San Juan City Hospital
Endocrinology, Diabetes & Metabolism

Prevention, Management and Diagnosis of Diabetes

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- March 27, 2021

Disclosure

Industry Relationship	Company Name	Role
Advisor/Consultant	Merck Medtronic	Consultant Consultant/Speaker
Industry Research	Eli-Lilly Enanta Pharmaceuticals	PI / Sub-PI Sub-PI

Objectives

- Know the prevalence of T2DM in Puerto Rico
- Review the screening methods for diagnosis prediabetes and diabetes
- Review the current recommendations and standards of care for the management of Prediabetes
- Review the current recommendations and standards of care for the management of type 2 diabetes.
- Lipids management in primary and secondary prevention of cardiovascular disease in patients with diabetes.
- Review recent advances in the therapeutic options available for glycemic control including it’s cardiovascular risk reduction

Question 1

- A 45-year-old Hispanic without medical history comes to the office for evaluation. Her only medication is a multivitamin. She does not a have a family history of type 2 diabetes.
- Physical examination
  - BMI: 26
  - BP: 125/82 mmHg

In addition to lifestyle modifications, which is of the following is the next best step management regarding diabetes risk.

- A. Perform screening now
- B. Perform screening in 2 years
- C. No need to perform Diabetes screening.
- D. Perform screening if starts symptoms such as polyuria, polydipsia and polyphagia.

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

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥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 (≥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 ≥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.

Classification and Diagnosis of Diabetes:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019; 42 (Suppl. 1): S13-S28

Criteria for the Diagnosis of Diabetes

Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

OR

2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT

OR

A1C ≥6.5%

OR

Random plasma glucose ≥200 mg/dL (11.1 mmol/L)

American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2019; 42 (Suppl. 1): S13-S28

Prediabetes*

FPG 100–125 [illegible]
(5.6–6.9 mmol/L): IFG

IMPAIRED FASTING GLUCOSE

OR

2-h plasma glucose 140–199 mg/dL
(7.8–11.0 mmol/L): IGT

IMPAIRED GLUCOSE TOLERANCE

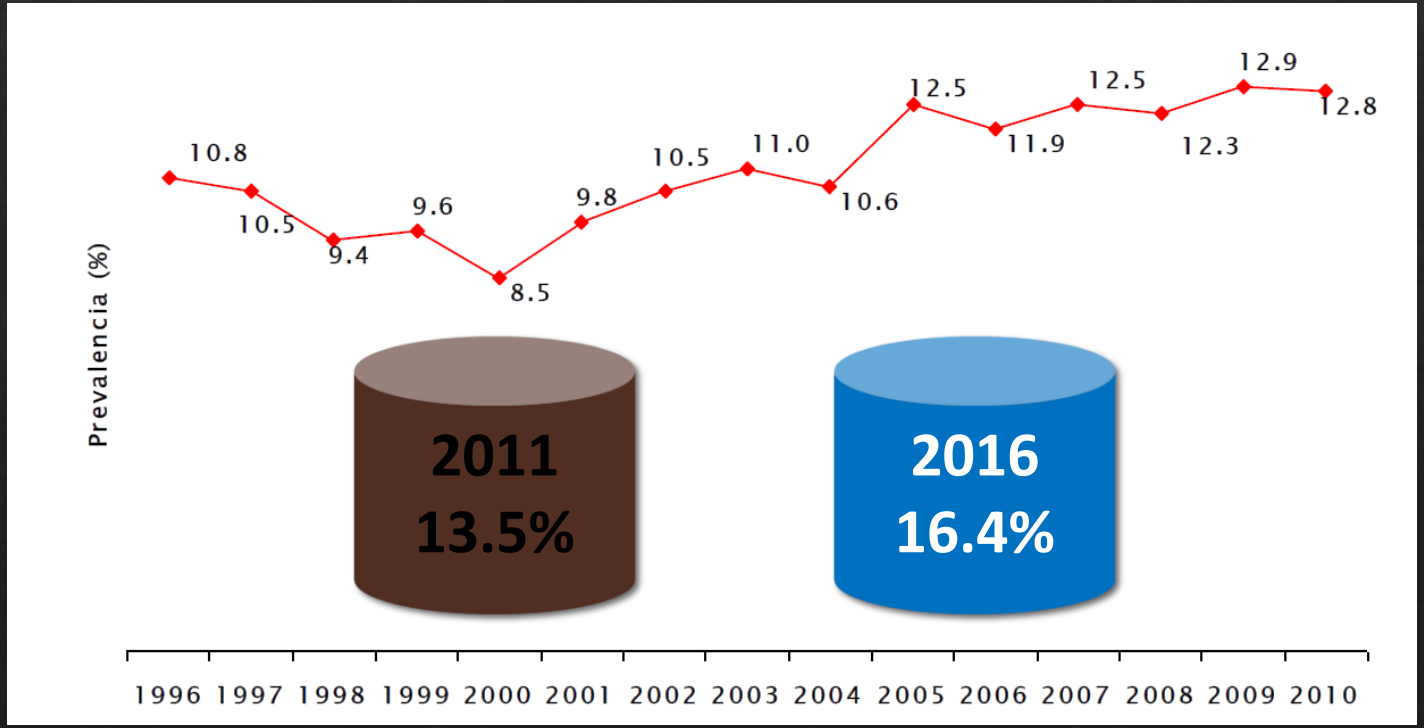
OR

A1C 5.7–6.4%

*** For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.**

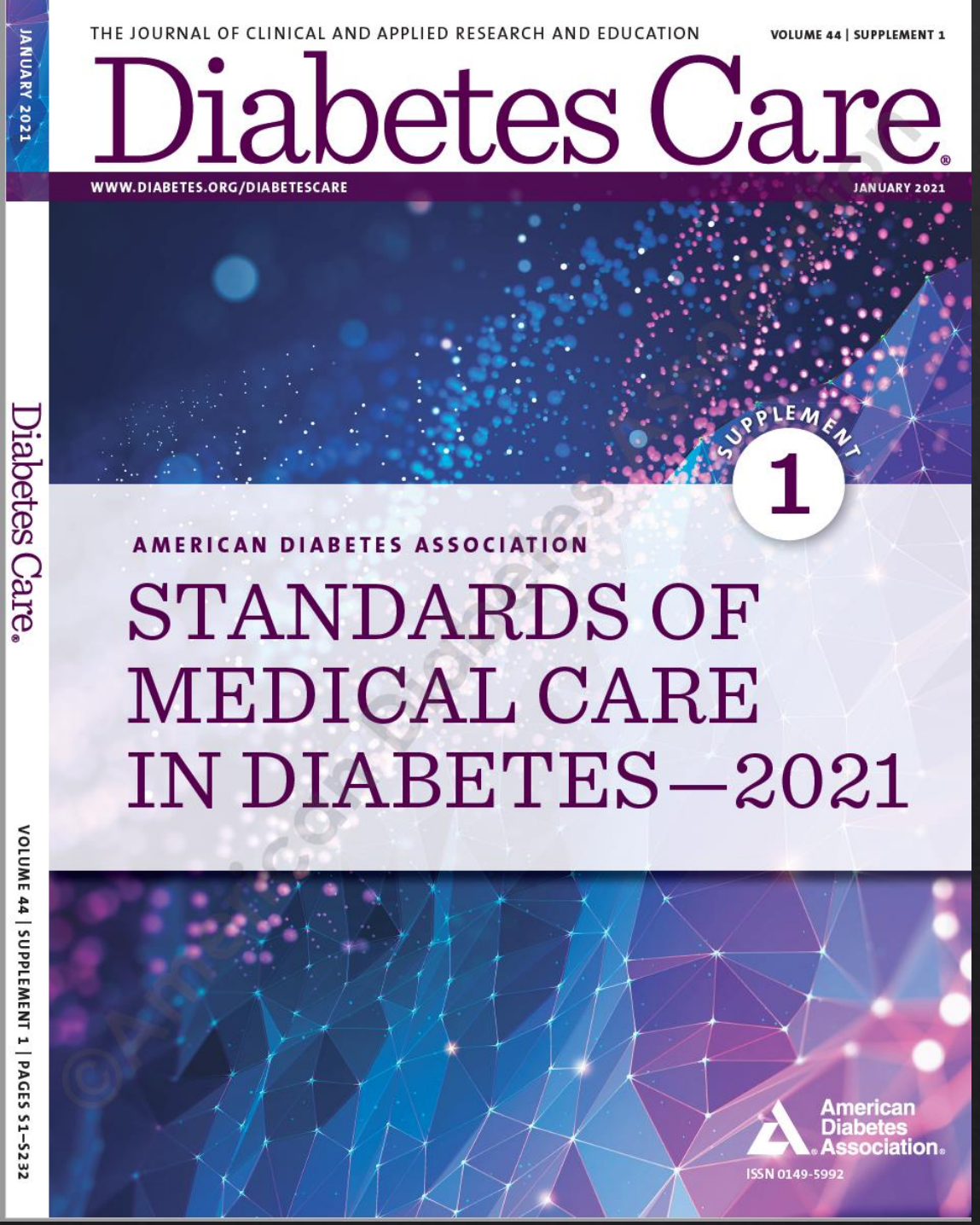
American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. *Diabetes Care* 2019; 42 (Suppl. 1): S13-S28

PREVALENCIA DE DIABETES EN PUERTO RICO, BRFSS, 1996-2010



2020 :16.8%

df.org/our-network/regions-members/south-and-central-america/members/90-puerto-rico.html/Accessed march10,2021



Standards of Medical Care in Diabetes - 2021

American Diabetes Association®

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AMERICAN COLLEGE OF ENDOCRINOLOGY

AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2020

 | DOI 10.4158/CS-2019-0472

Classification of Diabetes

- Type 1 diabetes
  - β-cell destruction
- Type 2 diabetes
  - Progressive insulin secretory defect
- Gestational Diabetes Mellitus (GDM)

Other specific types of diabetes due to other causes:

- Monogenic diabetes syndromes
- Diseases of the exocrine pancreas (cystic fibrosis)
- Drug- or chemical-induced diabetes

Classification and Diagnosis of Diabetes:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019; 42 (Suppl. 1): S13-S28

Question 2

A 39-year-old obese man is referred after a fingerstick blood glucose measurement at a health screening fair at work was documented to be 115 mg/dL (9.9 mmol/L). He had recently eaten lunch. His medical history is notable for dyslipidemia that is well controlled on simvastatin, gout, and obesity.

On physical examination, his blood pressure is 132/78 mm Hg and his BMI is 41.5 kg/m2. Acanthosis nigricans is present, but there are no other notable findings on physical examination.

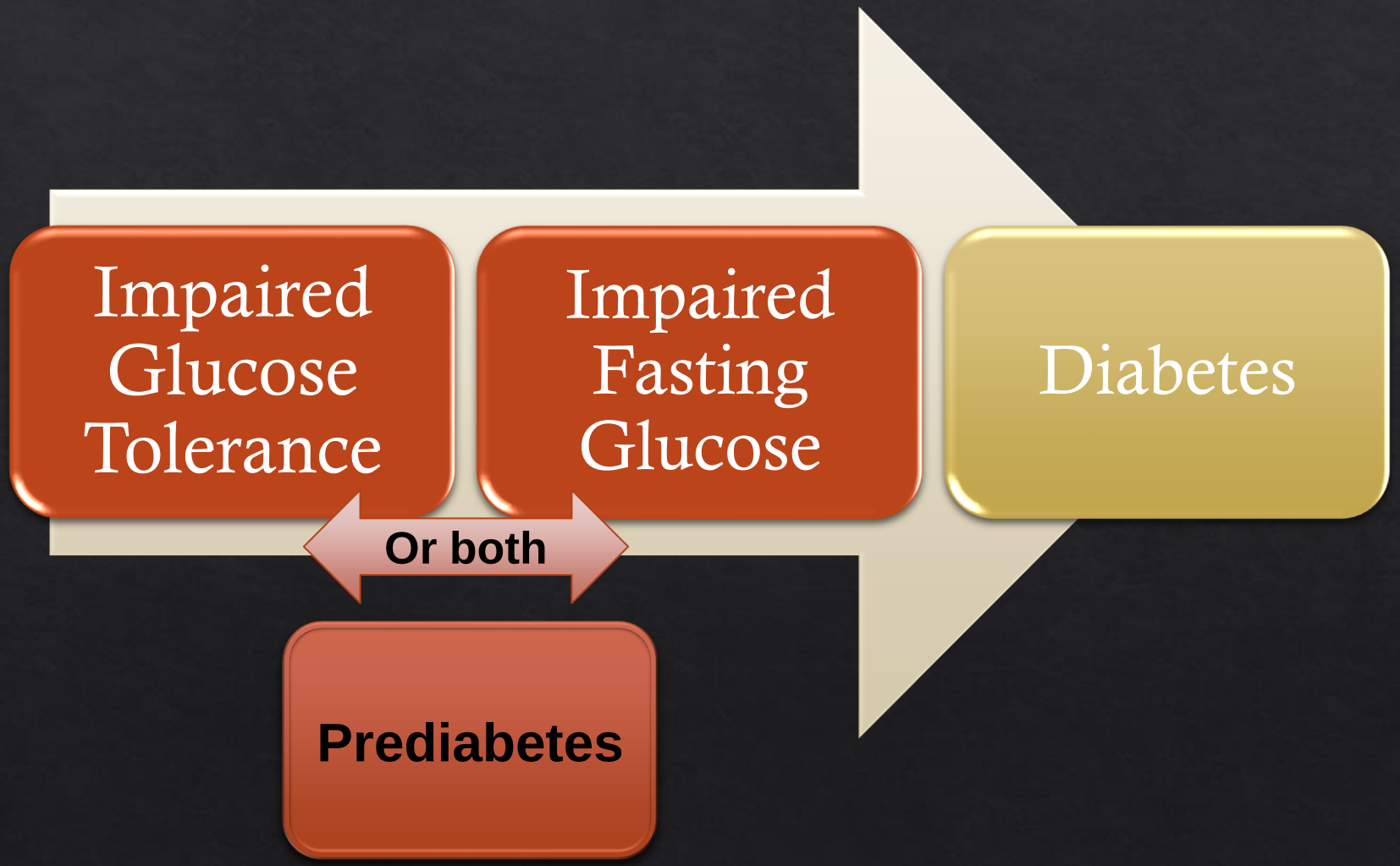
You reassess his glycemic status:

- Fasting plasma glucose (laboratory) = 119 mg/dL (70-99 mg/dL) (SI: 6.6 mmol/L [3.9-5.5 mmol/L])
- Hemoglobin A1c = 6.3% (4.0%-5.6%) (SI: 49 mmol/mol [20-38 mmol/mol])

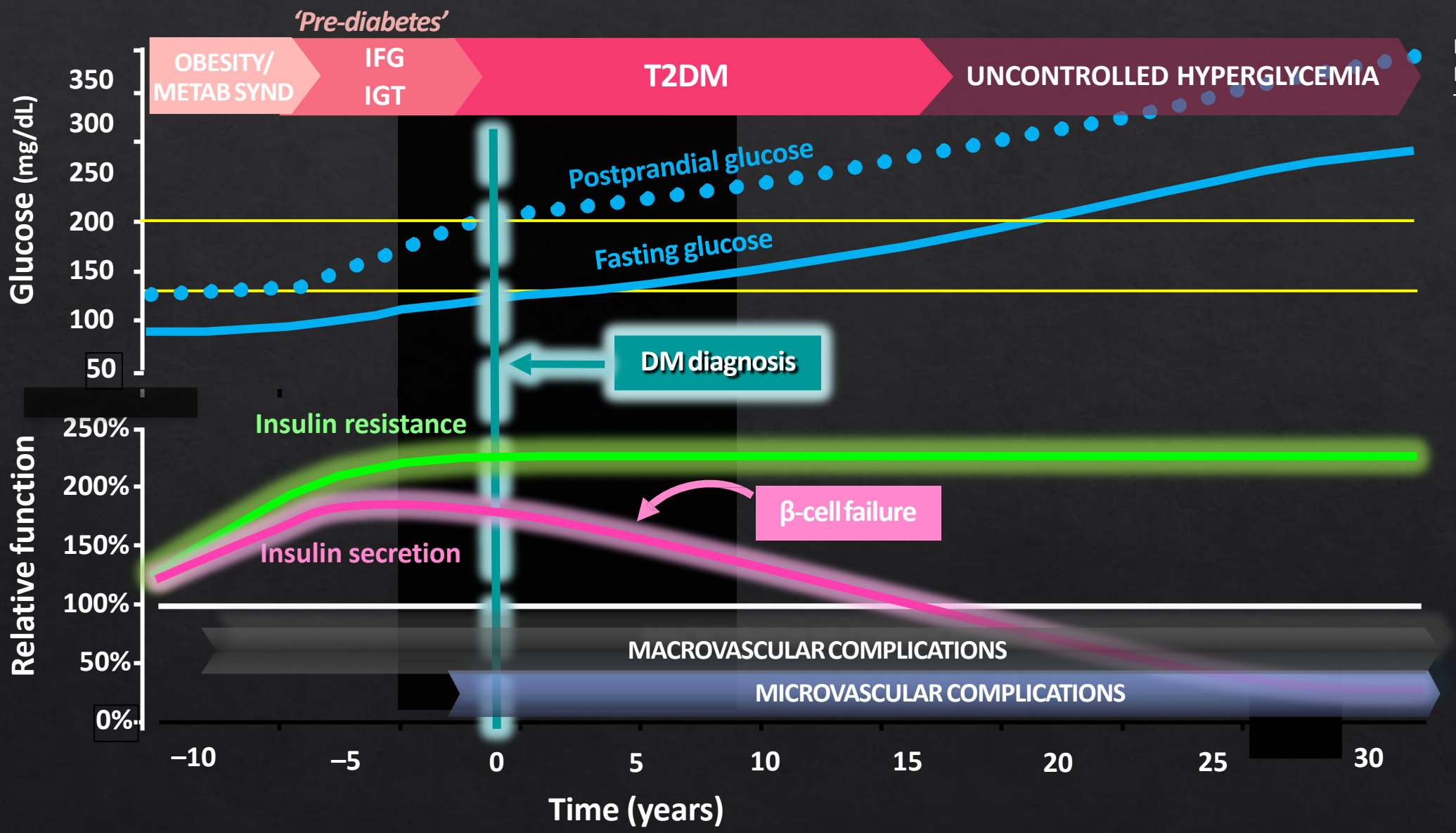
What is the next best step of management

