DIABETES COMPLICATIONS

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OUTLINE

- Microvascular complications
  - Diabetic nephropathy
  - Diabetic retinopathy
  - Diabetic neuropathy
- Macrovascular complications
  - Coronary artery disease
  - Peripheral artery disease
  - Stroke

CASE 1

- 26 yo male patient recently diagnosed with type 1 diabetes (T1D) after an episode of DKA, comes to you to stablish care. After hospitalization, patient is doing well adjusting to how to live with diabetes. He is measuring his BG 4x day ranging from 100-150 mg/dL fasting and pre-meals, and is compliant with insulin regimen. On PE: BP:125/80, HR 80, BMI 22, no signs of lipodystrophy on abdomen (area of insulin injection). He had some time to research about diabetes and is concerned about if he can have already any complications.

QUESTION 1

- How long does usually take for a patient with type 1 diabetes to develop long-term complications?

a) 2 years

b) 5 years

c) 7 years

d) 10 years

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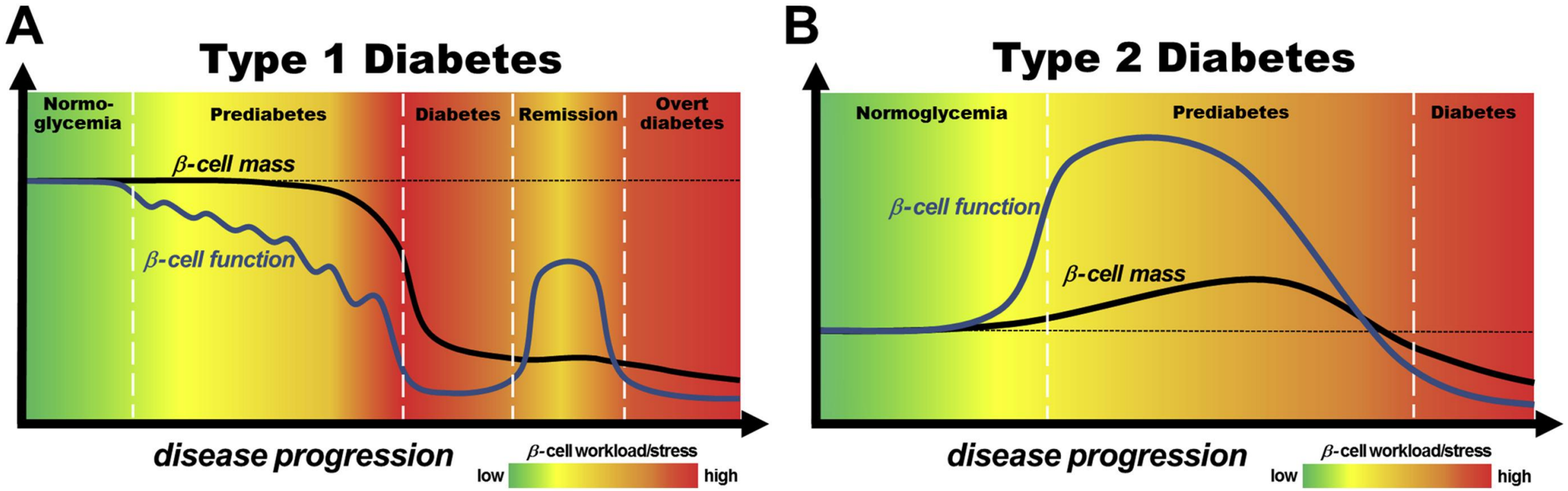
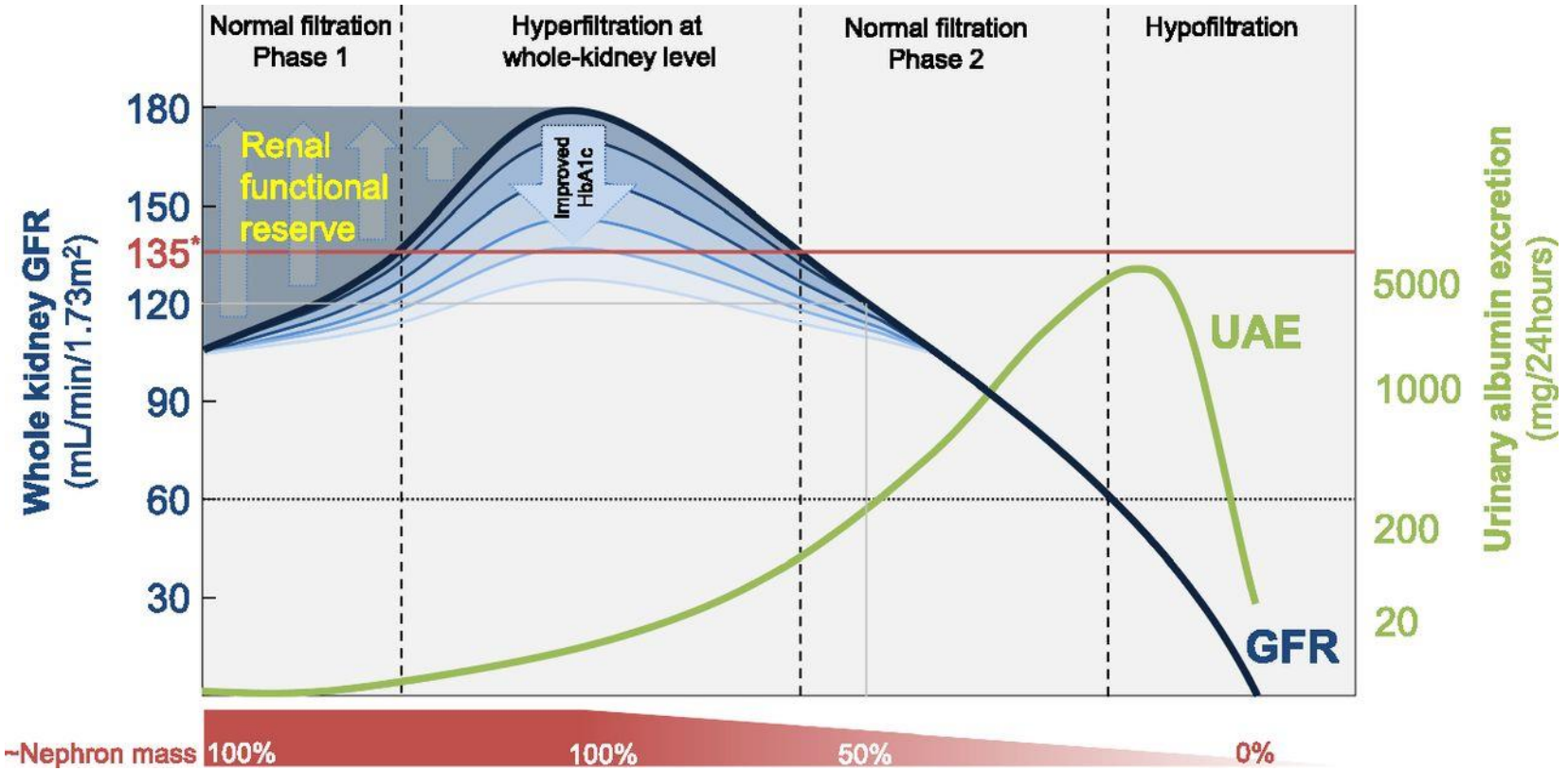
PATHOGENESIS OF DIABETES



Chen C. Molecular Metabolism. 2017.

Classic course of whole-kidney GFR and UAE according to the natural (proteinuric) pathway of DKD. Peak GFR may be seen in prediabetes or shortly after diabetes diagnosis, and can reach up to 180 ml/min in the case of two fully intact kidneys.



