



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Chronic Complications in Diabetes: Exploring Through Cases

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**CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE**



**HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL**

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- *Clinical focus:* Diabetes care in complex patient populations
- *Research focus:* Health outcomes research and care model design for people with diabetes

Disclosures

Research funding paid directly to institution:

Abbott Industries

Diabetes related- conditions abound

Amputations

Arthritis

Asthma

Blindness

Cancer

Chronic skin rash

Cirrhosis

Coronary artery disease

Dementia

Depression

Falls and Fractures

Gallstones

Gastroparesis

Glaucoma

Hearing Loss

Heart failure

Hypertension

HypoG related Trauma

Hypoglycemia

Infection

Infertility

Kidney failure

Miscarriage/stillbirth

Neuropathy

Obesity

Pancreatitis

Peripheral vascular disease

Retinopathy

Stroke

Tendonitis/tenosynovitis

Vaginal yeast infection

And there are more....

Diabetes and Comorbidity Big Picture & Management Pearls

Brief overview: “glucose hypothesis” and prevention

Case 1: Neuropathy and Diabetic Foot

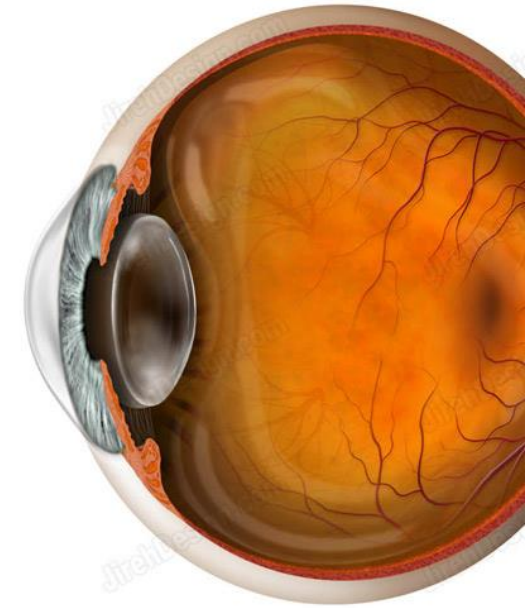
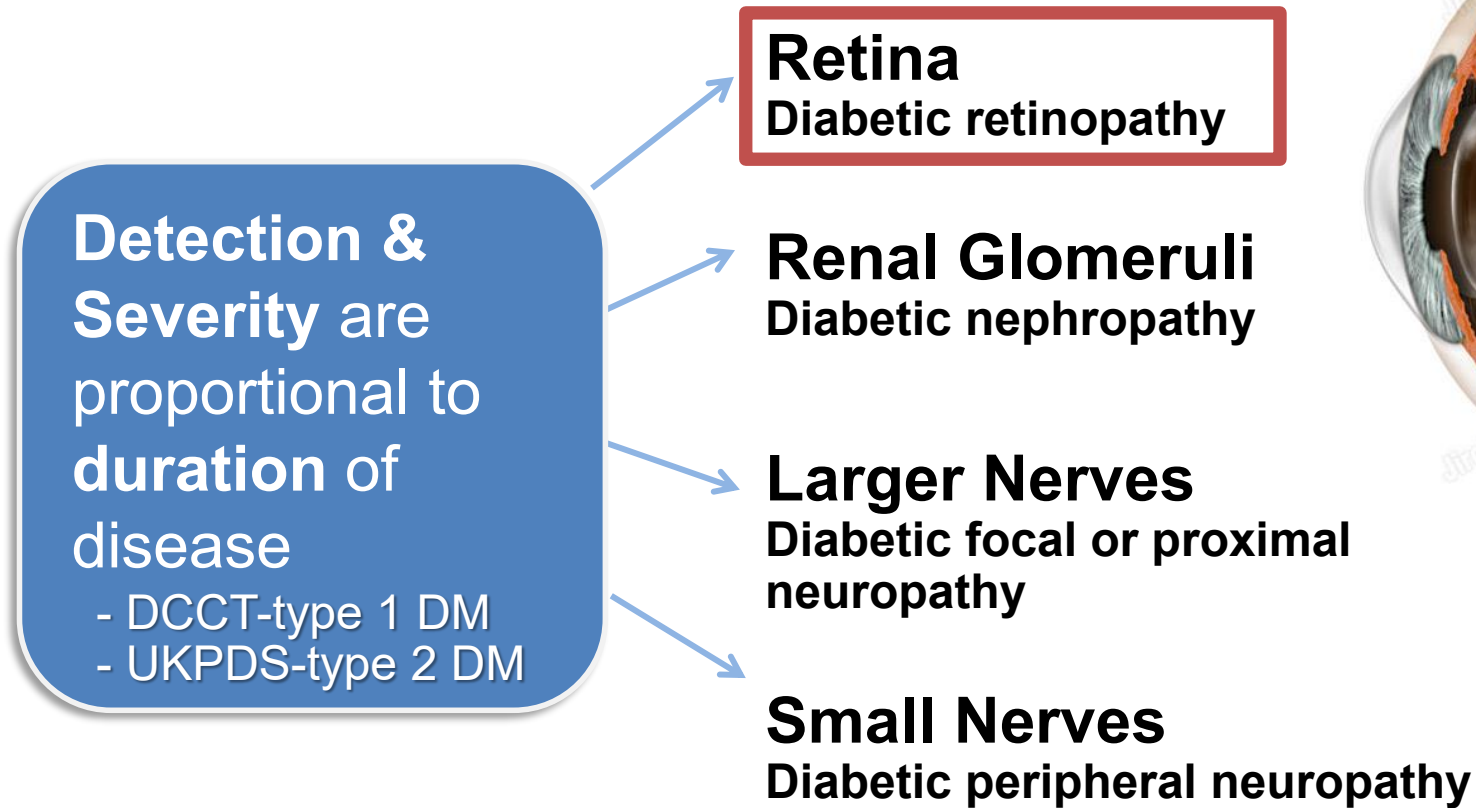
Case 2: Retinopathy

