Diabetes-Related Complications - What Can Primary Care Providers Do?

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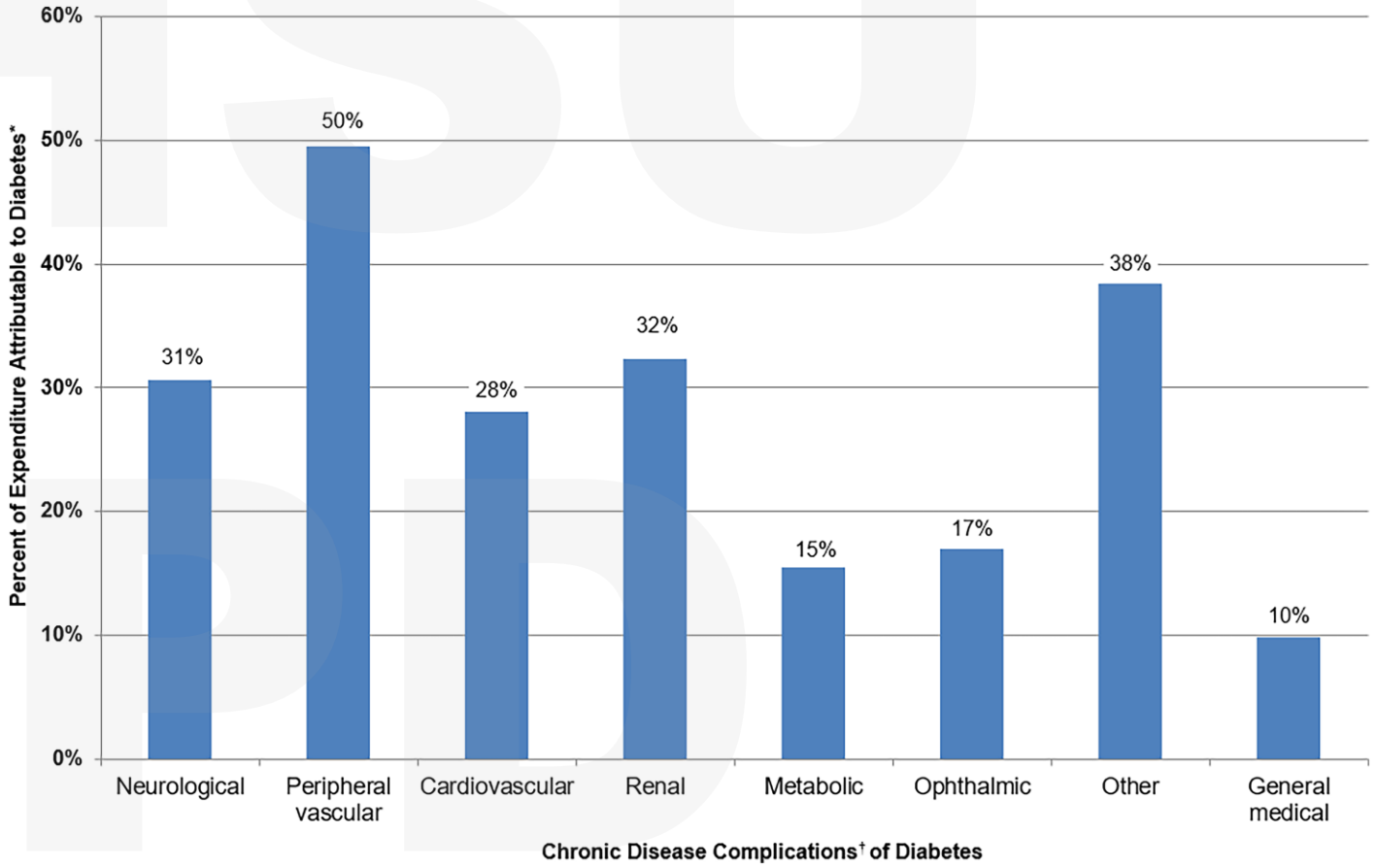
Objectives

1. Categorize diabetes-related complications
2. Review screening, detection, and management of diabetes-related complications

Diabetes-Related Complications, Cost

- 2022 total cost of diabetes in USA estimated at $412.9 billion
  - $306.6 billion direct medical costs, $106.3 billion indirect
- 1 in 4 healthcare dollars in USA is put toward diabetes-related care
- Medical expenditures are 2.6 times higher for people with diabetes than without



American Diabetes Association®

Diabetes Care. 2023;47(1):26-43. doi:10.2337/dci23-0085

Diabetes-Related Complications

- Generally Fall into 3 broad categories

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1. Macrovascular Complications

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   a) Coronary Artery Disease
   b) Peripheral Artery Disease
   c) Stroke

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2. Microvascular Complications

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1. Macrovascular Complications
   a) Coronary Artery Disease
   b) Peripheral Artery Disease
   c) Stroke
2. Microvascular Complications
   a) Retinopathy
   b) Neuropathy
   c) Nephropathy

Diabetes-Related Complications

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1. Macrovascular Complications
   a) Coronary Artery Disease
   b) Peripheral Artery Disease
   c) Stroke
2. Microvascular Complications
   a) Retinopathy
   b) Neuropathy
   c) Nephropathy
3. Metabolic

Diabetes-Related Complications

- Generally Fall into 3 broad categories

1. Macrovascular Complications
   a) Coronary Artery Disease
   b) Peripheral Artery Disease
   c) Stroke
2. Microvascular Complications
   a) Retinopathy
   b) Neuropathy
   c) Nephropathy
3. Metabolic
   a) MASLD
   b) obesity

Diabetes-Related Complications

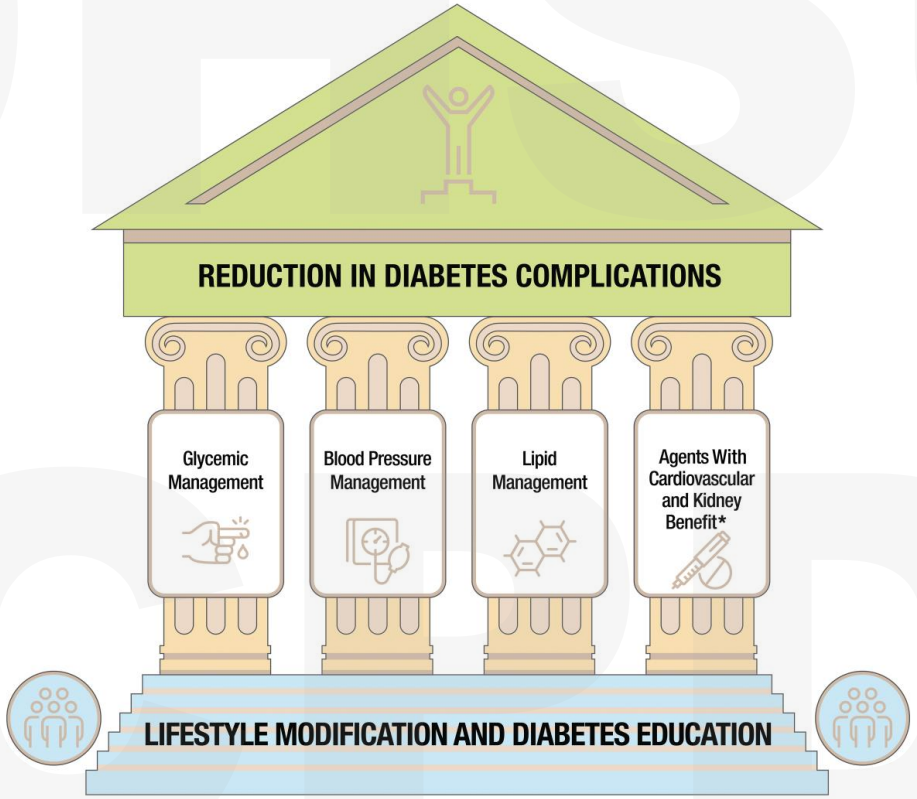

Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

American Diabetes Association; 4. 2024.

Cardiovascular Disease in Persons with Diabetes

- “ASVCD is leading cause of morbidity and mortality for individuals with diabetes”
- Estimated cost of $39.4 billion in CV -related spending per year associated with diabetes
- Heart failure hospitalizations two-fold higher in persons with diabetes
- Largest benefits are seen when multiple risk factors for ASCVD are addressed simultaneously (BP, diabetes, lipids)

American Diabetes Association; 10. Cardiovascular Disease and Risk Management.

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- Heart failure hospitalizations two-fold higher in persons with diabetes
- Largest benefits are seen when multiple risk factors for ASCVD are addressed simultaneously (BP, diabetes, lipids)
- ***There have been significant improvements in 10-year CHD risk among US adults with diabetes over the past decade due to more aggressive management- Morbidity and Mortality have decreased!*** (Buse et al., 2007) (Ali et al., 2013) (Gaede et al., 2016)

American Diabetes Association; 10. Cardiovascular Disease and Risk Management.

Cardiovascular Disease in Persons with Diabetes Screening/Detection

- Blood pressure every visit, general goal <130/80 in those with diabetes and other CV risk factors, if this can be achieved without "undue treatment burden"
- Assessment of family history
  - High Risk: males with MI <55 years, females <65 years
- Lipid profile at initial evaluation and annually

American Diabetes Association; 10. Cardiovascular Disease and Risk Management.

Cardiovascular Disease in Persons with Diabetes Management

- Lifestyle:
  - Restriction of sodium intake to < 2300 mg/day
  - At least 150 minutes of moderate-intensity exercise weekly
    - “Can talk, but cannot sing” while doing this degree of exercise
  - 8-10 servings per day of fruits and vegetables
  - 2-3 servings per day of low fat dairy products
  - Avoidance of excessive alcohol consumption
    - (</=2 servings/day in men, </=1 serving/day in women)

American Diabetes Association; 10. Cardiovascular Disease and Risk Management.

