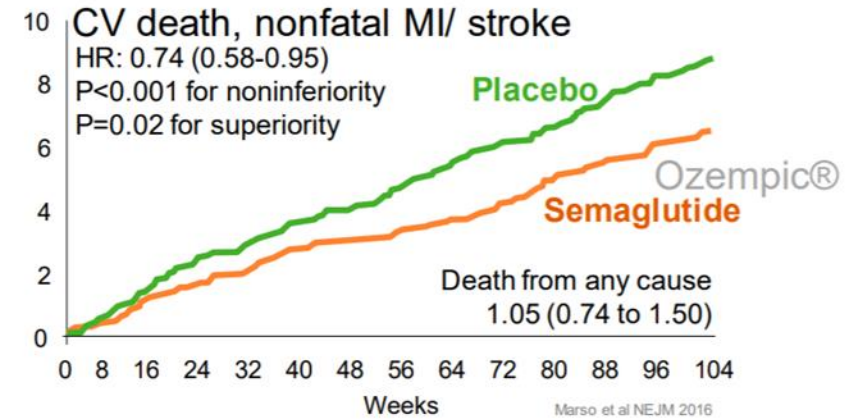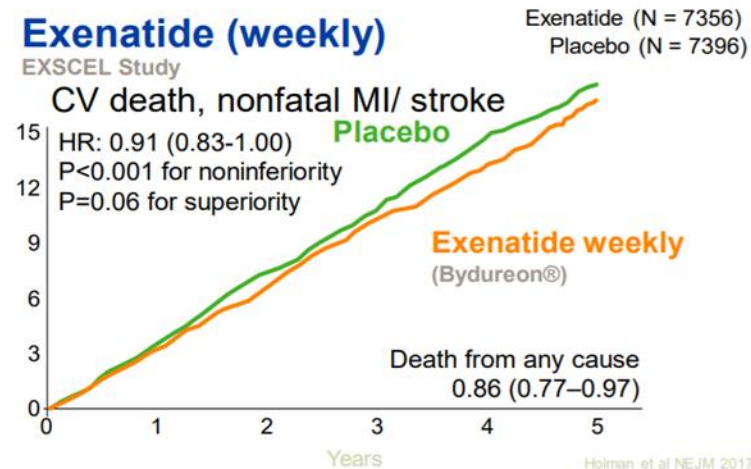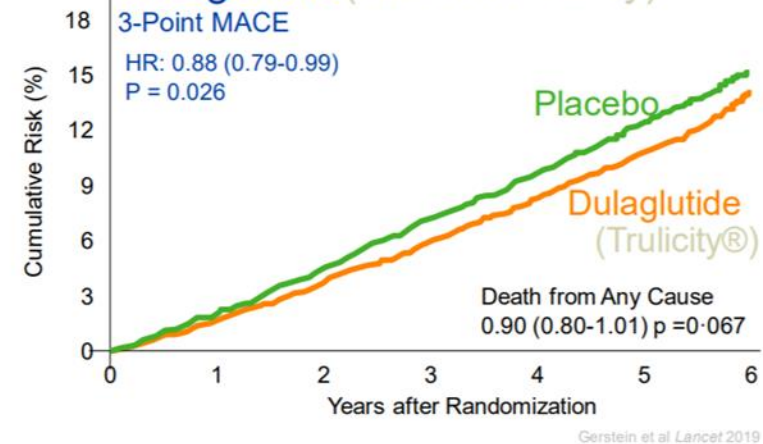
GLP-1 RAs reduce new macroalbuminuria in CVOT

Study	Favours GLP-1RA	HR with 95% CI	Weight (%)
ELIXA		0.81 [0.66, 0.99]	16.91
LEADER		0.74 [0.60, 0.91]	16.03
SUSTAIN-7		0.54 [0.37, 0.78]	5.18
EXSCEL		0.79 [0.64, 0.97]	16.08
REWIND		0.77 [0.68, 0.87]	45.80
Overall		0.76 [0.68, 0.86]	

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$

Test of $\theta_i = \theta_j$: $Q(4) = 3.96$, $p = 0.41$

0.50 0.75 1.00 1.25 1.50
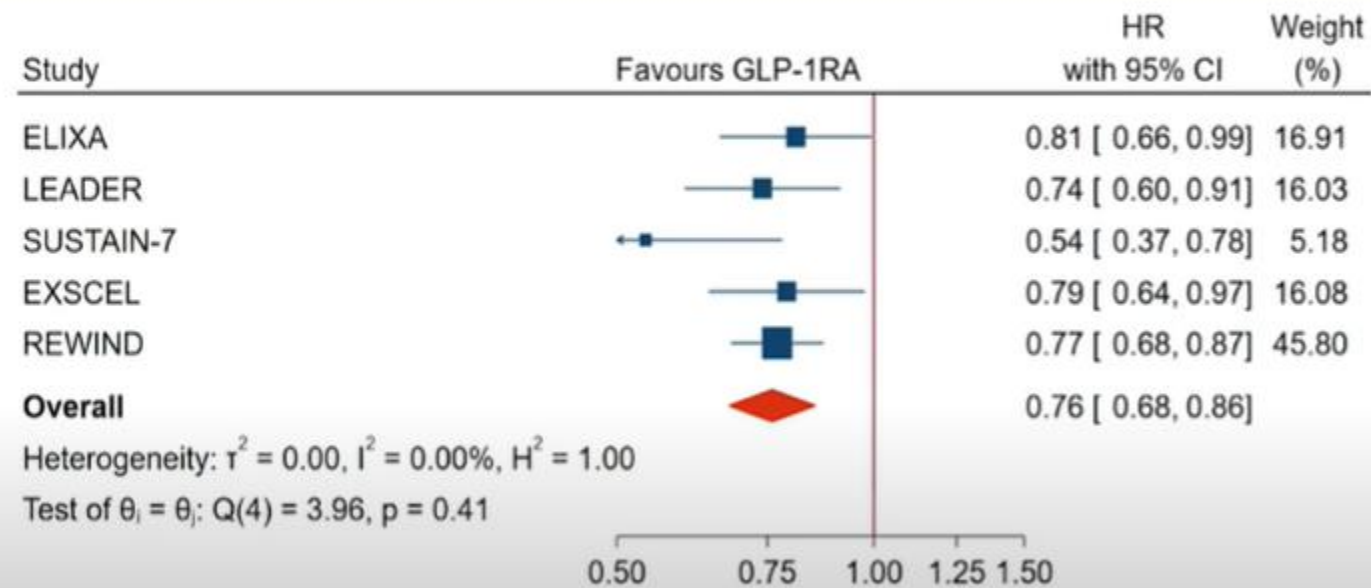
Random-effects empirical Bayes model
Knapp-Hartung standard errors

Giugliano et al. DOM (2019)

FDA has granted Liraglutide, Semaglutide, and Dulaglutide Additional CV Indications

In adults with T2DM + established CVD…

In adults with T2DM + established CVD or high CV risk

Liraglutide → ↓ MACE

Dulaglutide → ↓ MACE

Semaglutide → ↓ MACE

Consensus of Diabetes Organizations: Diabetes Management

Management of type 2 diabetes: consensus of diabetes organizations

Elaena Quattrocchi BS, PharmD, FASHP, CDE, Tamara Goldberg BS, PharmD, BCPS, Nino Marzella BS, MS, PharmD

Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Pharmacy

Table 2. Treatment goals for adult patients with type 2 diabetes.[7,10,19,20,86]

	ADA/EASD	AACE/ACE	IDF	ACP	Endocrine Society
HbA1c Individual Goal					
%	<6.5	<6.5	<7.0	7–8	<7.0
mmol/L	48	48	53	53	53
HbA1c General Goal					
%	<7.0	<6.5	<7.0	7.0–8.0	<7.0
mmol/L	53				
HbA1c >65 Years Old Goal					
%	<7.5–<8.5				>7.0–8.5
mmol/L	58–69				53–69
Fasting Plasma Glucose Goal					
mg/dl	80–130	<110	<110		
mmol/L	4.5–7.2	<6	<6		
Postprandial Plasma Glucose Goal					
mg/dl	<180	<140	<180		
mmol/L	<10	<7.8	<10		

AACE, American Association of Clinical Endocrinology; ACE, American College of Endocrinology; ACP, American College of Physicians; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; HbA1c, glycated hemoglobin; IDF, International Diabetes Federation.