Case 3: Complex obesity

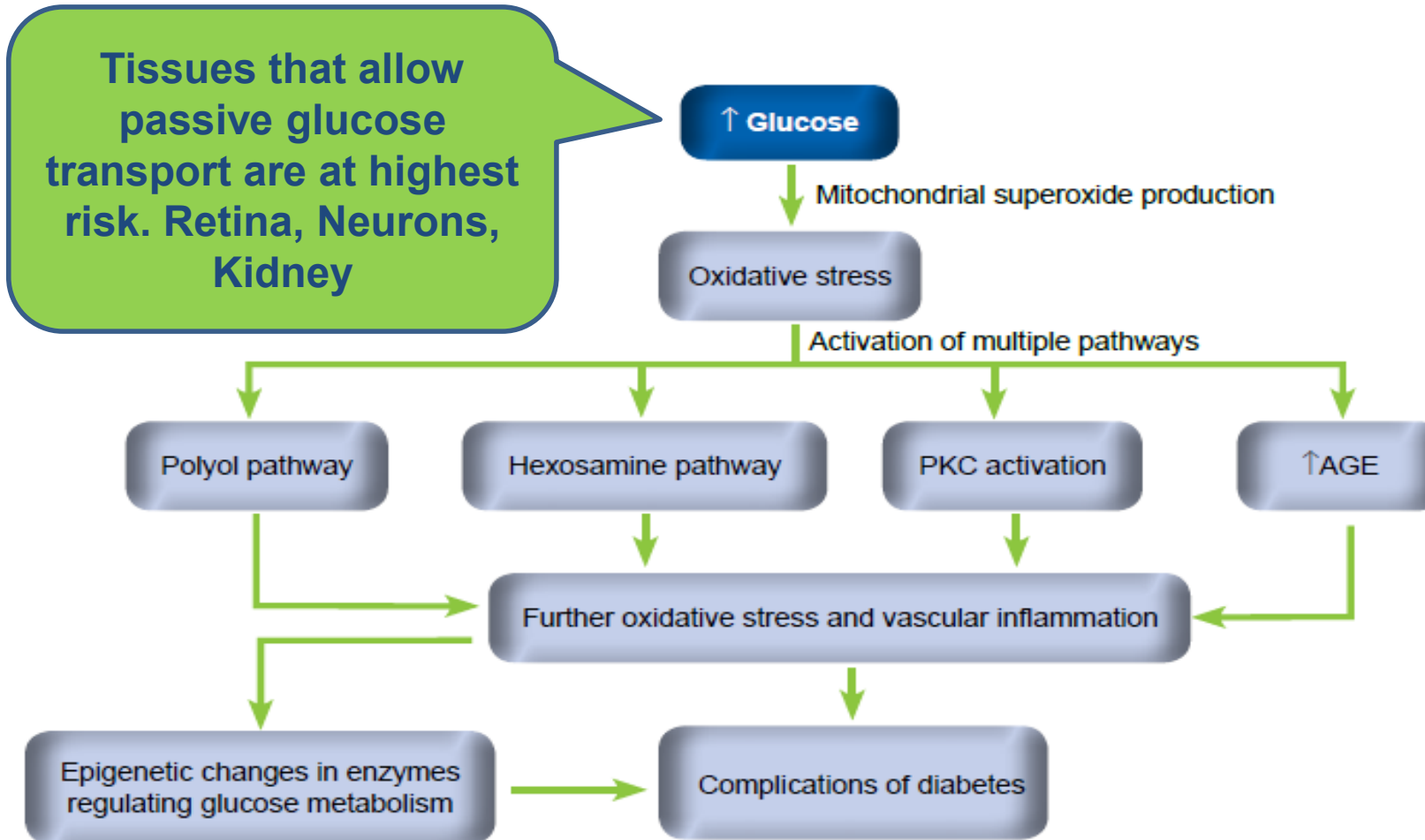
Case 4: CVD: focus on Heart Failure

Prevention Power: The Glucose Hypothesis

Microvascular Capillary and Arteriole Dysfunction

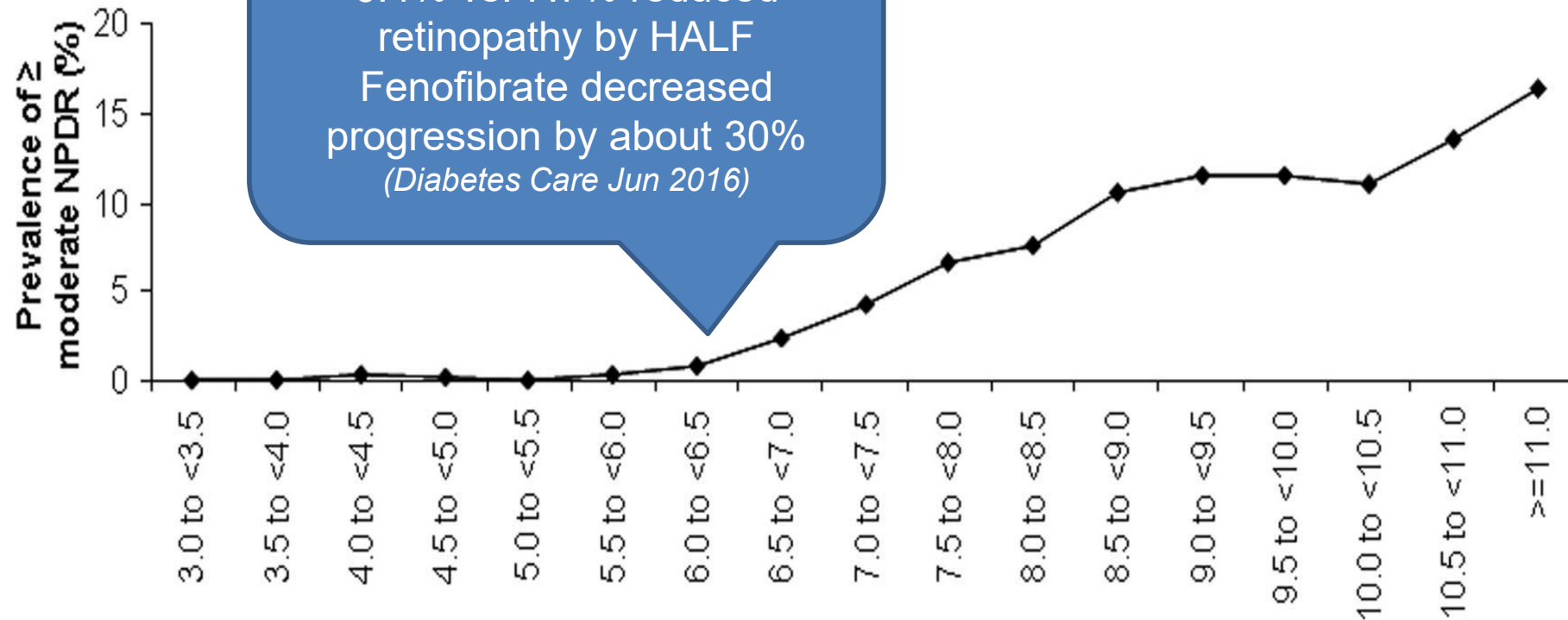


Mechanisms of Hyperglycemia-induced Tissue Damage



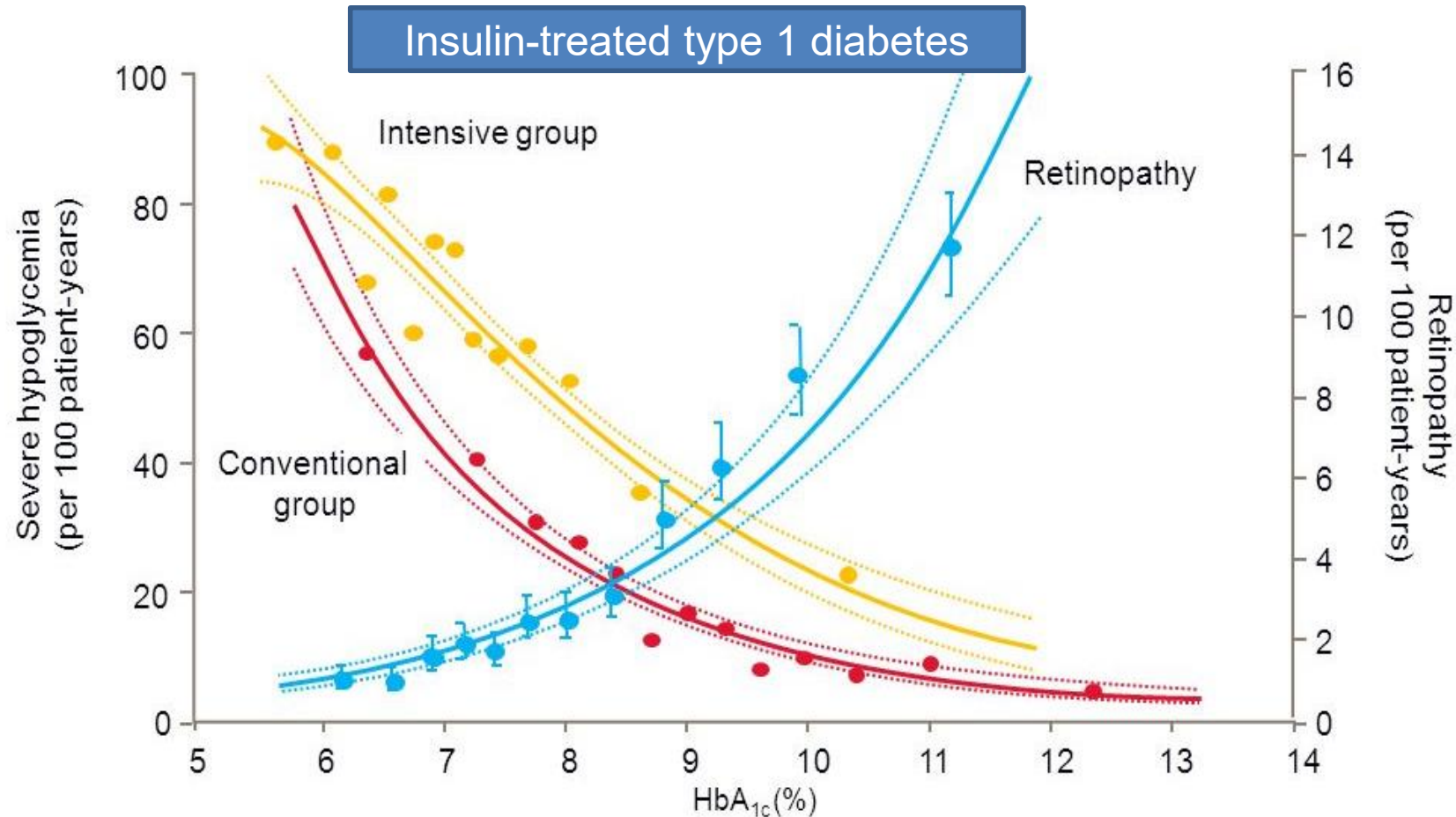
AGE - Advanced glycation end products; PKC - Protein kinase C

Microvascular disease progresses with higher average glucose level



Prevalence of moderate non-proliferative retinopathy by 0.5% intervals in participants aged 20–79 years. DETECT-2 Study.

The “clinician’s conundrum” is minimized with new medications and tools



The Other modifiable Risk Factors for **Microvascular** Complications in Diabetes

- **Cigarette smoking**
- **Dyslipidemia**
- **Hypertension**

Prevention Power: Screening over a Lifetime

Screening: Knowledge is Power

- **Fundoscopy exam**

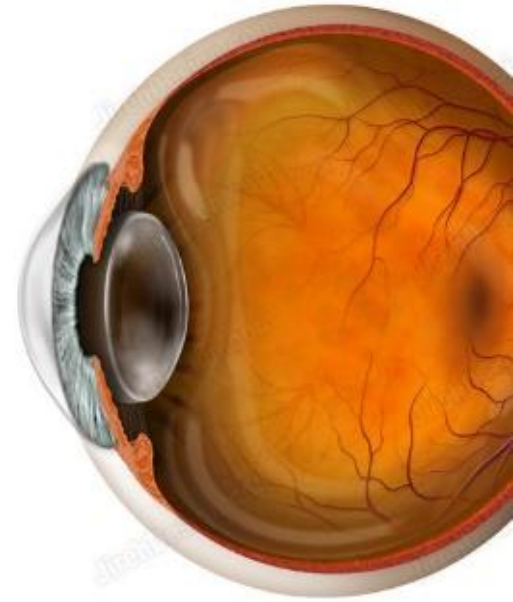
- Within 5 years of diagnosis of T1DM
- At time of diagnosis for T2DM
- Subsequent examinations: annually but every 2 yrs may be considered for well-controlled DM after ≥ 1 normal exams
- Prior to or in early pregnancy

- **Urine microalbumin**

- Annual UACR and serum Cr & eGFR in T1DM ≥ 5 years duration and in all T2DM starting at diagnosis
 - Urine albumin: creatinine ratio (UACR) on spot collection (mg/g Cr)
 - Because of variability in UAE: 2 specimens within 3-6 mo.