Lennart Tonneijck et al. JASN 2017;28:1023-1039

JASN Journal of the American Society of Nephrology

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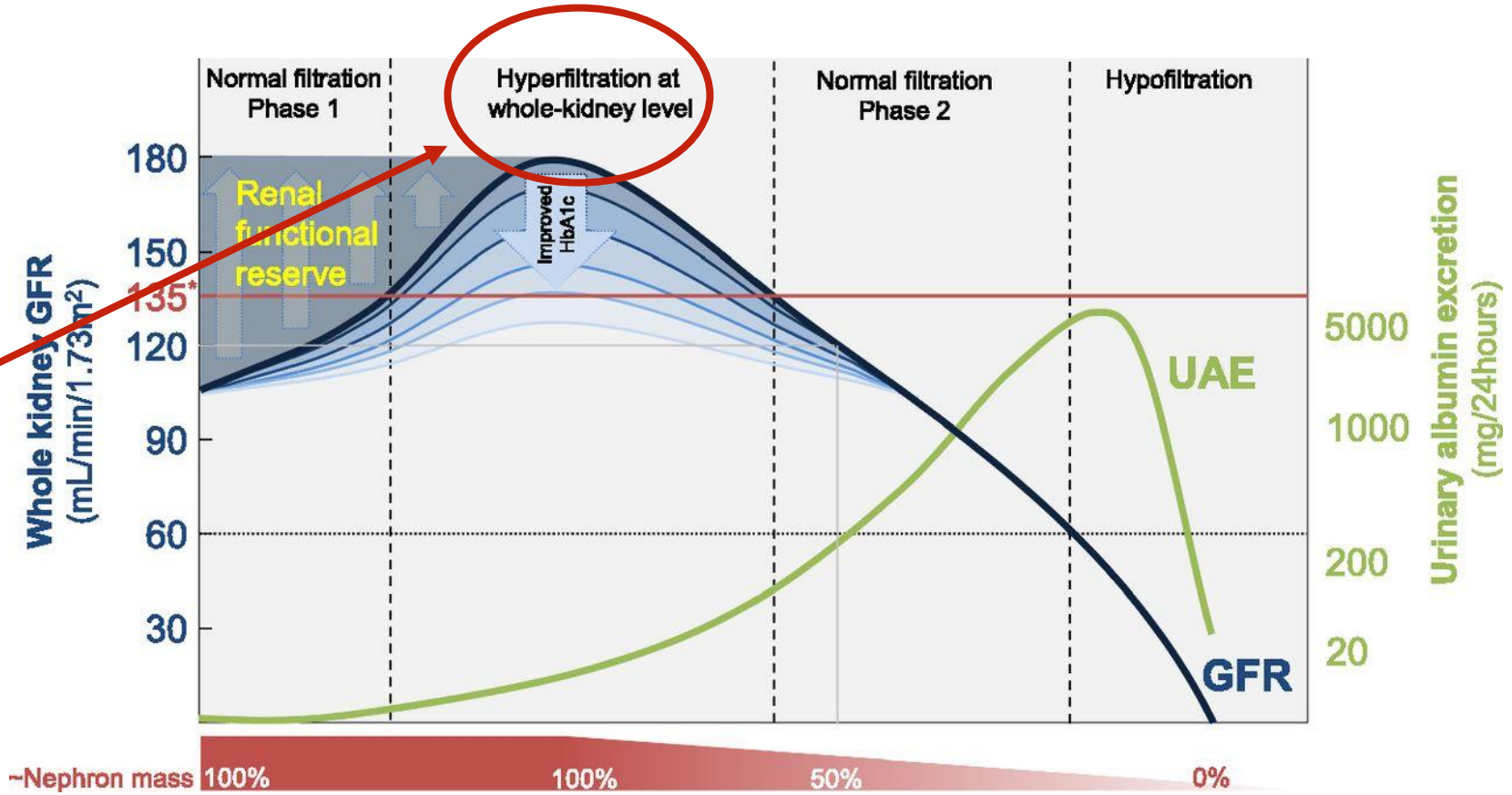
Pre-diabetes
Early diabetes
Obesity



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DIABETIC KIDNEY DISEASE (DKD)

- Screening
  - Who to screen:
    - T1D → duration ≥ 5 years
    - T2D → at diagnosis
    - all patients with co-HTN
  - At least once a year:
    - urinary albumin (e.g., spot urinary albumin–to–creatinine ratio)
    - eGFR

ADA – 2019 Standards of Care

DIABETIC KIDNEY DISEASE (DKD)

- Treatment
  - To reduce the risk or slow the progression of DKD
    - Optimize glucose control
    - Optimize BP control
  - Dietary protein:
    - Non dialysis-dependent DKD: ~ 0.8 g/kg body weight/day
    - Patients on dialysis: higher levels of dietary protein intake
- Monitor urinary albumin–to–creatinine ratio
- ACEi or ARB **NOT** recommended for primary prevention

ADA – 2019 Standards of Care

- If patient had type 2 diabetes and was found to have deteriorating GFR to 49 ml/min/1.73/m^2, despite being on good BG on metformin and BP control and on Lisinopril. what diabetic agent could you use to assist on stabilization of kidney function?

a) Insulin
b) Dulaglutide
c) Pioglitazone
d) Canagliflozin

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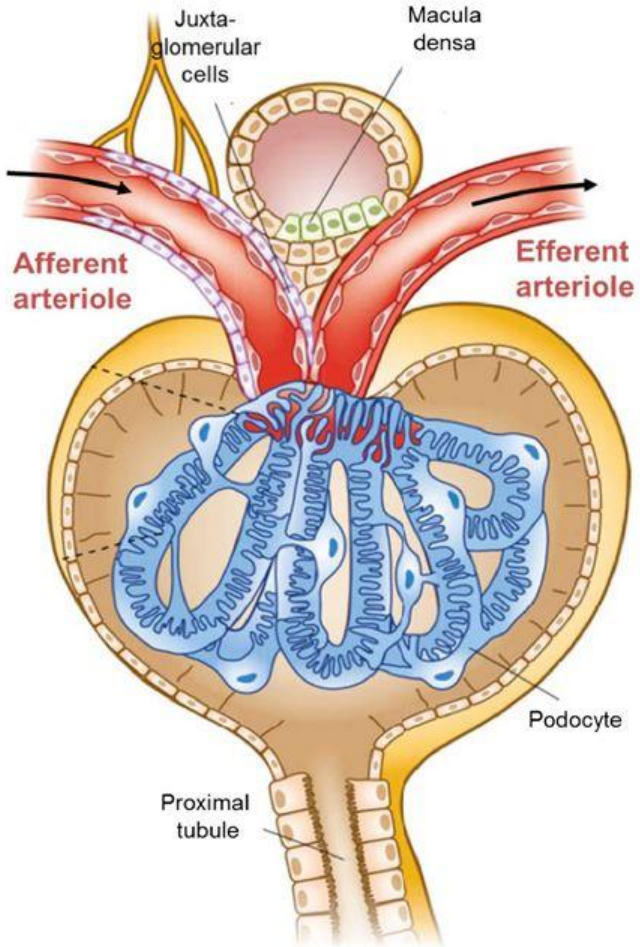
Schematic (net) effect of factors implicated in the pathogenesis of glomerular hyperfiltration in diabetes.

Factors causing a net reduction of <u>afferent</u> arteriolar resistance
Vascular factors
Nitric oxide bioavailability
COX-2 prostanoids
Kalikrein-kinins
Atrial natiuretic peptide
Angiotensin(1-7)
Hyperinsulinemia *per se*
Tubular signals
Inhibition of tubuloglomerular feedback (macula densa signals)