AACE Considerations for Individualized Glycemic Target Selection

Glycemic Targets

A1C ≤6.5% For patients without concurrent serious illness and at low hypoglycemia risk

For patients with concurrent serious illness and at risk for hypoglycemia **A1C >6.5%**
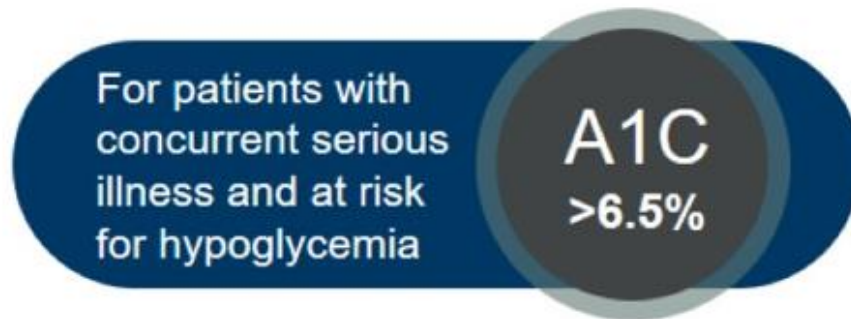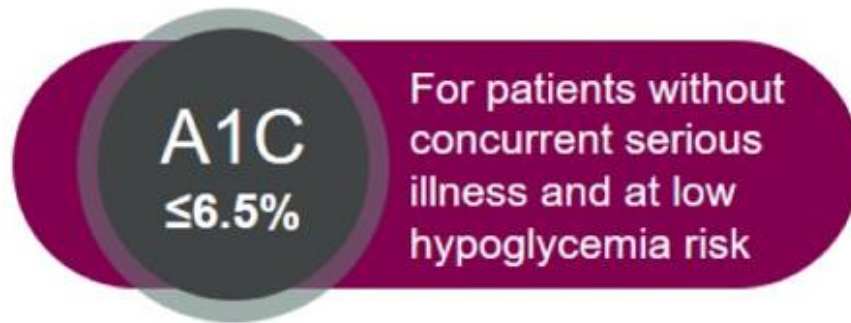
Adjustments Based On:

- Age
- Duration of diabetes
- Comorbid conditions
- Hypoglycemia risk
- Patient motivation
- Adherence
- Life expectancy

GLYCEMIC CONTROL ALGORITHM

ADA 2020 Standards of Care
Antihyperglycemic Medication in T2D: Overall Approach

First-Line Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

Indicators of High-Risk or Established ASCVD, CKD or HF

NO

Consider Independently of Baseline A1C or Individualized A1C Target

ASCVD PREDOMINATES
- Established ASCVD
- Indicators of high ASCVD risk (age≥55 years with coronary, carotid or lower extremity artery stenosis> 50% or LVH)

PREFERABLY
GLP-1 RA with proven CVD benefit*

OR

SGLT-2i with proven CVD benefit* if eGFR adequate

If A1C above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT-2i, choose agents demonstrating CV safety:
- For patients on a GLP-1 RA, consider adding SGLT-2i with proven CVD benefit*
- DPP-IVi if not on GLP-1 RA
- Basal insulin
- TZD
- SU

HF or CKD PREDOMINATES
- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30-60mL/min/1.73m² or UACR > 30mg/g, particularly UACR > 300mg/g

PREFERABLY
SGLT-2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate†

OR

If SGLT-2i not tolerated or contraindicated or if eGFR less than adequate, add GLP-1 RA with proven CVD benefit*

If A1C above target

Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
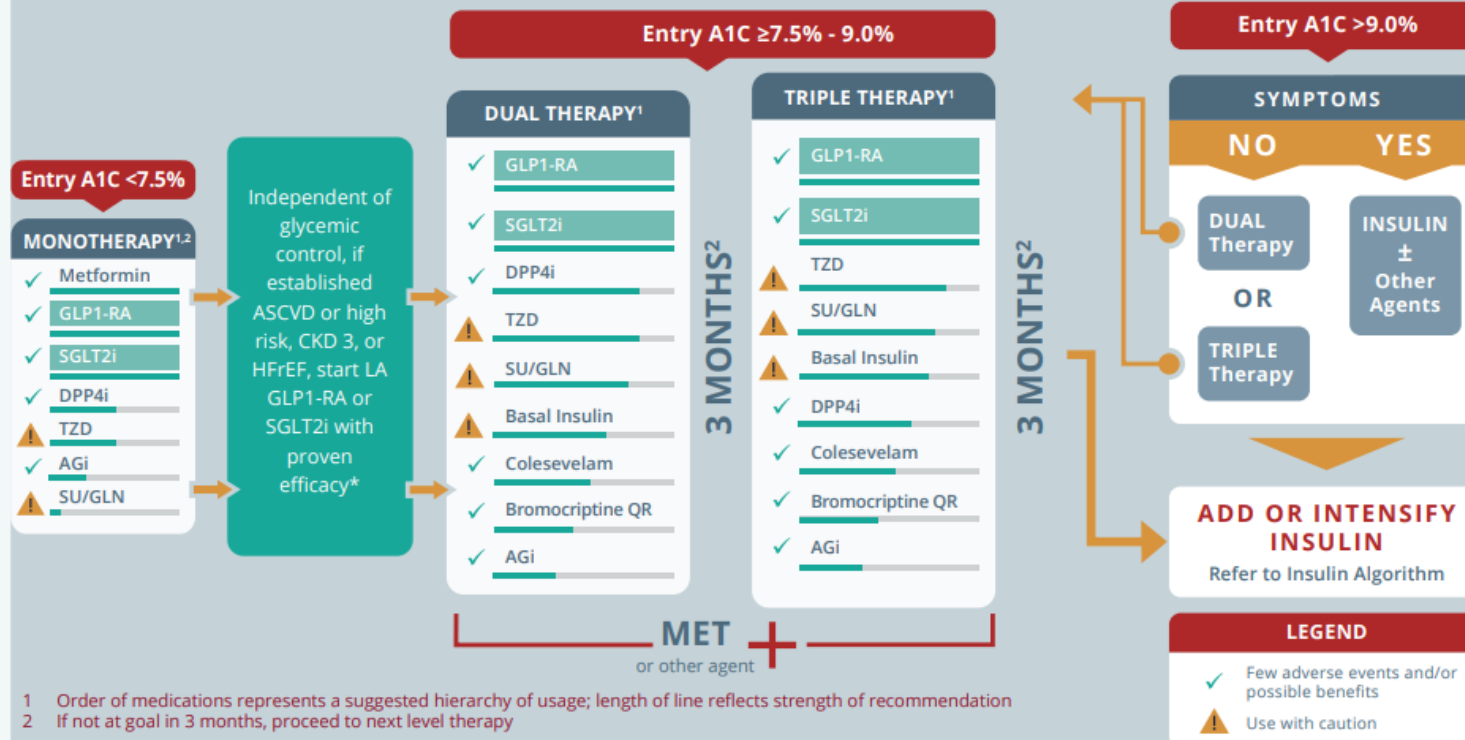- For patients on SGLT-2i, consider adding GLP-1 RA with proven CVD benefit.*
- DPP-IVi (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin
- SU