- **Foot exam**

- Annual inspection (vascular, deformity, active lesions) and monofilament (risk of amputation)
- **Foot exam at every visit for patients with prior ulcer/amputation/high risk**
- Podiatrist: abnormal monofilament, deformities, vascular, nail hygiene



Case 1: Ralph

- **A 62-year-old man with T1D for 25 years, CAD and HTN presents to your office for annual examination.**
- He has missed 2 appointments with his endocrinologist in the last year. Last retinal exam was 3 years ago (notable for early macular edema). He is taking all medications as prescribed.
- Finally returns due to significant pain in his toes and sometimes feet, comes and goes but can be sharp and “stinging”
- **PE:** BP 128/78 mm Hg, HR 82 beats per minute, BMI is 24. He is alert and oriented.
- **Diabetic foot exam:** absent vibration sensation in the 1st toe and ankle bilaterally. He is insensate to monofilament on noncalloused areas of the dorsal aspect of his 1st toe and 5th metatarsal on the right and the 5th metatarsal on the left. There is normal skin tone and peripheral pulses, + hammertoes diffusely, no red areas.

Case 1: Ralph

Which statement about the Semmes-Weinstein monofilament exam (SWME) findings is true?

- A. The SWME was developed in the 1960s by vascular surgeons to predict amputation risk
- B. Absent sensation on the SWME predicts Falls in the following year
- C. The sensitivity to detect diabetic peripheral neuropathy (DPN) is 60% when compared with nerve conduction study
- D. Vibration sensation loss is detectable later than SWME sensation loss in common DPN
- E. DPN is diagnosed with SWME when at least 2 of the tested sites are insensate

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the Semmes Weinstein monofilament examination (SWME)



- Developed in the 1960s by psychologists Florence Semmes and Sidney Weinstein to measure sensory loss in the **hands** of patients with brain injury
- The most sensitive method is to test **three** sites at highest risk of ulceration where any insensate areas yields a positive screen for DPN
- Using this method, the sensitivity is 90% when compared with the nerve conduction study
- VA data shows a + test predicts falls
- Loss of or early extinguished vibration sensation using 128 Hz tuning fork can be detected **earlier**

Distal Symmetric (Sensorimotor) Polyneuropathy (DSPN or DPN)

- Most common & widely recognized DN
 - Numbness, Tingling in a stocking/glove distribution
 - Pain/dysesthesia when C-fibers are involved
- Classified as :
 - Small Fiber Neuropathy (“C fiber” – PAIN)
 - Large Fiber Neuropathy (motor, vibration, touch/pressure)
 - Mixed Type Neuropathy (most)
- **Exclude B12 deficiency (up to 30% lifetime risk for longterm metformin users!), monoclonal gammopathy, hypothyroidism and uremia especially if early in disease course**



Treatment of small c-fiber “painful” DPN

- Pregabalin and duloxetine are approved by the FDA , Health Canada, and the European Medicines Agency for the treatment of neuropathic pain in diabetes; Tapentadol ER is opiate approved by FDA
- Gabapentin is still most widely studied at doses of 1800 mg to 3600 mg daily (1200 mg to 3600 mg gabapentin encarbil)
- Outcome used : 50% pain intensity reduction
 - associated with less sleep interference, fatigue, and depression, as well as better quality of life, function, and work.
 - **Over half of those treated with gabapentin will not have worthwhile pain relief but may experience adverse events (NNT = 4-8; NNTH = 12-27)**

Finnerup NB,. Lancet Neurol. 2015;14(2):162-173

Wiffen PJ, et al. Gabapentin for chronic neuropathic pain in adults.

Cochrane Database Syst Rev. 2017 Jun 9;6:PubMed PMID: 28597471;

Beyond gabapentin for DPN

- **Pregabalin**
 - Similar to or less effective than neurontin
- **SSRIs: Duloxetine**
 - Minimally effective, may have positive impact on coping
- **Amitriptyline**
 - Good for overnight control, sleep and mood
- **B Vitamin – like treatments**
 - Alpha-lipoic acid: antioxidant
 - Recommended dose 600mg QD or BID
 - Benfotiamine; derivative of thiamine
 - Fits with our understanding of pathophysiology but may be “too little too late” for most with pain - start earlier?
 - Modest impact in small RCTs, **but negligible side effects**
- **Topicals:**
 - Capsaicin, lidocaine patches; can help with more localized pain

Spinal Cord Stimulation for refractory Painful DPN



24-month outcomes, N= 216→> 187

Implanted cohort, 24-month follow-up

79.9%

mean pain
reduction

90.1%

≥50% pain
relief

65.7%

neurologic
improvement



10hz device (low
frequency)

Multicenter RCT in
the US sponsored
by NevCorp

QoL + sleep improved

Infection explant: 3.2%

Take-home: selected refractory PDN,
durable option

, Refractory DPN pain pathway

1 Confirm refractory PDN

Lower limb • ≥ 1 yr • pain $\geq 5/10$

2 Optimize basics

Glycemia • foot care • sleep • mood

3 Guideline-directed therapy

Duloxetine • gabapentinoid • TCA/topical • (Alpha lipoic acid)

4 Avoid opioid default

Short-term or last resort only

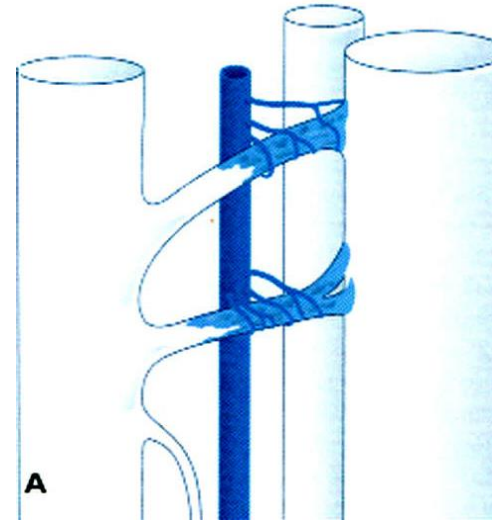
5 SCS referral

Pain/neuro • trial → implant

Focal Neuropathy

Vasculitis/ Interfascicular Infarction

- Mononeuropathy
- “Entrapment neuropathy”
- Older age
- Often a diagnosis of exclusion
- Painful, Self-limited, Resolves in 6-8 weeks, Rx: symptomatic relief



Cranial nerves: 3, 4, 6, 7

Ulnar, median, radial, femoral, **lateral femoral cutaneous (meralgia paresthetica)**,
medial and lateral plantar, peroneal, sural, sciatic, thoracic and abdominal nerves

Autonomic Neuropathy

DAN Prevalence:
1.9% to 90% depending
on tests used for diagnosis

Eye

- Abnormal pupillary reaction, with night blindness

Cardiovascular

- Sudden death, silent myocardial infarction
- Orthostasis
- Impaired peripheral vascular reflexes

Respiratory

- Failure of hypoxia-induced respiration

Gut

- Gustatory sweating
- Gastropareses
- Diarrhea
- Constipation
- Loss of anal sphincter tone and incontinence

Metabolic

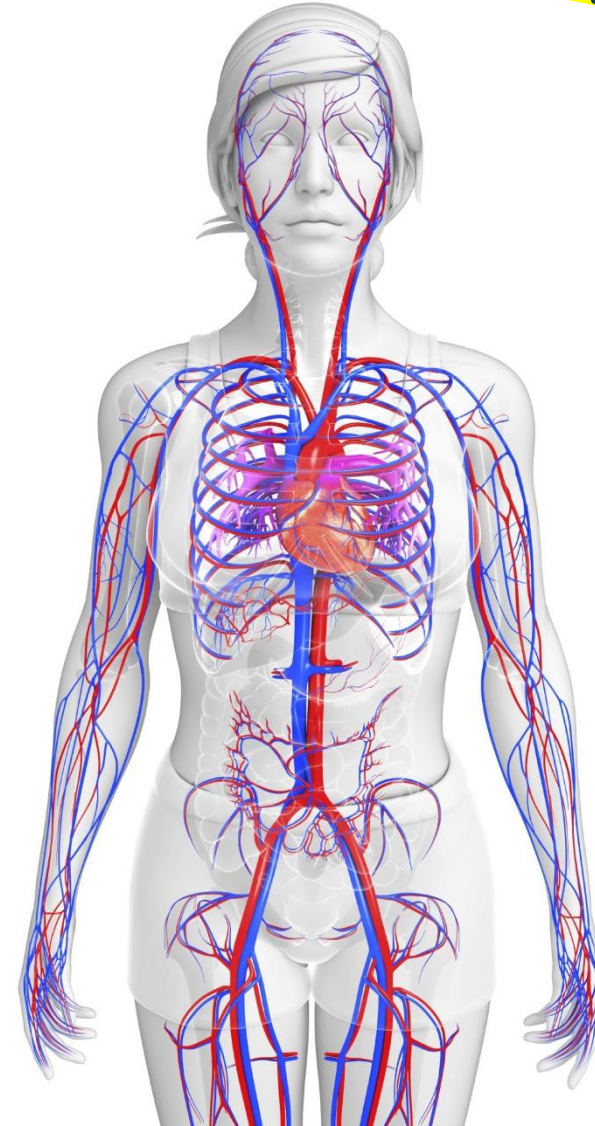
- Hypoglycemia unawareness
- Hypoglycemia unresponsiveness
- Hypoglycemia-associated autonomic failure

Genitourinary

- Overflow incontinence

Sexual

- Males: erectile dysfunction
- Females: decreased vaginal lubrication



CASE 2: Lucy (*no polling*)

Lucy is a 31-year-old woman with a 22-year history of type 1 diabetes mellitus. Her HA1c has ranged between 8-9% in the last 5 years related to difficulty focusing on herself after having a child. She also developed obesity with a BMI of 32 and new onset HTN. Her endocrinologist recommended starting Semaglutide for weight management.