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ACE-I
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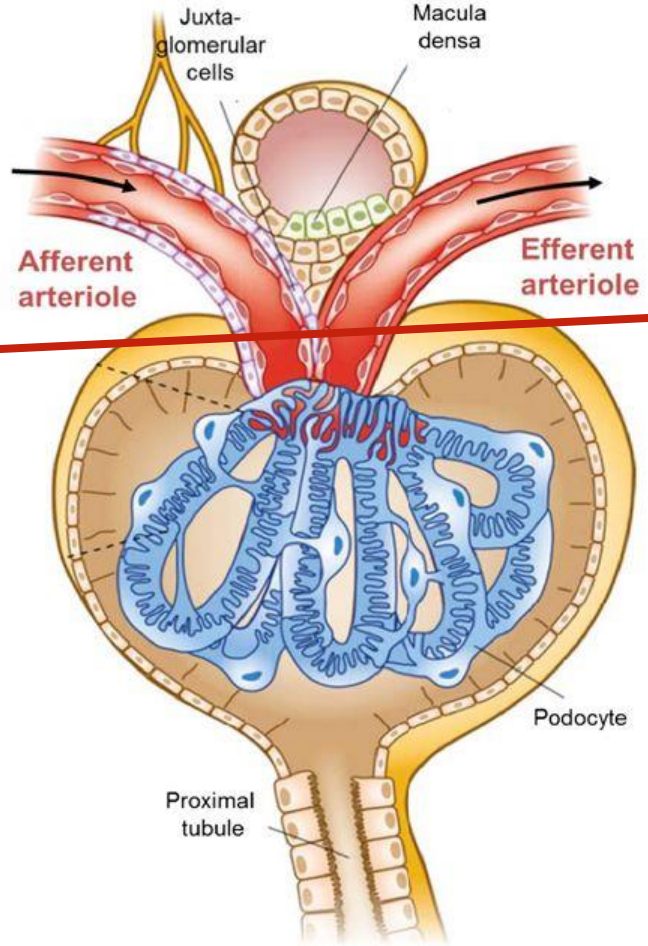

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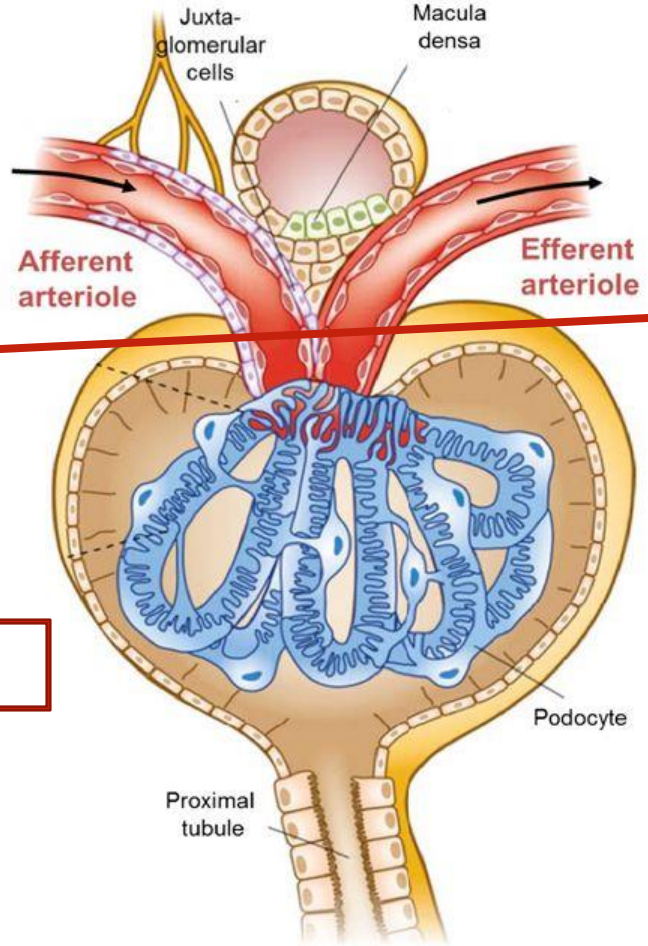

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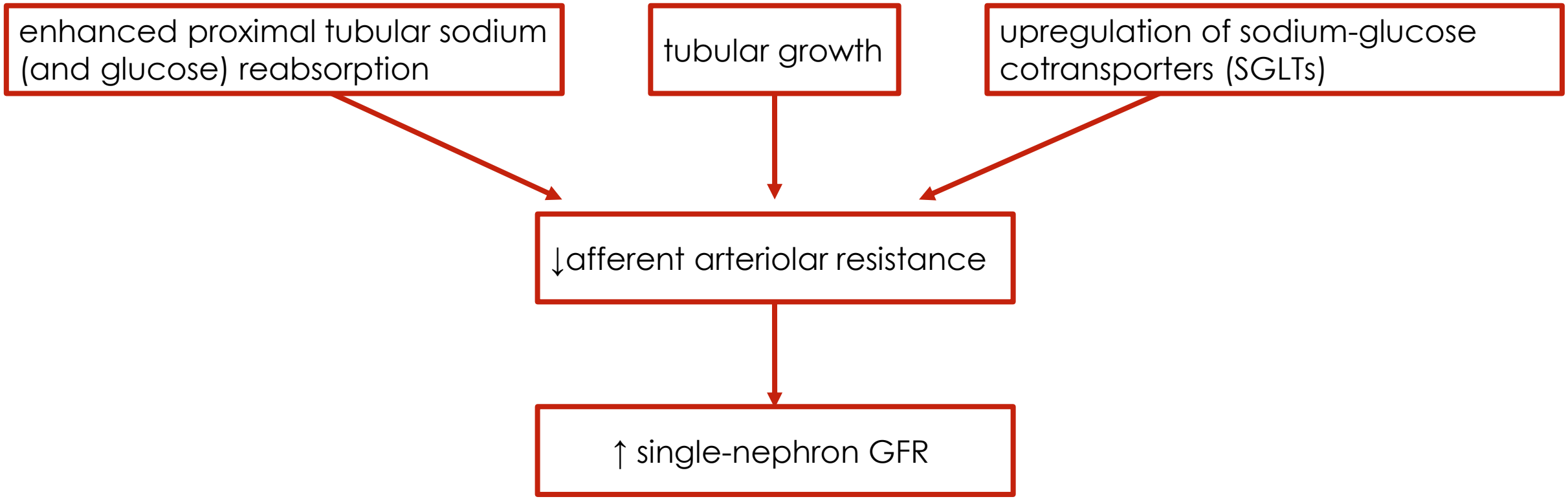
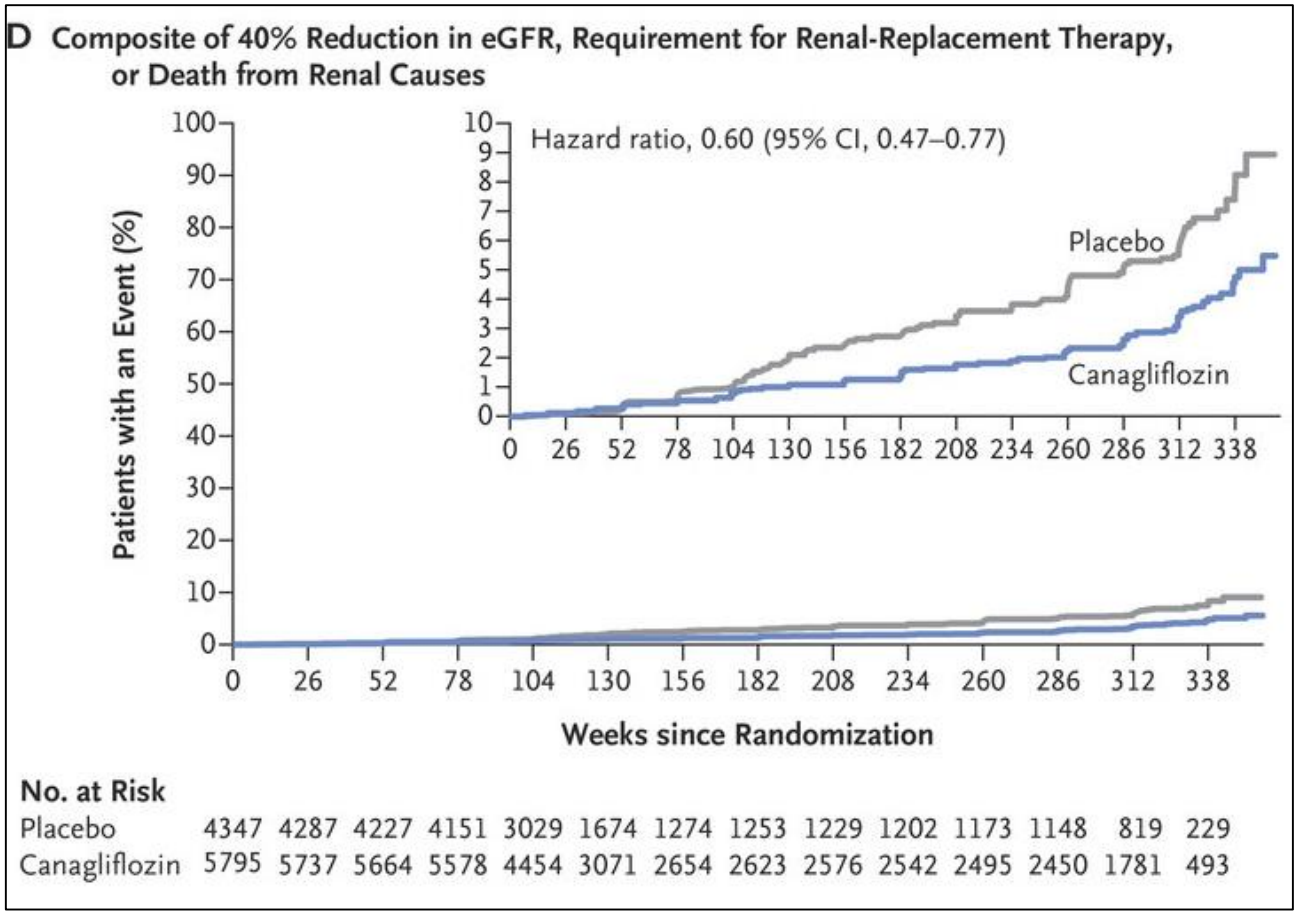


