CURRENT AND FUTURE STATE OF CARDIOVASCULAR DISEASE AND TYPE 2 DIABETES

Managing Macrovascular Complications In Patients with Diabetes

Faculty

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Disclosures

Jonathan Purnell, MD

- *Novo Nordisk*: Consultant, Advisory Board

Angela Thompson, DNP

- *Novo Nordisk*: Consultant, Focus Group

Jeff Unger, MD, FAAFP, FACE

- *Novo Nordisk:* Consultant, Speaker, Advisory Board, Primary Investigator; *Abbott Diabetes:* Consultant, Advisory Board, Speaker; *Allergan:* Speaker

Jonathan Weber, MA, PA-C

- *Nothing to disclose*

Accreditation Statements

- The AAFP has reviewed Current and Future State of Cardiovascular Disease and Type 2 Diabetes, and deemed it acceptable for AAFP credit. Term of approval is from 11/17/2020 to 11/16/2021. Credit approval includes the following session(s):
  - 1.00 Enduring Materials, Self-Study AAFP Prescribed Credit(s) - Case 3 - Managing Macrovascular Complications In Patients with Diabetes.
- This activity is approved for 1.0 contact hour(s) of continuing education by the American Association of Nurse Practitioners. Activity ID# 20104592. This activity was planned in accordance with AANP Accreditation Standards and Policies.
- This activity has been reviewed by the AAPA Review Panel and is compliant with AAPA CME Criteria. This activity is designated for 1.0 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation.
- The Endocrine Society designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™ and 1.0 ABIM Medical Knowledge MOC point. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Learning Objectives

- Review major risk factors for coronary artery disease, diabetic kidney disease (DKD) and heart failure in patients with type 2 diabetes mellitus (T2DM).
- Summarize the associations of T2DM, cardiovascular (CVD) and (DKD) and implications to the progression of cardiorenal syndrome (CRS) and cardiovascular mortality.
- Apply cardiovascular outcome trial (CVOT) results to provide guidance on appropriate pharmacologic interventions for patients with advanced diabetes related complications.
- Analyze the impact of hypoglycemia in patients with advanced coronary artery disease and discuss techniques for mitigating risk of hypoglycemia.
- Employ tools and techniques to improve adherence and long-term chronic disease outcomes.

AAFP

AANP
American Association of
NURSE PRACTITIONERS®

AAPA

ENDOCRINE
SOCIETY

Patient Case: Meet Tony

- 62-year-old male with diabetes x 12 years
- Complications include:
    - Multivessel CAD
    - DKD with eGFR= 38 (Stage 3B)
    - Charcot Arthropathy
- Works as a certified public accountant
- Married with 3 grown children
- No smoking or alcohol
- Medication List:
    - Metformin 1000 mg BID
    - Glipizide 10 mg BID
    - Valsartan 80 mg QD
    - Rosuvastatin 5 mg QD
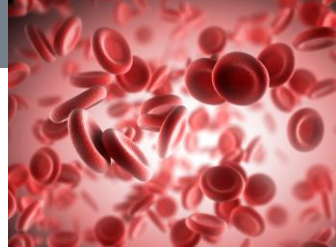- History of non-adherence to medications

CAD = Coronary Artery Disease
DKD = Diabetic Kidney Disease
eGFR = estimated Glomerular Filtration Rate

Image provided by © Obesity Action Coalition.

Patient Case: Tony

Physical Exam

- Weight: 325 pounds, Height: 6 feet, Body Mass Index (BMI): 42.9 kg/m^2;
- Blood Pressure: 160/96 mmHg, Pulse: 85 bpm
- HEART- S1, S2 with a fixed rate of 85 bpm. No evidence of beat-to-beat variability
- Lungs: Clear
- Abdomen: Enlarged liver span 12 cm
- Extremities: Charcot arthropathy
- Ankle-Brachial Index (ABI): 0.5 bilaterally (normal range above 0.8)

Labs

- A1C: 9.1 %
- eGFR: 38 mL/min/1.73
- Albumin Creatinine Ratio: 447 mg/gram
- Total cholesterol: 180
- Triglyceride: 190 mg/dL
- LDL cholesterol: 104 mg/dL
- HDL cholesterol: 38 mg/dL
- Non-HDL cholesterol: 142 mg/dL
- Hemoglobin/Hematocrit: 12.5/37
- Thyroid Stimulating Hormone: Normal
- Liver Function Tests: Within 2 x upper limits of normal.
- Testosterone: 125 ng/dL
- B12: Normal
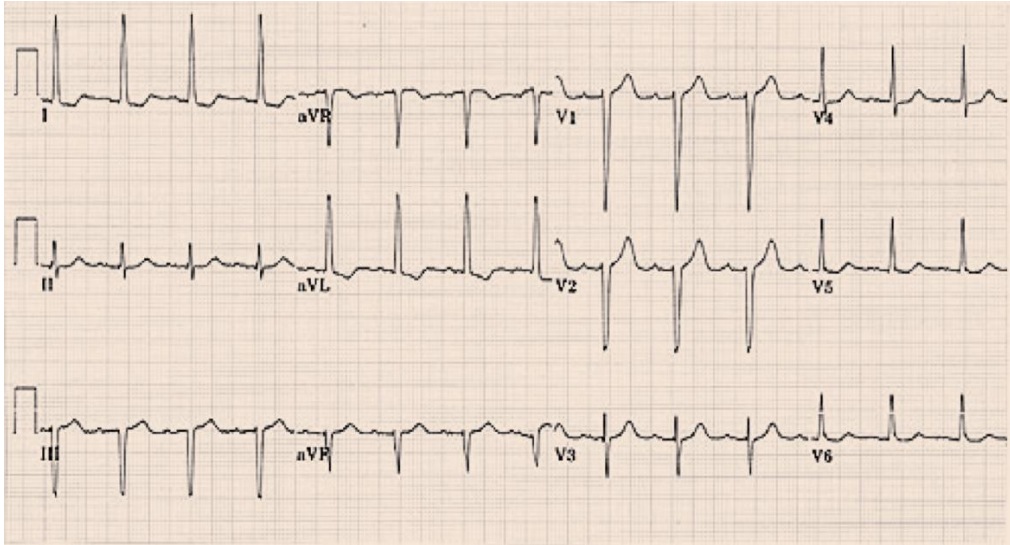
Patient Case: Meet Tony
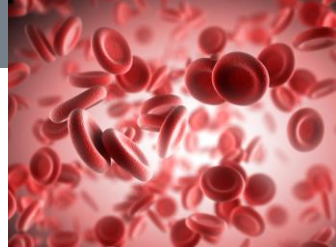
Home self-monitoring of blood glucose (SMBG) records for last 2 weeks:

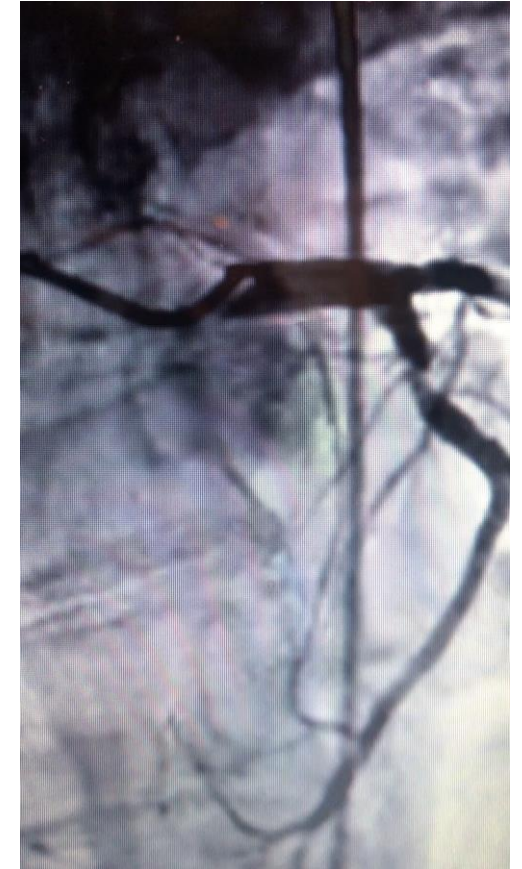|	Pre-Meal Capillary BG (mg/dL)
Breakfast (fasting)	188, 192, 201, 178, 199, 210, 186
Lunch	78 ,66, 62, 210, 63
Supper	220, 184, 197, 208, 224, 232, 205
Bedtime	210, 196, 330

BG = Blood Glucose
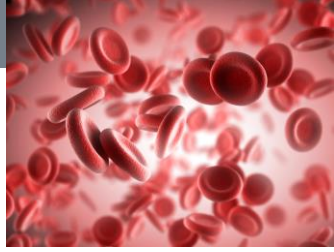
Tony's EKG and Echocardiogram

LVH and strain pattern
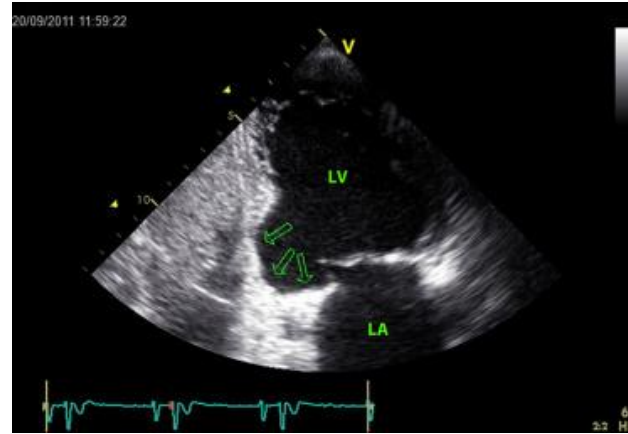
Echocardiogram showing severe CAD

Angiogram showing severe CAD

LVH = Left Ventricular Hypertrophy

Faculty Discussion Around Patient Case

Why is Tony off target?

What are his treatment priorities?

What would be your immediate choices for interventions?

Cardiovascular Risk in Type 2 Diabetes Mellitus (T2DM)

- Adults with type 2 diabetes have a 2-to-4-fold higher risk of cardiovascular morbidity and mortality than those without diabetes

  - Two-thirds of people aged $\geq$ 65 with diabetes die from heart disease

- Risk factors for CVD in type 2 diabetes include hyperglycemia, dyslipidemia, hypertension, renal disease, obesity, and smoking

- Led to FDA request for Cardiovascular Outcomes Trials (CVOTs)

  - 3-point MACE (Major Adverse CV Events) – composite of CV death, nonfatal myocardial infarction, and nonfatal stroke

 - 4-point MACE adds hospitalization for unstable angina to 3P-MACE

American Diabetes Association. *Diabetes Care*. 2016;39(Suppl 1):S60-S71.
American Heart Association. https://www.heart.org/en/health-topics/diabetes/why-diabetes-matters/cardiovascular-disease--diabetes.
Fox CS. *Trends Cardiovasc Med*. 2010;20(3):90-95.

Cardiorenal Syndrome

- Defined as disorders of the heart and kidneys whereby dysfunction in one may induce dysfunction in the other

- Dual and reciprocal interactions converge and promote organ damage and dysfunction in the heart and kidney
  - Poorly managed diabetes may also induce dysfunction in both

