DIABETES UPDATES FOR 2026

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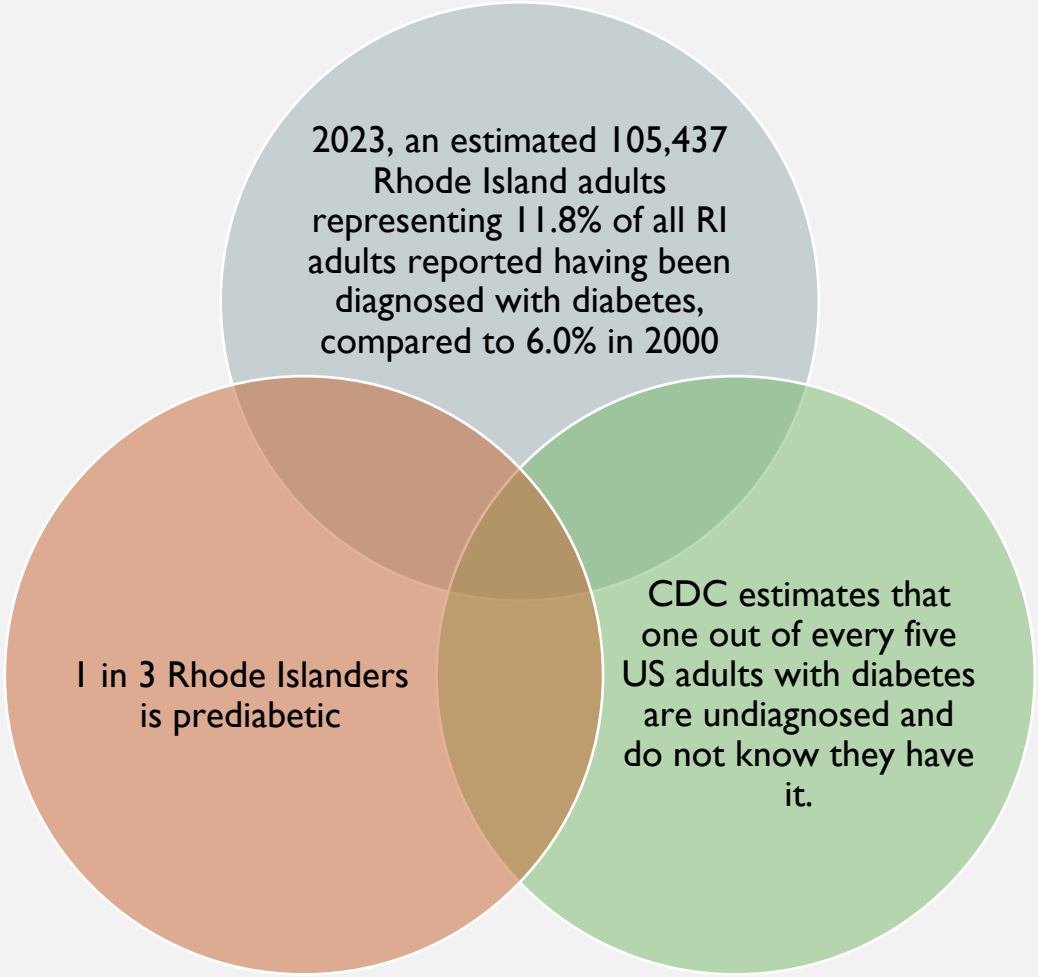
DISCLOSURES

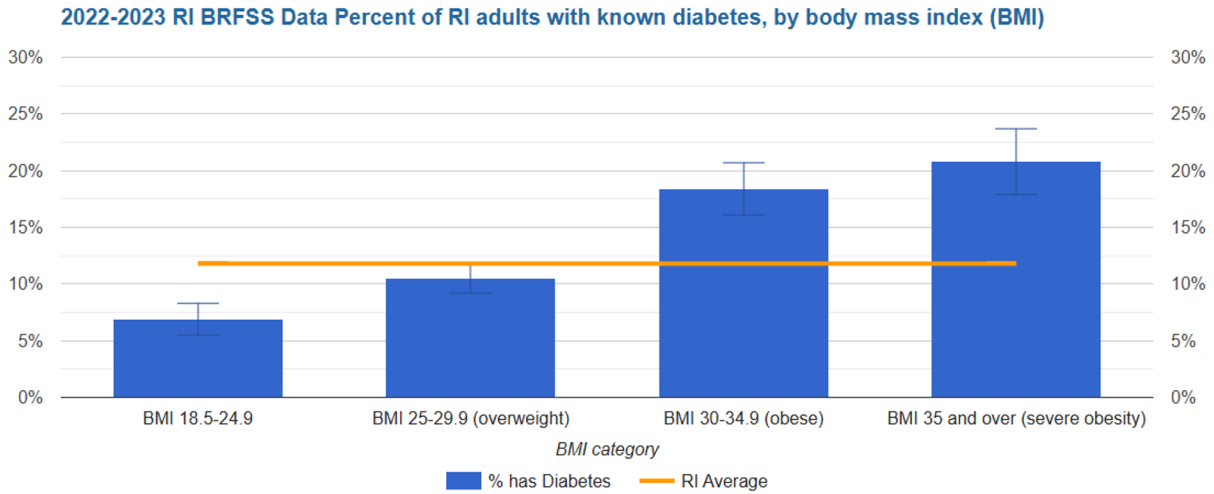
- None

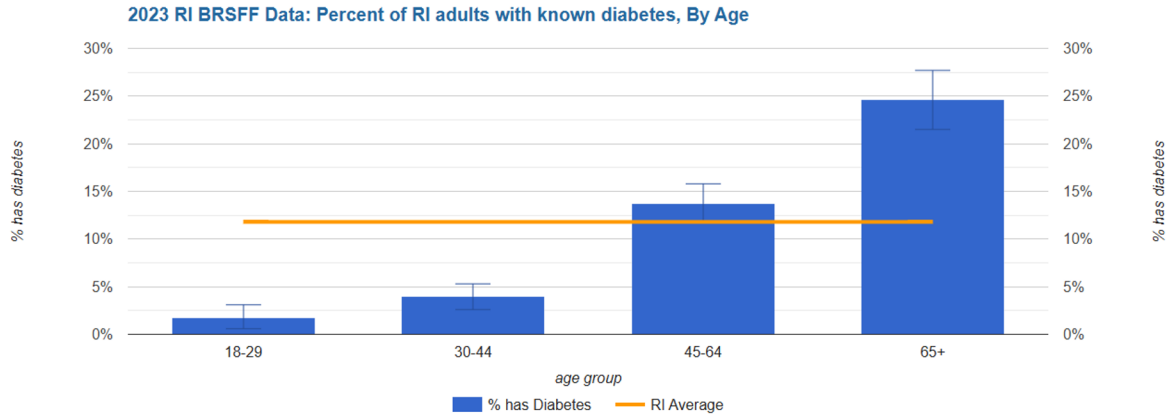
LEARNING OBJECTIVES

- Define the impact of Diabetes at the state level
- Utilize the changes in guidelines for Diabetes classifications
- Review updated age-related DM care recommendations
- Incorporate patient-centered care and programs available to patients in RI into practice
- Discuss wellness as it relates to positive outcome with DM
- Recognize the changes in treatment and management of Diabetes according to co-morbidity
- Review DM medications and best use to cover additional co-morbidities
- Review recommendations for Gestational DM and Breastfeeding and DM
- Discuss technology application for DM care

RI DM STATS

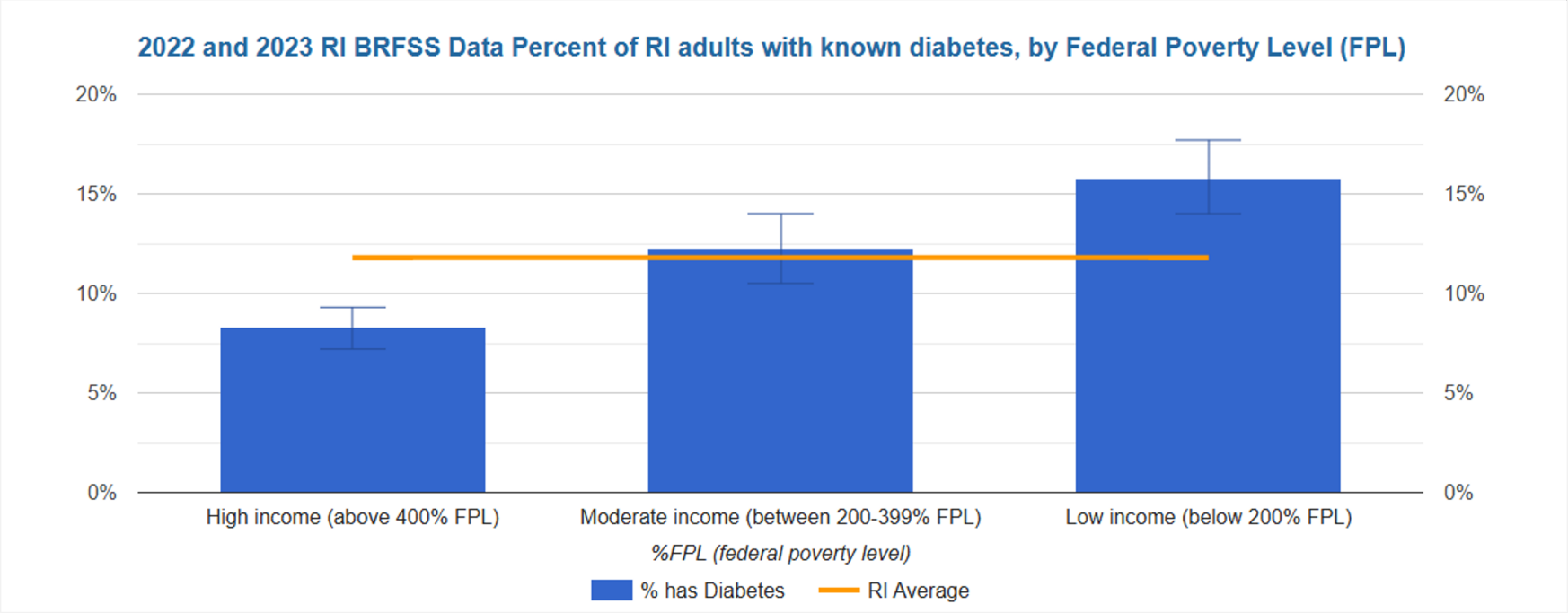

2023, an estimated 105,437 Rhode Island adults representing 11.8% of all RI adults reported having been diagnosed with diabetes, compared to 6.0% in 2000
1 in 3 Rhode Islanders is prediabetic
CDC estimates that one out of every five US adults with diabetes are undiagnosed and do not know they have it.





RI DIABETES

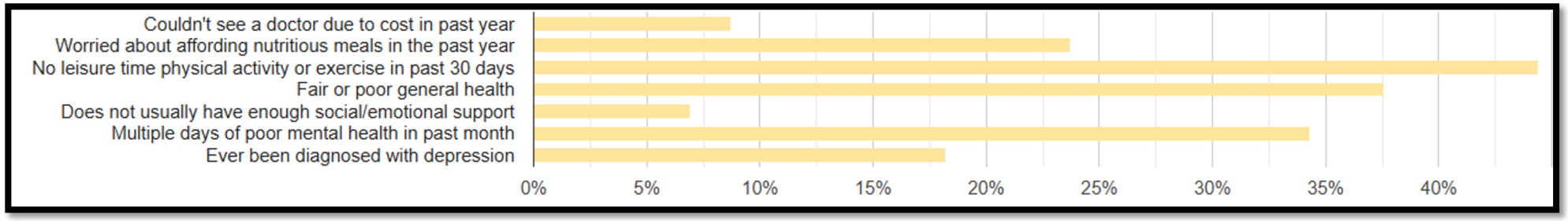
The risk of developing DM increases with age and weight



RI DIABETES

A lower socioeconomic status is associated with risk of DM, as people lack ready access to resources

PERCENTAGE OF RI ADULTS WITH DM WHO…



REVIEW OF TYPES OF DIABETES

Type 1 diabetes

- Due to autoimmune β-cell destruction
- Usually leading to absolute insulin deficiency
- Includes latent autoimmune diabetes in adults

Type 2 diabetes

- Due to a non-autoimmune progressive loss of adequate β-cell insulin secretion
- Frequently on the background of insulin resistance

Specific types of diabetes due to other causes

- Monogenic diabetes syndromes
- Diseases of the exocrine pancreas
- Drug- or chemical-induced diabetes

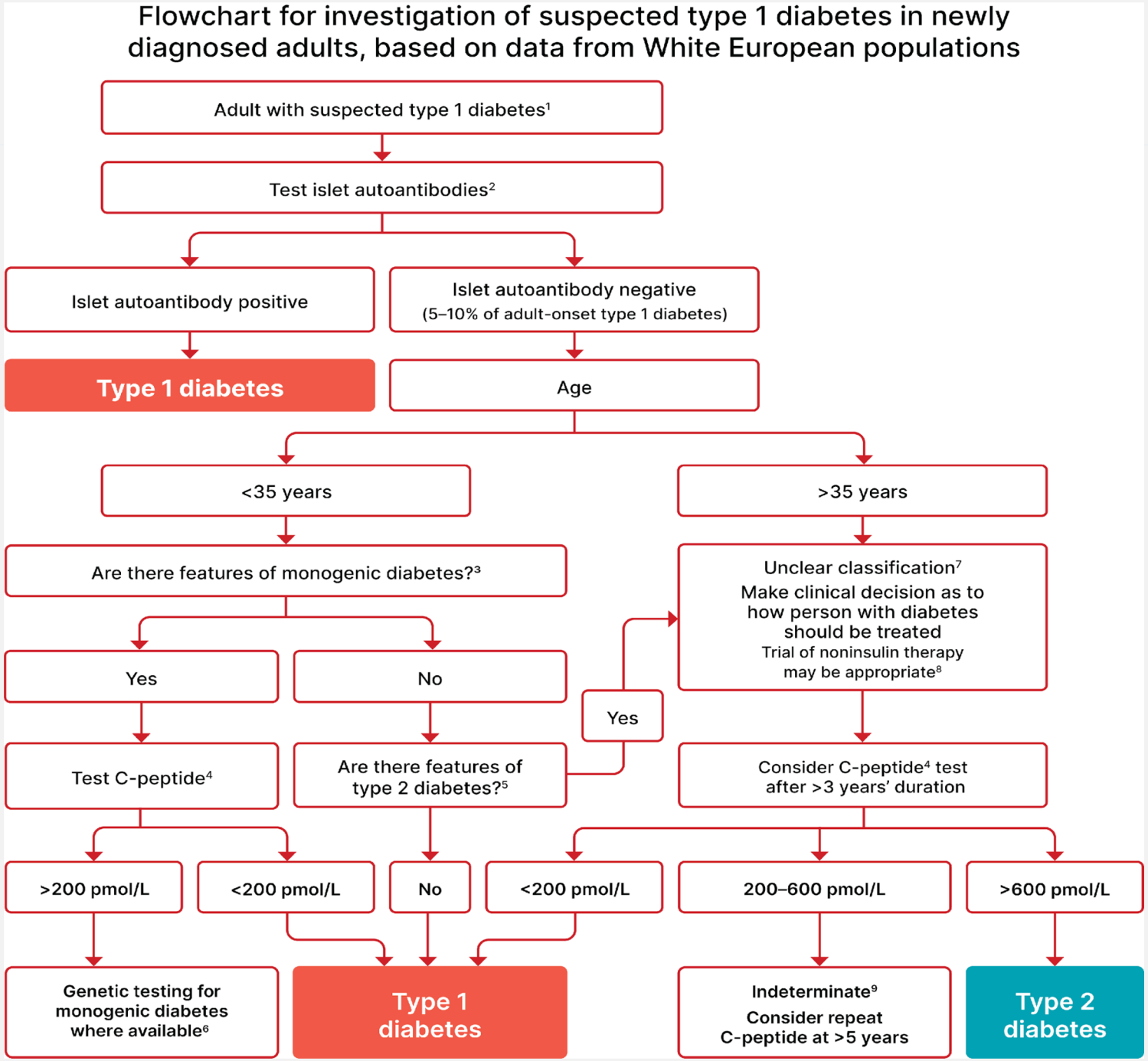
Gestational diabetes mellitus

- Diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation or other types of diabetes occurring throughout pregnancy, such as type 1 diabetes

American Diabetes Association®

From: **2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2026**

Diabetes Care. 2025;49(Supplement_1):S27-S49. doi:10.2337/dc26-S002



SCREENING TYPE 1 DM

Autoantibody-based screening for presymptomatic type 1 diabetes should be offered to those with a family history of type 1 diabetes or otherwise known elevated genetic risk

Screen for presymptomatic type 1 diabetes by testing autoantibodies against insulin (IA), glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2), or zinc transporter 8 (ZnT8)

Individuals with screening results positive for one or more islet autoantibodies should be evaluated for stage 3 (overt) type 1 diabetes (using A1C, urinalysis, and/or plasma glucose), which would require prompt clinical management and education.

Individuals with multiple confirmed islet autoantibodies and without overt type 1 diabetes have a high risk for progression to stage 3 type 1 diabetes and should be referred to a specialized center for metabolic staging, education, and consideration of prevention trials or approved treatments (e.g., teplizumab).

Individuals with a single confirmed IA-2 autoantibody should be monitored similarly to individuals with multiple islet autoantibodies, as IA-2 autoantibody positivity is an independent risk factor for progression. Individuals with a single confirmed islet autoantibody should undergo repeat antibody testing every 6 months to 3 years (depending on age) to assess for persistence or seroconversion.

Standardized islet autoantibody tests are recommended for classification of diabetes in adults who have phenotypic risk factors that overlap with those for type 1 diabetes (e.g., younger age at diagnosis, unintentional weight loss, ketoacidosis, or short time to insulin treatment).

Type 1 Diabetes Progression

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity	• Autoimmunity	• Autoimmunity
	• Normoglycemia	• Dysglycemia	• Overt hyperglycemia
	• Presymptomatic	• Presymptomatic	• Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies - GAD, glutamic acid decarboxylase (primary) - islet antigen 2, or - Zinc transporter 8 (ZnT8)	• Islet autoantibodies Dysglycemia: Elevated IFG and/or IGT • FPG 100–125 mg/dL • 2-h PG 140–199 mg/dL • A1C 5.7–6.4% or ≥10% increase in A1C	• Autoantibodies may disappear over time (5-10% may not express antibodies) • Diabetes diagnosed by standard criteria

STANDARDS OF CARE | DECEMBER 12 2022

2. Classification and Diagnosis of Diabetes: *Standards of Care in Diabetes—2023* FREE

Diabetes Education SERVICES 25 years

www.DiabetesEd.net

SCREENING GUIDELINES FOR ADULTS

Criteria for screening for diabetes or prediabetes in asymptomatic adults
Testing should be considered in adults with overweight or obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in individuals of Asian ancestry) who have one or more of the following risk factors: • First-degree relative with diabetes • High-risk race, ethnicity, and ancestry (e.g., African American, Latino, Native American, Asian American) • History of cardiovascular disease • Hypertension (≥130/80 mmHg or on therapy for hypertension) • HDL cholesterol level <35 mg/dL (<0.9 mmol/L) and/or triglyceride level >250 mg/dL (>2.8 mmol/L) • Individuals with polycystic ovary syndrome • Physical inactivity • Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans, metabolic dysfunction-associated steatotic liver disease)
People with prediabetes (A1C ≥5.7% [≥39 mmol/mol], IGT, or IFG) should be tested yearly.
People who were diagnosed with GDM should have testing at least every 1–3 years.
For all other people, testing should begin at age 35 years.
If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.
Individuals in other high-risk groups (e.g., people with HIV, exposure to high-risk medicines, evidence of periodontal disease, history of pancreatitis) should also be closely monitored

SCREENING CRITERIA FOR TYPE II DIABETES

TABLE 2.2/2.5 Criteria for the Screening and Diagnosis of Prediabetes and Diabetes

	Prediabetes	Diabetes
A1C	5.7–6.4% (39–47 mmol/mol)*	≥6.5% (48 mmol/mol)†
Fasting plasma glucose	100–125 mg/dL (5.6–6.9 mmol/L)*	≥126 mg/dL (7.0 mmol/L)†
2-hour plasma glucose during 75-g OGTT	140–199 mg/dL (7.8–11.0 mmol/L)*	≥200 mg/dL (11.1 mmol/L)†
Random plasma glucose	–	≥200 mg/dL (11.1 mmol/L)‡

Adapted from Tables 2.2 and 2.5 in the complete 2022 Standards of Care. *For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range. †In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate samples ‡Only diagnostic in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

SCREENING YOUTH UNDER 18 TYPE II DM

Overweight ≥ 85th percentile for weight

Risk factors:

- Maternal history of DM or GDM during gestation
- DM 2 in first or second-degree relative
- Native American, African American, Latino or Asian American

Signs of Insulin resistance:

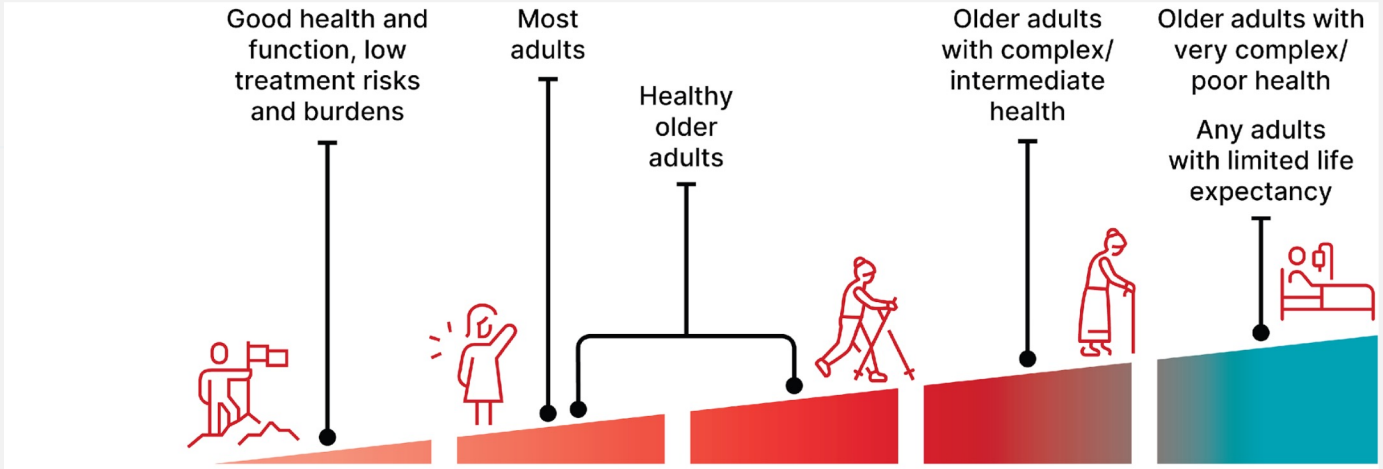
- Acanthosis nigricans
- Hypertension
- PCOS
- Dyslipidemia
- Small-for-gestational-age birth weight

From: **6. Glycemic Goals, Hypoglycemia, and Hyperglycemic Crises: Standards of Care in Diabetes—2026**

Diabetes Care.
2025;49(Supplement_1):S132-S149.
doi:10.2337/dc26-S006

Figure Legend:

Individualized A1C and CGM goals for nonpregnant adults. Select the glycemic goal based on individual health and function as described at the top of the figure. Consider modifying to a more or less stringent goal according to the factors listed in the table. Older adults are classified as healthy (few coexisting chronic illnesses, intact cognitive and functional status), as having complex/intermediate health (multiple coexisting chronic illnesses, two or more instrumental impairments to activities of daily living, or mild to moderate cognitive impairment), or as having very complex/poor health (long-term care or end-stage chronic illnesses, moderate to severe cognitive impairment, or two or more impairments to activities of daily living). Select glycemic goals that avoid symptomatic hypoglycemia and hyperglycemia in all individuals. Consider individuals' resources and support systems to safely achieve glycemic goals. Incorporate the preferences and goals of people with diabetes through shared decision-making. CGM, continuous glucose monitoring; TAR, time above range; TBR, time below range; TIR, time in range.



A1C goals	<6.5%	<7.0%	<7.5%	<8.0%	No A1C goal
CGM goals TIR:	—	>70%	—	>50%	—
• TBR <70	—	<4%	—	<1%	<1%
• TBR <54	—	<1%	—	<1%	<1%
• TAR >180	—	<25%	—	<50%	Avoid symptomatic hyperglycemia
• TAR >250	—	<5%	—	<10%	

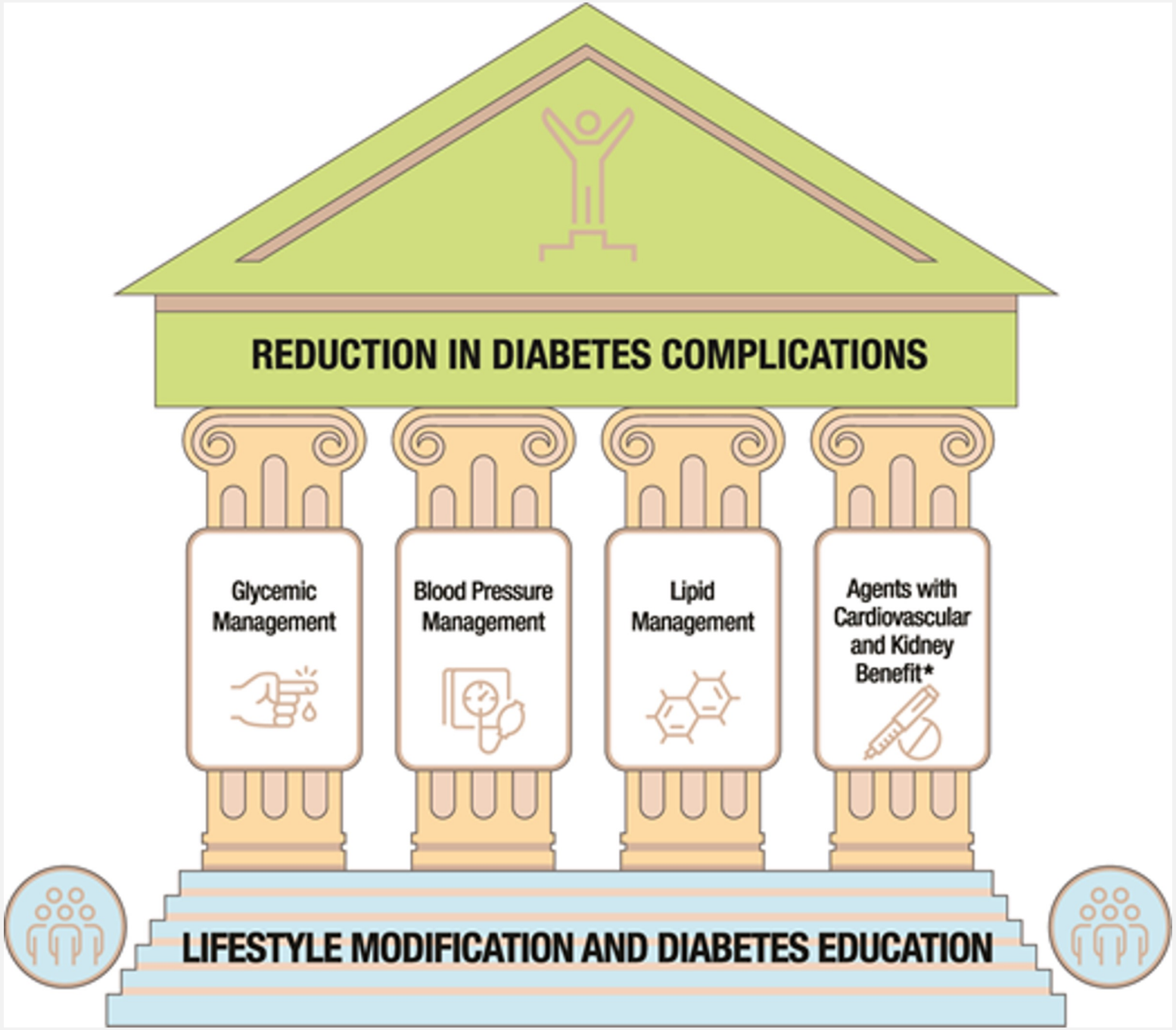
Modifying Factors

Favor more stringent goal	Favor less stringent goal
Short diabetes duration	Long diabetes duration
Low hypoglycemia risk	High hypoglycemia risk
Low treatment risks and burdens	High treatment risks and burdens
Pharmacotherapy with cardiovascular, kidney, weight, or other benefits	Pharmacotherapy without nonglycemic benefits
No cardiovascular complications	Established cardiovascular complications
Few or minor comorbidities	Severe, life-limiting comorbidities

IMMUNIZATIONS AND DM II

Table 4.3 Highly Recommended Immunizations For Adult Patients With Diabetes

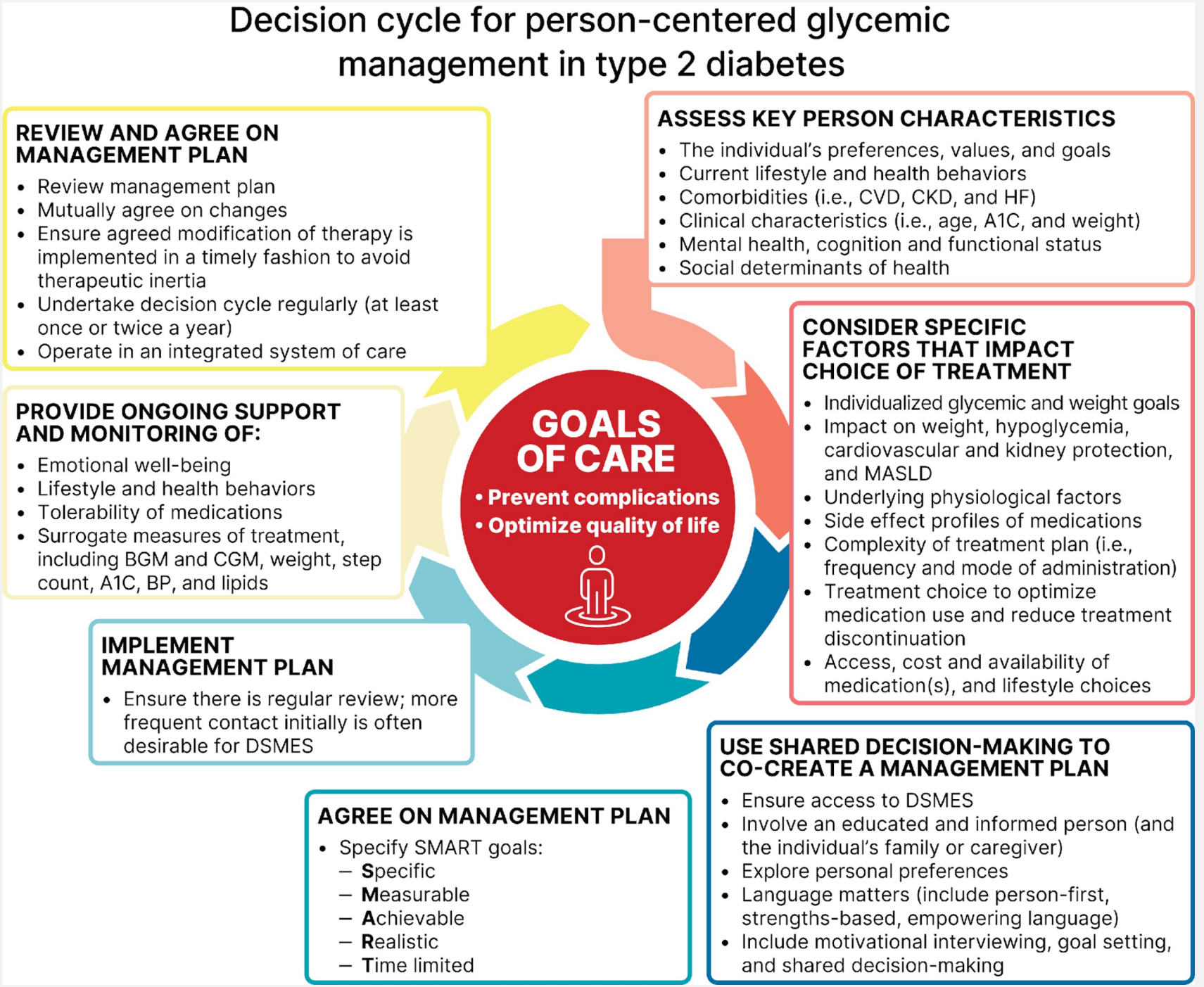
Vaccine	Recommendation
Hep B	<60 year of age; ≥60 year of age discuss with health care provider
HPV	≤26 years of age; 27-45 year of age may also be vaccinated against HPV after a discussion with health care provider
Influenza	All Patients; advised not to receive live attenuated influenza vaccine
PPSV23	• 19-64 year of age, vaccinate with Pneumovax • ≥65 years of age, obtain second dose of pneumovax, at least 5 years from prior Pneumovax vaccine
PCV20 or PCV15	• Adults ≥ 19 of age, with an immunocompromising condition • 19-64 year of ag, immunocompetent, no recommendation • ≥65 years of age, immunocompetent, have shared decision-making with health care provider
TDAP	All adults; pregnant woman should have an extra dose
Zoster	≥ 50 years of age
COVID-19	All people 6 months of age and older
RSV	Older adults ≥60 years of age with diabetes appear to be a risk group


REDUCTION IN DIABETES COMPLICATIONS
Glycemic Management
Blood Pressure Management
Lipid Management
Agents with Cardiovascular and Kidney Benefit*
LIFESTYLE MODIFICATION AND DIABETES EDUCATION

From: **4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2026**

Diabetes Care.
2025;49(Supplement_1):S61-S88.
doi:10.2337/dc26-S004

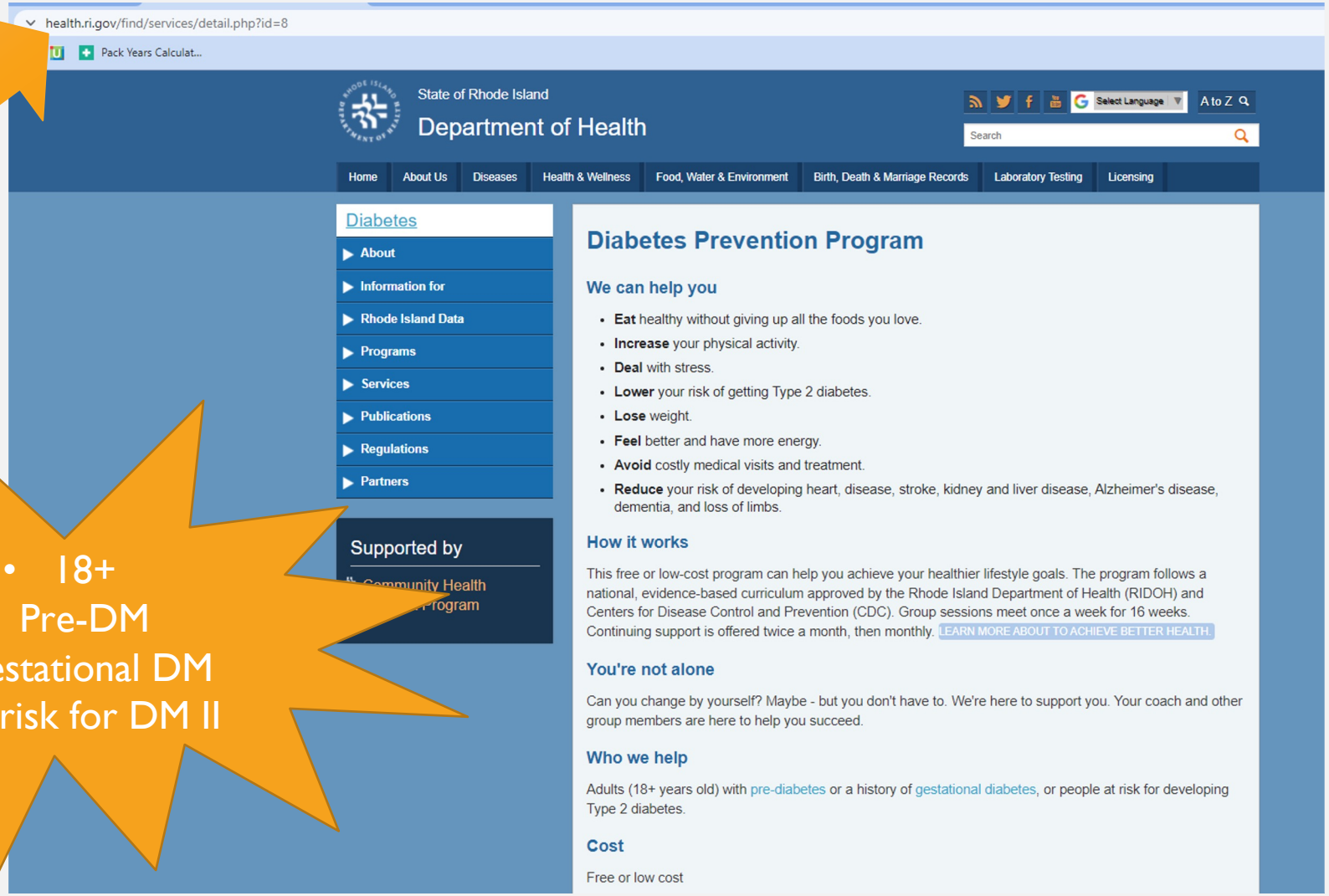
Decision cycle for person-centered glycemic management in type 2 diabetes



WHAT PROGRAMS ARE AVAILABLE IN RI?

https://health.ri.gov/find/services/detail.php?id=8

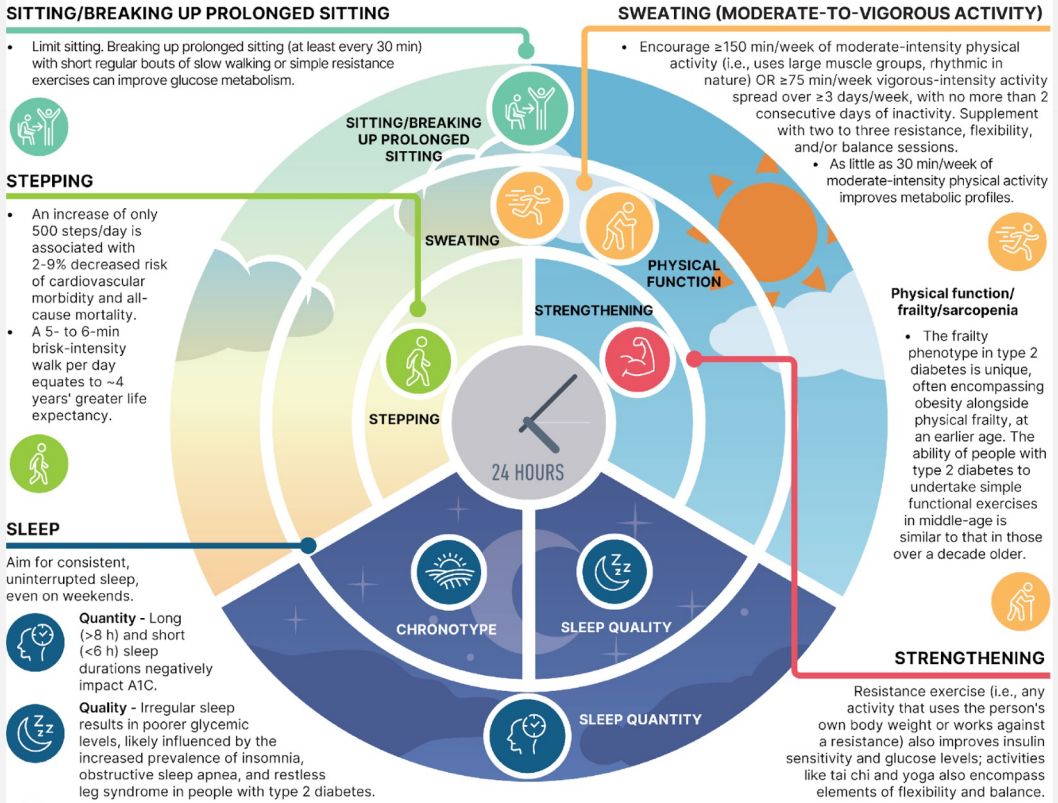
- 18+
- Pre-DM
- Gestational DM
- At risk for DM II



From: **5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: Standards of Care in Diabetes—2026**

Diabetes Care. 2025;49(Supplement_1):S89-S131. doi:10.2337/dc26-S005

Importance of 24-hour physical behaviors for type 2 diabetes



SITTING/BREAKING UP PROLONGED SITTING

- Limit sitting. Breaking up prolonged sitting (at least every 30 min) with short regular bouts of slow walking or simple resistance exercises can improve glucose metabolism.

STEPPING

- An increase of only 500 steps/day is associated with 2-9% decreased risk of cardiovascular morbidity and all-cause mortality.
- A 5- to 6-min brisk-intensity walk per day equates to ~4 years' greater life expectancy.

SLEEP

Aim for consistent, uninterrupted sleep, even on weekends.

Quantity - Long (>8 h) and short (<6 h) sleep durations negatively impact A1C.

Quality - Irregular sleep results in poorer glycemic levels, likely influenced by the increased prevalence of insomnia, obstructive sleep apnea, and restless leg syndrome in people with type 2 diabetes.

Chronotype - Evening chronotypes (i.e., night owl: go to bed late and get up late) may be more susceptible to inactivity and poorer glycemic levels than morning chronotypes (i.e., early bird: go to bed early and get up early).

SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)

- Encourage ≥150 min/week of moderate-intensity physical activity (i.e., uses large muscle groups, rhythmic in nature) OR ≥75 min/week vigorous-intensity activity spread over ≥3 days/week, with no more than 2 consecutive days of inactivity. Supplement with two to three resistance, flexibility, and/or balance sessions.
  - As little as 30 min/week of moderate-intensity physical activity improves metabolic profiles.

Physical function/ frailty/sarcopenia

- The frailty phenotype in type 2 diabetes is unique, often encompassing obesity alongside physical frailty, at an earlier age. The ability of people with type 2 diabetes to undertake simple functional exercises in middle-age is similar to that in those over a decade older.

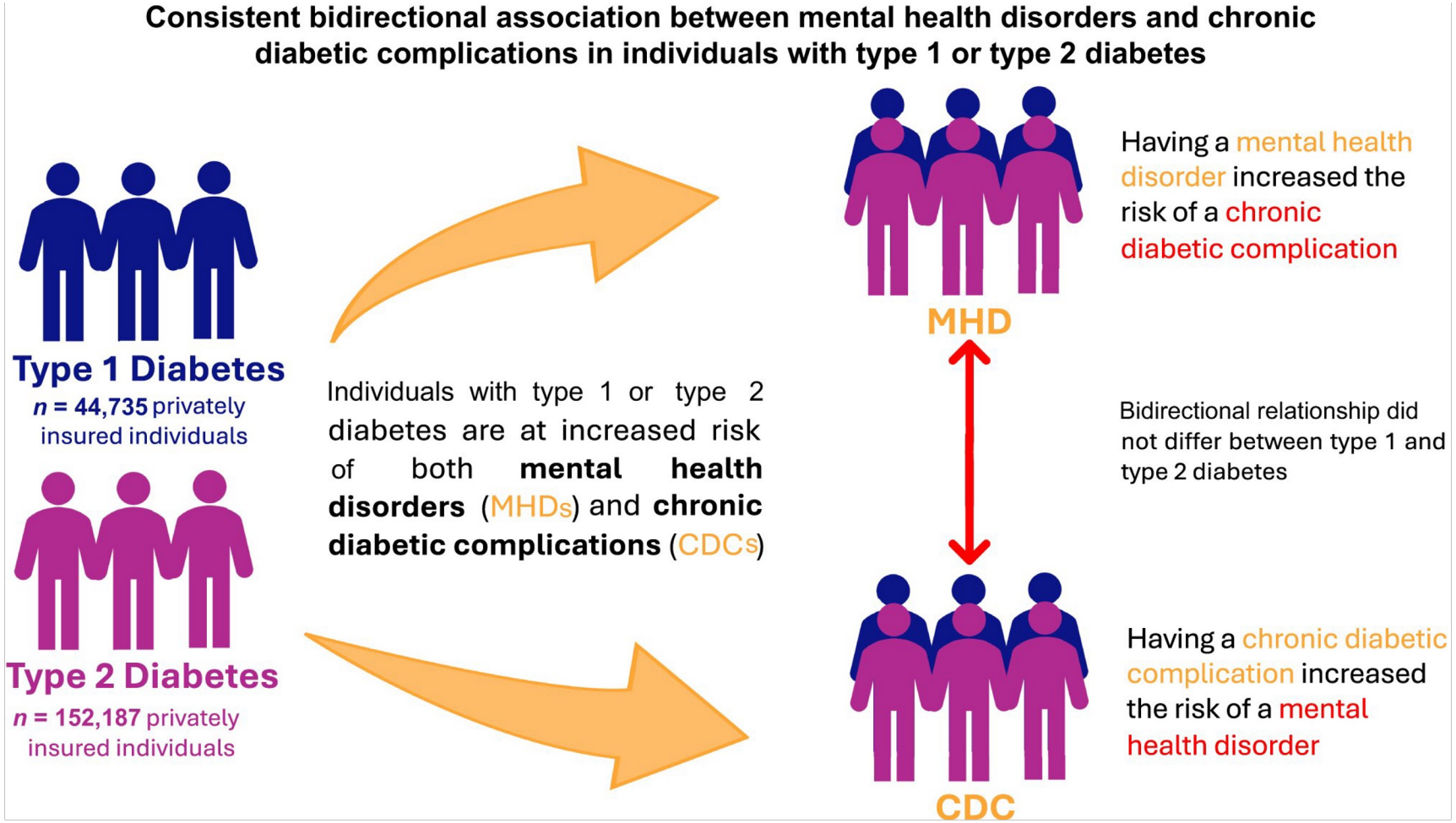
STRENGTHENING

Resistance exercise (i.e., any activity that uses the person's own body weight or works against a resistance) also improves insulin sensitivity and glucose levels; activities like tai chi and yoga also encompass elements of flexibility and balance.