Canagliflozin and cardiovascular outcomes - CANVAS study



renal-specific composite outcome:

- Reduction in eGFR
- Renal-Replacement Therapy
- Death from Renal Causes

Neal B et al. NEJM 2017

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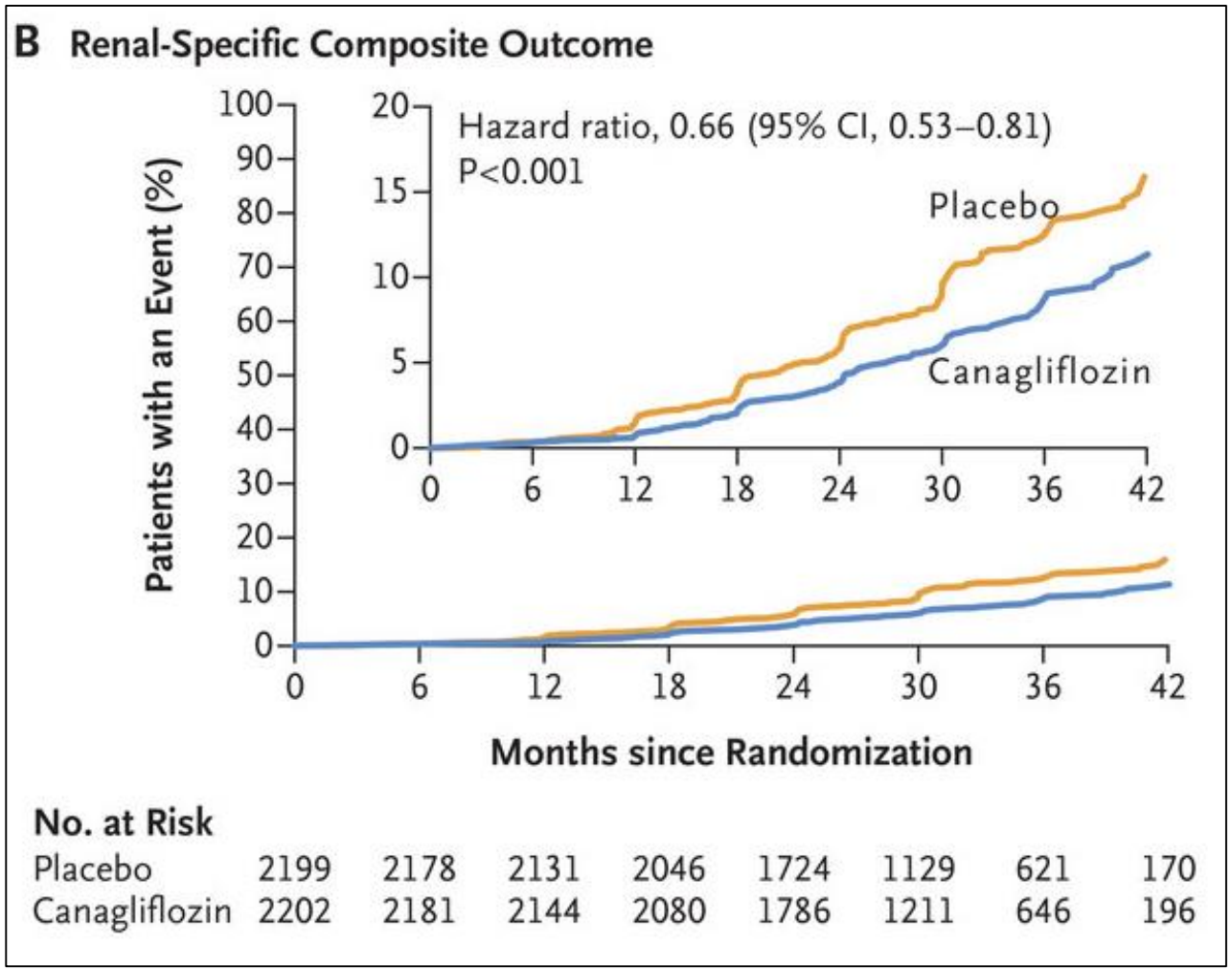
Canagliflozin and Renal outcomes - CREDENCE study



renal-specific composite outcome:

- End-stage kidney disease
- Doubling of serum creatinine level
- Renal death

V PERKOVIC ET AL. NEJM 2019.

The NEW ENGLAND JOURNAL of MEDICINE

METFORMIN AND CKD

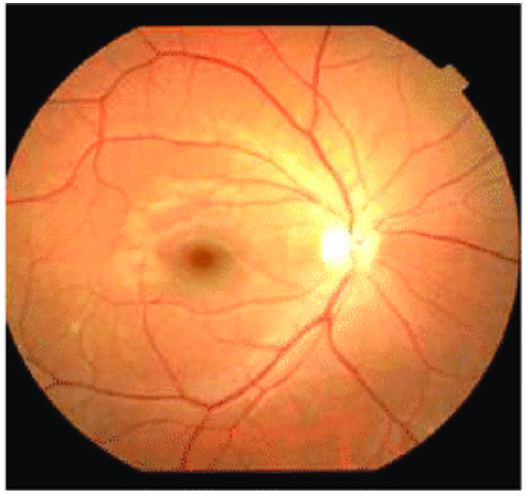
- Monitor eGFR at least yearly
- eGFR <30 mL/min/1.73 m^2 → Metformin contraindicated
- eGFR <45 mL/min/1.73 m^2 → Reassess benefits/risks
- eGFR <45 mL/min/1.73 m^2 → Do not initiate metformin
- eGFR 30–60 mL/min/1.73 m^2 →D/c metformin temporarily at the time of or before iodinated contrast imaging procedures

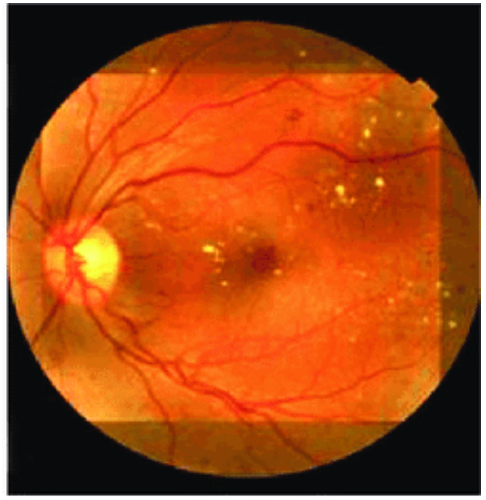
Within these constraints, metformin should be considered the first-line treatment for all patients with T2D, including those with CKD