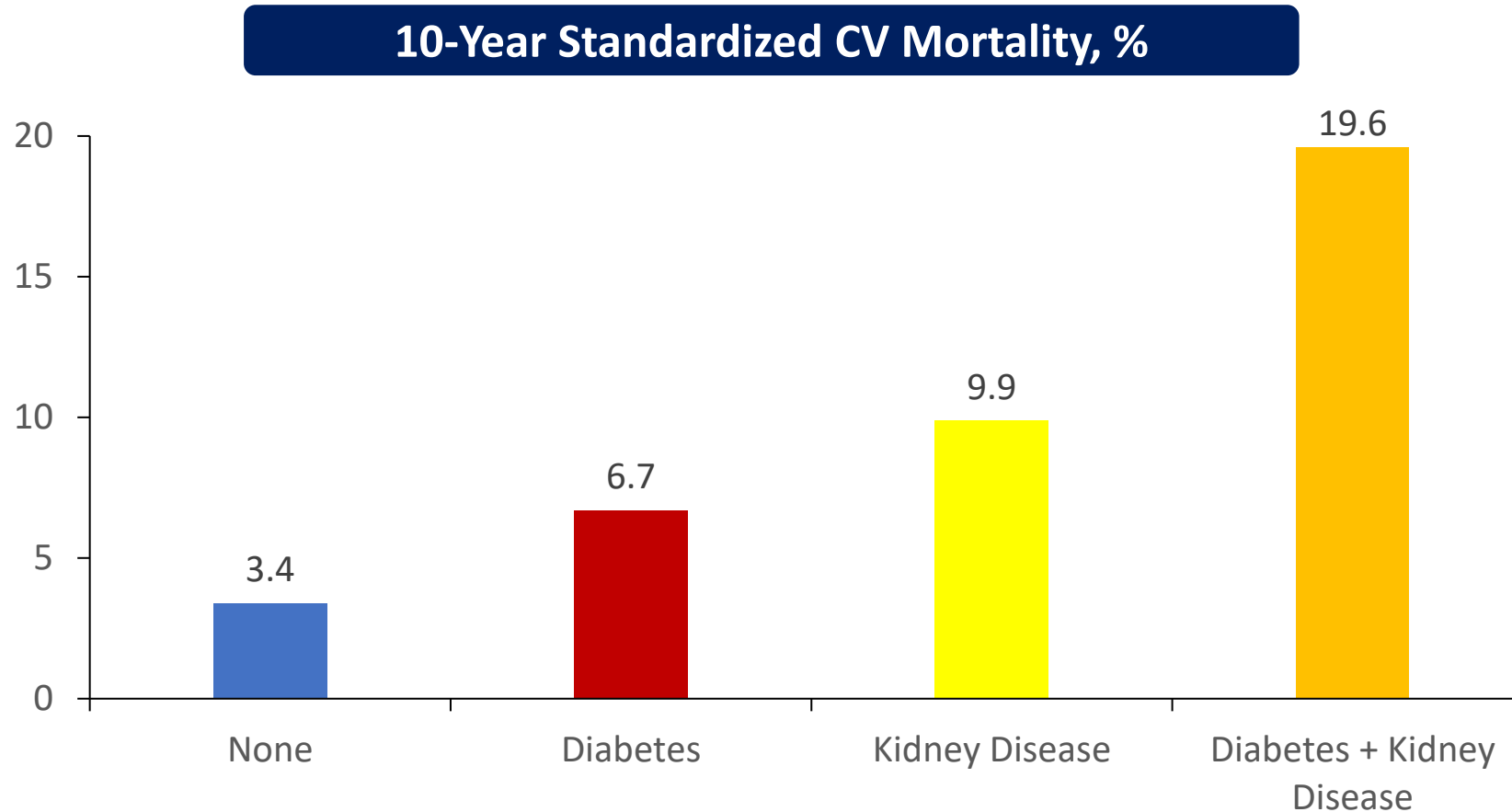- Deleterious outcomes are reinforced in a feedback cycle with accelerated progression
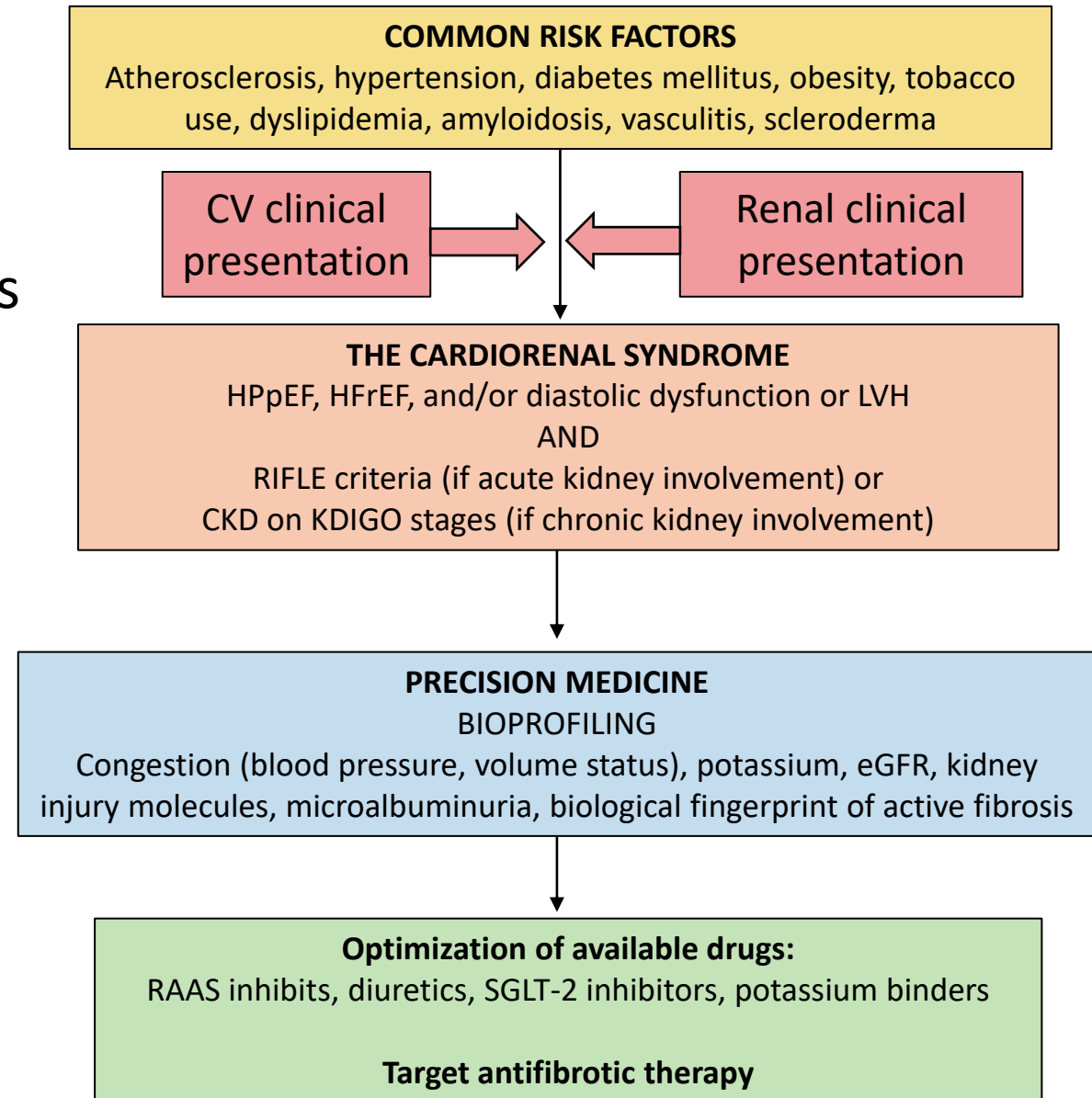
Ronco C, et al. *Eur Heart* J. 2010;31:703–711.
Karnib HH, et al. *Diabetes Res Clin Pract*. 2010;89:201-8.
Song MK, et al. *J Diabetes Res*. 2014;2014:313718.

COMMON RISK FACTORS
Atherosclerosis, hypertension, diabetes mellitus, obesity, tobacco use, dyslipidemia, amyloidosis, vasculitis, scleroderma

CV clinical presentation → ← Renal clinical presentation

THE CARDIORENAL SYNDROME
HPpEF, HFrEF, and/or diastolic dysfunction or LVH
AND
RIFLE criteria (if acute kidney involvement) or
CKD on KDIGO stages (if chronic kidney involvement)

PRECISION MEDICINE
BIOPROFILING
Congestion (blood pressure, volume status), potassium, eGFR, kidney injury molecules, microalbuminuria, biological fingerprint of active fibrosis

Optimization of available drugs:
RAAS inhibits, diuretics, SGLT-2 inhibitors, potassium binders

Target antifibrotic therapy

The Excess Risk of CV Mortality in T2DM is Concentrated in Patients With Kidney Disease

10-Year Standardized CV Mortality, %

- None: 3.4
- Diabetes: 6.7
- Kidney Disease: 9.9
- Diabetes + Kidney Disease: 19.6

Kidney disease magnifies risk of mortality

Afkarian M, et al. *J Am Soc Nephrol.* 2013;24:302-308.

Renal Dysfunction Increases Cardiovascular Mortality

KDIGO. *Kidney Int Suppl (2011)*. 2013;3(1):19-62.

UACR = Urine Albumin-to-Creatinine Ratio

16
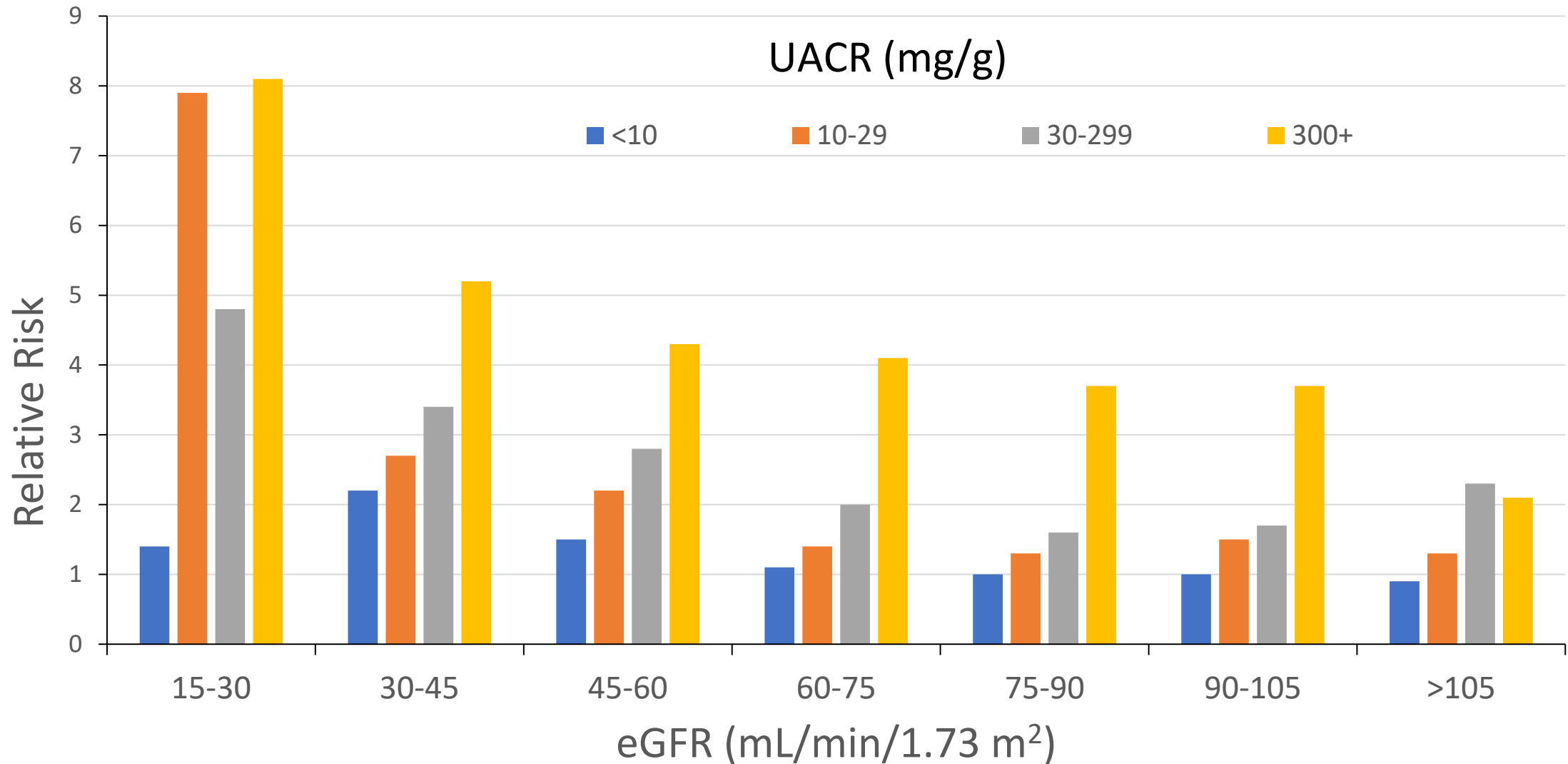
Albuminuria Can Occur Long Before eGFR Declines in DKD

Alicic RZ, et al. *Clin J Am Soc Nephrol*. 2017;12:2032-2045;
Afkarian M. *Pediatr Nephrol*. 2015;30:65-74.