- A. Lifestyle Modifications with target of 7% weight loss
- B. Start Metfomin 500 mg once daily
- C. Start dapagliflozin 10 mg once daily
- D. None of the above

Progression to Type 2 Diabetes



Pathophysiologic Progression of Type 2 Diabetes and Its Vascular Complications



IFG = impaired fas?ng glucose
IGT = impaired glucose tolerance
T2DM = type 2 diabetes mellitus

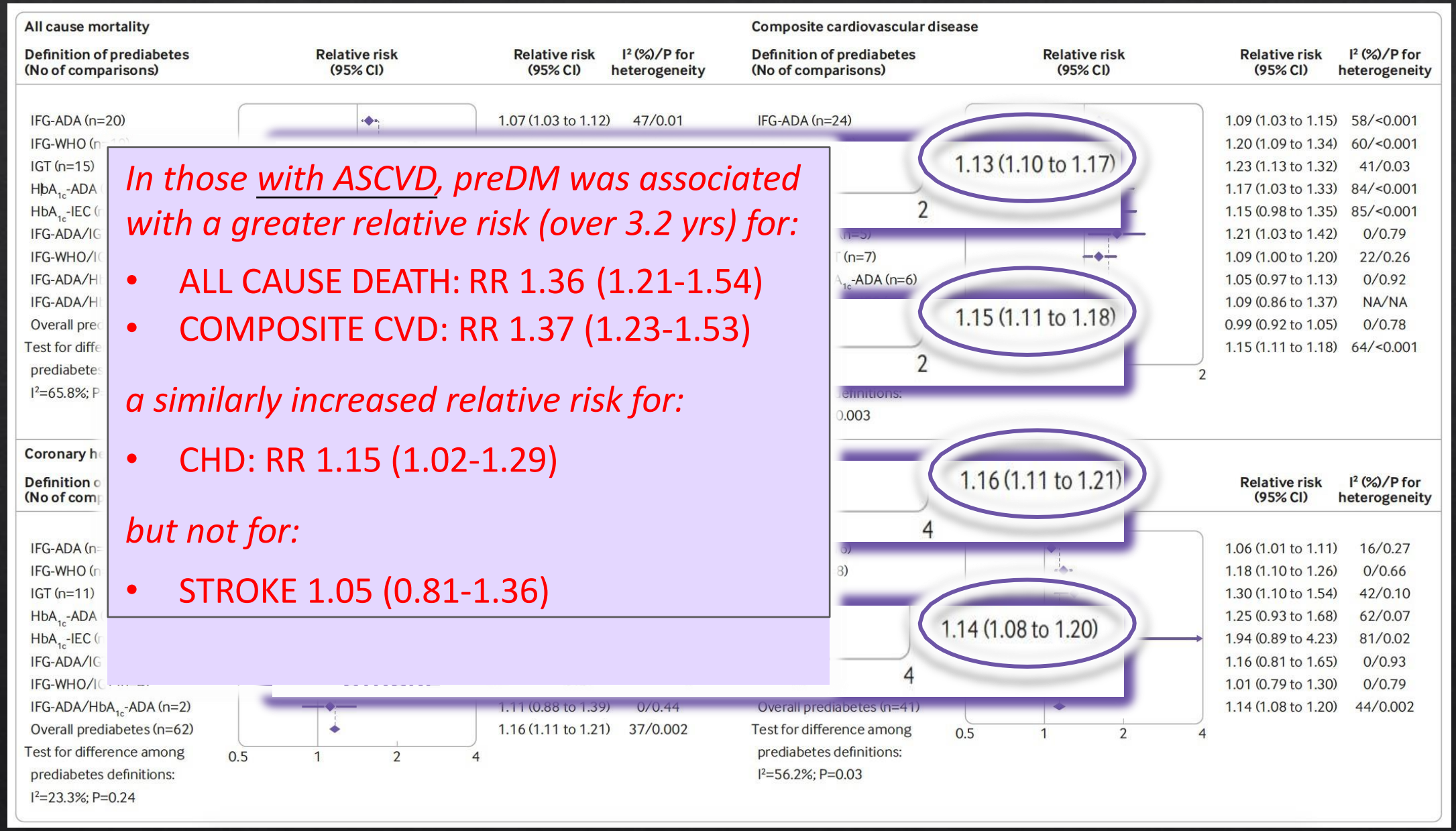
Adapted from:
Ramlo-Halsted BA et al. *Clin Diabetes* 2000;18:80-84

Association between preDM & all cause mortality and CVD

Studies: 129

People: 10,069,955

Follow-up: 9.8 yrs



In those with ASCVD, preDM was associated with a greater relative risk (over 3.2 yrs) for:

- ALL CAUSE DEATH: RR 1.36 (1.21-1.54)
- COMPOSITE CVD: RR 1.37 (1.23-1.53)

a similarly increased relative risk for:

- CHD: RR 1.15 (1.02-1.29)

but not for:

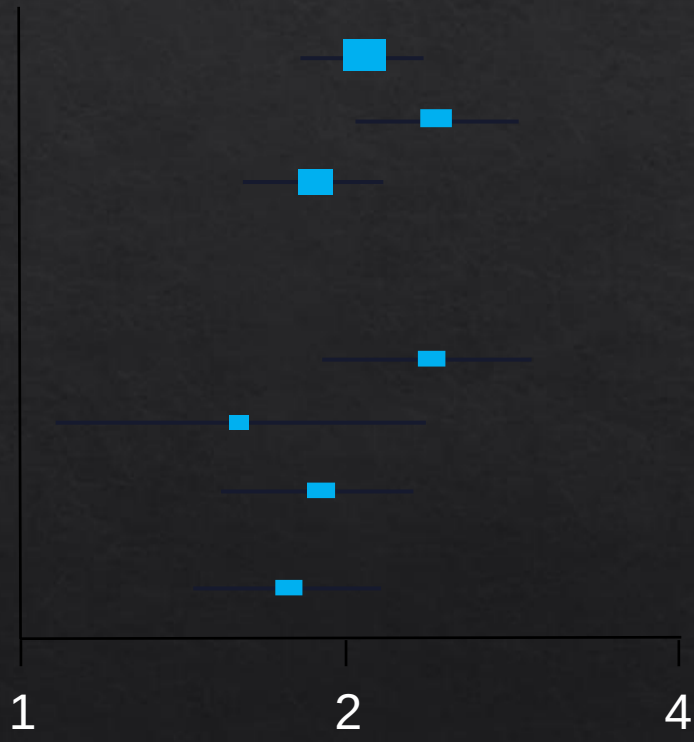
- STROKE 1.05 (0.81-1.36)

Cai X et al. BMJ 2020;370:m2297

T2DM Doubles the Risk for Macrovascular Outcomes

Meta-Analysis of 102 Prospective Studies[1]

	Number of Cases	HR (95% CI)	I^2 (95% CI)
Coronary heart disease[a]	26,505	2.00 (1.83-2.19)	64 (54-71)
Coronary death	11,556	2.31 (2.05-2.60)	41 (24-54)
Nonfatal MI	14,741	1.82 (1.64-2.03)	37 (19-51)
Stroke subtypes[a]			
Ischemic stroke	3,799	2.27 (1.95-2.56)	1 (0-20)
Hemorrhagic stroke	1,183	1.56 (1.19-2.05)	0 (0-26)
Unclassified stroke	4,973	1.84 (1.59-2.13)	33 (12-48)
Other vascular deaths	3,826	1.73 (1.51-1.98)	0 (0-26)



[a] Includes both fatal and nonfatal events.

Emerging Risk Factors Collaboration. *Lancet*. 2010;375:2215-22

Large T2DM Prevenaon RCTs: Lifestyle , DM or Obesity Meds

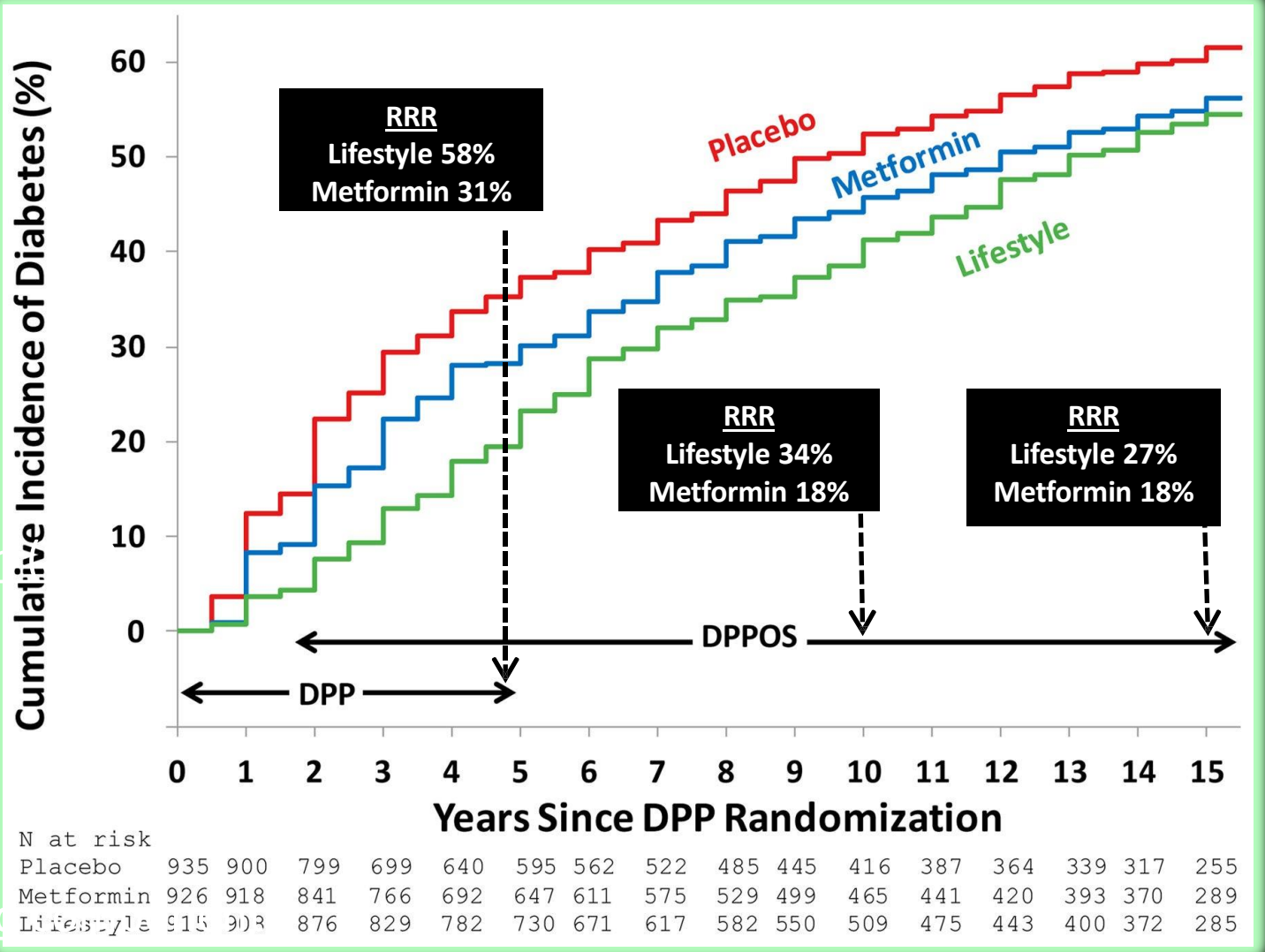
	Trial	Year	N	Subjects	Intervention	Duration	RRR
Lifestyle	Da Qing	1997	577	IGT	Lifestyle	~6 years	32%
	Finnish DPS	2001	522	IGT	Lifestyle	3.2 years	58%
	US DPP	2002	3234	IGT	Lifestyle	2.8 years	58%
Pharmacological Agents	US DPP	2002	3234	IGT	Metformin (biguanide)	2.8 years	31%
	STOP NIDDM	2002	1418	IGT	Acarbose (AGI)	3.3 years	25%
	XENDOS	2004	3305	IGT	Orlistat (lipase inhibitor)	~4 years	37%
	DREAM	2006	5269	IGT/IFG	Rosiglitazone (TZD)	3.0 years	62%
	NAVIGATOR	2010	9031	IGT + high CV risk	Nateglinide (meglitinide)	5.0 years	NS
	ACT NOW	2011	602	IGT	Pioglitazone (TZD)	2.4 years	72%
	ORIGIN*	2012	1456	IGT + high CV risk	Glargine (basal insulin)	6.2 years	20%
	CONQUER*	2014	866	Pre-DM / MetS	Phentermine/Topiramate	~2 years	79%
	IRIS*	2016	3876	Stroke + insulin resistance	Pioglitazone (TZD)	4.8 years	52%
	SCALE	2017	2254	Obesity + prediabetes	Liraglutide (GLP-1 RA)	~3 years	79%
	CAMELLIA*	2018	12,000	Overweight + high CV risk	Lorcaserin (serotonergic)	3.3 years	19%

* Not primary outcome

PanXR, Diabetes Care 1997;20:537; Tuomilehto J, *N Engl J Med* 2001;344:1343; Knowler WC, *N Engl J Med* 2002;346:393; Chiasson JL, *Lancet* 2002;359:2072; Torgerson JS, *Diabetes Care* 2004;27:155; Gerstein HC, *Lancet* 2006;368:1096; NAVIGATOR Study Group, *N Engl J Med* 2010;362:1463; Defronzo RA, *N Engl J Med* 2011;364:12; ORIGIN Trial Investigators, *N Engl J Med* 2012;367:319; Garvey WT, *Diabetes Care* 2014;37:912; Inzucchi SE, *Diabetes Care* 2016;39:1684; LeRoux CW, Lancet 2017;389:1399; Bohula EA *Lancet* 2018;392:2269; Inzucchi SE 80th Scientific Sesssions, ADA June 2020

Long-term follow-up of the DPP participants: DPP-OS

- 1996-2001
- 3234 persons with preDM (IGT + FPG >95)
- Interventions: Lifestyle change (7% body wt loss, 150 min exercise/wk) vs. metformin (850 mg BID), vs. placebo
- 2.8 yrs follow-up
- mean age, 51 yrs
- mean BMI, 34
- 45% minority groups
- DPPOS: Ongoing follow-up after randomized clinical trial completed