If A1C Above Individualized Target, Proceed as Below

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT-2i†	TZD
If A1C above target	If A1C above target	If A1C above target	If A1C above target
SGLT-2i OR TZD	SGLT-2i OR TZD	GLP-1 RA OR DPP-IVi OR TZD	SGLT-2i OR DPP-IVi OR GLP-1 RA

If A1C above target

Continue with addition of other agents listed above

If A1C above target

Consider addition of SU or basal insulin:
- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss‡   EITHER/ OR   SGLT-2i

If A1C above target	If A1C above target
SGLT-2i	GLP-1 RA with good efficacy for weight loss‡
If A1C above target	If A1C above target

If quadruple therapy required or SGLT-2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain. Preferably:
- DPP-IVi (if not on GLP-1RA) based on weight neutrality

If DPP-IVi not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:
- SU   -TZD   - Basal Insulin

COST IS A MAJOR ISSUE

SU	TZD
If A1C above target	If A1C above target
TZD	SU
If A1C above target	If A1C above target

Insulin therapy basal insulin with lowest acquisition cost
OR
Consider DPP-IVi OR SGLT-2i with lowest acquisition cost

American Diabetes Association. Standards of Medical Care in Diabetes—2020. *Diabetes Care*. 202;43(Suppl 1):S98-S110.

Treatment of Patients in Whom ASCVD Predominates

After metformin[a] and comprehensive lifestyle management (including weight management and physical activity), consider indicators of high ASCVD risk or established ASCVD, and use of SGLT2 inhibitors or GLP-1 receptor agonists with proven CVD benefit[b] regardless of baseline A1C or individualized A1C target.

ASCVD Predominates

- Established ASCVD
- Indicators of high ASCVD risk (age≥55 years with coronary, carotid or lower extremity artery stenosis> 50% or LVH)

Preferably, GLP-1 receptor agonist with proven CVD benefit[b]

----------------------------------OR----------------------------------

SGLT2 inhibitor with proven CVD benefit[b,c]

↓ A1C above goal

If further glycemic lowering is needed or patient is unable to tolerate GLP-1 receptor agonist or SGLT2 inhibitor, select medications demonstrating CV safety:

| For patients on a GLP-1 receptor agonist, consider adding SGLT2 inhibitor with proven CVD benefit[a] | DPP-4 inhibitor[e] | Basal insulin[f] | TZD[g] | SU[h] |

Patients Without Indicators of High Risk or Established ASCVD, HF or CKD: Need to Promote Weight Loss or Minimize Weight Gain

Metformin is first-line therapy

A1C above goal

Either/Or

SGLT2 inhibitor[a]

GLP-1 receptor agonist with good weight loss efficacy[b]

A1C above goal

GLP-1 receptor agonist with good weight loss efficacy[b]

SGLT2 inhibitor[a]

A1C above goal

Consider agents with lowest risk of weight gain, preferably DPP-4 inhibitors if not on GLP-1 receptor agonist.
Cautious addition of SU[c], Basal Insulin, TZD[d]

Patients Without Indicators of High Risk or Established ASCVD, HF or CKD: Need to Minimize Hypoglycemia

If not at A1C goal with metformin, continue metformin[a] and consider the drug classes below.

SGLT2 inhibitor[b]	GLP-1 receptor agonist	TZD	DPP-4 inhibitor
A1C above goal	A1C above goal	A1C above goal	A1C above goal
GLP-1 receptor agonist	SGLT2 inhibitor[b]	SGLT2 inhibitor[b]	SGLT2 inhibitor[b]
OR	OR	OR	OR
DPP-4 inhibitor	TZD	DPP-4 inhibitor	TZD
OR		OR	
TZD		GLP-1 receptor agonist	
A1C above Goal	A1C above Goal	A1C above Goal	A1C above Goal

Continue with addition of classes in the algorithm above

A1C above Goal

Consider SU[c] or basal insulin with lower risk of hypoglycemia[d]

Adapted from ADA Standards of Care [web annotation]. *Diabetes Care.* 2020; 43(Supplement 1):S1-S212.
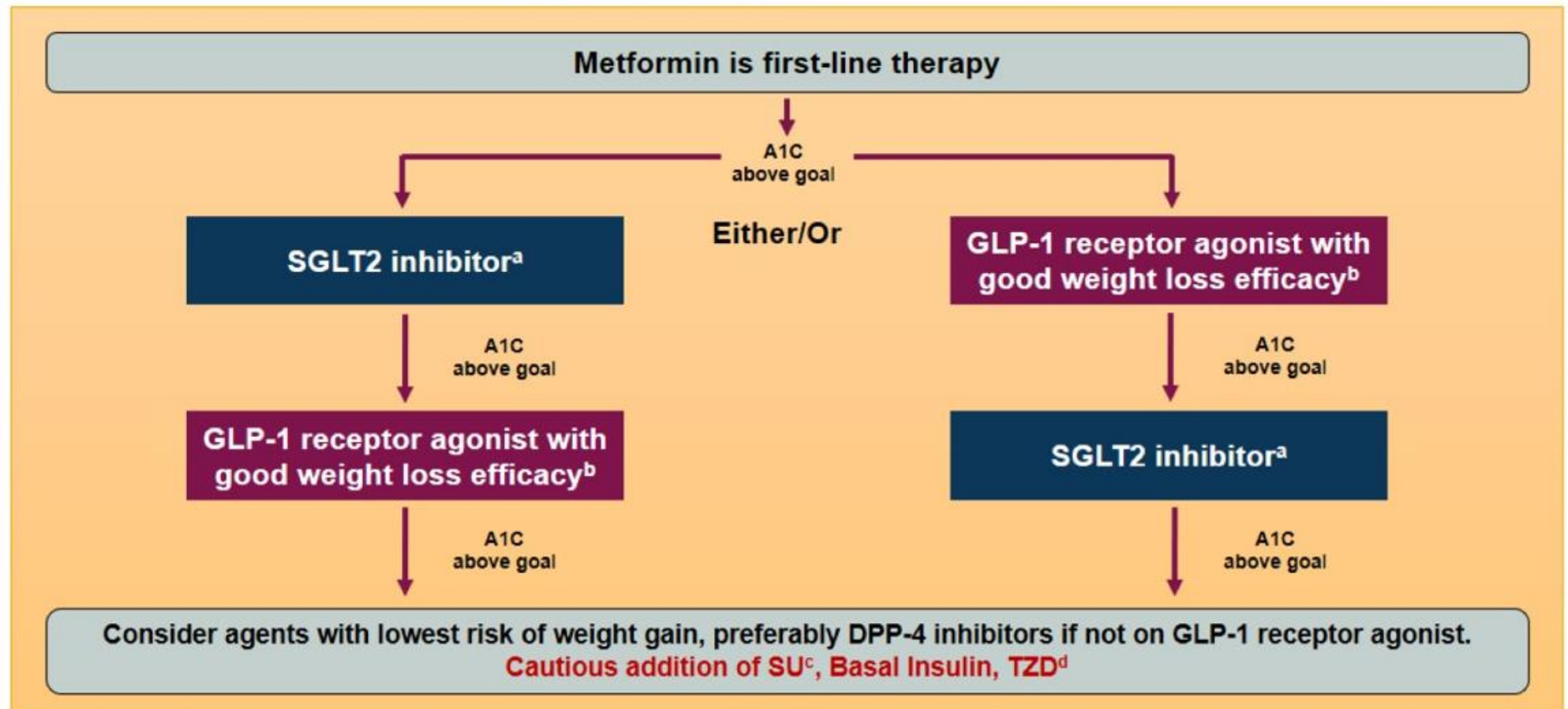
Treatment of Patients in Whom HF or CKD Predominates

After metformin[a] and comprehensive lifestyle management (including weight management and physical activity), consider presence of HF or CKD, and use of SGLT2 inhibitors or GLP-1 receptor agonists with proven CVD benefit regardless of baseline A1C or individualized A1C target.