17
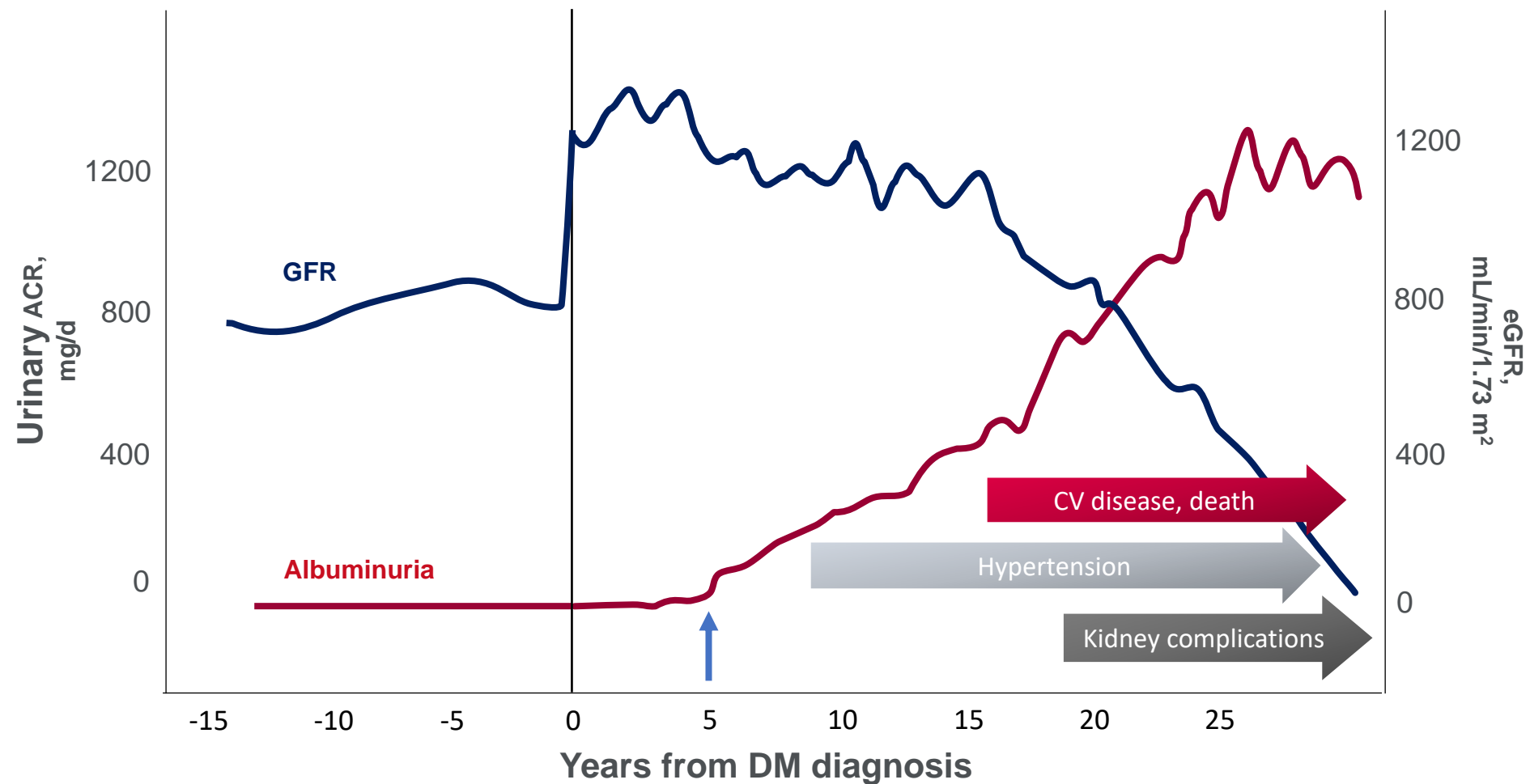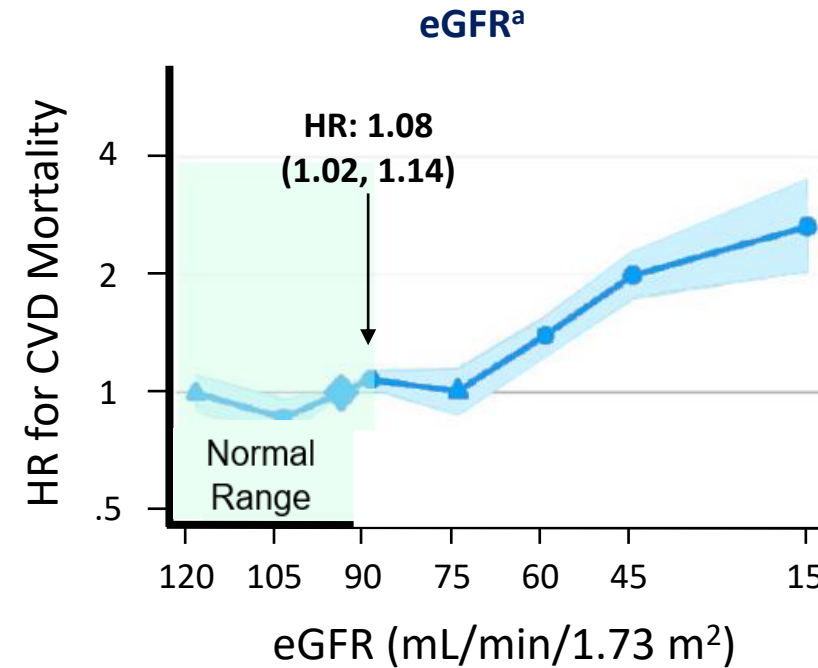
ACR Is an Independent Predictor of CV Mortality More so Than eGFR Across the Full Range of Kidney Function

CV Mortality

ACR[a]
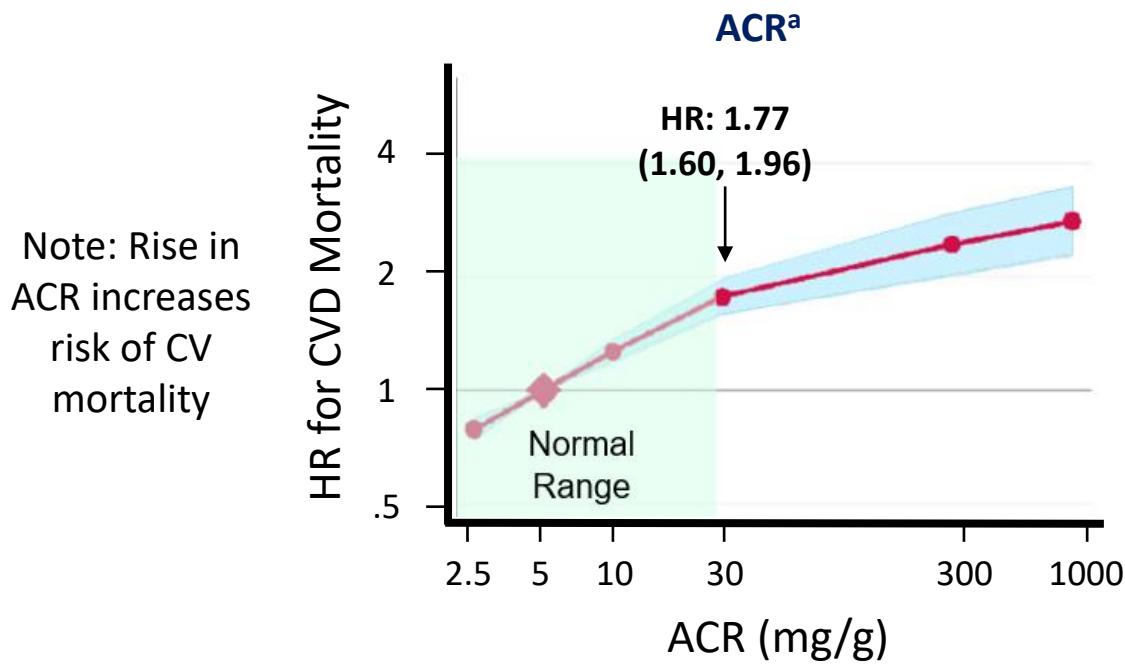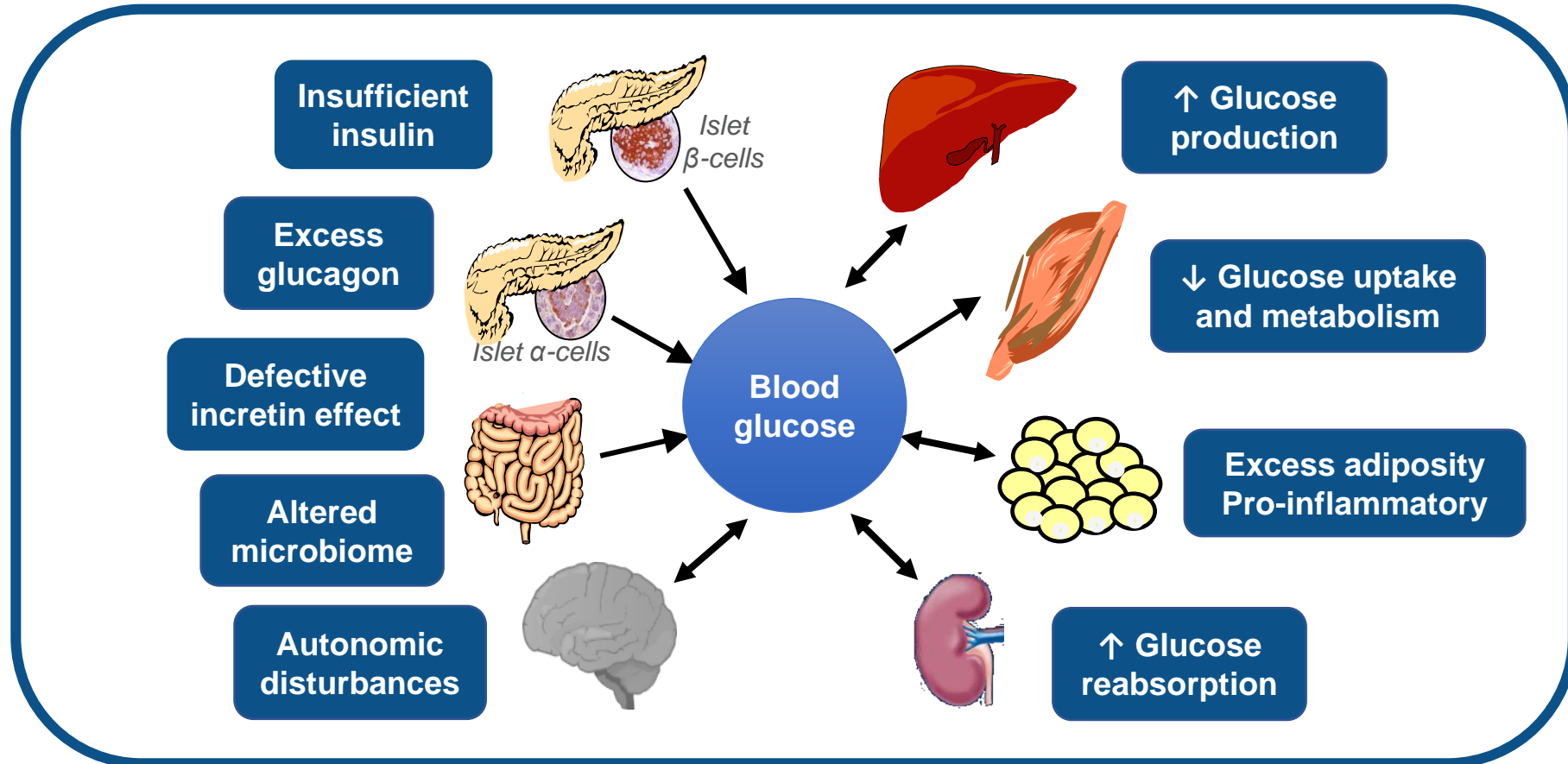
Note: Rise in ACR increases risk of CV mortality

HR: 1.77 (1.60, 1.96)

Normal Range

HR for CVD Mortality

ACR (mg/g)

eGFR[a]

HR: 1.08 (1.02, 1.14)

Decline in eGFR does not increase risk of CV mortality

Normal Range

HR for CVD Mortality

eGFR (mL/min/1.73 m^2)

Independent of each other and traditional risk factors, ACR ≥10 mg/g was significantly associated with increased CV mortality. eGFR was not until <60 mL/min/1.73 m^2

[a]Adjusted for each other (ACR or eGFR), age, gender, race, CVD history, systolic blood pressure, diabetes, smoking, and total cholesterol.