	Glucose/ insulin	Blood pressure	A1C	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓	↓	↓	↓	↑	↓	↑
STEPPING	↓	↓	↓	↓	↑	↓	↑
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓	↓	↓	↓	↑	↓	↑
STRENGTHENING	↓	↓	↓	↓	↑	↓	↑
ADEQUATE SLEEP DURATION	↓	↓	↓	↓	?	↓	↑
GOOD SLEEP QUALITY	↓	↓	↓	↓	?	↓	↑
CHRONOTYPE/CONSISTENT TIMING	↓	?	↓	?	?	↓	?

IMPACT OF PHYSICAL BEHAVIORS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ Higher levels of improvement (physical function, quality of life) ↓ Lower levels of improvement (glucose/insulin, blood pressure, A1C, lipids, depression)
? No data available
↑ Green arrows = strong evidence ↑ Yellow arrows = medium-strength evidence ↑ Red arrows = limited evidence



Graphical Abstract. Credit: *Diabetes Care* (2024).
DOI: 10.2337/dc24-0818

Treatment considerations for co-morbid depression and diabetes

CO-MORBIDITY
Patients with major depression have a twice as high risk of developing type-2 diabetes

Higher in women

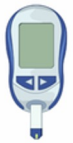
RISK FACTORS
Lifestyle factors
Genetic risk factors
Microbiota
Gut-brain axis

HPA axis and cortisol dysregulation
Pro-inflammatory state
Insulin signalling and neurotransmission

Depression management

Antidepressants:
SSRIs
SNRIs
↑Weight gain?
↔Glycemic control?

Antipsychotics:
↑Weight gain?
↔Glycemic control?



Anti-inflammatory agents:
↓Inflammation
↑Improvement in depressive symptoms?

Diabetes management

Anti-diabetics:
Metformin
Pioglitazone
GLP1-RAs
SGLT2Is
↑Improvement in depressive symptoms related to diabetes?
↑Cardio-renal benefit

Anti-inflammatory agents:
↓Inflammation
↑Improvement in depressive symptoms related to diabetes?

Translational Psychiatry (*Transl Psychiatry*)

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DIABETES AND OBESITY MANAGEMENT

Table 8.2

Median monthly (30-day) AWP and NADAC of maximum or maintenance dose of obesity pharmacotherapies

Medication name	Typical adult maintenance dose	AWP (median and range for 30-day supply)	NADAC (median and range for 30-day supply)
Sympathomimetic amine anorectic: approved for short-term use only			
Phentermine	8–37.5 mg daily	$43 ($3–$58)*	$2 ($2–$3)*
Lipase inhibitor			
Orlistat	60 mg t.i.d. (OTC)	$58 ($41–$90)	NA
	120 mg t.i.d. (Rx)	$675 ($520–$781)	$514 ($416–$611)
Sympathomimetic amine anorectic/antiepileptic combination			
Phentermine/topiramate ER	7.5 mg/46 mg daily	$238 ($238–$251)	NA
Opioid antagonist/antidepressant combination			
Naltrexone/bupropion ER	16 mg/180 mg b.i.d.	$750	NA
GLP-1 receptor agonist			
Liraglutide	3 mg daily	$1,619	$1,303
Semaglutide	2.4 mg once weekly	$1,619	$1,302
Dual GIP and GLP-1 receptor agonist			
Tirzepatide	5, 10, or 15 mg once weekly	$1,304**	$1,022

Table 8.1
Obesity pharmacotherapy in individuals with type 2 diabetes

Medication name	Weight Loss	Time frame for weight loss	Common side effects	Possible safety concerns and considerations
Sympathomimetic amine anorectic: approved for short-term use only				
Phentermine (183,184)†	• 15 mg q.d.; 7.4% • 7.5 mg q.d.; 6.6% • Placebo; 2.3%	28	Dry mouth, insomnia, dizziness, irritability, increased blood pressure, elevated heart rate	• Contraindicated for use in combination with monoamine oxidase inhibitors • Contraindicated with a history of cardiovascular disease • Do not use if at high risk for glaucoma due to risk of acute angle-closure glaucoma
Lipase inhibitor				
Orlistat (4,185)‡	• 120 mg t.i.d.; 9.6% • Placebo; 5.6%	52	Abdominal pain, flatulence, fecal urgency	• Contraindicated in cholestasis • Potential malabsorption of fat-soluble vitamins (A, D, E, K) and of certain medications (e.g., cyclosporine, thyroid hormone, anticonvulsants) • Rare cases of severe liver injury reported • Cholelithiasis reported • Nephrolithiasis reported. Monitor renal function and discontinue if oxalate nephropathy occurs
Sympathomimetic amine anorectic/antiepileptic combination				
Phentermine/topiramate ER (54,116)§	• 15 mg/92 mg q.d.; 9.8% • 7.5 mg/46 mg q.d.; 7.8% • Placebo; 1.2%	56	Constipation, paresthesia, insomnia, nasopharyngitis, xerostomia, increased blood pressure, nephrolithiasis	• Contraindicated for use in combination with monoamine oxidase inhibitors • Contraindicated during pregnancy due to risk of fetal harm with topiramate • Cognitive impairment associated with rapid dose titration or high initial doses • Caution with cardiovascular disease • Do not use if at high risk for glaucoma due to risk of acute angle-closure glaucoma
Opioid antagonist/antidepressant combination				
Naltrexone/bupropion ER (13,186)	• 16 mg/180 mg b.i.d.; 5% • Placebo; 1.8%	56	Constipation, nausea, headache, xerostomia, insomnia, elevated heart rate and blood pressure	• Contraindicated in people with unmanaged hypertension and/or seizure disorders • Contraindicated for use with chronic opioid therapy • Acute angle-closure glaucoma may occur • Increased blood pressure and heart rate may occur; monitor in people with cardiovascular and cerebrovascular disease **Boxed warning:** • Risk of suicidal behavior/ideation in people younger than 24 years old who have depression
GLP-1 receptor agonist				
Liraglutide (14,55,187)‖	• 3.0 mg q.d.; 6% • 1.8 mg q.d.; 4.7% • Placebo; 2%	56	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux, constipation)	• The following apply to both GLP-1 receptor agonists: • Provide guidance on discontinuation prior to surgical procedures to mitigate potential for pulmonary aspiration with general anesthesia or deep sedation • Pancreatitis: acute pancreatitis has been reported, but causality has not been established. Do not initiate if at high risk for pancreatitis and discontinue if pancreatitis is suspected • Biliary disease: evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected; avoid use in at-risk individuals • Gastrointestinal disorders (severe constipation and small-bowel obstruction/ileus progression) • Diabetic retinopathy: close monitoring of retinopathy in those at high risk (older individuals and those with longer duration of type 2 diabetes [≥10 years]) • Nonarteritic anterior ischemic optic neuropathy reported; rare incidence. Monitor for this during eye examinations • Impact on drug absorption: orally administered drug absorption may be impaired during dose titration (including oral contraceptives) • Gastrointestinal side effects: counsel on potential for gastrointestinal side effects; provide guidance on dietary modifications to mitigate gastrointestinal side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for those experiencing gastrointestinal challenges. Not recommended for individuals with gastroparesis • Hypoglycemia (with concomitant use of insulin or sulfonylurea) **Boxed warning:** • Risk of thyroid C-cell tumors in rodents; human relevance not determined; do not use in individuals with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2
Semaglutide (54,117,188)	• 2.4 mg weekly; 9.6% • 1.0 mg weekly; 7% • Placebo; 3.4%			
Dual GIP and GLP-1 receptor agonist				
Tirzepatide (109,189)	• 15 mg weekly; 14.7% • 10 mg weekly; 12.8% • Placebo; 3.2%	72	Gastrointestinal side effects (nausea, vomiting, diarrhea, esophageal reflux, constipation)	• Same as for GLP-1 receptor agonists, with addition of the following: • Monitor effects of oral medications with narrow therapeutic index (warfarin) or whose efficacy is dependent on threshold concentration • Advise individuals using oral contraceptives to switch to a nonoral contraceptive method or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation

PRE-DM AND METFORMIN THERAPY- DON'T FORGET TO USE IT

Consider Metformin Therapy to Prevent DM II for:

Adults with Pre-DM

- Most importantly in those aged 25-59 years with BMI **≥35**
- Fasting plasma **≥ 110 or A1C ≥6%**

Women with prior gestational DM

High risk patients on cancer treatments (PI3Kα inhibitor)

High-risk individuals treated with high-dose glucocorticoids

REMEMBER THE MEDICATION MANAGEMENT GUIDELINES AND BEST PRACTICES

Start SGLT-2 inhibitors to treat heart failure

SGLT-2 inhibitors now recommended in stage 4 CKD

Start Finerenone to treat CKD when SGLT-2 inhibitors are not tolerated

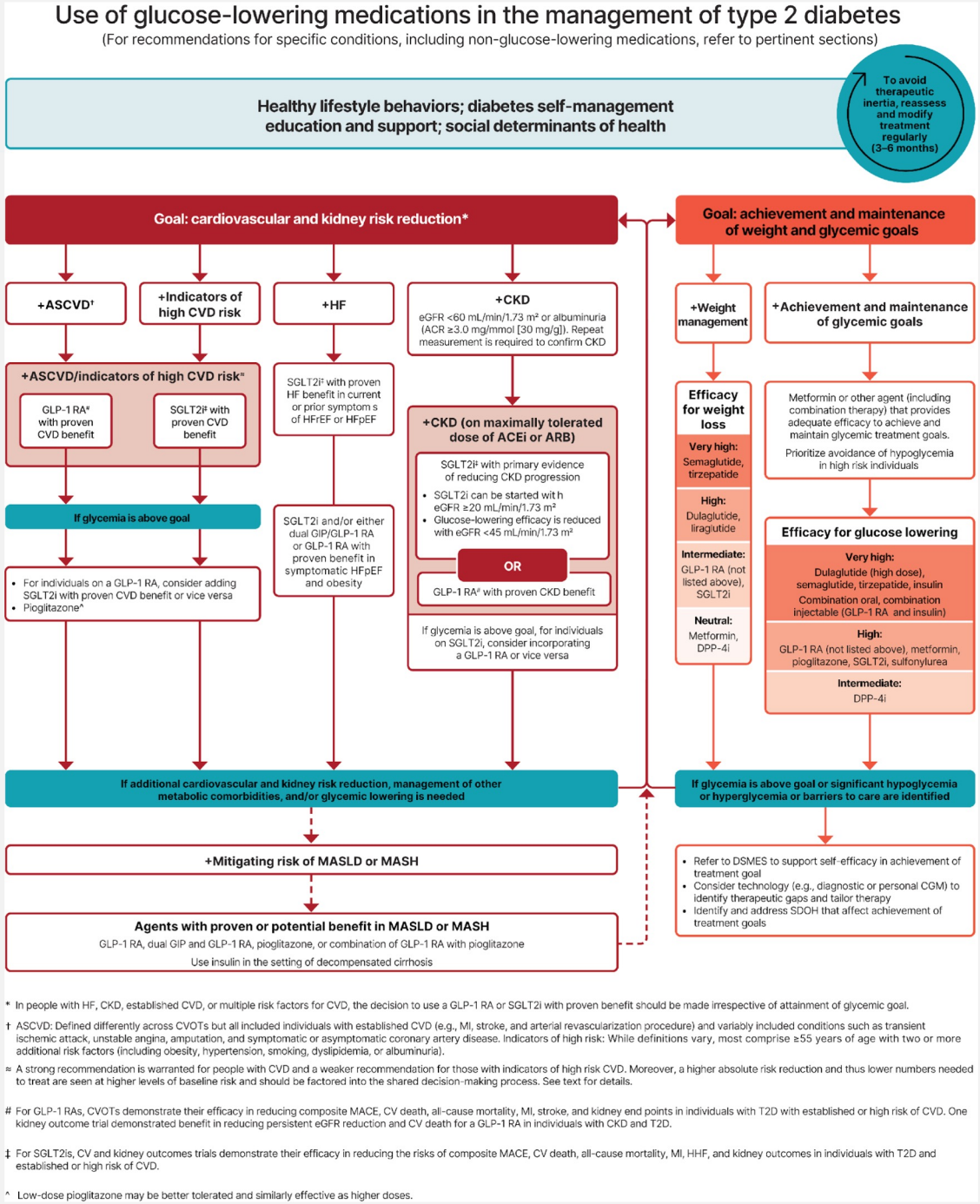
Consider adding GLP-1 to established insulin therapy as opposed to increasing insulin

Consider combining SGLT-2 inhibitor with GLP1 agonist for heart or kidney disease- could lower risk further

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	CHF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	▪ **FDA Black Box:** Risk of amputation (**canagliflozin**) ▪ Risk of bone fractures (canagliflozin) ▪ DKA risk (all agents, rare in T2DM) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide† > semaglutide > exenatide extended release	Neutral	High	SQ	Benefit: liraglutide	▪ Renal dose adjustment required (exenatide, lixisenatide) ▪ Caution when initiating or increasing dose due to potential risk of acute kidney injury	▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) ▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Potential risk of acute pancreatitis ▪ Joint pain

From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026**

Diabetes Care. 2025;49(Supplement_1):S183-S215. doi:10.2337/dc26-S009



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of attainment of glycemic goal.

† ASCVD: Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

≈ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

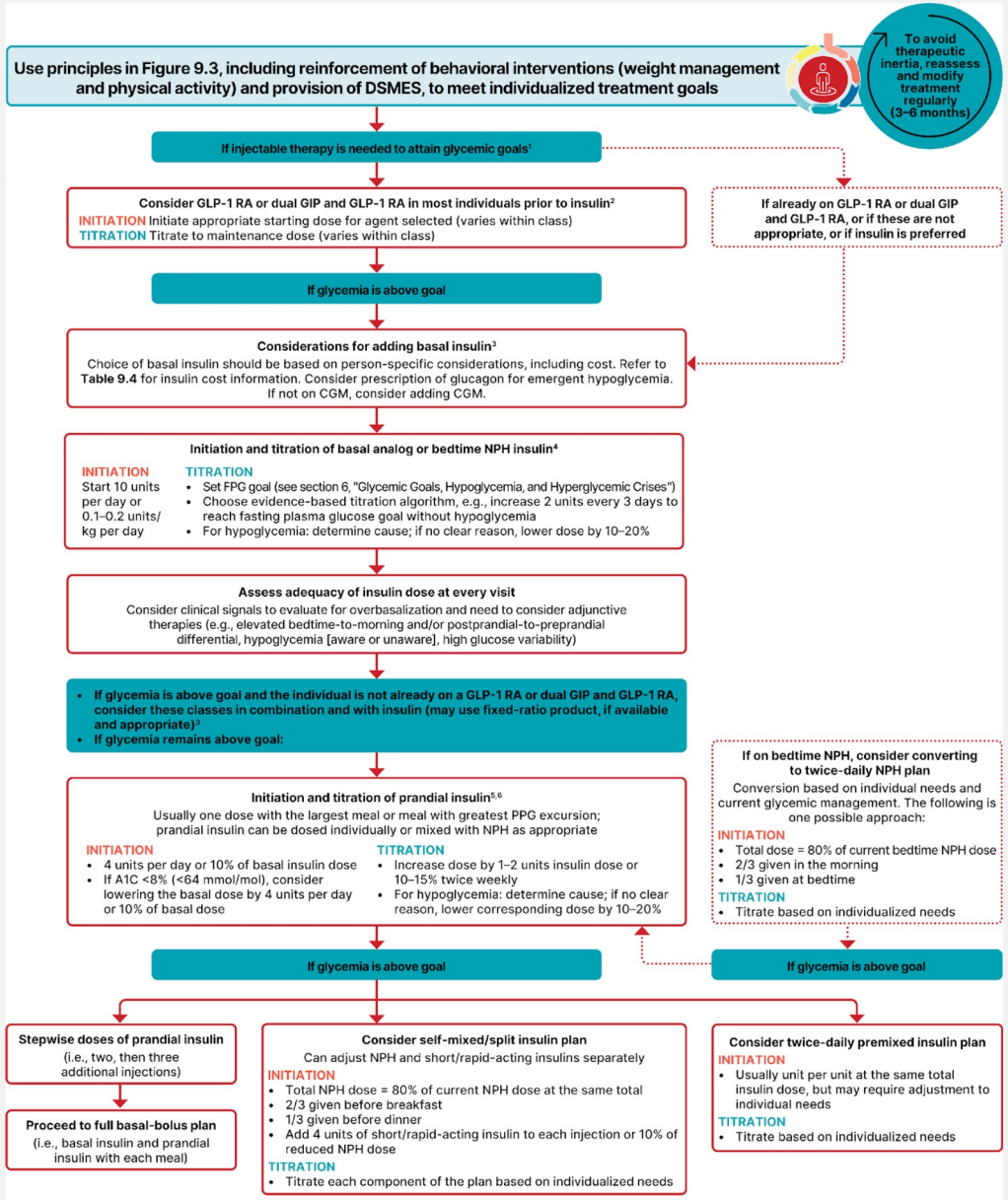
For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney end points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

‡ For SGLT2is, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HHF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

^ Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

From: **9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026**

Diabetes Care. 2025;49(Supplement_1):S183-S215. doi:10.2337/dc26-S009



1. Consider insulin as the first injectable if symptoms of hyperglycemia are present, when A1C or blood glucose levels are very high (i.e., A1C >10% [>86 mmol/mol] or blood glucose ≥300 mg/dL [≥16.7 mmol/L]), or when a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RAs, consider individual preference, glycemic lowering, weight-lowering effect, and frequency of injection. If CVD is present, consider GLP-1 RA with proven CVD benefit; oral or injectable GLP-1 RAs are appropriate.
3. For people on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (IDegLira or iGlarLixi).
4. Consider switching from evening NPH to a basal analog if the individual develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with a morning dose of a long-acting basal Insulin. Consider dosing NPH in the morning for steroid-induced hyperglycemia.
5. Prandial insulin options include injectable rapid- and ultra-rapid-acting analog insulins, injectable short-acting human insulin, or inhaled human insulin.
6. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin plan to decrease the number of injections required.

From: **11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2026**

Diabetes Care. 2025;49(Supplement_1):S246-S260. doi:10.2337/dc26-S011

Figure Legend:

Risk of CKD progression, cardiovascular disease risk, and mortality; frequency of visits; and referral to nephrology according to GFR and albuminuria. The numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by estimated GFR or albuminuria, with screening indicated once per year. For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e., every 1–3 months [deep red]) according to risks of CKD progression and CKD complications (e.g., cardiovascular disease, anemia, and hyperparathyroidism). These are general parameters based only on expert opinion and underlying comorbid conditions, and disease state must be taken into account, as should the likelihood of impacting a change in management for any individual. CKD, chronic kidney disease; GFR, glomerular filtration rate. Adapted from de Boer et al. (1).

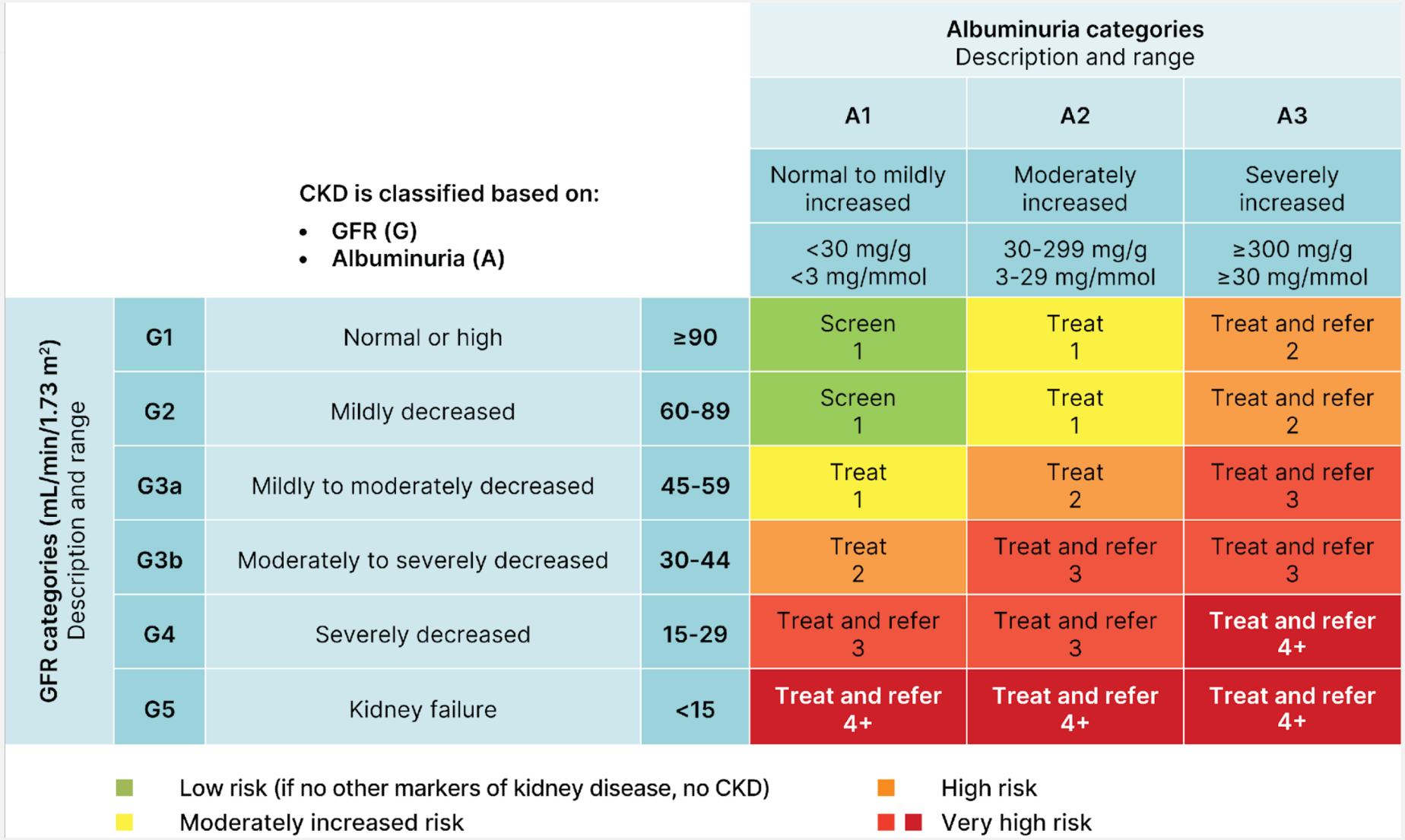


Table 11.1 Reasons to consider nondiabetic kidney diseases in a person with chronic kidney disease and diabetes

• Type 1 diabetes duration <5 years or no retinopathy
• Active urine sediment (e.g., containing red blood cells or cellular casts)
• Chronically well-managed blood glucose
• Rapidly declining eGFR
• Rapidly increasing or very high UACR (>300 mg/g) or urine protein/creatinine level (>500 mg/g)

Information adapted from Liang et al. (133). eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

American Diabetes Association®

MONITORING FOR CKD/DKD AND ASSOCIATED COMPLICATIONS

Table 11.2 Screening for selected complications of chronic kidney disease

Complication	Physical and laboratory evaluation
Blood pressure >130/80 mmHg	Blood pressure, weight, BMI
Volume overload	History, physical examination, weight
Electrolyte abnormalities	Serum electrolytes
Metabolic acidosis	Serum electrolytes
Anemia	Hemoglobin; iron, iron saturation, ferritin testing if indicated
Metabolic bone disease	Serum calcium, phosphate, PTH, vitamin 25(OH)D

Complications of chronic kidney disease (CKD) generally become prevalent when estimated glomerular filtration rate falls below 60 mL/min/1.73 m^2 (stage G3 CKD or greater) and become more common and severe as CKD progresses. Evaluation of elevated blood pressure and volume overload should occur at every clinical contact possible; laboratory evaluations are generally indicated every 6–12 months for stage G3 CKD, every 3–5 months for stage G4 CKD, and every 1–3 months for stage G5 CKD, or as indicated to evaluate symptoms or changes in therapy. 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

CKD/DKD INTERVENTIONS

Blood Glucose Management

- Goal A1C <7%

Bood Pressure Management

- Goal <130/80
- Treatment with ACE or ARB

Lifestyle Modification

- Decrease Salt/Protien
- Physical Activity
- Smoking Cessation
- Weight Loss

Non-Steroidal MRAs

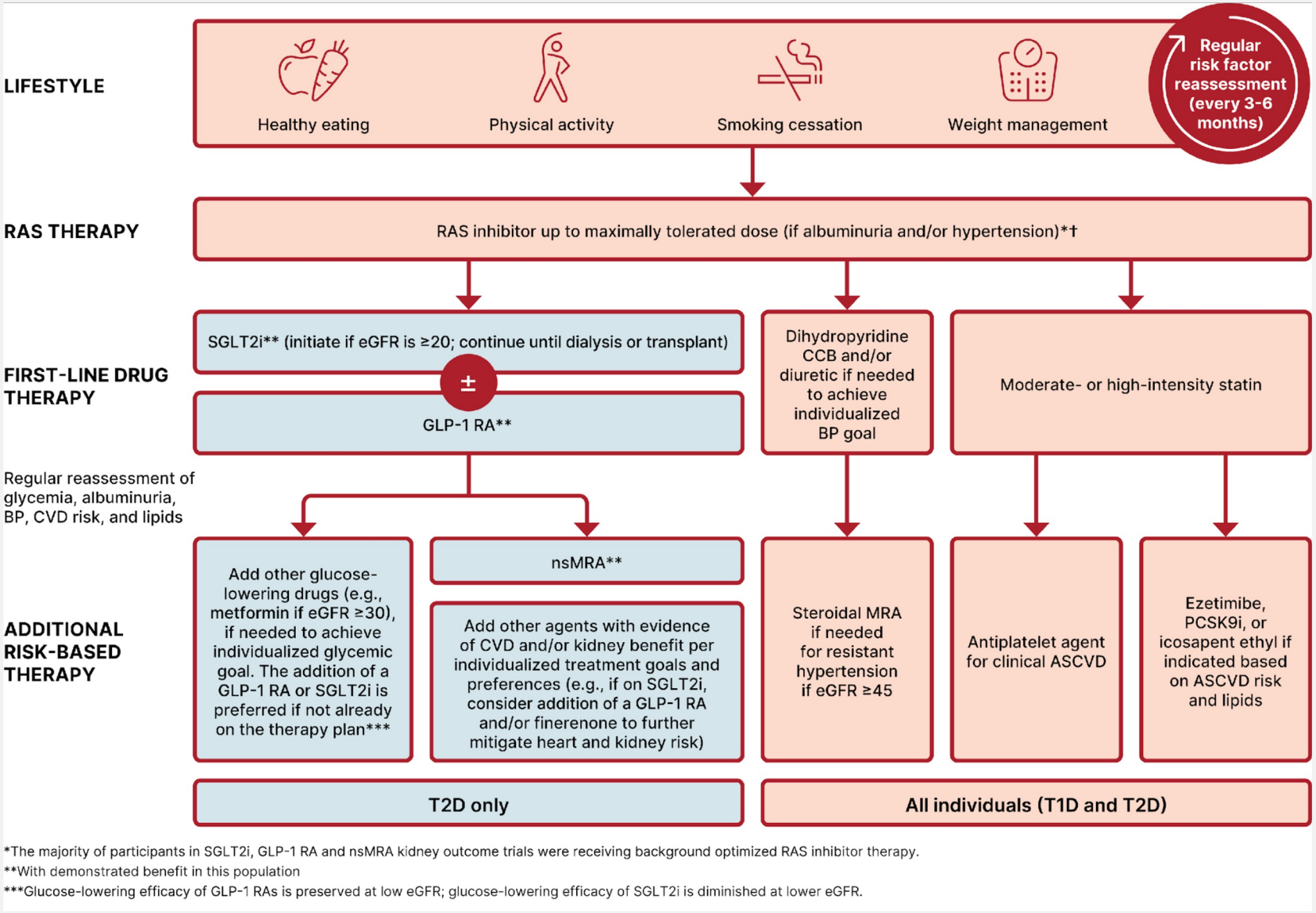
- Reduces CKD progression and cardiovascular events
  - CKD and albuminuria, if eGFR is **≥25 mL/min/1.73 m^2**
  - Potassium levels should be monitored 1 month after initiation.
- Use in conjunction with SGLT2 inhibitor for individuals with
  - Type 2 diabetes and urine albumin-to-creatinine ratio **≥100 mg/g with eGFR** 30–90 mL/1.73 m^2 on a renin-angiotensin-aldosterone system (RAS) inhibitor

From: **11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2026**

Diabetes Care. 2025;49(Supplement_1):S246-S260. doi:10.2337/dc26-S011

Figure Legend:

Holistic approach for improving outcomes in people with diabetes and CKD. Icons presented indicate the following benefits: BP cuff, BP lowering; glucose meter, glucose lowering; heart, cardioprotection; kidney, kidney protection; scale, weight management. eGFR is presented in units of mL/min/1.73 m^2. †ACEi or ARB (at maximal tolerated doses) should be first-line therapy for hypertension when albuminuria is present. Otherwise, dihydropyridine calcium channel blocker or diuretic can also be considered; all three classes are often needed to attain BP targets. †Finerenone is currently the only nsMRA with proven clinical kidney and cardiovascular benefits. ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HTN, hypertension; MRA, mineralocorticoid receptor antagonist; nsMRA, nonsteroidal mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; RAS, renin-angiotensin system; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes.



*The majority of participants in SGLT2i, GLP-1 RA and nsMRA kidney outcome trials were receiving background optimized RAS inhibitor therapy.
**With demonstrated benefit in this population
***Glucose-lowering efficacy of GLP-1 RAs is preserved at low eGFR; glucose-lowering efficacy of SGLT2i is diminished at lower eGFR.

American Diabetes Association®

From: **4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Care in Diabetes—2026**

Diabetes Care. 2025;49(Supplement_1):S61-S88.
doi:10.2337/dc26-S004

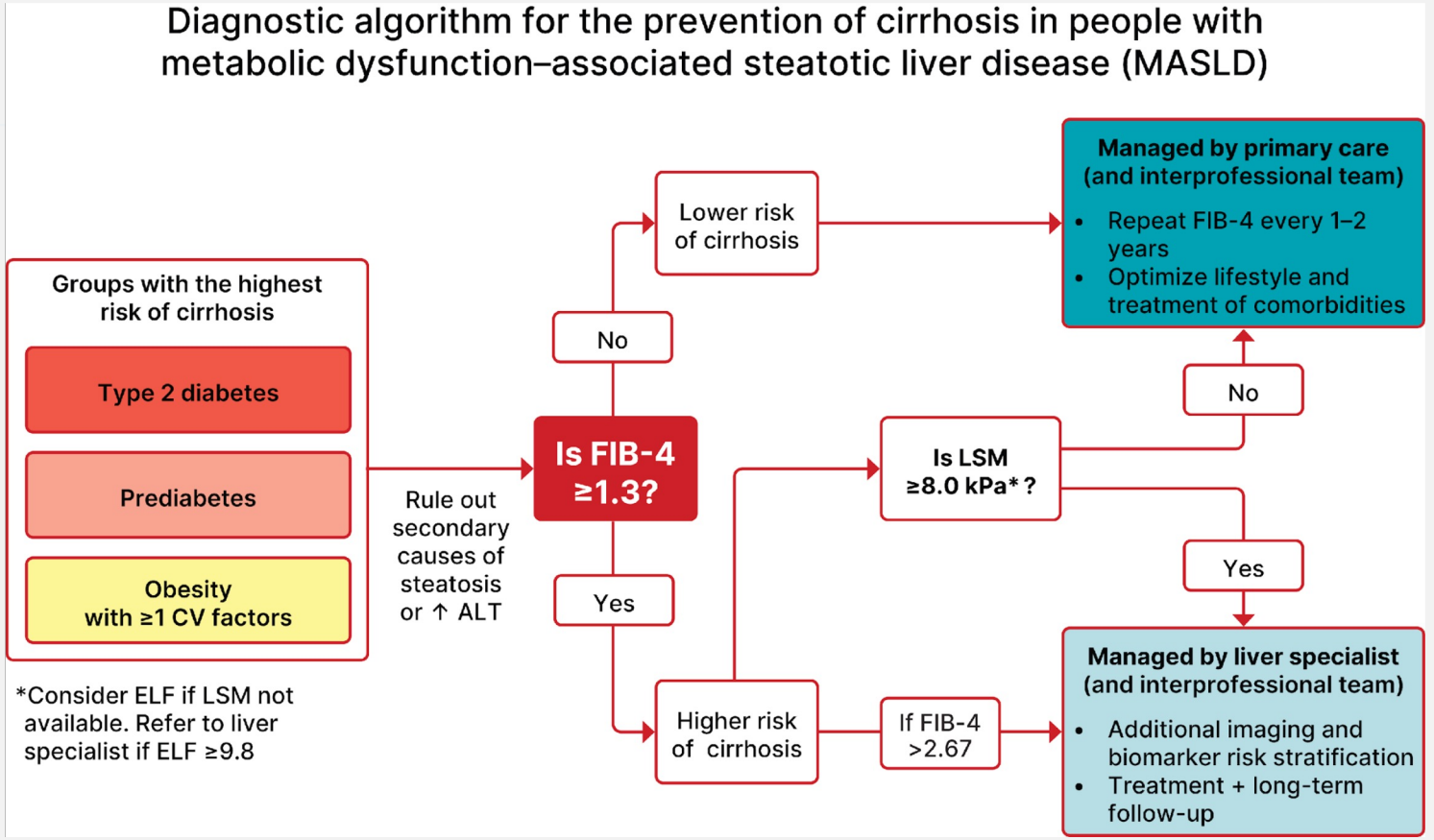
Table 2

Initial evaluation in patients with suspected nonalcoholic fatty liver disease

History and medical review	Investigations
Obesity	Liver biochemistries (ALT, AST)
T2D	Exclude/identify other liver diseases[a]
Metabolic syndrome	HBV and HCV serology (and viral load)
Alcohol intake	Auto antibodies (ANA, AMA, ASMA)
<14 drinks/wk for women	Serum ferritin, A1AT
<21 drinks/wk for men	Liver ultrasound: increased echogenicity
No known pre-existing liver disease	—

A1AT, α1 antitrypsin; AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti–smooth muscle antibody; HBV, hepatitis B virus; HCV, hepatitis C virus.

a NAFLD can coexist with other chronic liver diseases. Of note, 21% of patients with NAFLD may have elevations in autoantibodies in the absence of autoimmune hepatitis (85), and 20% may have high serum ferritin (>300 ng/mL in women and >450 ng/mL in men). Elevated serum ferritin is associated with advanced hepatic fibrosis (86) in patients with NAFLD.

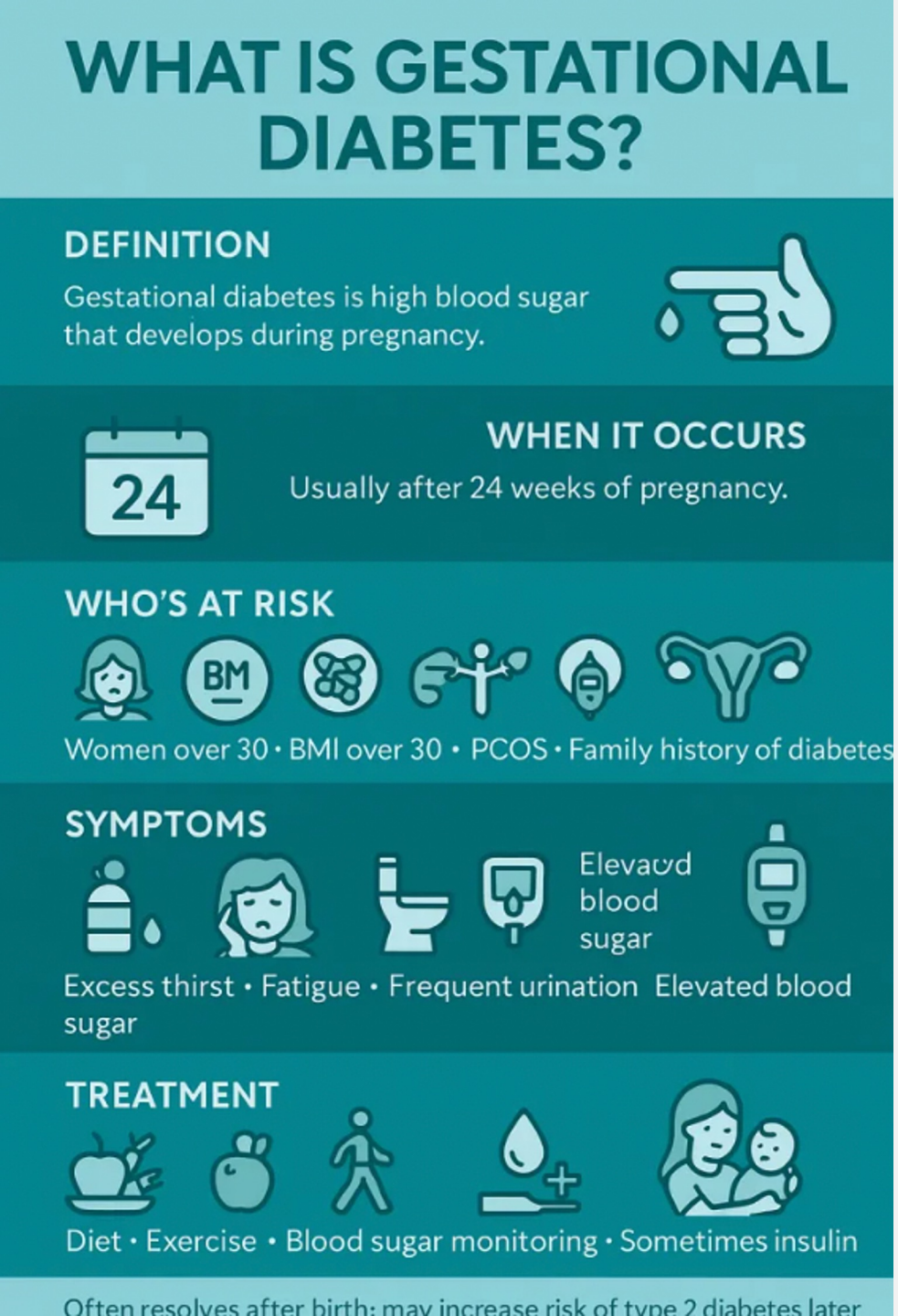


https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis

Table 6.8 Risk factors for hyperglycemic crises

Type 1 diabetes/absolute insulin deficiency
Younger age
Prior history of hyperglycemic crises
Prior history of hypoglycemic crises
Presence of other diabetes complications
Presence of other chronic health conditions (particularly in people with type 2 diabetes)
Presence of behavioral health conditions (e.g., depression, bipolar disorder, and eating disorders)
Alcohol and/or substance use
High A1C level
Insulin rationing
SGLT2 (SGLT1/2) inhibitor use
Social determinants of health

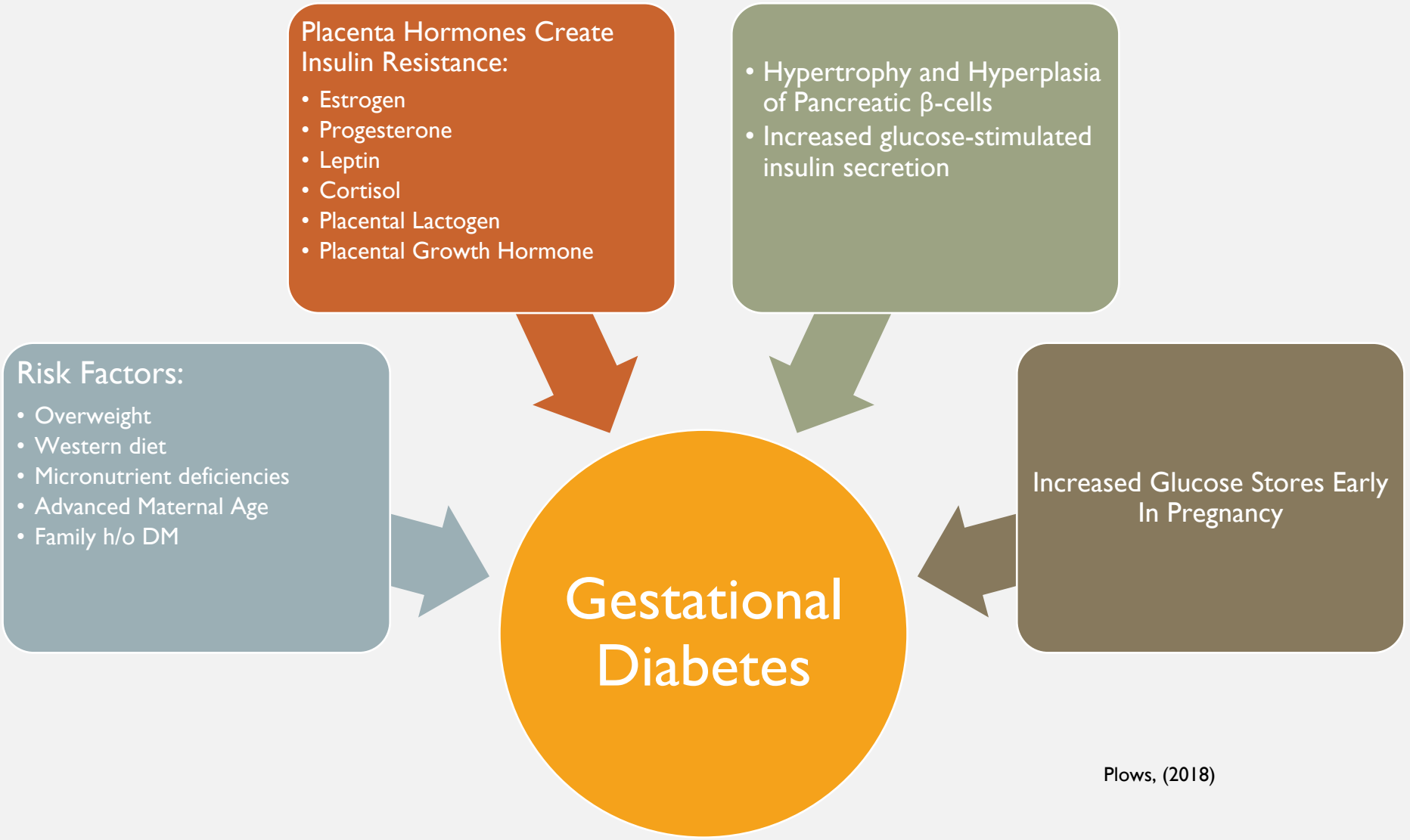
SGLT, sodium–glucose cotransporter. Data are from McCoy et al. (194), Gibb et al. (195), Randall et al. (196), Thomas et al. (197), and Borden et al. (198).