She was recently told by her ophthalmologist that she has early nonproliferative diabetic retinopathy. She is concerned about progression and losing her vision and asks what she can do to help prevent progression of this complication.

Retinopathy Diagnosis and Therapy



- Therapy for proliferative diabetic retinopathy and **macular edema** to stabilize and prevent vision loss
 - FIRST LINE: for Macular Edema and early PDR
 - Reduction in vascular endothelial growth factor (VEGF) by VEGF inhibitors
 - SECOND LINE: Laser photocoagulation- panretinal (PR) and focal (ME)
 - THIRD LINE: Intravitreal corticosteroid injection (ME)

Tight glycemic control (targeting lower than 7%) only helpful in younger cohorts (<65yo), appears not helpful in older adults

A word on semaglutide & the retina

- **The SUSTAIN-6 trial showed increased worsening of retinopathy requiring Rx in people with established DR (3% vs. 1.8% placebo)**
 - Rapid A1c lowering in baseline retinopathy may transiently worsen DR; coordinate ophthalmology for active disease
- **Nonarteritic Anterior Ischemic Optic Neuropathy**
 - New retrospective analysis: 3% overall prevalence in DM group; 1% not on sema, 7% rx sema
 - **Inconclusive:** Groups were not matched based on A1c or BP control – both risk factors for NAOIN
- **Ongoing FOCUS trial (NovoNordisk) will better establish these potential risks**

Case 3: Marsha

- 65 yo woman with type 2 diabetes since age 48, childhood-onset overweight, post-partum obesity in 30s. H/o preeclampsia. One year ago, she completed orientation to bariatric surgery through the local hospital program. However, in the interim she was diagnosed with uterine CA, and is s/p TAHBSO 4 months ago and doing well. Post op challenges included OSA (now on CPAP) and poor mobility due to osteoarthritis. She has also gained 15lbs.
- Regimen since surgery: Metformin 1000mg twice daily; dulaglutide 3mg weekly; valsartan 80, HCTZ 25, rosuvastatin 20

Key Data:

118 kg
BMI 48
GFR 68
A1c 9.8%

Vitals:

BP 152/84, pulse
82

Other Labs:

UACR: 50 mg/g Cr
LDL 120
HDL 26
Triglycerides 396

Case 3: *Question*

Which of the following is the best next therapeutic step?

- A. Referral to surgical weight loss program
- B. Add empagliflozin 10mg daily
- C. Switch dulaglutide 3mg to Tirzepetide 2.5mg weekly
- D. Add naltrexone 8mg/bupropion 90mg
- E. Increase dulaglutide to 4.5mg weekly

Case 3: *Question*

Diabetes regimen since surgery:
Glargine 60 units at bedtime, Metformin
1000mg twice daily; 4 other
medications for BP, lipid management

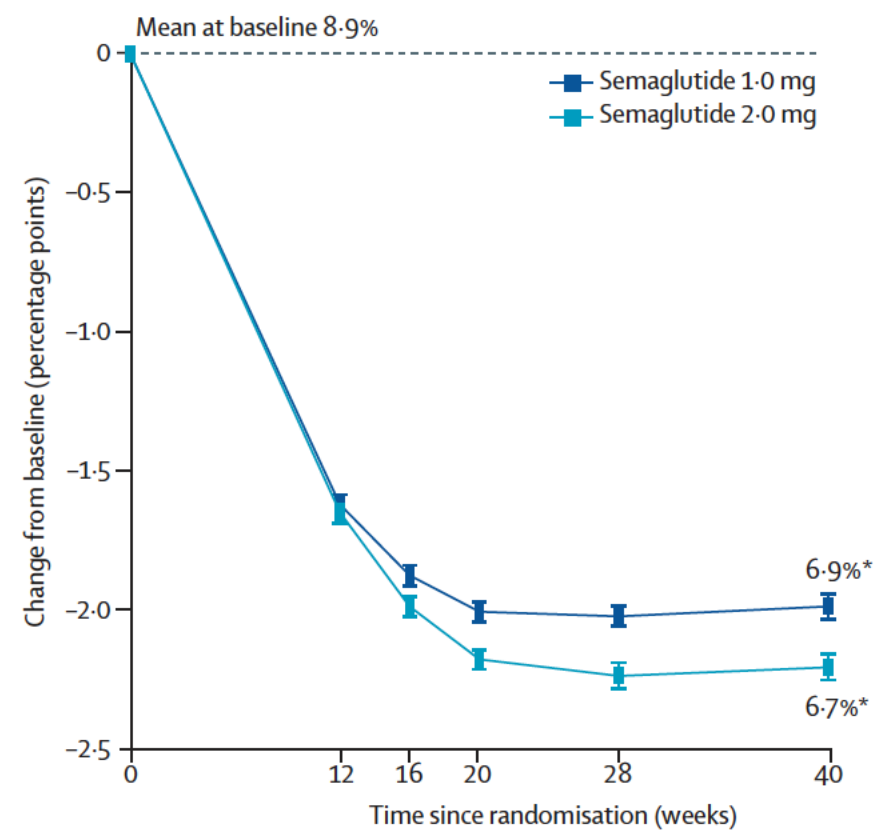
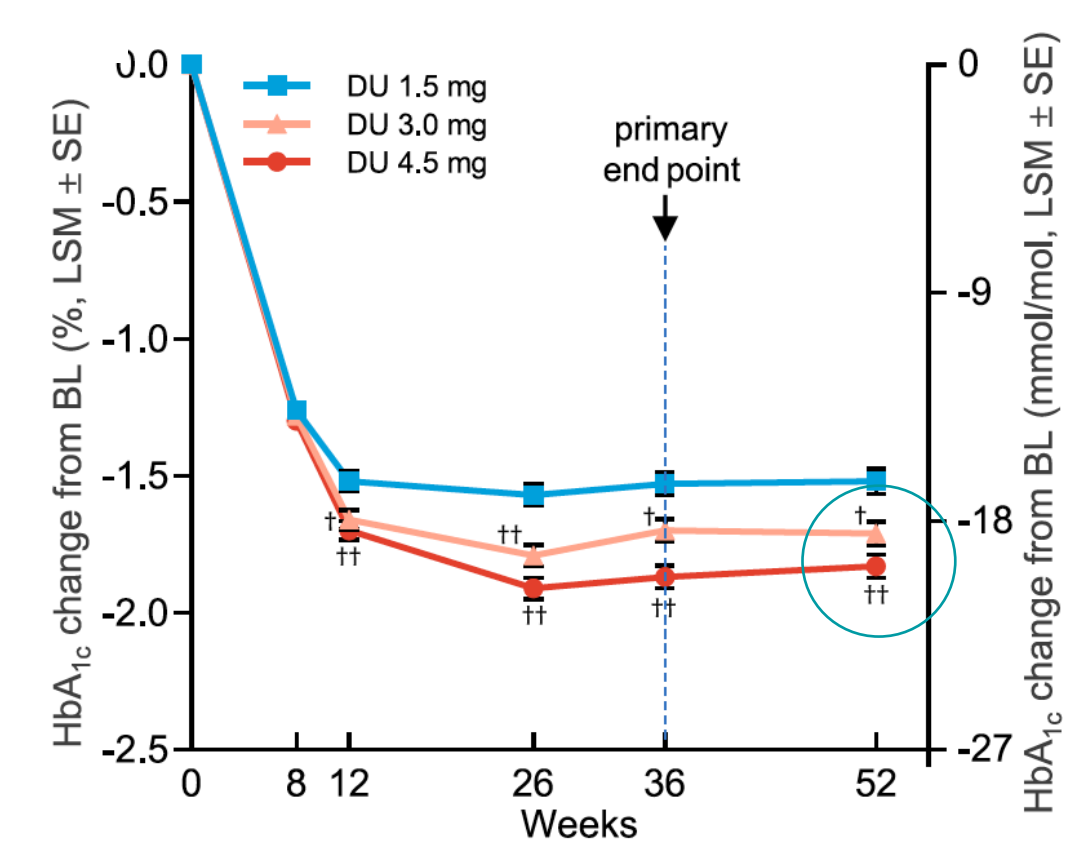
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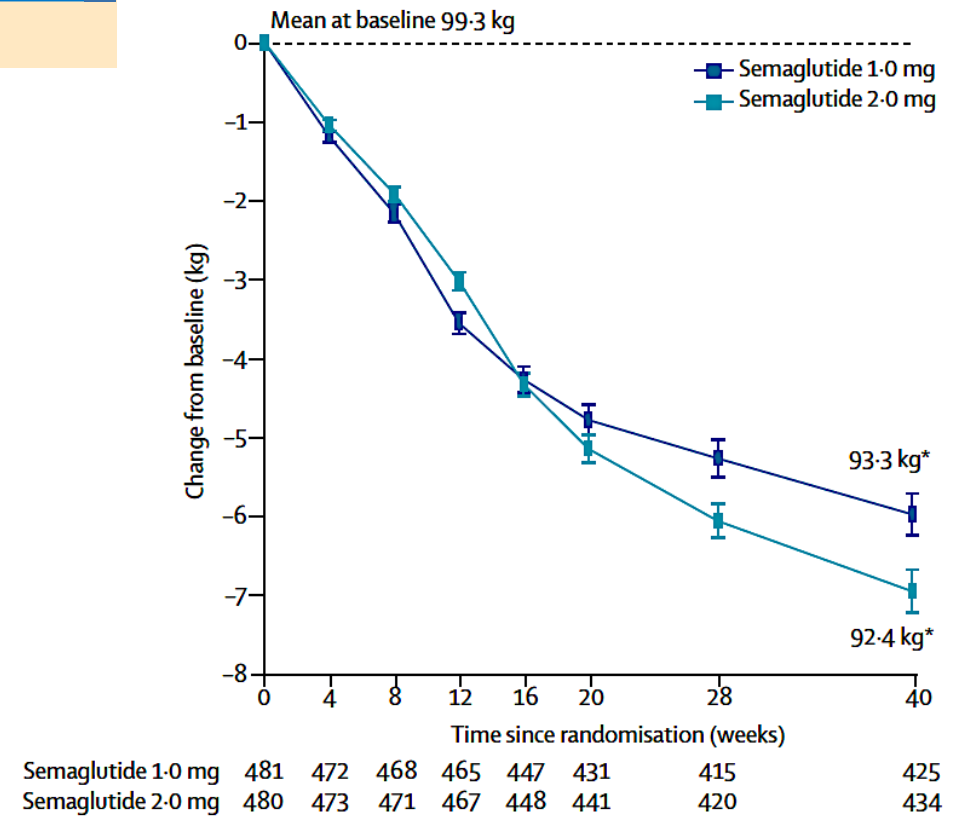
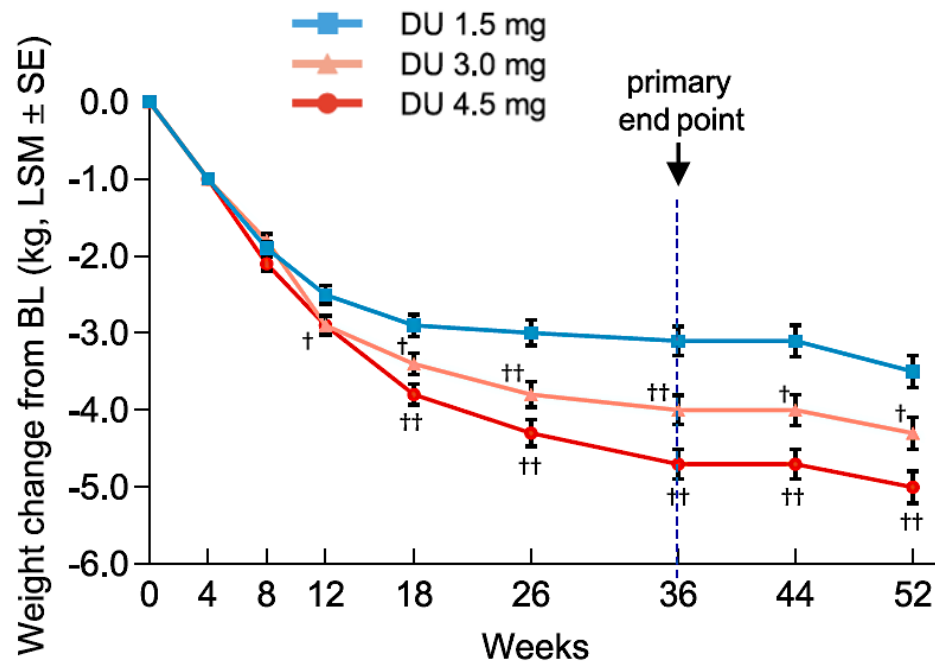
- **Weight reduction + glycemic control are imperative:** obesity complicated by OSA, OA and uterine adenocarcinoma.
- **Tirzepetide** : most effective incretin agent available for weight loss in people with diabetes (approx 10%), and glycemic control (A1c -2%). **Now indicated for OSA. SURPASS CVOT proved noninferior to dulaglutide for MACE**
- **Bariatric surgery**, specifically the *Roux en y* gastric bypass, is a life-extending option for her in the future. However, she just recently recovered from one surgery and would be advised to reduce both weight and A1c before surgery
- **Empagliflozin** is a weak glucose lowering and weight loss agent
- **Naltrexone/bupropion** achieves 5-8% weight loss in people without diabetes and <5% loss is expected in people with diabetes