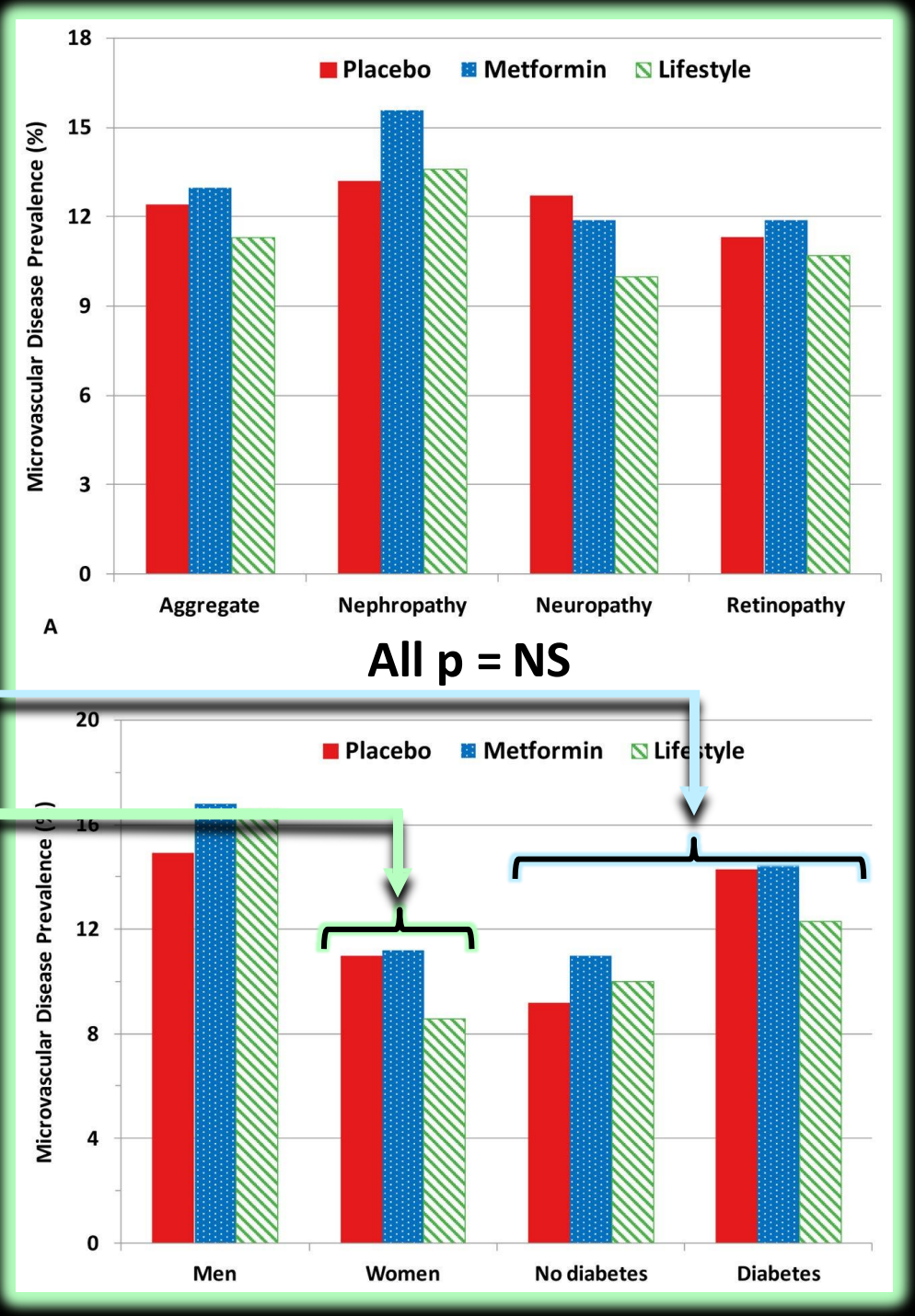
Knowler W *et al. N Engl J Med* 2002;346:393-403
DPP Research Group. *Lancet* 2009;374:1677-86
DPP Research Group. *Lancet Diabetes Endocrinol* 2015;3:86-75

Long-term follow-up of the DPP participants: DPP-OS

- *Microvascular outcomes*

Participants who did <u>not</u> develop T2D during DPP/DPPOS had a 28% lower (RR 0.72, p=0.01) aggregate microvascular disease prevalence than those who did develop T2D - for all treatment groups combined.

In women, the prevalence of aggregate microvascular outcome was 22% lower (RR 0.78, p=0.02) lower in the lifestyle group vs. metformin and 21% lower (RR 0.79, p=0.03) vs. placebo.



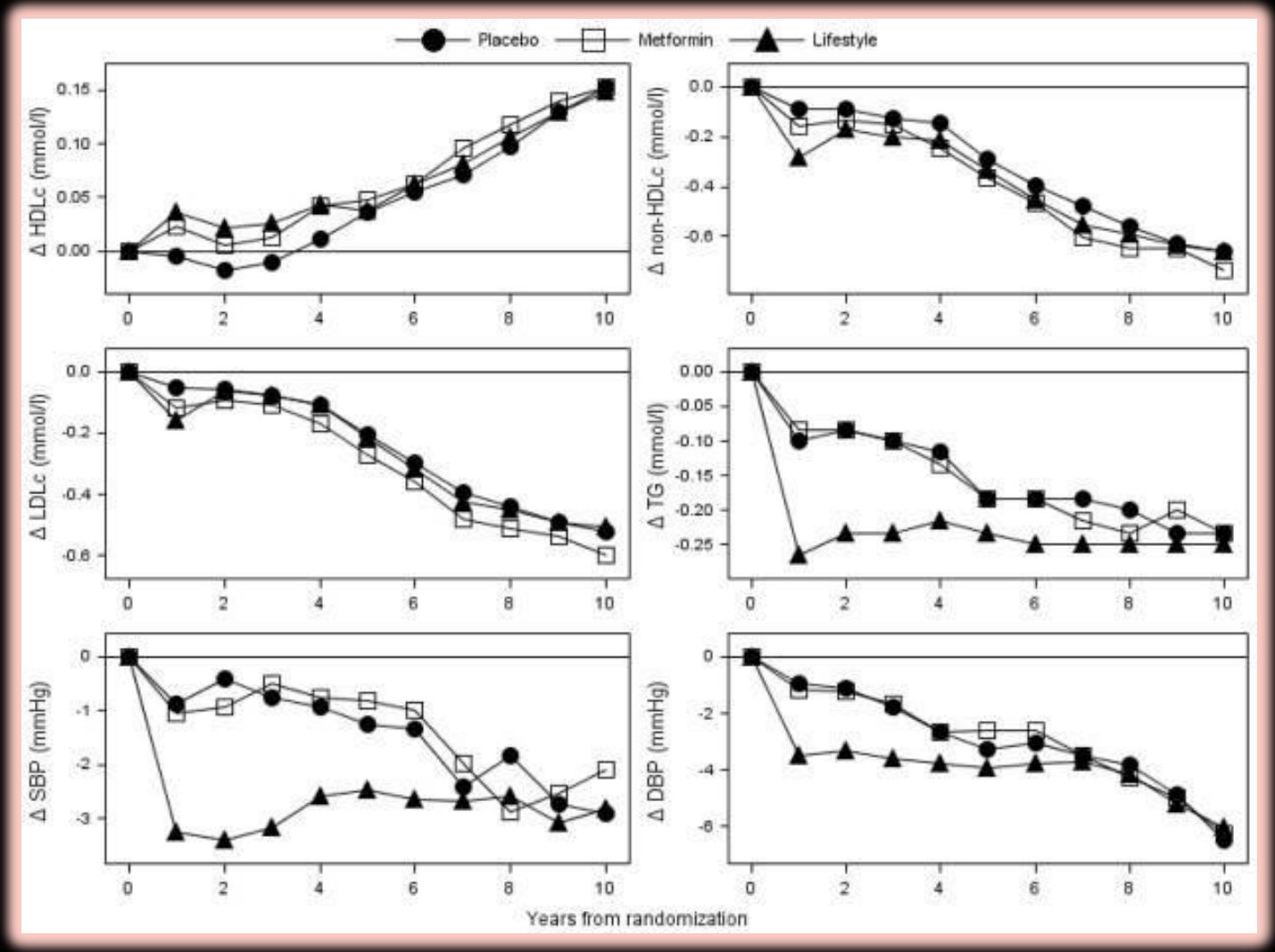
DPPOS OUTCOMES STUDY

Orchard TJ *et al. Diabet Med* 2013;30:46–55

Long-term (10-years) follow-up of the DPP participants: DPP-OS

- *Macrovascular outcomes*

- **Major improvements in SBP (↓ 2-3 mmHg) and DBP (↓ 5-6 mmHg) for LDL-C (↓ 18-21 mg/dl), HDL-C (↑ 5-6 mg/dl), and TGs (↓ 16-28 mg/dl) in all groups, with no between-group differences.**
- **Lipid (*P* <0.012) and BP (*P* <0.09) med use, however, was lower for the lifestyle group during DPP-OS.**



DPPOS OUTCOMES STUDY

Orchard TJ *et al. Diabet Med* 2013;30:46–55

Long-term (10-years) follow-up parMcipan

- *Macrova*

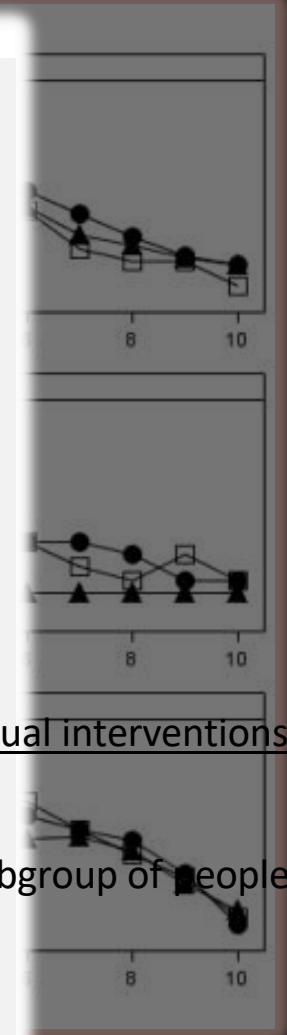
New Data from DPP-OS Shows Persistent Reduction of T2D Development Over 22-Year Average Follow-Up

- Prevention effects in original lifestyle group and metformin groups remain after 22 years: 25% & 18% ↓ risk of T2D, respectively, vs. placebo.
- Those who <u>did not</u> develop T2D had a significant 57% and 37% ↓ risk of retinopathy and nephropathy, respectively.

<u>MACE.</u>

- Despite the benefits seen with DM prevention overall, no significant benefit seen with the <u>individual interventions</u> outcomes
- However, there were favorable trends with metformin in stroke reduction and for MACE in the subgroup of people before age 45.

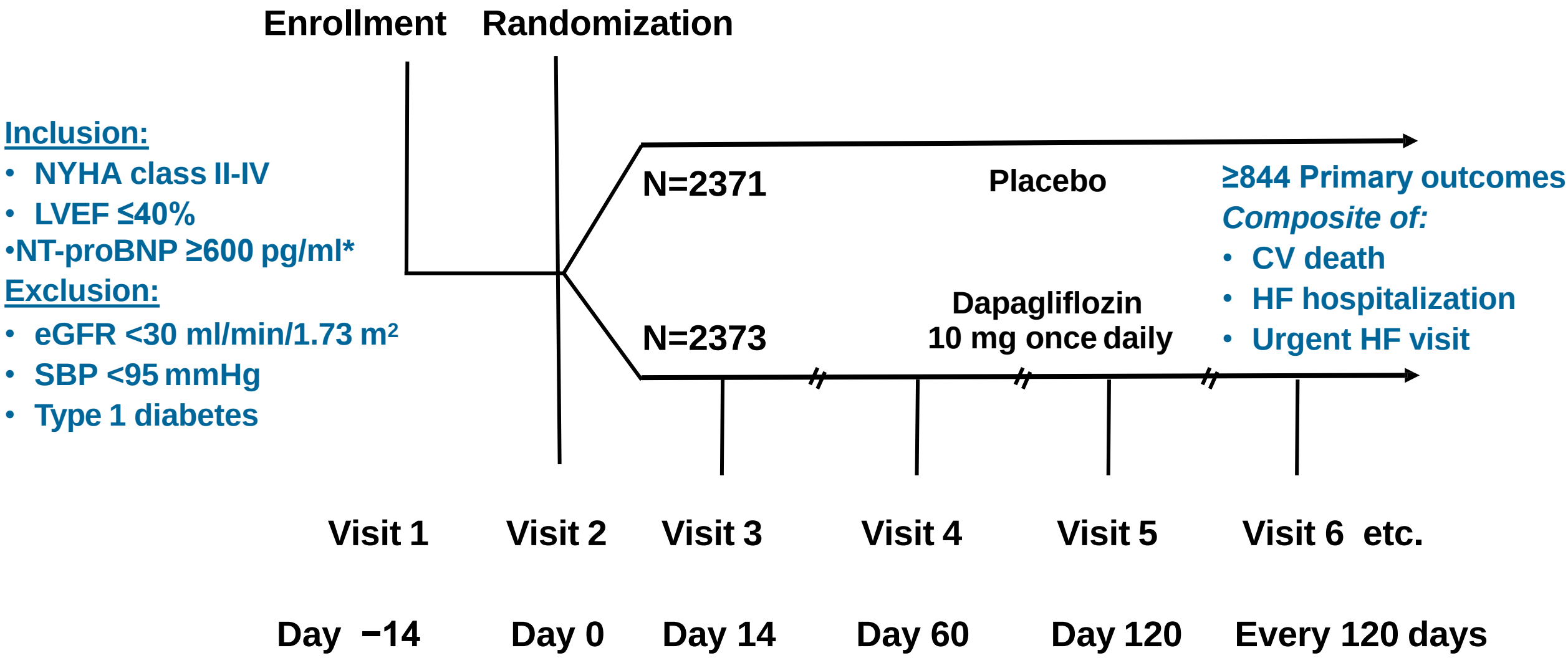
Nathan DM. *80th Scientific Sessions of the ADA*, June 2020



DPPOS OUTCOMES STUDY

Orchard TJ *et al. Diabet Med* 2013;30:46–55

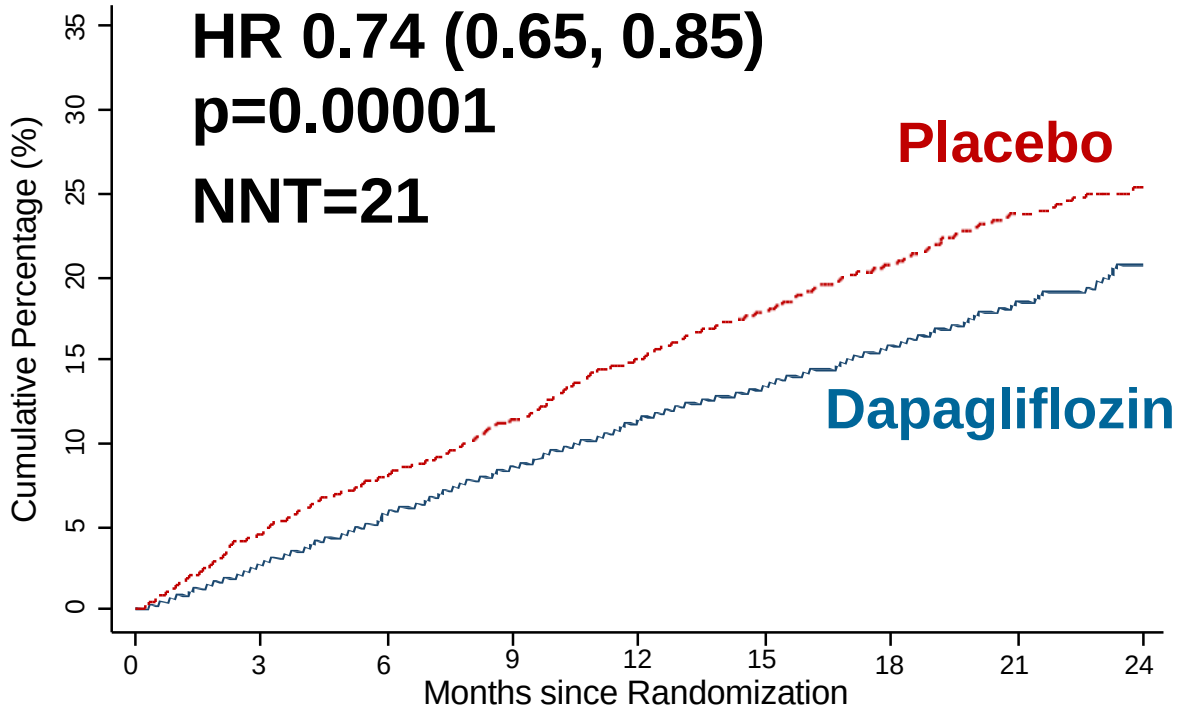
DAPA-HF Design



*≥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

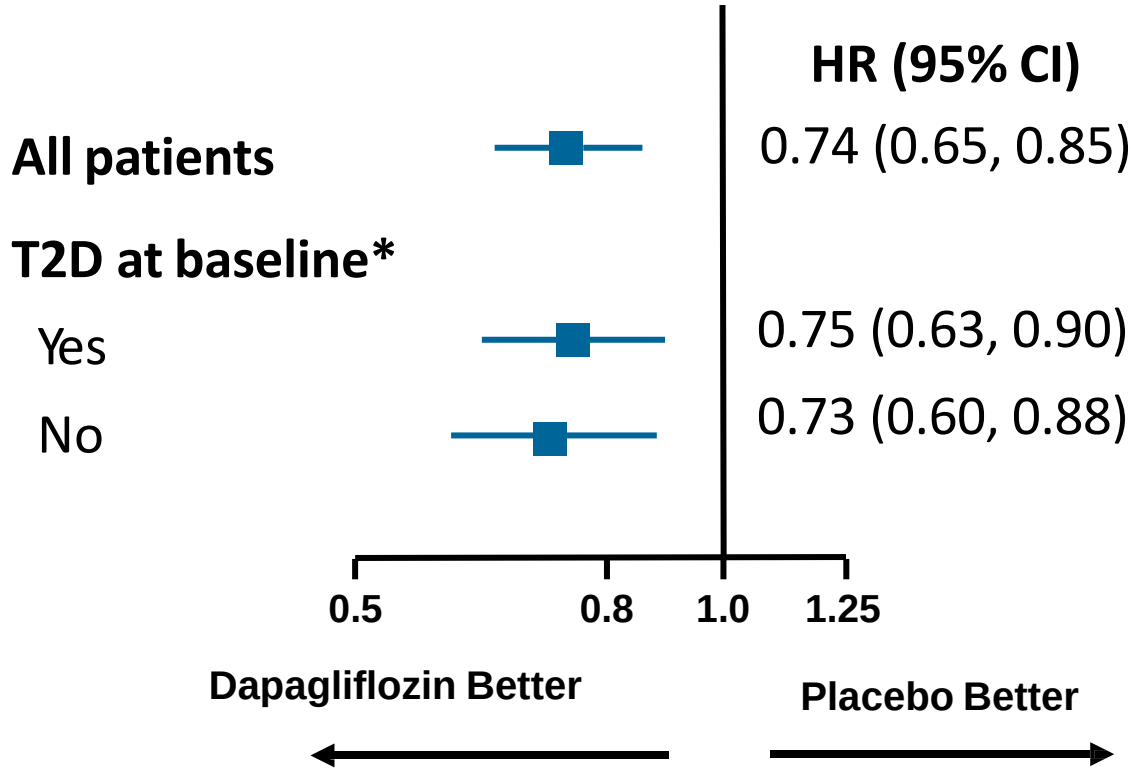
CV Death/HF hospitalization/Urgent HF visit



Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

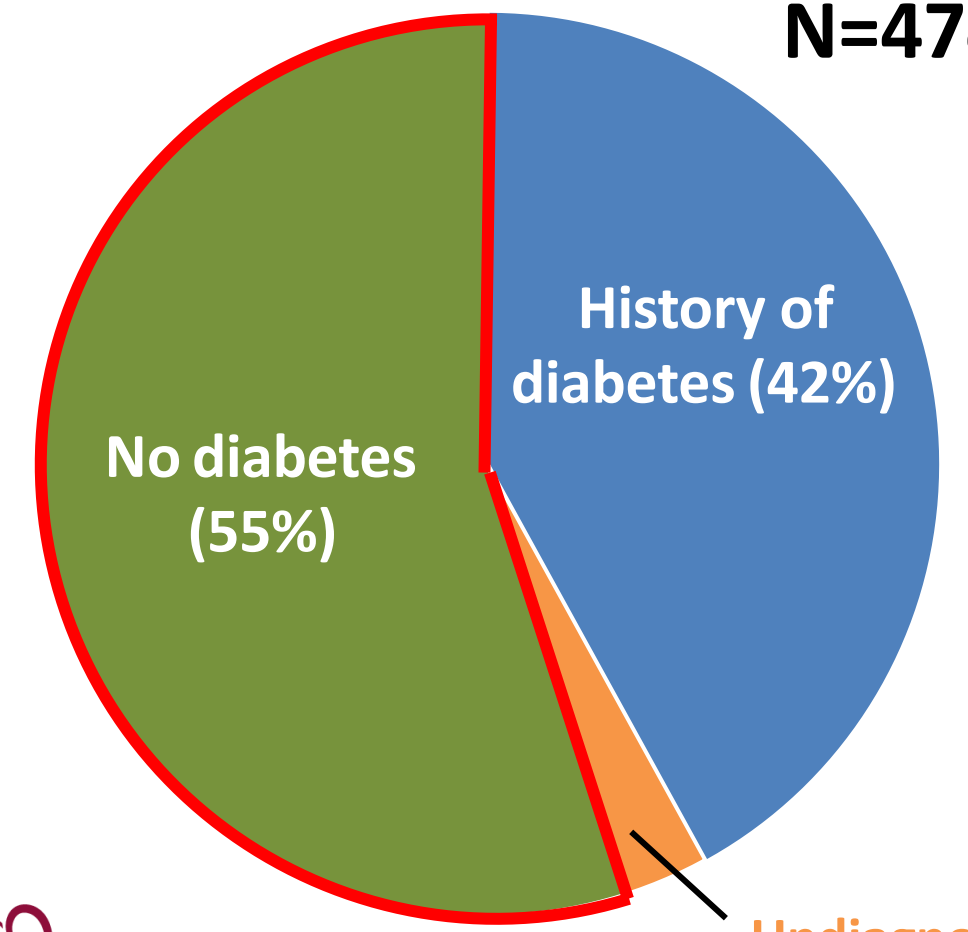
Similar benefit in patients with and without T2DM



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrolment and randomization visits.

McMurray et al. *N Engl J Med* 2019;38:1995-2008

Distribution of Patients by Glycemic Statu
HFrEF Population



DAPAHF

45%

History of diabetes (n=1983)

- Provided by investigators

Undiagnosed diabetes (n=156)

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

55%

No diabetes (n=2605)

- HbA1c <6.5% at Visits 1 and 2

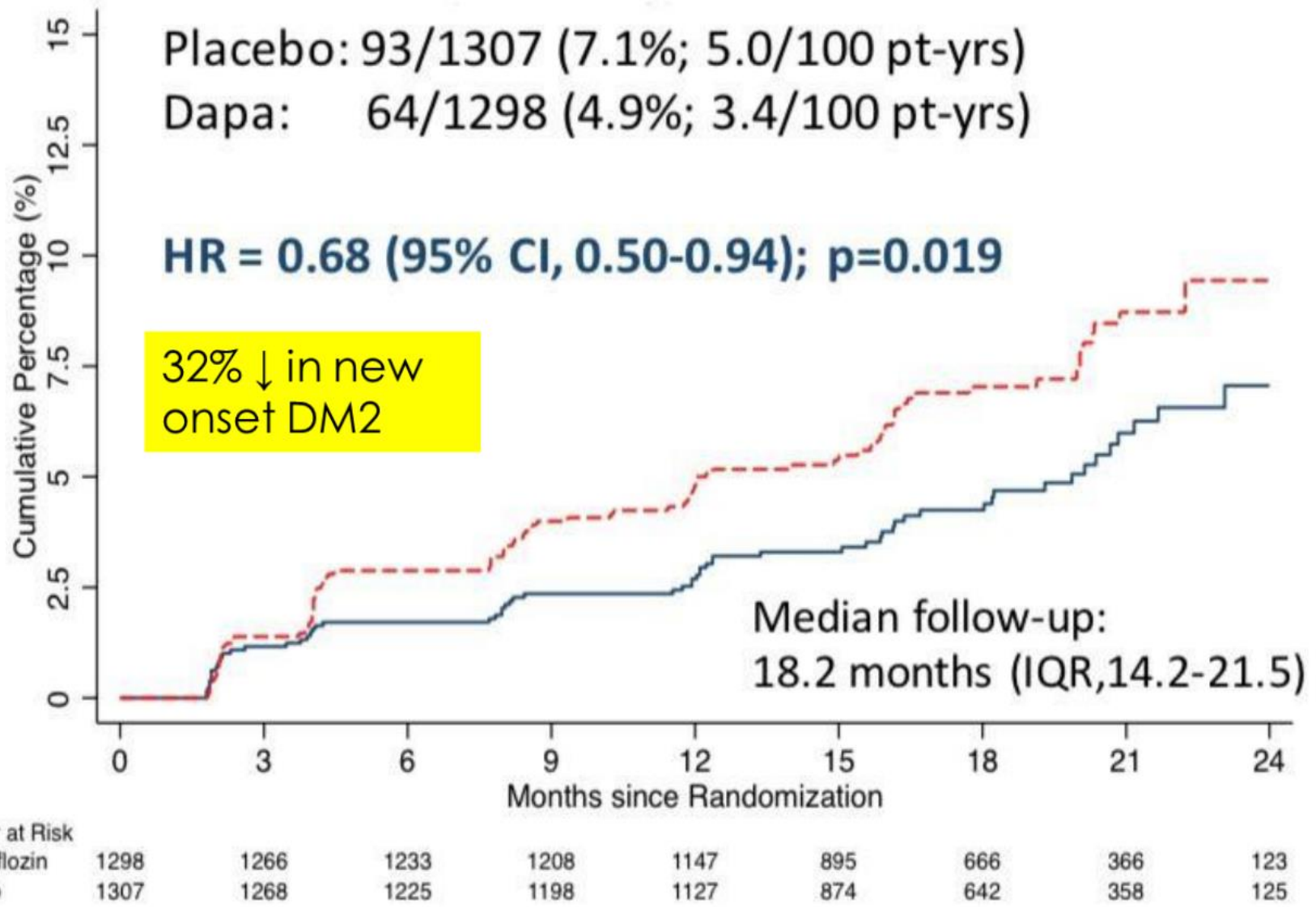
Petrie MC *et al. JAMA* 2020;323:1353-68

Results: 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



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

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

- DYSLIPIDEMIA ROUTE
- HYPERTENSION ROUTE

NORMAL GLYCEMIA

Progression

OVERT DIABETES

PROCEED TO GLYCEMIC CONTROL ALGORITHM

1 PRE-DM CRITERION

MULTIPLE PRE-DM CRITERIA

Intensify Weight Loss Therapies

Low-risk Medications
- Metformin
- Acarbose

Consider with Caution
- TZD
- GLP-1RA

If hyperglycemia persists

LEGEND

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

Type 2 Diabetes- a Chronic Degenerative Disease: Potential for Intervention

Most trials have captured brief vignettes in a chronic life-long disease.

DPP
FDPS
DaQing
STOPNIDDM
DREAM
IND-DPP

UKPDS

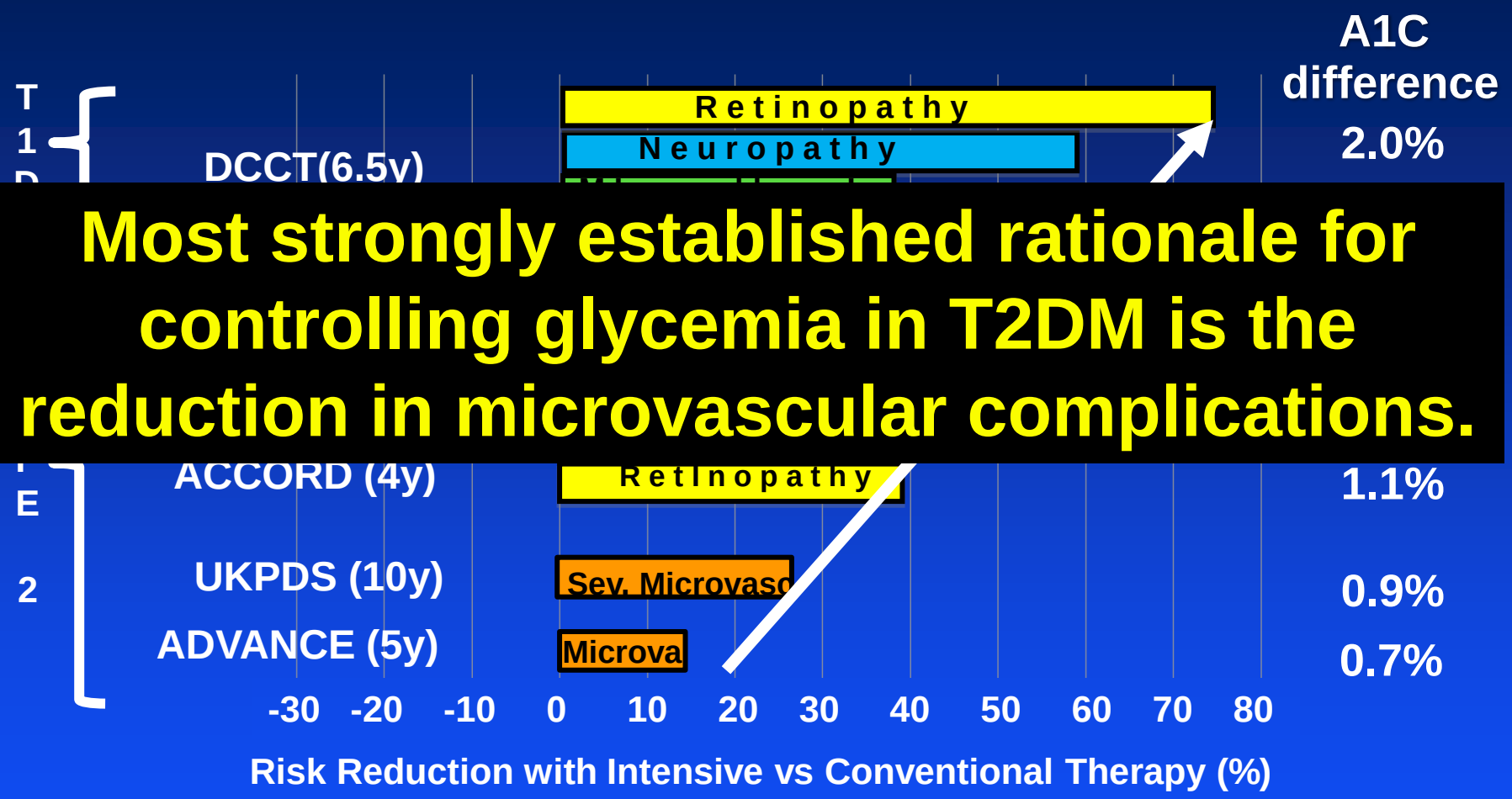
Look AHEAD Action for Health in Diabetes

ACCORD
ADVANCI

Mean DM duration ~11-14 years

CVD safety studies-Median F-U			
EMPA-Reg	3.1	CANVAS	2.4
LEADER	3.8	EXCSEL	3.2
SUSTA			2.6
CARO			1.3
DECLARE	4.2	ELIXA	2.1
REWIND	5.4	VERTIS	3.0

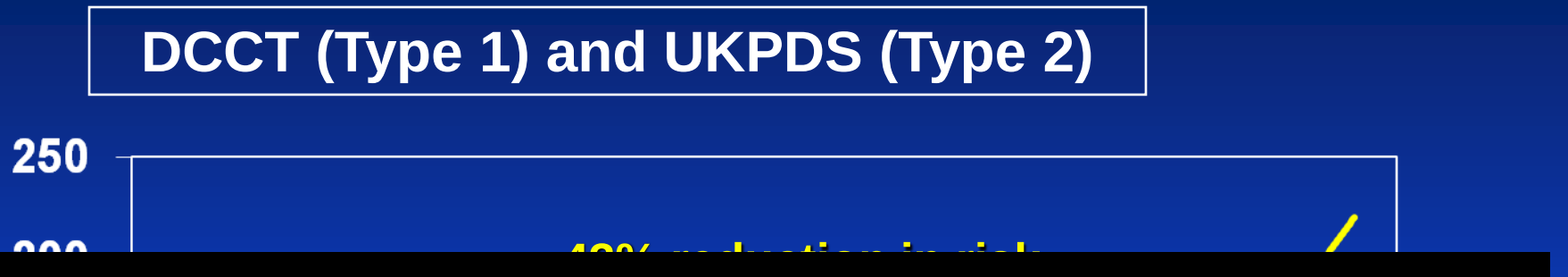
Metabolic Goals: Microvascular Benefits



Most strongly established rationale for controlling glycemia in T2DM is the reduction in microvascular complications.

Reduction in microvascular complications roughly proportional to A1c reduction.

Relationship between Glycemia and Microvascular Complications

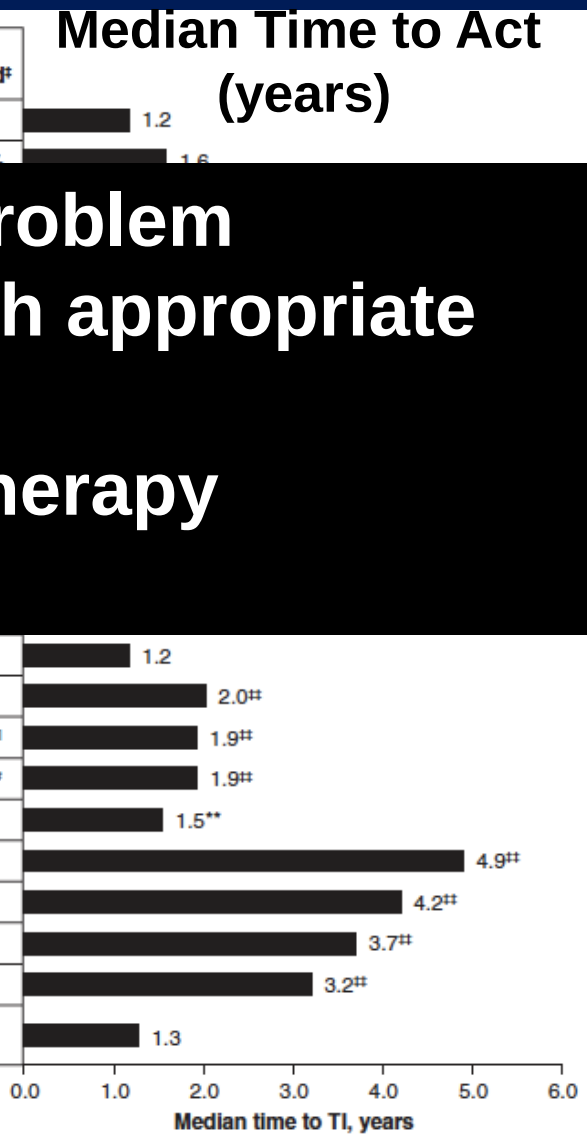


Although lower is better for microvascular complications in both type 1 and 2 diabetes, A1c of 7% was selected as the target as:

1) 7% was the A1c achieved in DCCT and UKPDS;
2) Absolute risks for complications quite low at HbA1c under 7%;
3) Balances benefits, risks and costs.