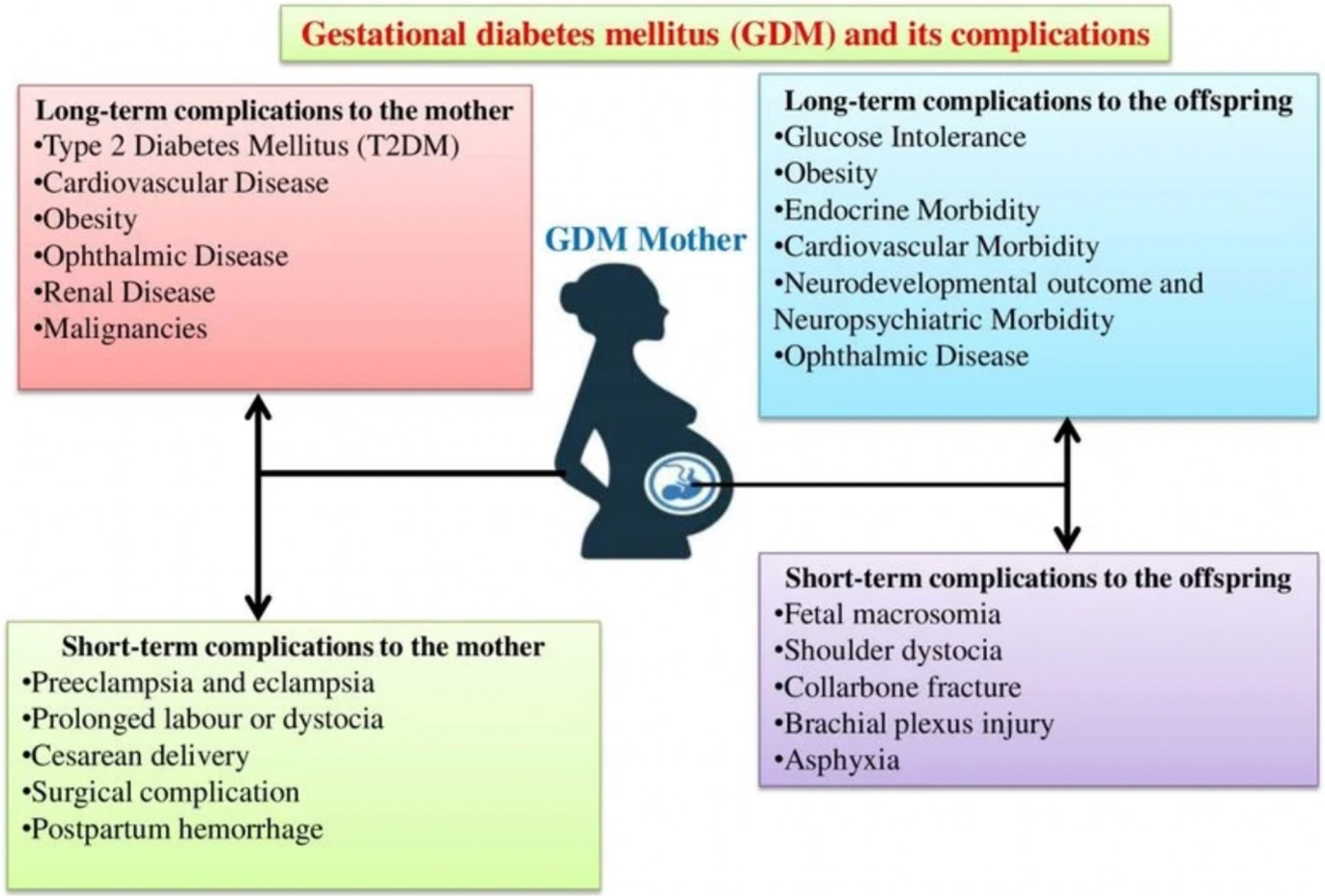
DEFINING GESTATIONAL DIABETES

- Condition that arises during pregnancy in which hormones made by the placenta lower insulin effectiveness
- Diagnosed 24-28 weeks of pregnancy with an initial glucose challenge test and follow-up glucose tolerance
- Treatment includes lifestyle changes such as diet and exercises, and medicine in severe cases
- It has implication for ongoing PRIMARY CARE SCREENING REQUIREMENTS

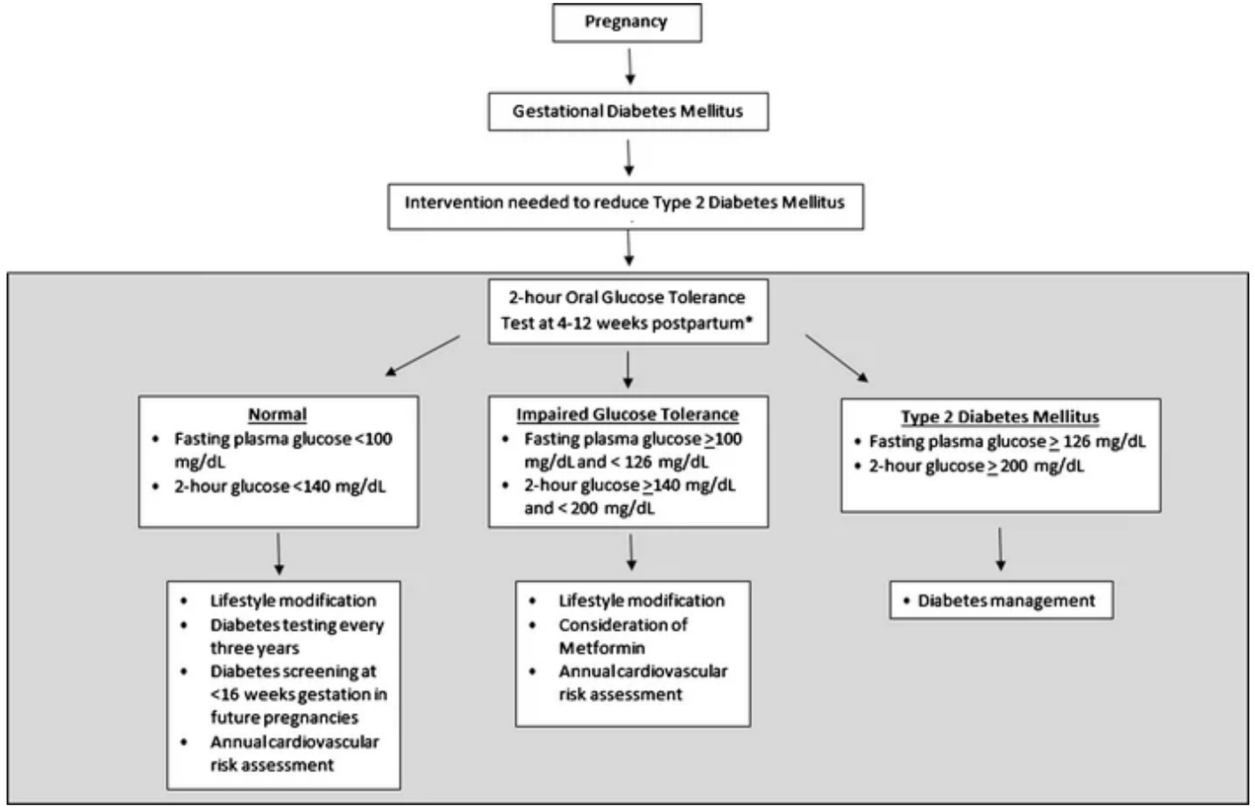
PATHOPHYSIOLOGY OF GESTATIONAL DM



Plows, (2018)



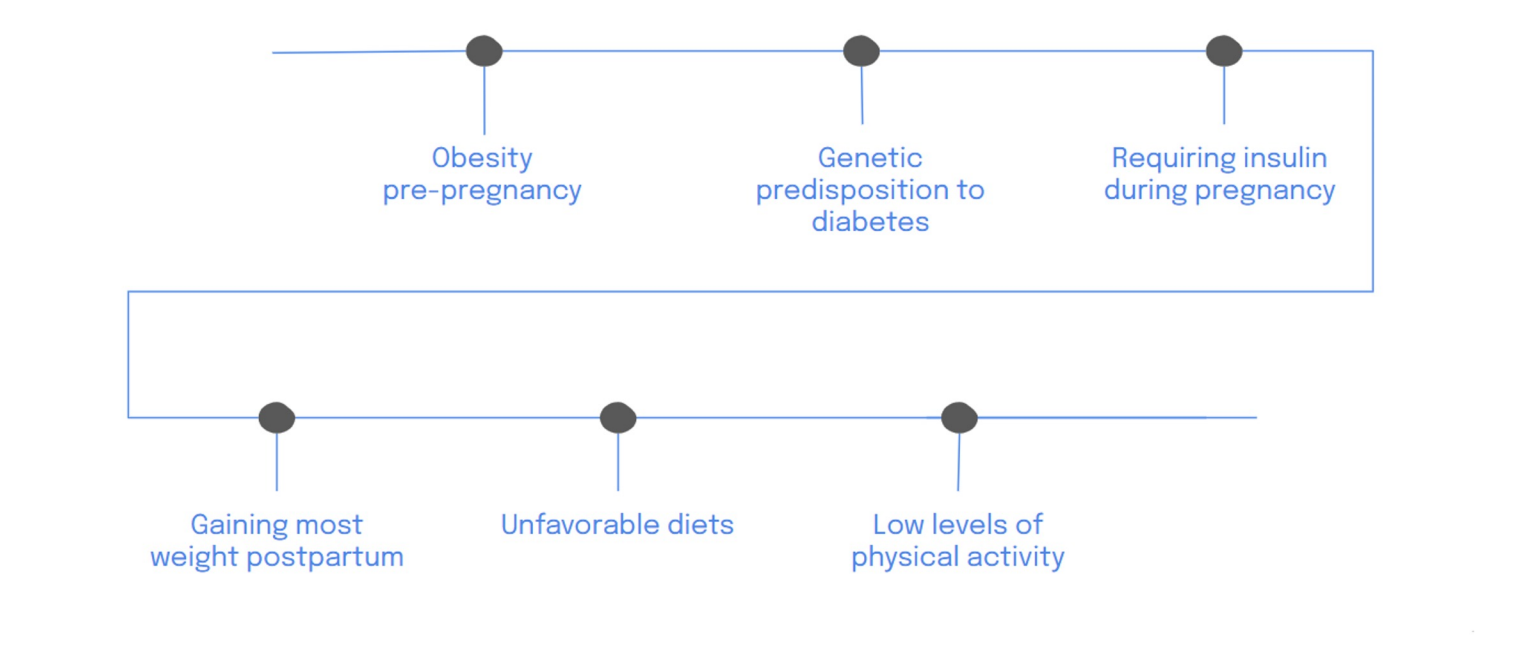
GESTATIONAL DIABETES COMPLICATIONS



GESTATIONAL DIABETES AFFECTS THE HEALTH TRAJECTORY

- Fasting Plasma Glucose Test
- 75-g, 2 hour glucose tolerance test
- 6-12 weeks after delivery, YEARLY if negative
- Monitor every 1-3 years indefinitely

INCREASE RISKS FOR DM II WITH HISTORY OF GESTATIONAL DM



Medication Safety in Pregnancy: Kidney-Protective Agents & Blood Pressure Management

Avoid potentially harmful kidney-protective medications in sexually active individuals of childbearing.

During pregnancy, the following medications are **contraindicated** because of risk of fetal harm:

- **ACE inhibitors**
- **ARBs**
- **MRAs**
- **SGLT2 inhibitors**
- **Neprilysin Inhibitors**

Antihypertensive medications considered safe and effective in pregnancy and for preconception planning include:

- **Methyldopa**
- **Labetalol**
- **Long-acting nifedipine**
- **Hydralazine** (typically for acute hypertension or severe preeclampsia)

Diuretics are not first-line for BP management in pregnancy, but may be used in **late pregnancy** when needed for volume control

Postpartum monitoring recommendations (ACOG):

- Individuals with gestational hypertension, preeclampsia, or superimposed preeclampsia should have **BP monitored in the hospital for 72 hours**, and again **7–10 days postpartum**
- Preeclampsia can occur up to 6 weeks postpartum
- **Long-term cardiovascular follow-up is recommended**, as these individuals have an increased lifetime risk of cardiovascular disease

The effect of breastfeeding on postpartum glucose tolerance and lipid profiles in women with gestational diabetes mellitus

Alexis Shub, Manisha Miranda, Harry M. Georgiou, Elizabeth A. McCarthy & Martha Lappas

International Breastfeeding Journal **14**, Article number: 46 (2019) | Cite this article

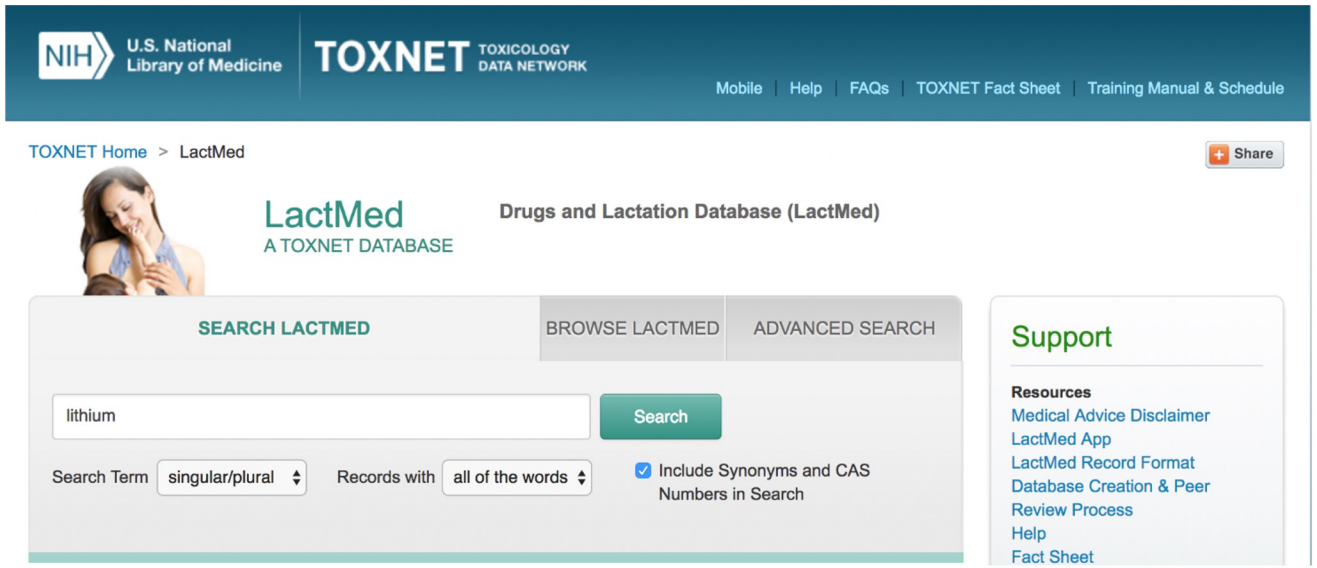
Women with Gestational DM who breastfed had a reduction in fasting glucose at six weeks postpartum compared to women who did not breastfeed

No significant change in lipid Profile

Conclusions: prevent DM II by breastfeeding, especially with history of Gestational Diabetes

LACTMED

- LactMed is a free, peer-reviewed, and regularly updated database from the National Institutes of Health (NIH) detailing the safety of over 1,800 drugs, herbal supplements, and chemicals for breastfeeding mothers and infants.



TECHNOLOGY AND DM

- Transitioning to Continuous Glucose Monitoring (CGM and Time in Range (TIR) over 14 days to calculate Glucose Management Indicator (GMI) for glucose management
- CGM for all children and adults who take insulin, including basal-only
- Auto Insulin Delivery for people with type I DM and adults and children on multiple daily injections
- Use the technology even while in hospitalized

LET'S GET IN RANGE

A1C and Estimated Average Glucose Levels

	A1C Percentage	Estimated Average Glucose (EAG)	
In-range	< 5.7%	< 117 mg/dL	6.5 mmol/L
Prediabetes	5.7-6.4%	117-137 mg/dL	6.5-7.6 mmol/L
Diabetes	> 6.4%	> 137 mg/dL	> 7.6 mmol/L
Increased risk of complications ↓	6.5%	140 mg/dL	7.8 mmol/L
	7.0%	154 mg/dL	8.6 mmol/L
	7.5%	169 mg/dL	9.4 mmol/L
	8.0%	183 mg/dL	10.1 mmol/L
	8.5%	197 mg/dL	10.9 mmol/L
	9.0%	212 mg/dL	11.8 mmol/L
	9.5%	226 mg/dL	12.6 mmol/L
	10%	240 mg/dL	13.4 mmol/L

Cleveland Clinic

CGM

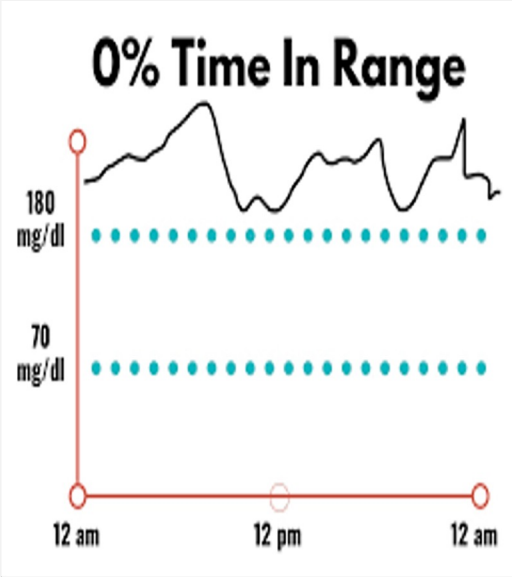
- Can be more or less stressful
- Continuous, robust data
- Real time monitoring
- Identify trends and fluctuations

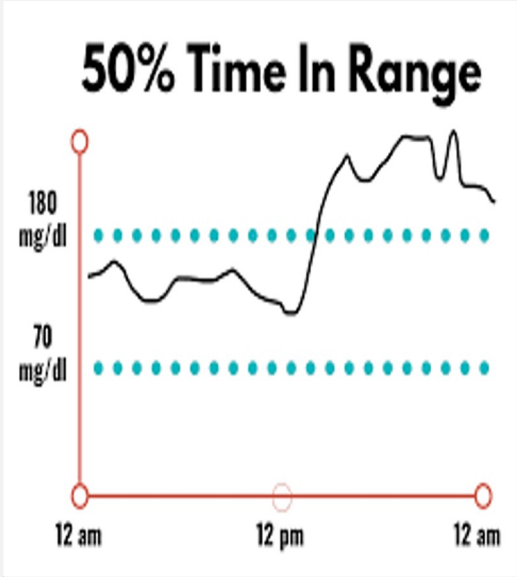
Glucometer

- More Invasive
- Periodic, limited data
- No real time monitoring
- Fails to capture trends and fluctuations

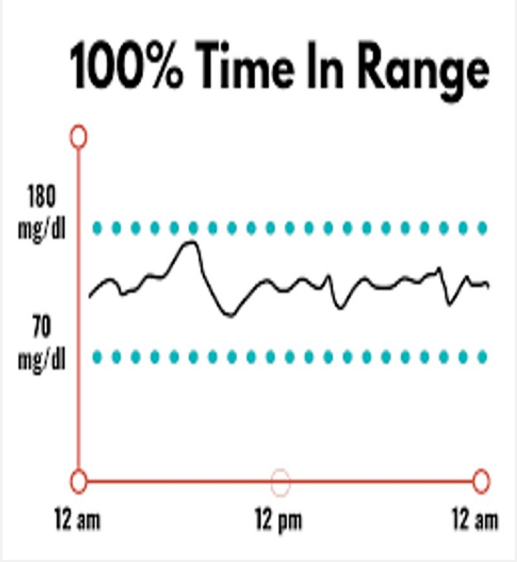
https://www.google.com/search?q=free+images+glucometer+vs+cgm&rlz=1C1CHBF_enUS941US942&sxsrf=ALeKk00DQ6t8tRx8dOEHRROOj-DJ4jmUag

DIABETES STANDARDS OF CARE



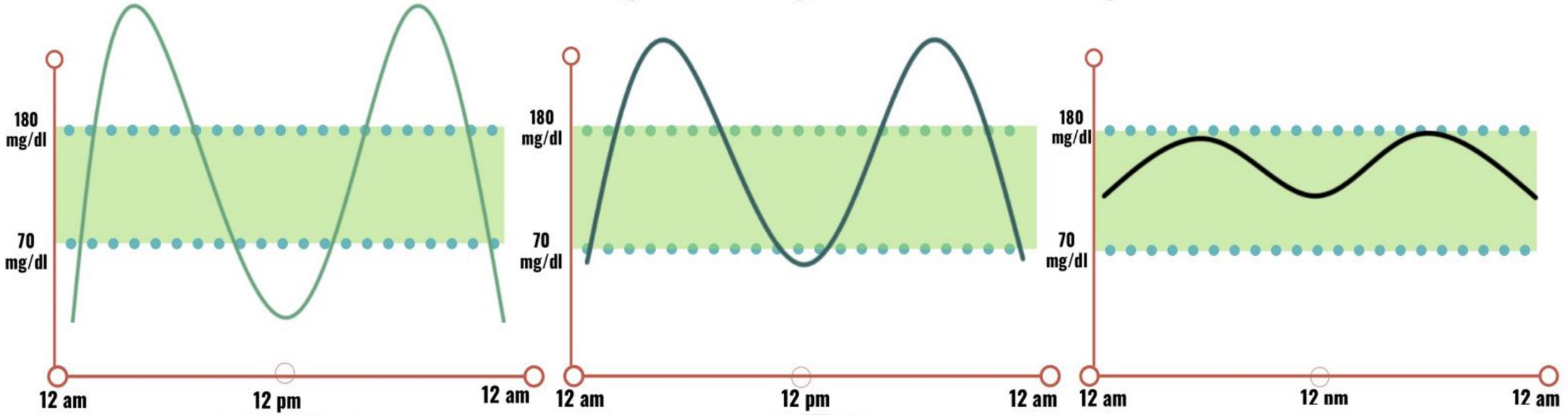


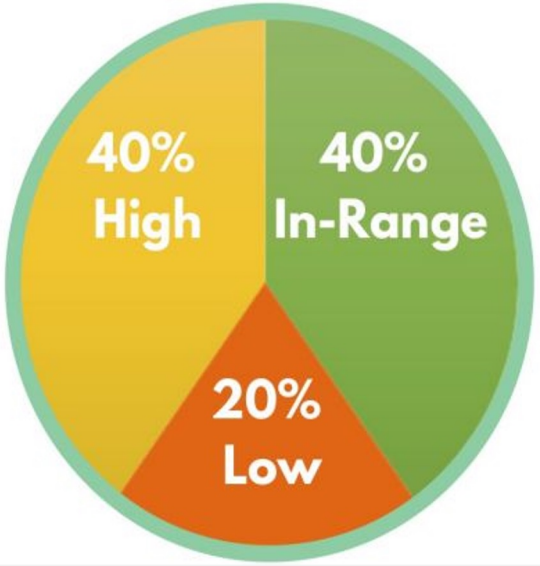
TIR GOAL 70%

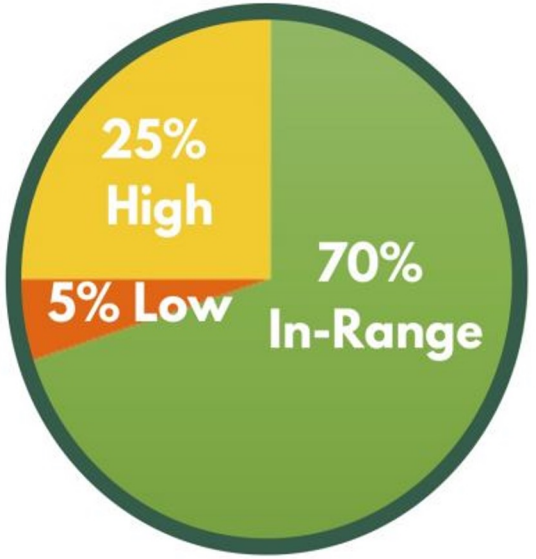


THE MANY FACES OF A 7% A1C

(and an average blood glucose of 154 mg/dl)







Blood glucometers have their own care limitations

CGM in comparison is a highly effective tool

- Provides real time data, patterns and trends
- Reveals previously unknown blood glucose patterns
- Assists providers effectively manage selected patients with T2D

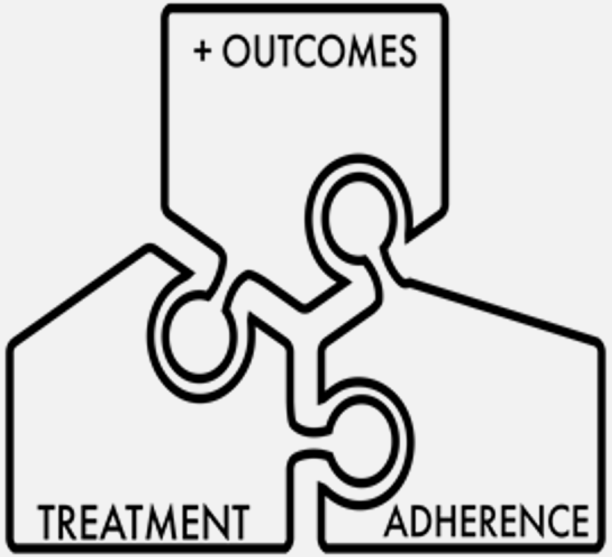
CGM increases patient disease state engagement

- Improves A1C control while mitigating hypoglycemia risk
- Helps prevent hospital readmissions
- Helps avoid unnecessary emergency room visits

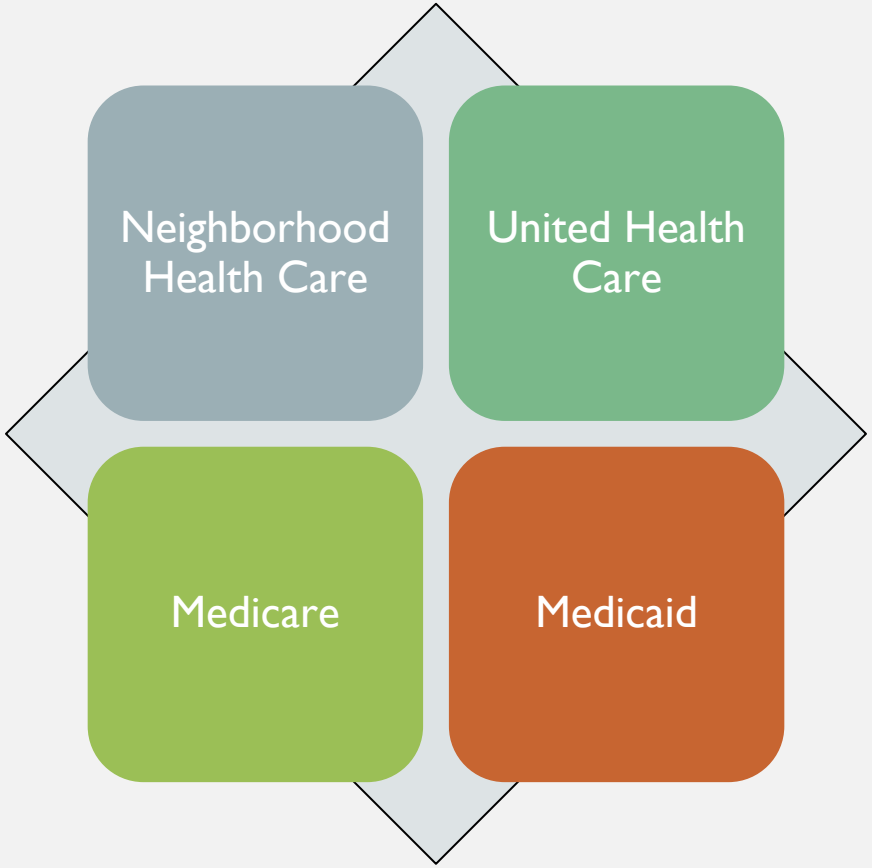
CGM may be a prudent cost strategy to improve T2D patient care

- Consider hypoglycemia cost implications vs the cost of technology

ADA recommends CGM to be most suitable for diabetes patients with insufficient and unsatisfied disease control and high risk of hypoglycemia



YES, YOU CAN GET CGM COVERED!



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THE BLEEDING HEART'S CUTTING EDGE: PHARMACOLOGIC ADVANCEMENTS IMPACTING CARDIAC MEDICINE

Justin Culshaw PharmD BCCCP
Brown University Health – Rhode Island Hospital

DISCLOSURES

Previously compensated as a consultant for GSK (GlaxoSmithKline) for vaccine related education from 5/2025 – 10/2025.

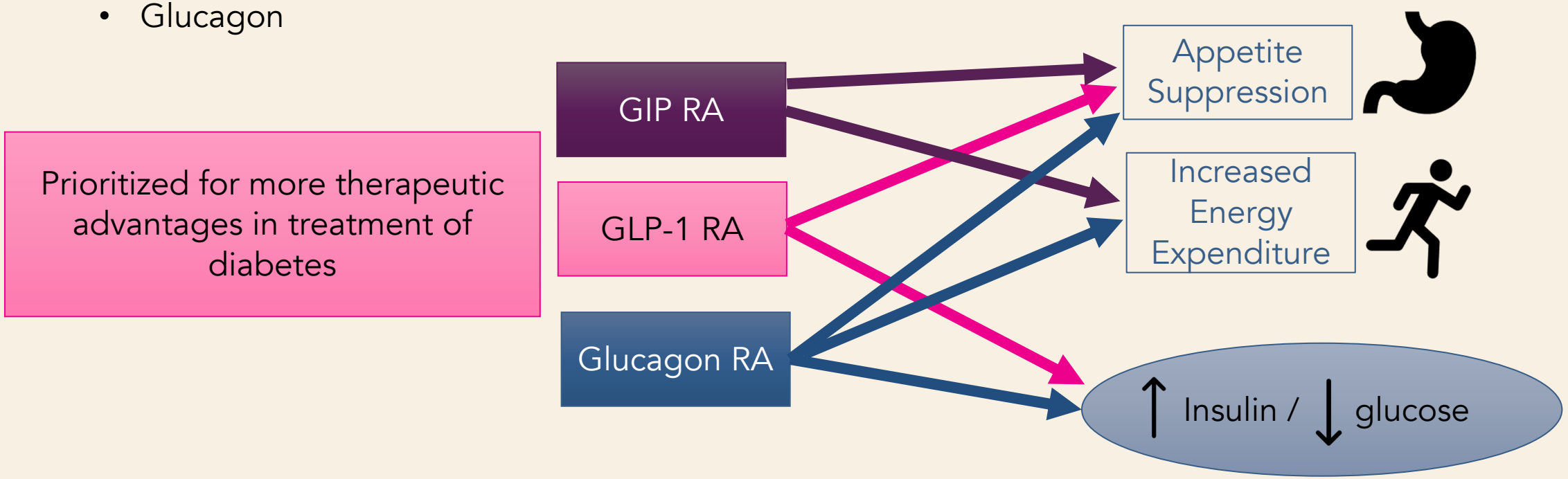
OBJECTIVES

1. Review pharmacologic mechanism advancements for approved GLP-1, PCSK-9, and disease-modifying amyloid therapy
2. Discuss emerging clinical practices and guidelines due to new drug substrates or expanded indications
3. Identify patients who newly are candidates for GLP-1 or PCSK9 therapy
4. Explore new substrates or indications for GLP-1, PCSK-9, and disease-modifying amyloid therapy medications currently in clinical development

GLUCAGON-LIKE PEPETIDE-1 RECEPTOR AGONISTS (GLP-1 RA)

INCRETIN HORMONE PHARMACOLOGIC TARGETS

- Patients with diabetes mellitus secrete less endogenous incretin hormones stimulated by caloric intake
  - Glucose-dependent insulinotropic peptide (GIP)
  - Glucagon-like peptide-1 (GLP – 1)
  - Glucagon



Toft-Nielsen Mbet al. J Clin Endocrinol Metab. 2001;86(8):3717–23.
Meier JJ. Nat Rev Endocrinol. 2012;8:728-742.

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AGONISTS, 2005 - 2017

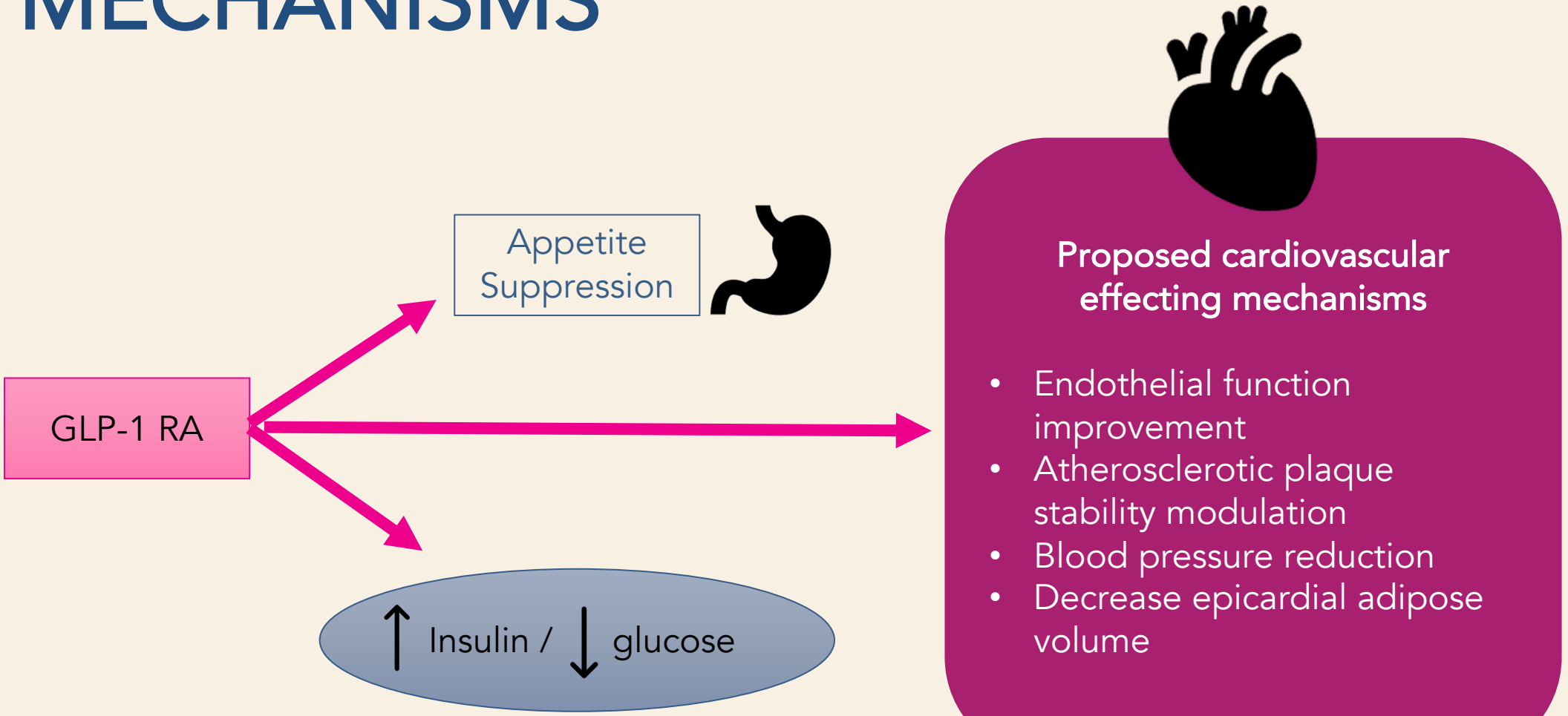
Counseling Points	Incr satiety, and transient, mild nausea may occur if they attempt to eat while feeling full
Administration	Subcutaneously; semaglutide oral
Benefits/Risk	§ A1c –lowering potential: 0.8 – 1.9% § Weight Effect: loss § Hypoglycemia risk: low § **HF benefit: neutral** § **MACE benefit: dulaglutide, liraglutide, semaglutide** § **CKD benefits: dulaglutide, liraglutide, semaglutide**

TIRZEPATIDE (MOUNJARO)

Approved 2022 for Diabetes

Mechanism of action	**GIP and GLP-1 RA**: glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist that increases glucose-dependent insulin secretion, decreases inappropriate glucagon secretion, and slows gastric emptying
Counseling Points	GI side effects – dietary modifications and titration
Adverse effects	**GI (decr appetite, diarrhea, nausea)**, injection site reaction, pancreatitis, tachycardia, AKI
Benefits/Risk	§ **Weight loss: very high,** 2 to 3 kg/6 months § CV and renal effects…

GLP-1 RA CARDIOVASCULAR MECHANISMS

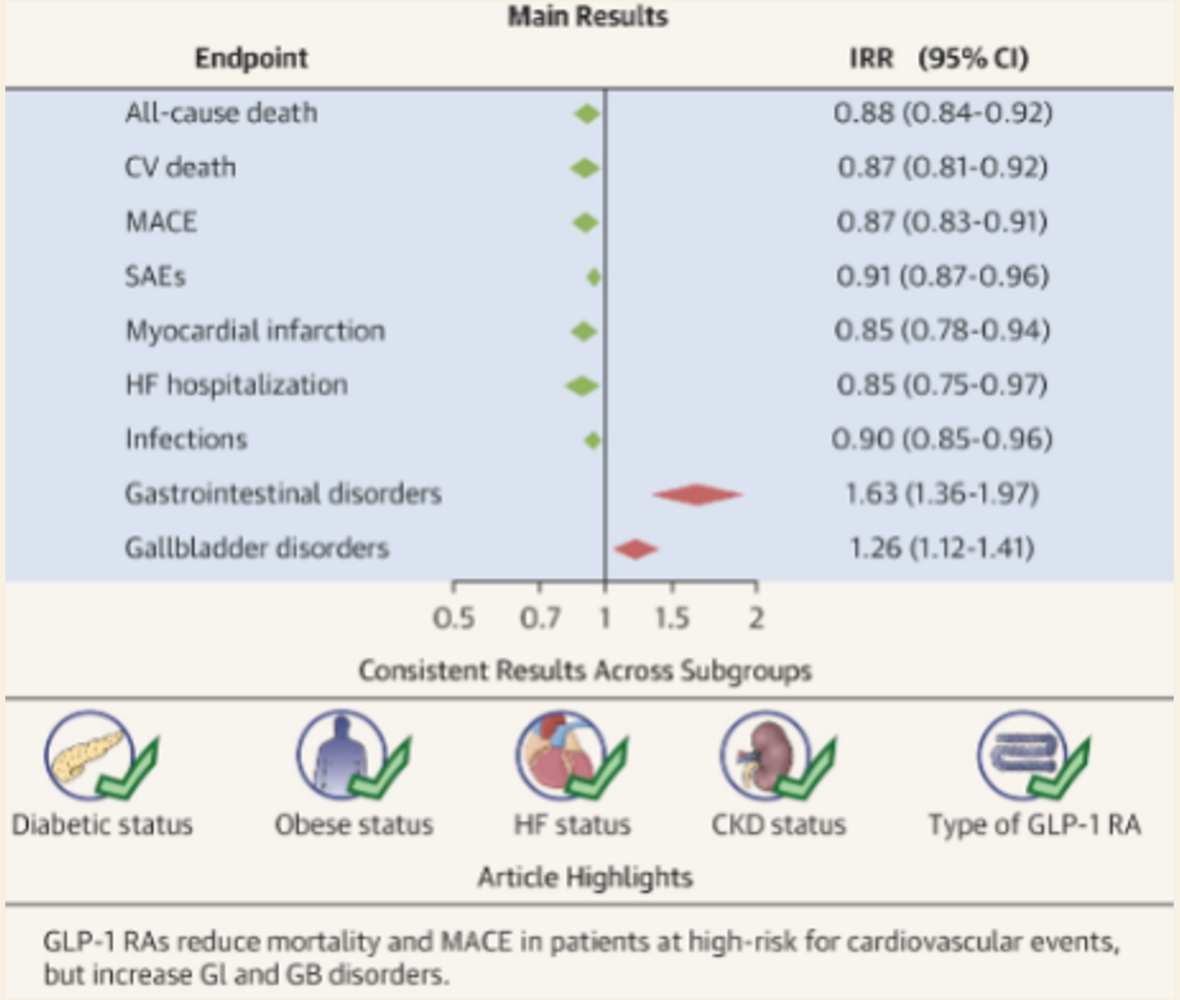


Galli M, et al. JACC 2025;86(20):1805-1819

CARDIOVASCULAR EFFECTS AND TOLERABILITY OF GLP-1 RA

Systematic Review Meta-analysis

- 21 randomized trials of GLP-1 RAs
- 99,599 patients at high risk of cardiovascular events
- Main outcomes: All-cause death, CV death, MACE and SAEs



Galli M, et al. JACC 2025;86(20):1805-1819

SURPASS-CVOT

Question: Does tirzepatide – a dual incretin agonist of GLP-1 and GIP receptors – impact cardiovascular outcomes?

Design

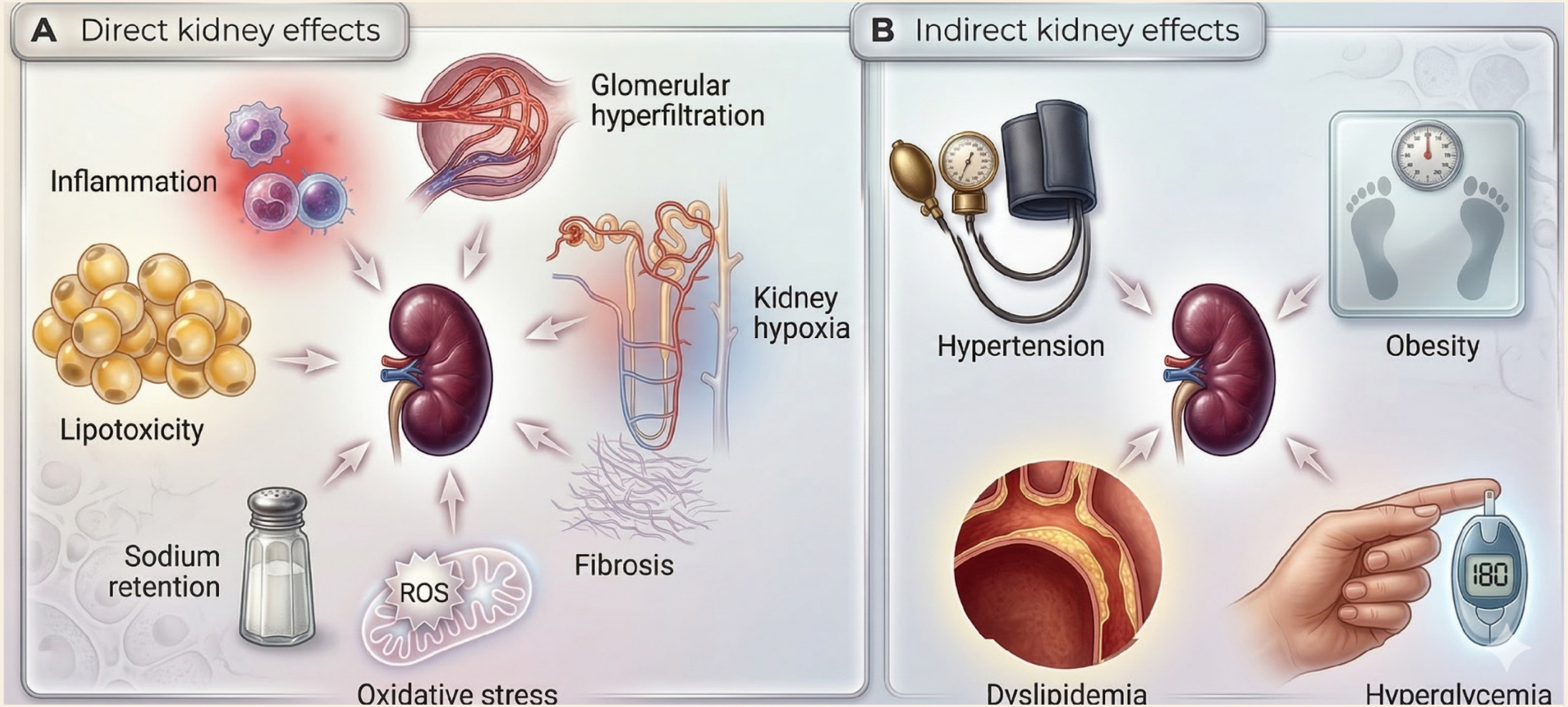
- Double blind randomized non-inferiority trial
- Active comparator controlled
- 13,165 adults with T2DM
  - Tirzepatide, N=6586
  - Dulaglutide, N=6579

Results

- No significant difference in **death from cardiovascular causes, MI, or stroke**
  - Hazard ratio, 0.92 (95.3% CI, 0.83 to 1.01) p=0.003 for noninferiority
  - Similar incidence of any adverse event

Nicholls Sjet al. N Engl J Med. 2025 Dec 18;393(24):2409-2420.