Change in A1c with higher doses of dulaglutide and semaglutide in patients with type 2 diabetes



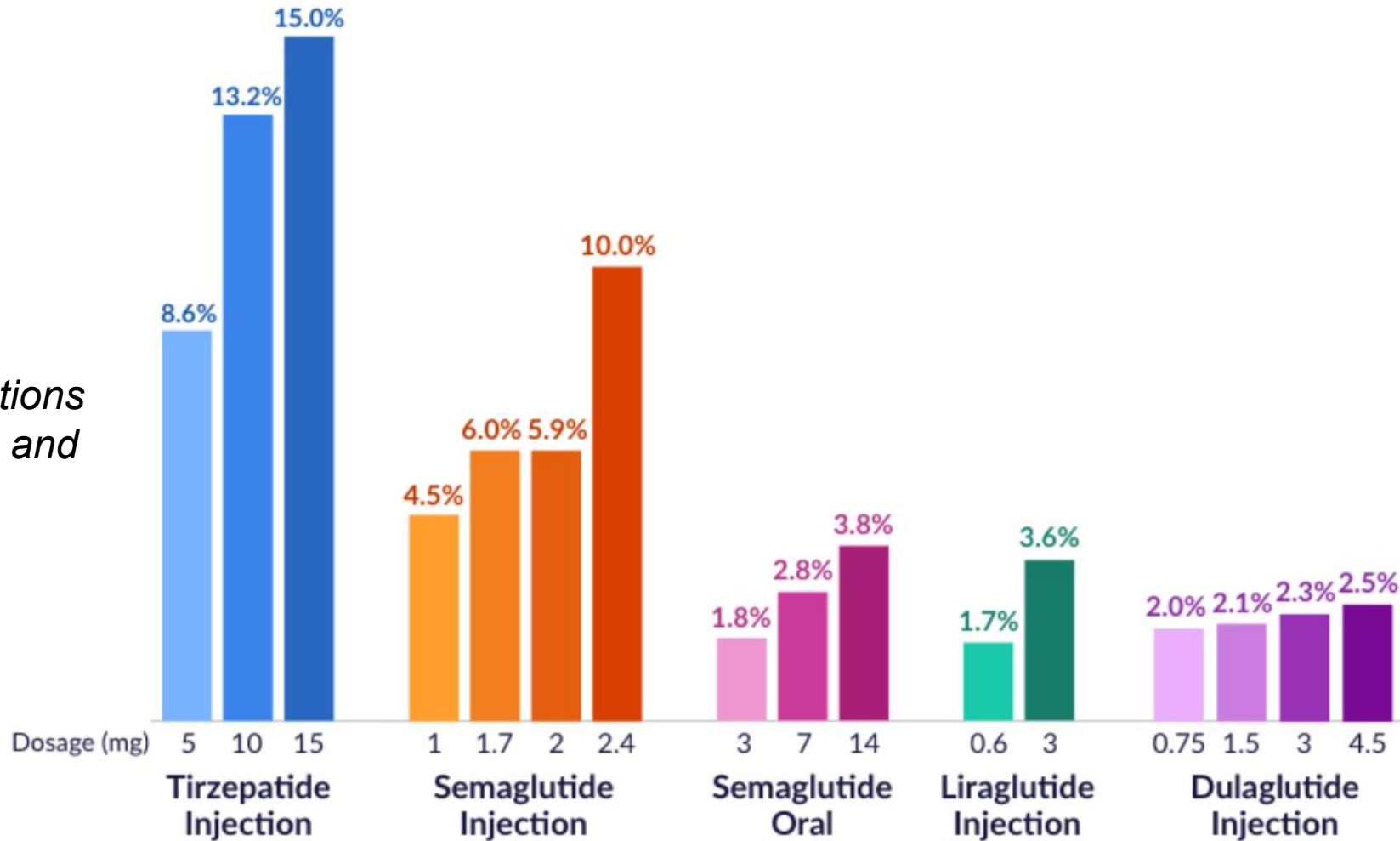
High Dose vs Low Dose GLP-1 RA, Dula vs. Sema: Change in weight.

Similar findings seen in “real world” data:
Lingvay I et al. [J Clin Endocrinol Metab. 2022; s](#)



Median weight loss by the peak dosage of the GLP-1 receptor agonist prescribed within year of starting

Note: Study populations include people with and without diabetes



N=413,557 patients

"Median Weight Loss After One Year by Peak Dosage," 2024. EpicResearch.org

Complex obesity: looking back at the liver

Marsha's perioperative laboratory test results:

Triglycerides = 396mg/dL

AST = 51 U/L (20-48 U/L) (SI: xx μ kat/L [0.33-0.80 μ kat/L])

ALT = 65 U/L (10-40 U/L) (SI: xx μ kat/L [0.17-0.67 μ kat/L])

INR= 1.0 (normal)

Platelets = 151

FIB-4 score was calculated to be **2.22** (Low <1.3; Intermediate **1.3-2.67**; High >2.67).