18

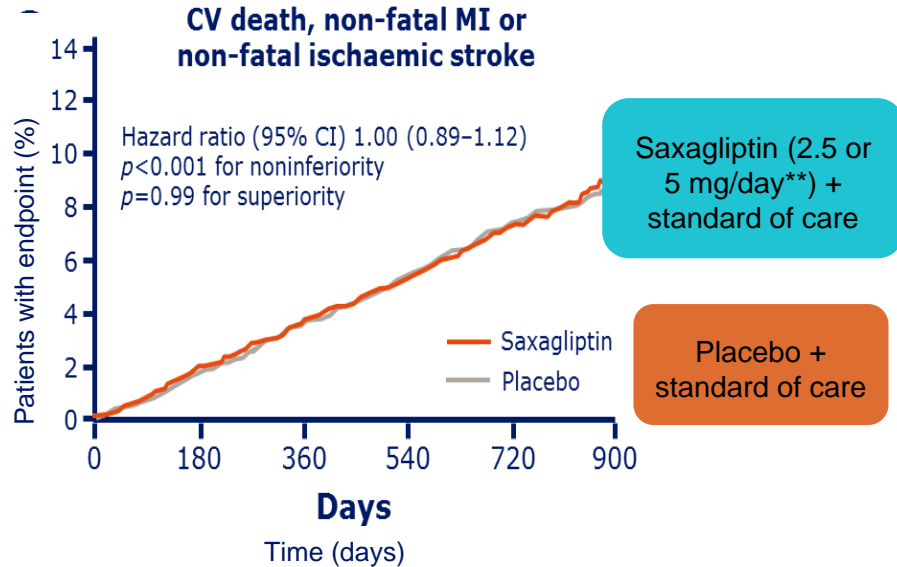ACR = Albumin-to-Creatinine Ratio

HR = Hazard Ratio

Hyperglycemia Has Many Sources That Can Be Addressed Using Drug Therapies

Multiple causes require multiple treatment options

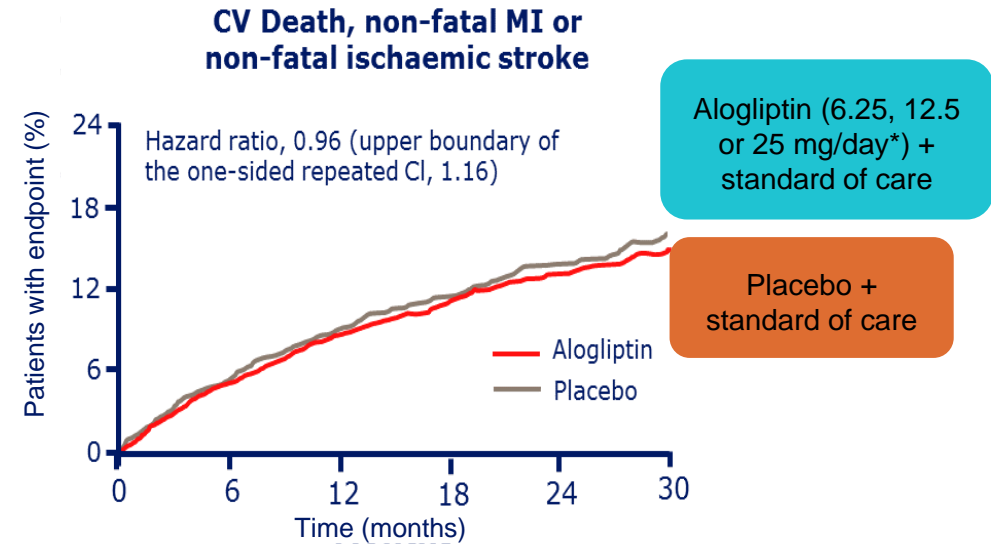Bailey CJ. *Clin Pharmacol Ther* 2015;98(2):170-84

Diabetes Trials Without CVOT Benefit

SAVOR-TIMI-53: Saxagliptin[1]

CV death, non-fatal MI or non-fatal ischaemic stroke

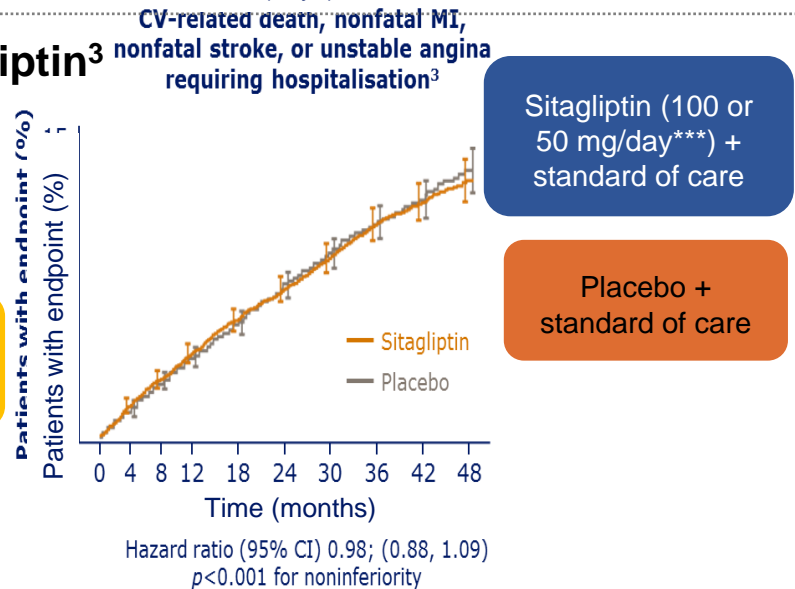Hazard ratio (95% CI) 1.00 (0.89–1.12)
$p<0.001$ for noninferiority
$p=0.99$ for superiority

T2D; HbA$_{1c}$ 6.5–12.0%; ≥40 years + CVD; ≥55 (men) or ≥60 (women) years + CV risk factors (n=16,492)
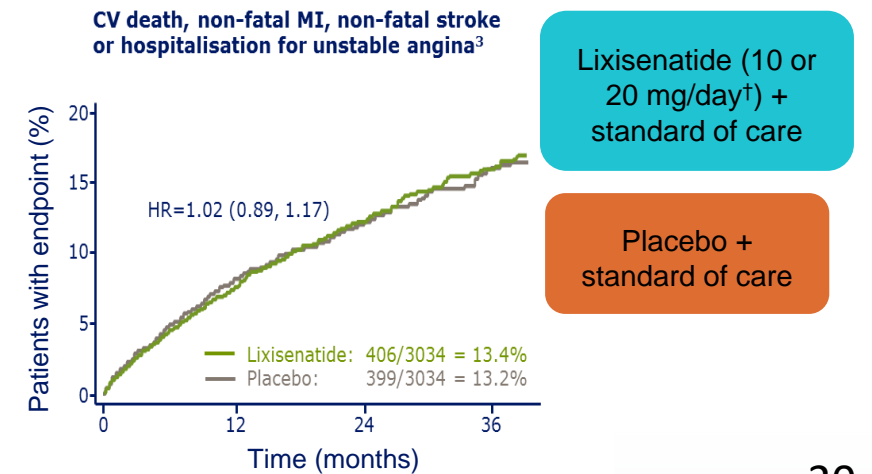
Saxagliptin (2.5 or 5 mg/day**) + standard of care

Placebo + standard of care

EXAMINE: Alogliptin[2]

CV Death, non-fatal MI or non-fatal ischaemic stroke

Hazard ratio, 0.96 (upper boundary of the one-sided repeated CI, 1.16)

T2D; HbA$_{1c}$ 6.5–11.0%; ACS within 15–90 days (n=5380)

Alogliptin (6.25, 12.5 or 25 mg/day*) + standard of care

Placebo + standard of care

TECOS: Sitagliptin[3]

CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalisation[3]

T2D; HbA$_{1c}$ 6.5–8.0%; ≥50 years; CVD history (n=14,671)

Sitagliptin (100 or 50 mg/day***) + standard of care

Placebo + standard of care

Hazard ratio (95% CI) 0.98; (0.88, 1.09)
$p<0.001$ for noninferiority

ELIXA: Lixisenatide[4]

CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina[3]

HR=1.02 (0.89, 1.17)

T2D; HbA$_{1c}$ 5.5–11.0%; ACS within 180 days (n=6068)

Lixisenatide (10 or 20 mg/day†) + standard of care

Placebo + standard of care

Lixisenatide: 406/3034 = 13.4%
Placebo: 399/3034 = 13.2%

1. Scirica BM, et al. N Engl J Med 2013; 369:1317-1326; 2. White WB, et al. N Engl J Med 2013; 369:1327-1335; 3. Green JB, et al. N Engl J Med 2015; 373:232-242; 4. Pfeffer MA, et al. N Engl J Med 2015; 373:2247-2257

EMPA-REG (empagliflozin) Trial Demonstrates <u>Rapid</u> Improvement in 3-Point MACE for SGLT2i
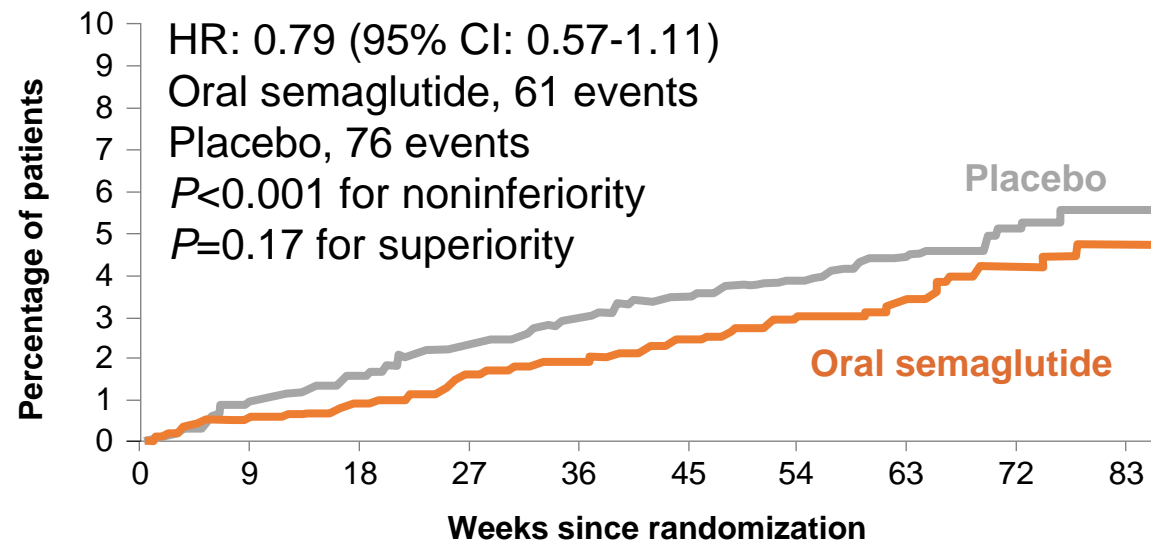

Cumulative incidence of the primary outcome

Placebo

P=0.04 for superiority
Hazard ratio, 0.86 (95.02% CI, 0.74-0.99)

Empagliflozin

14% risk reduction

Cumulative incidence of death from CV causes

P<0.001
Hazard ratio, 0.62 (95% CI, 0.49-0.77)

38% risk reduction

Hospitalization for heart failure

P=0.002
Hazard ratio, 0.65 (95% CI, 0.50-0.85)

35% risk reduction

Month

21

Zinnan B, et al. *N Engl J Med* 2015; 373:2117-2128.