GLP-1 RA MECHANISMS IN CKD



Cooper ME, et al.. J Clin Invest. 2025 Nov 3;135(21):e194749

FLOW TRIAL – SEMAGLUTIDE IN T2DM WITH CKD

Design

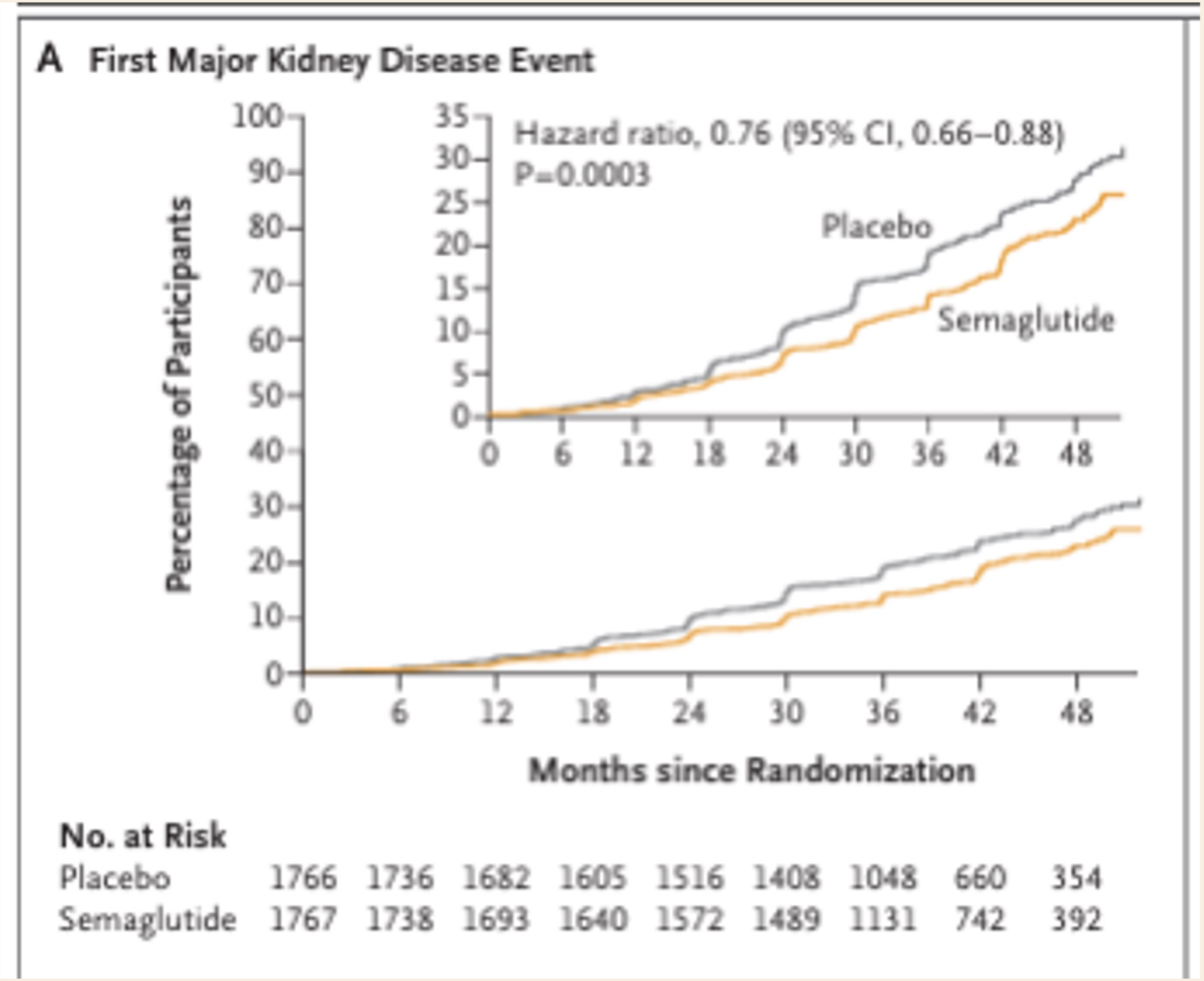
- International, double blind, randomized, placebo – controlled trial
- 1:1 semaglutide or placebo
  - 8-week dose escalation regimen
  - SGLT2 or MRAs allowed
- 3,533 adults with T2DM and high-risk CKD
  - Median 66.6 years old, 30.3% female
  - Mean eGFR 47 ml/min/1.73m^2
  - Median urinary albumin-to-creatinine ratio of 567.6

Primary Outcome

- Major kidney disease event (composite endpoint)
  - Initiation of long-term dialysis
  - Kidney transplant
  - Sustained * eGFR reduction to <15 ml/min/1.73m^2
  - Sustained >50% reduction in eGFR from baseline
  - Death from kidney-related or cardiovascular case

*28 days

Perkovic Vet al. N Engl J Med. 2024 Jul 11;391(2):109-121. Epub 2024 May 24.



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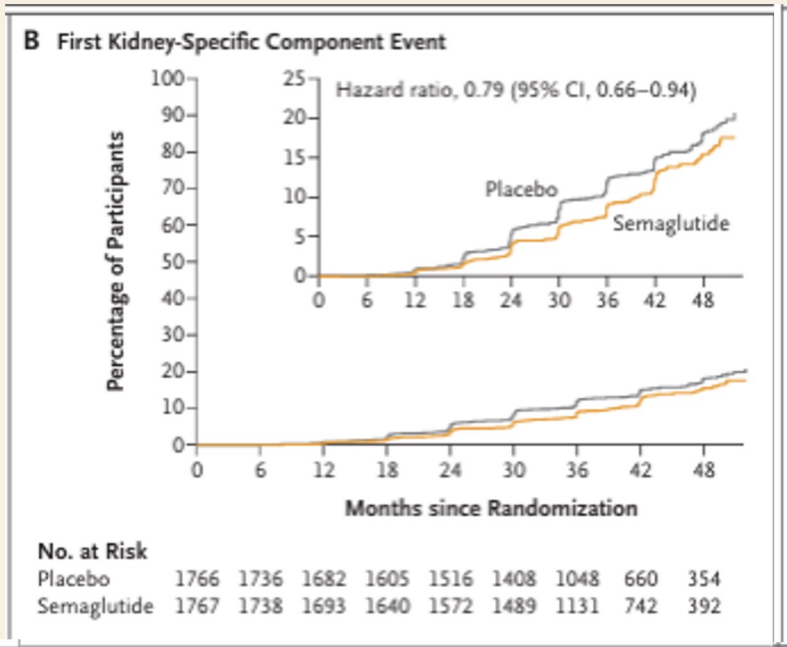
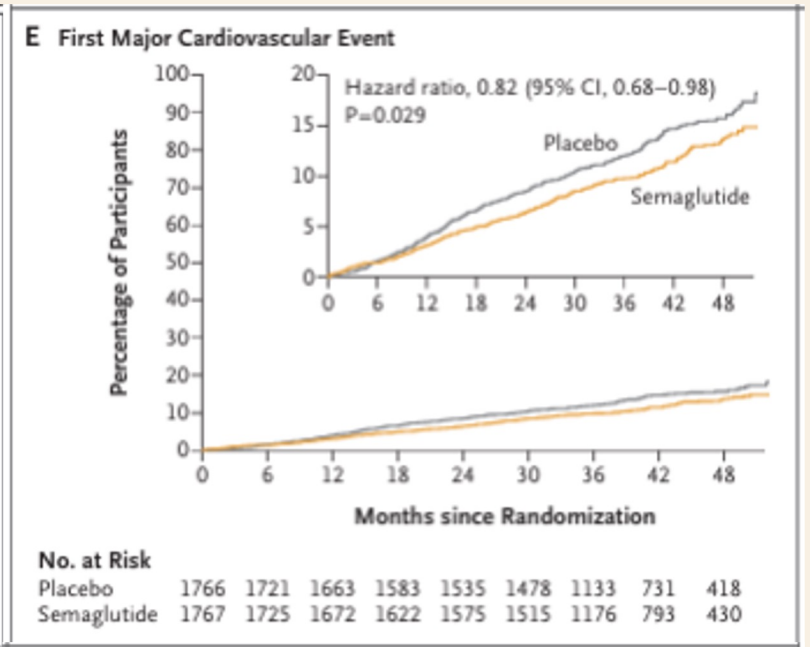
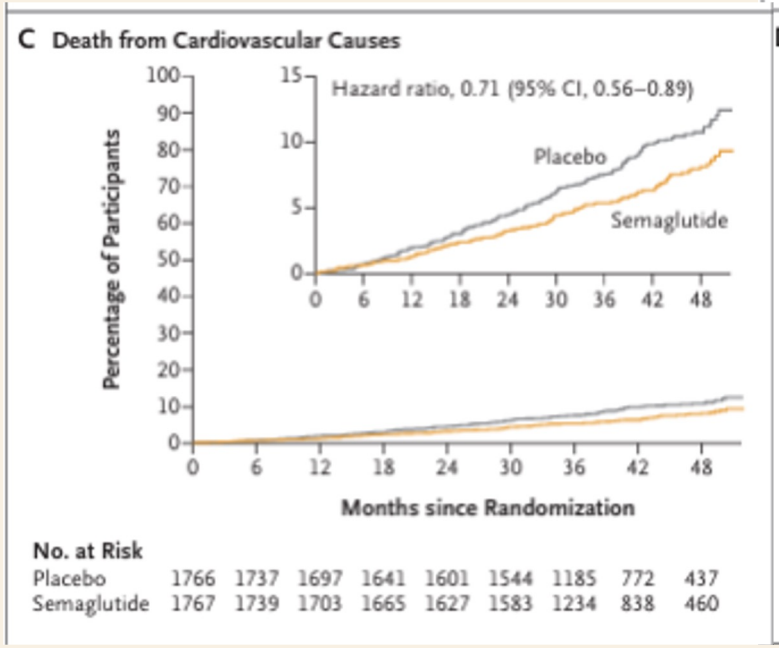
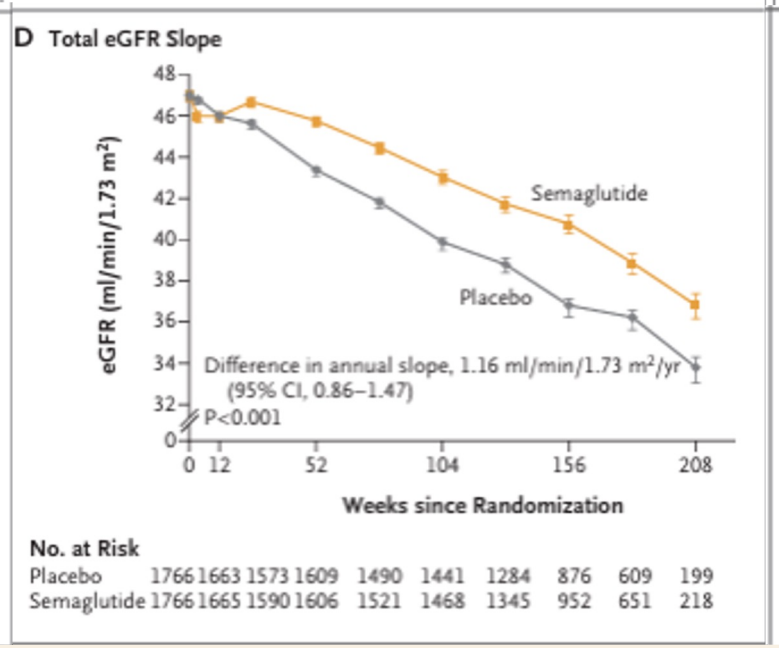
Perkovic Vet al. N Engl J Med. 2024 Jul 11;391(2):109-121. Epub 2024 May 24.

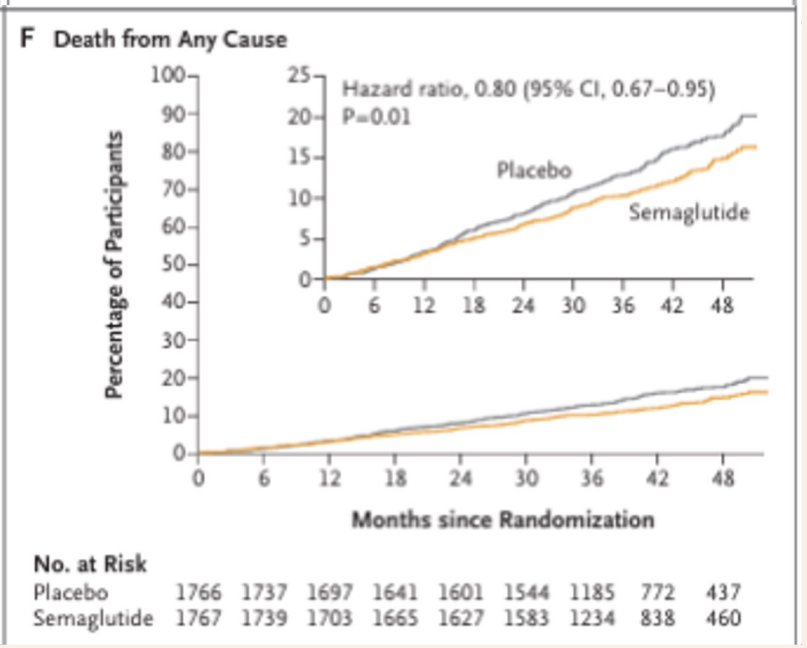
B) Persistent ≥50% reduction in eGFR
C) Death from cardiovascular causes
D) Total eGFR slope
E) a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes)
F) Death from any cause.











Perkovic Vet al. N Engl J Med. 2024 Jul 11;391(2):109-121. Epub 2024 May 24.

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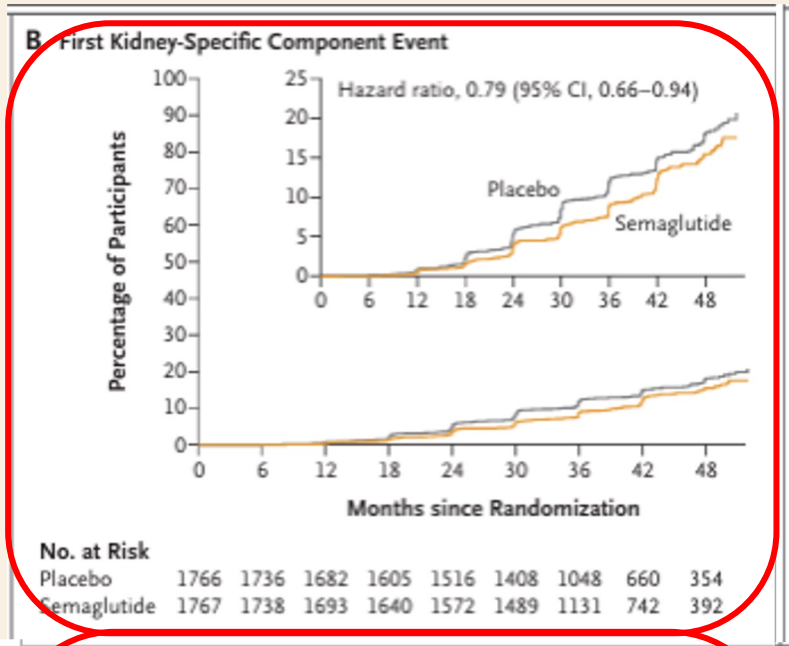

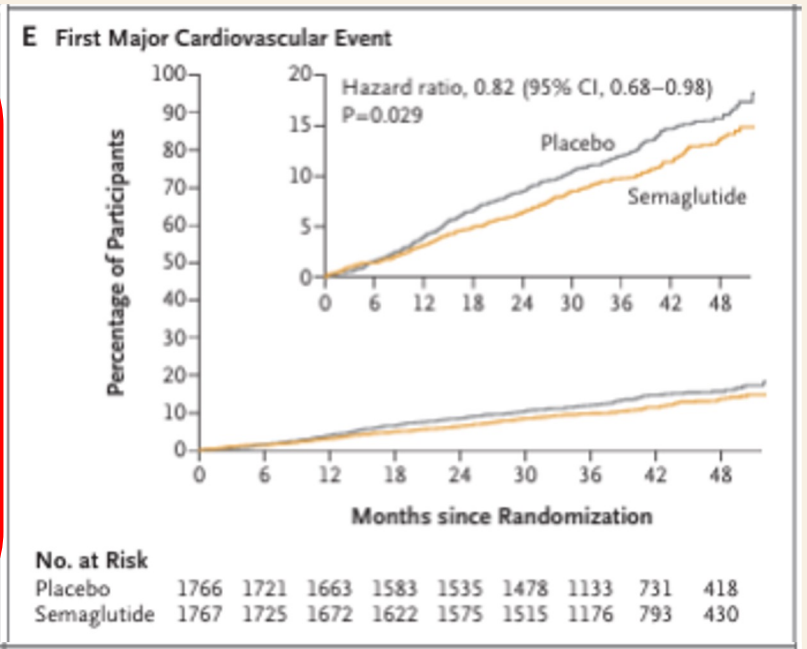

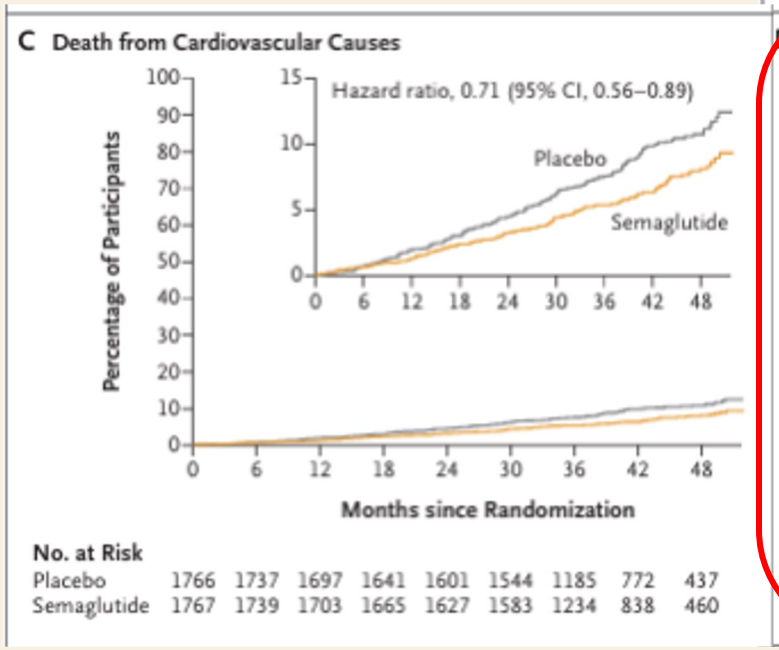

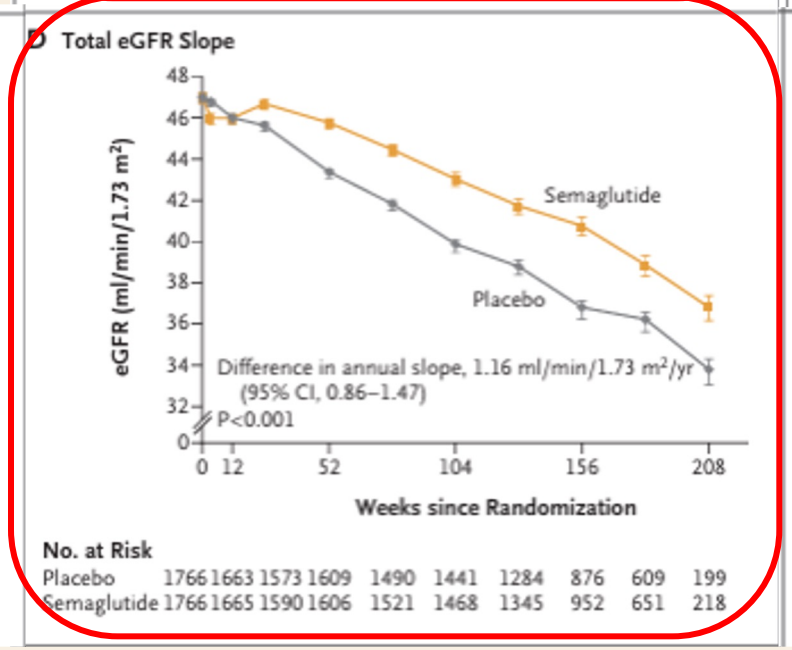

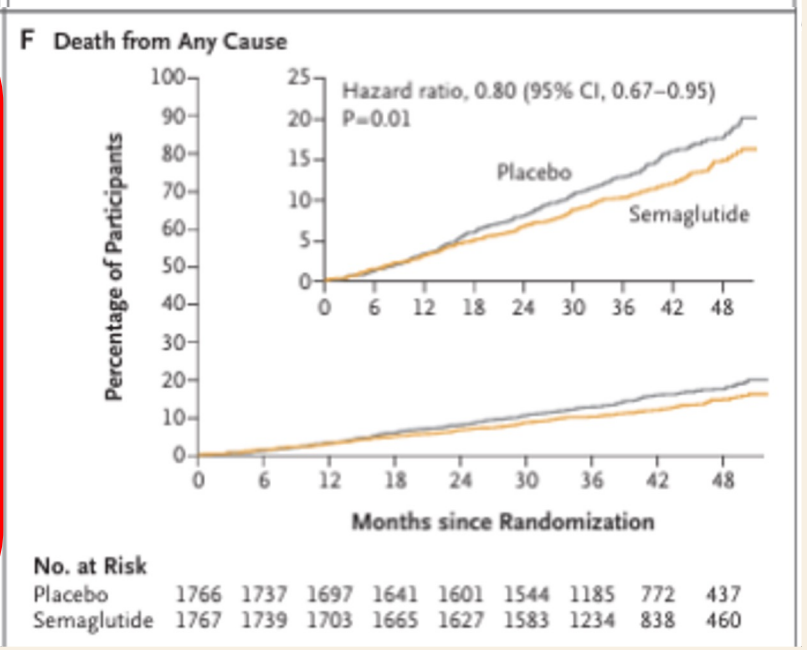

Perkovic Vet al. N Engl J Med. 2024 Jul 11;391(2):109-121. Epub 2024 May 24.

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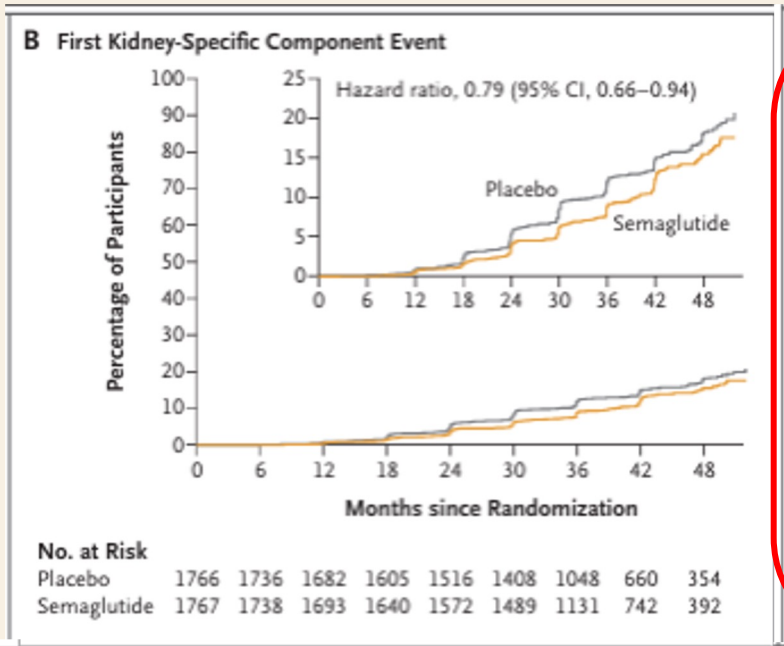
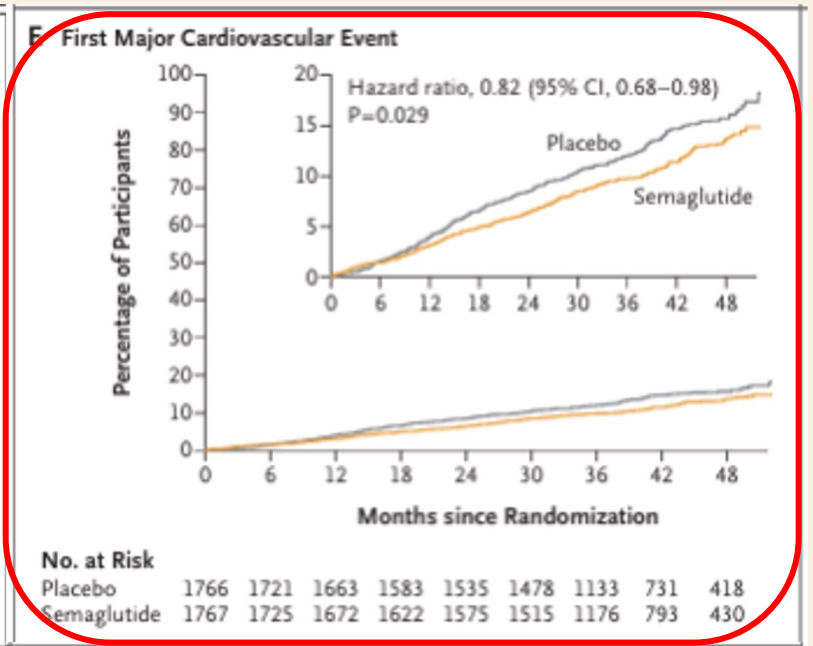
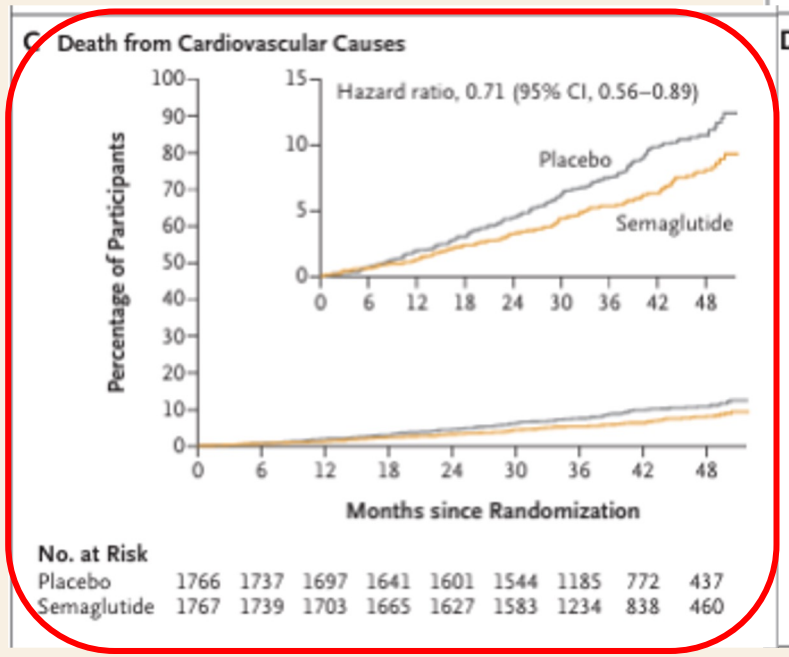
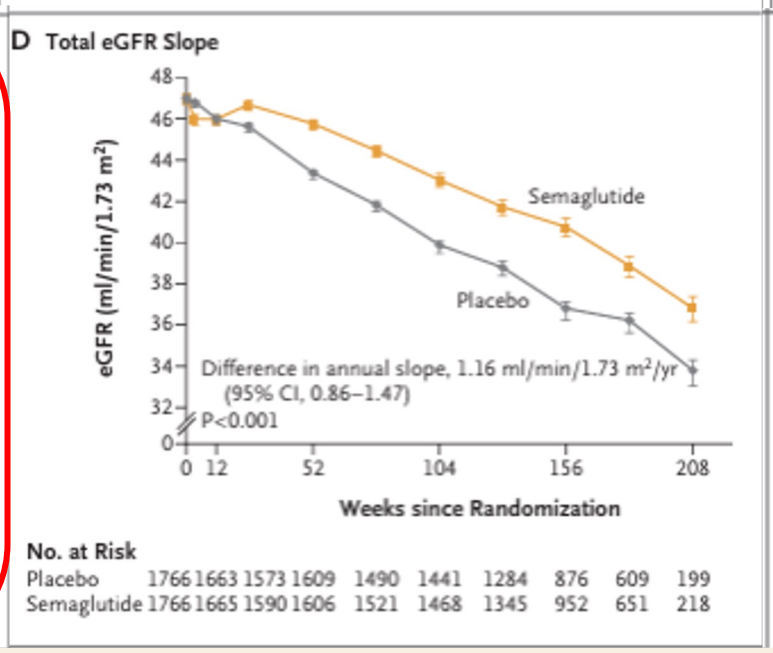
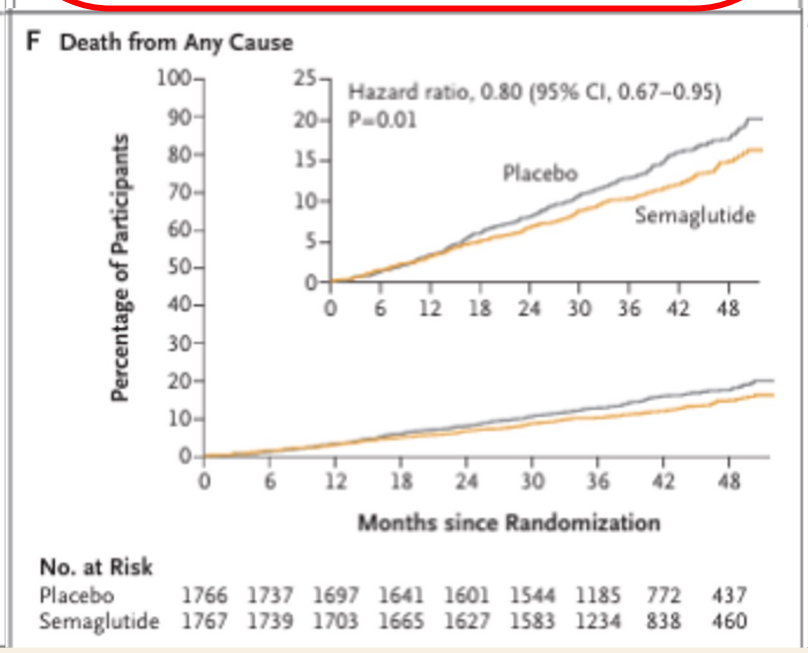








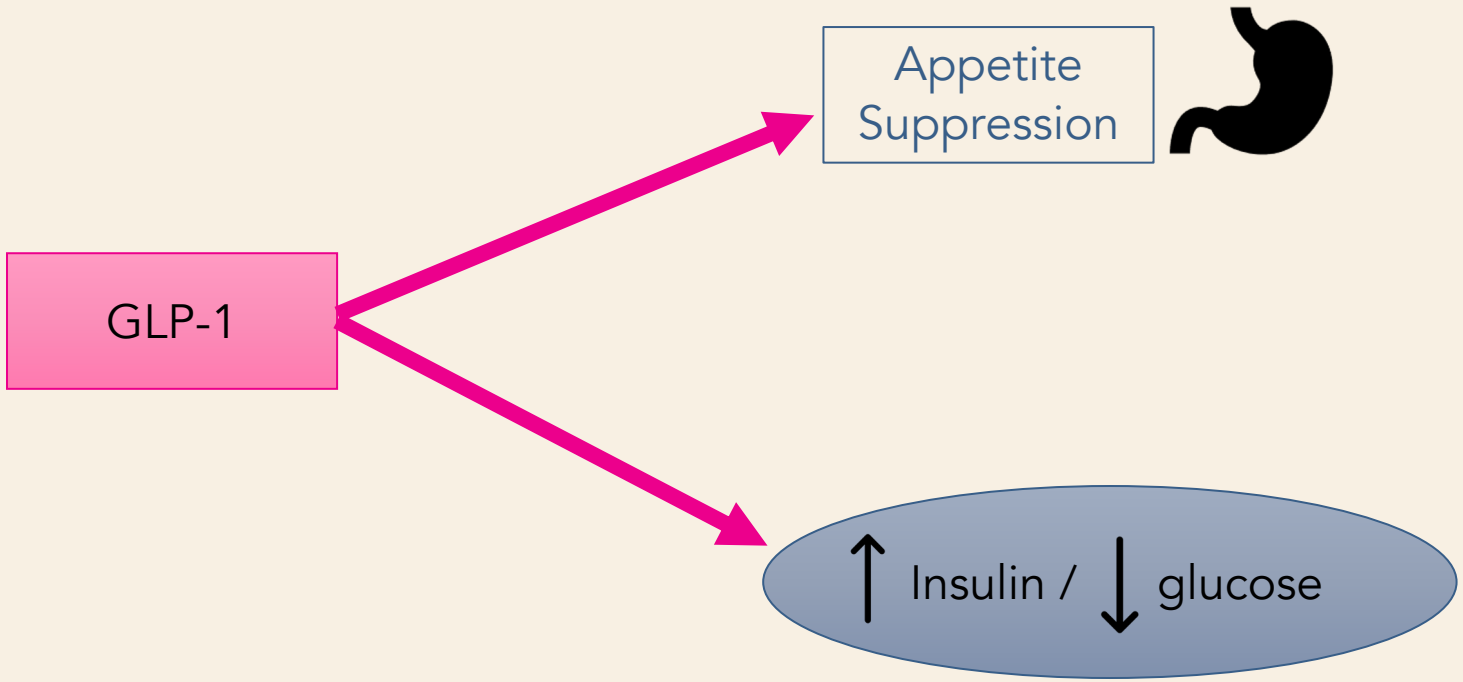


Perkovic Vet al. N Engl J Med. 2024 Jul 11;391(2):109-121. Epub 2024 May 24.

EVOLUTION OF INCRETIN-BASED MECHANISMS

GLP-1 mono-agonists

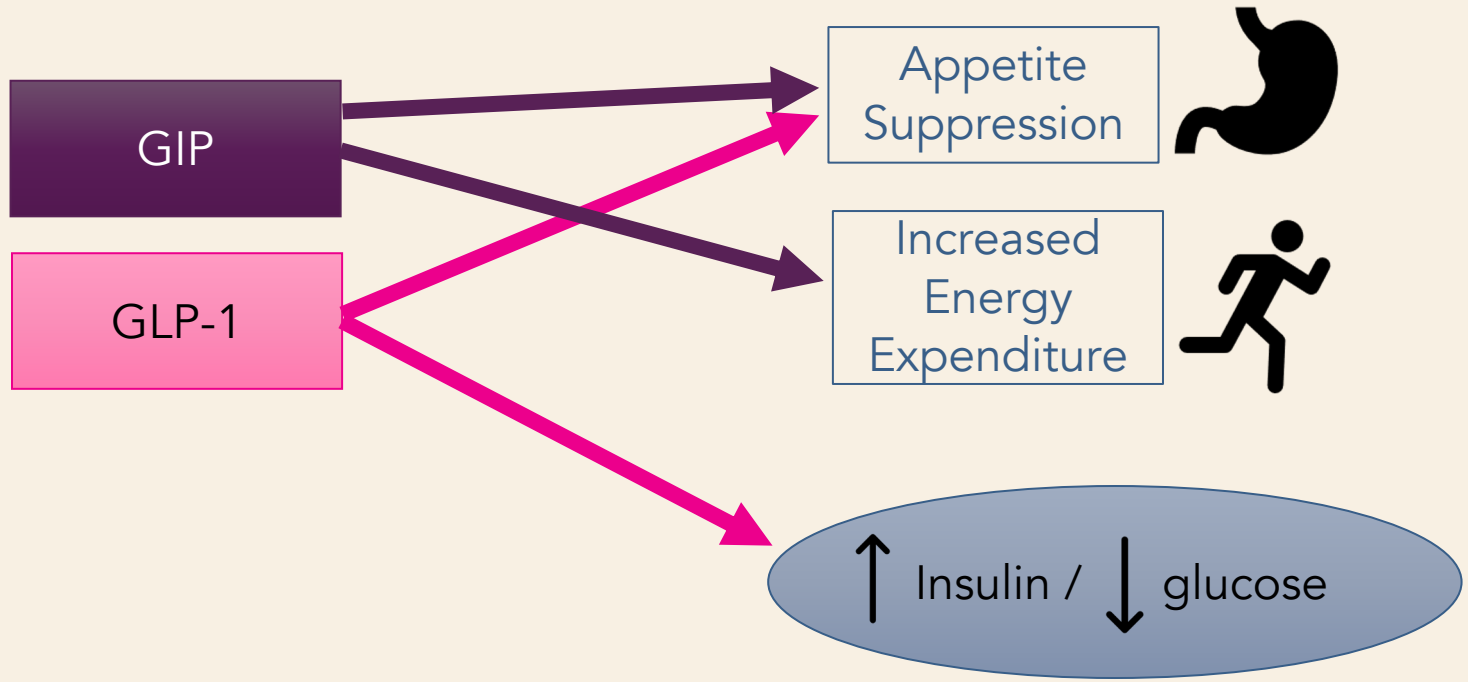
- Exenatide (Byetta)
- Exenatide ER (*Bydureon)*
- Liraglutide (Victoza)
- Dulaglutide (Trulicity)
- Semaglutide (Ozempic)



EVOLUTION OF INCRETIN-BASED MECHANISMS

GLP-1 dual-agonist

Tirzepatide (Mounjaro)

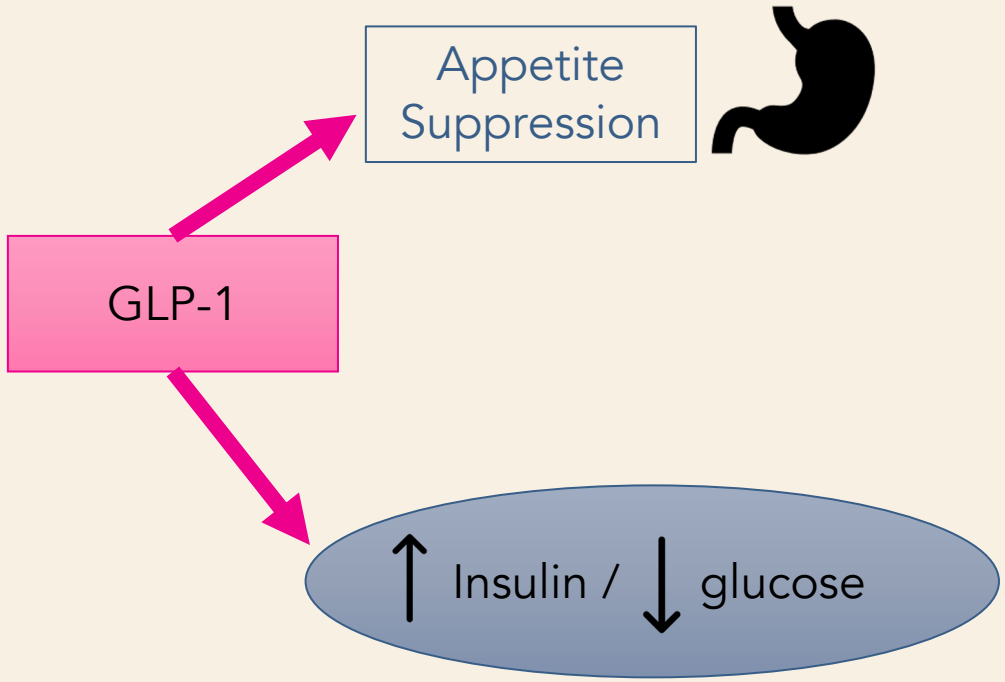


EMERGING AGENT

GLP-1 mono-agonist

Aleniglipron (pending phase III trials)

- Phase 2 trials for this daily oral pill showed 11–15% weight loss at 36 weeks.
  - N = 230 adults with a weight related comorbidity plus
    - Obesity and body mass index (BMI) of 30kg/m² or higher
    - Overweight with a BMI of 27kg/m² or higher

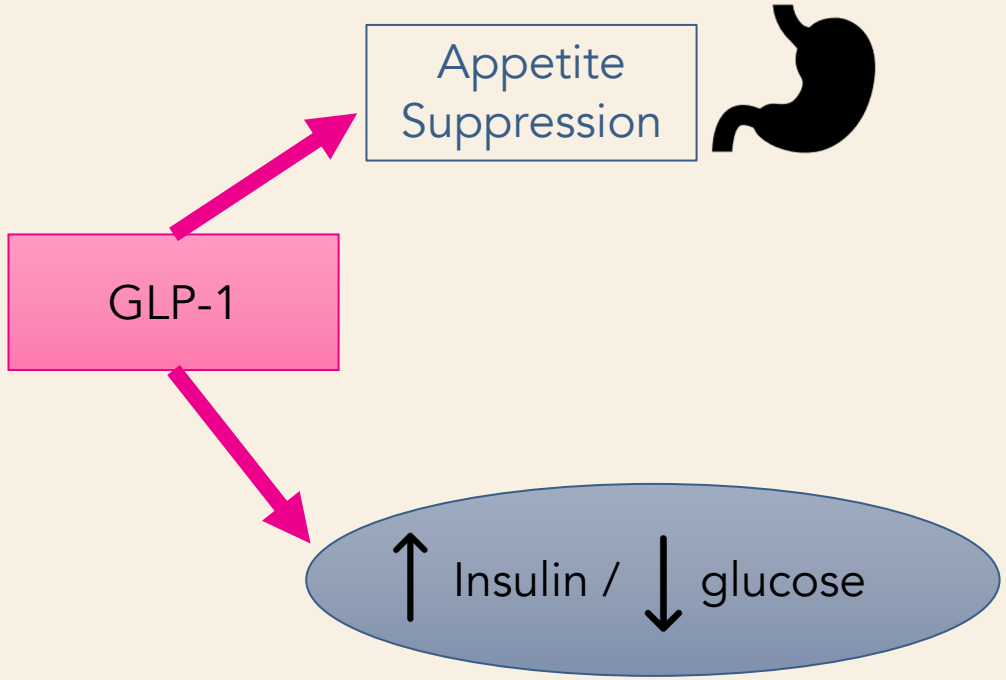


Șeremet OC, et al. Medicina (Kaunas). 2025 Oct 23;61(11):1902

EMERGING AGENT

GLP-1 non-peptide mono-agonist

Orforglipron (pending phase III trials)



- Preliminary phase 3 data
  - Weight loss up to 12.4%
  - improved cardiovascular/metabolic factors in patients with obesity
- Small Molecule, non-peptide Structure
  - Enhanced stability given molecular size
  - high affinity, low-efficacy agonism
  - potentially lower receptor desensitization and prolonging efficacy
  - Enhanced GI tract stability allowing for once daily dosing agnostic to timing

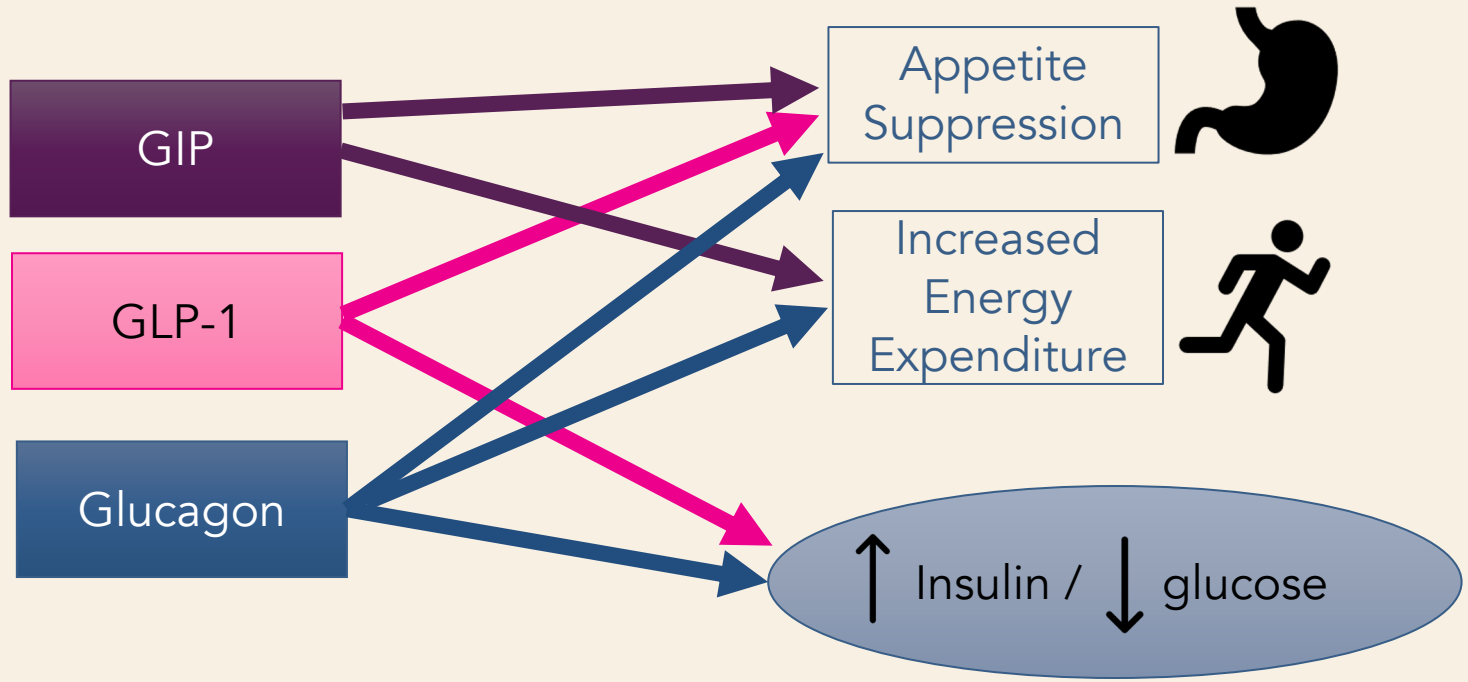
Rosenstock Jet al. Lancet. 2026 Feb 26:S0140-6736(26)00202-

EMERGING AGENT

GLP-1 tri-agonist

Retatrutide (pending phase III trials)

Showed weight loss of 23–24% in trials, with Phase 3 trials concluding in early 2026.