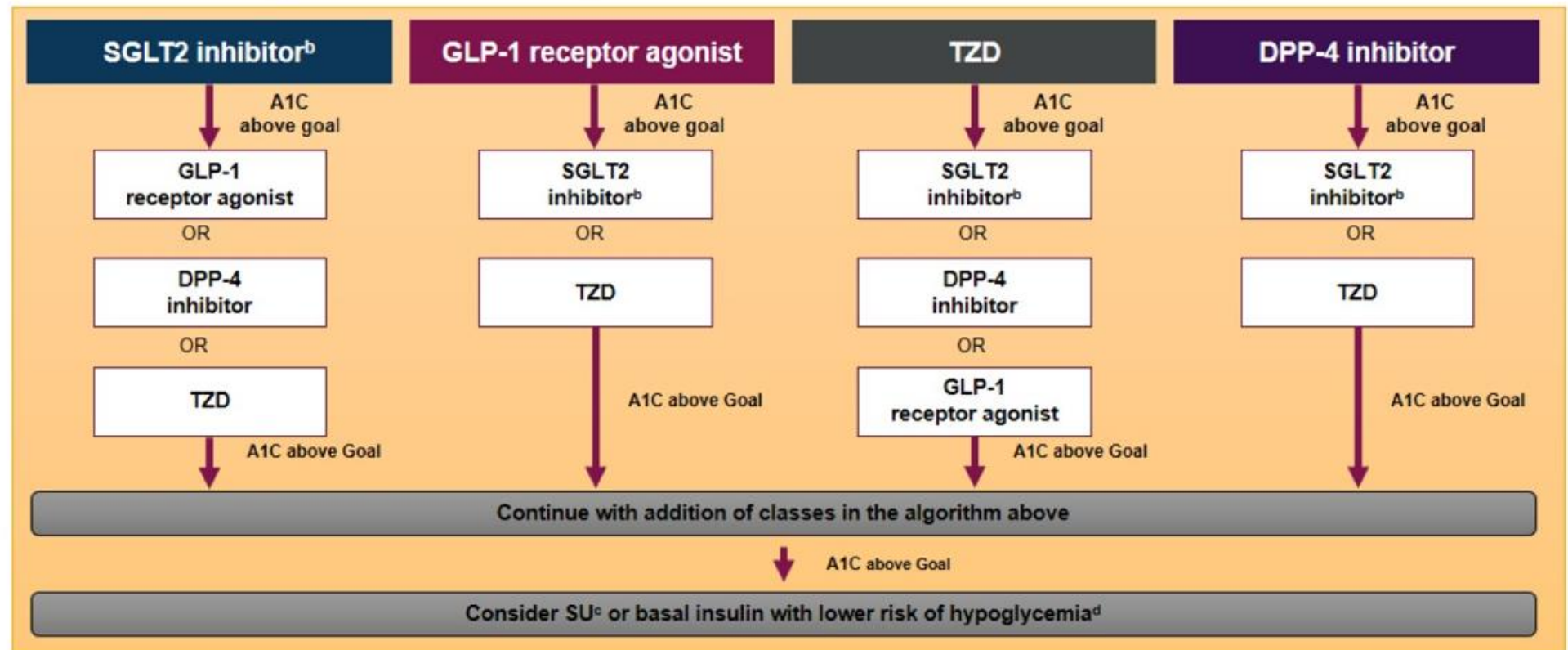**HF or CKD Predominates**

- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30-60mL/min/$1.73m^2$ or UACR > 30mg/g, particularly UACR > 300mg/g

Preferably SGLT2 inhibitor[b] with evidence of reducing HF and/or CKD progression in CVOTs[c]

-----OR-----

If SGLT2 inhibitor not an option[d], add GLP-1 receptor agonist with proven CVD benefit[e]

↓ A1C above goal

If further glycemic lowering is needed or patient is unable to tolerate GLP-1 receptor agonist or SGLT2 inhibitor, select medications demonstrating CV safety:[f]

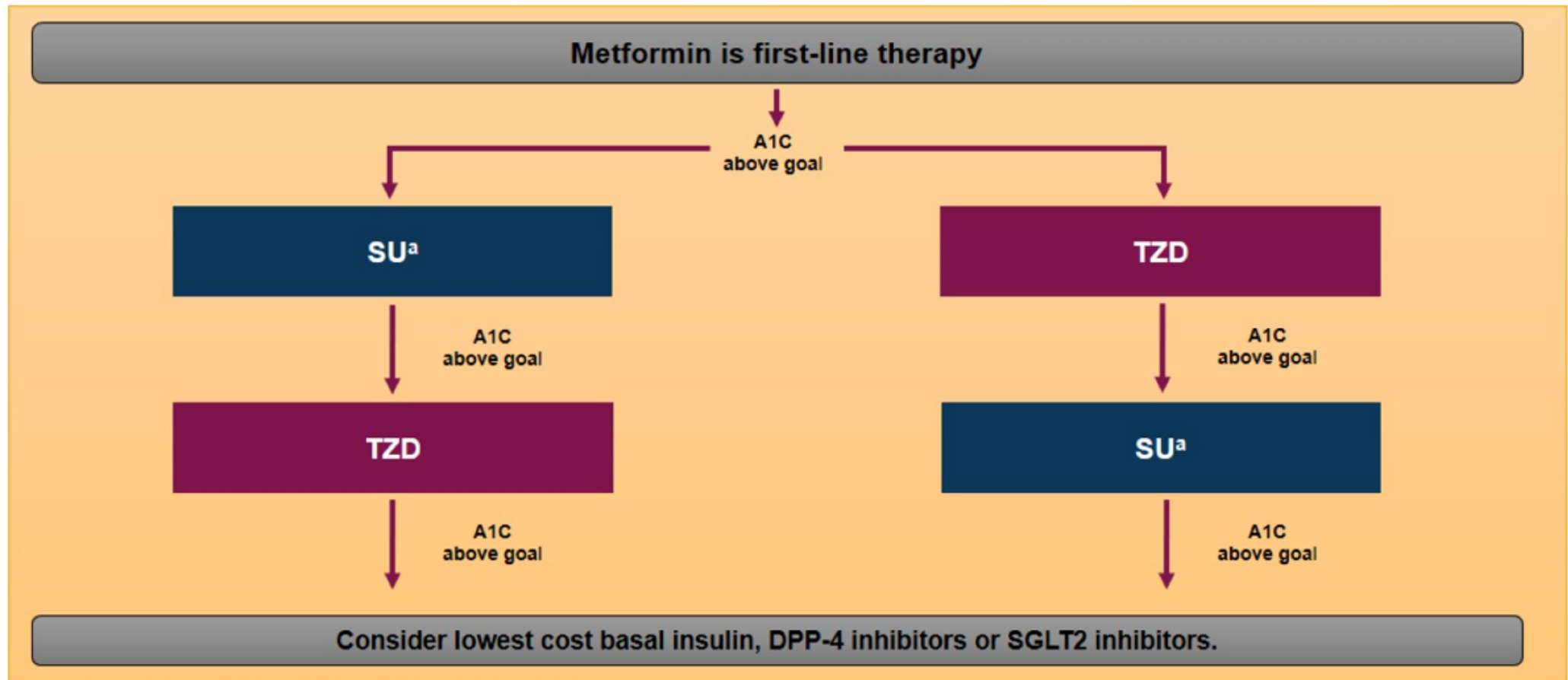| For patients on a SGLT2 inhibitor, consider adding GLP-1 receptor agonist with proven CVD benefit[a]	DPP-4 inhibitor (not SAXA) in HF[g]	Basal insulin[h]	SU[i]

Patients Without Indicators of High Risk or Established ASCVD, HF or CKD: Cost Issues

Metformin is first-line therapy

A1C above goal

SU[a]

TZD

A1C above goal

TZD

SU[a]

A1C above goal

A1C above goal

A1C above goal

Consider lowest cost basal insulin, DPP-4 inhibitors or SGLT2 inhibitors.