SGLT2i = Sodium/glucose cotransporter-2 inhibitors

GLP-1 RA Semaglutide Injection – SUSTAIN 6

CV Mortality, Nonfatal MI, or Nonfatal Stroke

HR: 0.74 (95% CI: 0.58-0.95)
P<0.001 for noninferiority
P=0.02 for superiority

— Semaglutide
— Placebo

Y-axis: **Patients with event, %** (0, 5, 10, 15, 20)
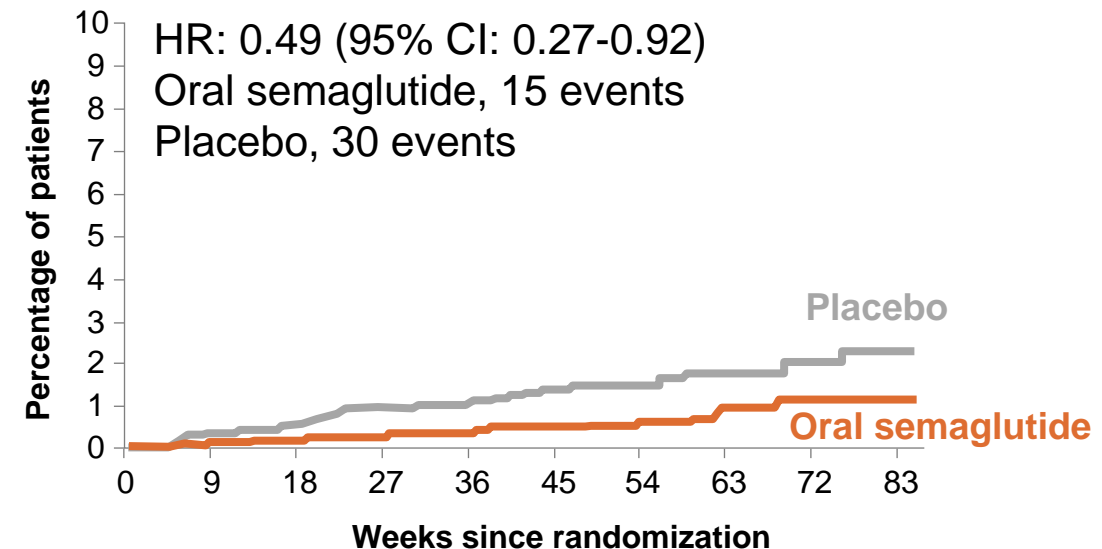X-axis: **Weeks since randomization** (0, 16, 32, 48, 64, 80, 96, 109)
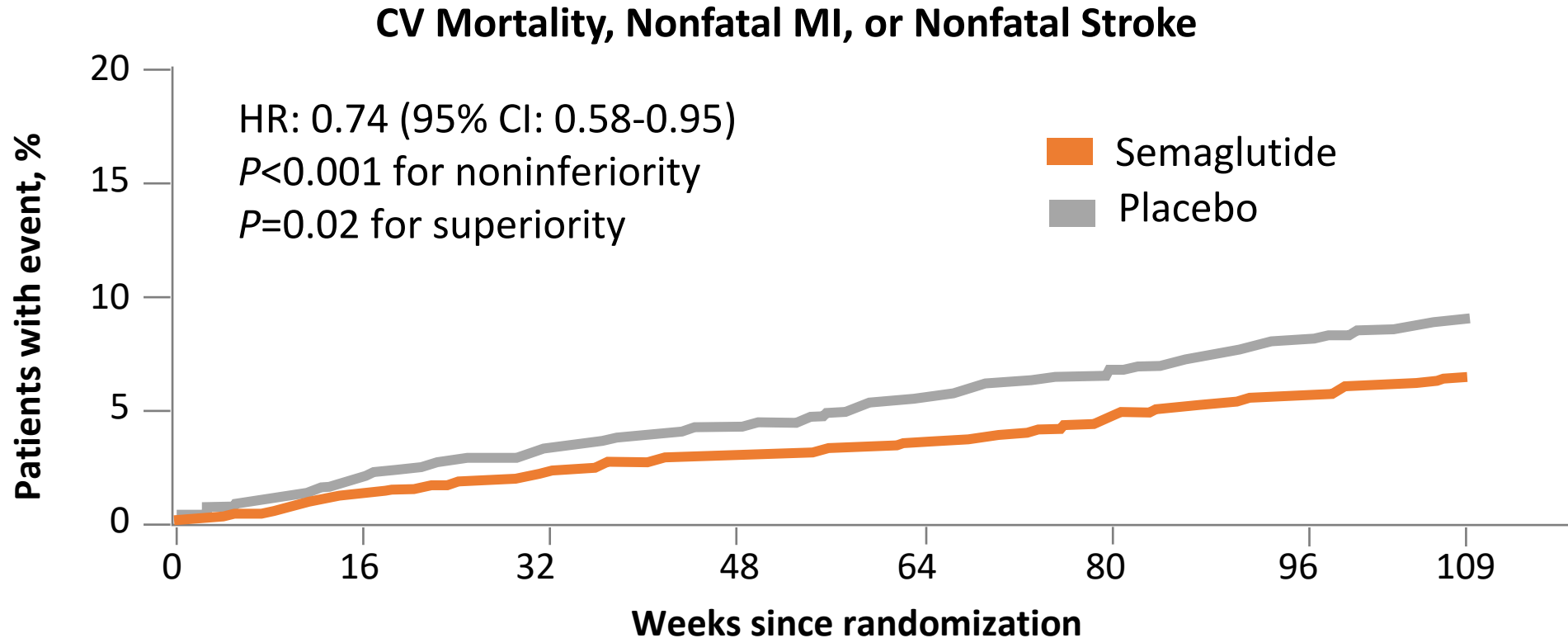
- Rates of CV mortality and nonfatal MI are similar between groups, and rate of stroke is lower in semaglutide group
- Rates of new or worsening nephropathy are lower in semaglutide group, but retinopathy complications are higher

22

Oral GLP1-RA Semaglutide – PIONEER 6
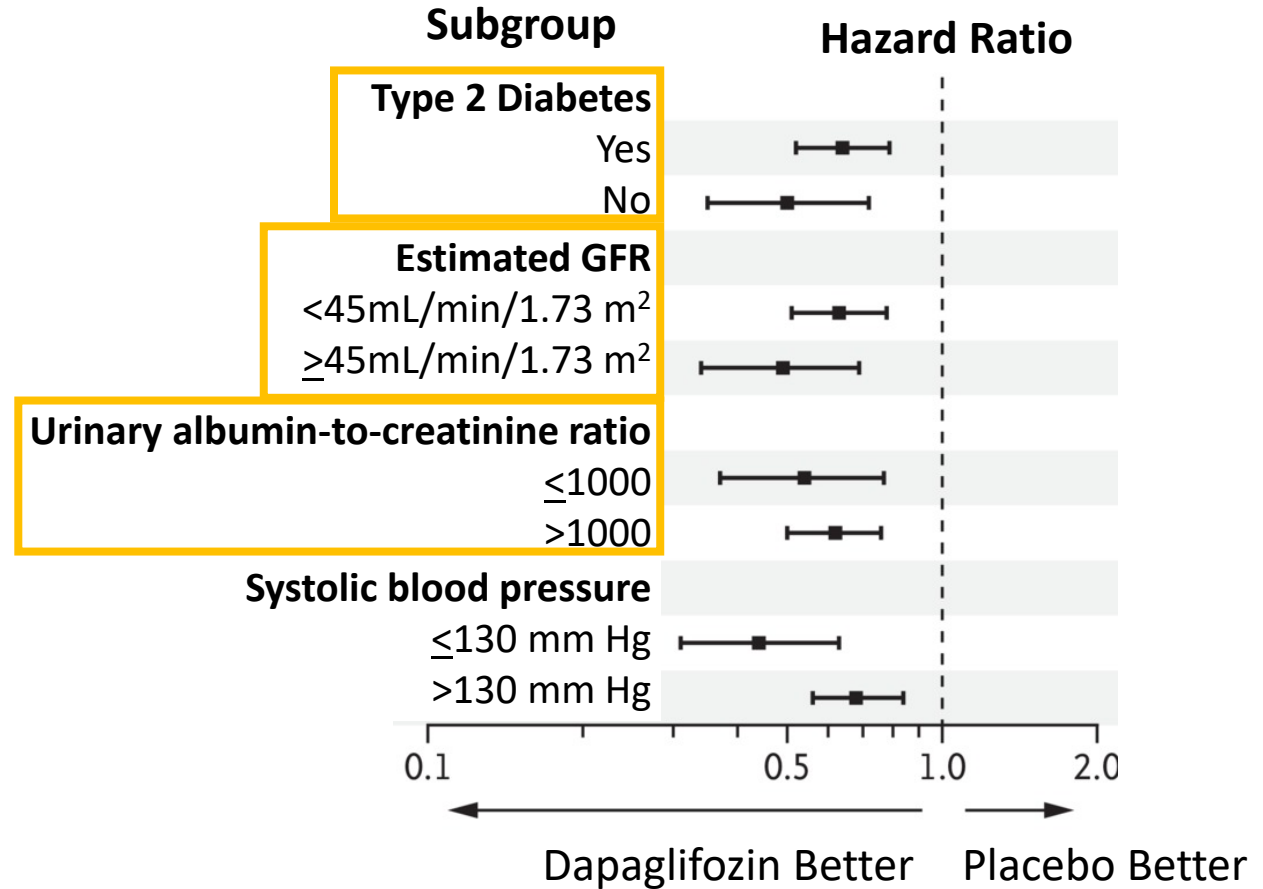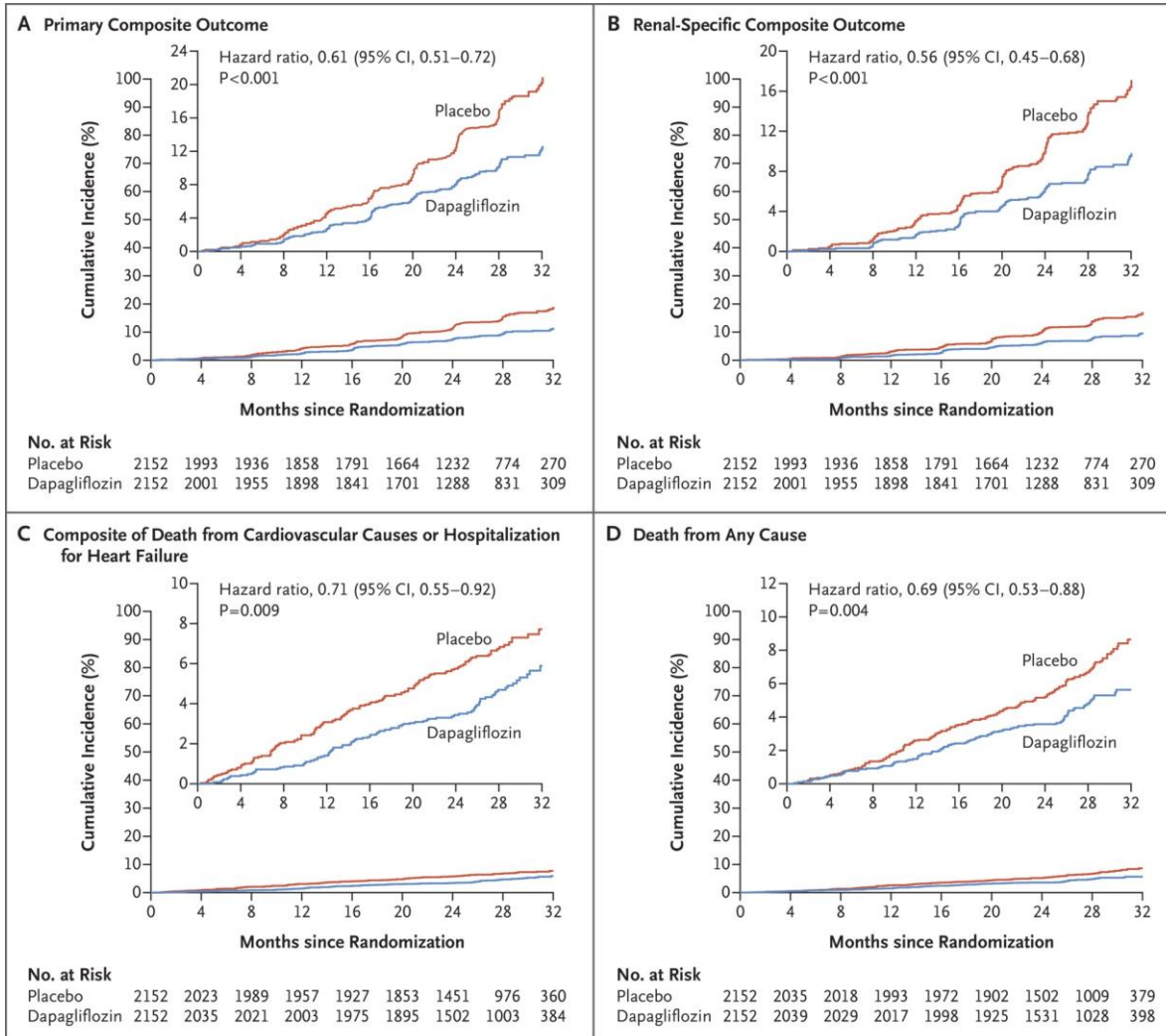
Composite Primary Outcome

HR: 0.79 (95% CI: 0.57-1.11)
Oral semaglutide, 61 events
Placebo, 76 events
P<0.001 for noninferiority
P=0.17 for superiority

Placebo

Oral semaglutide

Percentage of patients

Weeks since randomization

Death From Cardiovascular Causes

HR: 0.49 (95% CI: 0.27-0.92)
Oral semaglutide, 15 events
Placebo, 30 events

Placebo

Oral semaglutide

Percentage of patients

Weeks since randomization

- HR of death from any cause: 0.51 (95% CI: 0.31-0.84)

- No difference in rates of stroke or nonfatal MI between groups

- Gastrointestinal events leading to discontinuation were more common in oral semaglutide group vs placebo

23

Mansoor H, et al; *N Engl J Med* 2019; 381:841-851

GLP-1 RA = Glucagon-Like Peptide 1 Receptor Agonist

Meta-analysis of GLP-1 RAs:
CV Mortality, Nonfatal MI, or Stroke

Agent	GLP-1 RA, n/N (%)	Placebo , n/N (%)	HR (95% CI)	P Value
Lixisenatide	400/3034 (13)	392/3034 (13)	1.02 (0.89-1.17)	.776
Liraglutide	608/4668 (13)	694/4672 (15)	0.87 (0.78-0.97)	.015
Semaglutide	108/1648 (7)	146/1649 (9)	0.74 (0.58-0.95)	.016
Exenatide-QW	839/7356 (11)	905/7396 (12)	0.91 (0.83-1.00)	.061
Overall			0.90 (0.82-0.99)	.033

0.5   1.0   2.0

Favors GLP-1 RA   **Favors placebo**

Bethel MA, et al. *Lancet Diabetes Endocrinol*.2018;6(2):105-113.