Katsi V, et al. Biomolecules. 2025 May 30;15(6):796.

Ongoing trials with incretin-based therapies			
Name	Population	Agent	Outcome
REMODEL	CKD, T2DM	Semaglutide	Multiparametric MRI parameters
ASCEND PLUS	T2DM	Semaglutide	5-Point MACE
PRECIDENTD	T2DM	Open label GLP-1	4-Point MACE
ACHIEVE-4	T2DM + CV disease	orforglipron	4-Point MACE
SURMOUNT-MMO	Overweight or obese	tirzepatide	4-Point MACE
TREASURE-CKD	Obesity w/wo T2DM + CKD	tirzepatide	Kidney Oxygenation
TRIUMPH-Outcomes	Obesity w/wo ASCVD +/- CKD	retatrutide	4-Point MACE, 4-point kidney composite ESRD, CV/renal death
J1I-MC-GZBU	Obesity w/wo T2DM + CKD	retatrutide	Iohexol measured eGFR

Cooper ME, et al. J Clin Invest. 2025 Nov

GLP-1 RA FOR WEIGHT LOSS

OBESITY EPIDEMIC

- Chronic, relapsing disease
- Over 1 billion people affected worldwide
- 3.7 million obesity related deaths in 2024
    - 12% of deaths from noncommunicable diseases worldwide
- $3 trillion USD / year by 2030 in global costs

Celletti F, et al. JAMA. 2026 Feb 3;335(5):434-438

COMPARATIVE EFFECTIVENESS AND SAFETY OF GLP-1 RA FOR WEIGHT REDUCTION

Design

- Meta-Analysis of Placebo Controlled trials
- 55 clinical studies
  - N= 16,269
  - Included
    - GLP-1RA mono-agonists, dual-agonist, and tri-agonist

Results

Guo H, et al. Obes Pillars. 2025 Jan 30;13:100162.
Rubin R. JAMA. 2026 Feb 24;335(8):653-655

2025 WHO OBESITY GLP-1RA GUIDELINES

- As of October 2025, 12 GLP-1 therapies have been approved for indications in type 2 diabetes and/or obesity
- Over 40 agents—including multireceptor agonists—are in active development

Recommendation 1:

In adults living with obesity, GLP-1 therapies may be used as a long-term treatment for obesity. (conditional recommendation, moderate certainty evidence)

Recommendation 2:

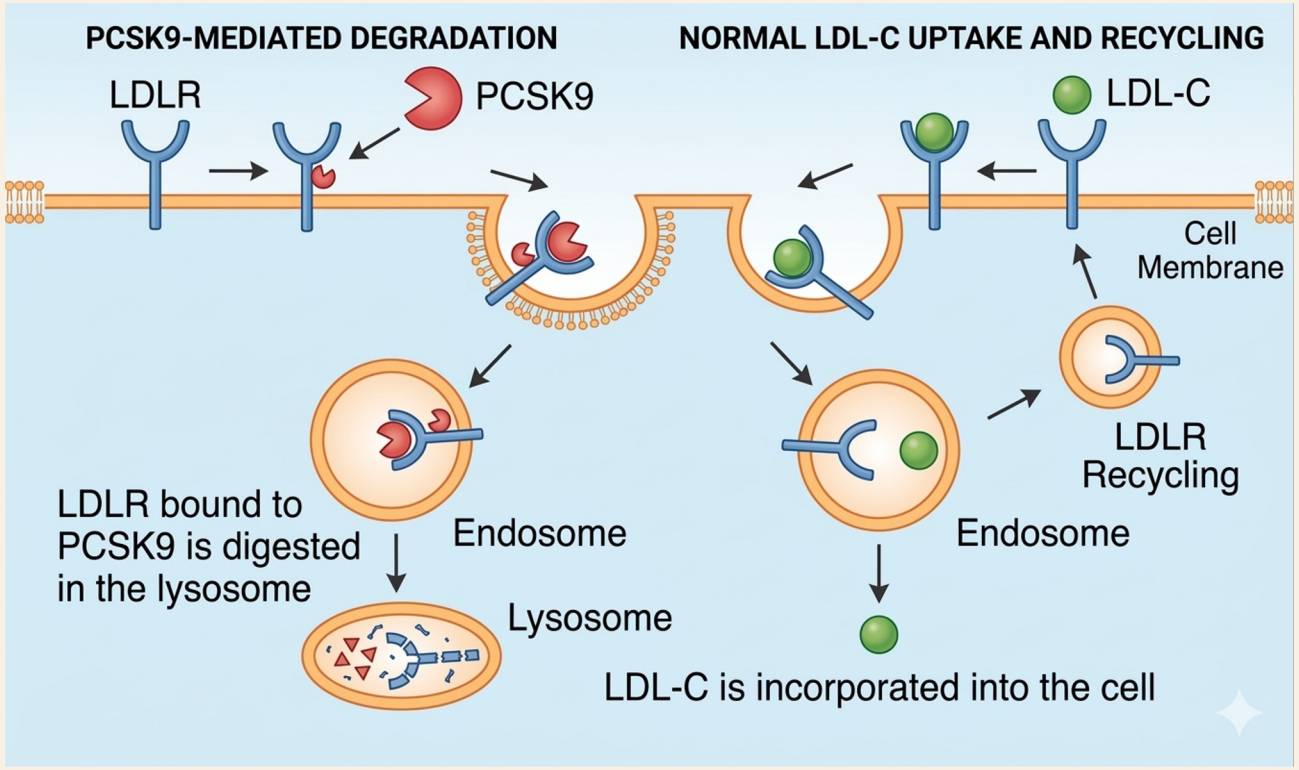
In adults living with obesity who are prescribed GLP-1 therapies, intensive behavioral therapy may be provided as part of a comprehensive multimodal clinical algorithm.

Guo H, et al. Obes Pillars. 2025 Jan 30;13:100162.
Rubin R. JAMA. 2026 Feb 24;335(8):653-655

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (**PCSK9**) INHIBITORS

PCSK9 INHIBITORS

MOA: Bind to the PCSK9 protein and blocks action on the LDL receptors, therefore allowing more LDL receptors to be present on the liver to remove LDL from the blood.



Pokhrel Bet al. PCSK9 Inhibitors. [Updated 2024 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448100/

PCSK9 INHIBITORS

Alirocumab (Praluent®)
Evolocumab (Repatha®)
Monoclonal antibodies, available as subcutaneous injections.

FDA Indications:
Alirocumab: adjunct to diet and maximally tolerated statin therapy for:

- **Heterozygous** familial hypercholesterolemia
- Pts w/ clinical ASCVD who require additional LDL lowering to get to goal

Evolocumab:

- Patients with clinical ASCVD + primary hyperlipidemia (LDL >190)
- **Homozygous** Familial Hypercholesterolemia

Pokhrel Bet al. PCSK9 Inhibitors. [Updated 2024 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448100/

PCSK9 INHIBITORS

- Side Effects:
  - Injection site reactions
  - Diarrhea
  - Myalgia
  - Influenza
  - Cough
  - Confusion, memory impairment
  - Hypersensitivity reactions (rare)
- Contraindication:
  - Hypersensitivity reactions
    - Including severe vasculitis
- Monitoring Parameters:
  - LDL-C within 4-8 weeks of initiation
  - Hypersensitivity reactions

Pokhrel Bet al. PCSK9 Inhibitors. [Updated 2024 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448100/

PCSK-9 INHIBITORS AND CV BENEFIT

- GLAGOV trial:
  - Evolocumab in patients with existing CAD on a statin
    - Evolocumab arm with reduced percent atheroma volume vs placebo (-0.95%, p <0.001 vs +0.05%, p=0.78) and plaque regression (64.3% vs 47.3%, p <0.001)
- FOURIER Trial:
  - Evolocumab vs placebo in patients with Cardiovascular disease
    - Composite cardiovascular death, MI, stroke, hospitalization for unstable angina, or cardiovascular revascularization occurred in 9.8% of evolocumab treated patients versus 11.3% of placebo (HR 0.85, 95% CI 0.79-0.92, p <0.001)
- ODYSSEY OUTCOMES Trial:
  - Alirocumab in patients with ACS within 1-12 months on high intensity statin
    - Composite death from CAD, nonfatal MI, fatal or nonfatal ischemic stroke, or UA requiring hospitalization occurred in 9.5% of alirocumab vs 11.1% of placebo treated patients (HR 0.85, 95% CI 0.78-0.93, p<0.001)

Nicholls SJ, et. al. JAMA. 2016;316(22):2373-84.
Sabatine MS, et. al. N Engl J Med. 2017; 376:1713-22.
Schwartz GG, et. al. N Engl J Med. 2018;379:2097-2107.

VESALIUS-CV

- Benefit in patients without previous myocardial infarction or stroke?

Design

- Double blind randomized placebo controlled
- 12,257 adults with atherosclerosis or DM, no previous MI or stroke
  - Evolocumab, N=6129
  - Placebo, N=6128

Results

- Median 4.6 year follow up
- Reduced 3-point MACE (HR 0.75 [95% CI, 0.65-0.86]; p<0.001)
- Reduced 4-point MACE (HR 0.81 [95% CI, 0.73-0.89]; p<0.001)

Bohula EA, et al. N Engl J Med. 2026 Jan 8;394(2):117-127.

EMERGING AGENTS

- Enlicitide (under investigation)
  - CORALreef study
    - Appears safe and efficacious for LDL-lowering at 52 week follow up, however long-term effects unknown
- Several other agents in active investigation
- Meta-analysis of 3 randomized controlled trials of oral PCSK9, reductions in
  - LDL-C levels (MD = -47.83%; 95% CI: -54.91, -40.74; P < .00001)
  - triglycerides (MD = -11.65%; 95% CI: -15.44, -7.87; P < .0001)
  - apolipoprotein B (MD = -38.71%; 95% CI: -45.48, -31.93; P < .00001)
  - lipoprotein(a) (MD = -19.80; 95% CI: -25.60, -14; P < .0001)

Ballantyne et al. JAMA. 2026 Jan 13;335(2):129-139
Ho VQT et al.. J Clin Lipidol. 2026 Jan;20(1):31-43

EMERGING TREATMENTS FOR CARDIAC AMYLOIDOSIS

CARDIAC AMYLOIDOSIS
DEFINITION AND TYPES

A restrictive cardiac myopathy resulting from the deposition of amyloid fibrils in the myocardial inter-stadium

- AL amyloidosis, where the amyloid fibrils are composed of monoclonal immunoglobulin light chains
- ATTR amyloidosis, where the amyloid fibrils are composed of the transthyretin protein
  - Variant (ATTRv)
    - Primary polyneuropathy (Val30Met), cardiomyopathy (Val122Ile, Leu111Met, Ile68Leu), and mixed phenotype (T60A)
  - Wild-type (ATTRwt)

Kittleson MM, et al.. *J Am Coll Cardiol*. 2023;S0735-1097(22)07423-X.

CARDIAC AMYLOIDOSIS
VARIANT (ATTRV)

SINGLE-NUCLEOTIDE POLYMORPHISMS IN THE TRANSTHYRETIN (*TTR*) GENE INDUCE TTR INSTABILITY AND MISFOLDING

ATTR Mutation	Clinical Manifestations	Geographic Location/Ethnicity
Val30Met (Met30)	Peripheral neuropathy ≫ cardiac involvement	Portugal Sweden Japan
Thr60Ala (Ala60)	Peripheral neuropathy = cardiac involvement	England Northern Island
Val122Ile (Ile122)	Cardiac involvement ≫ peripheral neuropathy	African African American Afro Caribbean

Ruberg FL, .*J Am Coll Cardiol*. 2019;73(22):2872-2891.

CARDIAC AMYLOIDOSIS

EPIDEMIOLOGY AND PROGNOSIS

Type of Cardiac Amyloidosis	Epidemiology	Prognosis
AL	12,000 patients 5,000-7,000 new cases are identified annually in the United States	6 months (without disease-specific treatment) 5.5 years (With contemporary management and early diagnosis)
ATTRwt	>100,000 persons 10 % of Heart failure patients Male > Female Increases with age	3.5 years
ATTRv	Unknown Val122Ile (pV142I) found in 3.4% of African Americans	4 to 5 years

Grogan M. *J Am Coll Cardiol*. 2016;68(10):1014-1020.
Gonzalez-Lopez E,. *European heart journal.* 2015;36(38):2585–94.
Quock TP. *Blood Adv*. 2018;2:1046-53.

CARDIAC AMYLOIDOSIS

AMYLOIDOSIS CLINICAL PRESENTATION

Amyloidosis type	Frequency of heart Involvement	Usual extracardiac signs
AL	70%	Nephropathy, proteinuria, autonomic dysfunction, polyneuropathy, macroglossia, spontaneous bruising, liver involvement
ATTRwt	100%	Carpal tunnel syndrome, lumbar spinal stenosis, ruptured biceps tendon
ATTRv	30-100% depend on the mutation	Polyneuropathy, orthostatic hypotension, vitreous opacities, gastrointestinal problems

Garcia-Pavia. *Eur Heart J*. 2021;42(16):1554-1568.

CARDIAC AMYLOIDOSIS

CARDIAC AMYLOIDOSIS RED FLAGS

Clinical	• Hypotension or normotensive if previous hypertensive
ECG	• Pseudoinfarct pattern
	• Low/decreased QRS voltage to degree of LV thickness
	• AV conduction disease
Laboratory	• Disproportionally elevated NT-proBNP to degree of HF
	• Persisting elevated troponin levels
Echocardiogram	• Granular sparkling of myocardium
	• Increased right ventricular wall thickness
	• Increased valve thickness
	• Pericardial effusion

Garcia-Pavia. *Eur Heart J*. 2021;42(16):1554-1568.

CARDIAC AMYLOIDOSIS
DIAGNOSIS

Invasive
All types

- Cardiac biopsy
- OR
- Extracardiac biopsy + CMR, and Echo criteria

Non-Invasive
Only for ATTR

- Grade 2 or 3 cardiac uptake at diphosphonate scintigraphy
- &
- Negative serum free light chains
- Negative urine and serum immunofixation
- (serum protein electrophoresis with immunofixation; urine protein electrophoresis with immunofixation)
- &
- CMR, and Echo criteria

Garcia-Pavia. *Eur Heart J*. 2021;42(16):1554-1568.

NEED FOR EARLIER DIAGNOSIS AND REFERRAL

Progress:

- Awareness of cardiac amyloidosis has increased
- Significant advances in non-invasive diagnostic tools
  - cardiac magnetic resonance imaging (CMR)
  - technetium pyrophosphate scan

Room for improvement:

Consider cardiac amyloidosis for any congestive heart failure patient with progressive diastolic dysfunction, especially if with:

- Bilateral carpal tunnel syndrome
- Numbness, tingling or pain in the hands or feet
- Spinal stenosis
- Spontaneous rupture of the biceps tendon

CARDIAC AMYLOIDOSIS
DISEASE MODIFYING TREATMENT – TTR STABILIZERS

Mechanism: Prevents tetramers from dissociating by binding to the T4 binding site on TTR

Drug	Approval year			Outcomes
		ATTRv	ATTRwt	
Tafamidis (Vyndaqel/Vyndamax))	2019	X	X	Significantly reduce disease progression and mortality
Acoramidis (Attruby)	2024	X	X	Reducing mortality and hospitalization rates

Hanna M, et al. JACC Adv. 2022 Dec 14;1(5):100148.
Gillmore J et al. N Engl J Med. 2024 Jan 11;390(2):132-142

CARDIAC AMYLOIDOSIS
DISEASE MODIFYING TREATMENT – TTR SILENCER

Mechanism: inhibit TTR gene expression within hepatocytes by inhibiting mRNA transcription, thus reducing the production of the circulating amyloid precursor

Drug	Approval year			Outcomes
		ATTRv	ATTRwt	
Vutrisiran (Amvuttra)	2022	X		Reduced • all-cause mortality • cardiovascular events • Hospitalizations • urgent heart failure visits Preserved functional capacity and quality of life
	2025	X	X	

Fontana M, et al. N Engl J Med. 2025 Jan 2;392(1):33-44.

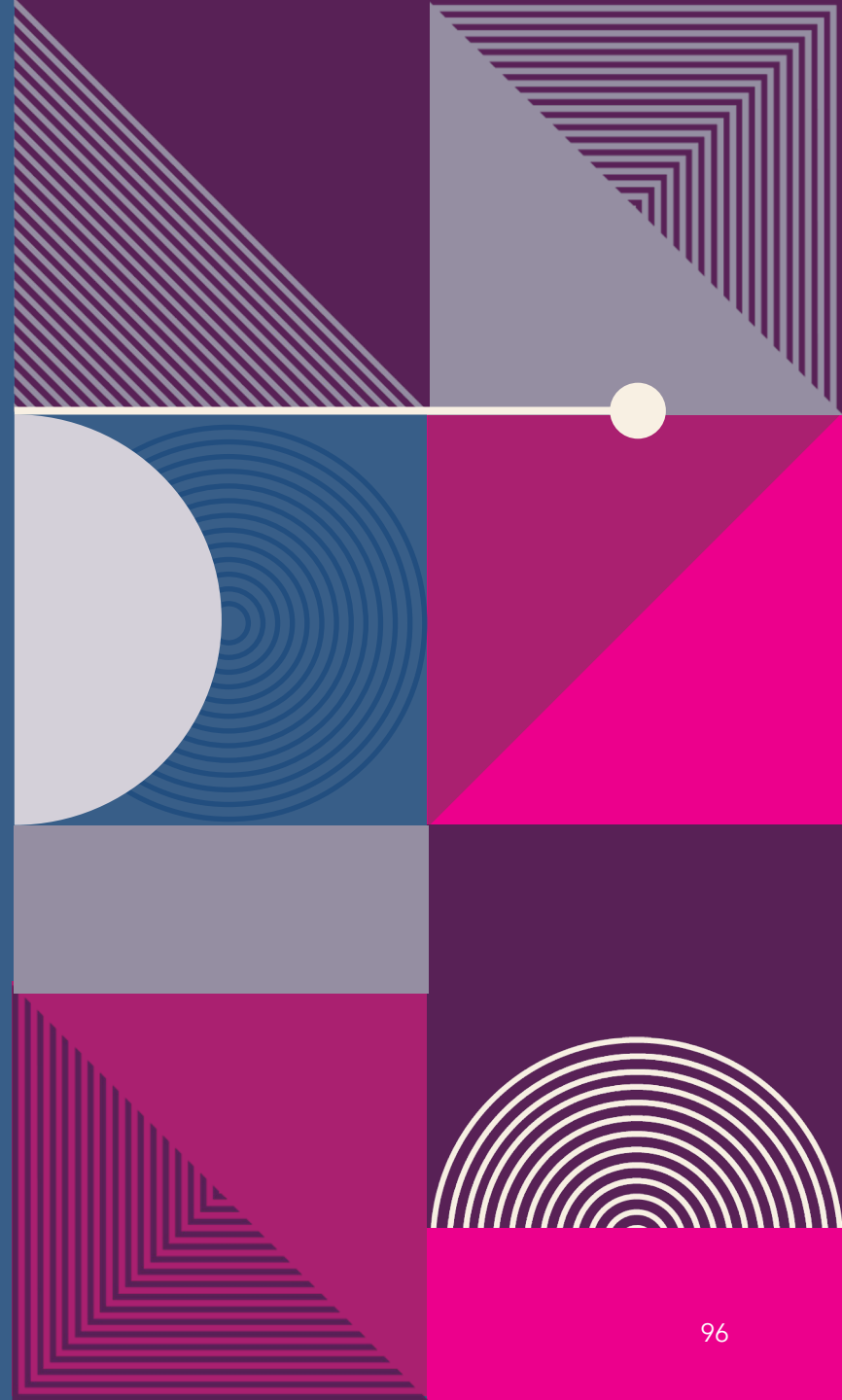
CARDIAC AMYLOIDOSIS
EMERGING DISEASE MODIFYING TREATMENT – TTR DEPLETERS

- Current therapies (stabilizers/silencers) slow progression
- TTR Depleters aim to reverse organ damage
- Monoclonal antibody therapy
  - binds to misfolded TTR amyloid fibrils
  - triggers immune mediated amyloid deposit removal via phagocytes
- Ongoing phase III clinical trials
  - Target both ATTRwt and ATTRv

Garcia-Pavia P et al. N Engl J Med. 2023 Jul 20;389(3):239-250.

KEY TAKEAWAYS

- Variety of important pharmacotherapeutic advancements impending, building on years of research
- Patient populations benefitting from GLP-1, PCSK-9, and disease-modifying amyloid therapy medications are expanding, including treatment options for
  - Primary obesity or overweight diagnosis
  - Atherosclerosis without prior stroke or MI
  - Disease-state revolutionizing therapy for ATTR cardiomyopathy



THE BLEEDING HEART'S CUTTING EDGE: PHARMACOLOGIC ADVANCEMENTS IMPACTING CARDIAC MEDICINE

Justin Culshaw PharmD BCCCP
Brown University Health – Rhode Island Hospital

MENOPAUSE AND PERIMENOPAUSE CARE FOR THE PRIMARY CARE PROVIDER

Michelle L. Blade Mello DNP, FNP-C, CNM

CONFLICT OF INTEREST

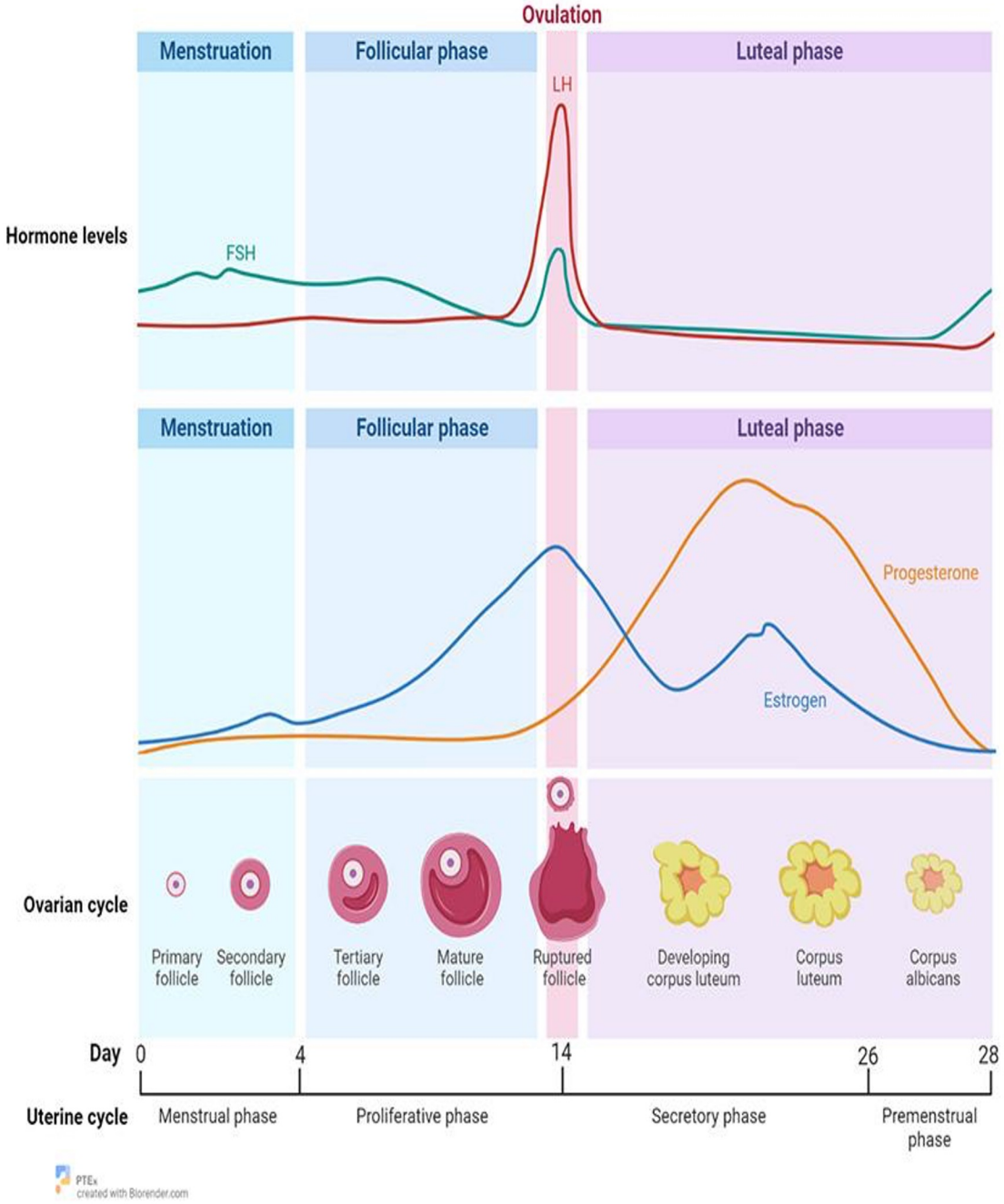
- Organon speaker – training providers on the insertion/removal of Nexplanon birth control implant

OBJECTIVES

- Define perimenopause and menopause
- Differentiate normal perimenopausal/menopausal changes from red-flag symptoms
- Compare hormonal pharmacologic options
- Recognize and manage genitourinary syndrome of menopause (GSM)

OBJECTIVES

- **Apply current evidence-based guidelines**
- **Develop an individualized treatment plan**
- **Identify clinical scenarios that require consultation or referral**
- **Enhance confidence**



OVARIAN HORMONES OF THE MENSTRUAL CYCLE

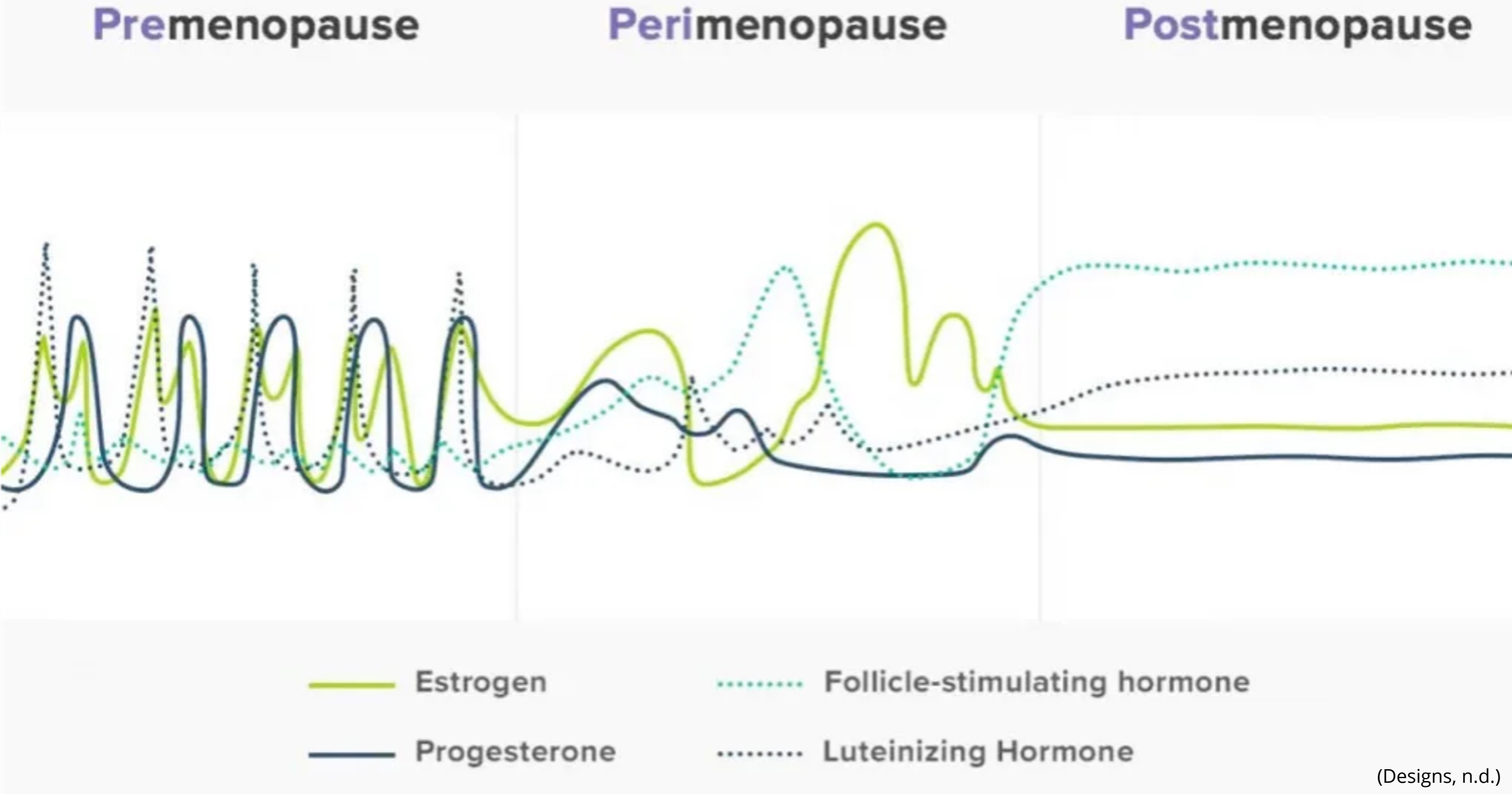
Follicle-Stimulating Hormone (FSH): Produced by the pituitary gland, it stimulates the growth of ovarian follicles during the follicular phase

Luteinizing Hormone (LH): Also from the pituitary, a surge in LH triggers ovulation midcycle

Estrogen: Produced by the developing follicle, it stimulates the proliferation of the endometrium. High levels of estrogen trigger the LH surge.

Progesterone: Produced by the corpus luteum, it makes the uterine lining receptive to implantation and supports early pregnancy

(Luteinising hormone (LH) | Pathology Tests Explained. Fig. 1. 2023)


Premenopause
Perimenopause
Postmenopause
Estrogen
Progesterone
Follicle-stimulating hormone
Luteinizing Hormone

(Designs, n.d.)

WHAT IS THE DIFFERENCE BETWEEN PERIMENOPAUSE AND MENOPAUSE?

- **Perimenopause** – begins up to 10 years before menopause, with fluctuating estrogen/progesterone, irregular menses, vasomotor symptoms, and still can ovulate.
  - Can begin in 30's and 40's

- **Menopause** – no menses for 12 consecutive months
  - Low estrogen/progesterone, and no ovulation

Perimenopause VS Menopause

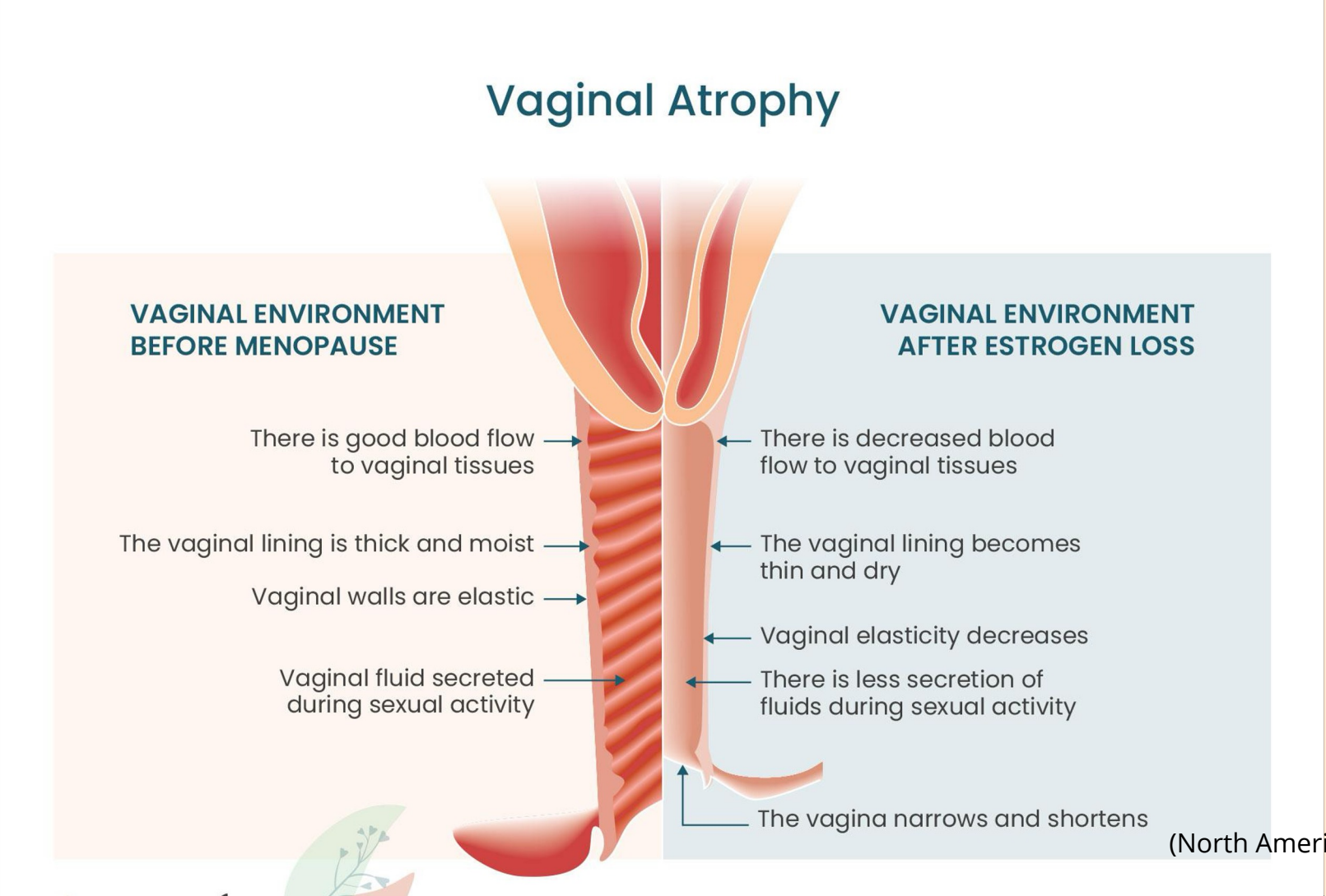
SYMPTOMS	PERIMENOPAUSE	MENOPAUSE
Period changes	Irregular periods	No periods
Hot flashes & night sweats	Yes	Yes
Vaginal dryness	Yes	Yes
Sleep disturbances	Yes	Yes
Changes in sexual desire	Yes	Yes
Mood swings	Yes	Yes
Headaches & brain fog	Yes	Yes
Painful sex	Yes	Yes
Urinary changes	Yes	Yes

(ACOG, 2025)
(Dalal & Agarwal,fig 1, 2015)
(Menopause Basics | Office on Women's Health, 2025)
(UpToDate, 2026)

Perimenopause Stages & Symptoms

SYMPTOM/CHANGE	VERY EARLY PERIMENOPAUSE	EARLY PERIMENOPAUSE	LATE PERIMENOPAUSE	MENOPAUSE TRANSITION
CYCLE REGULARITY	Regular cycles; PMS changes	Irregular cycles; variable timing	Skipping cycles; heavy bleeding	Absent cycles; menopause
SLEEP DISTURBANCE	Intermittent insomnia; subtle changes	Night sweats; frequent insomnia	Pronounced sleep disruption	Sleep disturbance wanes, but persists
MOOD CHANGES	Intensified PMS/mood swings	Anxiety, irritability, emotional swings	Depression, mood instability peaks	Mood generally stabilizes
HOT FLASHES	Rare or mild	Occasional, increasing	Frequent, severe	Gradually diminish
BLEEDING PATTERNS	Heavier flow possible	Irregular, unpredictable bleeding	Heavy, prolonged, skipped cycles	Absent
JOINT PAIN	Rare; subtle aches	Emerging, variable	Common; pronounced	Could persist
ESTROGEN CHANGE	High, peaks normal; start fluctuating	Increasing variability; spikes & drops	Sharp decline; consistently lower	Stable low levels

GENITOURINARY SYMPTOMS OF MENOPAUSE (GSM)



(North American Menopause Society, 2022)
(*Vaginal Changes*, 2025)

EVOLUTION OF MHT

- 1942 - MHT gained FDA approval
- 1960’s – MHT became widely used
- Mid 1970’s – MHT was associated with increased endometrial cancer risk, which was found to be mitigated by the addition of progesterone in newer research. Progesterone was added, and MHT use continued.
- 2002 and 2004 - Administrators of a study known as the Women’s Health Initiative (WHI) halted their research, announcing the risks outweighed the benefits of MHT.

(Makary et al., 2025)

WHI STUDY

- This estrogen plus progestin study was a randomized, double-blind, placebo-controlled primary prevention trial designed to test the effects of hormone therapy on chronic disease. **This was an estrogen-only study**
- **Target Population:** 27,347 postmenopausal women, aged 50–79 years, with or without a uterus.
- **Average Age: 63.2 years.**
- **Time Since Menopause: The average participant was more than a decade past the onset of menopause**, with many initiating hormone therapy long after symptoms ceased.
- **Setting:** 40 U.S. clinical centers.

(Marson et al., 2013)
(Makary et al., 2025)

WHI STUDY RESULTS

- **E + P arm:**
  - Conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day)
  - **Stopped in 2002, approx. 5 years after starting, due to a significant, unexpected rise in invasive breast cancer, CHD, CVA, and PE.**

- **E ONLY arm:**
  - Conjugated equine estrogens (CEE, 0.625 mg/day)
  - **Stopped in 2004, approx. 7 years after starting, due to an increased risk of CVA.**

- **Benefits recognized:** Improved bone health, reduced fracture risk, and no increased CHD risk when started between 50-59 and within 10 years of menopause

(Makary et al., 2025)

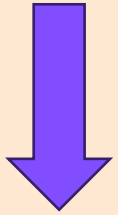
WHI STUDY FLAWS

- **Improper Age Demographic:** Older demographic.
- **The Timing Hypothesis:** Started too late.
- **Limited Hormone Types:** One type of high-dose CEE and MPA
- **Use of Oral vs. Transdermal Methods:** Only oral was tested.
- **Misleading Risk Reporting:** The results were reported in terms of **relative risk** rather than **absolute risk**, which exaggerated the perception of danger for the general public.

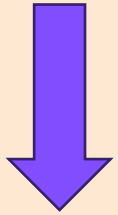
(Makary et al., 2025)

EVOLUTION OF MHT

- WHI scare – don’t use hormones, it’s dangerous



- Lowest dose, shortest time



- 2022 Menopause guidelines - Shared decision making

UPDATE OF BLACK BOX WARNINGS ON HORMONE REPLACEMENT THERAPY – NOVEMBER 2025

The FDA's hormone therapy label updates include

- **Removal of boxed warnings** (cardiovascular disease, stroke, breast cancer, probable dementia), except for the boxed warning in systemic estrogen labels for endometrial cancer with unopposed estrogen in women with a uterus.
- **Removal of the recommendation to prescribe hormone therapy at the lowest effective dose for the shortest duration**—treatment decisions are individualized and fall within the clinical judgment of a clinician in discussion with a patient.
- **Tailored safety information**: Instead of applying identical class-based language across all hormone therapy labels, safety data will be revised to reflect risks most relevant to each specific type of hormone therapy product (eg, combined estrogen plus progestogen vs estrogen alone).

(Makary et al., 2025)

UPDATE OF BLACK BOX WARNINGS ON HORMONE REPLACEMENT THERAPY – NOVEMBER 2025

The FDA's hormone therapy label updates include

- For the topical **vaginal estrogen-only drug label**, the emphasis is on the safety findings most relevant to topical vaginal use and not the broader warnings associated with systemic exposure.
- **Timing information for systemic hormone therapy**: Labels will include updated guidance on initiating treatment in women younger than 60 years or within 10 years of menopause onset to optimize the benefit-risk balance.

(Makary et al., 2025)

BENEFITS OF MHT

Estrogens

- **Vasomotor symptom relief**
- **Decrease in GSM symptoms**
- **Bone loss prevention**
- **Ease mood swings, irritability, “brain fog”**
- **may improve heart health, maintain blood vessel elasticity, and lower type 2 diabetes risk** (If started within 10 years of menopause)

Progestins

- **Uterine protection – main benefit**
- **Improved sleep and reduced anxiety**
- **Vasomotor symptom relief**
- **Bone loss prevention**
- **Cardiovascular health**

(North American Menopause Society, 2022)

RISKS AND SAFETY CONSIDERATIONS

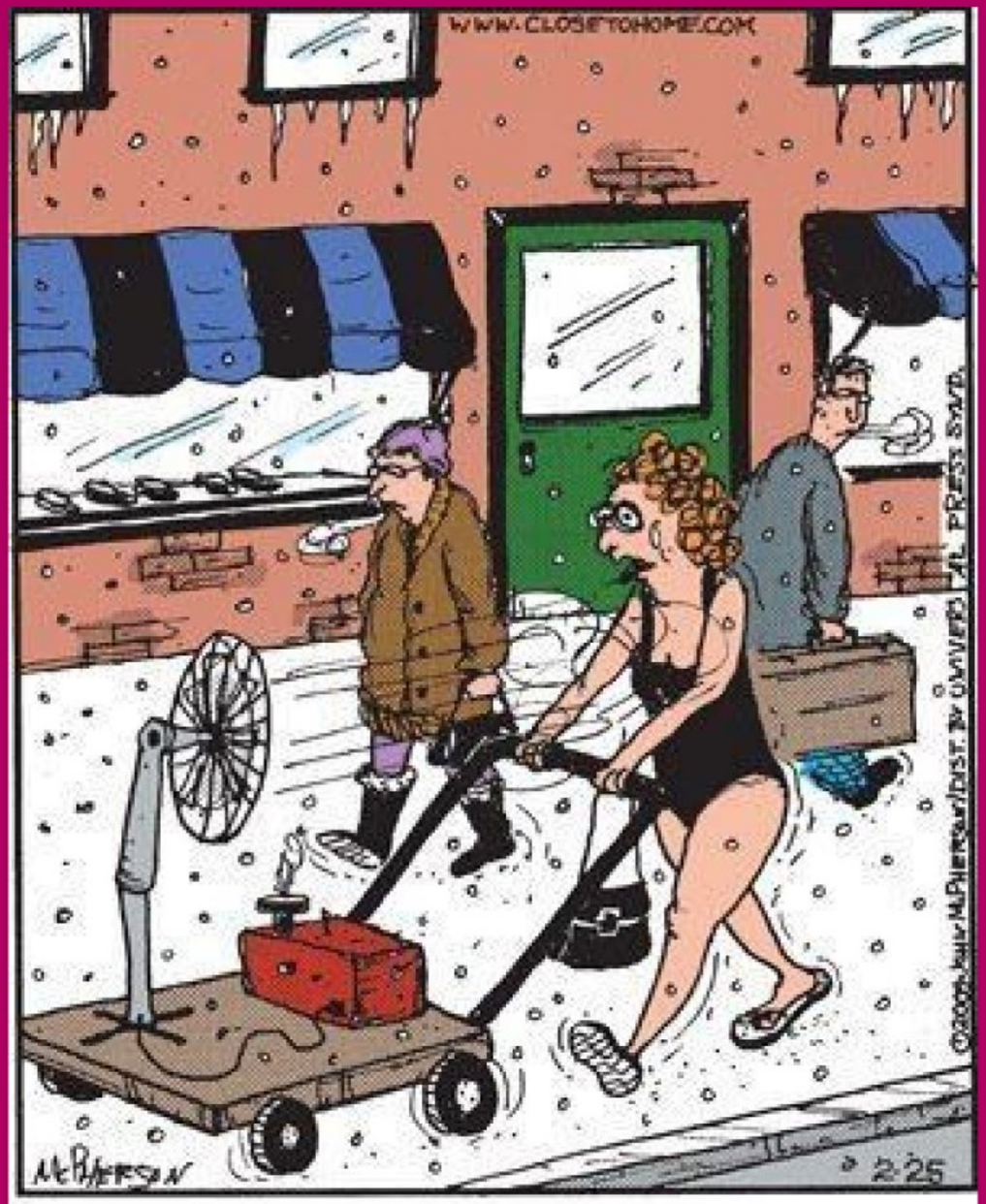
Estrogens

- **Cardiovascular disease**
- **Probable dementia (when initiated 65 or older)**
- **Malignant neoplasms**
- **Endometrial Cancer (unopposed)**
- Increased risk of hypercalcemia in women with breast cancer or bone metastases
- Risk of estrogen-induced hypocalcemia with preexisting hypoparathyroidism (may need to increase thyroid hormone doses if taken concomitantly
- Increased risk of gallbladder disease
- *Exacerbation of endometriosis***
- Increase risk of DVT

Progestins

- **Cardiovascular disease**
- **Probable dementia (when initiated 65 or older)**
- **Malignant neoplasms**
- May elevate blood pressure
- Severe hypertriglyceridemia that may lead to pancreatitis
- Impaired liver function and/or cholestatic jaundice – affects metabolism
- *Fluid retention may occur***
- *May cause transient dizziness and drowsiness***

(North American Menopause Society, 2022)



Kathy's hot flashes were becoming severe.