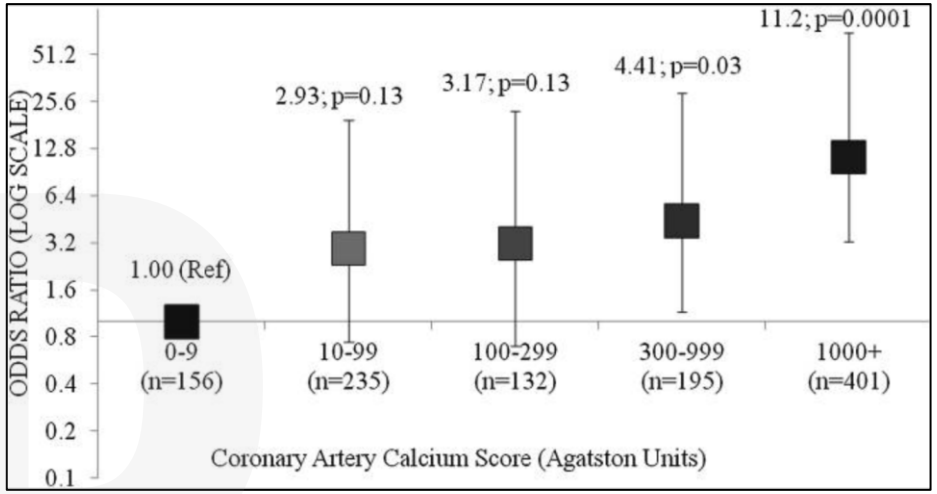
Cardiovascular Disease in Persons with Diabetes Monitoring

Coronary Artery Calcium Score (CAC): when to use?

- Not routinely recommended for screening due to cost and radiation exposure in otherwise 'higher-risk population'

Agarwal et al., 2013 completed on average a 7.4 year follow up on 1,123 persons with T2DM from the Diabetes Heart Study

- Separated into groups depending on CAC scores
- CAC predicted CVD mortality and meaningfully reclassified participants into risk category based on scoring



Conclusions:

- Can consider CAC use in patients who are hesitant to utilize lipid lowering therapy or want more information about their individualized risk
- Generally out of pocket cost is around $200

Agarwal, et al., 2013

Cardiovascular Disease in Persons with Diabetes Monitoring

B-type natriuretic peptide (BNP): when to use?

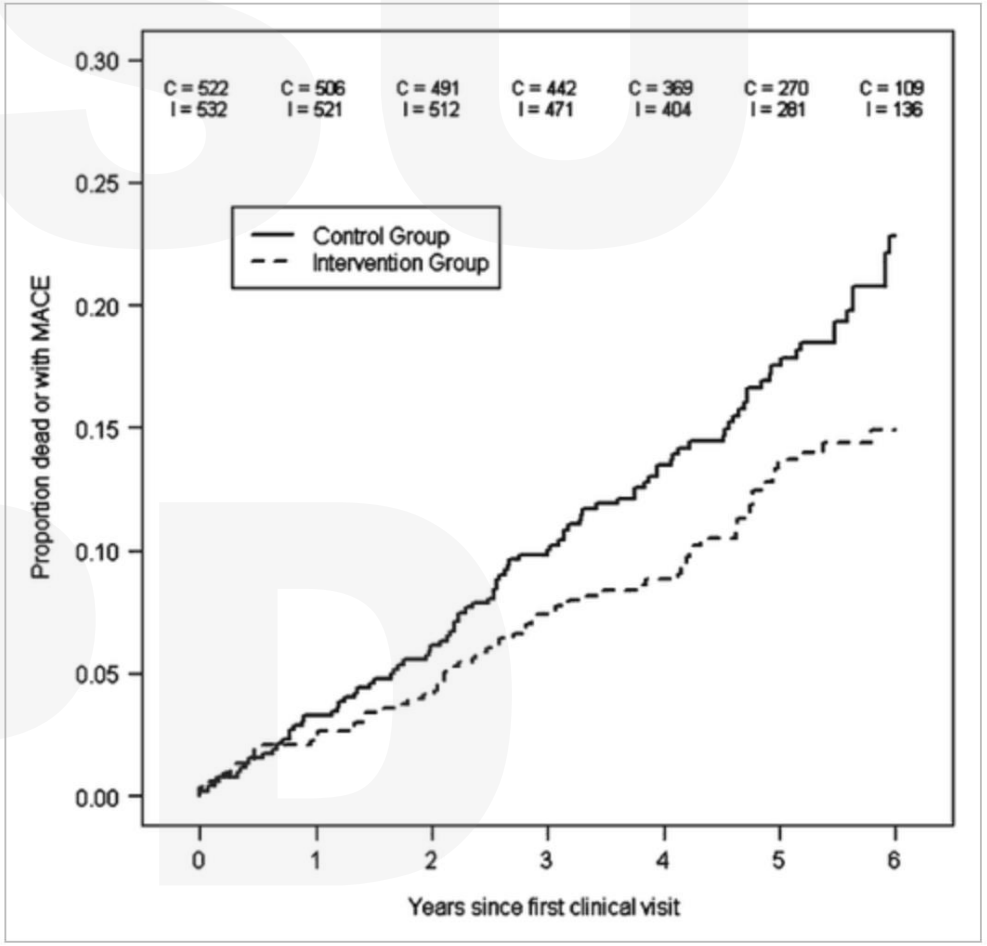
- Adults with diabetes are at increased risk for asymptomatic cardiac functional abnormalities (stage B heart failure), progression to symptomatic HF is more likely in persons with diabetes

ElMaghwary et al., 2014 completed a randomized control trial (2005-2011) of 1,374 persons with CV risk factors to continue routine primary care or undergo BNP testing.

- Participants with elevated BNP completed TTE and collaborative care with cardiology and PCP
- Primary end point of LV dysfunction and HF was significantly reduced in intervention group

Conclusions:

- Consider screening adults with T2DM by measuring BNP
- Obtain TTE in those with abnormal BNP value



European J of Heart Fail, Volume: 17, Issue: 7, Pages: 672-679, First published: 03 July 2015, DOI: (10.1002/ejhf.286)

Cardiovascular Disease in Persons with Diabetes Management

- Management
  - Antihypertensives:
    - Drug classes demonstrated to reduce CV events in persons with diabetes:
      - ACE-I, ARB, thiazide-like diuretics, dihydropyridine CCBs
    - In persons with established diabetes and CAD: ACE-I/ARB are first line
  - Cholesterol lowering agents:
    - For persons with diabetes aged 40-75 years w/o ASCVD, moderate-intensity statin therapy is recommended in addition to lifestyle modifications (ADA:10. Recommendation 10.18.)
    - For persons with diabetes aged 40-75 and ASCVD risk factors, target LDL <70 mg/dL (ADA;10. Recommendation 10.20.)
    - ***"Rule of 6"*** → for every doubling of statin therapy, expect a 6% reduction in LDL

American Diabetes Association; 10. Cardiovascular Disease and Risk Management.

Cardiovascular Disease in Persons with Diabetes Management

SGLT2 Inhibitors: "Constitute key treatment approach to reduce CVD and heart failure outcomes in people with diabetes" (ADA 2024)

- Empagliflozin: EMPA-REG OUTCOME Trial (established T2DM and CVD) mean f/u 3.1 yrs
  - reduced relative risk of hospitalization for heart failure by 35%
  - Reduced CV death by 38% vs 5.9% in placebo
- Canagliflozin: CANVAS and CANVAS-R Trials (T2DM 66% hx of CVD) mean f/u 3.6 yrs
  - Reduced composite outcome of CV death, MI, or stroke vs. placebo (26.9 vs 31.5 per 1,000 patient-years)
- Dapagliflozin: DECLARE-TIMI 58 Trial (T2DM and 40% hx of ASCVD)
  - Lower rate of CV death or hospitalization for HF vs placebo (4.9% vs 5.8%)
  - No difference seen in CV

American Diabetes Association; 10. Cardiovascular Disease and Risk Management.

Cardiovascular Disease in Persons with Diabetes Management

GLP1 Receptor Agonists:

- Semaglutide: SUSTAIN-6 trial (T2DM, 83% known CVD), 2 year f/u
  - MACE occurred in 6.6% treatment vs 8.9% placebo
- Dulaglutide: REWIND trial (T2DM, 32% known CVD), 5.4 yrs median f/u
  - MACE occurred in 12% treatment group vs 13.4% placebo
- Liraglutide: LEADER trial (T2DM and >80% known CVD), 3.8 yrs median f/u
  - MACE occurred 13% in treatment group vs 14% placebo
  - Death from CV causes 4.7% in treatment group vs 6% placebo