Scope of the Problem: Therapeutic Inertia

First author, year	Country	Study period	*N**	Index treatment	TI (addition to index treatment)	Patients who received TI, %†	HbA1c threshold‡
						64	≥7.0%
						Not reported	7.0–7.9%
						78	≥7.5%‖
Lin, 2015[43]	USA	2007–2012	79,805	≥1 OAD	OAD or injectable	48	≥7.0%
						50	Variable¶
						50	Variable#
Ajmera, 2015[18]	USA	2007–2012	16,653	2 OADs	OAD or insulin	49	≥8.0%
Rubino, 2007[54]	UK	2000–2006	2,501	≥2 OADs	Insulin	34	≥8.0%
						31	≥9.0%
Khunti, 2016[38]	UK	2004–2013	6,072	Basal insulin	Bolus or premix insulin or GLP-1 RA	31	≥7.5%
						Not reported	≥8.0%
Schwab, 2016[56]	USA	2008–2009	8,463	Any drug(s)	OAD or injectable or switch	Not reported	≥9.0%

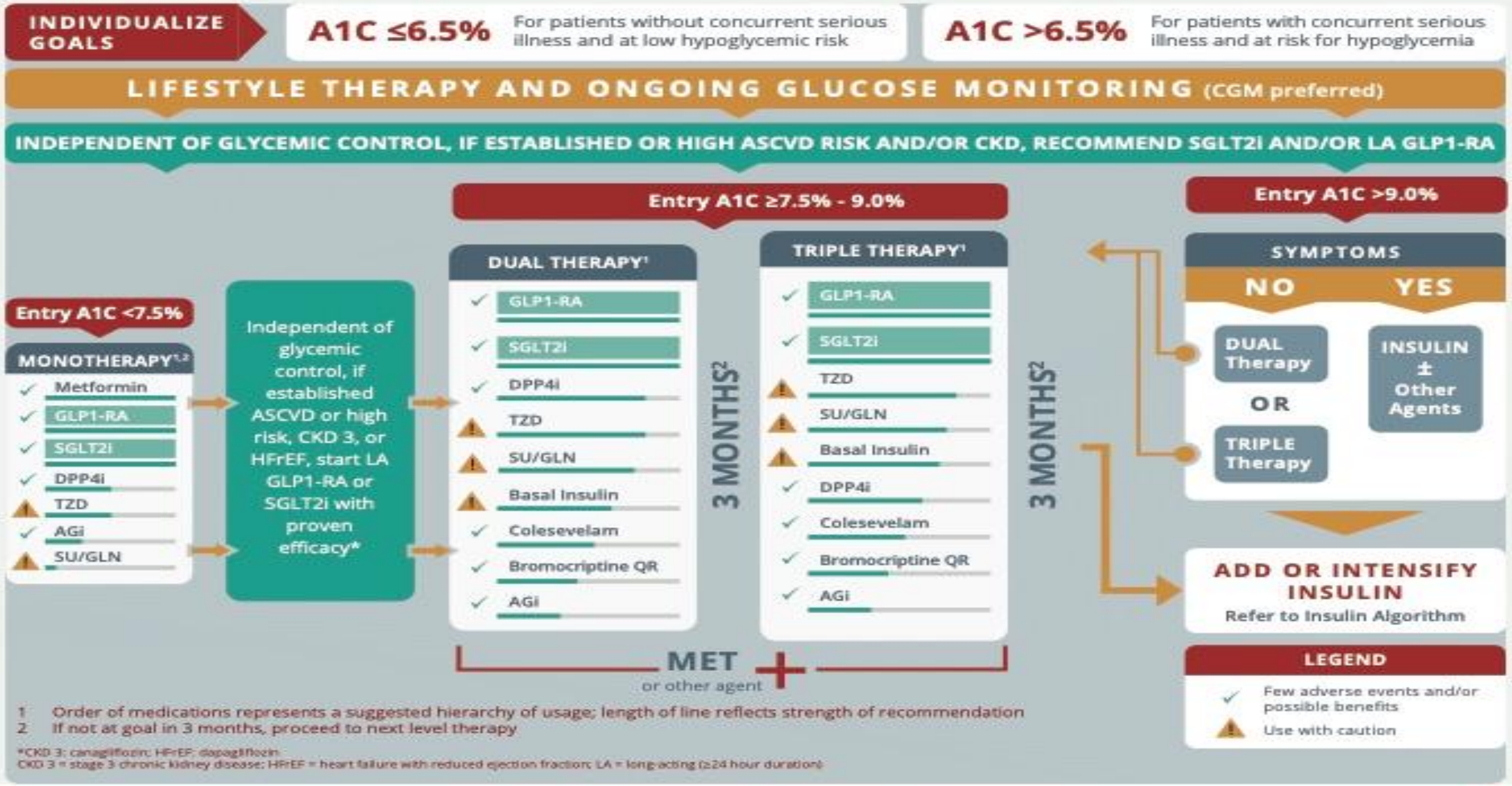


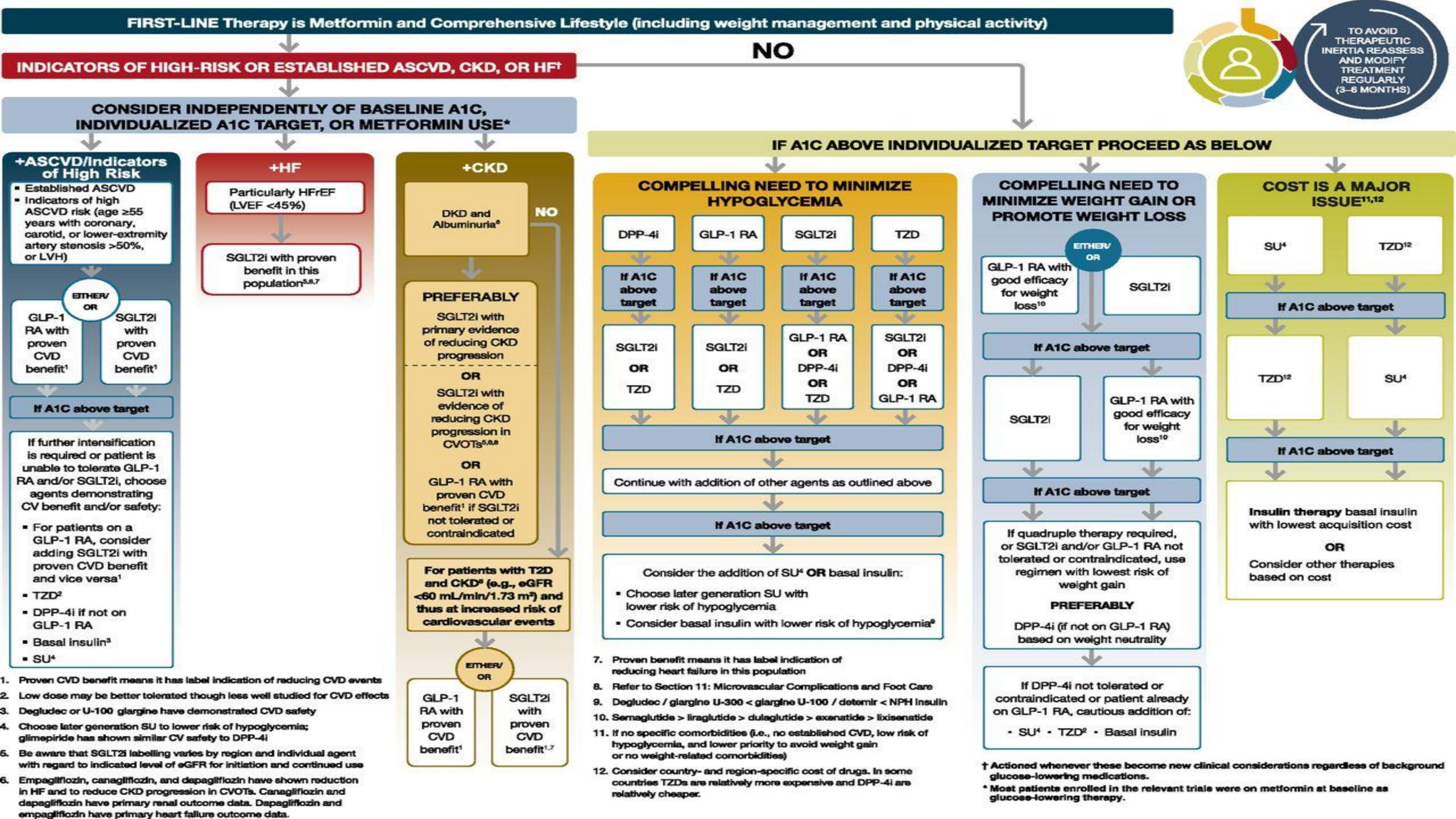
Summary of Scope of Problem

- Not all patients with type 2 reach appropriate metabolic goals
- Clinicians are slow to change therapy

Khunti K, 2018
Diabet Obes Metab

GLYCEMIC CONTROL ALGORITHM





1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

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

Glycemic Control Not at Goal*

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**

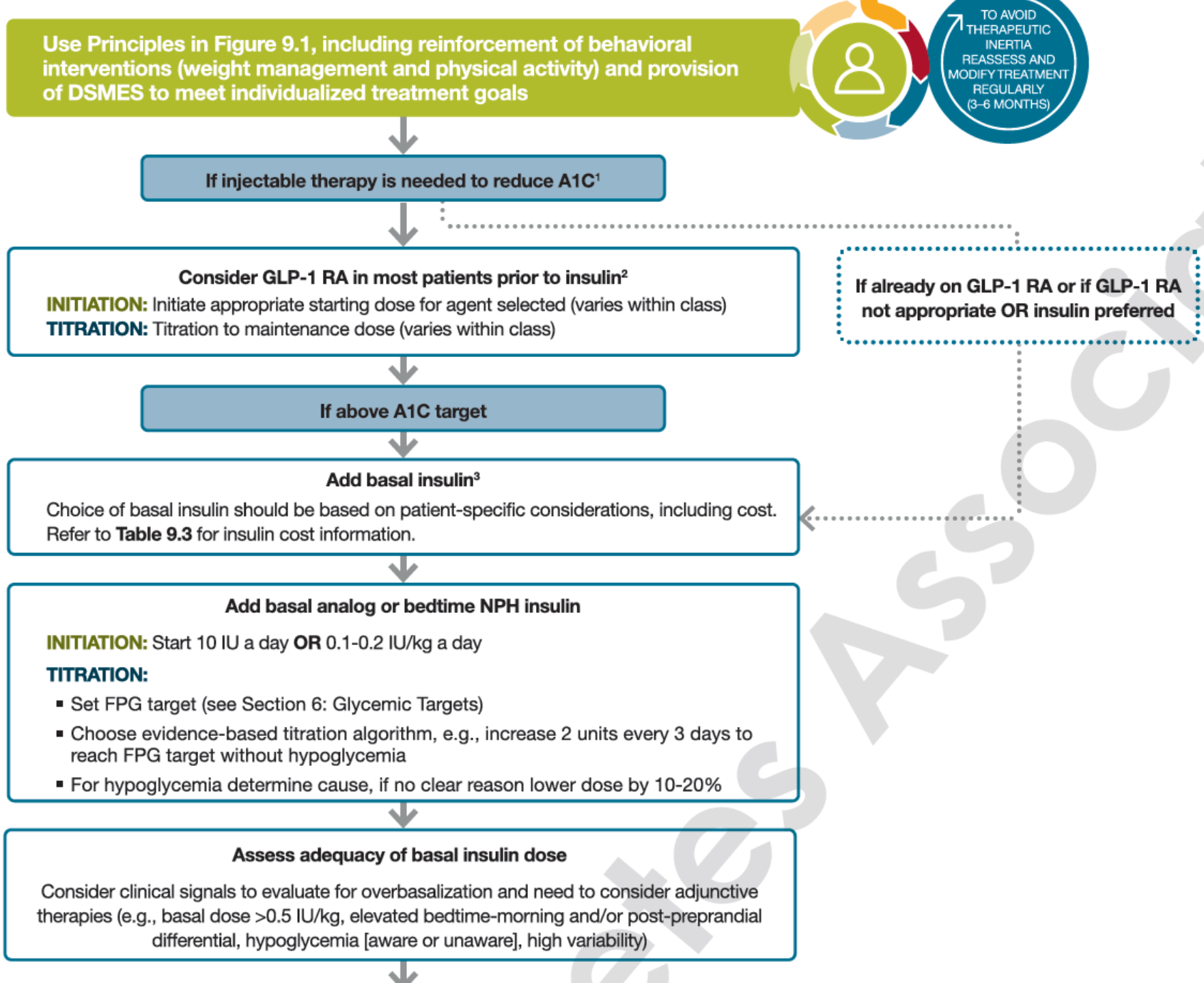
Basal Bolus

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

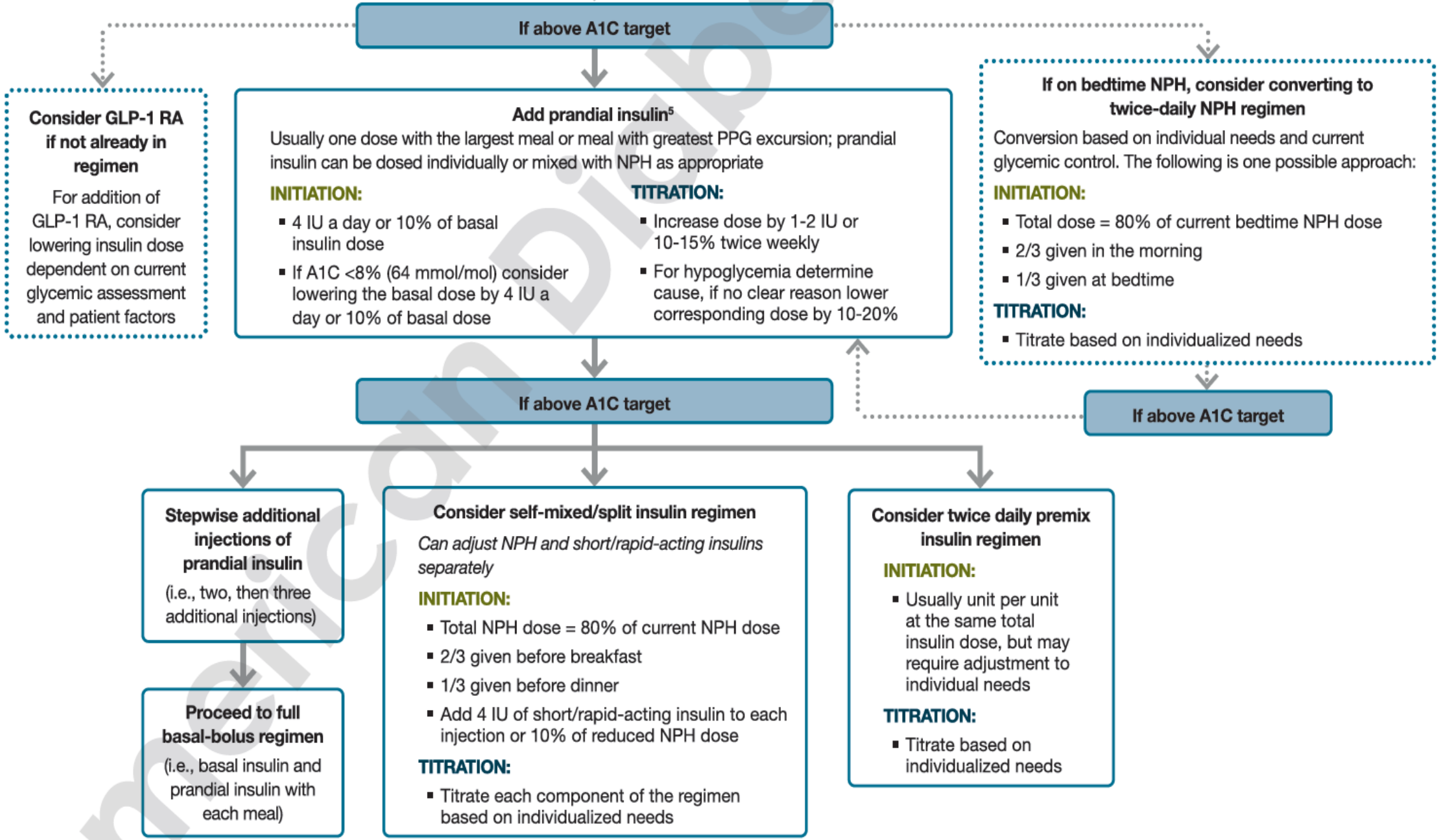
- **Start: 50% of TDD in three doses before meals**