CASE STUDY 1 - KATHY

59 y/o who wants to talk about menopause care.

She entered menopause at 50 y/o, and HRT was discouraged from considering hormones at that time.

Friends are talking about how great HRT is, and she wants to explore treatment.

Having night sweats, poor sleep quality, joint stiffness, and low libido.

PMHx HTN, IFG. No Thromboembolism.

PSHx: None.

1st degree relative with Breast Cancer.

TREATMENT APPROACH – STEPWISE IMPLEMENTATION

- First visit - start with patient education and goals assessment
- What does she care about? What does she consider a win? What are her fears? Does she want fewer UTIs? Less dyspareunia and vaginal dryness? Less hot flashes? Osteoporosis prevention?
- How does she like to learn? Books, Instagram, podcasts, YouTube… Give homework – encourage research.
  - Menopause.org

TREATMENT APPROACH – STEPWISE IMPLEMENTATION

Prescribe vaginal tx for GSM

	Composition	Mechanism of Action
CEE	Mixture of equine estrogens (estrone, equilin)	Directly activate estrogen receptors to improve lubrication and tissue thickness
Estradiol		Directly activate estrogen receptors to improve lubrication and tissue thickness
DHEA	A prohormone that acts locally, converting into testosterone and estrogens	Because it is converted into both estrogens and testosterones, it may improve tissue integrity and sexual response better than estrogen alone.

Preparation		United States trade name	Available strength(s)	Suggested regimen
Estrogens				
Conjugated estrogen	Vaginal cream	Premarin	0.625 mg conjugated estrogens per g of cream	0.5 g of cream intravaginally administered once daily for 2 weeks, then reduce to twice weekly
Estradiol	Vaginal cream	Estrace	100 mcg estradiol per g of cream	0.5 g of cream intravaginally administered once daily for 2 weeks, then reduce to twice weekly
	Vaginal Insert	Imvexxy	4 mcg or 10 mcg estradiol per vaginal insert	Insert 1 softgel intravaginally once daily for 2 weeks, followed by twice weekly.
		Vagifem, Yuvafem	10 mcg estradiol per vaginal insert	Insert 1 tablet intravaginally once daily for 2 weeks, followed by twice weekly.
	Vaginal Ring	Estring	7.5 mcg estradiol per day, released over 90 days	Insert ring in vagina, remove and replace every 90 days
DHEA				
Prasterone	Vaginal Insert	Intrarosa	6.5 mg prasterone per vaginal insert	Insert 1 suppository intravaginally once daily

CASE STUDY 1 - KATHY

Visit 1: Education/goal setting (fewer hot flashes and better sleep). Wants to avoid osteoporosis.

Refer to Menopause.org

Rx given: Vaginal estrogen: Vagifem 10 mcg 2 x a wk after a 2 wk daily loading dose.

Visit 2 (2-3 months later): assess vaginal estrogen (doing well – less dryness).

Looked at Menopause.org, talked to her friends, wants to stop her hot flashes, and is afraid of osteoporosis.

TREATMENT APPROACH – STEPWISE IMPLEMENTATION

Systemic Hormone Therapy

	Composition	Why?
Estradiol		Structurally identical to the main product of the premenopausal ovary
Progestogens	Micronized progesterone **(bioidentical)**	Added to all women with an intact uterus to prevent endometrial hyperplasia (which can occur in as little as 6 months of unopposed estrogen)

IS MY PATIENT A CANDIDATE FOR MENOPAUSAL HORMONE THERAPY (MHT)?

Safe option for healthy, symptomatic women who are within 10 years of menopause onset or younger than age 60 years and who do not have contraindications to MHT.

Things to consider:

- Patient age
- Impact of symptoms on quality of life
- The patient's calculated risks for cardiovascular disease and breast cancer

IS MY PATIENT A CANDIDATE FOR MENOPAUSAL HORMONE THERAPY (MHT)?

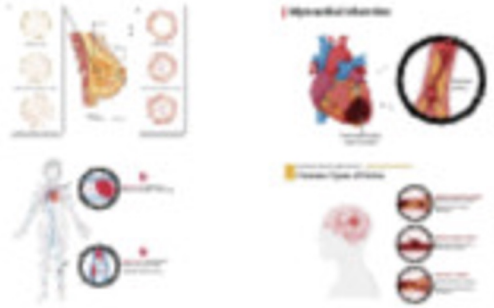
CVD Risk Assessment

10-year CVD risk	Years since menopause onset
	< 10 years
Low (<5%)	MHT ok
Moderate (5 to 10%)	MHT ok (choose transdermal)
High(>10%)	Avoid MHT

https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/

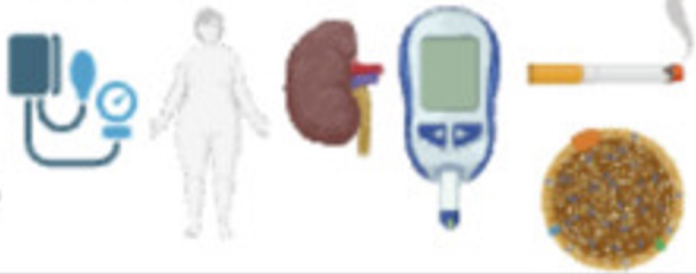
(Zoee D'Costa et al., 2025)

High Risk Groups, consider non MHT



Known ASCVD or ASCVD 10 year risk ≥7.5%
PREVENT 10 or 30 year risk ≥7.5%
Subclinical Atherosclerosis/PAD
SCAD
Stroke, TIA
Breast CA, Estrogen sensitive endometrial CA
Unexplained temporary vaginal bleeding
Menopause >10 years ago or age >60

Intermediate Risk Groups, control CV risk factors before initiation of HT



ASCVD 10 year risk 5-7.4%
PREVENT 10 or 30 year risk 5-7.4%
Metabolic Syndrome
CKM stage 1-2
SLE
Migraines with Aura

Low Risk Groups, may initiate HT

ASCVD 10 year risk <5%
PREVENT 10 or 30 year risk <5%
CKM Stage 0
Menopause <10 years, age <60
CAC score = 0

(Dastmalchi et al., 2025)

IS MY PATIENT A CANDIDATE FOR MENOPAUSAL HORMONE THERAPY (MHT)?

Breast Cancer Risk Assessment

Risk Category	5-year NCI or IBIS Breast Cancer Risk Assessment (%)	Suggested Approach
Low	<1.67	MHT ok
Intermediate	1.67 to 5	Caution
High	> 5	Avoid

https://bcrisktool.cancer.gov/

CASE STUDY 1 - KATHY

ASCVD 2.9%. **NCI 5-year risk 2.3%**

****Risk/Benefit discussion****

Desires transdermal estrogen and progesterone

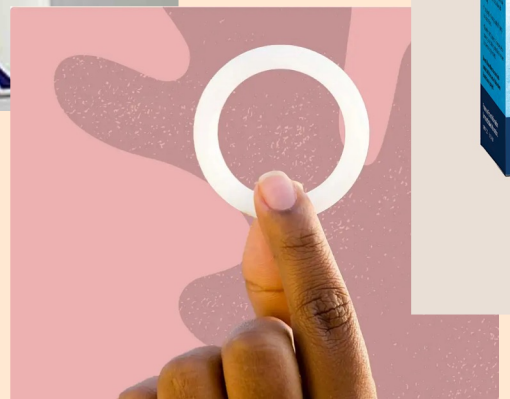
ESTROGEN PREPARATIONS - PATCHES

The goal is to start around 0.05 mg; lower doses will not provide symptom relief.

Drugs and U.S. Brand Names	Available strengths
Estradiol patches	
Alora (twice weekly)	0.025, 0.075, 0.1 mg per day
Minivelle, Lyllana¶ (twice weekly)	0.025, 0.0375, 0.05, 0.075, 0.1 mg per day
Vivelle-Dot, Dotti¶ (twice weekly)	0.025, 0.0375, 0.05, 0.075, 0.1 mg per day
Climara¶ (weekly)	0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg per day
Menostar (weekly)	0.014 mg per day
Estradiol-progestin patches	
Combi-Patch (twice weekly)	0.05 mg estradiol/0.14 mg norethindrone, 0.05 mg/0.25 mg per day
Climara Pro (weekly)	0.045 mg estradiol/0.015 mg levonorgestrel per day

ESTROGEN PREPARATIONS - GEL, SPRAY, VAGINAL RINGS

The goal is to start around 0.05 mg; lower doses will not provide symptom relief.



Drugs and US Brand Names	Available Strengths
Topical gel	
EstroGel 0.06%	0.75 mg estradiol per pump
Elestrin 0.06%	0.52 mg estradiol per pump
Divigel 0.1%	0.25, 0.5, 1 mg estradiol per pouch
Topical spray	
EvaMist	1.53 mg estradiol per spray
Intravaginal rings	
Femring	0.05 mg estradiol per day over 3 months, 0.1 mg estradiol per day over 3 months

Drugs and US Brand Names	Available Strengths
Oral estradiol*	
Estrace¶	0.5, 1, 2 mg
Oral esterified estrogen*	
Menest	0.3, 0.625, 1.25 mg
Oral CEEs*	
Premarin	0.3, 0.45, 0.625, 0.9, 1.25 mg
Oral estrogen-progesterone combination	
Bijuva	0.5 mg estradiol/100 mg progesterone, 1 mg/100 mg
Oral estrogen-progestin combinations	
Activella, Amabelz, Mimvey¶	0.5 mg estradiol/0.1 mg norethindrone acetate, 1 mg/0.5 mg
Angeliq	0.5 mg estradiol/0.25 mg drospirenone, 1 mg/0.5 mg
Prempro$^{\Delta}$	0.3 mg CEE/1.5 mg medroxyprogesterone, 0.45 mg/1.5 mg, 0.625 mg/2.5 mg, 0.625 mg/5 mg
Fyavolv, Jinteli¶	2.5 mcg ethinyl estradiol/0.5 mg norethindrone acetate, 5 mcg/1 mg
Oral CEEs and bazedoxifene	
Duavee	0.45 mg CEE/20 mg bazedoxifene

PROGESTERONE

(Joo et al., 2021)
(UpToDate, 2026)

Drugs and US Brand Names	Available Strengths
Micronized Progesterone (Preferred)	
Crinone	200 mg once daily for 12 days each month OR 100 mg once daily continuously
Endometrin	
Prometrium	
Medroxyprogesterone Acetate	
Provera	5-10 mg/day for 12 days each month OR 1.25-2.5 mg daily continuously
Levonorgestrel-releasing intrauterine device (LNG-IUS)	
Mirena, Liletta (52 mg)	Uterine protection for 5 years

CASE STUDY 1 - KATHY

She wants estrogen/progesterone patch, but it is too expensive with her insurance

– rx changed to Climara 0.05 mg weekly (originally cut in half to avoid breast tenderness) and Prometrium 100 mg/day daily.

Visit 3 (2-3 months later): Hot flashes have improved, but not gone. Increase Climara to 0.06 mg weekly, continue progesterone 100 mg/day continuously.

Visit 4 (2-3 months later): Hot flashes gone, sleep improved. Libido is still low.

TREATMENT APPROACH – STEPWISE IMPLEMENTATION

Testosterone Therapy

Preparation	Dose
Topical	
1% Gel (eg, AndroGel 1%,* Testim, Vogelxo)	5 mg applied daily to the thigh/calf

(Parish et al., 2021)

TESTOSTERONE THERAPY

Consider if, after 4-6 months, libido is still low.

- Lima bean-sized amount on calf/ankle daily
- 1 tube should last 7-10 days
- Reasonably affordable – a 30-tube box (10-month supply) is less than $100 on GoodRx.

(Scott & Newson, 2020)

CASE STUDY 1 - KATHY

Visit 4: Rx testosterone 1%, 5 mg topically daily.

Visit 5 (6 months later):

Hot flashes resolved

Dyspareunia gone

Sexual desire improved

“I feel like myself again.”

CASE STUDY 2 - MELISSA

48 y/o who wonders if she is in perimenopause.

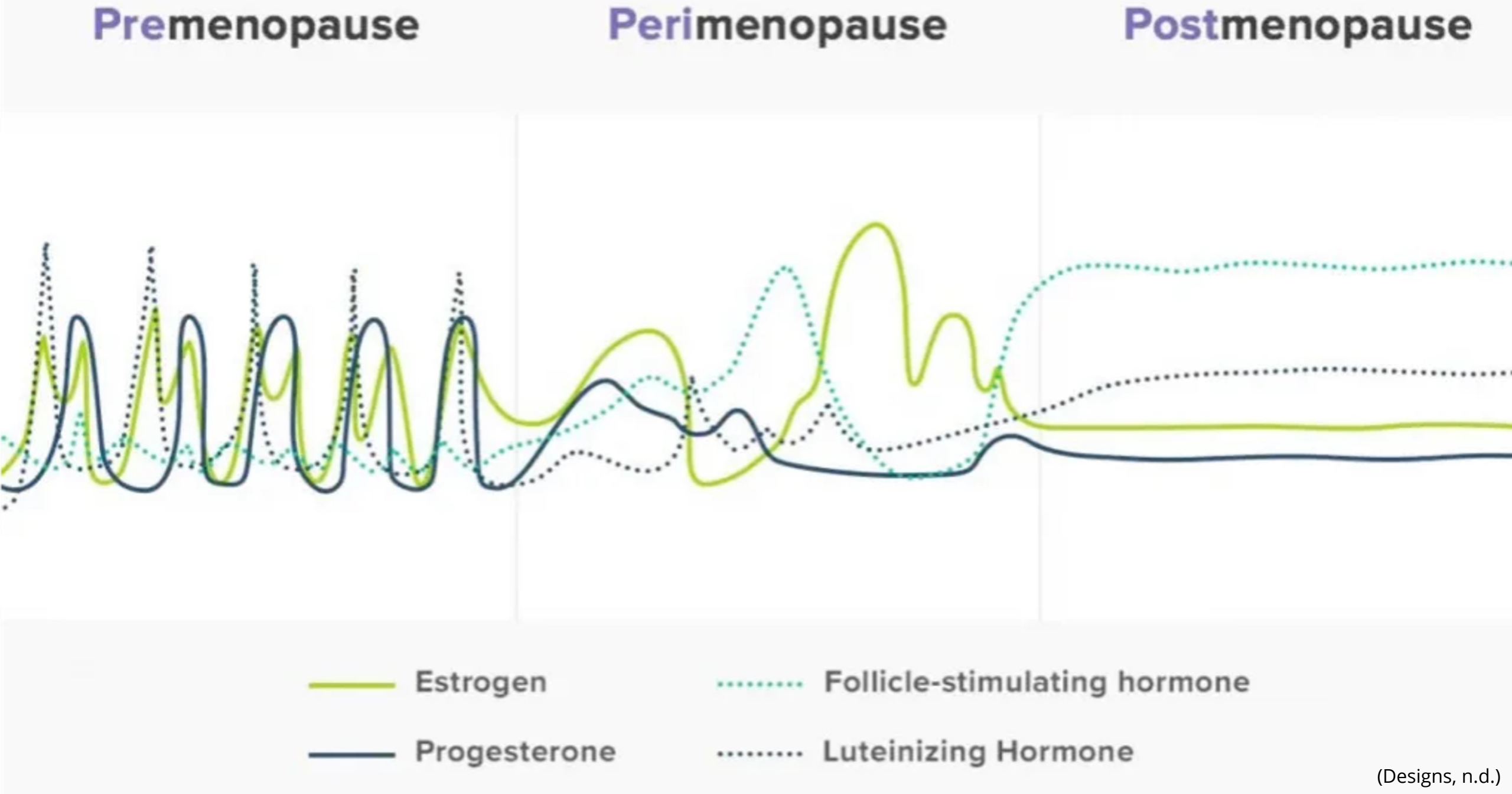
She has irregular, heavy menses and insomnia. She follows Mary Claire Haver, Tamsen Fadal, and Dr. Caissa Troutman on Instagram and at Midlife ReMDy. She wonders if hormones will help.

Having hot flashes, poor sleep quality, and joint stiffness.

PMHx: Depression and obesity. no thromboembolism.

PSHx: None.

FHx: Mo: hypothyroidism and HTN, Fa: HTN and DM.


Premenopause
Perimenopause
Postmenopause
Estrogen
Progesterone
Follicle-stimulating hormone
Luteinizing Hormone

(Designs, n.d.)

PERIMENOPAUSE APPROACHES

Status Quo	Birth Control “Elegant”	MHT “Gas Tank”
No Treatment – “ride out the waves”	Eliminate the highs/lows – shut down the ovaries and add back hormones	Will only eliminate the lows, and not stop the highs – will not let the gas tank get below “half a tank”

FINAL TIPS & TAKEAWAYS

- MHT includes shared decision-making.
- Vaginal estrogen for GSM is safe for everyone – start early, and they can take long term
- Transdermal MHT are 1st line, as they avoid the hepatic first-pass metabolism
- Work up abnormalities before starting MHT
- Take the easy ones – there are about 10 million women experiencing menopausal symptoms each year, and 4100 Menopause Society Certified Practitioners
- When in doubt – refer!
- Keep learning –
  - Menopause.org
  - Review the 2022 Menopause Society Hormone Therapy Guidelines

"Night sweats and hot flashes are nature's way of lowering your heating bill so you can save more money for your retirement."

REFERENCES

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THANK YOU

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NURSE PRACTITIONER

RI

ALLIANCE OF RHODE ISLAND

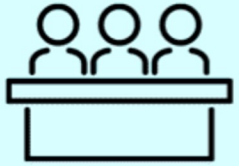
LEGISLATIVE UPDATE

DENISE COPPA, PHD, APRN-CNP, FNP-C, FAAN

ANNE NEUVILLE, DNP, APRN-CNP, FNP-BC

THE OFFICE

Step 1:
Bill is drafted.



Step 2:
Bill is introduced.

Step 3:
The Bill goes to committee. Members of the committee may hold hearings to better understand the implications of the bill, and the bill may be considered "dead" if the committee does not act on the bill.

Step 4:
The Subcommittee considers the bill. Subcommittees have specializations on a certain topic and may decide to conduct their own studies and hold their own hearings. The subcommittee must hold a vote to refer a bill back to the full committee.

Step 5:
The Committee marks up the bill. Committee members may propose amendments to the bill and must vote to refer a bill back to the full chamber of Congress.

Step 6:
The full chamber votes on the bill. There is additional debate about the bill, and the full chamber must vote to approve any amendments. The bill is then passed or defeated by the members voting.

Step 7:
The bill is passed and sent to the other chamber. The bill follows the same route through committees and finally to the floor. The chamber may approve the bill as received, reject it, ignore it, or change it. Congress may form a conference committee to resolve differences between the House and Senate versions of the bill. The bill dies if the conference committee is unable to reach an agreement. If the conference committee reaches an agreement, the House and Senate vote to approve a conference report.

Step 8:
The bill passes both chambers of Congress goes to the president. Once the president signs the bill, it becomes law. If the President vetoes a bill, Congress may attempt to override the veto. If both chambers of Congress pass the bill again by a two-thirds majority, the bill becomes law.

https://www.genome.gov/about-genomics/policy-issues/How-Bill-Becomes-Law

- HOW THE BILL BECOMES A LAW

ri state legislature website

SENATE BUNDLES HEALTH CARE BILLS

PATIENTS & PROVIDERS

- S 3059: PBM OVERSIGHT
- S 2563: study cost effectiveness of Medicaid drugs
- S 3060: BH covers 7 days of post hosp care w/o prior auth
- S 2379: vaccination schedule set by DOH can be followed by director

HEALTH CARE WORKFORCE

- S 3062: create loan repayment for primary care grads who stay
- S3064: funding for URI med school
- S 3057: establish primary care commission to support workforce retention

S 2806 EQUAL PAY FOR HEALTH CARE WORKERS

- **Whenever any policy of health insurance provides for reimbursement for any service which is within the lawful scope of practice of a duly licensed and certified nurse practitioner, as defined in § 5-34-3, including prescribing or dispensing drugs, a primary care or mental health service, provided by a licensed physician, the insured under the policy is entitled to reimbursement for such service, whether it is performed by a physician licensed by the board of medical licensure and discipline or by a duly licensed nurse practitioner**
- **WORKING ON SISTER BILL IN HOUSE**

S 2831/ H 7686 PRIMARY CARE TRAINING SITES PROGRAM
S 2118/ H7634 – NCQA certification

For the fiscal year 2026 and thereafter, the State of Rhode Island shall appropriate the sum of two million seven hundred thousand dollars ($2,700,000) to the primary care training sites program for the purpose of supporting its training for physicians, nurse practitioners and physician assistants, established pursuant to the provisions of this chapter. The funds appropriated under this section shall be administered by the department of health.

S 2033/ H 7185 PROTECTION OF HCP ACT

(a) Notwithstanding any other provision in this chapter to the contrary, the prescription label for medication abortion prescription drugs may include the name of the dispensing healthcare practice instead of the name of the dispenser.

(b) For purposes of this section, “medication abortion prescription drugs” means substances used in the course of medical treatment intended to induce the termination of a pregnancy including, but not limited to, mifepristone and misoprostol

H 7634 MENTAL HEALTH LAW

- Nothing contained herein shall be deemed to contravene the provisions of § 5-37-14, and no physician or ~~surgeon~~ advanced practice registered nurse (APRN) licensed to practice in this state, or having a privilege to practice in this state, and having met the requirements either of the statute or of this chapter, shall be made to answer in any court for his or her participation in any proceeding under this chapter except upon a showing of actual fraud or gross, willful or wanton negligence; provided further, that no physician or ~~surgeon~~ APRN shall be made to answer in any court for any damage or injury to any person or thing arising out of a patient's enjoyment and/or exercise of rights protected by this chapter including, without limitation, discharge, where the enjoyment and/or exercise of the rights, or any of them, are in contravention of either the written orders or prescription or advice of a physician or ~~surgeon~~ APRN.

S 2111/ H 7278: Telemedicine

online adaptive interviews, remote patient monitoring devices, audiovisual communications, including the application of secure video conferencing or store-and-forward technology to provide or support healthcare delivery, which facilitate assessment, diagnosis, counseling and prescribing treatment, and care management of a patient's health care while such patient is at an originating site and the healthcare provider is at a distant site, consistent with applicable federal laws and regulations. "Telemedicine" does not include an email message or facsimile transmission between the provider and patient, or an automated computer program used to diagnose and/or treat ocular or refractive conditions.

H 7740 SEDATION BILL

- REINTRODUCED

Registered nurses (RNs) and advanced practice registered nurses (APRNs), other than licensed certified registered nurse anesthetists (CRNAs), as defined in this chapter, and RNs enrolled in a nurse anesthesiology training program approved by the Council on Accreditation of Nurse Anesthesia Educational programs (COA) or its predecessors or successors, shall not administer agents that are primarily used and classified as general anesthetics for minimal, moderate, deep sedation, or general anesthesia including, propofol, Etomidate, sodium thiopental, methohexital, or volatile gases (e.g. sevoflurane, isoflurane, desflurane), nor shall any RN or Non CRNA APRN administer or manage deep sedation or general anesthesia for any diagnostic, 12 therapeutic, or surgical procedures using any drug or medication.

WHEN YOU CAN’T GET TO THE OFFICE

- HOW TO SUBMIT WRITTEN TESTIMONY

Image generated by the author, by way of Chat CPT


THE UNIVERSITY OF RHODE ISLAND
Betty Rambur, PhD, RN, FAAN
Routhier Endowed Chair for Practice and Professor of Nursing
Vice Chair, Medicare Payment Advisory Commission
NOTE: Views presented are those of the author and do not necessarily represent those of any of her affiliations.

Disclosures

Dr. Rambur is the author of two textbooks, one on health care regulation and one on health care finance, economics and policy for nurses.

She is the Routhier Endowed Chair for Practice at the University of Rhode Island and Vice Chair of the Medicare Payment Advisory Commission.

Image generation citations/prompts reported at the end of this slide deck.

All views presented are hers and do not necessarily represent any of her affiliations.

Objectives—Following This Presentation Participants Will Be Able To

- Describe the impact of U.S. health care costs on societal and economic stability, and the overlooked distinction between insurance premiums and the true cost of care.

- Explain NP opportunities arising from new Medicare payment models

- Consider effect of market consolidation on NP practice options and patient access

- Assist patients' ability to distinguish between services offered within Medicare Advantage vs traditional Medicare

- Provide leadership in emerging state and federal cost and transparency initiatives, including the use of all-payer claims databases to improve benchmarking, accountability, and value-driven health care

- Define strategies for fostering NP entrepreneurship and innovation within current constraints

Window of Opportunity

Current era---focus on affordability

Reduction of impeding regulation

Market approaches

Value focus

NOTE: FEE-FOR-SERVICE IS NOT OUR FRIEND

AND, IT IS NOT OUR NATION'S FRIEND

Image by way of Chat GPT

IMPACTS

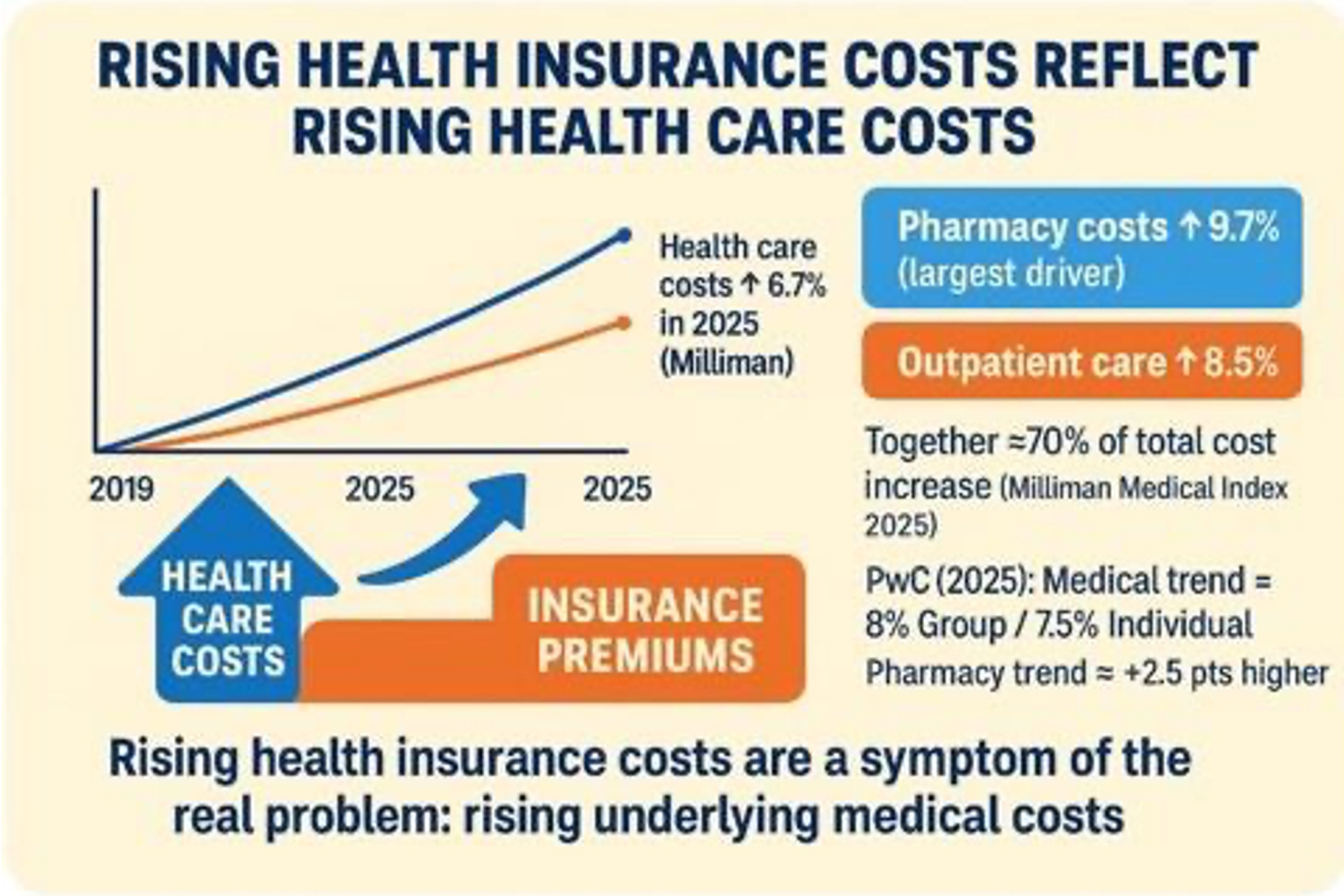
Individuals and Families

Taxpayers

Employers

Easy to blame insurance companies, BUT….

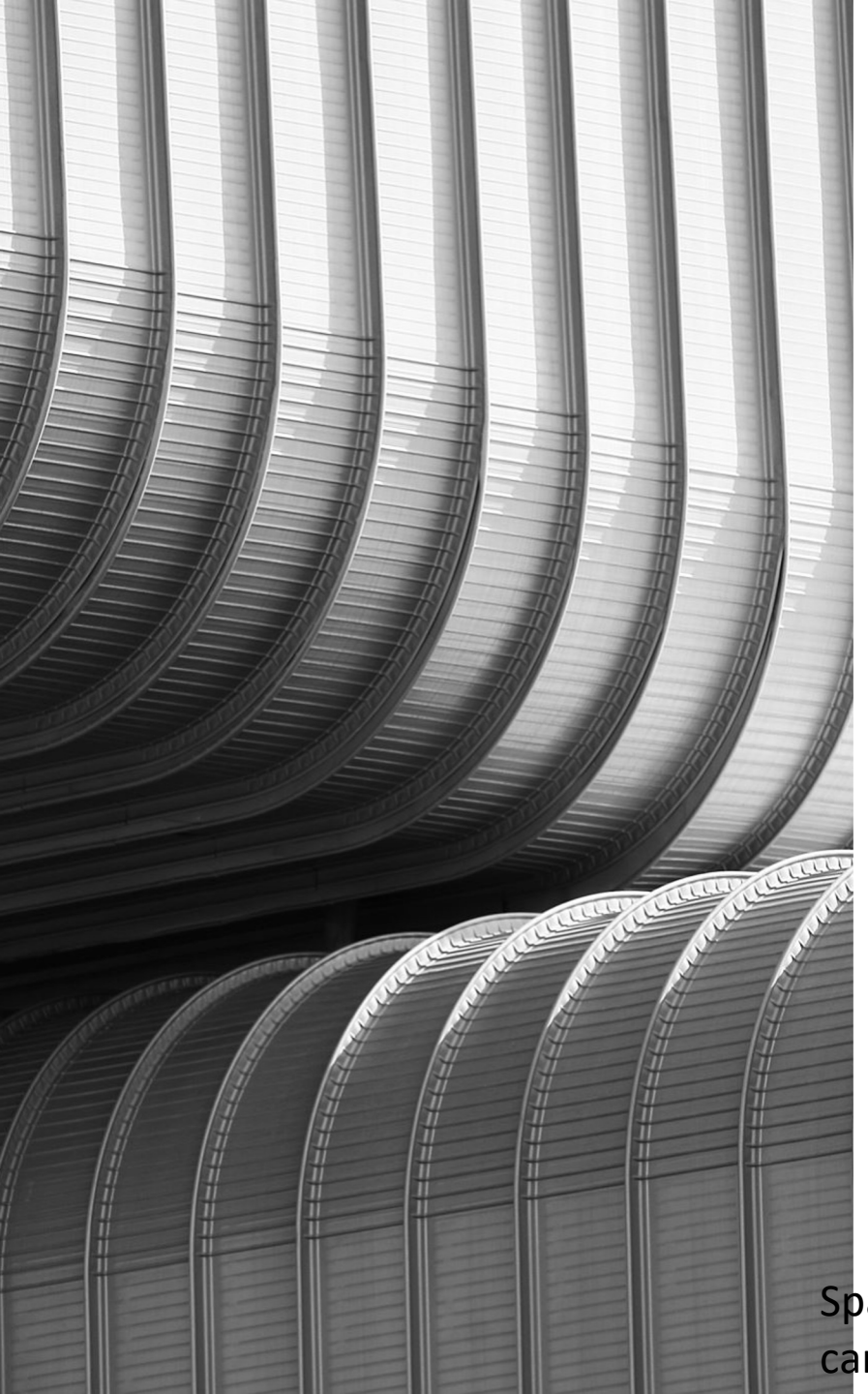
Request—can we help taxpayers and policy makers understand that the cost of health insurance is a reflection of health care costs



Everyone hates pre-authorization…but we (providers) have earned it!

Image by way of CHAT GPT

Image by way of CHAT GPT



COST of CARE

- Prohibitive for more & more Americans
- Nearly half say it difficult to afford health care
- Three in 10 say they or their family had problems paying for healthcare
- 36% of adults have skipped or postponed needed care because of costs

Sparks et al 2025. https:www.kff.org/health-costs/americans-challenges-with-health-care-costs/

Why Don't 'Traditional Market Forces' Improve Outcomes and Decrease Costs?

Health care is a vulnerable "purchase"—traditionally, 80% of health care costs driven by MD/DO decision-making

- Cost to the patient/taxpayers is revenue for providers

Costs are not transparent—neither is the value of the intervention

Most quality measure are weak, financial incentives don't align with societal need

Many barriers for "competitors" to enter the market-

Increasing market consolidation

National Health Expenditure $5.3 Trillion!!!!—And Growing

Drivers of Spending??

"It's the Prices, Stupid"—Reinhardt et al, 2023, reiterated in 2019 by Anderson et al

"It is Not the Prices, Stupid"—Chernow, 2026

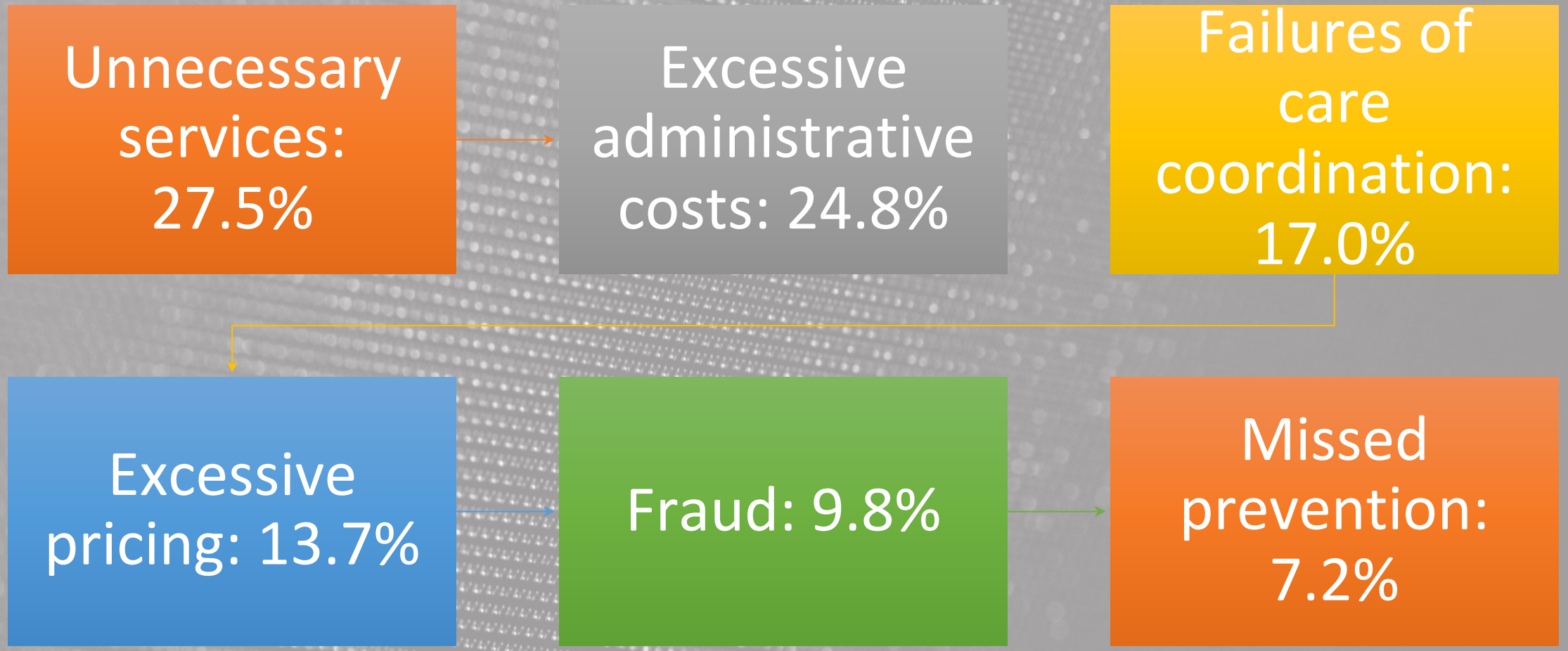
- Driver is the volume of services used &
- The intensity of those services

Chernow, M. (2026, January 15). Growth in national health expenditures: its' not the prices, stupid. *Health Affairs Forefront.* Doi:10.1377/forefront.20260113.24167

Fraud, Waste, and Abuse

THESE CONVERSATIONS WILL CONTINUE OR ACCELERATE…BUT THEY ARE NOT THE SAME THING!

US *National Health Expenditures* $5.2 trillion/year—1/3 of which is waste or low value care



Berwick, D. M., & Hackbarth, A. D. (2012). Eliminating waste in US health care. *JAMA*, *307*(14), 1513–1516. https://doi.org/10.1001/jama.2012.362

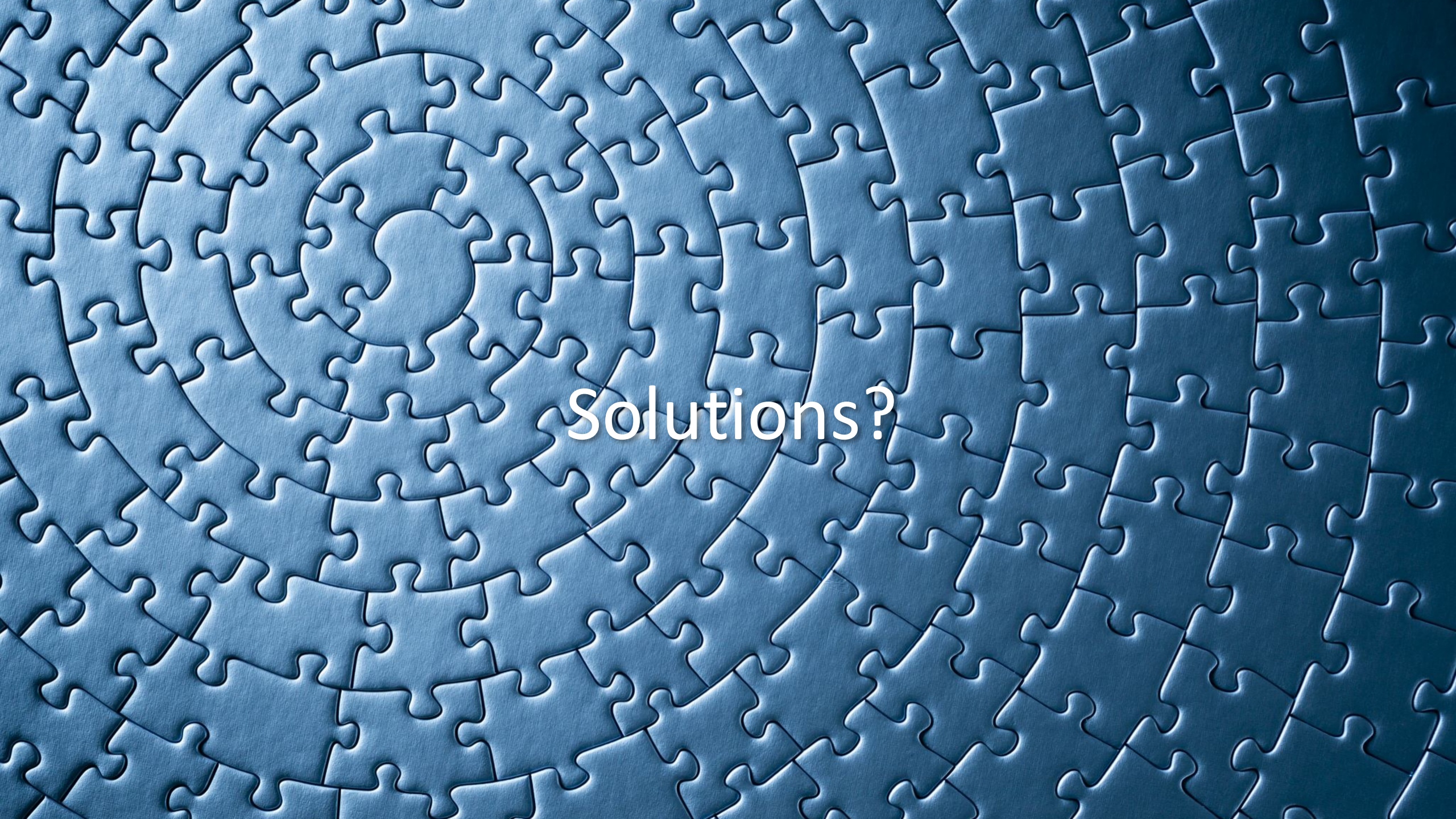
Image by way of CHAT GPT

The Paradox of Too Little and Too Much

Overtreatment causes harm—financially, physically, emotionally.

- **Cascade of tests**
- **Cascade of treatments**—some of which **cause harm**
- Turns people into patients sometimes "**victims**"

Image by way of CHAT GPT


Solutions?

Financing reform?

Image by way of Chat GPT

Financing : Committing to Health for All, Health Care for All, or Insurance for All?

SINGLE PAYER?
MULTIPAYER?
“SOCIALIZED MEDICINE?

- Financing reform vs payment reform
- But what do they “cover’”?
  - Cost sharing in most wealthy nations
  - Basic or comprehensive benefits?