2020 ADA Standards of Care:
Decision Cycle for Patient-Centered Glycemic Management

- Review management plan
- Mutual agreement on changes
- Ensure agreed modification of therapy is implemented in a timely fashion to avoid clinical inertia
- Decision cycle undertaken regularly (at least once/twice a year)

Review and Agree on Management Plan

Assess Key Patient Characteristics

- Current lifestyle
- Co-morbidities ie, ASCVD, CKD, HF
- Clinical characteristics i.e. age, A1C, weight
- Issues such as motivation and depression
- Cultural and socio-economic context

- Emotional well-being
- Check tolerability of medication
- Monitor glycemic status
- Biofeedback including SMBG, weight, step count, A1C, BP and lipids

Ongoing Monitoring and Support Including:

Goals of Care
- **Prevent Complications**
- **Optimize Quality of Life**

Consider Specific Factors Which Impact Choice of Treatment

- Individualized A1C target
- Impact on weight and hypoglycemia
- Side effect profile of medication
- Complexity of regimen i.e. frequency, mode of administration
- Choose regimen to optimize adherence and persistence
- Access, cost and availability of medication

- Patients not meeting goals generally should be seen at least every 3 months as long as progress is being made; more frequent contact initially is often desirable for DSMES

Implement Management Plan

Shared Decision-Making

Specify SMART Goals:
- **Specific**
- **Measurable**
- **Achievable**
- **Realistic**
- **Time limited**

Agree on Management Plan

- Involves an educated and informed patient (and their family/caregiver)
- Seeks patient preferences
- Effective consultation includes motivational interviewing, goal setting and shared decision making
- Empowers the patient
- Ensure access to DSMES

Adapted from ADA Standards of Care. *Diabetes Care*. 2020; 43(Supplement 1):S38.

A1C = glycated hemoglobin; ADA = American Diabetes Association; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CKD = chronic kidney disease; DSMES = diabetes self-management education and support; HF = heart failure; SMBG = self-monitored blood glucose.

American Diabetes Association. Standards of Care in Diabetes 2020. *Diabetes Care*. 2020; 43(supplement 1): S1-S212.

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Key Recommendation for Overall Health Assessment (Endocrine Society)

Step 1: Assessing overall health

Overall Health Category	Group 1: Good Health	Group 2: Intermediate Health	Group 3: Poor Health
Patient characteristics	No comorbidities **or** 1-2 non-diabetes chronic illnesses* **and** No ADL$^\epsilon$ impairments and ≤1 IADL impairment	3 or more non-diabetes chronic illnesses* **and/or** Any one of the following: mild cognitive impairment or early dementia ≥2 IADL impairments	Any **one** of the following: End-stage medical condition(s)** Moderate to severe dementia ≥2 ADL impairments Residence in a long-term nursing facility

Reasonable glucose target ranges and HbA1c by group

← Shared decision-making: individualized goal may be lower or higher →

Step 2: Identify HbA1c and glucose targets

Overall Health Category		Group 1: Good Health	Group 2: Intermediate Health	Group 3: Poor Health
Use of drugs that may cause hypoglycemia (e.g., insulin, sulfonylurea, glinides)	No	Fasting: 90-130 mg/dL Bedtime: 90-150 mg/dL <7.5%	Fasting: 90-150 mg/dL Bedtime: 100-180 mg/dL <8%	Fasting: 100-180 mg/dL Bedtime: 110-200 mg/dL <8.5%$^¥$
	Yes$^£$	Fasting: 90-150 mg/dL Bedtime: 100-180 mg/dL ≥7.0 and <7.5%	Fasting: 100-150 mg/dL Bedtime: 150-180 mg/dL ≥7.5 and <8.0%	Fasting: 100-180 mg/dL Bedtime: 150-250 mg/dL ≥8.0 and <8.5%$^¥$

*Does not include diabetes ** e.g. metastatic cancer, oxygen requiring COPD, ESKD on HD, advanced HF.
ADL: Activities of daily living (e.g. eating, bathing, dressing)
IADL: Instrumental activities of daily living (e.g. managing money, doing housework)

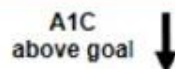LeRoith, D., et al. J Clin Endocrinol Metab 104: 1520–1574, 2019

Intensifying to Injectable Therapy

GLP-1 receptor agonists are preferred to insulin in most clinical settings

If injectable therapy is needed to reduce A1C[a]

↓

GLP-1 receptor agonist for most patients prior to insulin[a,b]

A1C above goal ↓

Add basal insulin[c]

↓

Add basal analog or bedtime NPH insulin

A1C above goal despite adequate titration of basal analog or bedtime NPH[d] or once basal dose >0.5 IU/kg or FPG at target ↓

Add prandial insulin

Concomitant Drug or Class	Recommended Action When Initiating Combination Injectable Therapy
Metformin	Continue treatment.
SGLT2 inhibitor	In patients with suboptimal blood glucose control, especially those requiring large insulin doses, adjunctive use may help to improve control and reduce amount of insulin needed; consider potential side effects
DPP-4 inhibitor	Discontinue
TZD	In patients with suboptimal blood glucose control, especially those requiring large insulin doses, adjunctive use may help to improve control and reduce amount of insulin needed; consider potential side effects
SU	Discontinue

ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)

A1C <8%

TDD 0.1–0.2 U/kg

A1C >8%

TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** >180 mg/dL: add 20% of TDD
  - **FBG** 140–180 mg/dL: add 10% of TDD
  - **FBG** 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - **BG** <70 mg/dL: 10% – 20%
  - **BG** <40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

*Glycemic Goal:

- <7% for most patients with T2D; fasting and premeal BG <110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

INTENSIFY (Prandial Control)

Add GLP1-RA

Or SGLT2i Or DPP4i

Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals

- Start: 10% of basal dose or 5 units

Basal Bolus

- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg

- Start: 50% of TDD in three doses before meals

Glycemic Control Not at Goal*

Insulin titration every 2–3 days to reach glycemic goal:

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently >140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently <70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG <40 mg/dL: 20% - 40%