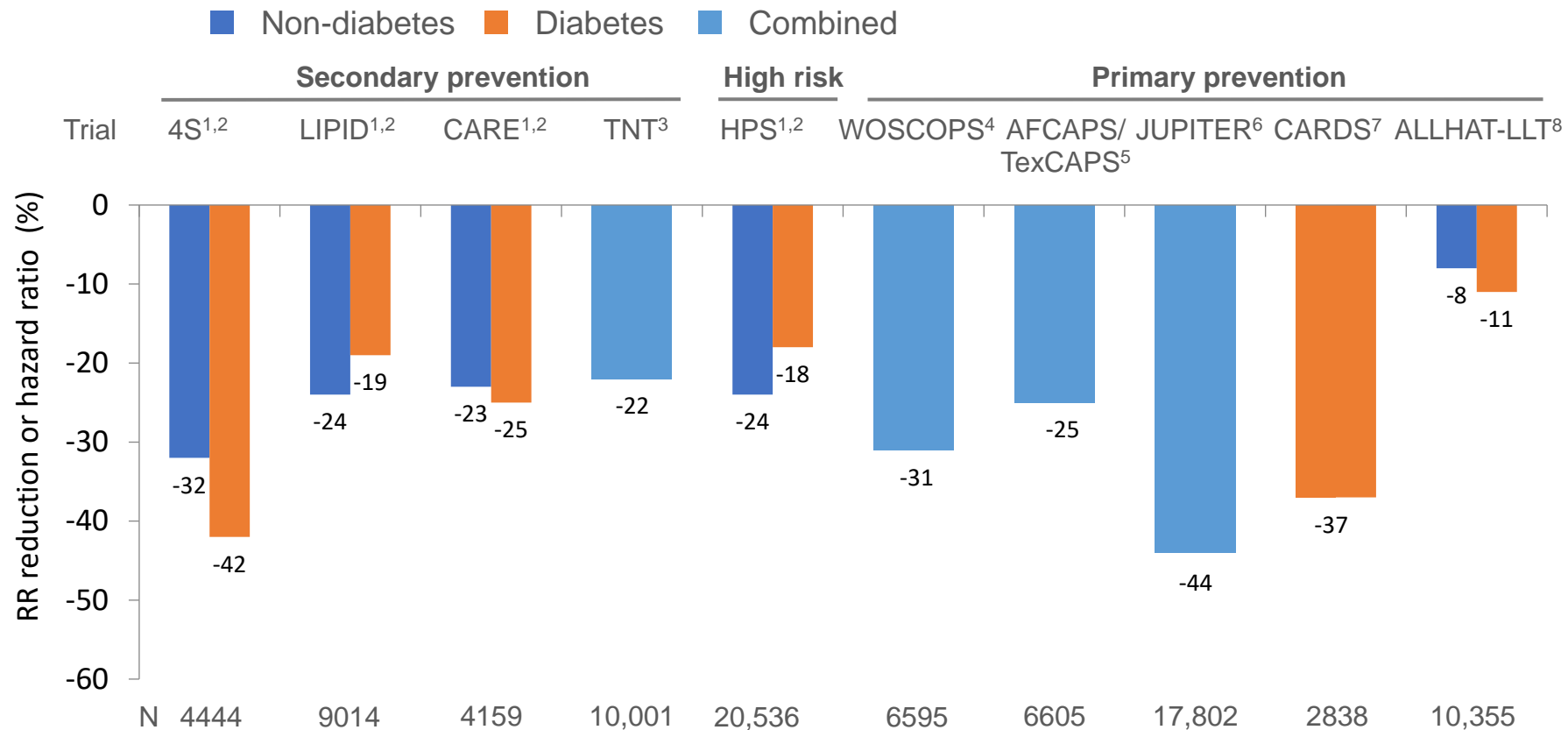# Dapagliflozin in Patients with Chronic Kidney Disease
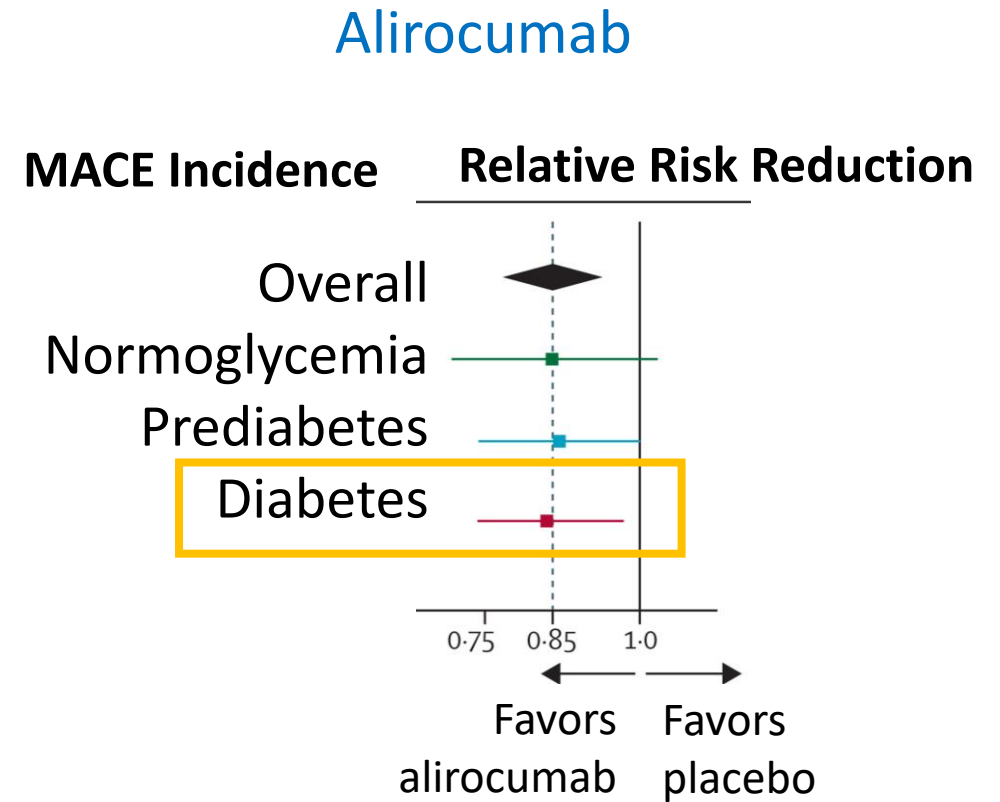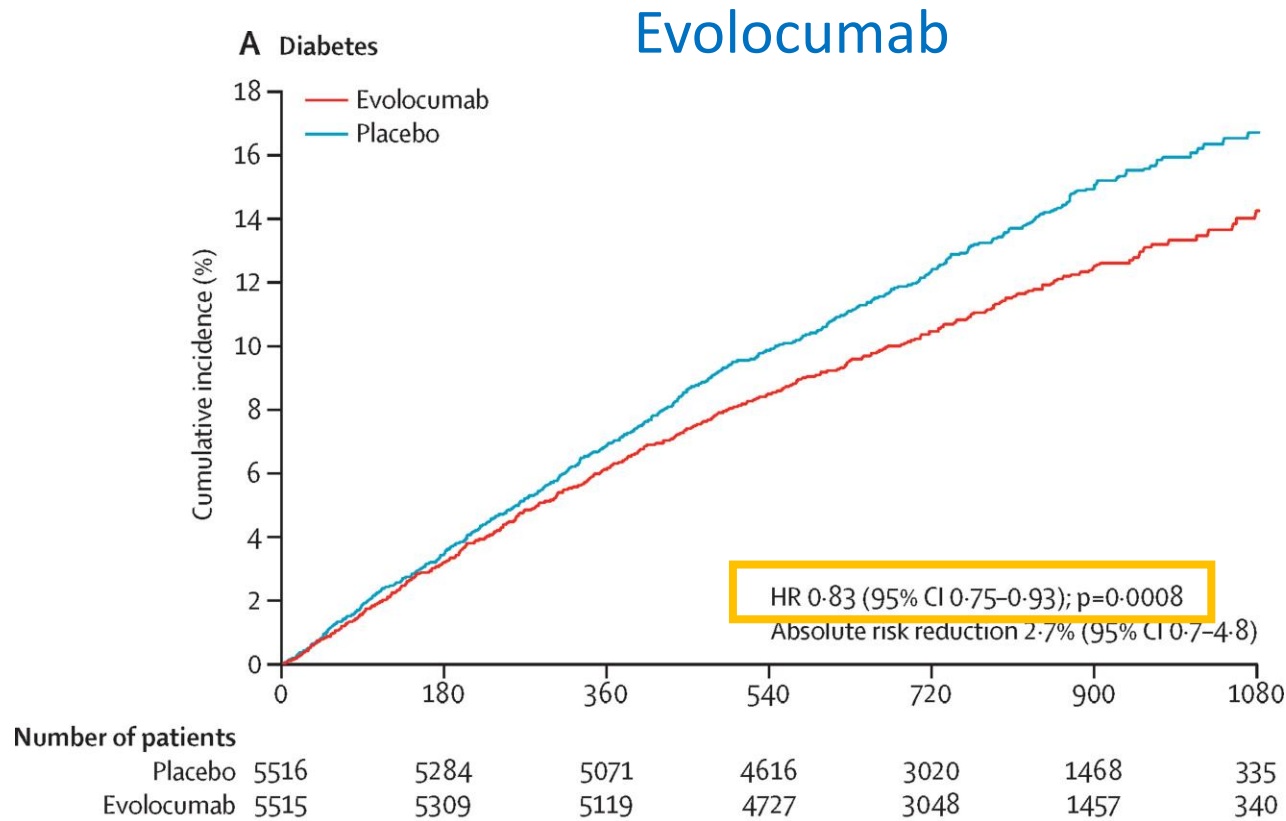
Small Reductions in BP Reduce Risk in High CV Risk Patients
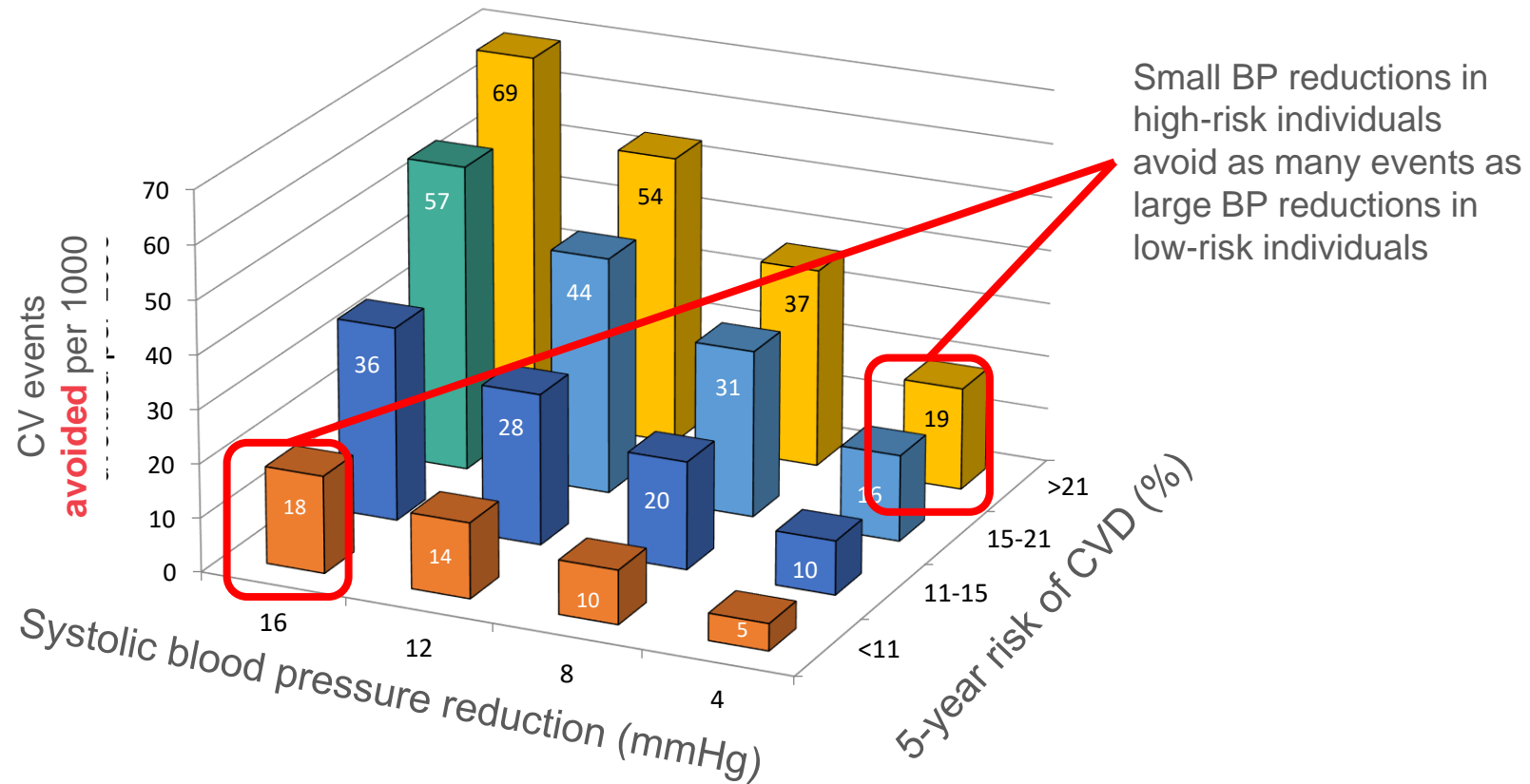
Small BP reductions in high-risk individuals avoid as many events as large BP reductions in low-risk individuals

Bethel MA, et al. *Lancet Diabetes Endocrinol*.2018;6(2):105-113

Statin Therapy: A Pivotal Role in Reducing CV Risk

1. Ryden et al. *Eur Heart J* 2007;28:88–136. 2. Libby. *J Am Coll Cardiol* 2005;46:1225–8. 3. LaRosa et al. *N Engl J Med* 2005;352:1425–35.
4. Shepherd et al. *N Engl J Med* 1995;333:1301–8. 5. Downs et al. *JAMA* 1998;279:1615–22. 6. Ridker et al. *N Engl J Med* 2008;359:2195.
7. Colhoun et al. *Lancet* 2004:364:685–96. 8. ALLHAT-LLT. *JAMA* 2002:288:2998–3007.