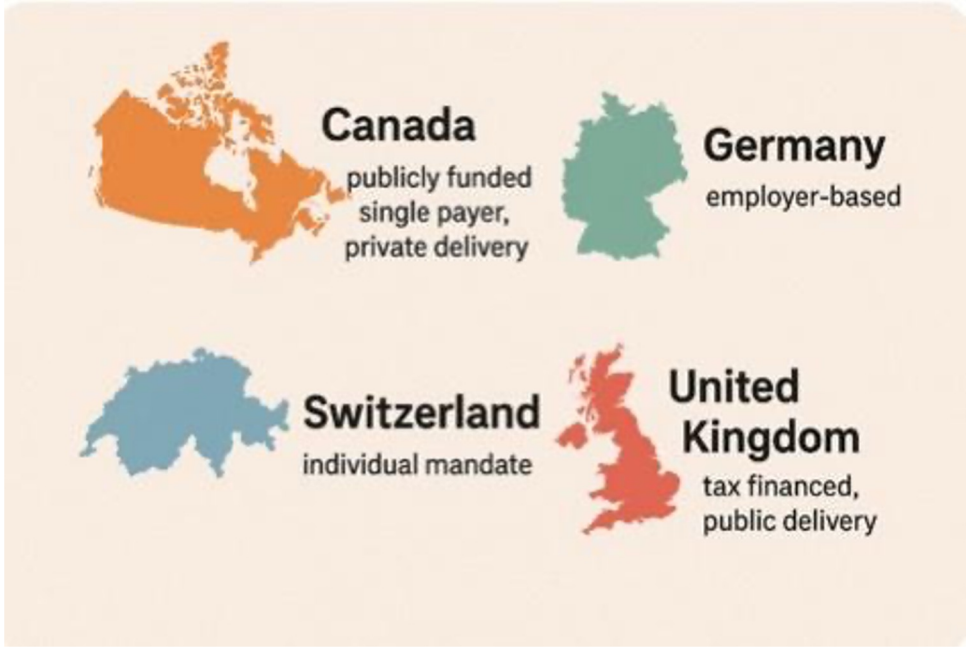


Image by way of CHAT GPT

Essential Strategies for NPs

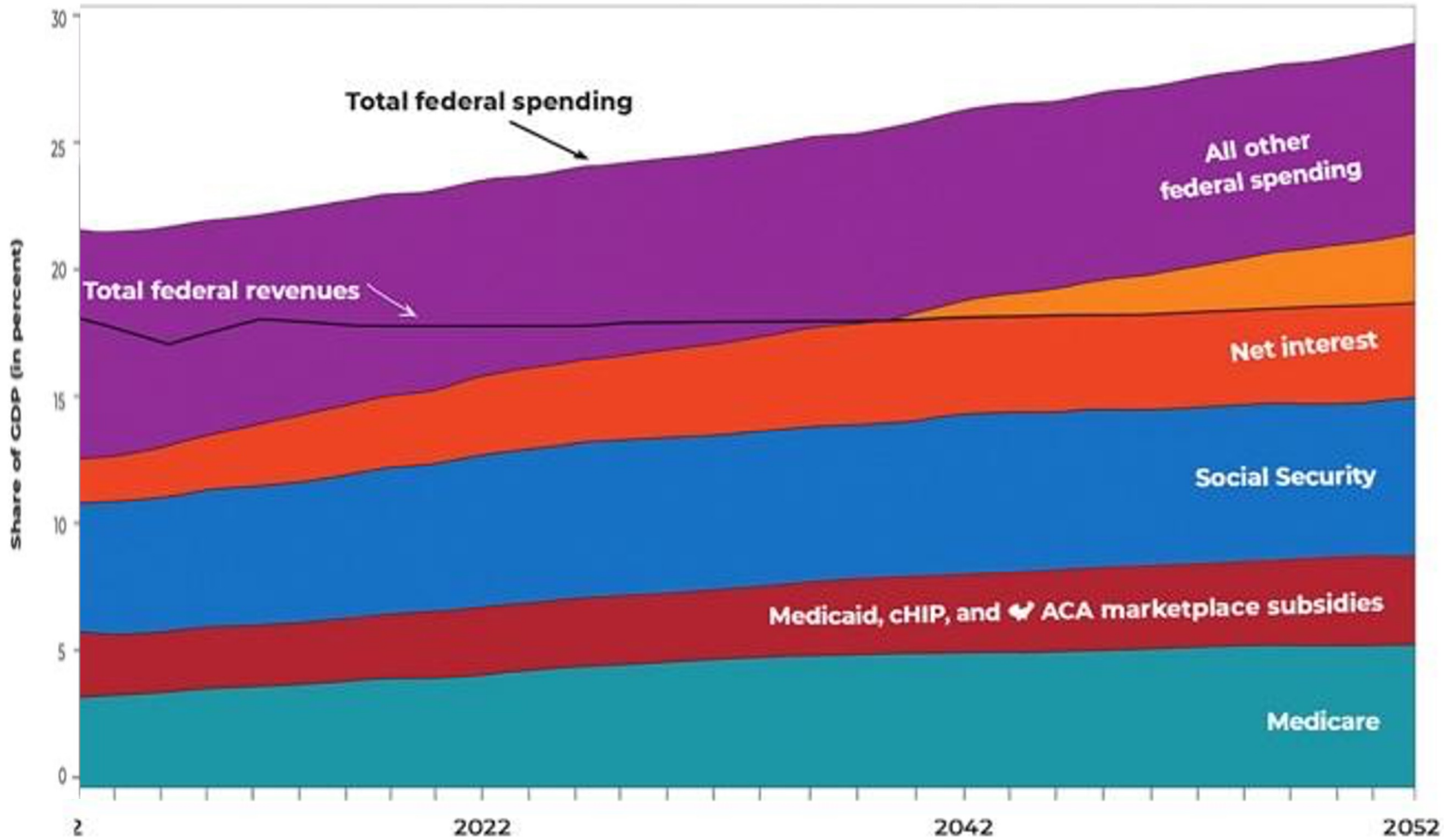
Value-barons—root out low value care. Embrace cost containment and market-based approaches. Essential to embrace economics as an ethical imperative

Translate what we know to public audiences—lay press

WHY AN *ETHICAL* OBLIGATION?

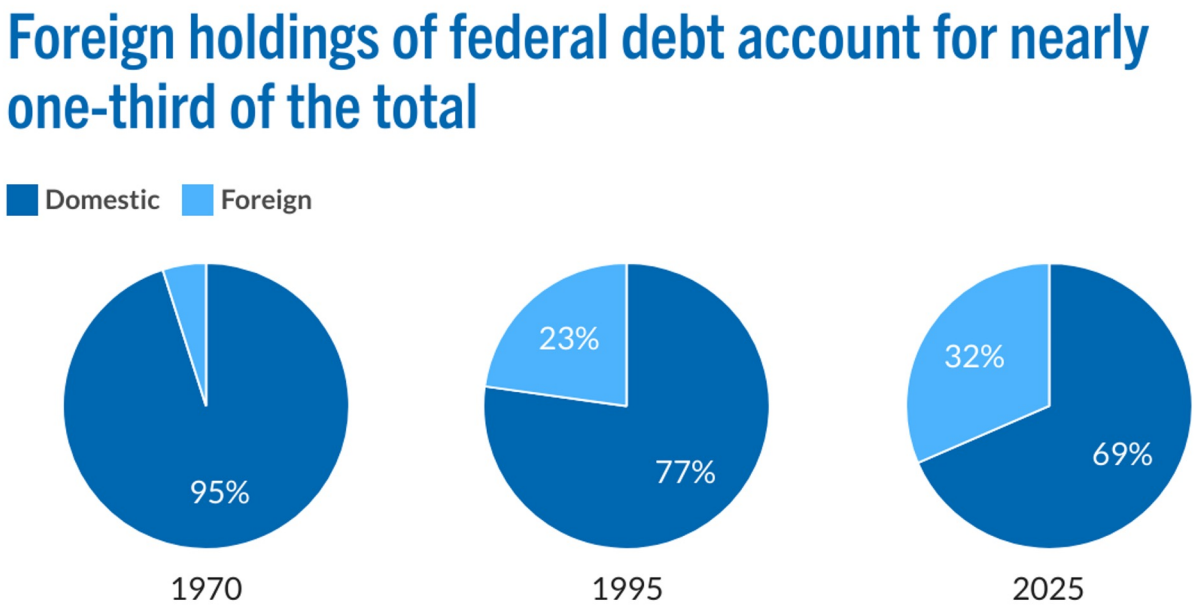
Image by way of CHAT GPT

Spending on Medicare, other major health programs, Social Security, and net interest is projected to exceed total federal revenues by 2041



The Deficit- > $38.9 trillion—increase $2 trillion in 2025

- $113, 638 for each person in the US
- Who owns us?
- Increasingly, other nations



$39,000,000,000,000

Sources: Office of Management and Budget and Source: U.S. Department of the Treasury

Note: Data reflect debt held by the public at the end of the fiscal year.

PETER G. PETERSON FOUNDATION

CMS Medicare Payment Model Changes

- CMS is refining Medicare payment models to strengthen value-based care
- Focus on fewer models with clearer accountability and measurable results
- Recent changes reflect policy direction, not retreat, from value-based payment
- These shifts will increasingly affect physician and APP reimbursement

What CMS Changed

- Several CMMI alternative payment models ended early due to limited savings
- CMS is consolidating its model portfolio around higher-impact approaches
- Increased emphasis on total cost of care and measurable outcomes
- Shift toward models that include downside risk over time

Direction of Travel: Where Medicare Is Headed

- From volume → value
- From voluntary pilots → sustained payment models
- From upside-only incentives → shared risk arrangements
- From process metrics → outcome-focused measures

What This Means for Clinicians

- Care delivery efficiency will increasingly affect reimbursement
- Documentation, care coordination, and quality reporting remain critical
- Practices aligned with value-based infrastructure will be better positioned
- Expect continued evolution rather than stability in payment programs

Bottom Line

1

CMS is focusing, not abandoning value-based care

2

Payment models will increasingly reward outcomes and efficiency

3

Understanding these shifts is essential for future clinical sustainability

New Value Based Initiatives

- ACCESS (Advancing Chronic Care with Effective Scalable Solutions)
  - 10 -year model (if found to lower costs/improve outcomes can become permanent)
  - Deploys innovative technology
  - Focuses on conditions affecting 2/3+ of Medicare population
    - Hypertension
    - Diabetes
    - Chronic musculoskeletal pain
    - Depression

NPs--THIS HAS YOUR NAME/ FINGERPRINTS ALL OVER IT!!!!

TEAMS-Transforming Episode Accountability Model

- MANDATORY—741 acute care hospitals https://www.cms.gov/team-model-participant-list
- A prospectively set payment for an episode of care (bundled payment) through 30 days post discharge
- Includes lower joint replacement
- Hip and femur fracture
- Coronary artery bypass
- Major bowel
- Varying financial risk and reward

Some are Deploying AI

- WISeR (Wasteful & Inappropriate Service Reduction Model)
- Uses AI for pre-authorization—savings shared with AI company
- Prior auth is new for traditional Medicare
- *Technically* voluntary in NJ, OH, OK, TX, AZ, WA

Rural Health Transformation Program

- $50 billion--All 50 states
- Aim is to expand access to care in rural states
- Strengthen the rural health care workforce
- Support innovation
- Modernize facilities

I don’t think they can do this without you (NPs)

Medicare Ambulatory Specialty Model

Note: Medical provider groups oppose, concerned about lower reimbursement

Prescription Drug Prices

Inflation Reduction Act--Negotiated prices on 10 common, expensive drugs; 15 for 2027

BALANCE Model-(Better Approaches to Lifestyle and Nutrition for Comprehensive hEalth) GLP1 price negotiation, among other lifestyle interventions

Most Favored Nation Status—policy designed to ensure US drug prices are not more than the lowest price paid in other developed nations. Voluntary, Trump RX; includes GLP1s (details missing at this time) (Cubanski, 2026) https://www.kff.org/quick-take/president-trump-proposes-codifying-mfn-drug-pricing-deals-but-key-details-are-missing/).

“Great Healthcare Plan”—Announced by President January 2026

- Aims to codify into law voluntary price negotiations
- Make more meds available over the counter
- Billions in subsidies to people rather than insurance subsidies
- Transparency in claims, denials, wait times, prices

Congressional Health Funding Proposal: Telehealth & PBM Provisions—January 20, 2026; Key Elements Relevant to Nurse Practitioners

- Extends Medicare telehealth flexibilities, including home as an originating site
- Prevents abrupt expiration of pandemic-era virtual care authorities
- Continues Hospital-at-Home and related care model waivers
- Includes negotiations on Pharmacy Benefit Manager (PBM) transparency and pricing practices
- Part of short-term federal health funding legislation—not a permanent fix

What about State-led initiatives?

Nine states with formal adoption of cost growth targets (MA, OR, RI, CT, DE, VT, NJ, WA, CA…others considering)

States focusing on price transparency (AK, CO, AZ, IN, TX, OK, WA,VA)

25 states have an operational all-payer claims data base, interest from at least five more

PRICE TRANSPARENCY IS KEY—BUT, what about value transparency? Governmental payers, taxpayers, and insurance plans increasingly asking--

What are people paying for?

What are people getting, both short and long term?

NPs can play a key role as a translator in this space

Translating Value in Medicare

Translating Value in TM vs MA

TRADITIONAL MEDICARE

- USUALLY NO PRIOR AUTH
- CHOICE OF PROVIDER
- NO OUT-OF-POCKET MAX UNLESS BY A SUPPLEMENT

MEDICARE ADVANTAGE

- MEDICARE FROM A PRIVATE COMPANY
- NARROWER NETWORKS AND PRE-AUTH
- TRADE OFF IS PERKS LIKE GYM MEMBERSHIP
- TWO TYPES—HMO AND PPO
- HMO GENERALLY DOES NOT PAY FOR CARE RECEIVED OUT OF NETWORK

Important Opportunity—I-SNPs (Institutional Special Needs Plans)

Clinical Leadership & Care Delivery

Primary/lead clinician for long stay-residents

Provide comprehensive primary or chronic care management

Regular onsite, urgent, & follow-up evals

Interdisciplinary Care Coordination

- Lead & coordinate interdisciplinary care teams (nursing, social work, pharm, therapies)
- Align care with resident's goals
- Reduce (disorientating) avoidable hosp. & readmissions

Important Opportunity—I-SNPs Institutional Special Needs Plans

Outcomes & Cost Stewardship

Management of chronicity, prevention, early intervention

Reduce unnecessary care, ED visits, hospital stays

Advance value-based care by decreasing costs and improving outcomes

Resident-Centered, Goal-Concordant

- Engages families/residences in shared decision-making
- Integrates hospice/palliative care/advanced care planning
- Focus on human dignity/choice/resident autonomy

NO ONE IS GOING TO INVITE US TO THE TABLE

- SO, WE NEED TO SHOW WHAT WE CAN BRING TO THE TABLE
- INVITE OURSELVES
- FOCUSING ON COST AND VALUE IS A SURE TICKET IN!

FINAL QUESTION

ARE NP PROGRAMS PROVIDING ENOUGH FOUNDATIONAL EDUCATION IN ECONOMICS?

IF NOT, HOW DO WE ADDRESS THAT?

One Final Note—How Do We Get Rid of "Incident To Billing"

Winning argument

Its not transparent

Its not cost effective

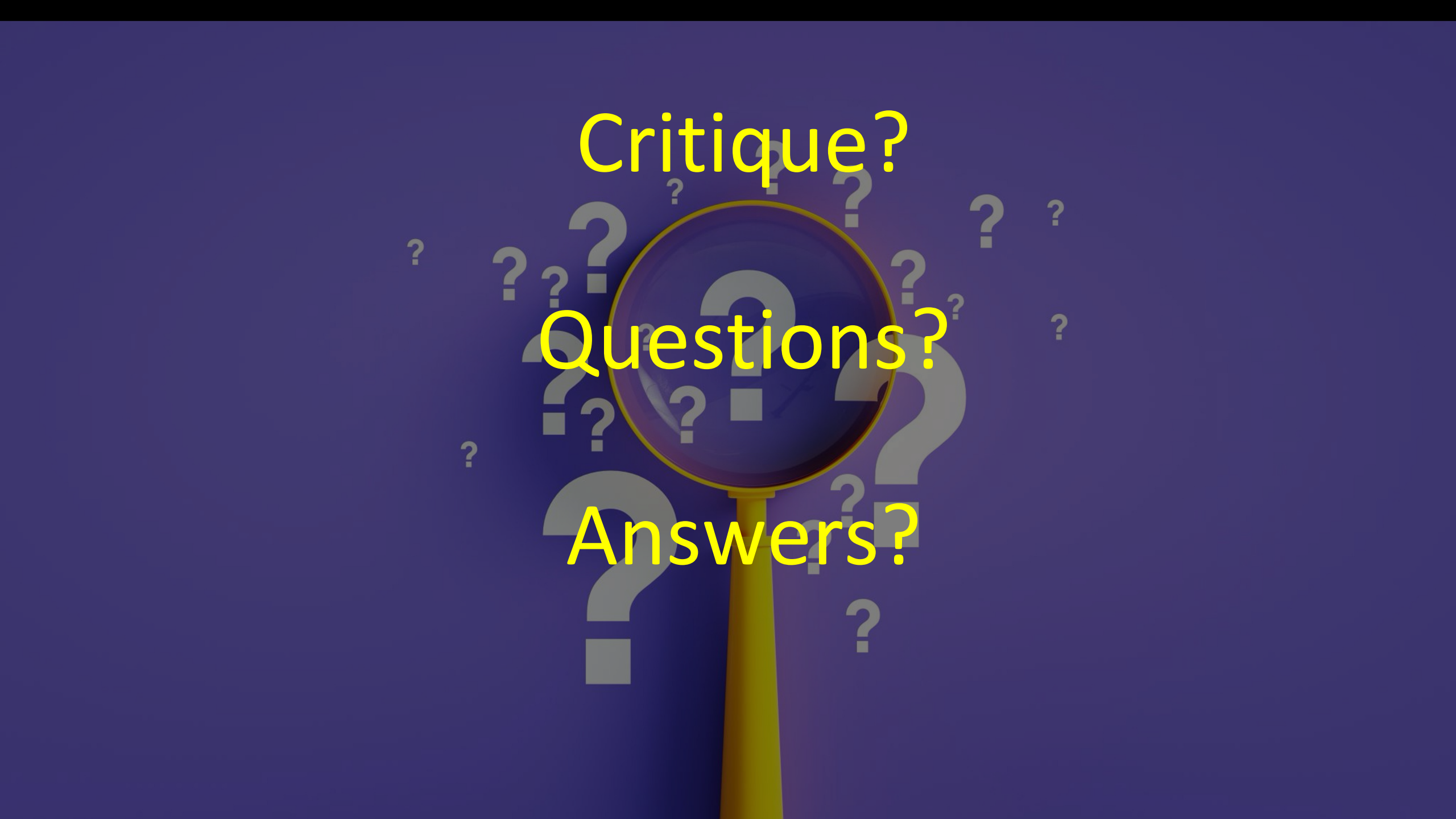
- Higher Health Care Costs
  - Higher insurance premiums
  - Higher taxes
- Higher Cost Sharing

Image Generation

- Slide 1-Image generated by the author, Chat GPT, prompt = “create an image for a slide that says: Unleashing the Full Power of Nurse Practitioners--Navigating Payment Policy, Cost, Containment, and Innovation in the US Health Care system. Now is our time.”
- Slide 2-URI Standard template
- Slides 3-5, 7, 10-14, 17, 20, 23-47. Microsoft PowerPoint “Designer” Generated.
- Slide 6—Image generated by the author, Chat GPT prompt= “Create an image for a slide that illustrates that fee for service reimbursement in health care fuels excessive costs but is revenue for providers.” This can be on one slide or two.
- Slide 8-Image generated by the author, Chat GPT prompt=“Create an image that reflects that the cost of health insurance is a result of underlying health care costs.
- Slide 9—Image generated by the author, Chat GPT, prompt=”Create an interesting, colorful image for a slide that states that health care cost containment is an ethical imperative”
- Slide1 5—Image generated by the author, Chat GPT, prompt=”Create an image that illustrates the tension between a patient’s concern with cost and the MDs benefit:’ Patient states: “The cost of care is outrageous”. MD states smugly, “You’re also overtreated.”
- Slide 16—Image generated by the author, Chat GPT prompt,=“Create an image suitable for a PowerPoint slide with the title “the Paradox of Too Little and Too Much”. Include overtreatment harm, the cascade of tests, the cascade of treatments. Finish with a bullet that states it “Turns people into patients.”
- Slide 18-Image generated by the author, Chat GPT prompt=“Create an image that suggests that universal health care coverage is a magical mirror, whereby some see free access to all care and others see excessive regulations and cost.”
- Slide 19-Image generated by the author, Chat GPT prompt=“Create an image of four nations (Canada, Germany, Switzerland, and UK) that bullets the health care financing system in that nation.”
- Slide 21-Image generated by the author, Chat GPT, prompt= “Create an image of Lady Justice”
- Slide 22—Image generated by the author, Chat GPT, using a back and white image of this data from the Medicare Payment Advisory Commission, prompt=“update this graph, ensuring the data are correct, to be brightly colored and easier to follow.”

Chat GPT version GPT-5.2

Microsoft PowerPoint Version 16.661 (22101101)


Critique?
Questions?
Answers?

The Surge of Male Mortality : ED, Testosterone & Men's Cardiometabolic Health: An Emerging Epidemic

Martin Miner MD
Co-Director Men's Health Center
Clinical Professor of Family Medicine & Urology
Alpert School of Medicine
Brown University
Providence, RI

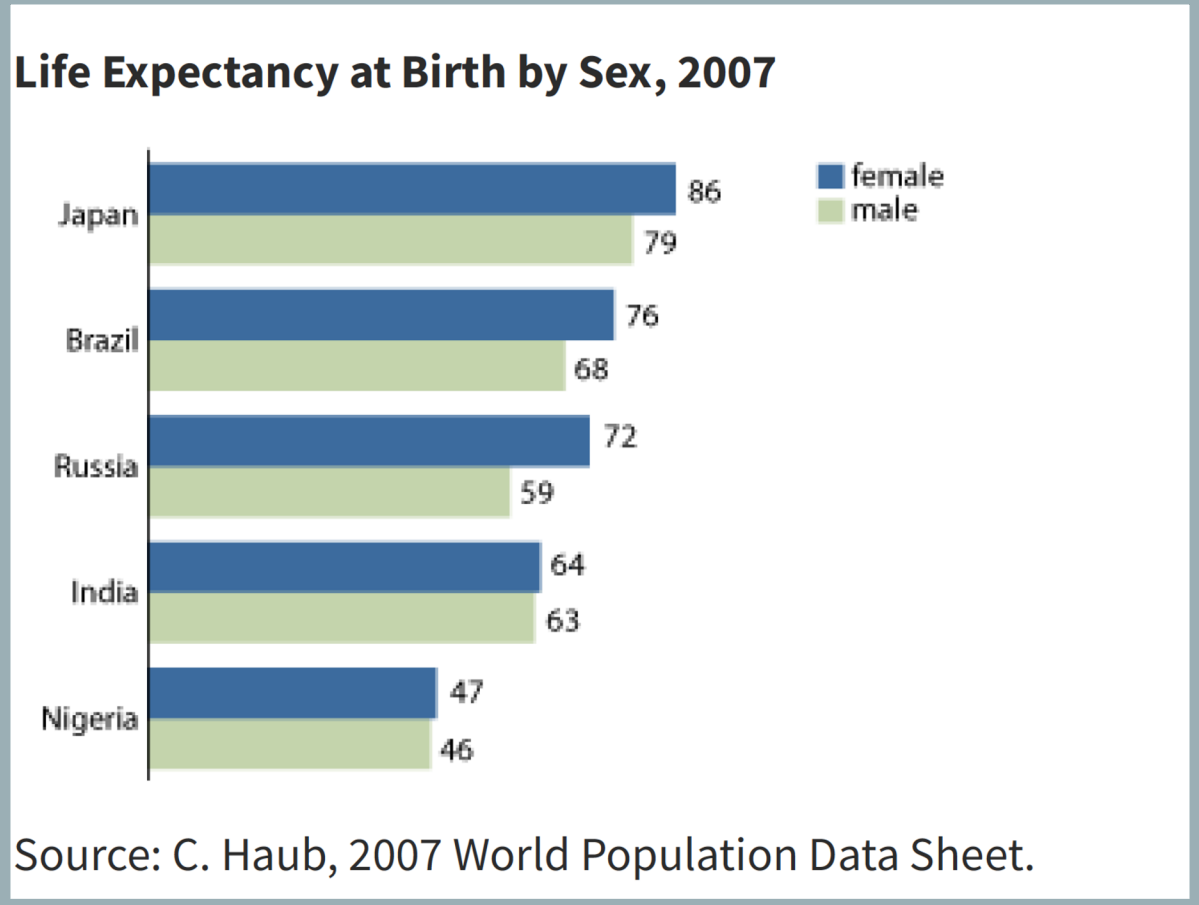
Disclosures

- Halozyme: Advisor, Literature Support, Consultant
- Tolmar: Advisor (ADT), Literature Support
- Verity Pharm: Consultant
- HIMs: Advisor for Cardiometabolic Health
- AUA ED & Peyronie's Guidelines: 2018 & Current

References available upon request

The Male Mortality Gap

- Men live **5-13 years shorter** than women globally
- Russia: 13-year gap; United States: 5-year gap
- Higher mortality rates in 9 of 10 leading causes of death
- Economic burden: $480 billion annually



What drives this higher mortality?

Root Causes of Male Mortality Gap

- Risky, unhealthy behaviors & high-risk activities
- Higher rates of smoking & heavy alcohol use
- Employment in hazardous occupations
- **PRIMARY DRIVER:** Poor cardiometabolic health
- Low healthcare engagement: 44% no annual PE
- Men utilize healthcare 69% less than women

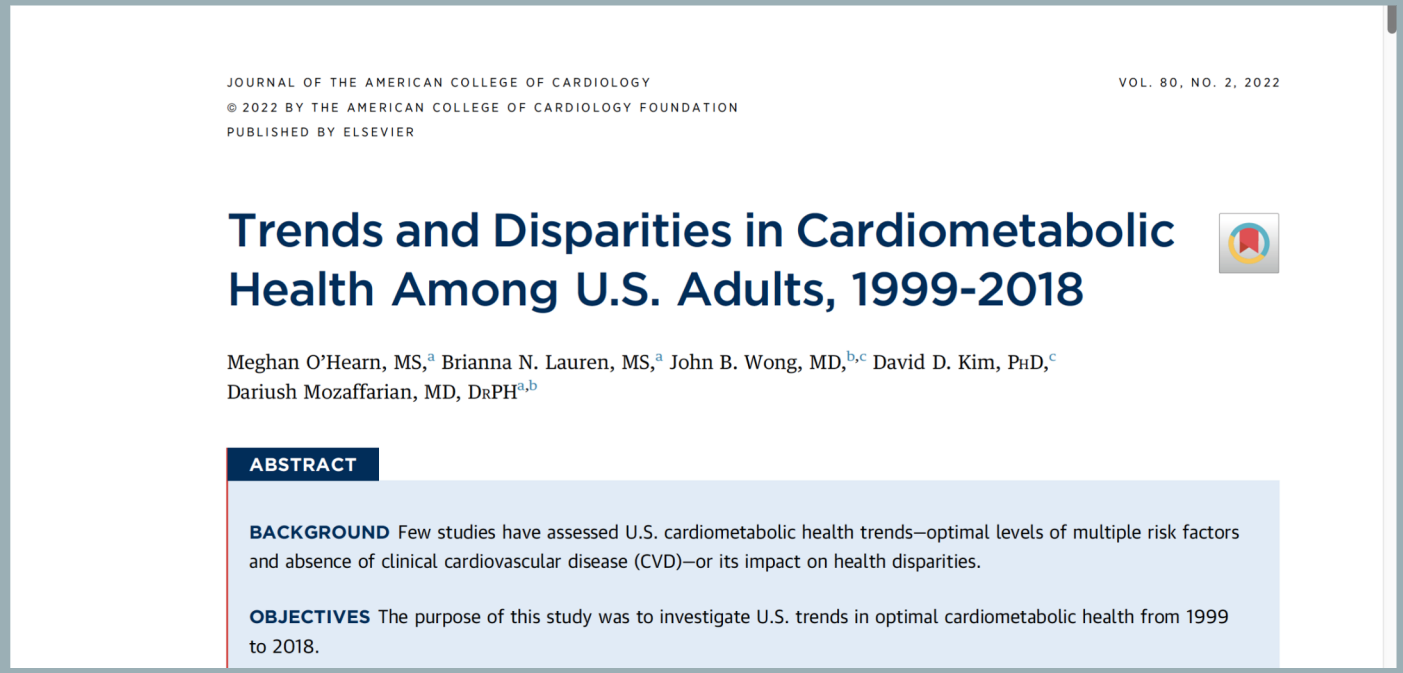
O'Hearn et al. J Am Coll Cardiol. 2022;80:138-151

The Cardiometabolic Health Crisis

(2017-18)

- **Only 6.8%** of US adults have good cardiometabolic health (
- **Decline from 7.7%** over 20 years 1999

- Disparities by age, sex, education, race, ethnicity
- "Diet, unhealthy weight gain, poor glucose levels worsening"
- Affects all socioeconomic and



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 80, NO. 2, 2022
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PUBLISHED BY ELSEVIER

Trends and Disparities in Cardiometabolic Health Among U.S. Adults, 1999-2018

Meghan O'Hearn, MS,[a] Brianna N. Lauren, MS,[a] John B. Wong, MD,[b,c] David D. Kim, PhD,[c] Dariush Mozaffarian, MD, DrPH[a,b]

ABSTRACT

BACKGROUND Few studies have assessed U.S. cardiometabolic health trends—optimal levels of multiple risk factors and absence of clinical cardiovascular disease (CVD)—or its impact on health disparities.

OBJECTIVES The purpose of this study was to investigate U.S. trends in optimal cardiometabolic health from 1999 to 2018.

O'Hearn et al. J Am Coll Cardiol. 2022;80:138-151

Chronic Disease: Diabetes & Pre-diabetes

In the US:

29.3 million diagnosed diabetes

9.7 million undiagnosed diabetes

115.9 million pre-diabetes

- Treatment costs: >$348 billion annually (pre-GLP1)
- Prevalence increasing across all demographics

CDC, National Diabetes Statistics

Chronic Disease: Obesity

41.9% of US adults obese (2017-2020)

9.2% with severe obesity

Cost: >$400 billion annually (employers & employees)

- Increased from 30.5% in 1999-2001
- **42% of Americans** have ≥2 chronic conditions

CDC NHANES Data, 2017-2020

The Problem:

- US has a "sick care" system, not preventive health system
- Chronic disease costs spiraling out of control
- **Solution needed:** Primary prevention & restorative health
- Challenge: How to engage men in self-care?

- **Key insight: Male sexual function is gateway to men's health**

Men's Health: Integrated Approach & Sexual Health

ED correlates with all major chronic diseases

Men's Health and Sexual Medicine are correlated with all major chronic disease areas and impact men across all racial, ethnic and socio-economic and geographical boundaries. The goal of the Men's Health Clinician is to find and fix the root cause of the problem. Must Include a ***Cardiometabolic w/u:***

CARDIOVASCULAR DISEASE

- Sleep Disorders
- Ischemic Heart Disease
- Hypertension & Dyslipidemia
- Peripheral Artery Disease
- Chronic Renal Failure

DIABETES

- Diabetes
- Metabolic Syndrome
- Overweight and Obesity

ERECTILE DYSFUNCTION

LOW TESTOSTERONE

LUTS Secondary to BPE

MENTAL HEALTH

- Depression
- Anxiety
- Stress

BEHAVIORAL MODIFICATION

- Nutrition Fitness Smoking
- Alcohol & Liver Disease
- Gut Biome & Bone Health

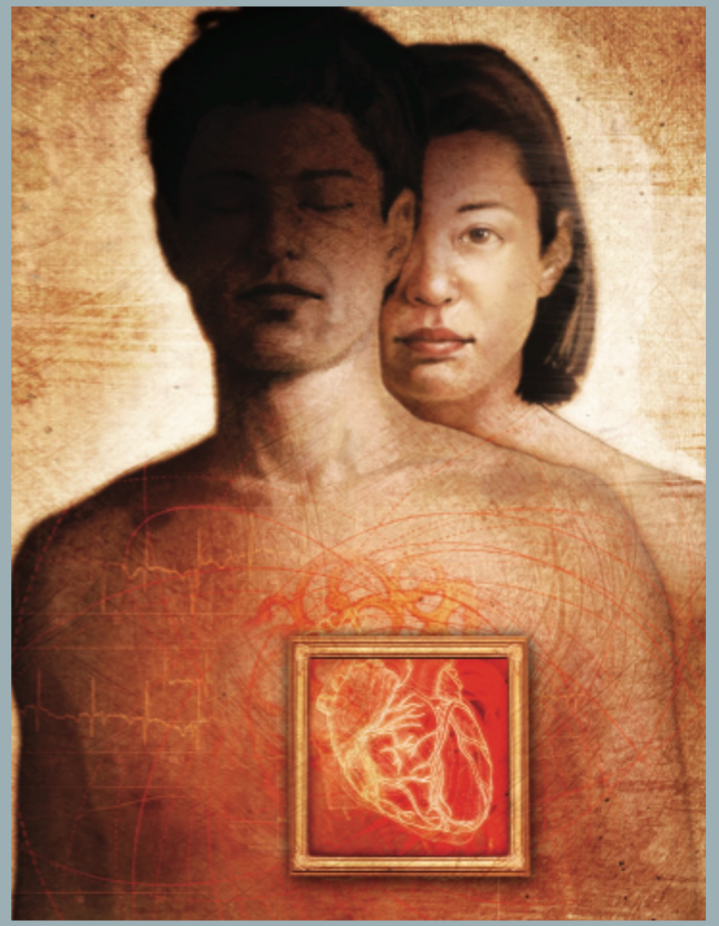
UROLOGY

- Chronic Prostatitis
- Prostate Cancer & Restoration
- Peyronie's Disease

Erectile Dysfunction & Cardiovascular Disease

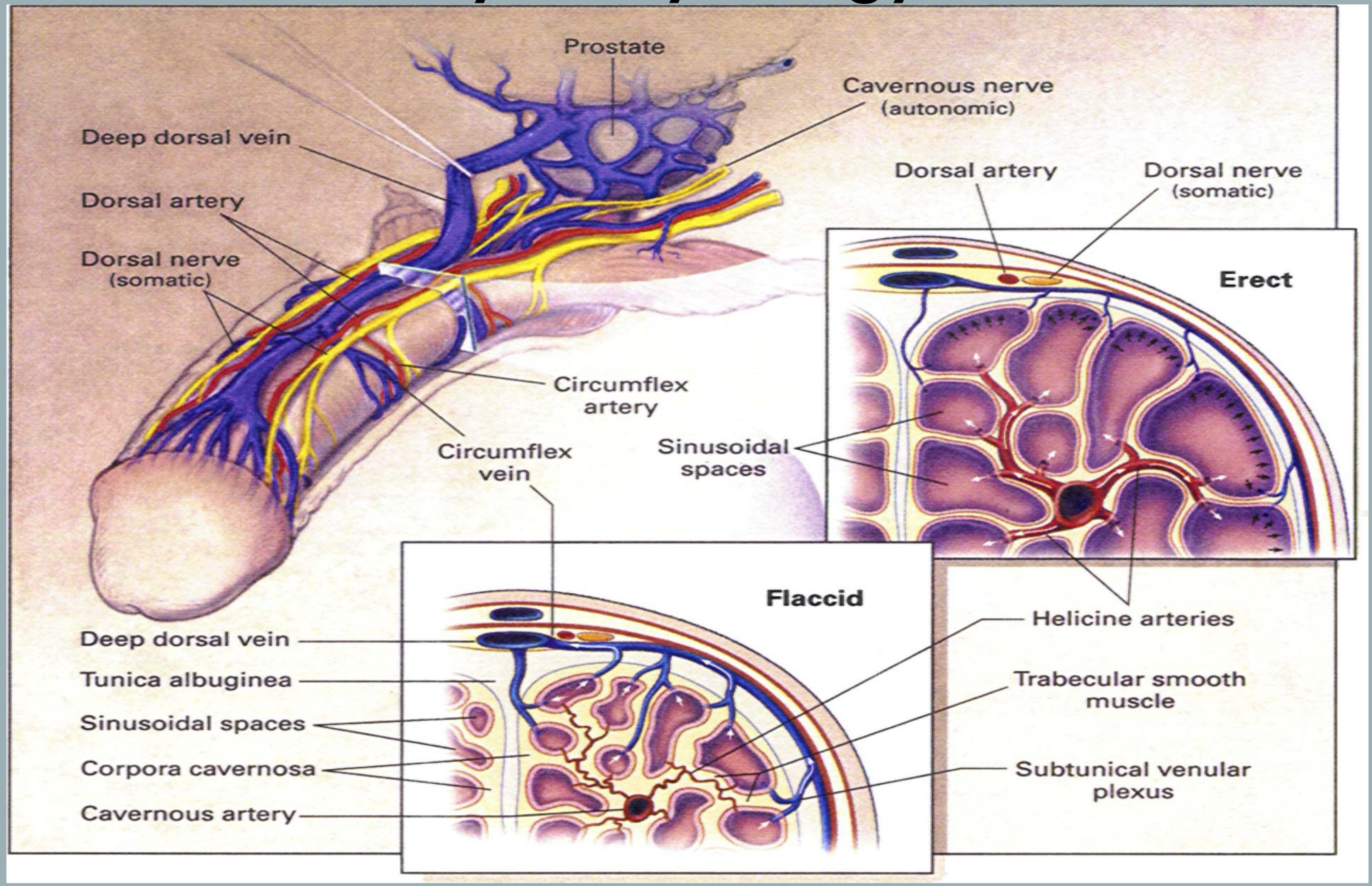
ED is a **predictor of CVD** morbidity and mortality

- ED represents early endothelial dysfunction
- Indicates smooth muscle dysfunction & atherosclerosis
- Offers opportunity for **early risk-adjusted treatment**
- Goal: Reduce cardiovascular events



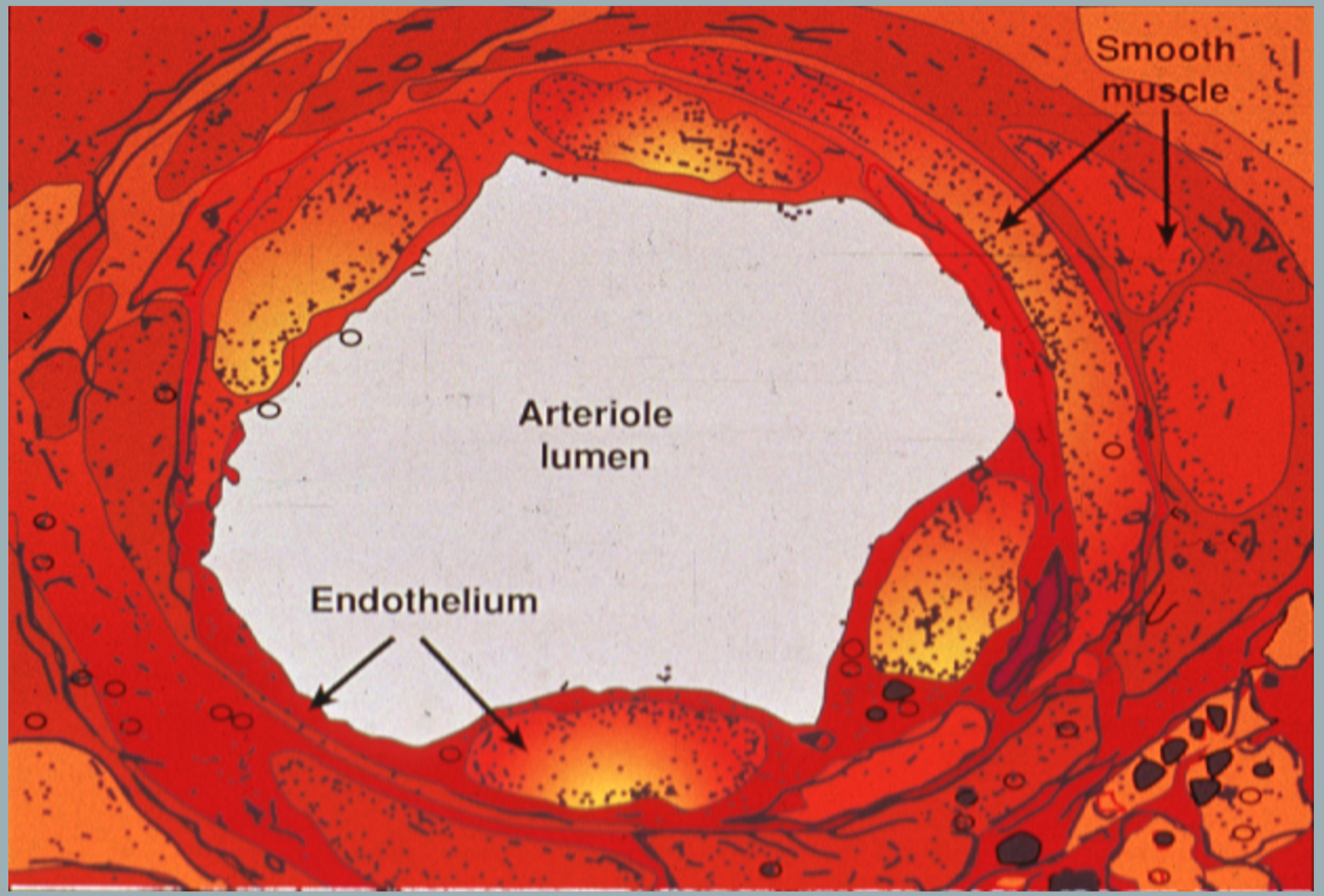
Böhm M, et al. Circulation. 2010;121(12):1439-1446.
ONTARGET/TRANSCEND Studies

Penile Anatomy & Physiology



- Corpus cavernosum: Smooth muscle & sinusoids
- Endothelium: Produces nitric oxide (NO)
- NO → cGMP → smooth muscle relaxation
- Erection requires intact vascular & neurologic function
- **Key:** Penile endothelium mirrors

The Endothelium: A Living Organ



- Lines all blood vessels (60 trillion cells)
- Produces nitric oxide (vasodilation)
- Regulates platelet function & thrombosis
- **Endothelial dysfunction:** Early atherosclerosis sign
- Present in ED, hypertension, diabetes, smoking

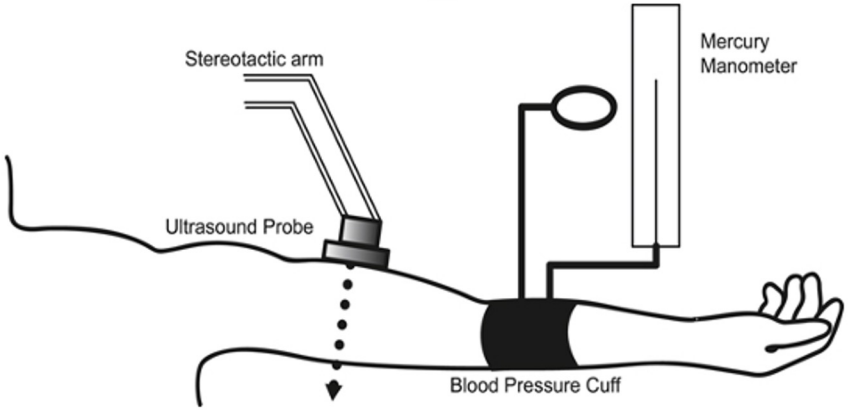
Penile endothelium dysfunction = Systemic vascular dysfunction

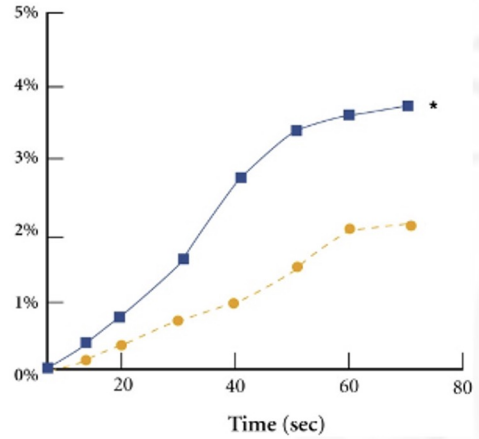
ED as Early CVD Marker: Kaiser/Billups

J Am Coll Cardiology 2004

- 30 men with ED and no other clinical cardiovascular disease vs. 27 age-matched controls without ED

Lab Results	NI Subjects (27)	ED Patients (30)
Tot Chol (mg/dl)	193.1 ± 8.6	203.6 ± 7.6
Trigly (mg/dl)	130.7 ± 18.4	115 ± 11.5
HDL-C (mg/dl)	47.9 ± 3.9	47.7 ± 2.4
LDL-C (mg/dl)	118.5 ± 7.0	128.2 ± 6.8
Glucose (mg/dl)	92.9 ± 2.1	90.0 ± 1.6
Lipo a (mg/dl)	24.3 ± 10.3	22.4 ± 3.7
Homocys (mg/dl)	9.2 ± 0.3	8.9 ± 0.5





Significantly reduced in erectile dysfunction patients (**circles**) versus normal control subjects (**squares**) over the whole time period (p=0.014).