Insulin Pump Therapy

Insulin type	How it is delivered	Expiration date	Onset	Peak	Duration
Rapid Acting					
Admelog	Pens and vials	28 days	15-30 min	30 min-2 ½ hrs	4-5 hours
Afrezza inhaled powder	4, 8 and 12 unit Cartridges	3 days	3-7 min	12-15 min	1 ½-3 hours
Apidra	Vials and pens	28 days	10-20 min	30 min-1 ½ hrs	2-4 hours
Fiasp	Vials and pens	28 days	15-20 min	1 ½- 2 hours	5 hours
Humalog, U-100 and U-200	Vials, pens and cartridges refills	28 days	10-20 min	30 min-1/12 hrs	3-5 hours
Novolog	Vials, pens and cartridges refills	28 days	10-20 min	1-3 hours	3-5 hours
Short Acting **					
Regular	Vials and pens (varies by brand)	31-42 days	15-30 min	2 ½-5 hours	4-12 hrs
U-500 (5x the concentration)	Vials and pens	28 days	30 min	4-8 hours	18-24 hrs
Intermediate Acting **					
NPH (created in 1946)	Vials and pens (varies by brand)	31-42 days	1-2 hours	4-12 hours	14-24 hrs
Long Acting					
Basaglar	Vials and pens	28 days	3-4 hours	No peak +	11-24 hrs
Lantus	Vials and pens	28 days	3-4 hours	No peak +	11-24 hrs
Levemir	Vials and pens	42 days	3-4 hours	No peak +	6-23 hrs
Toujeo, U-300	Pen only	42 days	6 hours	No peak	24-36 hrs
Tresiba, U-100 and U-200	Pen only	56 days	1 hour	9 hours	36-42 hrs
Combination					
NPH/Regular 70/30	Vials and pens	31-42 day vial 10 day pen	30 min	50 min-2 hrs 6-10 hrs	18-24 hrs
Rapid acting 70/30	Vials and pens	28 day vial 14 d pen	15-30 min	1-4 hours	18-24 hrs
Rapid acting 75/25	Vials and pens	28 d vial 10 d pen	15-30 min	1-6 ½ hours	12-24 hrs
Rapid acting 50/50	Vials and pens	28 d vial 10 d pen	15-30 min		

MiniMed™ 670G

PROS
- Integrated Enlite 3 Continuous Glucose Monitor (CGM)
- Automatically adjusts basal insulin delivery based on data from CGM
- Bluetooth Bayer Contour Next Link Meter with remote bolusing.

CONS
- Enlite 3 CGM has accuracy issues
- Medtronic belt clip does not pivot so pump must be unclipped to view screen
- Screen is small
- Not a touch screen

Omnipod® DASH

PROS
- Only tubeless insulin pump
- Sleek touch screen personal diabetes manager
- Bluetooth Bayer Contour Next Meter
- Automatic insertion of cannula with the press of a button (great for toddlers)

CONS
- No integrated CGM
- Not capable of automatically adjusting insulin delivery or suspending delivery
- Holds only 200 units of insulin
- Must change pod every 3 days

t:slim X2™

PROS
- Smallest insulin pump on the market
- Integrated Dexcom CGM is very accurate
- Automatically adjusts basal insulin based on data from CGM
- Pump software can be updated

CONS
- No link meter
- Tubing connector looks medical
- Rechargeable battery can be a con for some users

For every absolute 10% change in %TIR, there was a 0.8% change in HbA1C.
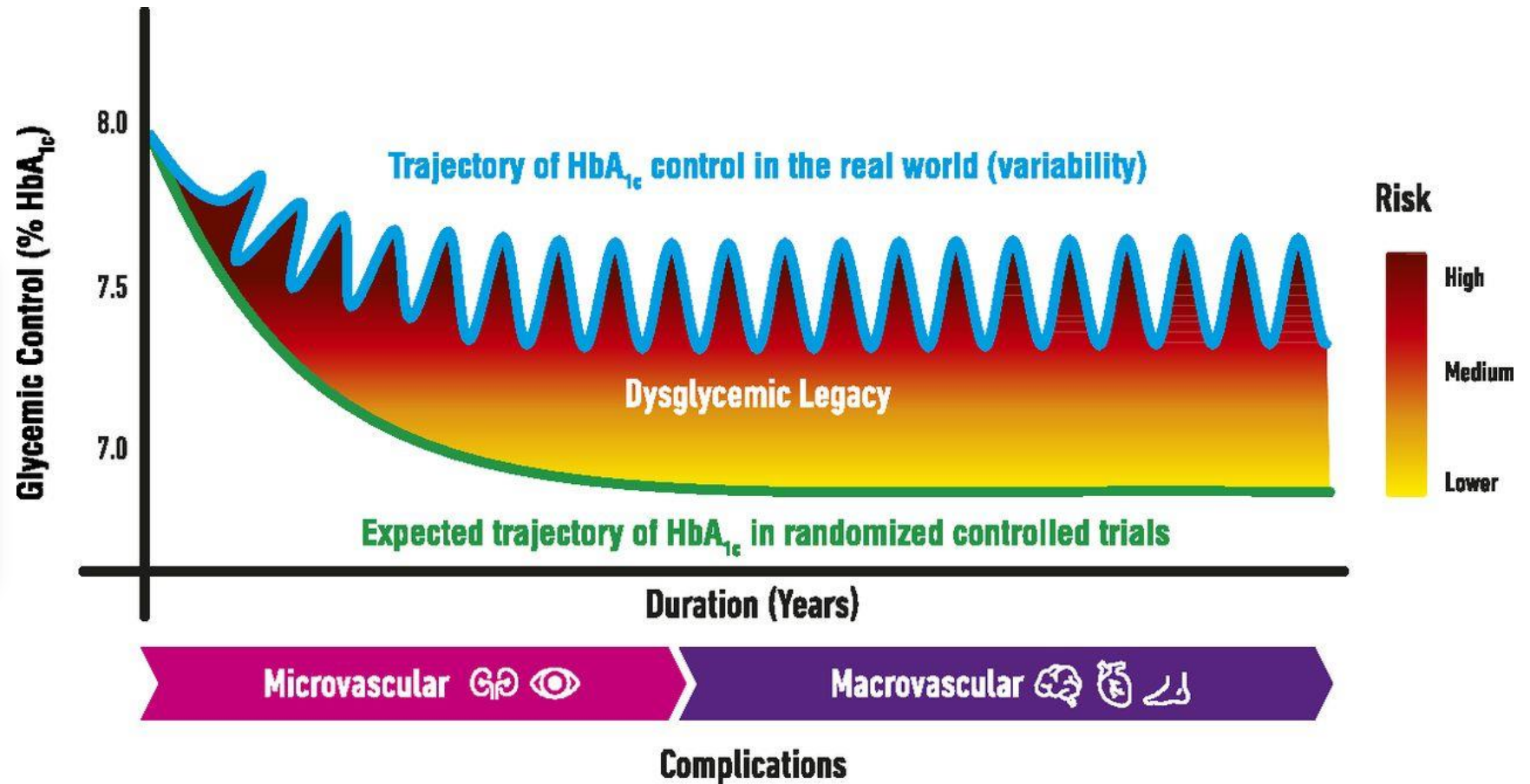
A schematic representation of the effects of early intensive glycemic control in preventing initial microvascular complications and then macrovascular complications several years later. Failure to initially control and maintain glycemia at diagnosis or sustained glycemic variability leads to the dysglycemic legacy of diabetes complications.