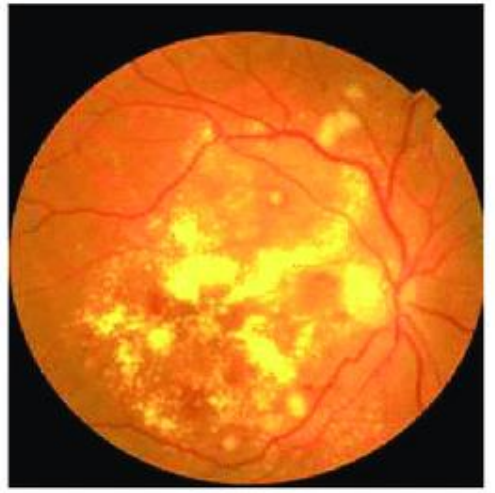
FDA guidance + ADA 2019 Standards of Care

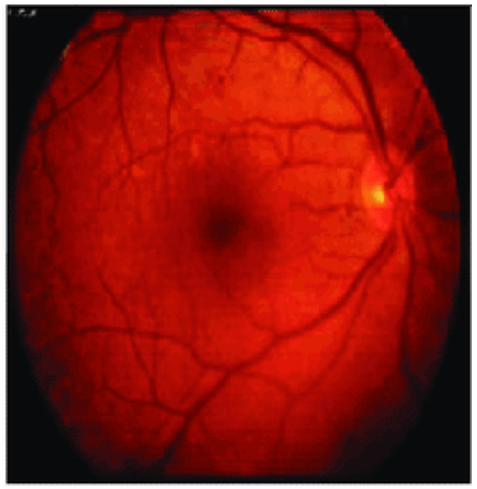
CASE 2

- A 56 yo female patient with type 2 diabetes for 10 years, HTN, and HLP, comes to you for follow up. She reports that she went to her ophthalmologist. She reports that her retinal exam revealed proliferative diabetic retinopathy (PDR). What are the findings on a retinal exam that indicate proliferative diabetic retinopathy?

a) 

b) 

c) 

d) 

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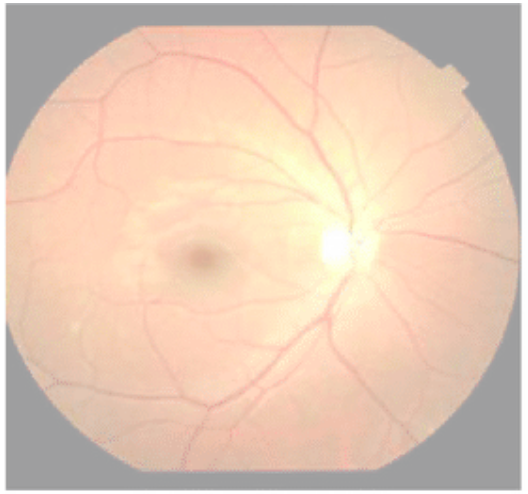
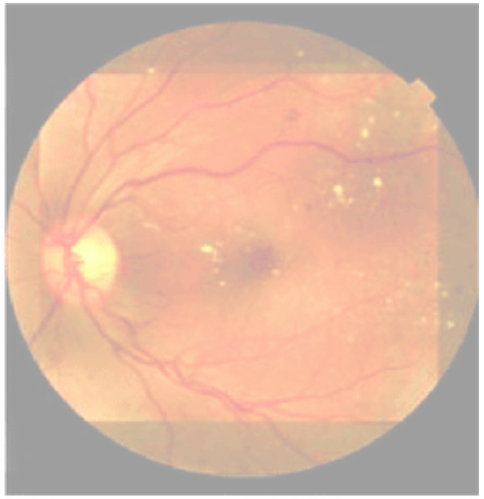
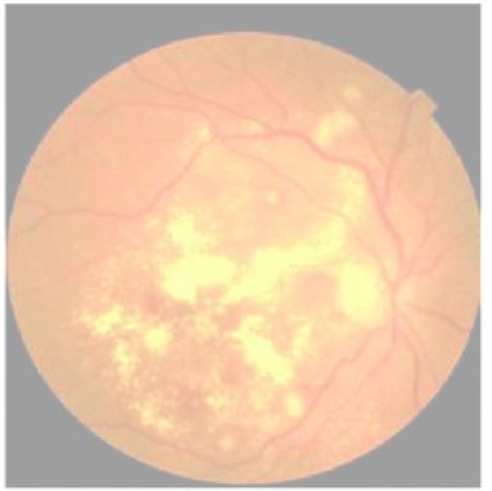
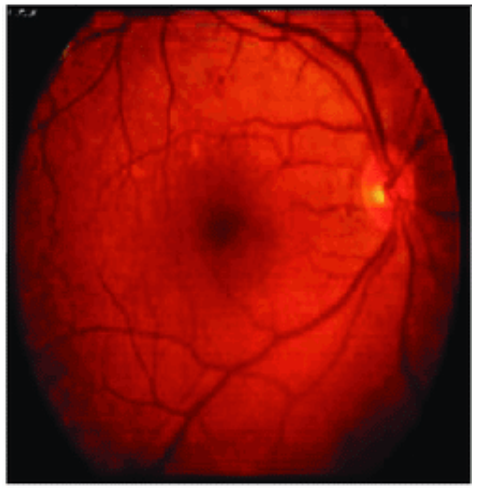
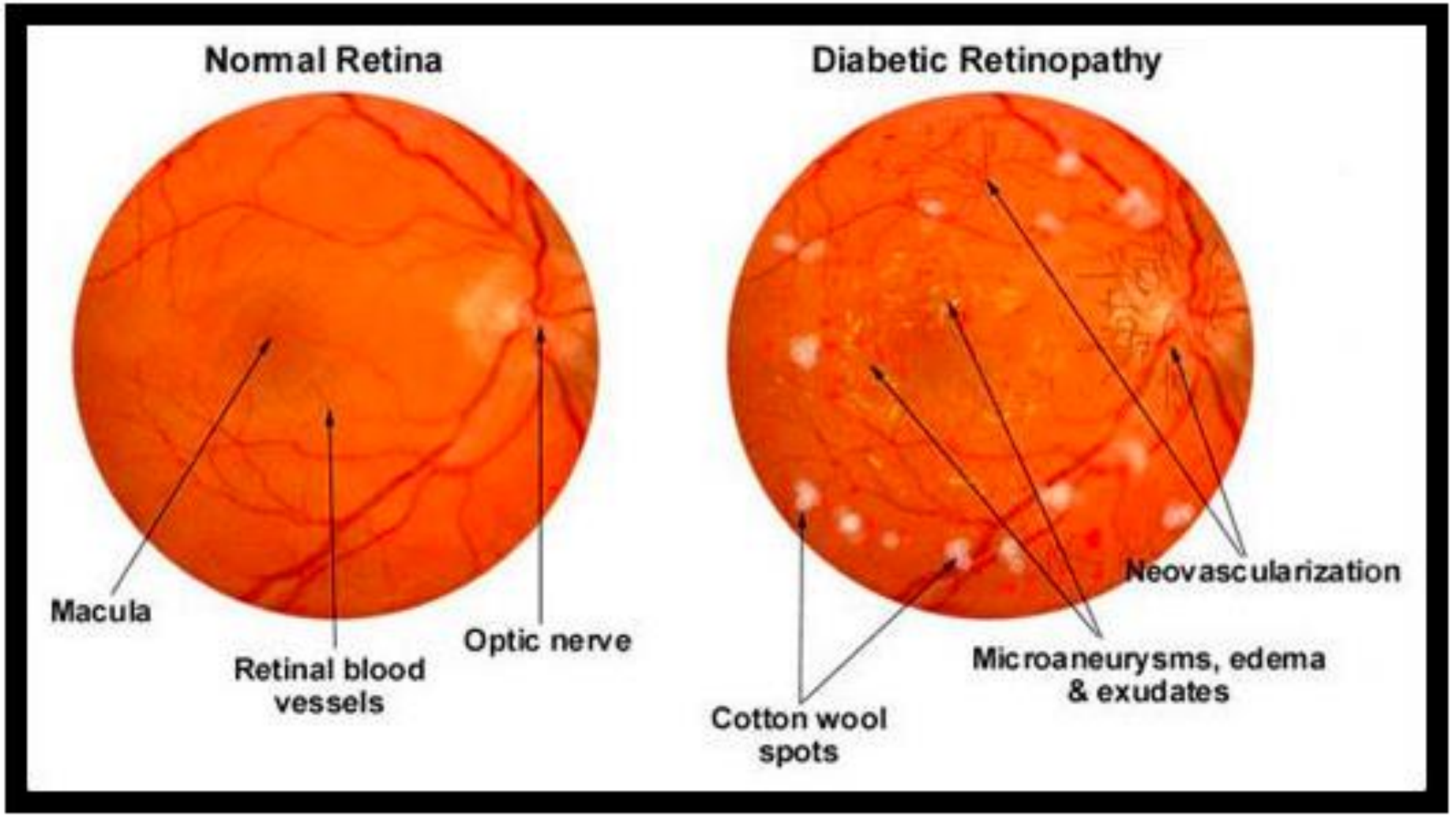
a) 

b) 

c) 

d) 