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%

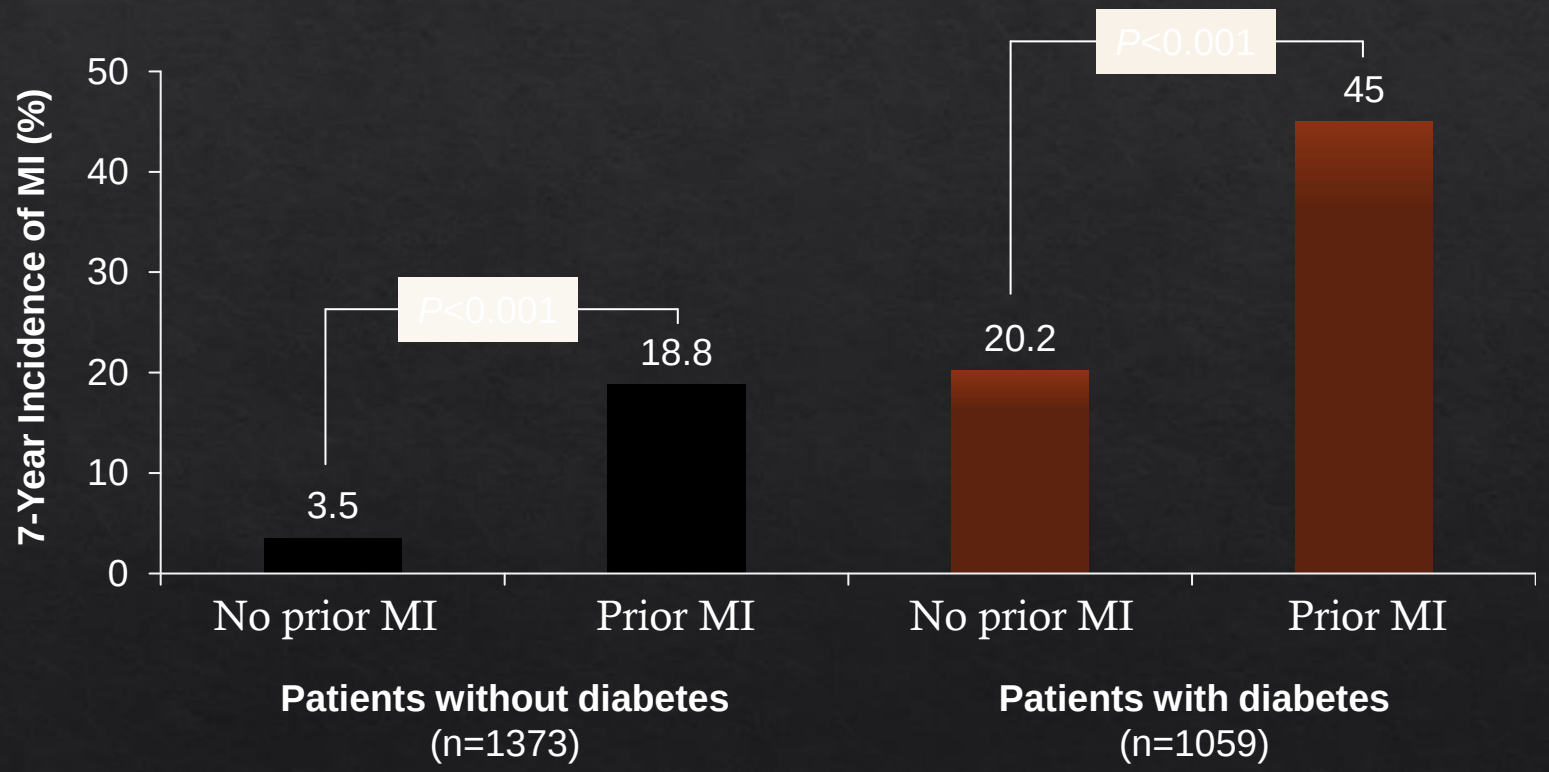

Use Principles in Figure 9.1, including reinforcement of behavioral interventions (weight management and physical activity) and provision of DSMES to meet individualized treatment goals
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
If injectable therapy is needed to reduce A1C[1]
Consider GLP-1 RA in most patients prior to insulin[2]
INITIATION: Initiate appropriate starting dose for agent selected (varies within class)
TITRATION: Titration to maintenance dose (varies within class)
If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred
If above A1C target
Add basal insulin[3]
Choice of basal insulin should be based on patient-specific considerations, including cost. Refer to Table 9.3 for insulin cost information.
Add basal analog or bedtime NPH insulin
INITIATION: Start 10 IU a day OR 0.1-0.2 IU/kg a day
TITRATION:
Set FPG target (see Section 6: Glycemic Targets)
Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG target without hypoglycemia
For hypoglycemia determine cause, if no clear reason lower dose by 10-20%
Assess adequacy of basal insulin dose
Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., basal dose >0.5 IU/kg, elevated bedtime-morning and/or post-preprandial differential, hypoglycemia [aware or unaware], high variability)

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT



SHOULD ANTIHYPERGLYCEMIC THERAPY BE FOCUSED ON REDUCING CARDIOVASCULAR RISK?

Diabetes and Cardiovascular Risk

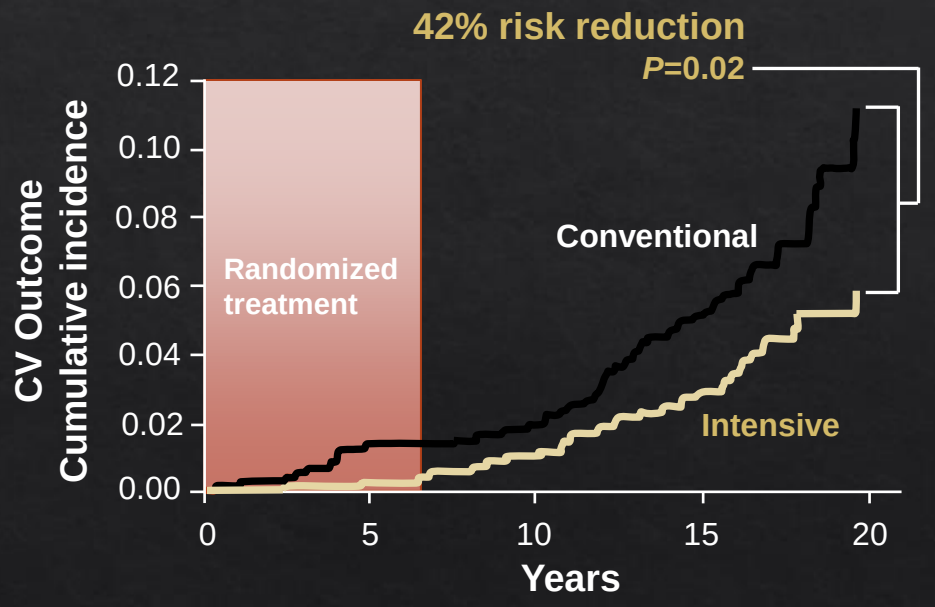


MI, myocardial infarction.

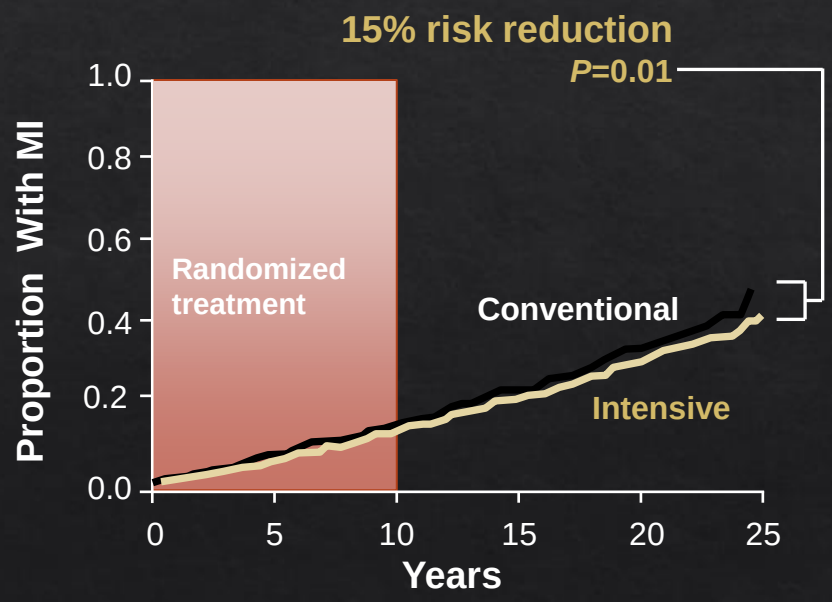
Haffner SM, et al. *N Engl J Med*. 1998;339:229-234.

Intensive Glycemic Control Reduces Long-term Macrovascular Risk

DCCT
T1D, 5-6 years duration
(N=1441)



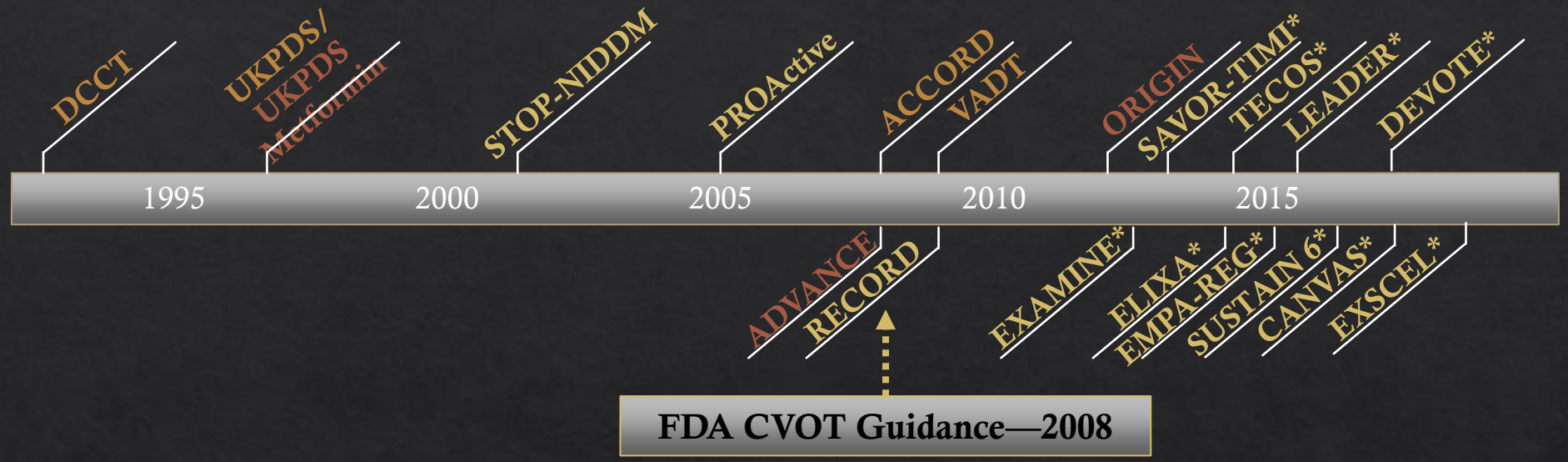
UKPDS
T2D, newly diagnosed
(N=4209)



CV, cardiovascular; DCCT, Diabetes Control and Complications Trial; MI, myocardial infarction; T1D, type 1 diabetes; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study.

Nathan DM, et al. *N Engl J Med*. 2005;353:2643-2653. Holman RR, et al. *N Engl J Med*. 2008;359:1577-1589.

Timeline of Major Diabetes Outcomes Trials



Blue = Intensive vs standard control using same set of glucose-lowering agent(s)
Purple = Intensive control with a specific agent vs standard care
Red = Placebo- or active-controlled study
* = FDA-mandated cardiovascular safety trial

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CANVAS, Canagliflozin Cardiovascular Assessment Study; DCCT, Diabetes Control and Complications Trial; DEVOTE, Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG, EMPA-REG OUTCOME trial; Exenatide Study of Cardiovascular Event Lowering; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ORIGIN, Outcome Reduction with an Initial Glargine Intervention; PROActive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; SUSTAIN, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Cardiovascular Outcomes Trials: A Brief History

- 2008 FDA guidance mandating assessment of CV safety of all antihyperglycemic agents in RCTs
  - Designed as noninferiority studies to demonstrate study drug was not associated with more MACE than placebo
    - Some study designs tested for superiority if noninferiority criteria were met
  - Primary endpoint: composite of cardiovascular death, nonfatal MI, and nonfatal stroke
    - Some primary endpoints included additional components

MACE = major adverse cardiovascular events; RCTs, randomized controlled trials.

FDA. Guidance for industry: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf.

Large CV Outcomes Trials in Diabetes (Non-Insulin)

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	sulfonylurea	placebo
N	16,500	5,400	14,700	6,000	8,300
Results	2013	2013	2015	2017	2017

Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP1-RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide
Comparator	placebo	placebo	placebo	placebo	placebo
N	16,500	14,700	6,000	5,400	8,300
Results	2016	2015	2016	2018	2019

Study	EMPA-REG	CANVAS	DECLARE	NCT01986881
SGLT-2-i	empaglifozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
N	7,020	4,330	17,160	3900
Results	2015	2017	2019	2020

HARMONY
Albiglutide
Placebo
9,463
2018

Preliminary

MACE Events in CVOTs with GLP1 Receptor Agonists

		Cardiovascular Benefits				
	Subjects with Established CVD	Non-Fatal MI	Non-Fatal CVA	CV Death	3-Pt MACE	Comments
Liraglutide **LEADER** 9340 Patients	~81%	Neutral	Neutral	**Positive**	**Positive**	3-Pt MACE Driven by significant ↓ in CV death Relative risk reduction ~22%
Semaglutide SQ **SUSTAIN-6 Study** 3297 Patients	~83%	Neutral	**Positive**	Neutral	**Positive**	3-Pt MACE Driven by significant ↓ in non-fatal CVA Relative risk reduction ~39%
Semaglutide PO **PIONEER-6 Study** 3183 Patients	~85%	Neutral	Neutral	**Positive**	**Positive**	3-Pt MACE Driven by significant ↓ in CV death Relative risk reduction ~51%
Lixisenatide **ELIXA STUDY** 6068 Patients	100%	Neutral	Neutral	Neutral	Neutral	NA
Exenatide **EXCEL Study** 14752 Patients	~73%	Neutral	Neutral	Neutral	Neutral	3-Pt MACE Barely missed significance, HR 0.91 (p=0.06) Relative risk reduction ~9%
Albiglutide **HARMONY Study** 9463 Patients	100%	**Positive**	Neutral	Neutral	**Positive**	3-Pt MACE Driven by significant ↓ in fatal and non-fatal MI Relative risk reduction ~25%
Dulaglutide **REWIND Study** 9901 Patients	~31%	UNK	UNK	UNK	**Positive**	Full results not released/published

Hupfer C, Mudaliar S. Diab Obes Metab, 2019

MACE Events in CVOTs with SGLT2 Inhibitors

		Cardiovascular Benefits					
	Subjects with Established CVD	Non-Fatal MI	Non-Fatal CVA	CV Death	3-Pt MACE	CV Death, HHF (Pre-specified Primary Endpoint)	Comments
Empagliflozin **EMPA-REG** 7020 Patients	100%	Neutral	Neutral	**Positive**	**Positive**	NA	3-pt MACE Driven by significant ↓CV death Relative Risk Reduction 38%
Canagliflozin **CANVAS Program** 10142 Patients	66%	Neutral	Neutral	Neutral	**Positive**	NA	3-pt MACE HR 0.86 Relative Risk Reduction 14%
Dapagliflozin **DECLARE-TIMI** 17160 Patients	41%	Neutral	Neutral	Neutral	Neutral	**Positive**	Driven by significant ↓CV death Relative Risk Reduction 51%

Hupfer C, Mudaliar S. Diab Obes Metab, 2019

FDA News Release

Canagliflozin (*Invokana*) Gets FDA Nod for CV Protection

Megan Brooks

October 31, 2018

8 Read Comments

Add to Email Alerts

The US Food and Drug Administration (FDA) has approved the sodium-glucose cotransporter type 2 (SGLT2) inhibitor canagliflozin (*Invokana*, Janssen) to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes who have established cardiovascular disease (CVD).