Continuous Glucose Monitor Comparison

	DEXCOM G6	GUARDIAN 3	Freestyle Libre 2	Eversense
Days of sensor wear	10	7	14	90
Integration with pump	Tandem t:slim Control-IQ (and older Basal-IQ)	Yes and No: The Guardian 3 is part of the 670g hybrid closed-loop insulin pump system. The Guardian Connect is a stand alone CGM that does not connect to any pump.	No	No
Cost	Transmitter: $300 every 90 days Sensors: $420 for 30 day supply Receiver (not necessary if using smartphone): $380 one time purchase	Rechargeable Transmitter: $1100 (1 year warranty, may last longer) Sensors: $450 for box of 5 (35 day supply)	Sensors: $135 for 28 day supply Reader (not necessary if using smartphone): $175	$1400 for sensor, transmitter, and supplies, plus cost of insertion in doctor's office. Limited time Eversense Bridge program limits the cost to $99 plus insertion
Smartphone integration	Android, iOs, Apple Watch	Android, iOs	Android, iOs	Android, iOs, Apple Watch
Data sharing	Up to 10 people with Dexcom Follow app (Apple, Google	Up to 4 people with CareLink™ Connect web app (Apple, Google)	Up to 20 people with LibreLinkup app (Apple, Google)	Up to 5 people with Eversense Now app
Separate receiver available	yes	No	Yes	No
Water resistance	8 feet for up to 24 hours	7.5 feet for 10 minutes	3 feet or for 30 minutes	1 meter (about 3 feet) for 30 minutes

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

DYSLIPIDEMIA

LIFESTYLE THERAPY (Including Medically Assisted Weight Loss)

LIPID PANEL: Assess ASCVD Risk

STATIN THERAPY
If TG >500 mg/dL, fibrates, Rx-grade OM-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C- lowering therapies

Repeat lipid panel; assess adequacy, tolerance of therapy

Intensify therapies to attain goals according to risk levels

RISK LEVELS	HIGH	VERY HIGH	EXTREME	RISK LEVELS:
	DESIRABLE LEVELS	DESIRABLE LEVELS	DESIRABLE LEVELS	**HIGH*:** DM but no other major risk and/or age <40
LDL-C (mg/dL)	<100	<70	<55	**VERY HIGH*:** DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking, CKD3,4)
Non-HDL-C (mg/dL)	<130	<100	<80	
TG (mg/dL)	<150	<150	<150	**EXTREME*:** DM plus established clinical CVD
Apo B (mg/dL)	<90	<80	<70	

If not at desirable levels: Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

To lower LDL-C: Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin
To lower Non-HDL-C, TG: Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
To lower Apo B, LDL-P: Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin
To lower LDL-C in FH:** Statin + PCSK9i

If TG 135-499: Add icosapent ethyl 4 g/day if high ASCVD risk on maximally tolerated statins

Assess adequacy & tolerance of therapy with focused laboratory evaluations and patient follow-up

* EVEN MORE INTENSIVE THERAPY MIGHT BE WARRANTED   ** FAMILIAL HYPERCHOLESTEROLEMIA

HYPERTENSION

GOAL: SYSTOLIC <130, DIASTOLIC <80 mm Hg

ACEi or ARB

For initial blood pressure >150/100 mm Hg: **DUAL THERAPY**

ACEi or ARB +
- Calcium Channel Blocker ✓
- ß-blocker ✓
- Thiazide ✓

If not at goal (2–3 months)

Add calcium channel blocker, ß-blocker or thiazide diuretic

If not at goal (2–3 months)

Add next agent from the above group, repeat

If not at goal (2–3 months)

Additional choices (α-blockers, central agents, vasodilators, aldosterone antagonist)

Achievement of target blood pressure is critical

Table 5. Overview of statin therapy.[28,30]

High intensity (decrease LDL-C >50%)	Moderate intensity (decrease LDL-C 30–<50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
Patients with ACS and LDL>50 mg/dL who could not tolerate high dose statins Use moderate-intensity statin and ezetimibe	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg

LDL-C, low-density lipoprotein cholesterol.

A CHANGING PARADIGM IN CARING FOR PATIENTS WITH TYPE 2 DIABETES AND CLINICAL CVD

| Medication	NNT to prevent a Death
Statins (for 5 years)	100
Anti-hypertensives (for 5 years)	125
Empagliflozin (for 3 years)	39
Liraglutide (for 3 years)	98

These benefits of GLP-1 receptor agonists and SGLT2 inhibitors emerged in trials were the drugs were added (versus placebo) in patients with CVD and an A1c >7%.

Krumholz, H and Lipska, K. JAMA. 2017 March 14; 317(10): 1017–1018
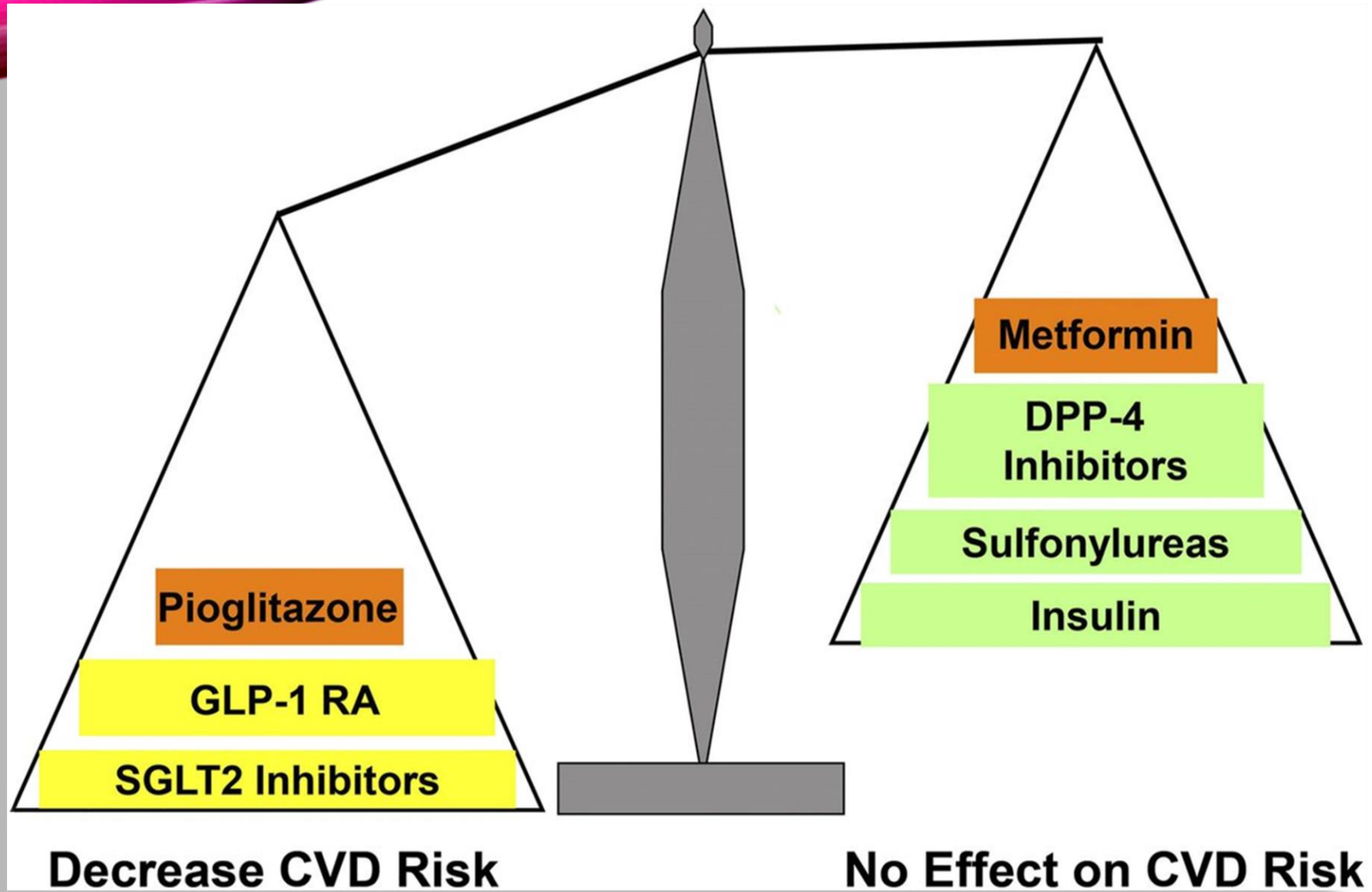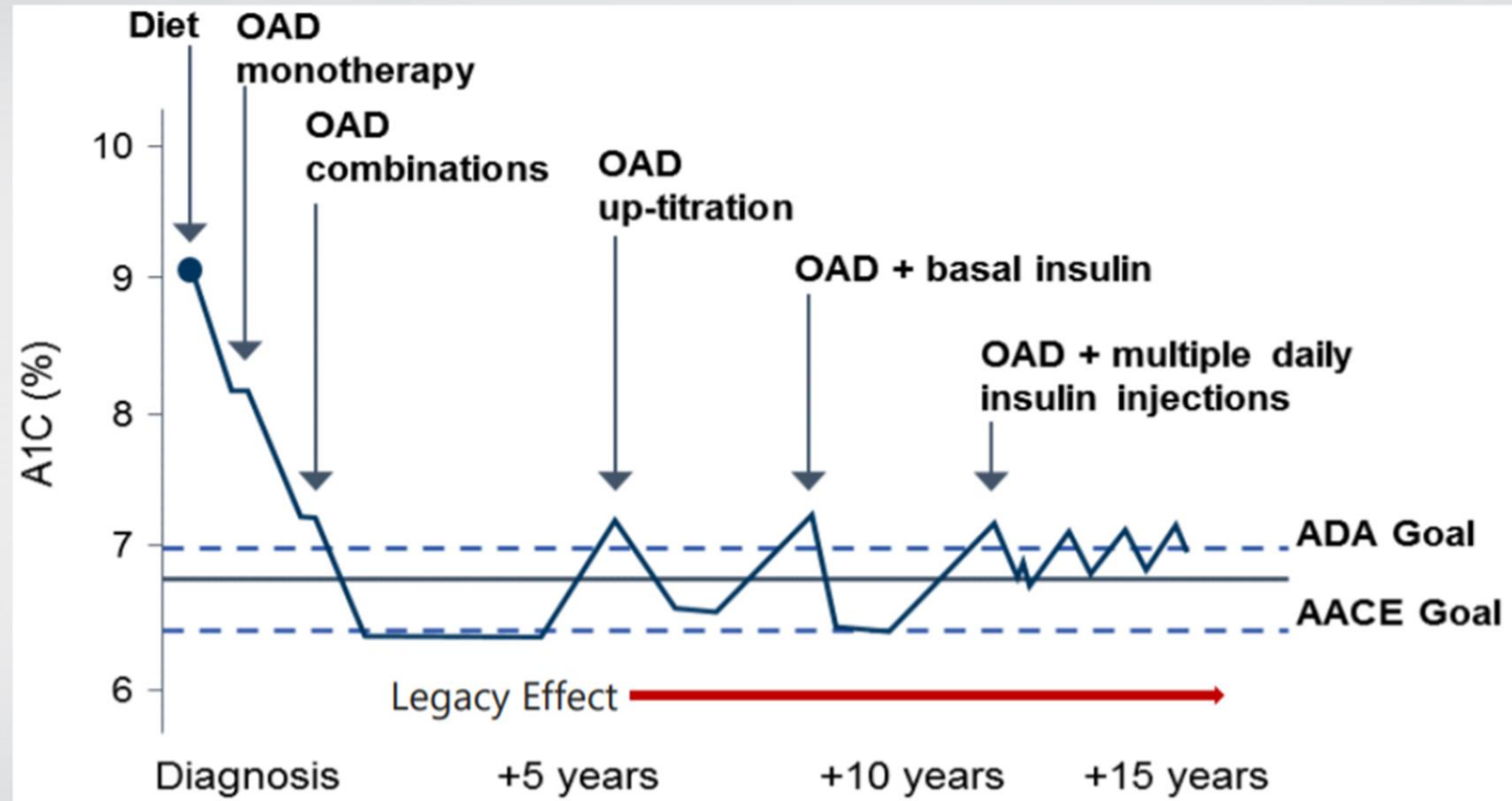
Real-World vs Clinical Trial Results