DIABETIC RETINOPATHY



DIABETIC RETINOPATHY

- To reduce the risk or slow the progression of diabetic retinopathy:
  - Optimize glycemic control
  - Optimize blood pressure control
  - Optimize serum lipid control

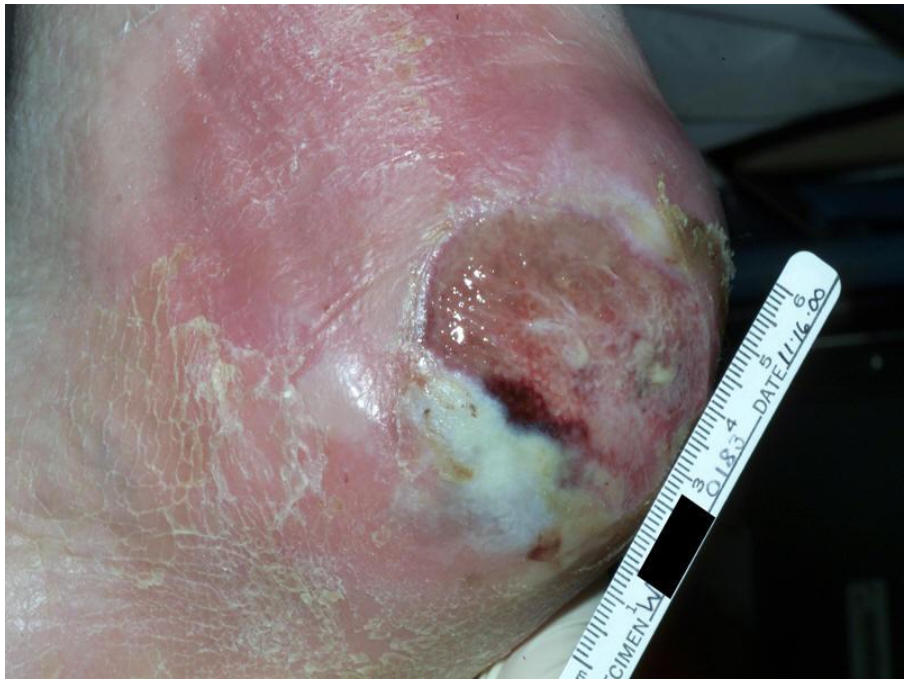
DIABETIC RETINOPATHY

- Screening
  - initial dilated eye examination
    - T1D: within 5 years after the onset of diabetes.
    - T2D: at the time of the diabetes diagnosis.
  - Follow up exams
    - No retinopathy ≥ 1 annual eye exam + BG well controlled → exams every 1–2y
    - Any diabetic retinopathy → dilated retinal examinations repeated annually
    - Progressing or sight threatening retinopathy → more frequent examinations

TREATMENT RETINOPATHY

- Management by experienced ophthalmologist if:
  - any level of macular edema
  - severe nonproliferative diabetic retinopathy (NPDR)
  - any proliferative diabetic retinopathy (PDR)
- Panretinal laser photocoagulation therapy (↓ risk of vision loss)
  - high-risk PDR
  - severe NPDR
- Intravitreous injections of anti–vascular endothelial growth factor (VEGF; ranibizumab)
  - not inferior to traditional panretinal laser photocoagulation
  - indicated to ↓ risk of vision loss in patients with PDR
  - indicated for central-involved diabetic macular edema
- Not a contraindication to aspirin therapy for cardioprotection

- This patient is also complaining of a burning pain on her feet, worsen at night, who is not allowing her to sleep sometimes, because the touch of the sheets on her feet are too painful. You perform a foot exam:



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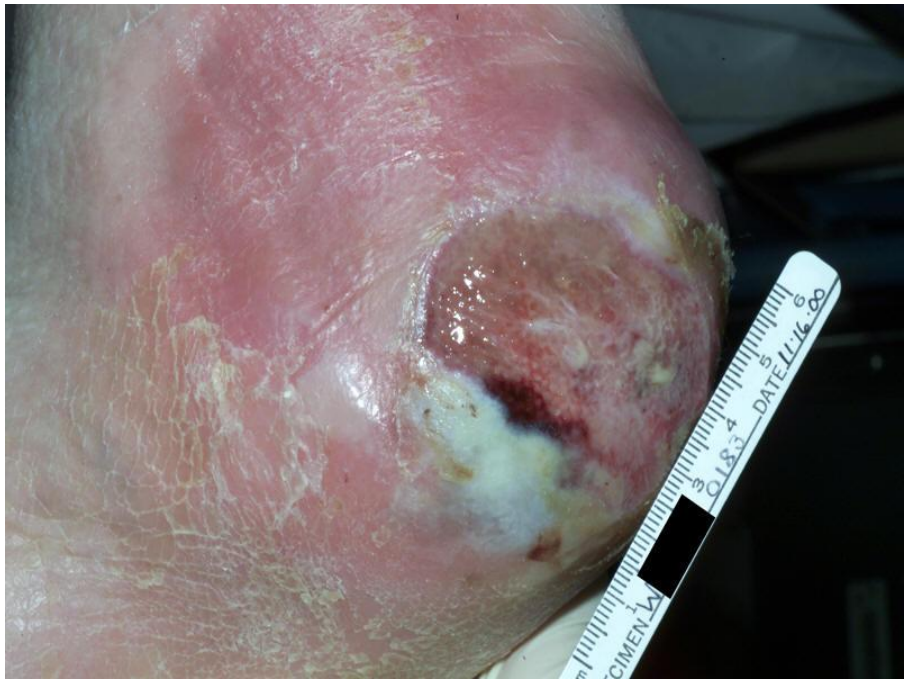

What are the most common microorganism that causes this?

a) Staphylococcus aureus & B hemolytic streptococcus
b) Staphylococcus aureus & Clostridium difficile
c) Staphylococcus aureus & Pseudomonas aeruginosa
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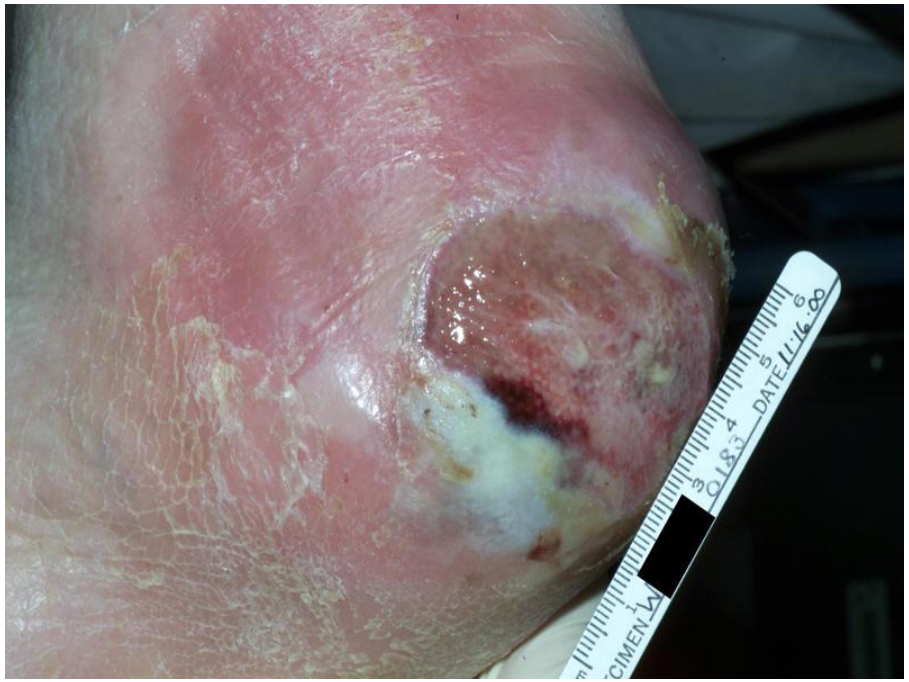