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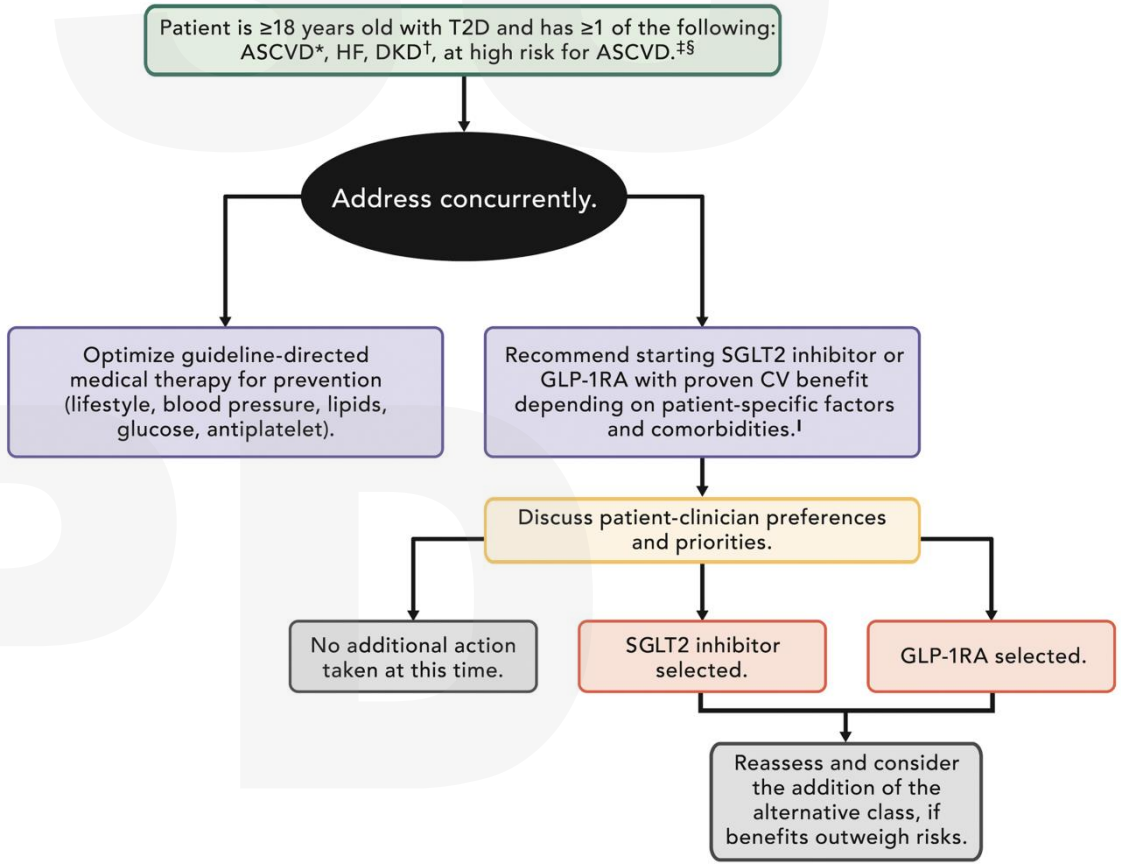
Cardiovascular Disease in Persons with Diabetes Management

Summary

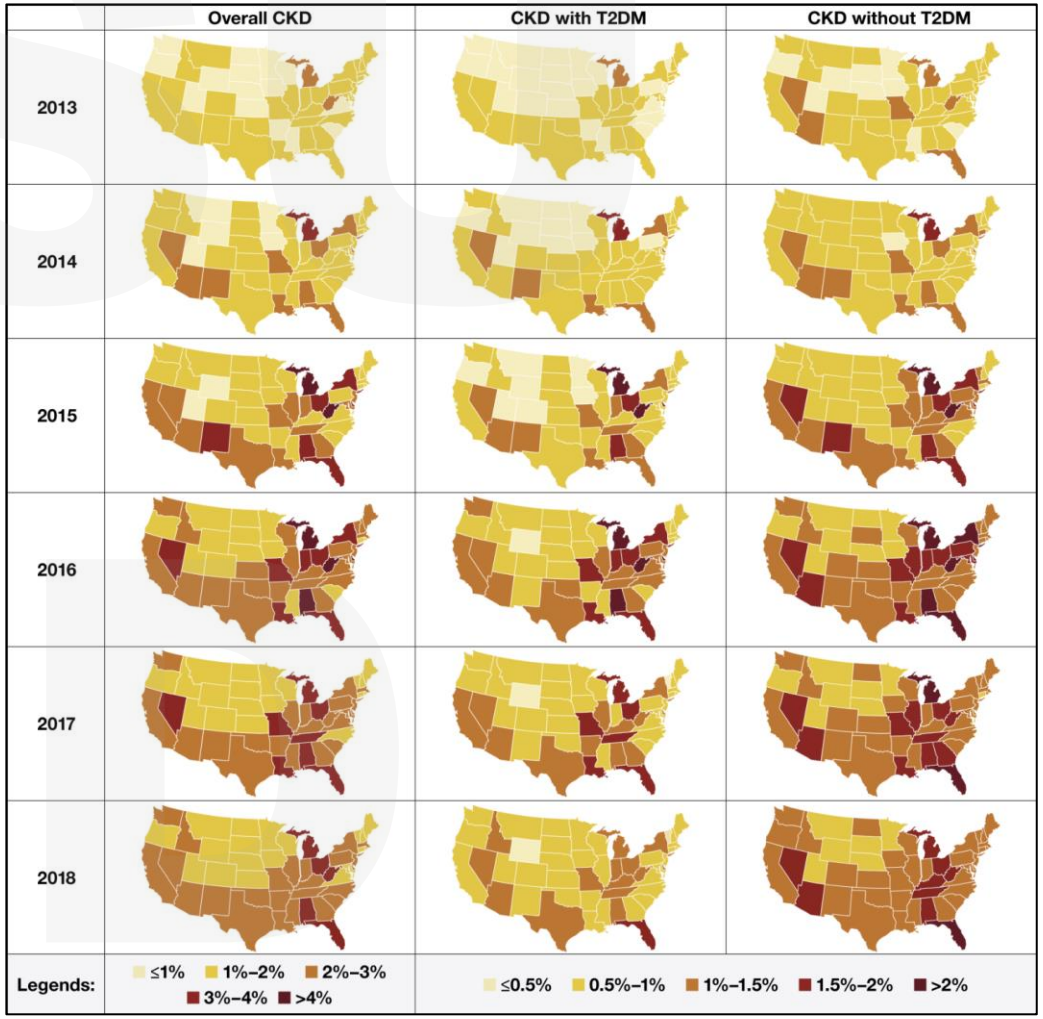
- GLP1-Receptor Agonists and SGLT-2 inhibitors reduce risk of MACE in persons with Type 2 DM and established ASCVD
- SGLT-2 inhibitors reduce risk of HF hospitalization in persons with known ASCVD or multiple risk factors , SGLT-2 inhibitors first line if clinically appropriate
- DPP4-inhibitors non-inferior to Sulfonylureas in regards to CV death
  - Sulfonylureas more likely to cause hypoglycemic complications
- Metformin can be used in persons with T2DM and stable heart failure
- Pioglitazone contraindicated in people with symptomatic heart failure



American Diabetes Association; 10. Cardiovascular Disease and Risk Management.

Kidney Disease in Persons with Diabetes

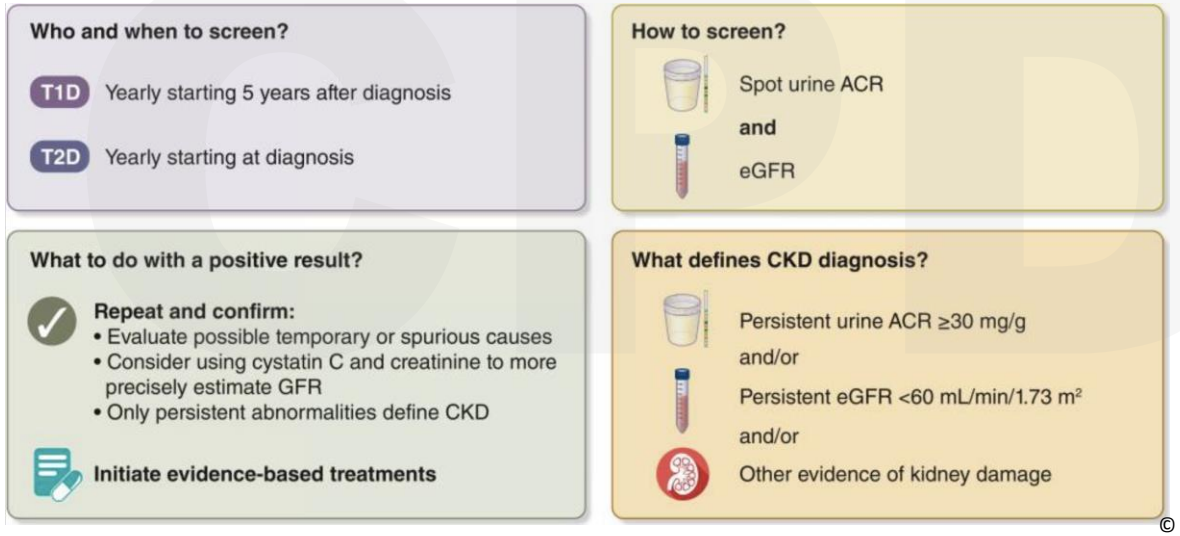
- CKD as a complication of diabetes occurs in 20-40% of persons with type 2 diabetes
- CKD due to diabetes is leading cause of ESRD in the USA
- Reminder, CKD may be present at time of type 2 DM diagnosis!



CKD Prevalence Among Patients With and Without Type 2 Diabetes: Regional Differences in the United States. Feng, Xue (Snow) et al.Kidney Medicine, Volume 4, Issue 1, 100385

Kidney Disease in Persons with Diabetes Screening

- Annual assessment of Urinary Albumin to Creatinine Ratio (UACR)
  - If abnormal (>30 mg/g), recommend to repeat 2 more times over 3-6 months to confirm albuminuria
  - Variations of >20% can occur between collections
- Annual assessment of eGFR
- Diabetic Kidney disease is a **clinical diagnosis**
  - Albuminuria and/or reduced eGFR in absence of other primary cause of kidney damage