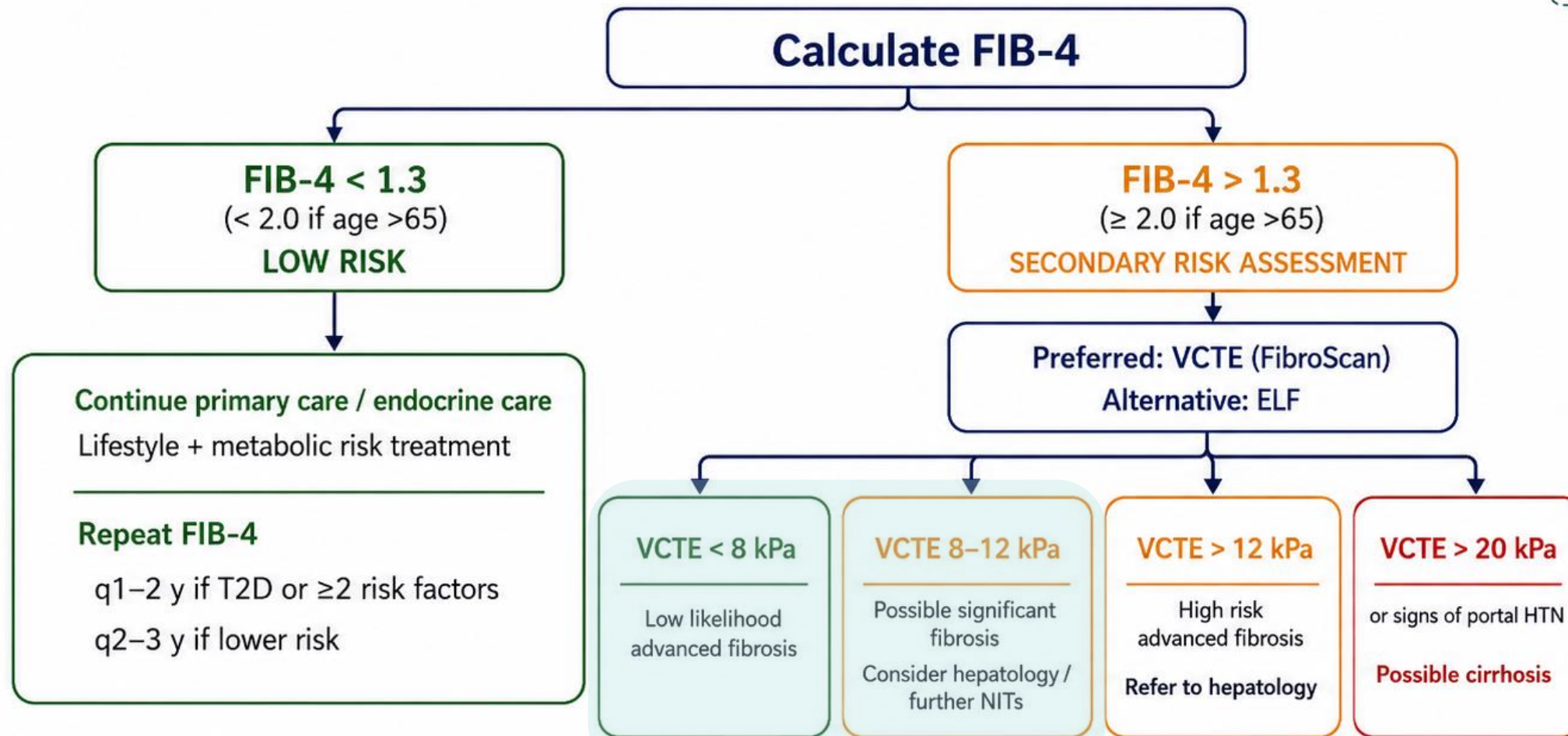
Vibration-controlled transient elastography was performed which showed a Liver Stiffness Measurement of **8.2 kPa** (Low Risk: <8kPa, **Indeterminate Risk: 8-12 kPa**, High Risk: > 12kPa).



MASLD Screening Algorithm

Start with FIB-4

$$\text{FIB-4} = \frac{\text{age} \times \text{AST}}{\text{platelets} \times \sqrt{\text{ALT}}}$$



Pearls:

- FIB-4 less accurate if age <35
- Use threshold 2.0 if age >65
- Avoid interpretation during acute illness

Rx: weight loss, GLP-1, statin → follow up

Diabetic Kidney Disease

- **Increased urinary albumin excretion corrected for urinary creatinine:**
 - Spot UACR ≥ 30 mg/g Cr or ≥ 30 mg/24 hr
- **Risk of functional decline is proportional to degree of albuminuria**
- **Very elevated (≥ 300 mg/24hrs)**
 - Predicts renal failure – accelerated by HTN & smoking
 - Indicates glomerular basement membrane disease
 - Occurs after ~ 17yrs of diabetes



Cardiovascular-Kidney-Metabolic (CKM) disease

- **Obesity, DKD and CVD overlap and the presence of one should lead to evaluation of the other**
- This relationship is seen in type 1 and type 2 diabetes
- **Cardiovascular mortality** in UKPDS and kidney disease
 - Normoalbuminuria: 1%/year
 - Microalbuminuria: 2%/year
 - Macroalbuminuria: 3.5%/year
 - CKD (elevated creatinine including ESRD): 12%/year



FLOW Trial: Semaglutide vs. placebo in DKD

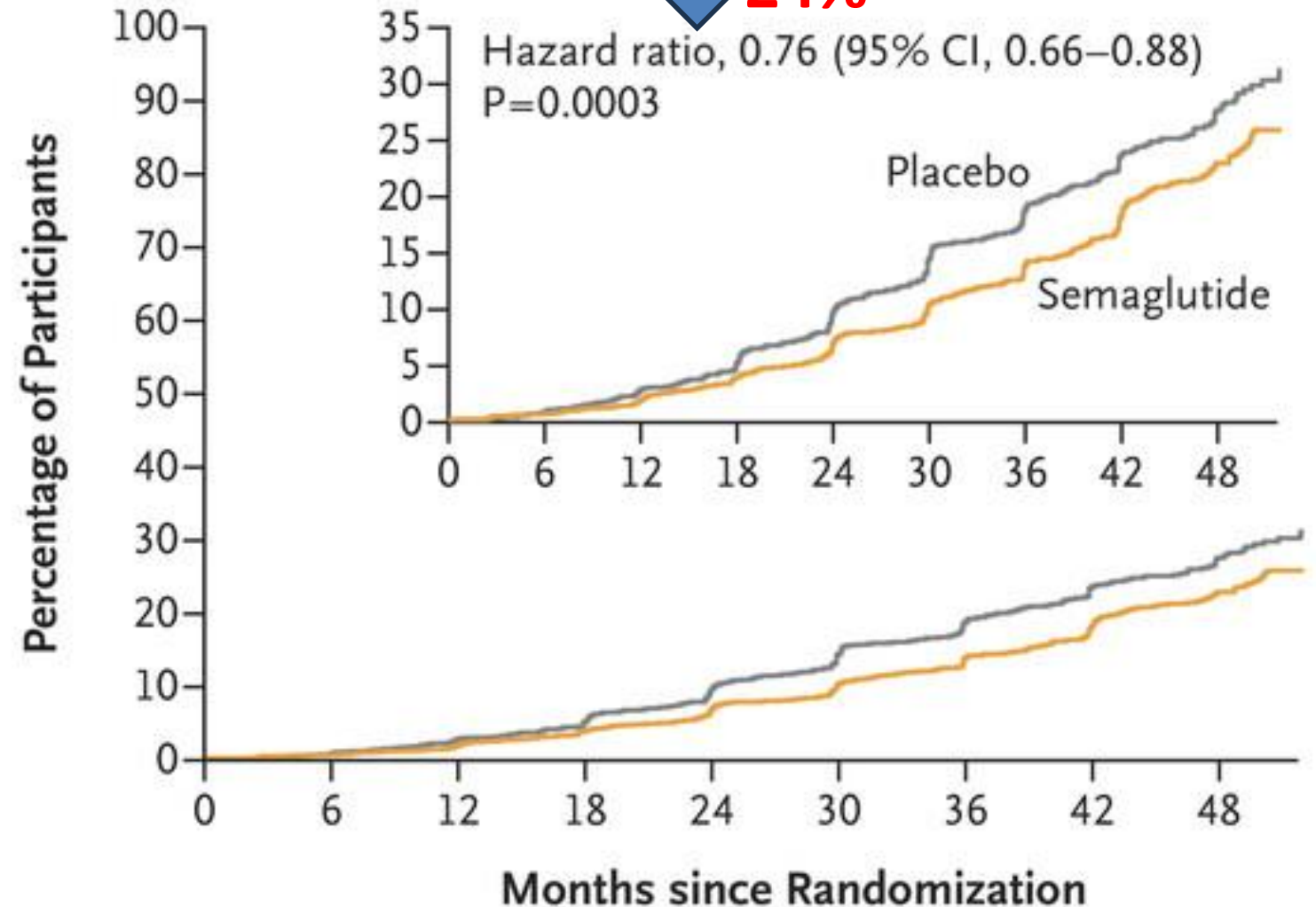
- N= 3534 people with type 2 diabetes and kidney disease
- Primary objective: delay in progression of CKD and a reduction in the risk of renal and cardiovascular mortality
 - **Endpoint: “First Major Kidney Disease Event”**
 - **onset of kidney failure, death from kidney failure; cardiovascular death; onset of persistent $\geq 50\%$ reduction in eGFR from baseline**
 - Stopped early due to efficacy at 48 weeks

FLOW primary outcome

Driven by CV event reduction...so ? Really good for the kidney or more the heart?