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DIABETIC NEUROPATHY

- Screening
  - Timing
    - T2D → at diagnosis
    - T1D → 5 years after the diagnosis
    - annually thereafter
  - Assessment for distal symmetric polyneuropathy
    - Small-fiber function: pinprick and temperature sensation
    - Large-fiber function: vibration perception and 10-g monofilament
    - Protective sensation: 10-gmonofilament (at least yearly)

TREATMENT FOR NEUROPATHY

- Optimize glucose control
  - prevent/delay the development of neuropathy in T1D
  - slow the progression of neuropathy in T2D
- Goals
  - to reduce pain related to diabetic peripheral neuropathy
  - To reduce symptoms of autonomic neuropathy
  - to improve quality of life
- Initial pharmacologic treatment options
  - Pregabalin
  - Duloxetine

CASE 3

- 55 yo male patient with hx of T2D for 8 year, HTN, HLP, and obesity come to the ED with chest pain radiated to the left upper extremity for 30 minutes. He reports that he stopped all his meds few months ago. On PE: BP 166/104 HR 94 BMI 35 , patient is diaphoretic. RRR no murmurs. Clear lungs. EKG shows ST elevation on V1-V5. A1c 8.5, creat 0.9, LDL 190, HDL 35. Besides medical therapy, patient undergoes to angiogram followed by angioplasty and stent placement on LAD. What is the optimal medical therapy for patient when he leaves the hospital?

a) Life-style change, Metformin, Rosuvastatin 40 mg, Clopidogrel, AAS 81mg, Metoprolol
b) Life-style change, Metformin, Liraglutide, Rosuvastatin 40mg, Clopidogrel, AAS 81 mg, Metoprolol
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d) Nothing, patient is not going to take anyways

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CORONARY HEART DISEASE

- Screening
  - In asymptomatic patients
    - routine screening is not recommended
    - It does not improve outcomes as long as atherosclerotic CVD risk factors are treated.
  - Investigate for coronary artery disease
    - atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort)
    - signs or symptoms of associated vascular disease
      - Carotid bruits
      - Transient ischemic attack
      - Stroke
      - Claudication
      - Peripheral arterial disease
    - electrocardiogram abnormalities (e.g., Q waves).

CASE 3

- He returns 3 months later. He lost 20 lbs, stopped smoking, is doing 30 min of walking 5x/week and taking his meds regularly. Denies symptoms. PE: BP 123/61 HR 64 BMI 31. A1c 7.5, LDL 68, Creat 0.9. What can you add on his regimen to reduce risk of a new CV event?

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c) Sitagliptin
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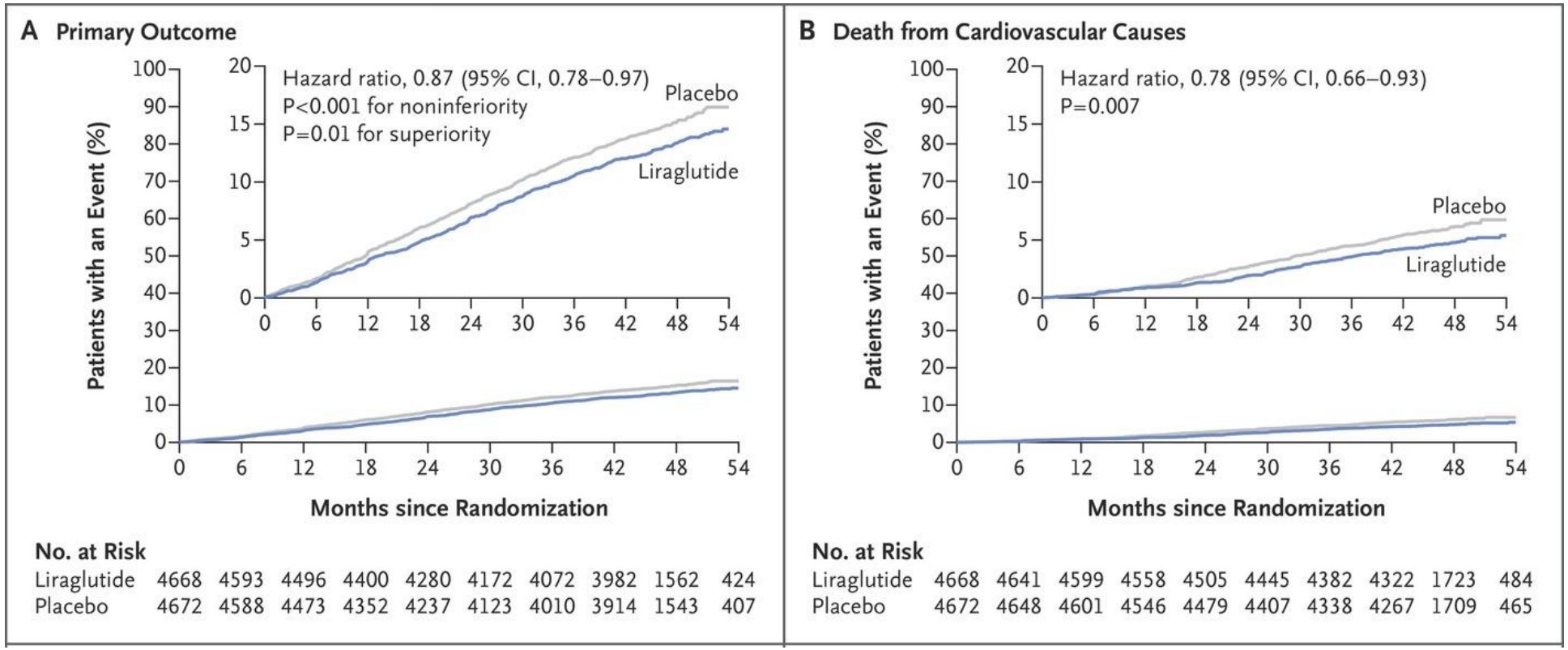
LIRAGLUTIDE AND CARDIOVASCULAR OUTCOMES - LEADER STUDY