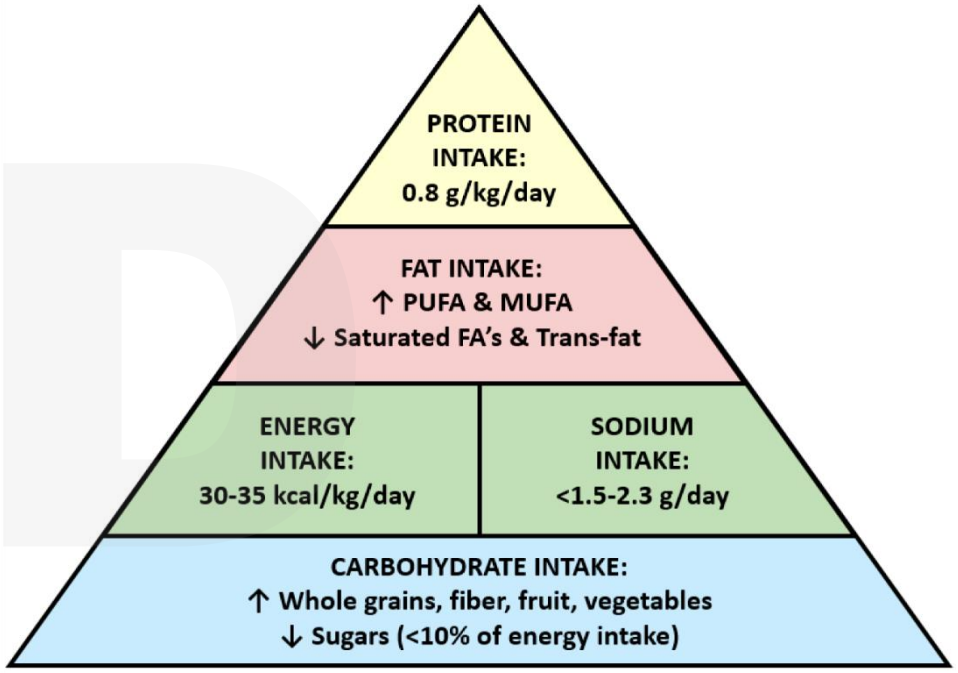


Kidney Disease in Persons with Diabetes Management

- Prevention: only primary preventions in persons with diabetes are:
  - Glucose control (Hgb A1C ≤ 7%)
  - Blood pressure control (<130/80)
  - ACEI/ARB do NOT prevent development of diabetes-related kidney disease

Kidney Disease in Persons with Diabetes Management

- Dietary Modifications:
  - Dietary protein limited to ~0.8 g/kg body weight per day
    - Shown to slow GFR decline and greater effect over time (de Boer et al., 2022)
  - Dietary sodium restriction of <2,300 mg/day



Ko et al., 2017. Dietary Approaches in Management of Diabetes Patients with Kidney Disease.

Kidney Disease in Persons with Diabetes Management

- ACE-I or ARB therapy reduce progression to ESRD in people with type 1 or 2 DM with established CKD and macroalbuminuria
  - Slow CKD progression in those with early stage kidney disease (UACR 30-299 mg/g creatinine)
  - Preferred first line agents for BP control in persons with diabetes and CKD
  - Recommended maximally tolerated doses of these agents for greatest benefit
  - Not superior to other antihypertensive agents in absence of albuminuria

American Diabetes Association; 11. Chronic Kidney Disease and Risk Management.

Kidney Disease in Persons with Diabetes Management

- SGLT2-inhibitors
  - Recommended for people with eGFR ≥ 20 at type 2 diabetes as they **slow CKD progression and reduce HF risk independent of glucose management**
- Empagliflozin: EMPA-REG OUTCOME Trial (established T2DM and CVD) mean f/u 3.1 yrs
  - Reduced risk of incident or worsening nephropathy by 39%
  - Reduced risk of doubling of serum creatinine by 44%
- Canagliflozin: CANVAS and CANVAS-R Trials (T2DM 66% hx of CVD) mean f/u 3.6 yrs
  - Reduced risk of progression of albuminuria by 27%
  - Reduced risk of reduction in eGFR, ESRD, or death from ESRD by 40%

American Diabetes Association; 11. Chronic Kidney Disease and Risk Management.

Kidney Disease in Persons with Diabetes Management

- SGLT2-inhibitors
  - Trials in advanced kidney disease and diabetes specifically
- Empagliflozin: EMPA-KIDNEY (CKD and 50% participants had T2DM)
  - Lower risk of progression of kidney disease and lower risk of death from CV disease (HR 0.72)
- Canagliflozin: CREDENCE trial (T2DM and CKD, 99% participants on ACEi or ARB)
  - Reduced risk of progression to ESRD by 32% vs placebo
  - 30% reduction in doubling of serum creatinine, renal or CV death in treatment group vs placebo
  - **Trial stopped early due to positive efficacy**
- Dapagliflozin: DAPA-CKD trial (67% w/ T2DM and CKD, others without T2DM)
  - Significant benefit in treatment group to delay in time to deline in eGFR, ESRD, CV or renal death

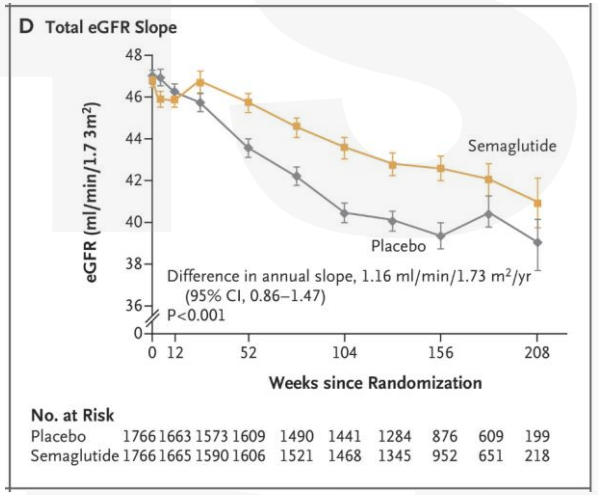
American Diabetes Association; 11. Chronic Kidney Disease and Risk Management.

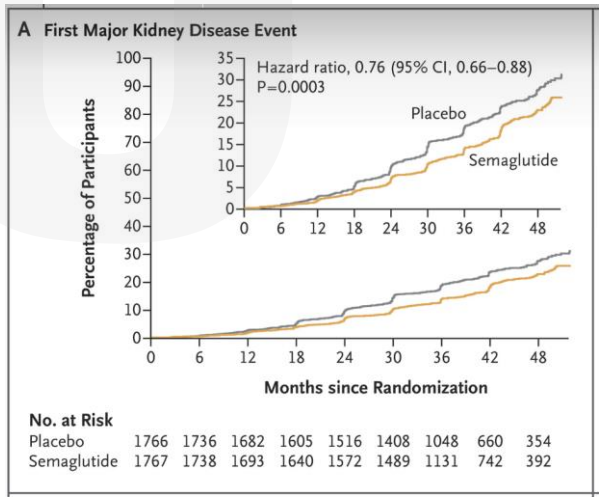
Kidney Disease in Persons with Diabetes Management

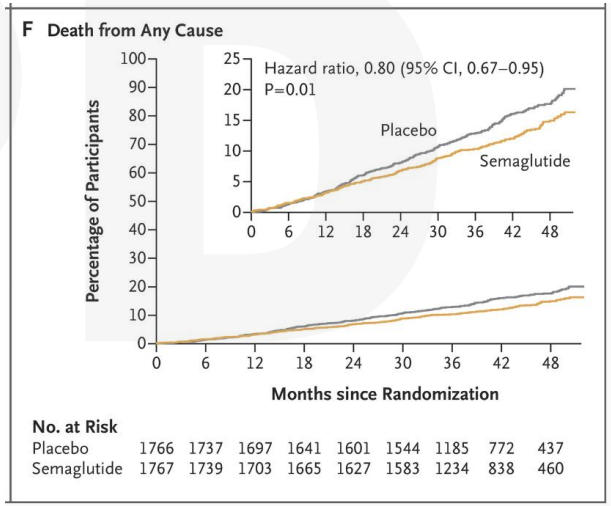
- Semaglutide
  - 2024 FLOW Trial (Semaglutide 1 mg weekly)
  - Double-blind, randomized placebo-controlled trial of 3533 participants with type 2 diabetes and CKD
  - Median f/u time of 3.4 years

Results:

- 24% lower relative risk of major kidney disease events in treatment group vs. placebo
- Slope in reduction of eGFR less in treatment vs placebo
- Risk of major CV event 18% lower in treatment group
- Risk of death of any cause 20% lower in treatment group







Perkovic et al., 2024. NEJM.

Neuropathy in Persons with Diabetes

- Up to 50% of diabetic peripheral neuropathy may be asymptomatic
- Distal symmetric polyneuropathy is the most common form and is often encountered in the primary care setting as the most common systemic complication of diabetes mellitus.
- No current treatments to reverse nerve damage once it has occurred
- Can slow progression with glycemic management

American Diabetes Association; 12. Retinopathy, Neuropathy, and Foot Care.

Neuropathy in Persons with Diabetes

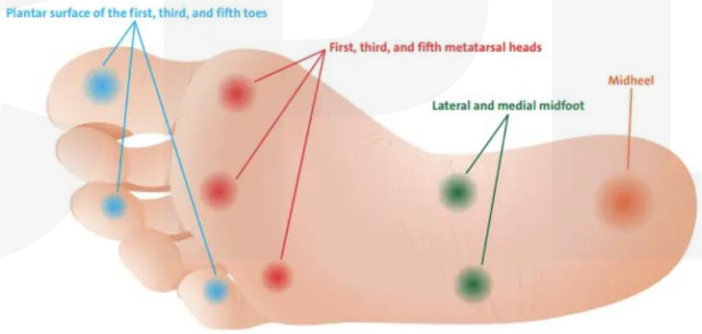
Heterogeneity in signs and symptoms based on affected nerve(s)

	Symptoms	Signs on Examination
Motor	Weakness	Weakness Atrophy Fasciculations Areflexia
Large-Fiber Sensory	Numbness Imbalance, falls Ataxia Paresthesias	Loss of vibratory sensation and/or proprioception Pseudoathetosis Sensory ataxia Areflexia
Small-Fiber Sensory	Numbness Pain	Loss of pain and/or temperature sensation
Autonomic	Postural dizziness Dry mouth, dry eyes, dry skin Early satiety Coldness or flushing Impotence Bladder dysfunction	Orthostatic hypotension Skin changes Loss of hair Hyperemia or cold, pale feet

Doughty et al., 2018

Neuropathy in Persons with Diabetes Screening

- Peripheral neuropathy
- Briefly examine patients feet at every diabetes appointment
- Type 2 DM at time of diagnosis and type 1 DM ≥ 5 years since diagnosis should undergo
  - Annual monofilament (10 g) testing and at least ONE of the following:
    - 128-Hz tuning fork testing (large fiber function)
    - temperature or pinprick sensation (small fiber function)



American Diabetes Association; 12. Retinopathy, Neuropathy, and Foot Care.