A First Major Kidney Disease Event

↓ **24%**



No. at Risk

Placebo	1766	1736	1682	1605	1516	1408	1048	660	354
Semaglutide	1767	1738	1693	1640	1572	1489	1131	742	392

FLOW: Kidney specific outcomes *also* positive

Table 2. Efficacy and Safety Outcomes.*

Outcome	Semaglutide (N = 1767)	Placebo (N = 1766)	Hazard Ratio (95% CI)	Estimated Difference (95% CI)	P Value
Primary outcome: major kidney disease events — no. (%)†	331 (18.7)	410 (23.2)	0.76 (0.66 to 0.88)	—	0.0003
Components of primary outcome — no. (%)					
Persistent ≥50% reduction from baseline in eGFR	165 (9.3)	213 (12.1)	0.73 (0.59 to 0.89)	—	—
Persistent eGFR <15 ml/min/1.73 m ²	92 (5.2)	110 (6.2)	0.80 (0.61 to 1.06)	—	—
Initiation of kidney-replacement therapy	87 (4.9)	100 (5.7)	0.84 (0.63 to 1.12)	—	—
Death from kidney-related causes	5 (0.3)	5 (0.3)	0.97 (0.27 to 3.49)	—	—
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Composite of kidney-specific components of the primary outcome	218 (12.3)	260 (14.7)	0.79 (0.66 to 0.94)	—	—
Confirmatory secondary outcomes					
Mean annual rate of change in eGFR — ml/min/1.73 m ²	−2.19	−3.36	—	1.16 (0.86 to 1.47)	<0.001

Case 4: Frank

- 61-year-old man with type 2 diabetes and nonischemic cardiomyopathy, heart failure with reduced ejection fraction (ejection fraction = 25%-30%), hypertension, obesity and chronic kidney disease, discharged from the hospital after acute heart failure exacerbation.
- Diabetes for 15 years.
- Regimen at discharge: insulin glargine, 25 units in the morning, and insulin aspart, 4 units with meals. Stopped taking the aspart insulin as it was too difficult.
- PE: BMI = 39 kg/m², jugular venous distension to the midneck, 2+ to 3+ lower-extremity edema, and reduced 10-g monofilament sensation below the knee.
- Laboratory tests show a Hemoglobin A1c of 6.7% and an estimated GFR of 32ml/min per 1.73 m² (normal = >60 mL/min per 1.73 m²)

Case 4: Question

Which of the following is the best second agent to use in combination with glargine insulin to achieve optimal disease control?

- A. dapagliflozin
- B. semaglutide
- C. none, no second agent is required
- D. linagliptin
- E. glimepiride

Case 4: Question

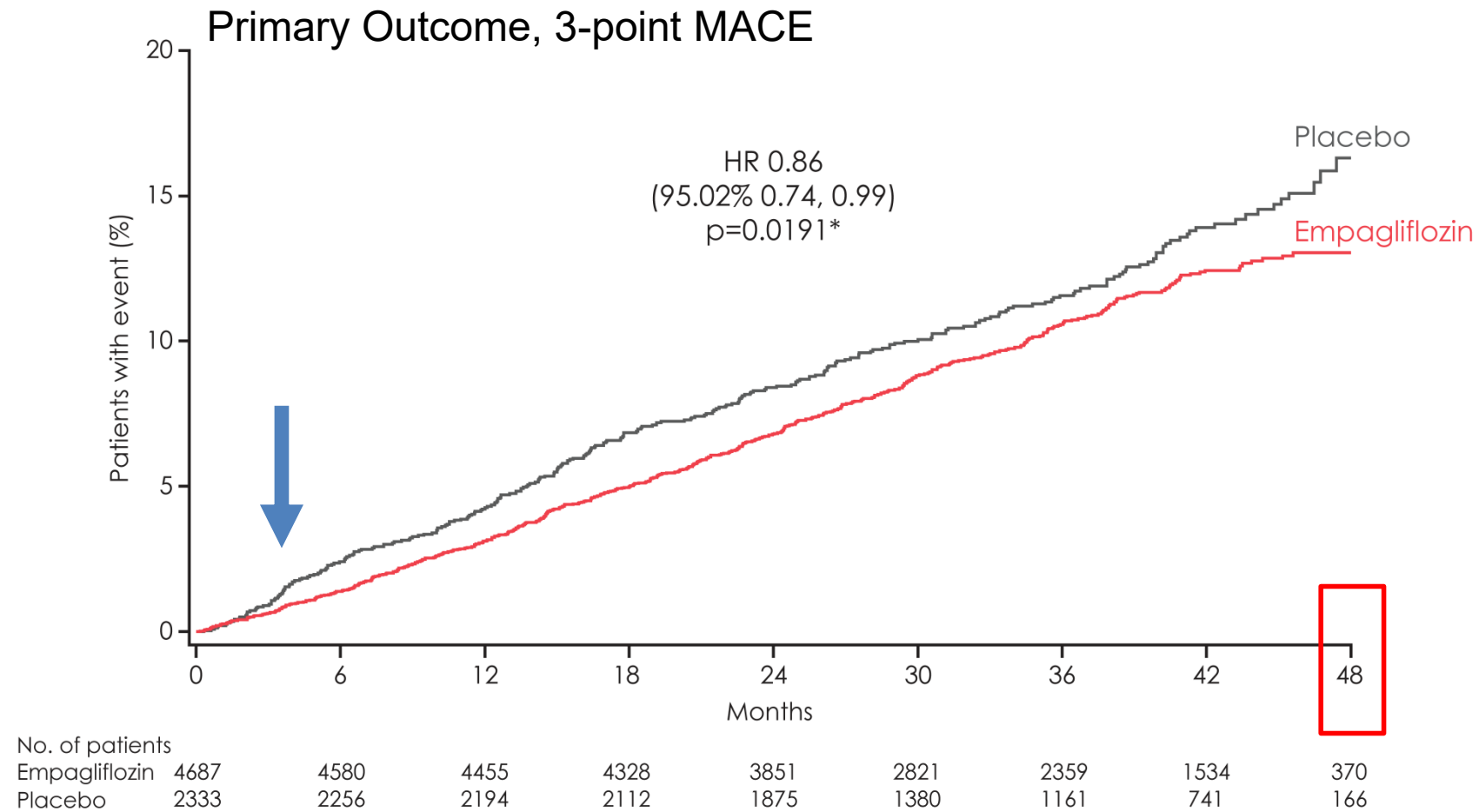
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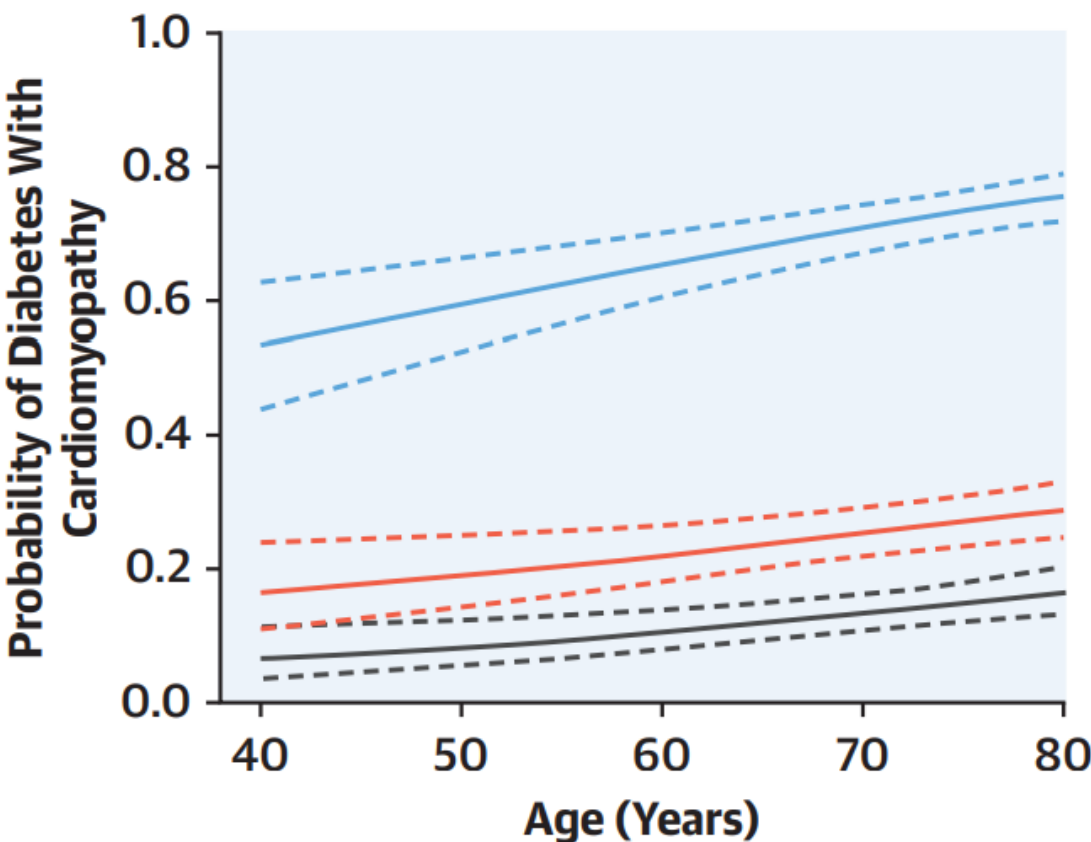
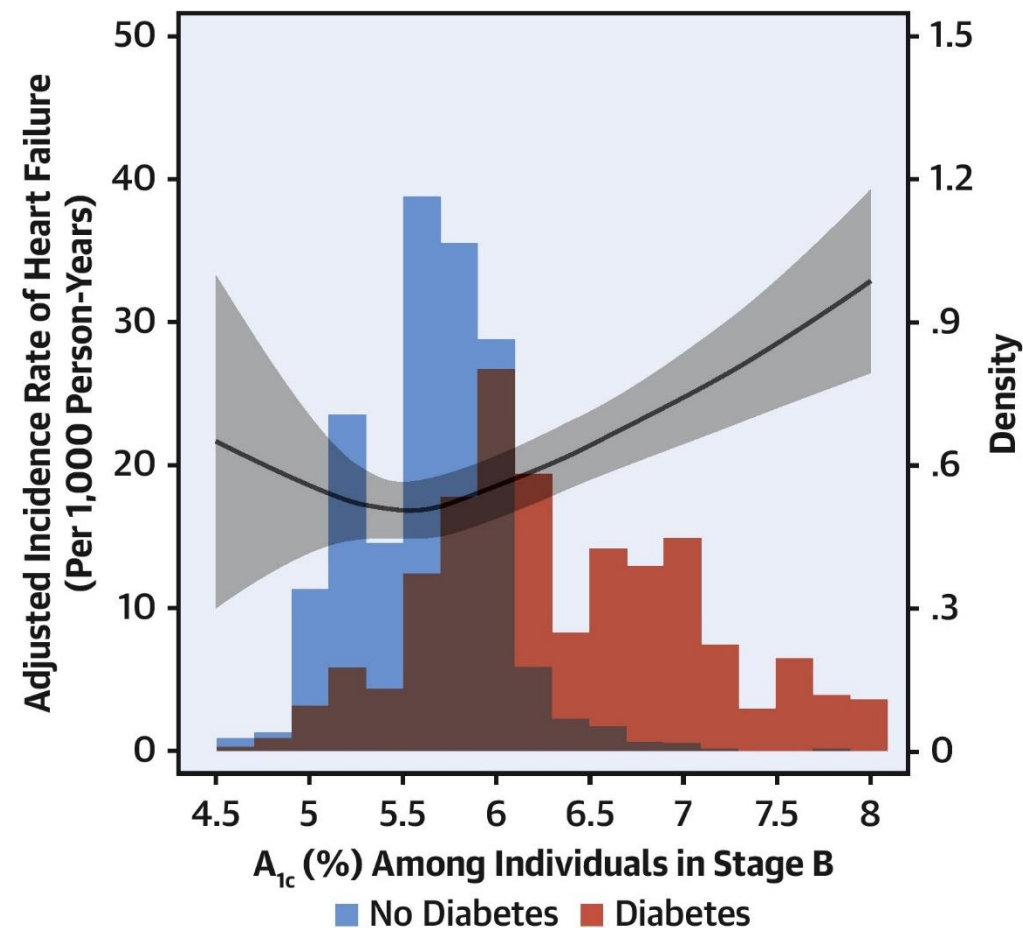
Case 4: *Explanation*