PCSK9 inhibitor Therapy Reduces Cardiovascular Disease Events

Evolocumab

Alirocumab

MACE Incidence   **Relative Risk Reduction**

Overall
Normoglycemia
Prediabetes
Diabetes

Favors alirocumab   Favors placebo

Sabatine MS, et al. *Lancet Diabetes Endocrinol.* 2017; 5: 941–50.
Ray KK, et al. *Lancet Diabetes Endocrinol*. 2019; 7: 618–28

29

PCSK9 = Proprotein convertase subtilisin/kexin type 9

It's More Than Glucose Control

There's also…	…And let's not forget…	Plus…	And now…
Antiplatelet therapy	Smoking cessation	Diabetes distress	Choose glucose-lowering medication shown to reduce cardiovascular risk *(when possible)*
Blood pressure	Regular examination of weight, eyes, mouth/teeth, feet, skin, kidneys	Quality of life	
Cholesterol			
Dietary			
Exercise			

Lifestyle Modification and Patient Education

MNT

Physical Activity

Smoking Cessation

Psychosocial Care

Diabetes Self-Management Education and Support

- Facilitating behavior change and well-being to improve health outcomes
- Patient-centered care with individualized management plan

ADA. *Diabetes Care*. 2020;43:S37-S47. ADA. *Diabetes Care*. 2020;43:S48-S65.
Evert AB, et al. *Diabetes Care*. 2019;42:731-54. Powers MA, et al. *Diabetes Care*. 2015;38:1372-82.

Treatment Goals: More Than Just the Sugar

	AACE[1]	ADA[2,3]
A1C, %	≤6.5	≤7.0
Fasting/premeal BG, mg/dL	<110	80-130
Postprandial, mg/dL	<140[a]	<180[b]
Blood pressure, mm Hg	<130/80	<140/90
LDL, mg/dL	<100 (<70) (<55)[c]	Based on risk

[a]2-hour postmeal; [b]Peak; [c]Lower goals recommended for high-risk cardiovascular disease.

1.   Garber AJ, et al. *Endocr Pract*. 2018;24(1):91-120;
2.   ADA. *Diabetes Care* 2018; 41(Supplement 1):S86-S104.

AACE = American Association of Clinical Endocrinologists
ADA = American Diabetes Association

Patient Case: Tony
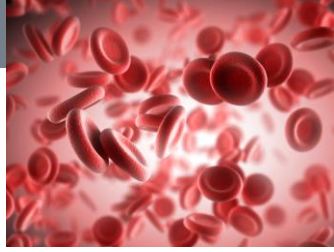
Known Complications

- DKD: Stage 3B
- CAD
- Diabetic retinopathy (DR)
- Obesity
- ? Nonalcoholic steatohepatitis (NASH)
- ? Obstructive sleep apnea (OSA)
- Low testosterone
- Autonomic neuropathy

Labs

- A1C: 9.1 %
- eGFR: 38 mL/min/1.73
- Albumin Creatinine Ratio: 447 mg/gram
- Total cholesterol: 180
- Triglyceride: 190 mg/dL
- LDL cholesterol: 104 mg/dL
- HDL cholesterol: 38 mg/dL
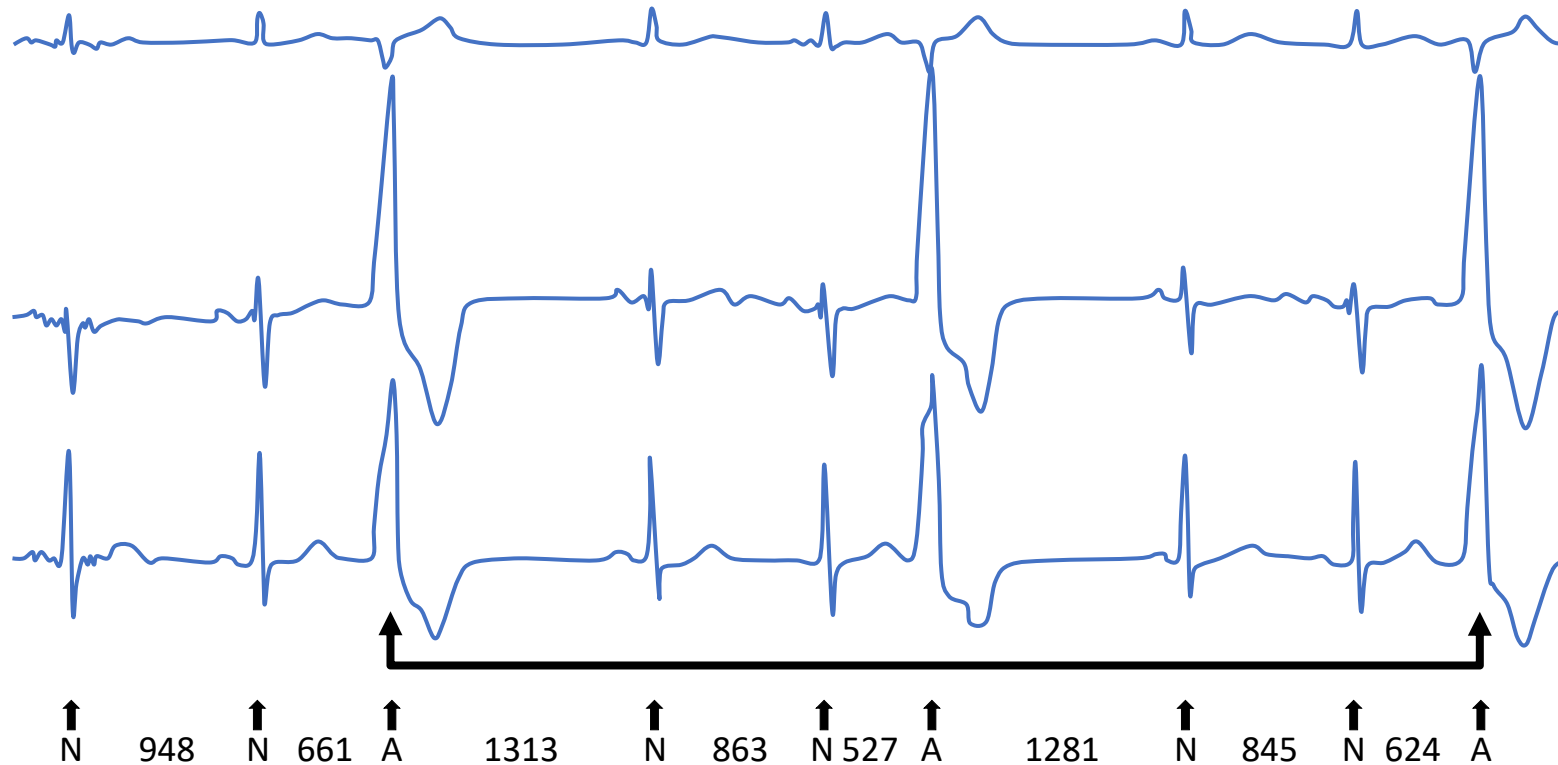- Non-HDL cholesterol: 142 mg/dL

Treatment Priorities

- Improve glucose control and minimize glycemic variability which increases risk of hypoglycemia and advancement of long-term complications
- Reduce CV risk - 2nd prevention
- Stabilize renal function and prevent progression of DKD
- Improve adherence
- Weight loss: achieved by lifestyle + carefully chosen meds for diabetes management and/or bariatric surgery

Frequency of Adverse Outcomes in Patients With T2D Experiencing Severe Hypoglycemia
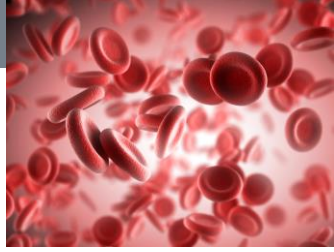

The median time from an episode of severe hypoglycemia until death in T2D is ≤ 1.6 years!

Conclusion – severe hypoglycemia is associated with a higher risk of mortality

Legend:
- Macrovascular event
- Microvascular event
- Death from any cause
- Cardiovascular death
- Noncardiovascular death

Y-axis: Num,ber of Adverse Outcomes (0, 5, 10, 15, 20, 25)

X-axis: Severe Hypoglycemia to Event, Months (0-12, 13-24, 25-36, 37-48)

Zoungas S, et al. *N Engl J Med*. 2010;363:1410-1418.

Example of Cardiac Arrhythmia: Sinus Bradycardia With Trigeminy

Glucose = 49 mg/dL

N   948   N   661   A   1313   N   863   N 527   A   1281   N   845   N 624   A

Chow E, et al. *Diabetes.* 2014;63:1738-1747.

35

Practical Tips for Treating Hypoglycemia

- Patient, family, and friends should be aware of hypoglycemia signs and symptoms

- Raise the targeted blood glucose level for 2 weeks to minimize risk of hypoglycemia and restore hypoglycemia awareness in high risk patients

- Have a plan to manage hypoglycemia (*e.g. Rule of 15*)
  - Test BG, if possible
  - Treat hypoglycemia with 15 grams of sugar or carbohydrates (e.g. ½ cup juice, 2-3 glucose tablets)
  - Wait 15 minutes and test BG again
  - Take additional 15 grams if necessary
  - Follow treatment of hypoglycemia with protein
  - Resume activity when feeling better and BG > 100 mg/dL
  - Glucagon

ADA. Hypoglycemia (low blood glucose).
http://www.diabetes.org/living-with-diabetes/treatment-and-care/blood-glucose-control/hypoglycemia-low-blood.html.
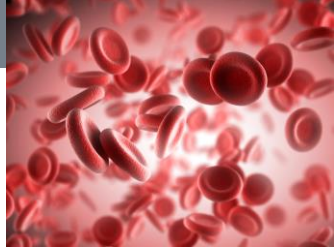
Patient Case: Tony's Treatment Plan

On initial visit, was taking:
- Metformin 500 mg BID
- Glipizide 10 mg BID
- Valsartan 80 mg QD
- Rosuvastatin 5 mg QD

New Treatment Plan:
- Begin semaglutide 0.25 mg/week
- Increase atorvastatin to 80 mg QD
- Consider use of PCSK9i
- Begin aspirin 81 mg QD
- Begin metoprolol 50 mg QHS
- Continue metformin 500 mg BID
- Increase losartan to 100 mg QD
- Consider referral to bariatric surgery

Labs
- A1C: 9.1 %
- eGFR: 38 mL/min/1.73
- Albumin Creatinine Ratio: 447 mg/gram
- Total cholesterol: 180
- Triglyceride: 190 mg/dL
- LDL cholesterol: 104 mg/dL
- HDL cholesterol: 38 mg/dL
- Non-HDL cholesterol: 142 mg/dL
- Hemoglobin/Hematocrit: 12.5/37
- Thyroid Stimulating Hormone: Normal
- Liver Function Tests: Within 2 x upper limits of normal.
- Testosterone: 125 ng/dL
- B12: Normal