Neuropathy in Persons with Diabetes Screening

- Autonomic neuropathy
- Type 2 DM at time of diagnosis and type 1 DM ≥ 5 years since diagnosis should undergo
  - Annual screening of symptoms: orthostatic dizziness, syncope, dry cracked skin, chronic diarrhea or constipation, erectile dysfunction, increase or decrease in sweating
  - Clinical signs: resting tachycardia, orthostatic hypotension, gastroparesis

American Diabetes Association; 12. Retinopathy, Neuropathy, and Foot Care.

Neuropathy in Persons with Diabetes Monitoring

- Peripheral Neuropathy
  - Most commonly starts with small fiber neuropathy presenting with peripheral pain and dysesthesia
  - Large fiber neuropathy causing numbness and loss of protective sensation (risk factor for diabetic foot ulceration)

American Diabetes Association; 12. Retinopathy, Neuropathy, and Foot Care.

Neuropathy in Persons with Diabetes Management

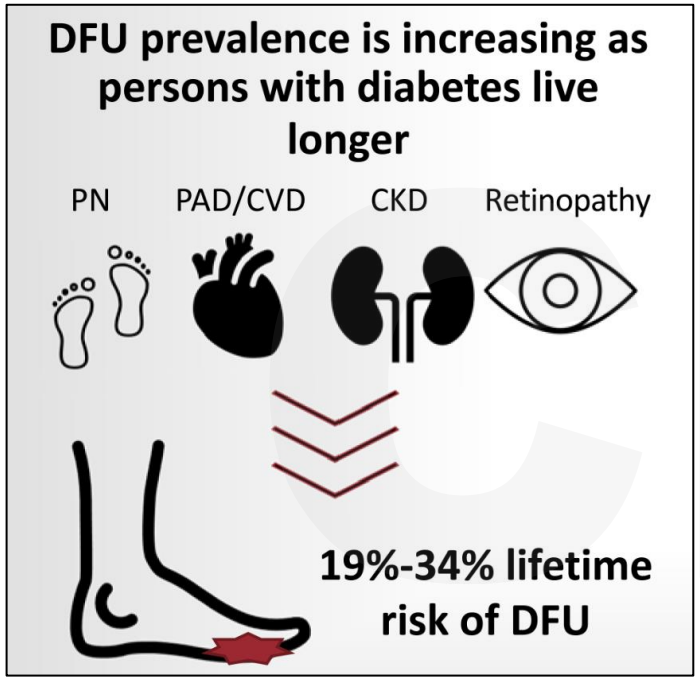
Neuropathic Pain

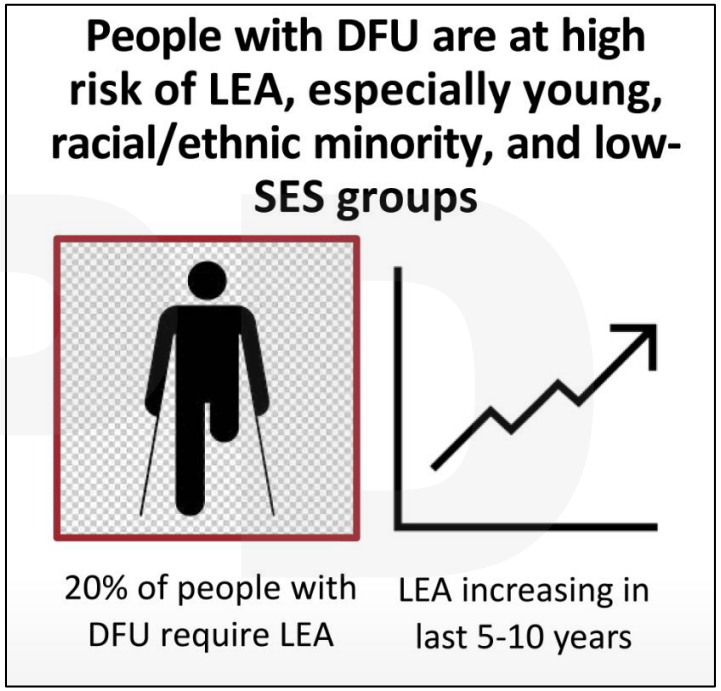
- Glycemic control and lifestyle modifications not shown to improve neuropathic pain
- Gabapentinoids: Pregabalin and Gabapentin
- SNRIs: duloxetine, Venlafaxine, Desvenlafaxine
- TCA: Amitriptyline
- Na Channel Blockers: Lamotrigine, lacosamide, carbamazepine, oxcarbazepine, valproic acid
- Capsaicin 8% patch, 0.075% topical cream

American Diabetes Association; 12. Retinopathy, Neuropathy, and Foot Care.

Foot Complications in Persons with Diabetes

- Multifactorial stemming from: peripheral arterial disease, neuropathy, and foot deformities
- Major cause of morbidity and mortality





Diabetes Care. 2022;46(1):209-221. doi:10.2337/dci22-0043

Foot Complications in Persons with Diabetes Screening

- Loss of protective sensation (LOPS) is vital indicator of peripheral sensory neuropathy and is assessed with 10 g monofilament exam

Table 12.1—International Working Group on the Diabetic Foot risk stratification system and corresponding foot screening frequency

Category	Ulcer risk	Characteristics	Examination frequency*
0	Very low	No LOPS and No PAD	Annually
1	Low	LOPS or PAD	Every 6–12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Every 3–6 months
3	High	LOPS or PAD and one or more of the following: • History of foot ulcer • Amputation (minor or major) • End-stage renal disease	Every 1–3 months

Adapted with permission from Schaper et al. (81). LOPS, loss of protective sensation; PAD, peripheral artery disease. *Examination frequency suggestions are based on expert opinion and person-centered requirements.

American Diabetes Association; 12. Retinopathy, Neuropathy, and Foot Care.

Foot Complications in Persons with Diabetes Screening

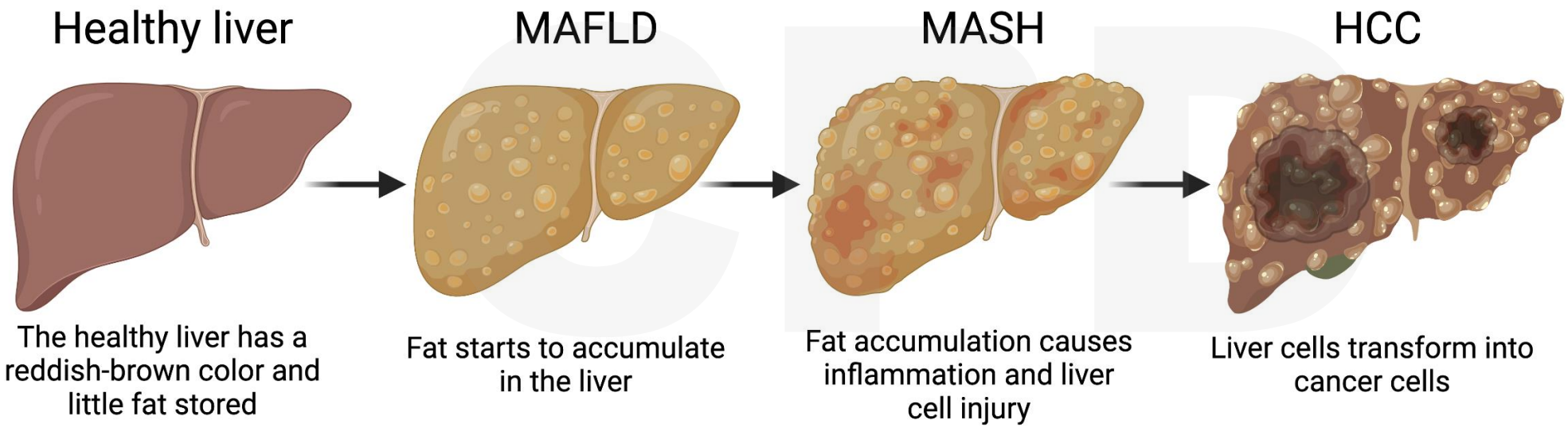
- Peripheral Arterial Disease
  - Symptoms: leg fatigue, claudication, rest pain relieved with dependency
  - Physical Exam: lower extremity pulses, capillary refill, rubor on dependeny and palor on elevation
  - **<u>Any persons exhibiting signs /symptoms of PAD:</u>** doppler arterial ultrasound

Foot Complications in Persons with Diabetes Management

- No / Low-Risk persons: education and self-care and monitoring of feet
- Moderate / high-risk persons: referral to specialist
- Customizable footwear, management of ingrown toe nails, use of moisturizers
- Daily self-evaluation of feet by patients