Conceptually, there is an efficacy gap between clinical trial results and real-world outcomes. Patients with diabetes in the real world are experiencing less meaningful and less sustained improvements resulting in an efficacy gap.

Edelman SV, et al. *Diab Care*. 2017;40(11):1425-1432.
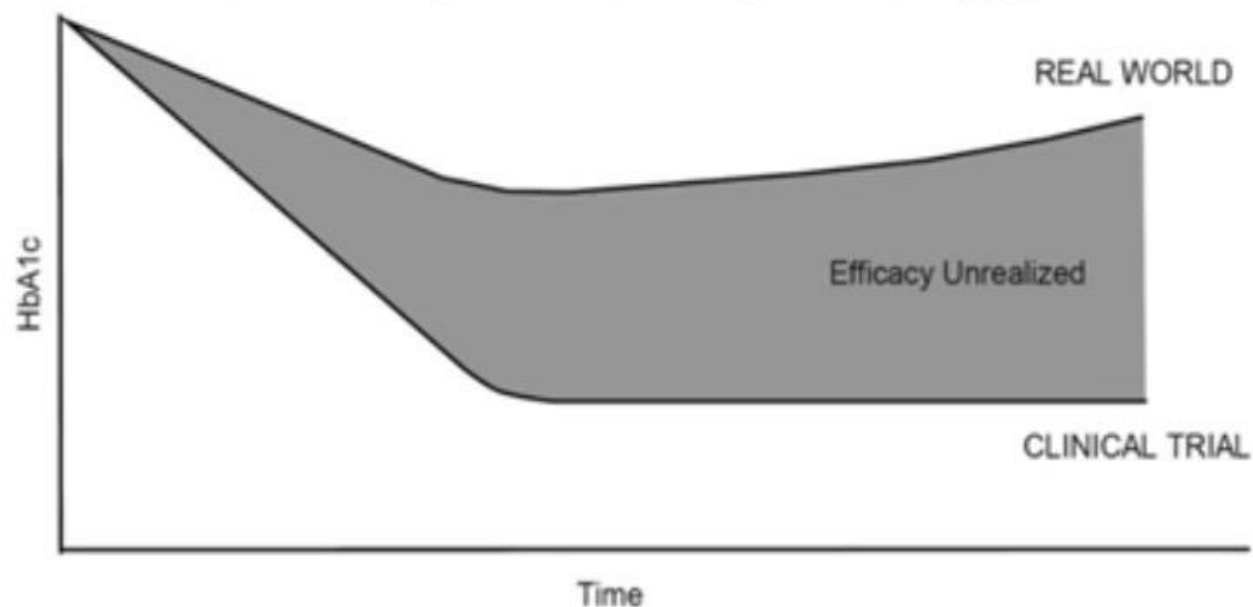
Clinical Inertia

"Treat to Target" Approach

Lovshin JA, Zinman B. Nat Rev Endocrinol. 2013;9(11):635-636.
Fu AZ et al. Diabetes Obes Metab. 2011;13(8):765-769.
(UKPDS F/U) Holman, R. R., et al. (2008). NEJM, 359, 1577-1589. doi:10.1056/NEJMoa0806470 (legacy effect)

Conclusion

- ✓ Effective ways to prevent diabetes include both lifestyle modification and drug therapy tailored to the individual.

- ✓ Glycemic control remains the central pillar of therapy; maintenance of blood glucose within a tight target range has well-established benefits on microvascular disease and if achieved early, the potential for macrovascular benefit over the long-term.

- ✓ Understanding of the underlying pathophysiology of T2DM, particularly cardio-renal-metabolic interplay, can allow a more rational approach to management.

- ✓ Newer therapies may be used to target specific physiological dysfunctions, maximizing the overall benefit to the patient in terms of body weight, adverse effects and cardiovascular risk factors

- ✓ The appropriate choice and timing of combination therapy as well as following treatment guidelines can optimize care for the individual patient.

Hope Smiles from the threshold of the year to come

Alfred Lord Tennyson