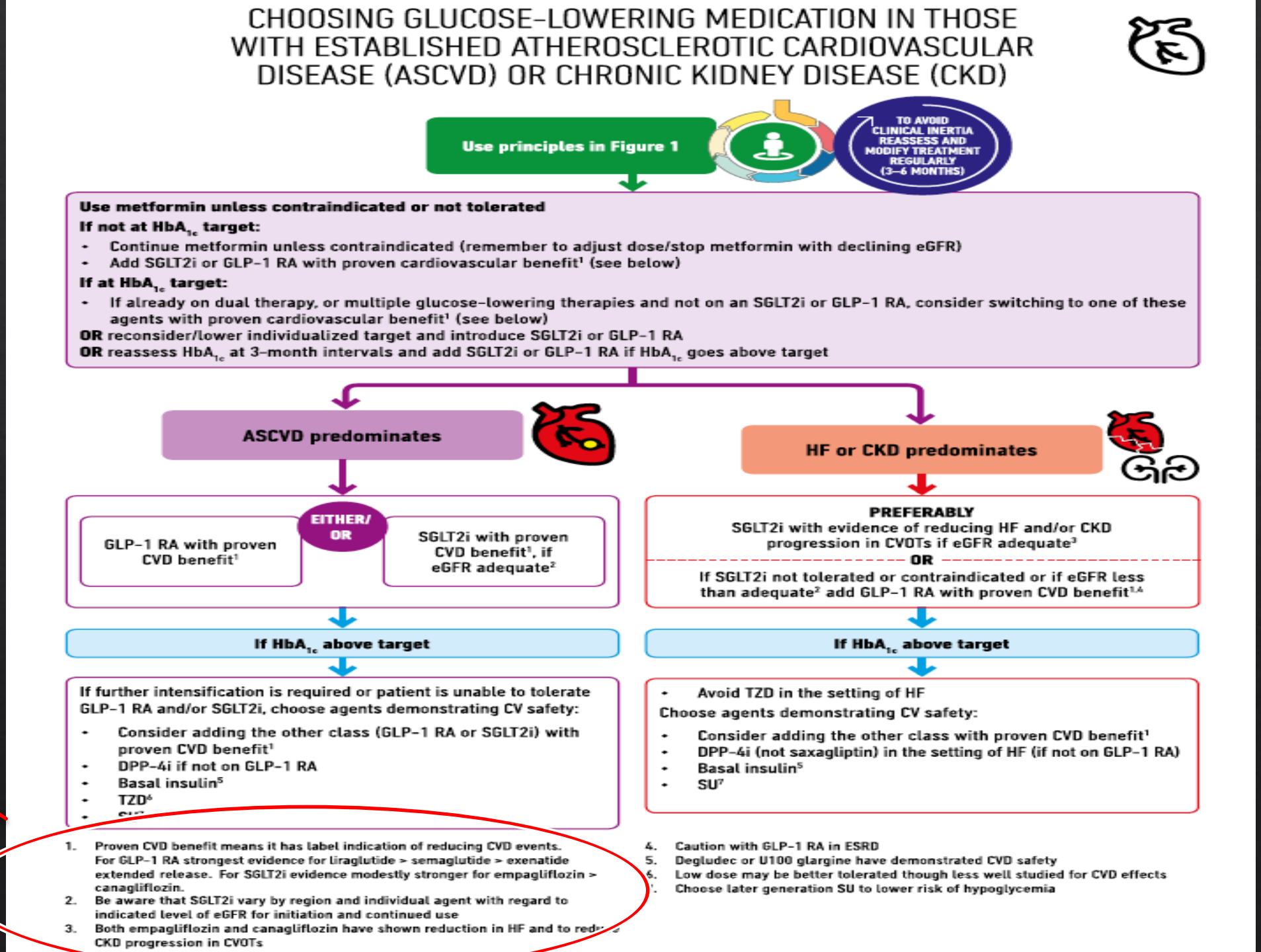
With FDA approval of the supplemental new drug application, canagliflozin becomes the first oral diabetes drug indicated to reduce the risk of myocardial infarction (MI), stroke, or death due to a cardiovascular cause, the company said in a news release.

Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

https://doi.org/10.2337/dci18-0033

SGLT2i:
empagliflozin ,canagliflozin
GLP1:
liraglutide > semaglutide > exenatide LAR

Now in SGLT2i:
Empagliflozin: CV death
Canagliflozin: nonfatal MI, nonfatal stroke and CV death
Dapaglifozin: Hospitalizations for HF



CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

In those WITHOUT established ASCVD OR CKD

Use principles in Figure 1

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

First–line therapy is metformin
If HbA_{1c} is ≥17 mmol/mol (1.5%) above individualized HbA_{1c} target consider early combination therapy

If HbA_{1c} above target

EITHER/ OR

GLP–1 RA with good efficacy for weight loss[1]

SGLT2i if eGFR adequate[2]

If HbA_{1c} above target

SGLT2i if eGFR adequate[2]

GLP–1 RA with good efficacy for weight loss[1]

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP–1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain
PREFERABLY
DPP–4i (if not on GLP–1 RA) based on weight neutrality

If DPP–4i not tolerated or contraindicated or patient already on GLP–1 RA, cautious addition of:
• SU[3] • TZD[4] • Basal insulin

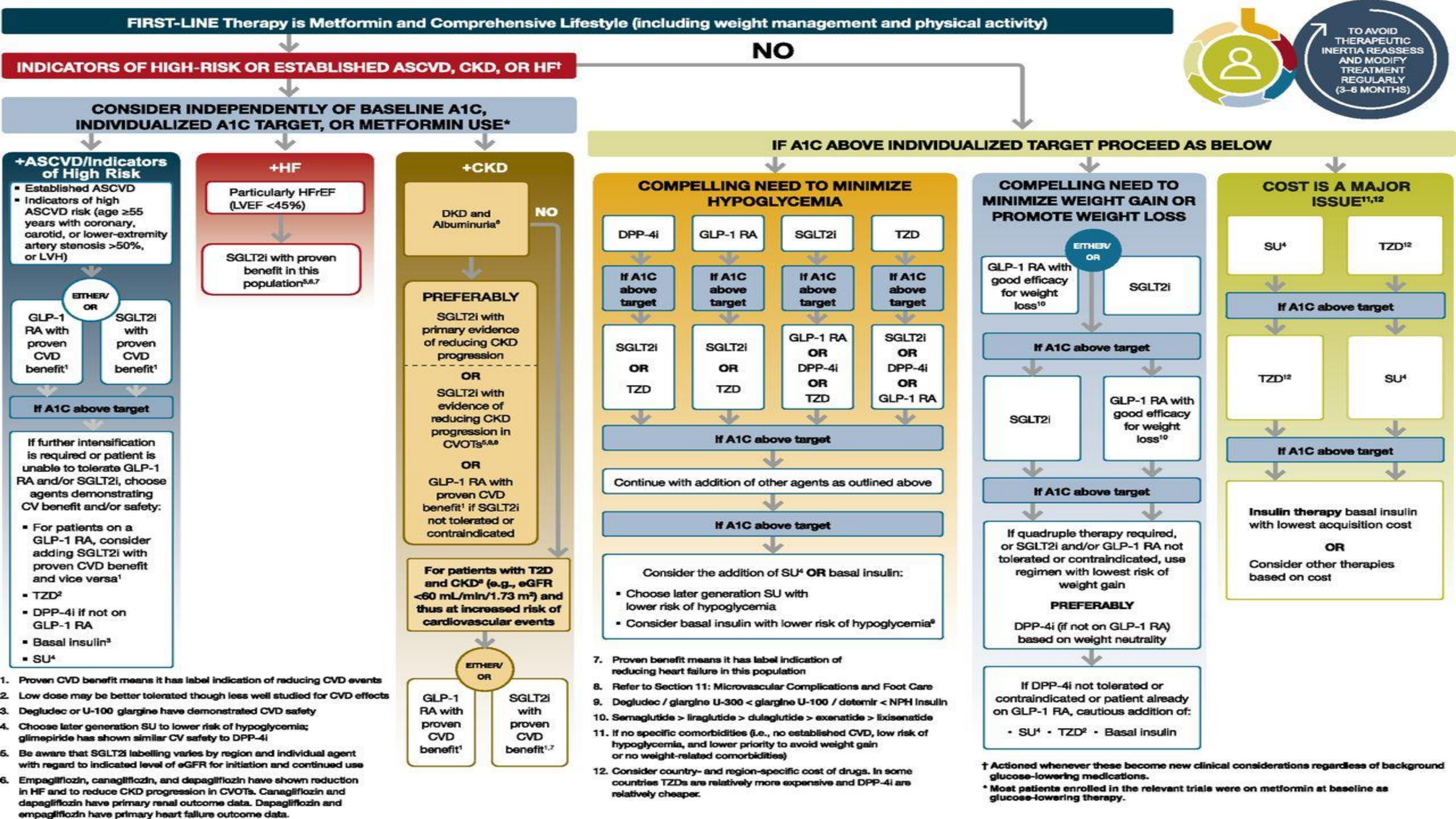
Implement strategies for maximizing weight loss

General lifestyle advice
- Medical nutritional therapy
- Eating patterns
- Physical activity

Non–surgical energy restriction for weight loss
Weight loss of 15 kg can lead to remission of T2DM in patient <6 years' duration, **consider evidence–based weight loss programs**

Consider medication for weight loss

Consider metabolic surgery



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

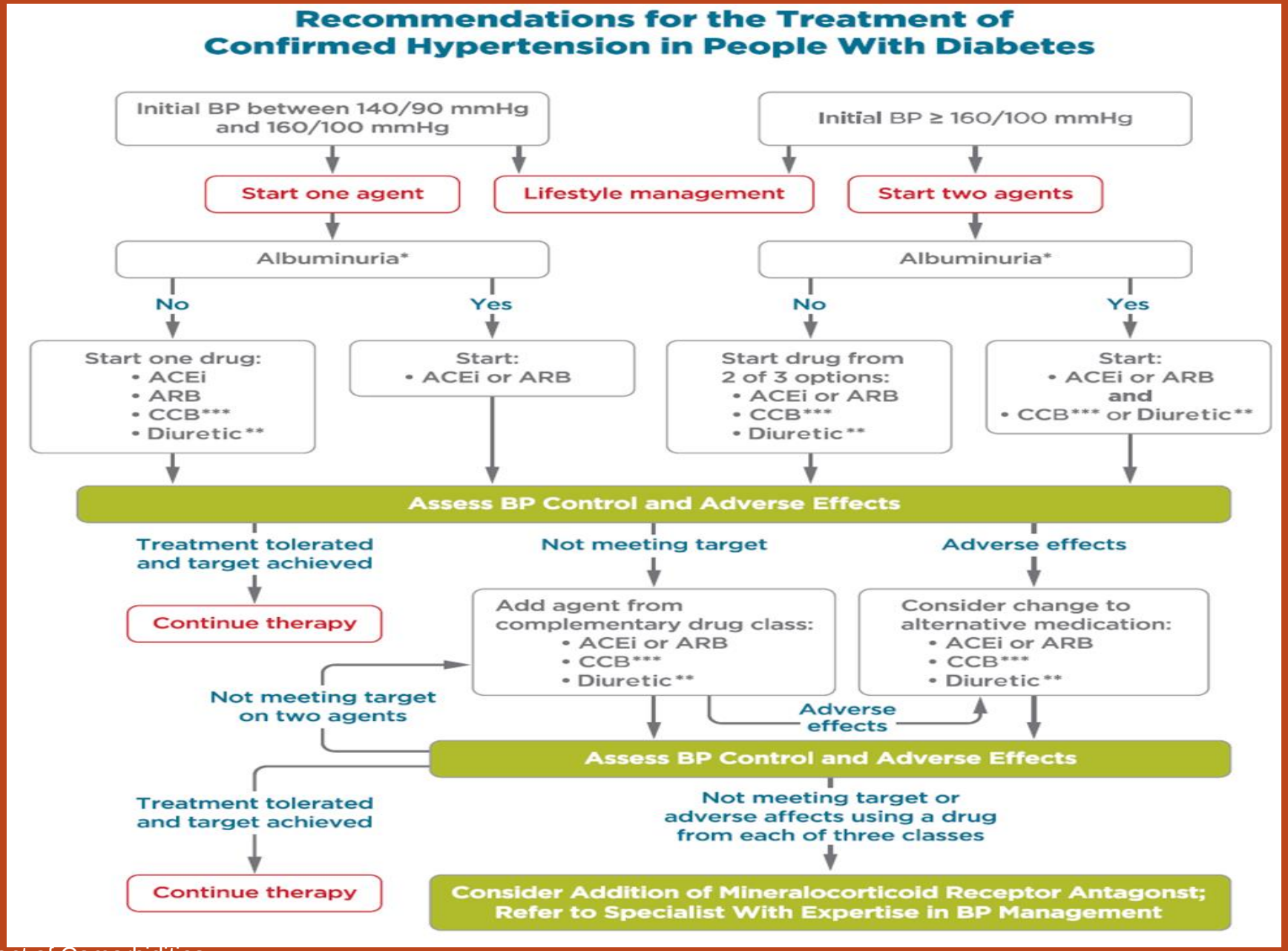
Algorithm for Individualizing Glycemic Targets

Ismail-Beigi F, Moghissi E, et al. *Ann Intern Med*. 2011;154:554-559.

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT

10.4 For individuals with diabetes and hypertension at higher cardiovascular risk (existing atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk >15%), a blood pressure target of <130/80 mmHg may be appropriate, if it can be safely attained. **C**

10.5 For individuals with diabetes and hypertension at lower risk for cardiovascular disease (10-year atherosclerotic cardiovascular disease risk <15%), treat to a blood pressure target of <140/90 mmHg. **A**



Comprehensive Medical Evaluation and Assessment of Comorbidities:
tandards of Medical Care in Diabetes - 2019. *Diabetes Care* 2018; 41 (Suppl. 1): S28-S37

Goal BP and Initial Therapy in Diabetes to Reduce CV / Renal Risk?

Group	Goal BP (mmHg)	Initial Therapy
ADA (2018)	<140/90;high risk <130/80	ACE Inhibitor/ARB (only if nephropathy or heart failure present)
ACC/AHA BP (2017)	<130/80	ACE Inhibitor/ARB*
KDIGO/KDOQI (NKF) (2013)	<140/90	ACE Inhibitor/ARB*
2014 Expert Panel Report (2013)	<130/80	ACE Inhibitor/ARB*
KDOQI (NKF) (2004)	<130/80	ACE Inhibitor/ARB*
JNC 7 (2003)	<130/80	ACE Inhibitor/ARB*
Am. Diabetes Assoc (2003)	<130/80	ACE Inhibitor/ARB*
Canadian HTN Soc. (2002)	<130/80	ACE Inhibitor/ARB*
Am. Diabetes Assoc (2002)	<130/80	ACE Inhibitor*
Natl. Kidney Foundation (2000)	<140/80	ACE Inhibitor
British HTN Soc. (1999)	<140/80	ACE Inhibitor
JNC VI (1997)	<130/85	ACE Inhibitor

* Indicates use with diuretic

INTENSIVE BLOOD PRESSURE MANAGEMENT MAY SAVE LIVES

WHAT'S THE BEST WAY TO TREAT HIGH BLOOD PRESSURE IN PATIENTS 50 AND OLDER?
The SPRINT trial enrolled more than 9,300 participants at UAB and other locations to find out. Investigators divided them into two groups:

STANDARD TREATMENT

TARGET: 140 mmHg Systolic BP

THERAPY:

Avg. 2 different blood pressure medications

INTENSIVE TREATMENT

TARGET: 120 mmHg Systolic BP

THERAPY:

Avg. 3 different blood pressure medications

RESULTS: ABOUT **30%** lower rates of heart attack, heart failure, and other cardiovascular events; ABOUT **25%** lower risk of death

among participants receiving intensive treatment

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Lifestyle Modifications

- Weight loss
- Sodium intake less than 2,300 mg /day
- Increase consumption of fruits and vegetables
  - 8-10 servings per day
- Alcohol intake
  - 2 for men
  - 1 for women
- Low fat dairy products
  - 2-3 servings per day

Table 10.2—Recommendations for statin and combination treatment in adults with diabetes

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

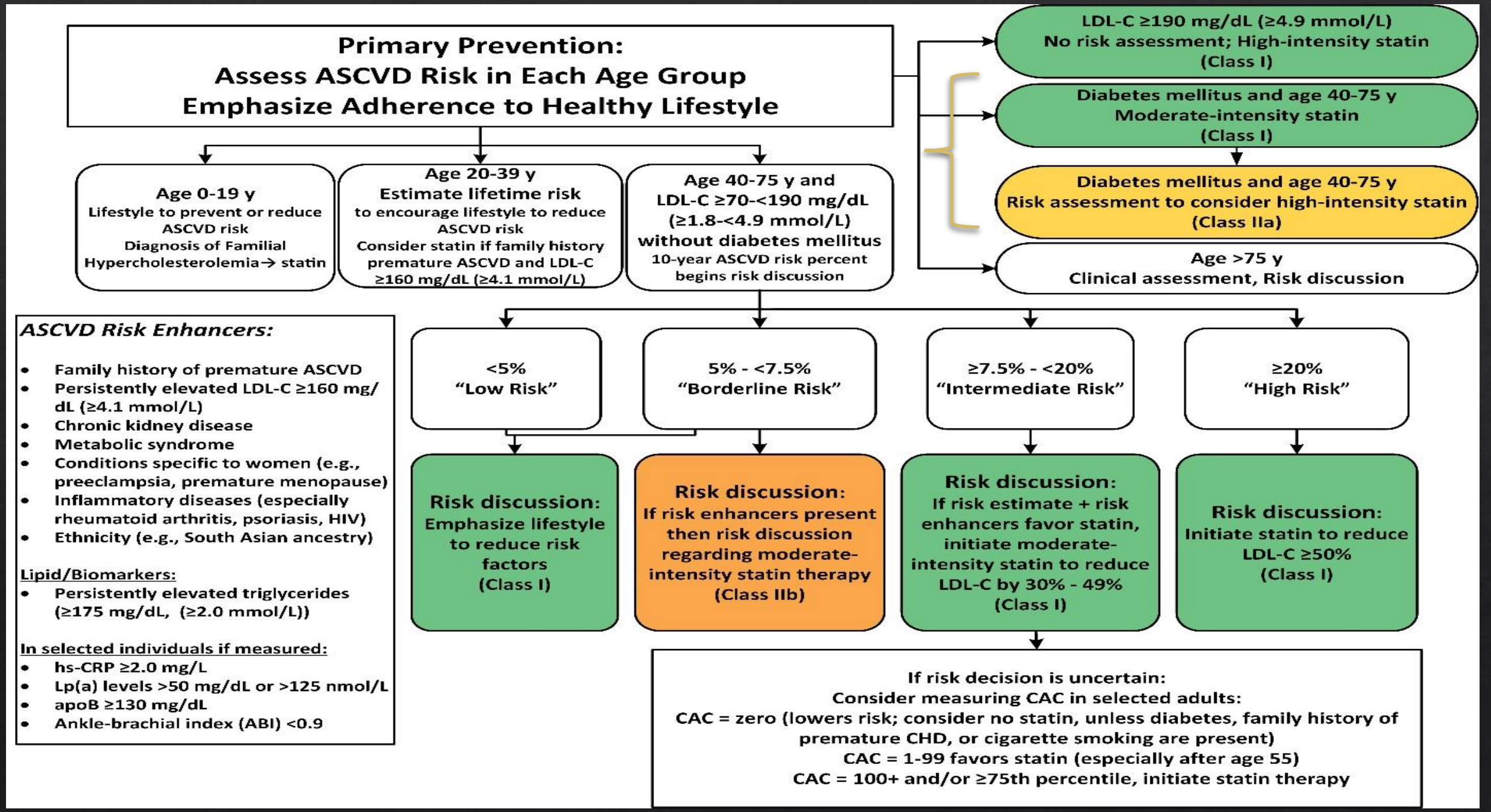

Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk
to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and
LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L)
without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
ASCVD Risk Enhancers:
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers:
Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))
In selected individuals if measured:
hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or >125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9
<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

Table 5. Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus

Risk Enhancers
• Long duration (≥10 years for type 2 diabetes mellitus (S.4.3-20) or ≥20 years for type 1 diabetes mellitus) • Albuminuria ≥30 mcg of albumin/mg creatinine • eGFR <60 mL/min/1.73 m^2 • Retinopathy • Neuropathy • ABI <0.9

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – DM or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10%-20% – DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS, acute coronary syndrome; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not recommended.