MASLD in persons with Diabetes

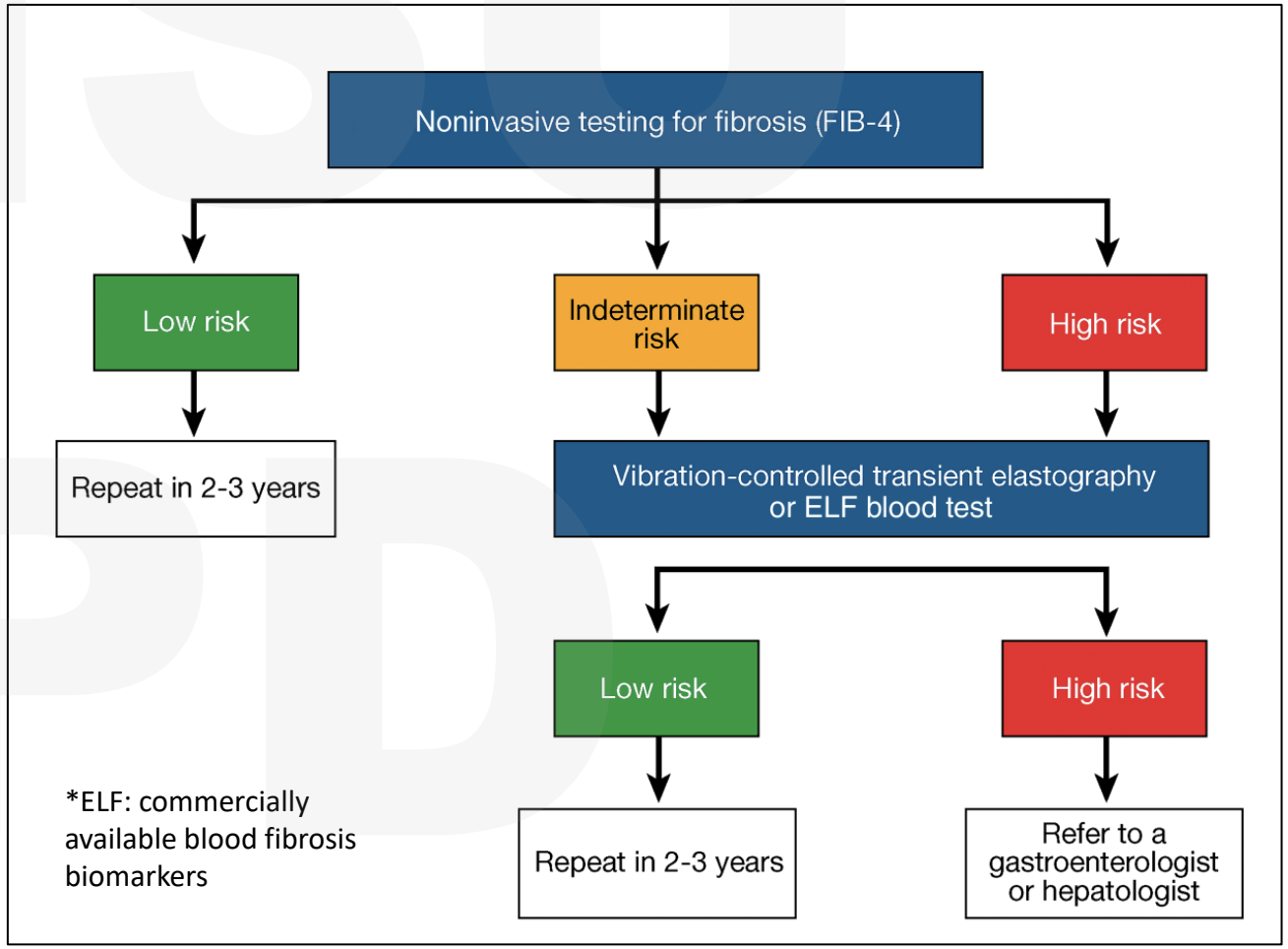
- Formally NAFLD (metabolic dysfunction-associated steatotic liver disease)
- Estimated that >70% of people with type 2 diabetes have MASLD (Lomonaco et al., 2021)
- Steatohepatitis develops in at least 50% of people with type 2 diabetes (Harrison, et al., 2021)
- #1 cause of death is CVD in those with Type 2 DM and MASLD (Duell et al., 2022)



MASLD in persons with Diabetes Screening

- **FIB-4 Score**: assessing for presence of advanced fibrosis
- Low risk: <1.3 (NPV 90%) (Sterling et al.,2006)
- Indeterminate:1.3-2.67
- High Risk:>2.67
- Pros:
  - Cost-effective initial screening
  - Labs readily accessible on routine screenings
- Cons:
  - artificially lowered results in those <35 years
  - Artificially raised results in those >65 years

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}}$$



American Diabetes Association Professional Practice Committee; 4. Comprehensive Medical Evaluation and Assessment of Comorbidities

MASLD in persons with Diabetes Management

Dietary Modifications:

- Restriction of high-fructose corn syrup intake to <20 g/d has been shown to improve MASH even in the absence of weight loss.
- **Fructose intake**; aggravates weight gain, stimulates intrahepatic triglyceride accumulation, and has been associated with worsening fibrosis and progression to NASH among patients with MASLD.
- Mediterranean style dietary habits have been shown to reduce hepatic fat and to improve insulin sensitivity independently of exercise and weight loss.
- Mediterranean diet was superior to a low-fat diet in reducing hepatic fat assessed by MRI, despite more modest weight loss (mean, ≈3 kg).
- **Mediterranean diet** is the only specific dietary pattern recommended by the European Association for the Study of the Liver/European Association for the Study of Diabetes/European Association for the Study of Obesity clinical practice guidelines for the treatment of MASLD and MASH.

Duell et al., 2022. AHA Scientific Statement.

MASLD in persons with Diabetes Management

Weight loss/exercise

- Exercise decreases hepatic steatosis, increases free fatty acid uptake in myocytes, and increases insulin sensitivity **independently** of weight loss.
- **10 %** weight reduction ~ with **resolution of MASH in 90%** on repeat liver biopsy.
- **5%** weigh loss ~ with only a **≈40% improvement in MASH resolution**.
- FDA approved weight-lowering medications may be appropriate and efficacious for achievement of sustained weight loss in some patients with BMI >30 kg/m2 or BMI >27 kg/m + comorbidities.
- The most efficacious intervention for achieving sustained major median weight loss of 21% to 30% is bariatric surgery. BMI >35

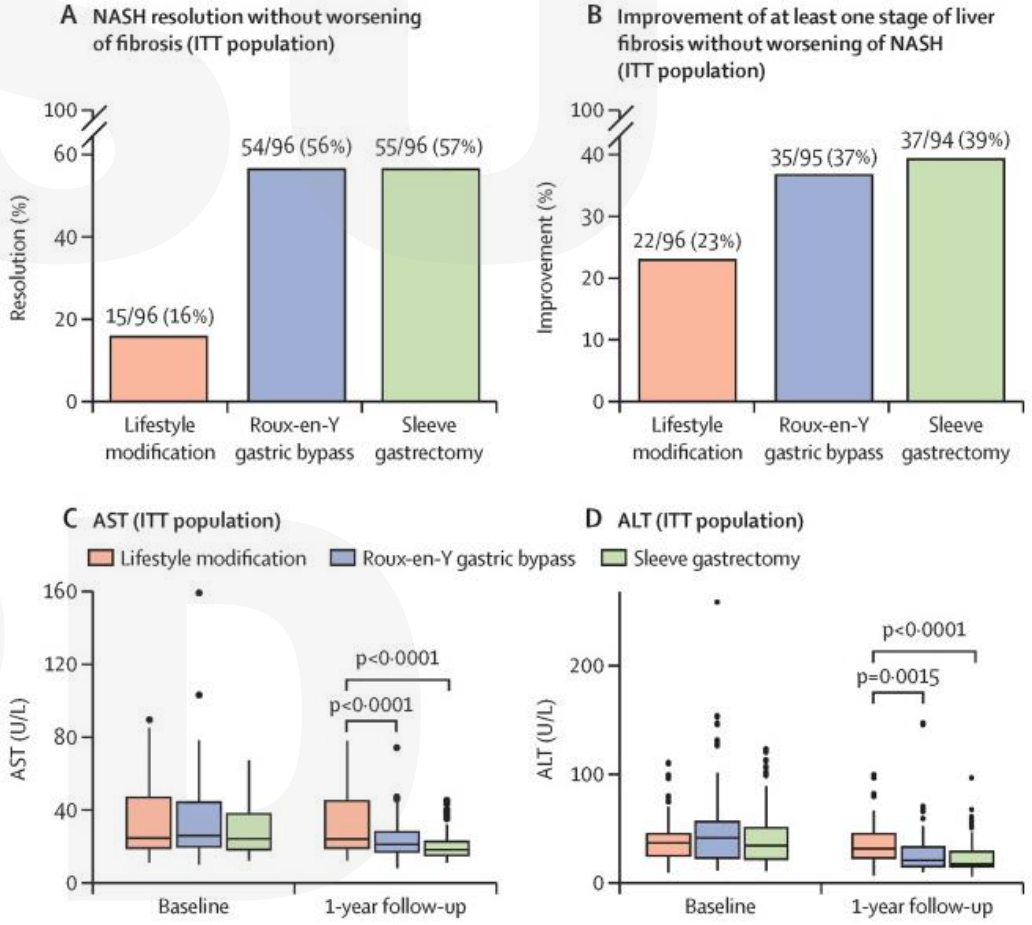


Figure 1 Primary endpoint, secondary endpoint, AST, and ALT results in the ITT population

Verrastro et al., 2023.

MASLD in persons with Diabetes Management

- **Semaglutide:** Randomized placebo-controlled 72-week study of 320 patients with biopsy-proven MASH with liver fibrosis stages 1 to 3. (Newsome et al., 2021)
  - Resolution of MASH with no worsening of fibrosis occurred in 40% treated with 0.1 mg daily, 36% with 0.2 mg daily, 59% with 0.4 mg daily, and 17% with placebo (P<0.001 for semaglutide 0.4 mg versus placebo)
  - No significant improvement in fibrosis stage between groups
- **Tirzepatide:** SYNERGY-NASH Phase 2 trial, 52 week randomized PCT of 190 patients w/ bx confirmed MASH (Loomba et al., 2024)
  - Resolution of MASH with no worsening of fibrosis occur in 44% treated with 5 mg weekly, 56% in 10 mg weekly, 62% in 15 mg weekly, and 10% in placebo
- **Pioglitazone:** When compared with placebo, pioglitazone improved liver function, reduced liver fat, and decreased NASH despite increasing body weight (Musso et al.,2017) (Ciardullo et al., 2023)
  - Contraindicated in cirrhosis, discontinue in those with transaminases >2.5 x ULN

Ciardullo et al., 2023

MASLD in persons with Diabetes Management

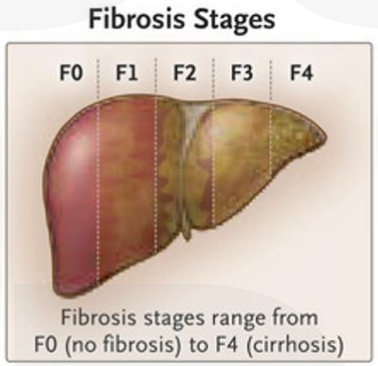
- Resmetirom *(Rezdiffra)*
- oral thyroid hormone receptor-beta (THRβ) agonist.
- Agonists of thyroid hormone receptor (THR)-β, which is prima found in the liver, can promote lipophagy, mitochondrial bioge and mitophagy, stimulating increased hepatic fatty acid β-oxidation.