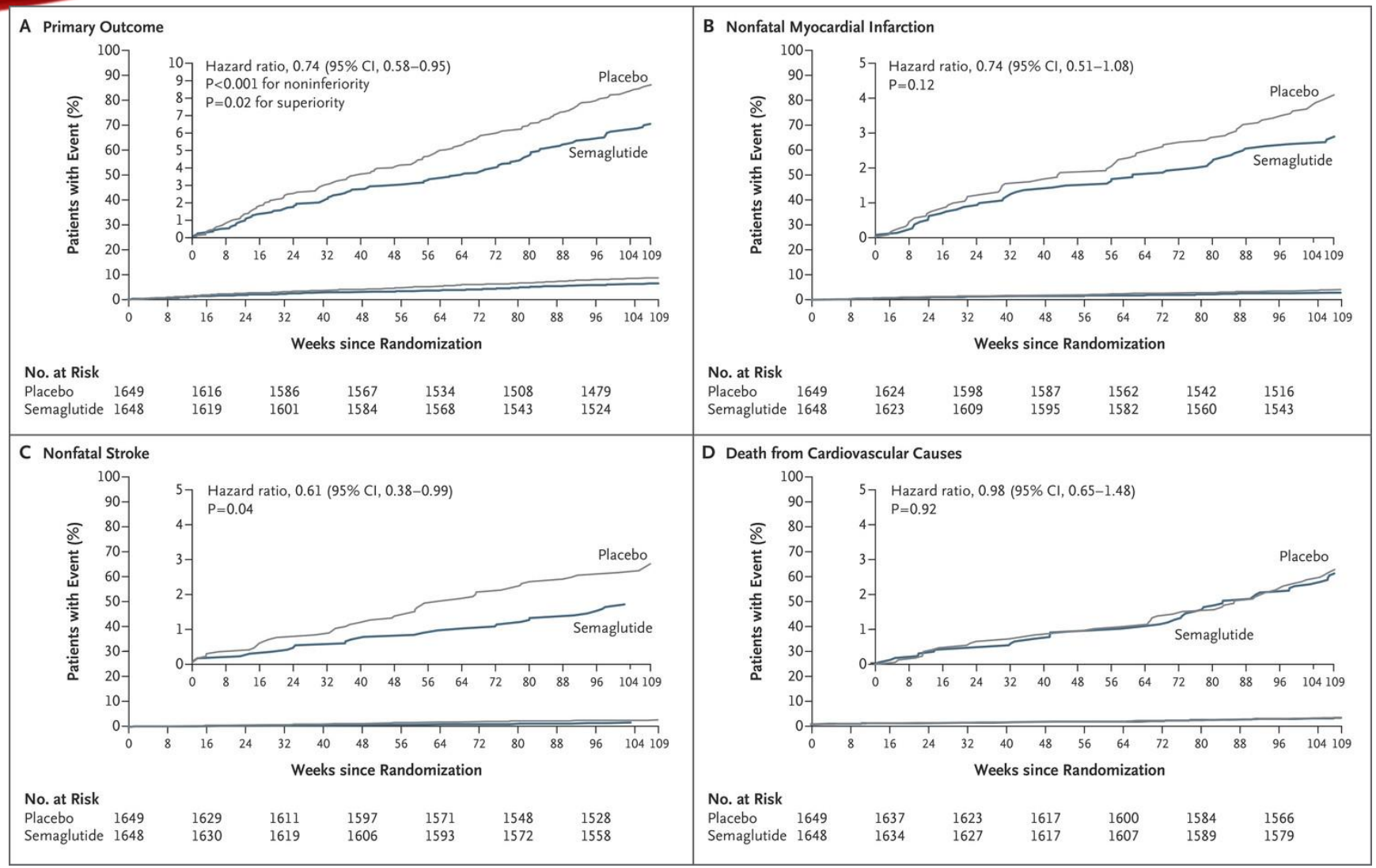
Primary outcomes:

- CV death
- MI
- Stroke

Marso, S.P. et al. 2016.

The NEW ENGLAND JOURNAL of MEDICINE

Semaglutide and cardiovascular outcomes - SUSTAIN-6 study



Marso, S.P. et al. 2017.

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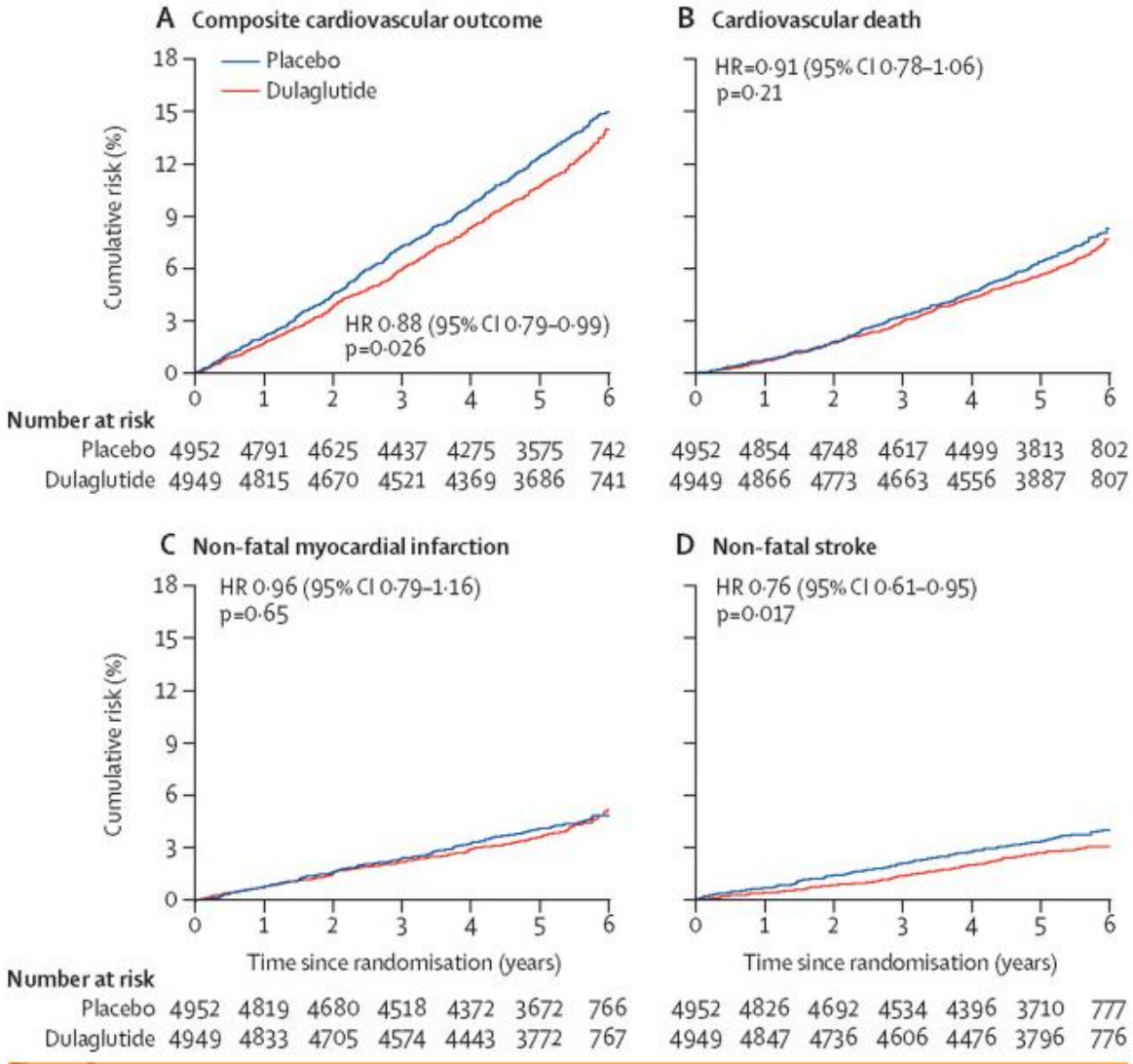
Dulaglutide And Cardiovascular Outcomes - REWIND STUDY



Gerstein, H.C. The Lancet. 2019

TREATMENT

- known atherosclerotic CVD → ACEi or ARB therapy
- If prior MI → beta-blockers for at least 2 y after the event
- T2D + stable CHF, metformin may be used if eGFR remains >30 mL/min
  - avoided in unstable or hospitalized patients with CHF
- T2D + established atherosclerotic CVD, antihyperglycemic therapy:
  - 1st: lifestyle management + metformin
  - 2nd: empagliflozin and liraglutide →proven to ↓ major adverse CV events/mortality
  - canagliflozin may be considered to reduce major adverse CV events

ADA 2019 Standard of Care

SUMMARY

- Microvascular complications typically presents after 5 years of T1D diagnosis, but may present at the time of T2D diagnosis
- Yearly screening: eye exam, comprehensive foot exam, urine albumin-to-creatinine ratio, eGFR
- ACEi or ARB and blood glucose control are paramount on treatment of DKD
  - Metformin use (when not contra-indicated)
  - Consider SGLT-2 i
- Laser therapy or VEGFi are treatment for severe diabetes retinopathy: PDR or severe NPDR
- Always exam the feet of patients with diabetes
- No screening for CVD, however aggressively treat BG, HTN and HLP to decrease risk for an event. Consider use of GLP1-RA or SGLT-2i

QUESTIONS?

Joslin Diabetes Center's 50-year medal.

Photo credit ©Joslin Diabetes Center

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