Patient Case: Tony's CGM

A1C = 9.1 %

Metformin 500 mg BID + glipizide 10 mg QD

3 months later: A1C = 7.2 %

Semaglutide 1 mg + Metformin 500 mg BID

38

CGM = Continuous Glucose Monitor

# The Disconnect Between Clinical Trials and Real-World Results
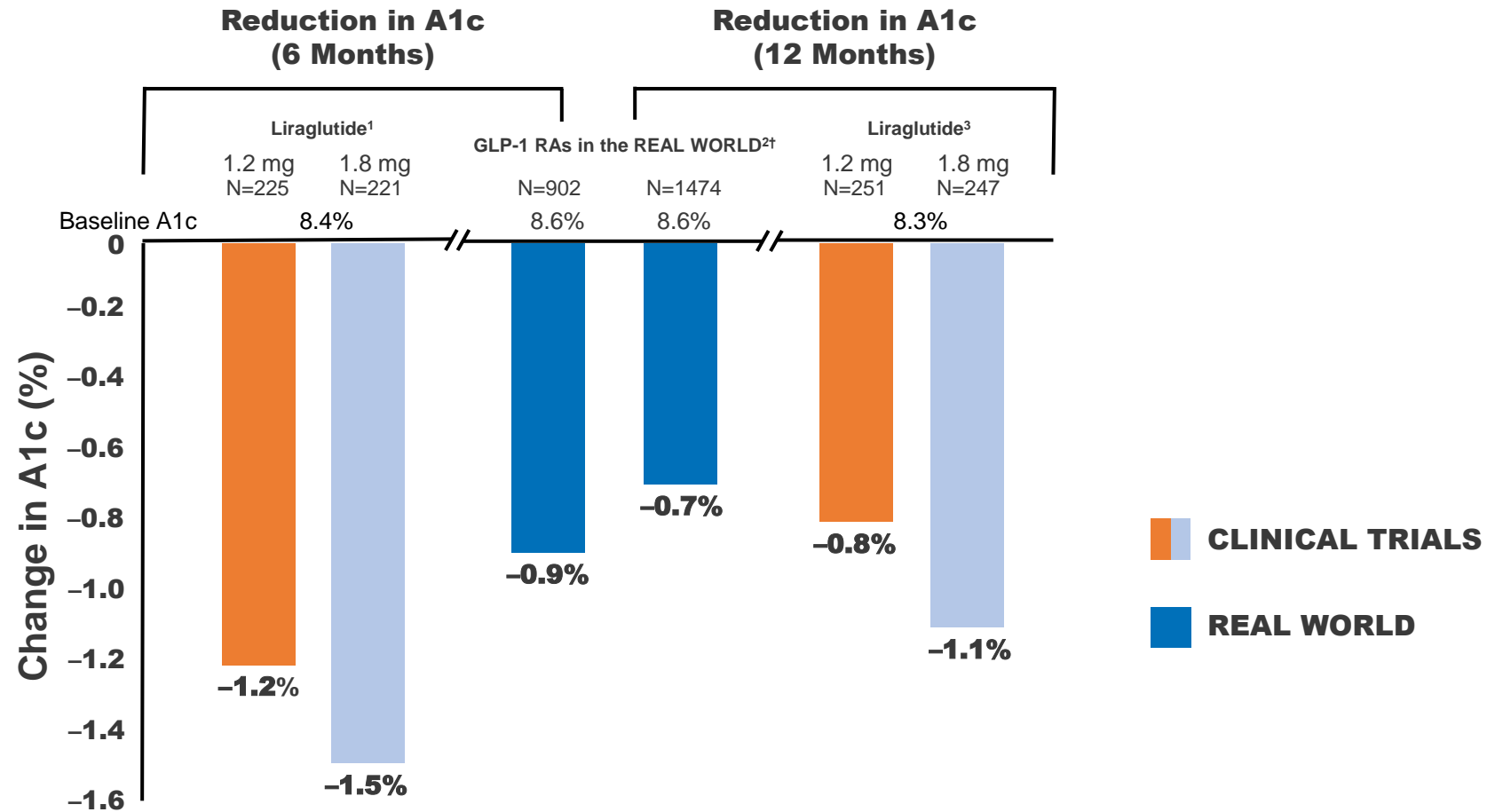
†Quintiles EMR database

N=1474 patients with T2D who were prescribed liraglutide or exenatide once weekly.

1. Pratley RE, et al. *Lancet.* 2010;375:1447-1456.
2. Singhal M, et al. ISPOR Annual International Meeting. May 16-20, 2015; Poster PDB10.
3. Garber A, et al. *Lancet.* 2009;373:473-481.

39

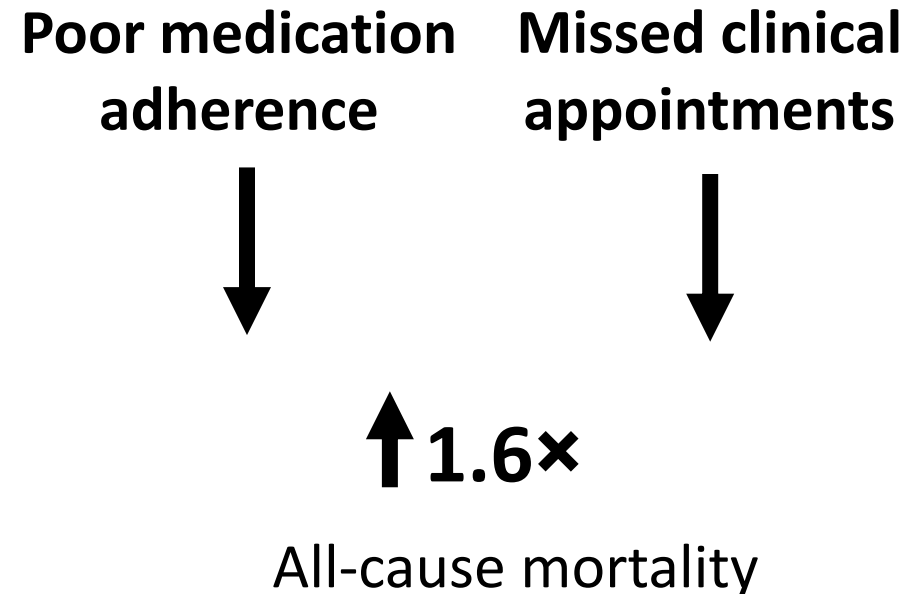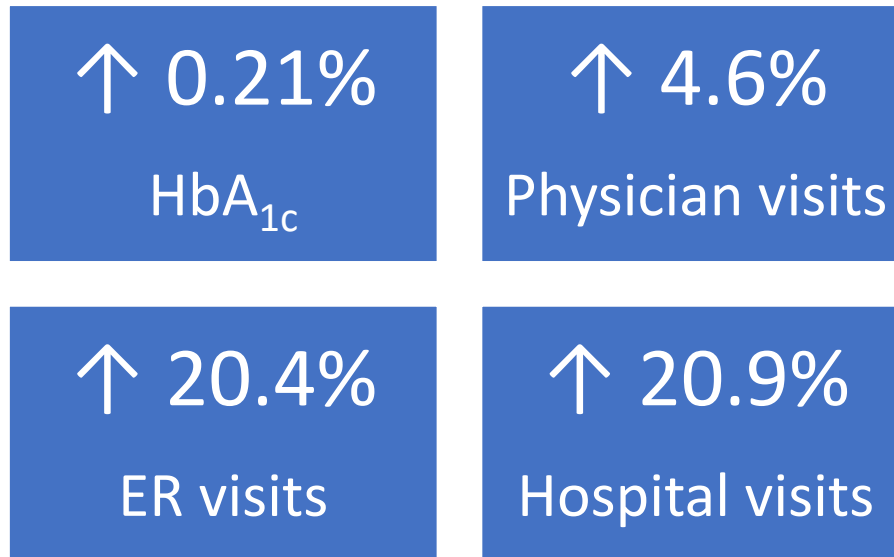# Patient Adherence with Medications for T2DM Is Suboptimal
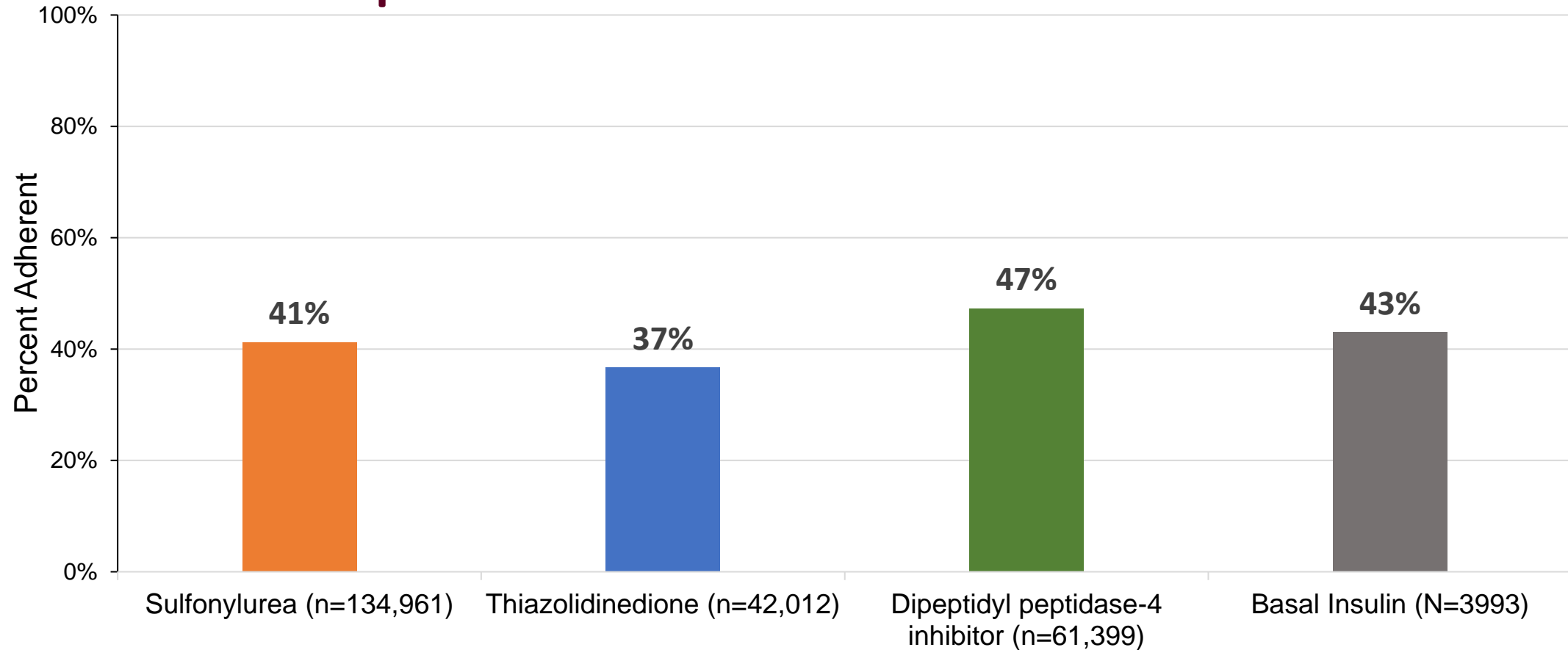
Adherence defined as: SU, TZD, DPP-4i: patients who maintained proportion of days covered ≥0.80 over 1 year
Basal insulin: patients with refill gap ≤90 days over 18 months

Farr AM, et al. *Adv Ther.* 2014;31(12):1287-1305.
Zhou FL, et al. *Diabetes Obes Metab.* 2018;20:1298-1301.

Medication NON-Adherence, Either Willful or Inadvertent, Can Include:

- Failing to fill or refill prescription
- Omitting a dose or taking medications at the wrong time
- Taking more or less of a medication than prescribed
- Prematurely discontinuing medication
- Inappropriate supplement use
- Taking medication with prohibited foods, liquids, other medications
- Improperly using administration devices (i.e., inhalers, syringes)

Consequences of Poor Medication Adherence

1-point drop in self-reported medication adherence (MMAS scale) is associated with:

| ↑ 0.21% HbA$_{1c}$ | ↑ 4.6% Physician visits |
| ↑ 20.4% ER visits | ↑ 20.9% Hospital visits |

Poor medication adherence ↓ **Missed clinical appointments** ↓

↑ **1.6×**

All-cause mortality

DiBonaventura M, et al. *Patient Prefer Adherence*. 2014;8:873-882;
Currie CJ, et al. *Diabetes Care*. 2012;35:1279-1284.

4 C's: Strategy to Assess Cultural Competency

- Call: What do you "call" your problem?
  - What do you think is wrong?
- Cause: What do you think caused your problem?
  - Gets at patient beliefs regarding source of the problem.
- Cope: How do you cope with your condition?
  - Have you done anything or seen anyone else to improve?
- Concerns: What are your concerns regarding the condition and/or recommended treatment?
  - What's the hardest thing right now? What do you fear the most?
  - How is this interfering with your life or ability to function?

43

Consequences of Care Deficient of Cultural Competence

- Patients may have untoward health consequences or poor quality of care and be dissatisfied with their care.

- Lower-quality patient-provider interactions are associated with decreased patient satisfaction in the healthcare provider.

  - African Americans, Asian Americans, Latinos & Muslims report that the quality of their care was diminished because of their ethnicity or race.

Diana L. Swihart; Romaine L. Martin. *Cultural Religious Competence In Clinical Practice*. March 2020.

Summary: Goals Of Diabetes Management

- Define and achieve glycemic targets (A1C, fasting and postprandial glycemia, as well as "time in target" for patients using continuous glucose sensors).

- Choose therapy that addresses both glucose lowering and the pathogenesis of T2D (ominous octet).

- Use medications that favor weight loss and minimization of hypoglycemia.

- Optimally address other established comorbidities.

  - Including high-intensity statins, aspirin, ACE/ARBs, SGLT-2 inhibitors, and GLP-1 RAs, as applicable.

- For patients at high risk for CVD, prescribe appropriate cardiovascular and reno-protective medications. Independent of glycemic targets.