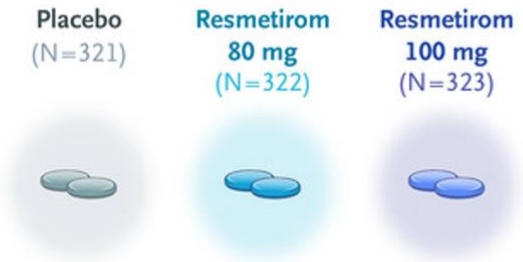
(Harrison S et al., 2024, NEJM)

MASLD in persons with Diabetes Management

MAESTRO-NASH

- Phase 3,multinational, double blinded, randomized and controlled trial.
- 966 patients with biopsy proven NASH with fibrosis F1B, F2,F3 assigned 1:1:1.
- Two primary end-points at week 52
  - Reduction in NAFLD activity score =>2
  - Reduction in fibrosis =>1 stage

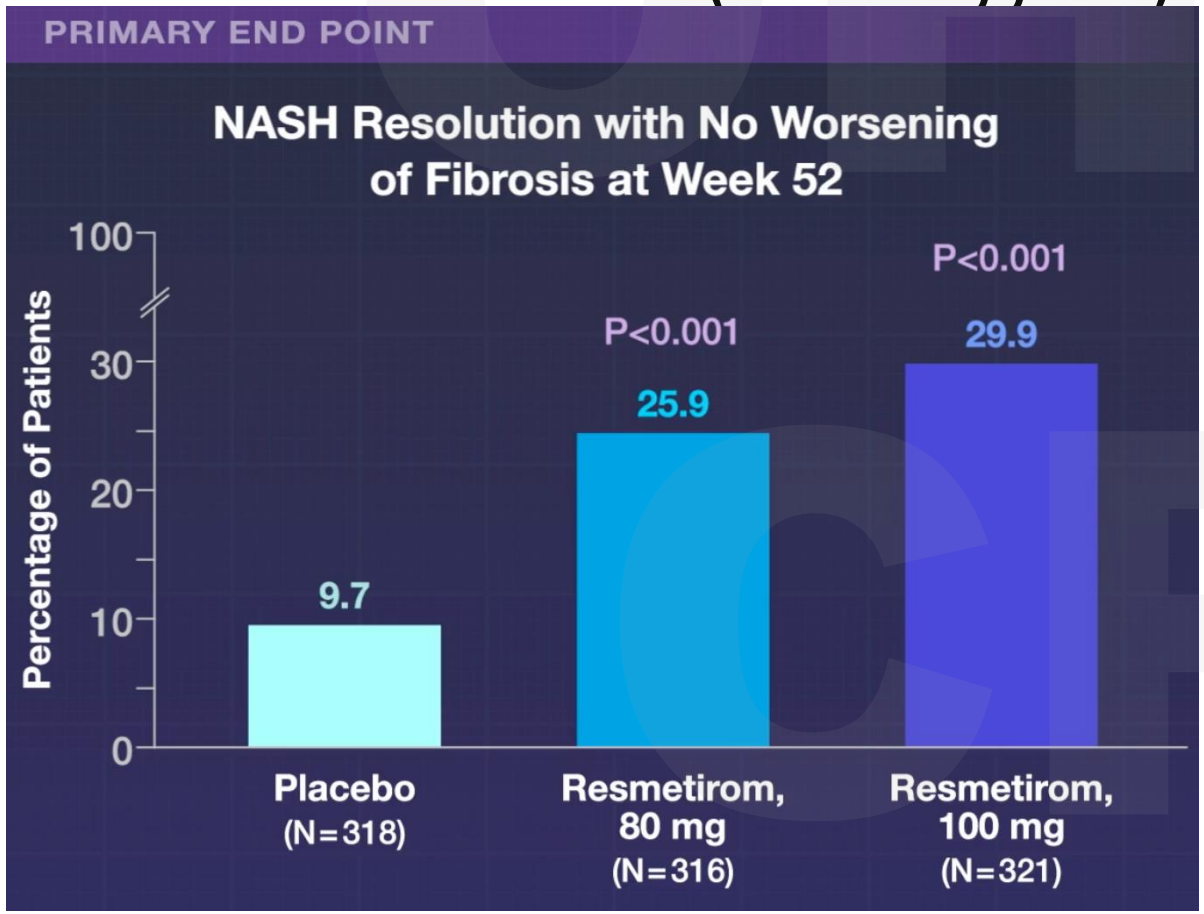


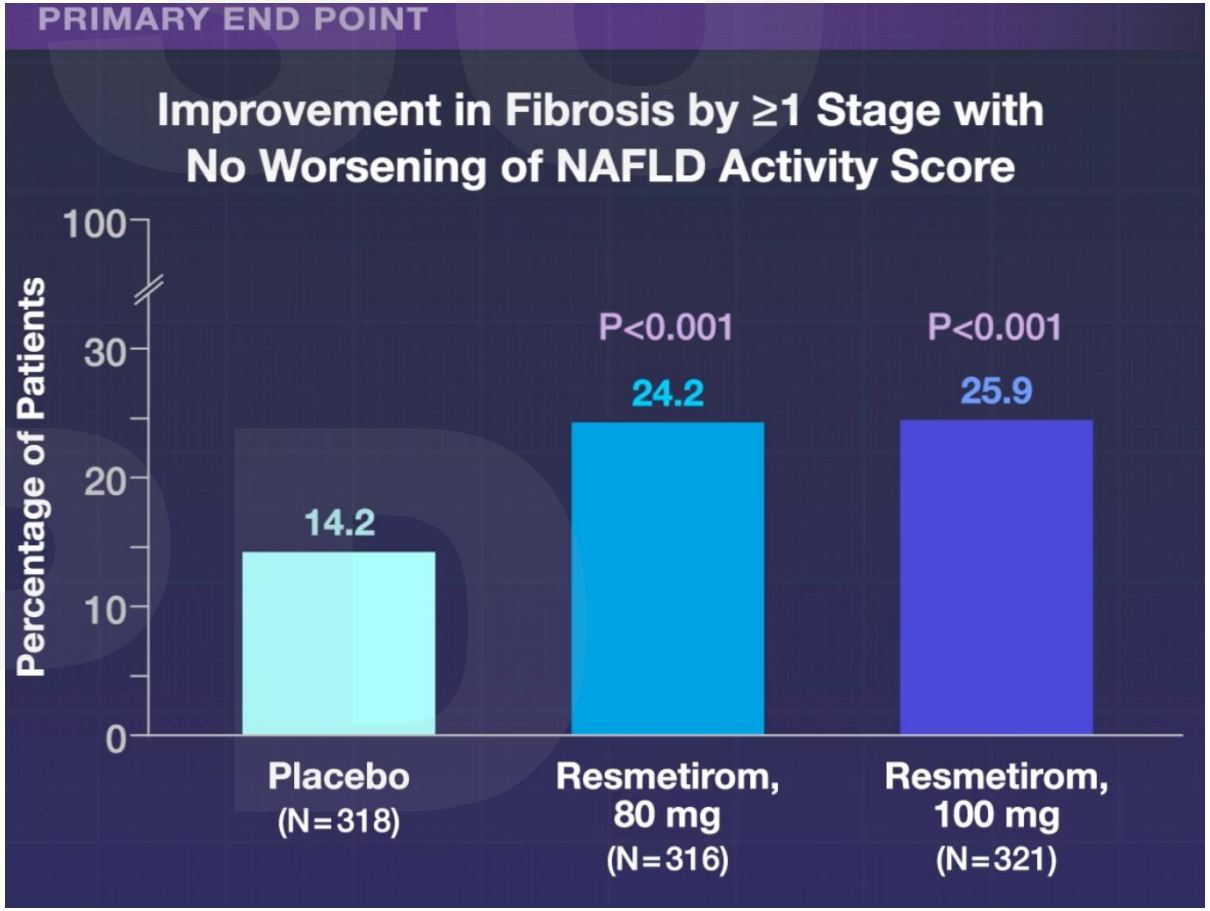


(Harrison S et al., 2024, NEJM)

MASLD in persons with Diabetes Management

Resmetirom (*Rezdiffra*)





(Harrison S et al., 2024, NEJM)

Retinopathy in persons with Diabetes

- Most common cause of new blindness in adults age 20-74 in US
- Glaucoma, cataracts, and other eye disorders occur earlier and more frequently in persons with diabetes
- Risk factors associated with retinopathy:
  - Hyperglycemia, nephropathy, hypertension, dyslipidemia

Retinopathy in persons with Diabetes Screening

- Adults with type 1 diabetes: initial screening eye exam within 5 years of diagnosis
- Adults with type 2 diabetes: initial screening exam at time of diagnosis
- If no evidence of retinopathy from one or more annual eye exams and glycemic control is at goal, can screen every 1-2 years

Retinopathy in persons with Diabetes Management

- Referral to ophthalmologist in setting of retinopathy or any level of diabetic macular edema

GLP1-RA

- Some association between worsening retinopathy and GLP1-RA therapy
  - Postulated that this may be related to acute improvements in glycemic control that are associated with initial worsening of retinopathy (Bethel et al.,2021)
  - No long term outcomes trials to assess retinopathy changes over time in this population