- **“Disease control”** refers to the concept all diabetes related conditions should be considered in the design of a treatment program (not just the A1c).
- **SGLT2i dapagliflozin:** reduces hospitalizations in individuals with heart failure, and reduce progression of CKD in those with diabetes and stage 3b and 4.
- **Dapagliflozin is recommended** in the setting of an eGFR as low as 20 to reduce the risk of eGFR decline, ESKD, CV death and hospitalizations due to CHF.
- **Semaglutide is a reasonable option as well for both weight reduction and improved functional status in the setting of heart failure. However, not studies in diabetes + heart failure with reduced ejection fraction.** The other options have either no benefit outside of glycemic control (linagliptin) or increase the risk of hypoglycemia and weight gain (glimepiride).

EMPAreg trial: Recognizing subclinical CHF



Heart Failure Incidence Is Higher in Diabetes and Increases with Age



N=4,774 adults with preclinical HF

Diabetes-Related Dementia: *Treatment Implications*



New Entity

Diabetes-related dementia: slower progression, no typical neuroimaging, linked to high A1C + long duration + frailty



GLP-1 Receptor Agonists

Significant ↓ in all-cause dementia

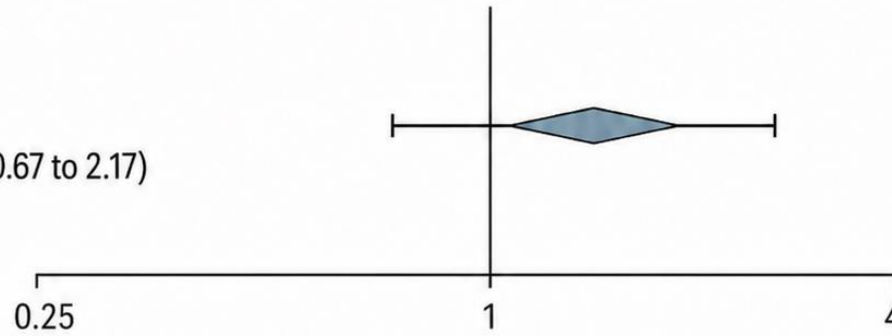
Meta-analysis evidence

GLP-1 RAs are likely protective against dementia

(no evidence for treatment benefit, Cummings JL, et al. Lancet. 2026 May.)

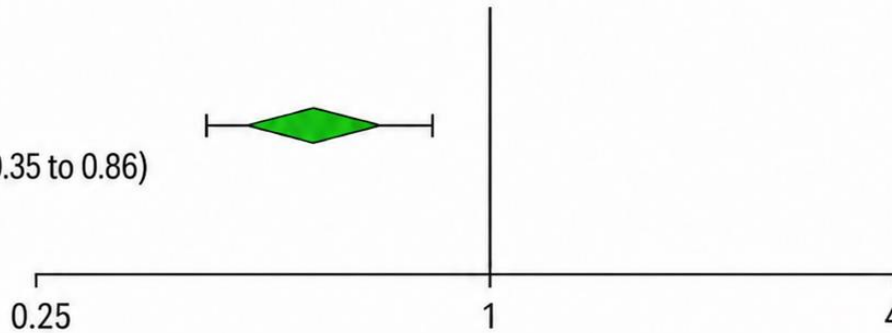
SGLT2i

OR 1.20 (95% CI 0.67 to 2.17)



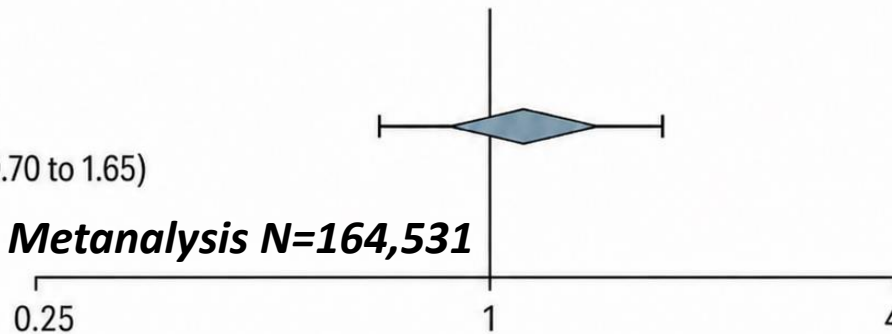
GLP-1RA

OR 0.55 (95% CI 0.35 to 0.86)



Pioglitazone

OR 1.07 (95% CI 0.70 to 1.65)



Metanalysis N=164,531

Odds ratio

GLP-1 and dementia studies:

- Hui et al. Journal of Alzheimer's Disease. 2025.
- Cummings et al. Lancet. 2026.
- Tang et al. JAMA Neurology. 2025.
- Nance et al. Alzheimer's & Dementia. 2025.
- Inoue et al. Annals of Internal Medicine. 2025.
- Tang et al. Journal of the American Geriatrics Society. 2023.
- Edison et al. Nature Medicine. 2025.
- Santos et al. Pharmaceuticals. 2026.
- Athauda et al. Journal of Clinical Investigation. 2026.

GLP1 RA vs. SGLT2i: *when you need to make a choice*

Prefer SGLT2i when
Heart failure
HA1c lower (<9)
Renal protection: GFR <60, significant albuminuria
Preference for oral medication
Contraindications to GLP1 RA are present, such as: - History of pancreatitis <i>with ongoing risk</i> - History of severe gastroparesis - History of medullary thyroid cancer or MEN2 (rare!!)

GLP1 RA vs. SGLT2i: *when you need to make a choice*

Prefer SGLT2i when	Prefer GLP1 RA when...
Heart failure	TIA/Stroke/MI/PAD
HA1c is lower (HA1c <9)	Weight loss is a priority
Renal protection: GFR <60, significant albuminuria	Renal protection: when glycemic control <i>and</i> ASCVD risk are priority
Preference for oral medication	eGFR <20
Contraindications to GLP1 RA are present, such as: - History of pancreatitis <i>with ongoing risk</i> - History of severe gastroparesis - History of medullary thyroid cancer or MEN2 (rare!!)	Relative Contraindications to SGLT2i are present, such as: - History of severe recurrent genital mycotic infections - History of recurrent UTI while on SGLT2i - History of diabetic ketoacidosis

MOC Reflective Statement

- **Microvascular complications are rising as early CV death rates have stabilized.**
- **Comprehensive goal-oriented care in diabetes is effective in reducing complication rates:** Glucose control, Weight control, Lipid control, Blood pressure control and Smoking avoidance/cessation
- **Achieve glucose control as early and for as long as safely possible.** Benefit wanes with age, risks increase
- **Microvascular and Macrovascular Events can be reduced by SGLT2 inhibitors and GLP-1 RA –based medications**

THANK YOU!



Questions?
Comments?

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Additional learning

Increases Fracture Risk over Time in Diabetes

- **T2DM patients have double the risk for fractures compared to controls**
- **Bone density may be normal** but bone quality is compromised, possibly due to accumulation of Advanced Glycation End products (AGEs)
- **Other risk factors for fracture**
 - Neuropathy
 - Hypoglycemia
 - Some medications (pioglitazone, canagliflozin)



Soft Tissue Complications in DM

- **Spectrum of involvement**

- Stiffness in hands and fingers (also called cheiroarthropathy)
- Tenosynovitis (a precursor to cheiroarthropathy and “trigger finger” when occurs in the hands)
- Adhesive capsulitis
- Dupuytren’s contracture
- Carpal Tunnel Syndrome

- **Incidence and risk factors not well studied in T2DM**

- Duration of diabetes and glucose control correlate with risk in Type 1 DM, unknown in type 2

When to refer to a hand surgeon?

- **Decreased functionality of the hand**
- **Pain**
- **The terrible trifecta:**
 - **Carpal Tunnel**
 - **Tenosynovitis (painful trigger finger)**
 - **Dupuytren's contracture**