Barter PJ, et al. *J Intern Med*. 2006;259:247-258; Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-494; Brunzell JD, et al. *Diabetes Care*. 2008;31:811-822; Cannon CP, et al. *N Engl J Med.* 2015;372(25):2387-2397; Grundy SM, et al. *Circulation.* 2004;110:227-239; Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Lloyd-Jones DM, et al. *Am J Cardiol*. 2004;94:20-24; McClelland RL, et al. *J Am Coll Cardiol*. 2015;66(15):1643-1653; NHLBI. NIH Publication No. 02-5215. 2002; Ridker PM, *J Am Coll Cardiol*. 2005;45:1644-1648; Ridker PM, et al. *JAMA*. 2007;297(6):611-619; Sever PS, et al. *Lancet*. 2003;361:1149-1158; Shepherd J, et al. *Lancet*. 2002;360:1623-1630; Smith SC Jr, et al. *Circulation*. 2006;113:2363-2372; Stevens RJ, et al. *Clin Sci*. 2001;101(6):671-679; Stone NJ. *Am J Med*. 1996;101:4A40S-48S; Weiner DE, et al. *J Am Soc Nephrol.* 2004;15(5):1307-1315.

Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

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on Behalf of the REDUCE-IT Investigators

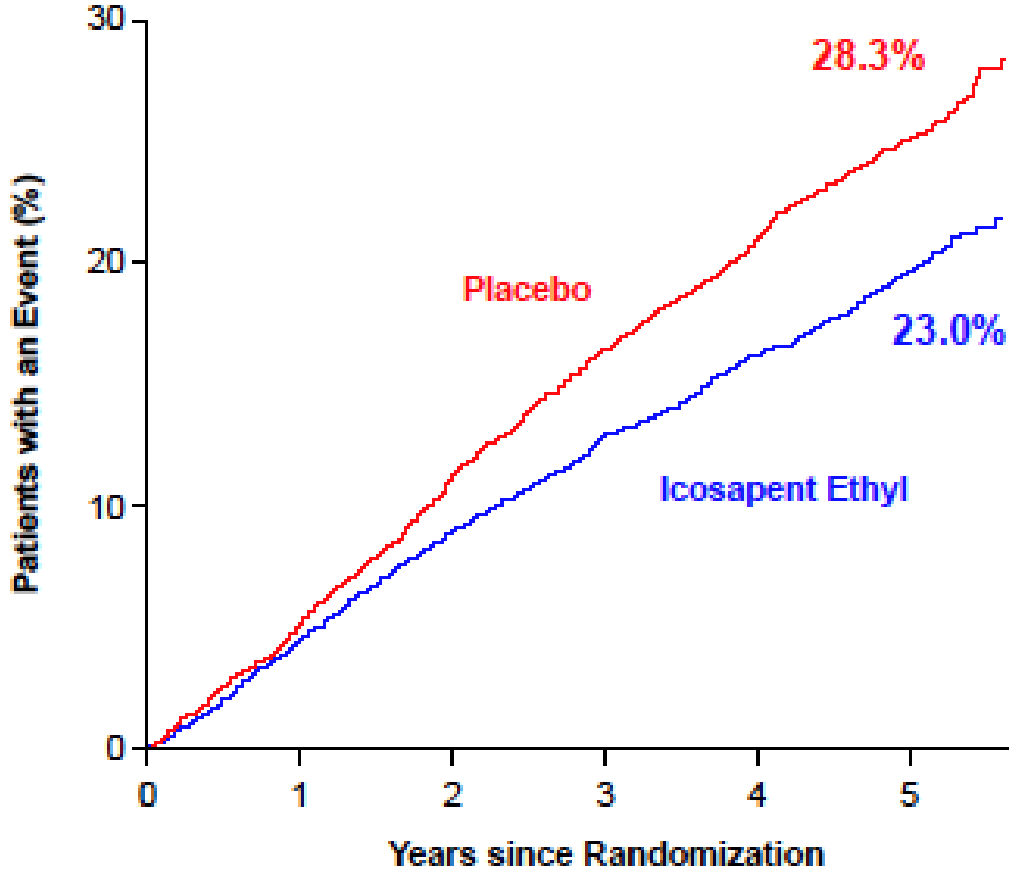
Key Inclusion Criteria – REDUCE-IT

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) *or* ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)
2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*
3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

*Due to the variability of triglycerides, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

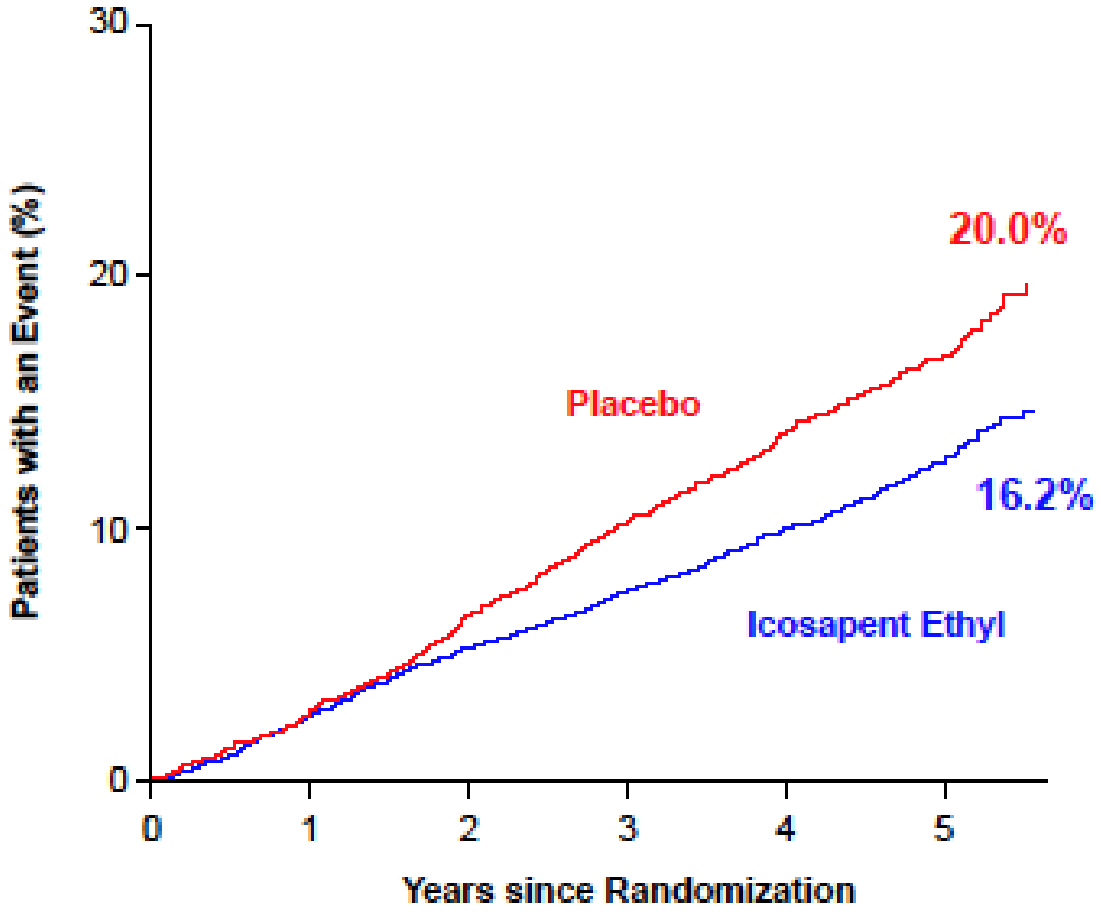
ARR = 4.8%

NNT = 21 (95% CI, 15–33)

P=0.00000001

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

RRR = 26.5%

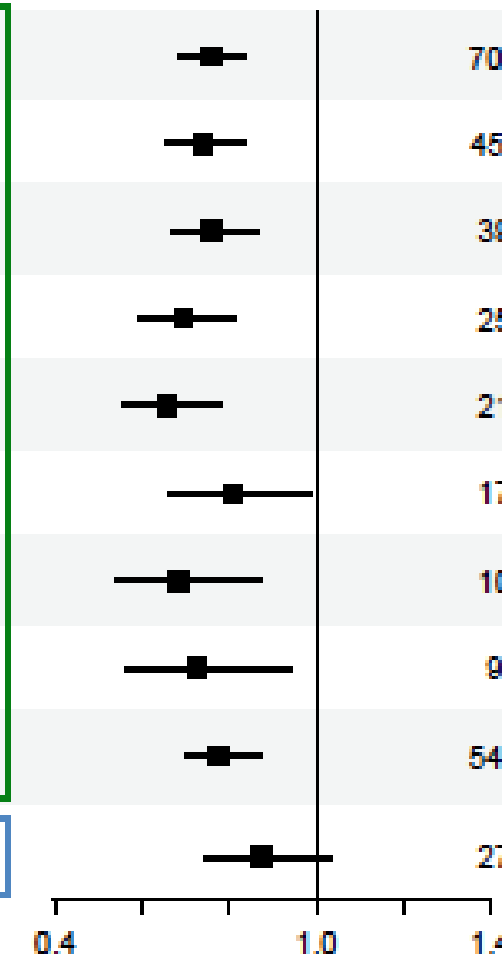
ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P=0.0000006

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018. Bhatt DL. AHA 2018, Chicago.

Prespecified Hierarchical Testing



Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09

RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018.

Updated ADA SOC March 27 2019 on Lipid management for CV Risk Reduction

- Based on the outcome of Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT)

- The *Standards of Care* now include a recommendation that icosapent ethyl be considered for patients with diabetes and atherosclerotic cardiovascular disease (ASCVD) or other cardiac risk factors on a statin with controlled LDL-C, but with elevated triglycerides (135-499) to reduce cardiovascular risk.

Antiplatelet Agents: Recommendations

- Use aspirin therapy (75-162 mg/day) as a secondary prevention strategy in those with diabetes and a history of ASCVD. A
- For patients with ASCVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. B
- Dual antiplatelet therapy (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for a year after an acute coronary syndrome A and may have benefits beyond this period. B

Cardiovascular Disease and Risk Management:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019; 42 (Suppl. 1): S113-S114

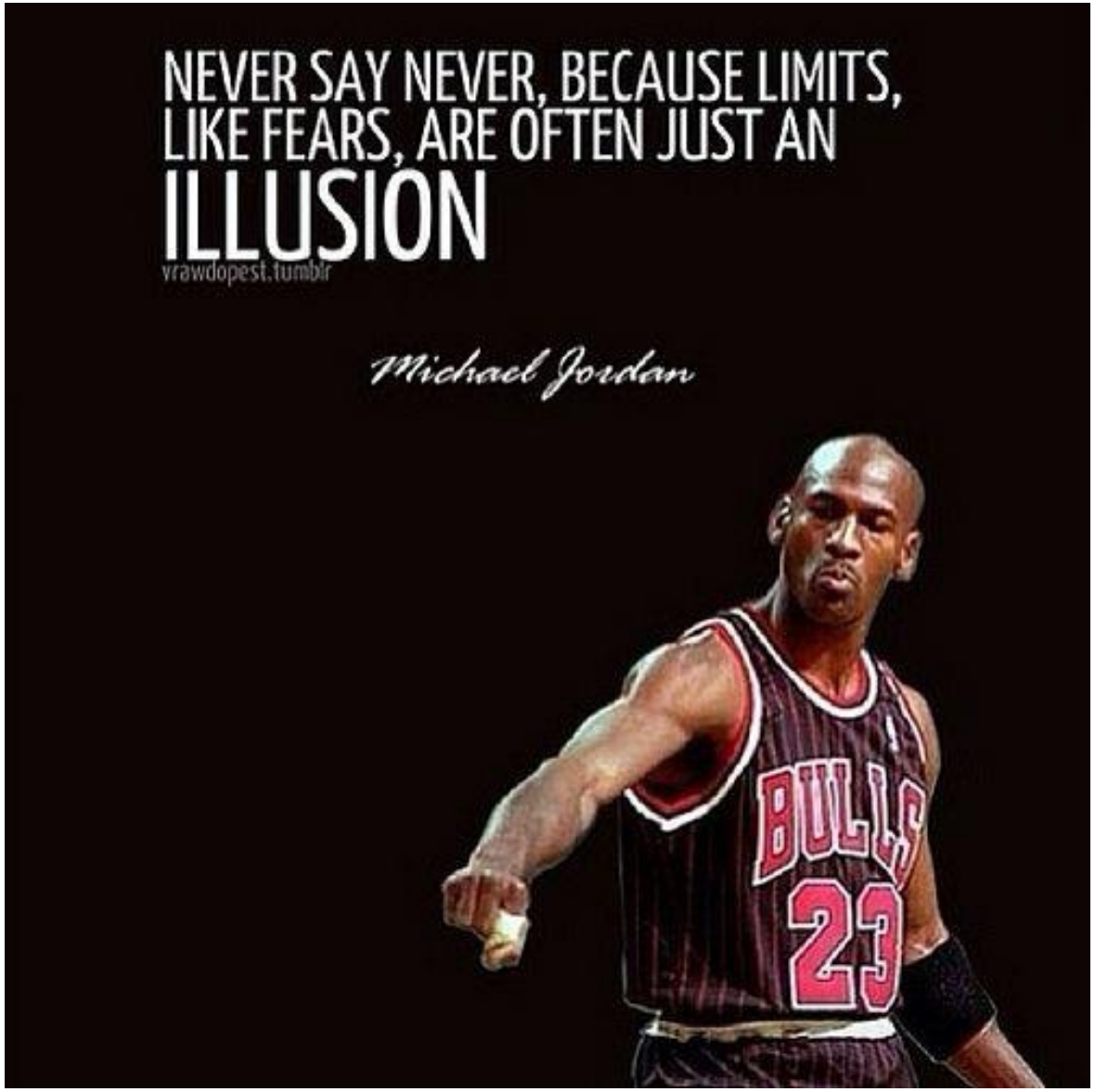
Antiplatelet Agents: Recommendations

- Aspirin therapy(75–162mg/day) **may be** considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a discussion with the patient on the benefits versus increased risk of bleeding. C

Cardiovascular Disease and Risk Management:
Standards of Medical Care in Diabetes - 2019. *Diabetes Care* 2019; 42 (Suppl. 1): S113-S114

Conclusion

- Effective ways to prevent diabetes include both lifestyle modification and drug therapy tailored to the individual.
- Although a new approach regarding management is pursued, glycemic control is still a main target.
- Patient with presence of ASCVD, Diabetic Kidney Disease and Heart Failure therapy should include medications with benefits regardless A1c
- Lipid lowering therapy should be always included in the diabetic patient.


NEVER SAY NEVER, BECAUSE LIMITS,
LIKE FEARS, ARE OFTEN JUST AN
ILLUSION
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Michael Jordan
BULLS
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QUESTIONS??