Osteoporosis in Persons with Diabetes

- 34% increased risk of fracture compared to age-matched persons without diabetes
- Hip Fracture risk increased by 1.79 times in persons with type 2 diabetes compared to those without (Wang et al.,2019)
  - Risk throughout life increased 40-70% compared to those without diabetes
  - Risk higher even in early stages of disease with higher BMD (Napoli et al.,2019)

Osteoporosis in Persons with Diabetes

- DEXA scan monitoring, every 2-3 years:
  - Adults with diabetes >65 years old
  - Younger persons with diabetes with high risk features
  - FRAX score does not accurately assess for diabetes, can add 10 years to age or reduce BMD by 0.5 SD T-Score (Ferrari et al., 2018)
- Maintenance of Vitamin D levels
- Appropriate daily intake of calcium
  - Generally 1200 mg / day in women
  - Generally 1000 mg / day in men

Table 4.5—General and diabetes-specific risk factors for fracture

General risk factors
- Prior osteoporotic fracture
- Age >65 years
- Low BMI
- Sex
- Malabsorption
- Recurrent falls
- Glucocorticoid use
- Family history
- Alcohol/tobacco abuse
- Rheumatoid arthritis

Diabetes-specific risk factors
- Lumbar spine or hip T-score ≤−2.0
- Frequent hypoglycemic events
- Diabetes duration >10 years
- Diabetes medications: insulin, thiazolidinediones, sulfonylurea
- A1C >8%
- Peripheral and autonomic neuropathy
- Retinopathy and nephropathy

American Diabetes Association Professional Practice Committee; 4. Comprehensive Medical Evaluation and Assessment of Comorbidities

Conclusions

- SGLT2-inhibitors and GLP1-RA have been shown to provide multiple benefits outside of glycemic control for persons with type 2 diabetes
- Regular foot evaluations allow for earlier detection of neuropathy and foot wounds
- MASLD is highly prevalent amongst persons with type 2 diabetes, FIB-4 is a cost-effective and fast screening tool to assess for fibrosis! And we have medications that can help!

References

1. Agarwal S, Cox AJ, Herrington DM, Jorgensen NW, Xu J, Freedman BI, Carr JJ, Bowden DW. Coronary calcium score predicts cardiovascular mortality in diabetes: diabetes heart study. Diabetes Care. 2013 Apr;36(4):972-7. doi: 10.2337/dc12-1548. Epub 2012 Dec 10. PMID: 23230101; PMCID: PMC3609509.
2. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care, 1999-2010. N Engl J Med 2013;368:1613–1624American Diabetes Association; 8. Cardiovascular Disease and Risk Management. *Diabetes Care* 1 January 2016; 39 (Supplement_1): S60–S71. https://doi.org/10.2337/dc16-S011
3. American Diabetes Association; 9. Microvascular Complications and Foot Care. *Diabetes Care* 1 January 2016; 39 (Supplement_1): S72–S80. https://doi.org/10.2337/dc16-S012
4. American Diabetes Association Professional Practice Committee; 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Care in Diabetes—2024*. *Diabetes Care* 1 January 2024; 47 (Supplement_1): S52–S76. https://doi.org/10.2337/dc24-S004
5. Bethel MA, Diaz R, Castellana N, Bhattacharya I, Gerstein HC, Lakshmanan MC. HbA1c change and diabetic retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: a meta-analysis and meta-regression. Diabetes Care 2021;44:290–296
6. Buse JB, Ginsberg HN, Bakris GL, et al.; American Heart Association; American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes
7. Ciardullo, S., Vergani, M., & Perseghin, G. (2023). Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes: Screening, Diagnosis, and Treatment. *Journal of Clinical Medicine*, *12*(17), 5597. https://doi.org/10.3390/jcm12175597
8. de Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, Rosas SE, Rossing P, Bakris G. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022 Dec 1;45(12):3075-3090. doi: 10.2337/dci22-0027. PMID: 36189689; PMCID: PMC9870667.
9. Doughty CT, Seyedsadjadi R. Approach to Peripheral Neuropathy for the Primary Care Clinician. *Am J Med*. 2018;131(9):1010-1016. doi:10.1016/j.amjmed.2017.12.042
10. Duell PB, Welty FK, Miller M, Chait A, Hammond G, Ahmad Z, Cohen DE, Horton JD, Pressman GS, Toth PP. Nonalcoholic Fatty Liver Disease and Cardiovascular Risk: A Scientific Statement From the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2022;42(6):e128-e145. doi:10.1161/ATV.0000000000000153
11. Emily D. Parker, Janice Lin, Troy Mahoney, Nwanneamaka Ume, Grace Yang, Robert A. Gabbay, Nuha A. ElSayed, Raveendhara R. Bannuru; Economic Costs of Diabetes in the U.S. in 2022. *Diabetes Care* 2 January 2024; 47 (1): 26–43. https://doi.org/10.2337/dci23-0085
12. Feng XS, Farej R, Dean BB, Xia F, Gaiser A, Kong SX, Elliott J, Lindemann S, Singh R. CKD Prevalence Among Patients With and Without Type 2 Diabetes: Regional Differences in the United States. Kidney Med. 2021 Nov 3;4(1):100385. doi: 10.1016/j.xkme.2021.09.003. PMID: 35072048; PMCID: PMC8767132.
13. Ferrari SL, Abrahamsen B, Napoli N, et al.; Bone and Diabetes Working Group of IOF. Diagnosis and management of bone fragility in diabetes: an emerging challenge. Osteoporos Int 2018;29:2585–2596
14. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–591
15. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, Labriola D, Moussa SE, Neff GW, Rinella ME, Anstee QM, Abdelmalek MF, Younossi Z, Baum SJ, Francque S, Charlton MR, Newsome PN, Lanthier N, Schiefke I, Mangia A, Pericàs JM, Patil R, Sanyal AJ, Noureddin M, Bansal MB, Alkhouri N, Castera L, Rudraraju M, Ratziu V; MAESTRO-NASH Investigators. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med. 2024 Feb 8;390(6):497-509. doi: 10.1056/NEJMoa2309000. PMID: 38324483.
16. Harrison SA, Gawrieh S, Roberts K, Lisanti CJ, Schwope RB, Cebe KM, Paradis V, Bedossa P, Aldridge Whitehead JM, Labourdette A, Miette V, Neubauer S, Fournier C, Paredes AH, Alkhouri N. Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort. J Hepatol. 2021 Aug;75(2):284-291. doi: 10.1016/j.jhep.2021.02.034. Epub 2021 Mar 18. PMID: 33746083.
17. Ko, Gang Jee, Kamyar Kalantar-Zadeh, Jordi Goldstein-Fuchs, and Connie M. Rhee. 2017. "Dietary Approaches in the Management of Diabetic Patients with Kidney Disease." *Nutrients* 9 (8): 824. https://doi.org/10.3390/nu9080824.
18. Koo DJ, Lee MY, Moon SJ, Kwon H, Lee SM, Park SE, Park CY, Lee WY, Oh KW, Cho SR, Jeong YH, Rhee EJ. Coronary Artery Calcium Score as a Sensitive Indicator of Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus: A Long-Term Cohort Study. Endocrinol Metab. 2023;38(5):568-577.
19. Ledwidge MT, O'Connell E, Gallagher J, Tilson L, James S, Voon V, Bermingham M, Tallon E, Watson C, O'Hanlon R, Barry M, McDonald K. Cost-effectiveness of natriuretic peptide-based screening and collaborative care: a report from the STOP-HF (St Vincent's Screening TO Prevent Heart Failure) study. Eur J Heart Fail. 2015 Jul;17(7):672-9. doi: 10.1002/ejhf.286. PMID: 26139583.
20. Lomonaco R, Godinez Leiva E, Bril F, Shrestha S, Mansour L, Budd J, Portillo Romero J, Schmidt S, Chang KL, Samraj G, Malaty J, Huber K, Bedossa P, Kalavalapalli S, Marte J, Barb D, Poulton D, Fanous N, Cusi K. Advanced Liver Fibrosis Is Common in Patients With Type 2 Diabetes Followed in the Outpatient Setting: The Need for Systematic Screening. Diabetes Care. 2021 Feb;44(2):399-406. doi: 10.2337/dc20-1997. Epub 2020 Dec 21. PMID: 33355256; PMCID: PMC7818321.
21. McDermott K, Fang M, Boulton AJM, Selvin E, Hicks CW. Etiology, Epidemiology, and Disparities in the Burden of Diabetic Foot Ulcers. *Diabetes Care*. 2023 Jan 2;46(1):209-221. doi:10.2337/dci22-0043.
22. Musso, G.; Cassader, M.; Paschetta, E.; Gambino, R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: A meta-analysis. *JAMA Intern. Med.* **2017**, *177*, 633–640.
23. Napoli N, Conte C, Pedone C, et al. Effect of insulin resistance on BMD and fracture risk in older adults. J Clin Endocrinol Metab 2019;104: 3303–3310
24. SleighPerkovic V, Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, Baeres FMM, Idorn T, Bosch-Traberg H, Lausvig NL, Pratley R; FLOW Trial Committees and Investigators. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. N Engl J Med. 2024 Jul 11;391(2):109-121. doi: 10.1056/NEJMoa2403347. Epub 2024 May 24. PMID: 38785209.t P. The HOPE Study (Heart Outcomes Prevention Evaluation). J Renin Angiotensin Aldosterone Syst. 2000 Mar;1(1):18-20. doi: 10.3317/jraas.2000.002. PMID: 11967789.
25. Sterling RK, Lissen E, Clumeck N, et. al. Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co-infection. Hepatology 2006;43:1317-1325.
26. Wang H, Ba Y, Xing Q, Du JL. Diabetes mellitus and the risk of fractures at specific sites: a meta-analysis. BMJ Open. 2019 Jan 3;9(1):e024067. doi: 10.1136/bmjopen-2018-024067. PMID: 30610024; PMCID: PMC6326306.