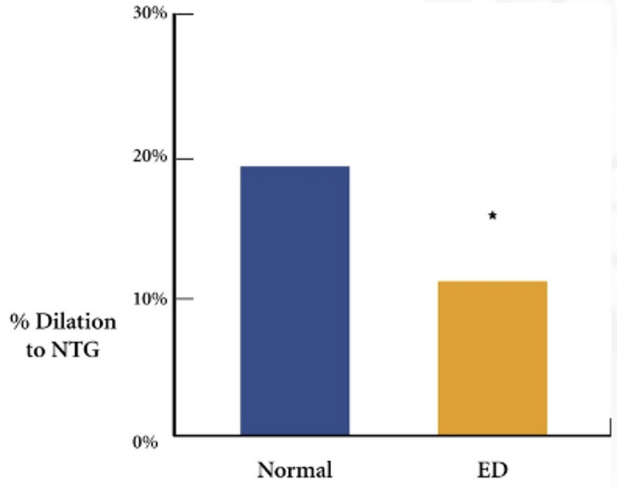


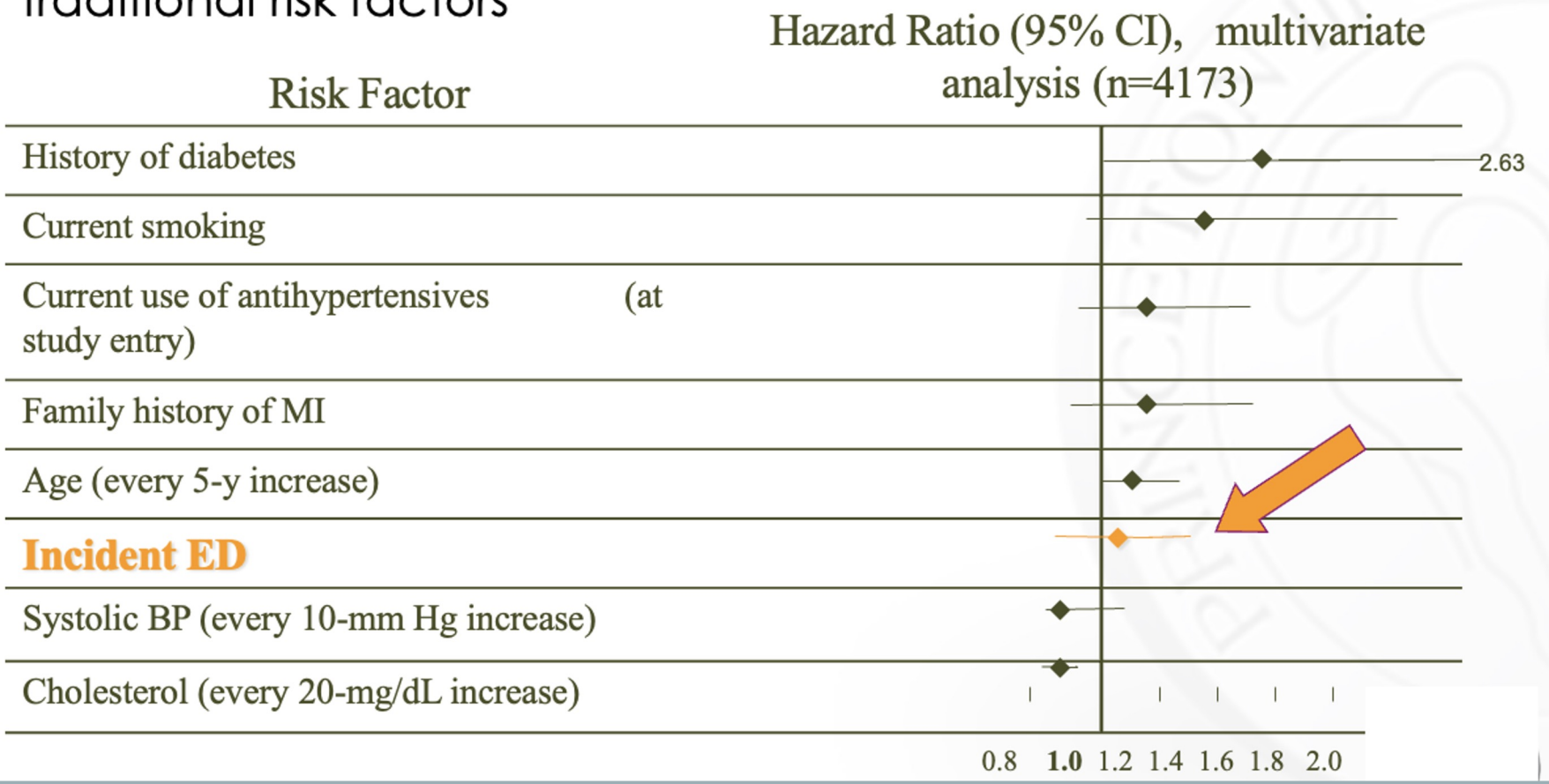
Figure 2. The vasodilator response to 0.4 mg sublingual nitroglycerin (NTG) was significantly impaired in erectile dysfunction (ED) patients versus normal control subjects (13.0 1.4% vs. 17.8 1.4%, p 0.02).

Kaiser JM, et al. J Am Coll Cardiol. 2004

PCPT Trial: ED as CVD Risk Factor

Thompson et al., JAMA 2005 10-Years 9500 Men: 1/2 ie Placebo Group Examined Q3 mo

Incident ED had an equal or greater effect on subsequent CV events of same magnitude as traditional risk factors



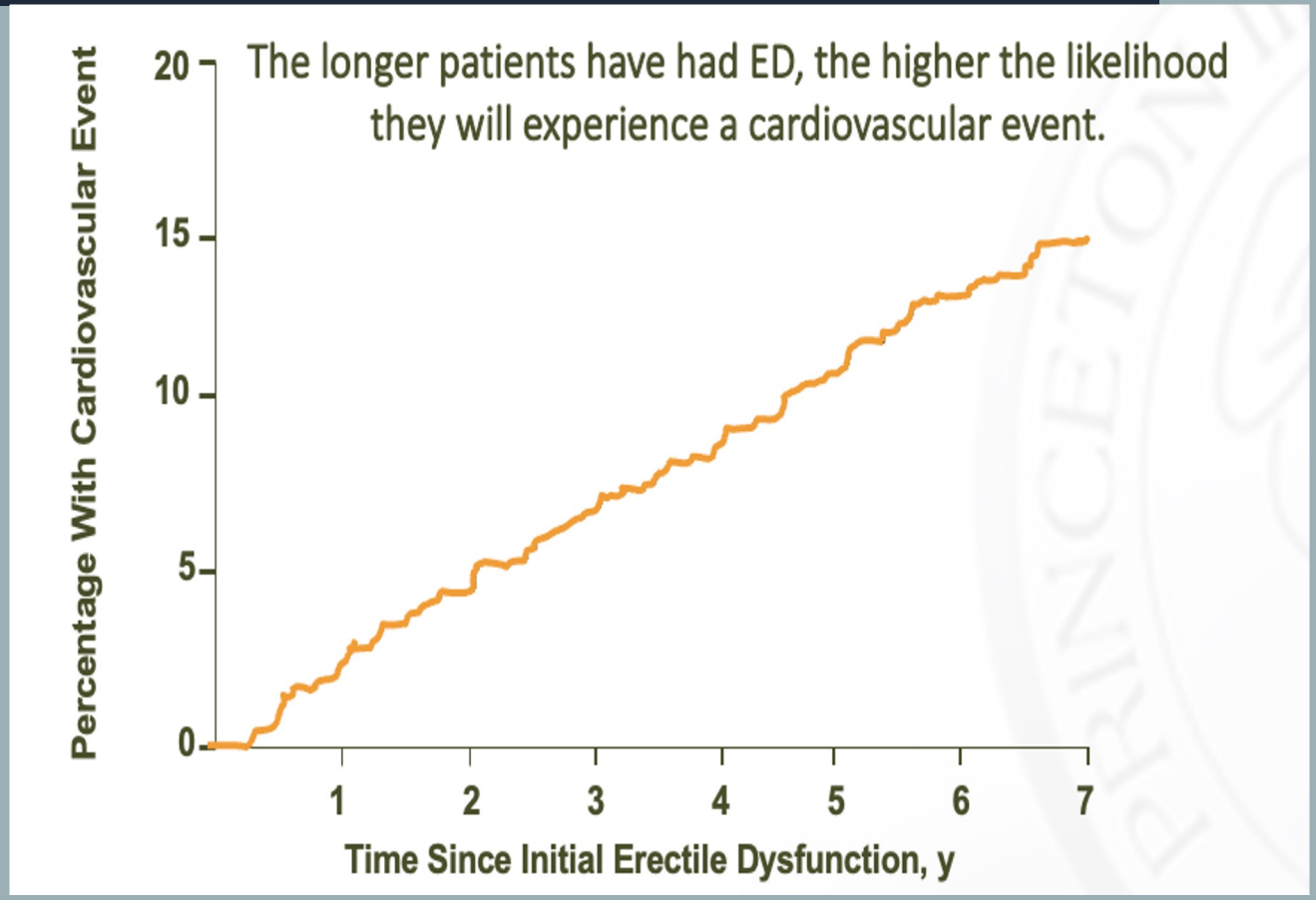
Thompson IM, et al. JAMA. 2005;294:2996-3002

PCPT: Time from ED to Cardiac Event

Incident ED predicted CV event in 11% of men

Time window: Up to 7 years prior to occurrence

- Of 4,247 men, 57% reported incident ED at 5 years
- Increased to 65% at 7 years
- The longer ED present, higher CV event likelihood
- **Critical window:** 2-5 years for intervention



JOURNAL of MEDICINE ®

All Men with Vasculogenic Erectile Dysfunction Require a Cardiovascular Workup

Martin Miner, MD,[a] Ajay Nehra, MD,[b] Graham Jackson, MD,[c] Shalender Bhasin, MD,[d] Kevin Billups, MD,[e,f] Arthur L. Burnett, MD,[f] Jacques Buvat, MD,[g] Culley Carson, MD,[h] Glenn Cunningham, MD,[i] Peter Ganz, MD,[j] Irwin Goldstein, MD,[k] Andre Guay, MD,[l] Geoff Hackett, MD,[m] Robert A. Kloner, MD, PhD,[n] John B. Kostis, MD,[o] K. Elizabeth LaFlamme, PhD,[p] Piero Montorsi, MD,[q] Melinda Ramsey, PhD,[p] Raymond Rosen, PhD,[r] Richard Sadovsky, MD,[s] Allen Seftel, MD,[t] Ridwan Shabsigh, MD,[u] Charalambos Vlachopoulos, MD,[v] Frederick Wu, MD[w]

[a]Departments of Family Medicine and Urology, Miriam Hospital and Brown University, Providence, RI; [b]Department of Urology, Rush University, Chicago, Ill; [c]Guy's & St. Thomas Hospital, London, UK; [d]Department of Medicine, Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Mass; [e]Department of Urologic Surgery, University of Minnesota, Minneapolis; [f]The James

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MAYO CLINIC

MAYO CLINIC PROCEEDINGS

CLINICAL PRACTICE GUIDELINES

The Princeton IV Consensus Recommendations for the Management of Erectile Dysfunction and Cardiovascular Disease

Tobias S. Köhler, MD; Robert A. Kloner, MD, PhD; Raymond C. Rosen, PhD; Arthur L. Burnett, MD, MBA; Michael J. Blaha, MD; Peter Ganz, MD; Irwin Goldstein, MD; Noel N. Kim, PhD; Tom Lue, MD, ScD; Kevin T. McVary, MD; John P. Mulhall, MD, MSc; Sharon J. Parish, MD; Hossein Sadeghi-Nejad, MD; Richard Sadovsky, MD; Ira D. Sharlip, MD; and Martin Miner, MD

Sexual Medicine Reviews, 2024, 00, 1–29
https://doi.org/10.1093/sxmrev/qeae043
Review

ISSM

OXFORD

Proceedings of PRINCETON IV: PDE5 inhibitors and cardiac health symposium

Raymond C. Rosen, PhD[1,*], Martin Miner, MD[2], Arthur L. Burnett, MD, MBA[3], Michael J. Blaha, MD, MPH[4], Peter Ganz, MD[5], Irwin Goldstein, MD[6], Noel Kim, PhD[7], Tobias Kohler, MD, MPH[8], Tom Lue, MD[9], Kevin McVary, MD[10], John Mulhall, MD, MSc[11], Sharon J. Parish, MD[12], Hossein Sadeghi-Nejad, MD, FACS[13], Richard Sadovsky, MD[14], Ira Sharlip, MD[9], Robert A. Kloner, MD, PhD[15]

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[2]Men's Health Center, Miriam Hospital, 180 Corliss St. 2nd Floor, Providence, RI 02904, United States
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Diagnosis and Treatment of Erectile Dysfunction for Reduction of Cardiovascular Risk

Ajay Nehra,* Graham Jackson, Martin Miner, Kevin L. Billups, Arthur L. Burnett, Jacques Buvat, Culley C. Carson, Glenn R. Cunningham, Irwin Goldstein, Andre T. Guay, Geoff Hackett, Robert A. Kloner, John Kostis, Piero Montorsi, Melinda Ramsey,† Raymond C. Rosen, Richard Sadovsky, Allen D. Seftel, Charalambos Vlachopoulos and Frederick C. W. Wu

From the Rush University Medical Center (AN), Chicago, Illinois, Guys and St. Thomas Hospitals London (GJ), London, Good Hope Hospital (GH), Birmingham and Andrology Research Unit, Developmental and Regenerative Biomedicine Research Group, The University of Manchester, Manchester Academic Health Science Centre, Manchester Royal Infirmary (FCWW), Manchester, United Kingdom, Family Medicine and Urology, Warren Alpert School of Medicine, Brown University (MM), Providence, Rhode Island, University of Minnesota, Minneapolis (KLB), Minnesota, The James Buchanan Brady Urological Institute, The Johns Hopkins Hospital (KLB, ALB), Baltimore, Maryland, Centre d'Etude et de Traitement de la Pathologie de l'Appareil Reproducteur et de la Psychosomatique (JB), Lille, France, University of North Carolina (CCC), Chapel Hill, North Carolina, Baylor College of Medicine and St. Luke's Episcopal Hospital (GRC), Houston, Texas, Alvarado Hospital (IG), San Diego, Good Samaritan Hospital and Department of Medicine, Keck School of Medicine at University of Southern California (RAK), Los Angeles, California, Center for Sexual Function/Endocrinology, Lahey Clinic Medical Center (ATG), Peabody, Tufts University School of Medicine (ATG), Boston and New England Research Institutes, Inc. (RCR), Watertown, Massachusetts, University

The Second Princeton Consensus on Sexual Dysfunction and Cardiac Risk: New Guidelines for Sexual Medicine

Graham Jackson, MD,* Raymond C. Rosen, PhD,† Robert A. Kloner, MD,‡§ and John B. Kostis, MD†

*Cardiothoracic Center, St Thomas' Hospital, London, UK; †University of Medicine and Dentistry of New Jersey—Robert Wood Johnson Medical School, New Brunswick, NJ, USA; ‡Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; §Heart Institute of Good Samaritan Hospital, Los Angeles, CA, USA

DOI: 10.1111/j.1743-6109.2005.00196.x

Princeton Consensus Panels: 25 Years

- **Started 1999:** Response to sildenafil patient surge
- **P1-P3:** Developed risk stratification for sexual dysfunction in CVD
- **P4 (2023):** Updated with ASCVD risk calculator & CAC scoring

Sex safety: MI risk increases from 1% to 1.01% baseline

Normal sex = 2-3 METS = (2 flights of stairs 10 seconds or walk 1 mile flat in 20 minutes)

Intense sex = 5-6 METS (4minutes standard Bruce protocol)

DeBusk R, et al. Am J Cardiol. 2000; Nehra A, et al. Mayo Clin Proc. 2012

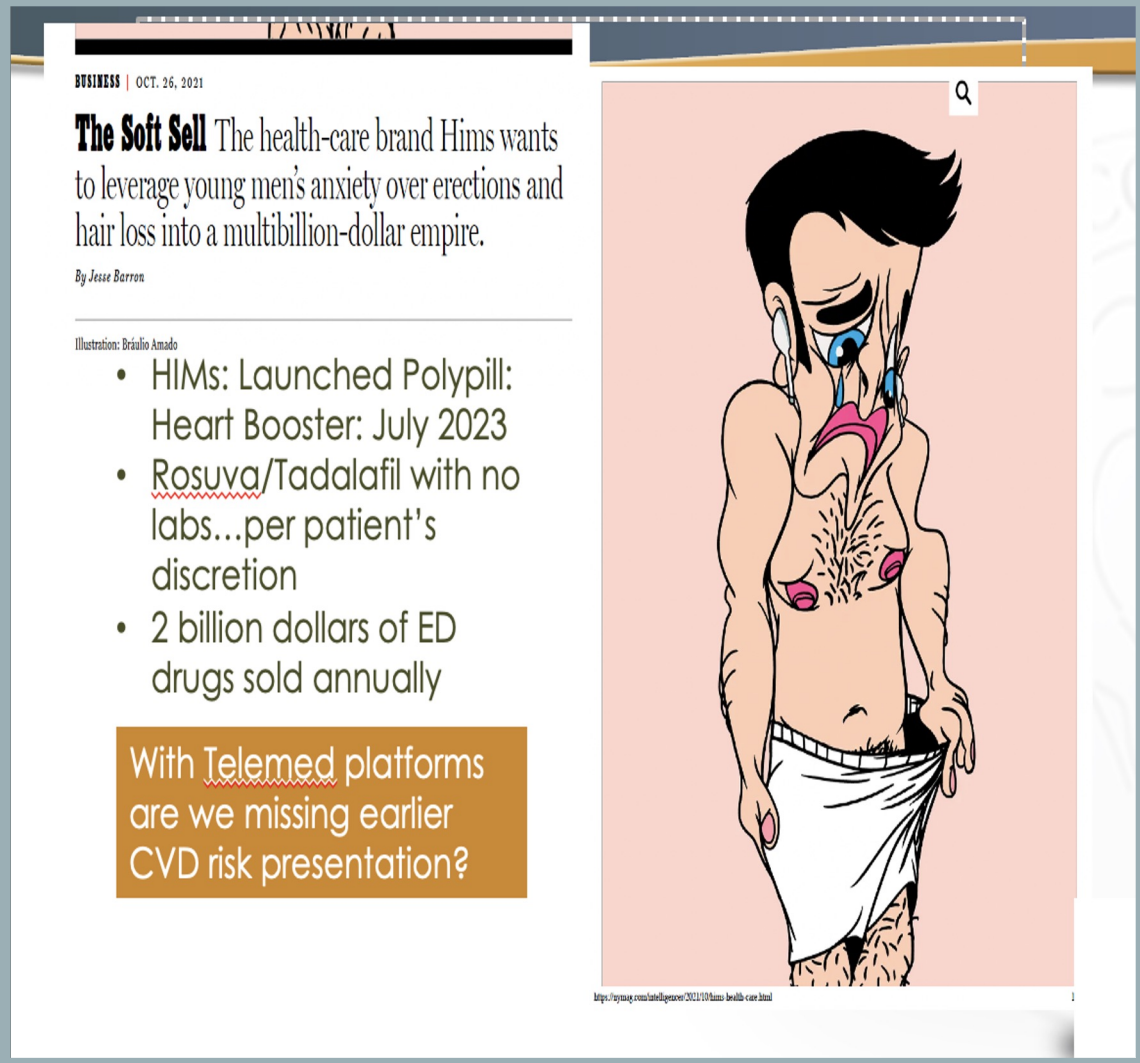
ED & CAD: Is Narrowing the Only Link?

- ½ to ⅔ of young men with MI have **no ED**
- Many men with severe ED **never develop MI**
- **However:** ED severity is strongly linked with CAD severity
- ED is **risk marker AND risk factor** for CVD onset
  Suggests: Multiple pathways beyond simple vessel narrowing

Telemedicine & ED: Missing the Connection?

- $2 billion in ED drugs sold annually at HIMS
- Telemedicine ED platforms gaining popularity
- **Risk:** Treating ED without CVD risk assessment
- Polypill approaches (e.g., Rosuvastatin/Tadalafil) without labs
- **Missing opportunity:** Early CVD risk detection

ED assessment must include some CVS Risk assessment



BUSINESS | OCT. 26, 2021

The Soft Sell The health-care brand Hims wants to leverage young men's anxiety over erections and hair loss into a multibillion-dollar empire.

By Jesse Barron

Illustration: Bráulio Amado

- HIMs: Launched Polypill: Heart Booster: July 2023
- Rosuva/Tadalafil with no labs…per patient's discretion
- 2 billion dollars of ED drugs sold annually

With Telemed platforms are we missing earlier CVD risk presentation?

Psychogenic ED: Also Harbinger of CVD Risk

- Bi-directional association: ED ↔ Depression
- Men with depression: 3x greater ED risk (Araujo, 1998)
- Onset depression → ED; Onset ED → mood deterioration
- **Meta-analysis (2017-2021):** Psychogenic ED linked to increased CVD risk (OR 1.57)

Psychogenic ED may predict CVD risk independent of vascular component

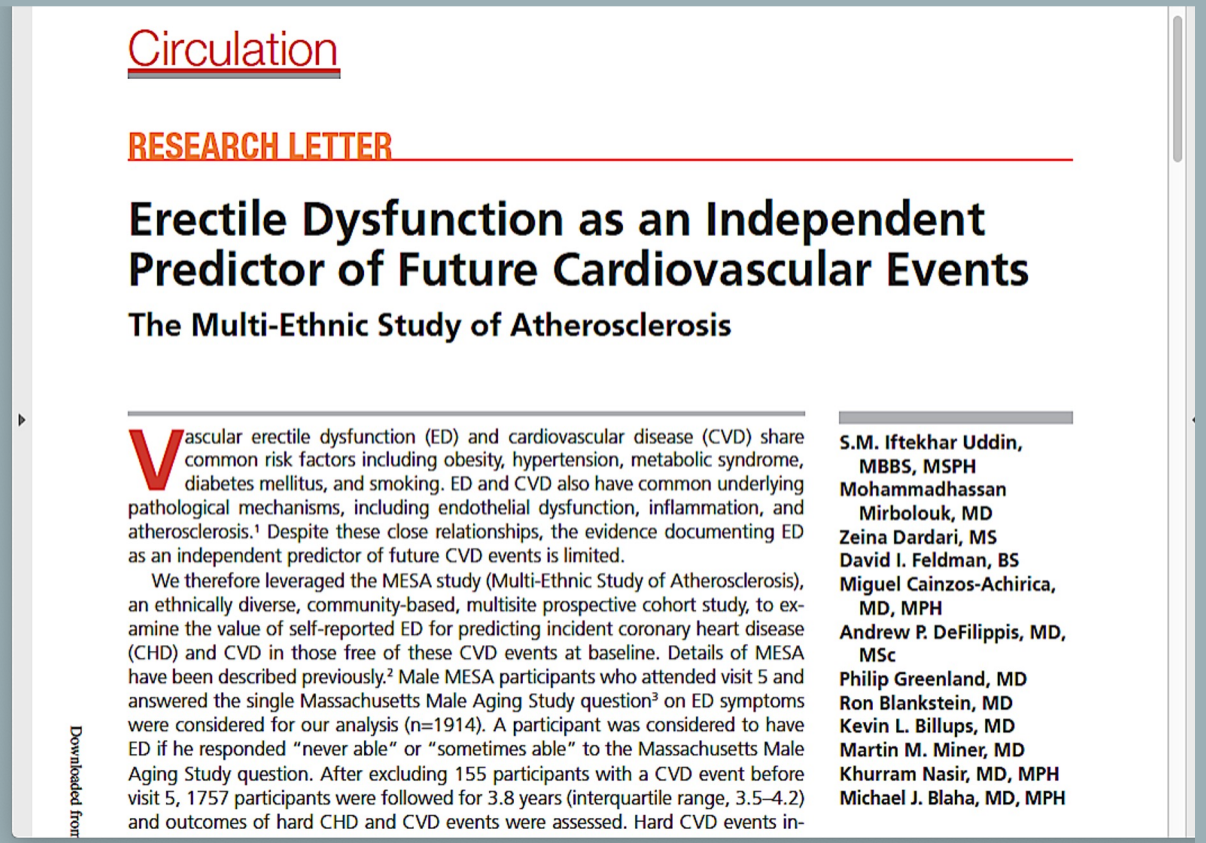
Araujo AB, et al. Psychogenic ED & CVD Risk Analysis

MESA: ED & Subclinical Atherosclerosis

Multi-Ethnic Study of Atherosclerosis (6,800 participants)

- 1,862 men free of CVD (mean age 59.5 yo) x 3.8 yrs
- Ethnicities: 42% White, 24% AA, 11% Asian, 23% Hispanic
- Increased CAC & CIMT at baseline → **future ED/CVD events**
- **Key finding:** ED linked to subclinical CAD detection

"In an ethnically diverse, community-based cohort, ED was found to be a significant ***independent*** *predictor of future hard CVD events after adjustment for traditional CVD risk factors, depression, and β-blocker use"*



Circulation

RESEARCH LETTER

Erectile Dysfunction as an Independent Predictor of Future Cardiovascular Events

The Multi-Ethnic Study of Atherosclerosis

Vascular erectile dysfunction (ED) and cardiovascular disease (CVD) share common risk factors including obesity, hypertension, metabolic syndrome, diabetes mellitus, and smoking. ED and CVD also have common underlying pathological mechanisms, including endothelial dysfunction, inflammation, and atherosclerosis.[1] Despite these close relationships, the evidence documenting ED as an independent predictor of future CVD events is limited.

We therefore leveraged the MESA study (Multi-Ethnic Study of Atherosclerosis), an ethnically diverse, community-based, multisite prospective cohort study, to examine the value of self-reported ED for predicting incident coronary heart disease (CHD) and CVD in those free of these CVD events at baseline. Details of MESA have been described previously.[2] Male MESA participants who attended visit 5 and answered the single Massachusetts Male Aging Study question[3] on ED symptoms were considered for our analysis (n=1914). A participant was considered to have ED if he responded "never able" or "sometimes able" to the Massachusetts Male Aging Study question. After excluding 155 participants with a CVD event before visit 5, 1757 participants were followed for 3.8 years (interquartile range, 3.5–4.2) and outcomes of hard CHD and CVD events were assessed. Hard CVD events in-

S.M. Iftekhar Uddin, MBBS, MSPH
Mohammadhassan Mirbolouk, MD
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Martin M. Miner, MD
Khurram Nasir, MD, MPH
Michael J. Blaha, MD, MPH

Circulation. 2019;138:540–542.

MESA: ED with Positive CAC Increases Risk

Men with ED + positive CAC:
90% increased risk of ASCVD events

- Following multivariate regression of traditional CHD risk factors
- CAC scoring identifies high-risk ED patients
- Enables risk stratification & intervention

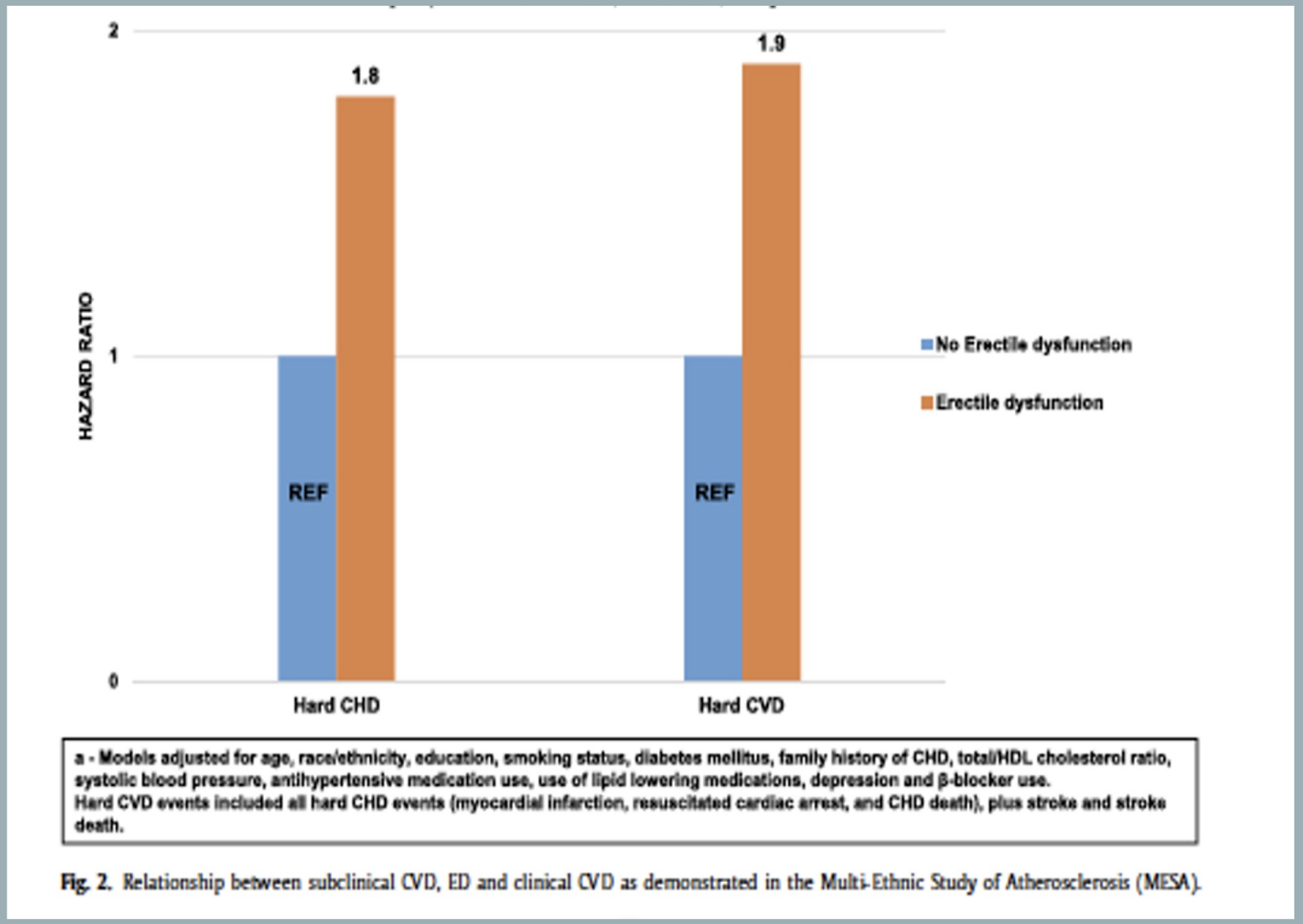


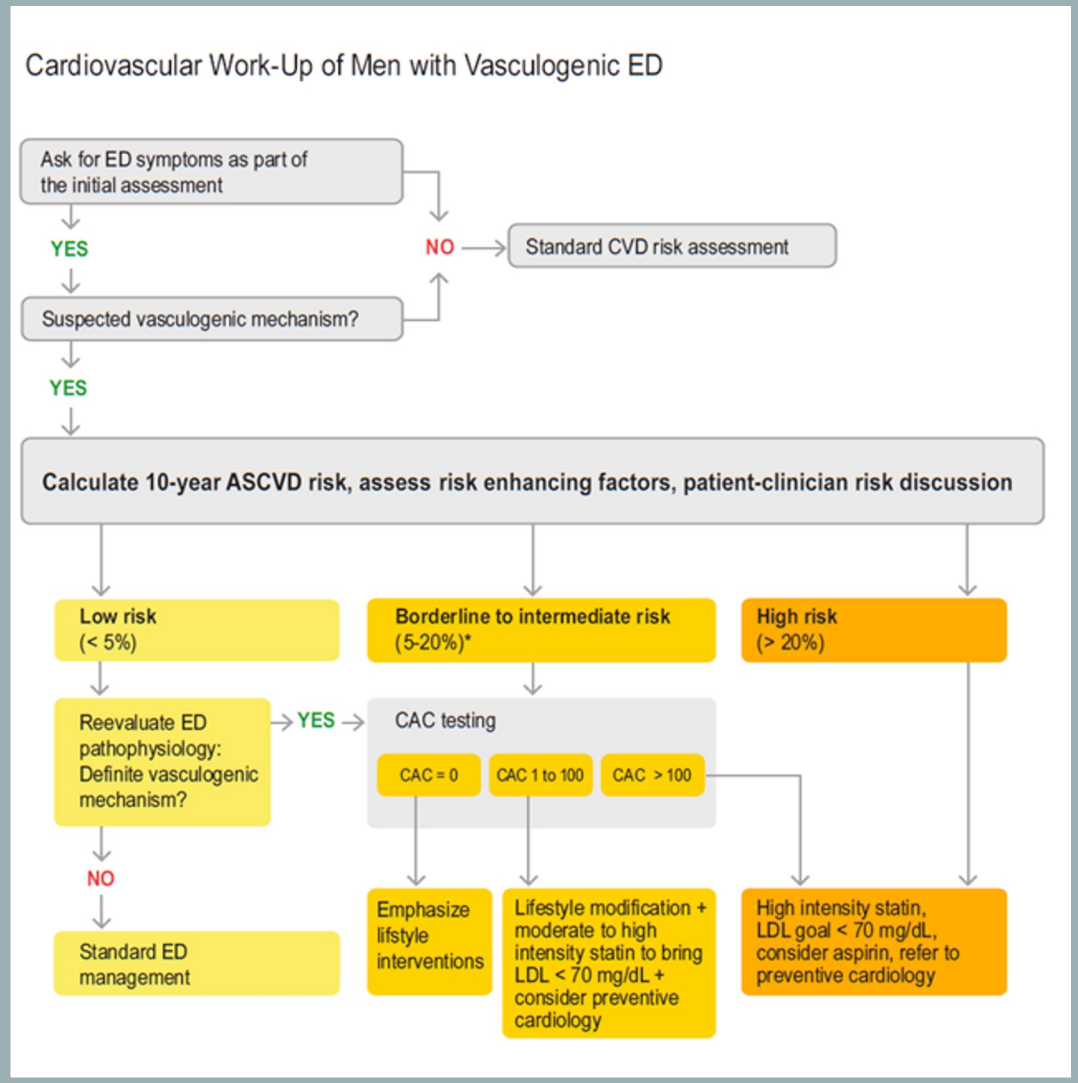
Fig. 2. Relationship between subclinical CVD, ED and clinical CVD as demonstrated in the Multi-Ethnic Study of Atherosclerosis (MESA).

Circulation. 2019;138:540–542.

P4 2023: ED Workup Algorithm

Step 1: Calculate 10-year ASCVD risk (ACC/AHA calculator)

- **Borderline-intermediate risk (5-20%):** Order CAC score
- **CAC = 0:** Lifestyle modification
- **CAC 1-100:** Moderate-high intensity statin + risk factor control
- **CAC >100:** High-intensity statin + preventive cardiology referral



CAC testing: Fast (10-15 min), affordable ($75-150), widely accessible

P4 Consensus 2023 Guidelines

Why Screen for ED: The Stakes

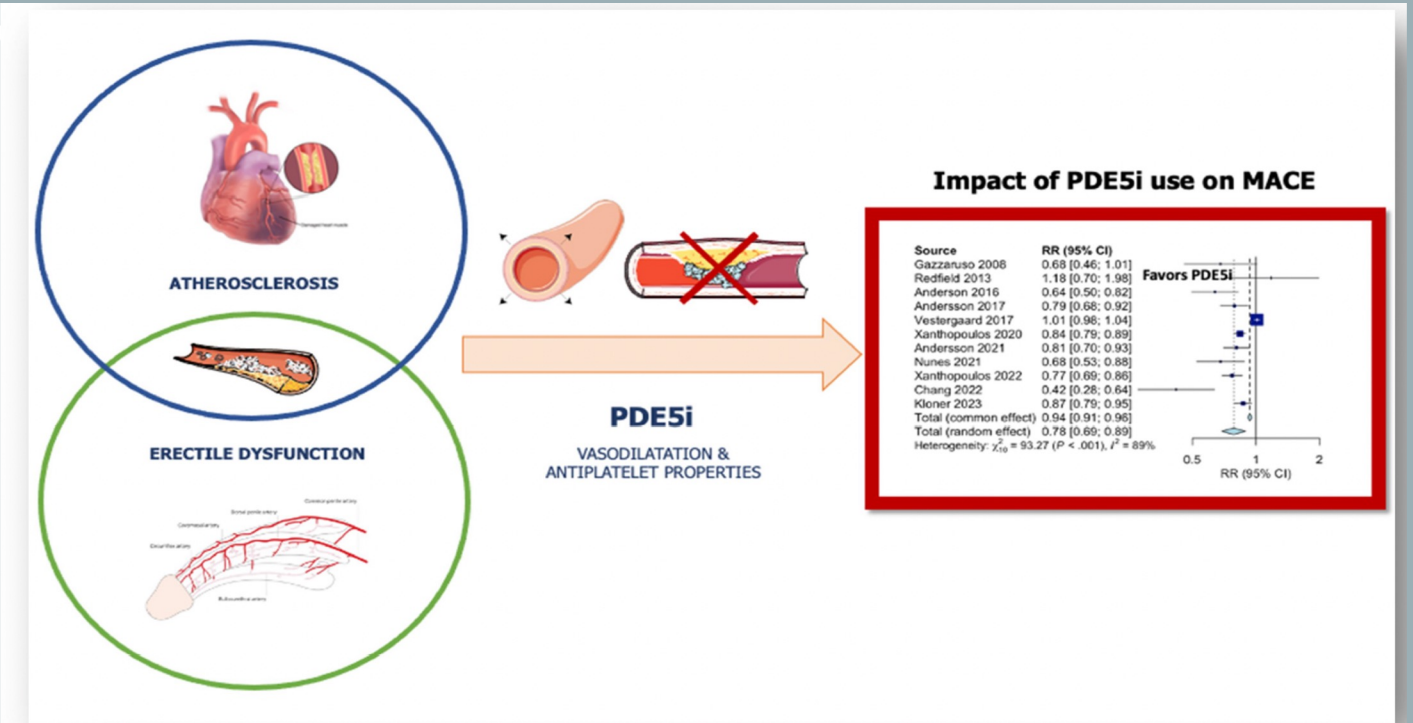
- CVD is leading cause of death; 50% die suddenly without symptoms

- "Given the connection between ED and CAD, it is both logical and strongly supported that erectile function can be improved by a healthy diet, exercise, weight loss, tobacco cessation, and stress reduction."

- "Improving erectile function with both lifestyle and pharmacologic interventions may reduce atherosclerotic risk and future CV events "

PDE5 Inhibitors: CVD Safety Profile

- 20 years of evidence supporting safety in CVD
- Mechanism: Inhibit phosphodiesterase → increase cGMP → NO-mediated vasodilation
- Also improve vascular function systemically
- Include: Sildenafil, tadalafil, vardenafil, avanafil
- **MACE reduction: 13%-34%**
- **Mortalit**



PDE5i Use & Mortality Reduction

Dose-response relationship observed

Regular PDE5i use associated with improved CV outcomes independent of ED

13% Reduction MACE; 25% Reduction in Mortality

adverse cardiovascular events and overall mortality in a large nationwide cohort of men with erectile dysfunction and cardiovascular risk factors: A retrospective, observational study based on healthcare claims and national death index data

Robert A. Kloner, MD, PhD[1,2,*], Eric Stanek, Pharm D[3,4], Christopher L. Crowe, MPH[3], Mukul Singhal, PhD[3], Rebecca S. Pepe, MPH[3], Julia Bradsher, PhD, MBA[1], Raymond C. Rosen, PhD[5]

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*Corresponding author: Huntington Medical Research Institute (HMRI), Pasadena, CA, USA. Email: robert.kloner@hmri.org

ut evidence

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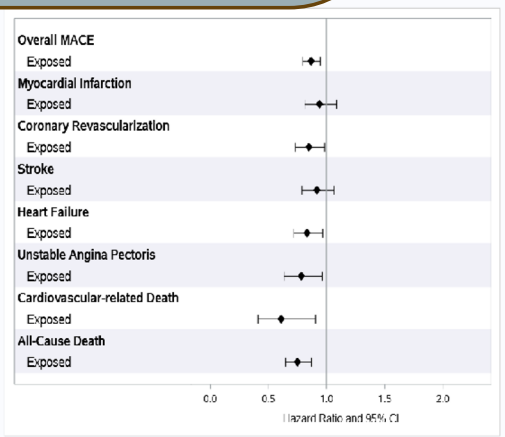
ard Ratios

MACE:

- **13%** reduction in rate of overall MACE
  - (HR= 0.87; 0.79-0.95) **P=0.001**
- Individual MACE Components:
  - Myocardial infarction (HR= 0.94; 0.81-1.09) P=0.399
  - Coronary revascularization (HR= 0.85; 0.73-0.98) **P=0.029**
  - Stroke (HR=0.92; 0.79-1.06) P=0.254
  - Heart failure (HR= 0.83; 0.72-0.97) **P=0.016**
  - Unstable angina (HR= 0.78; 0.64-0.96) **P=0.021**
  - Cardiovascular-related mortality (HR = 0.61; 0.41-0.90) **P=0.014**

Mortality:

- **25%** reduction in rate of overall mortality
  - (HR= 0.75; 0.65-0.87) **P<0.001**

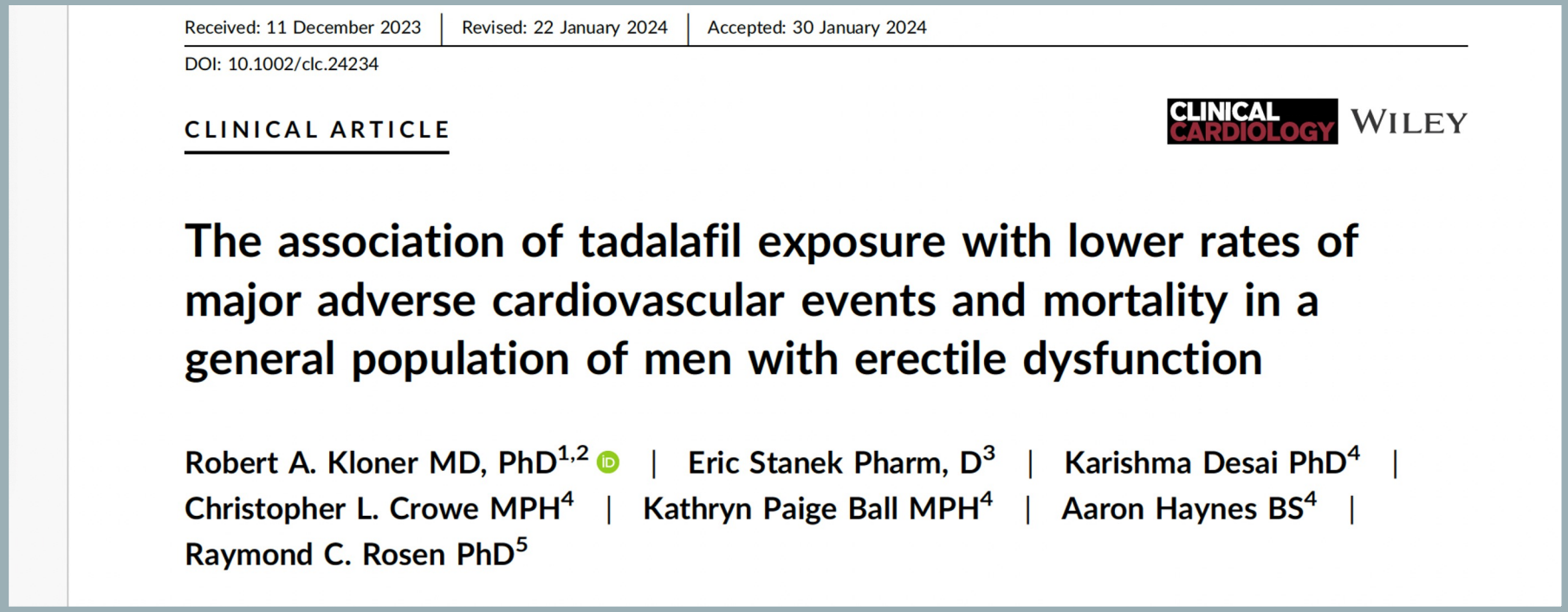


Median follow up was 24 months in the exposed group and 18 months in the non-exposed group.

Tadalafil: Specific CVD Benefits

Large US claims database analysis (8,156 exposed vs. 21,012 unexposed)
MACE reduction: **19%** (HR 0.81; p=0.007)
All-cause mortality: **44% reduction**

- Mean follow-up: 37 months
- Effect sustained over time



Received: 11 December 2023 | Revised: 22 January 2024 | Accepted: 30 January 2024

DOI: 10.1002/clc.24234

CLINICAL ARTICLE

CLINICAL CARDIOLOGY WILEY

The association of tadalafil exposure with lower rates of major adverse cardiovascular events and mortality in a general population of men with erectile dysfunction

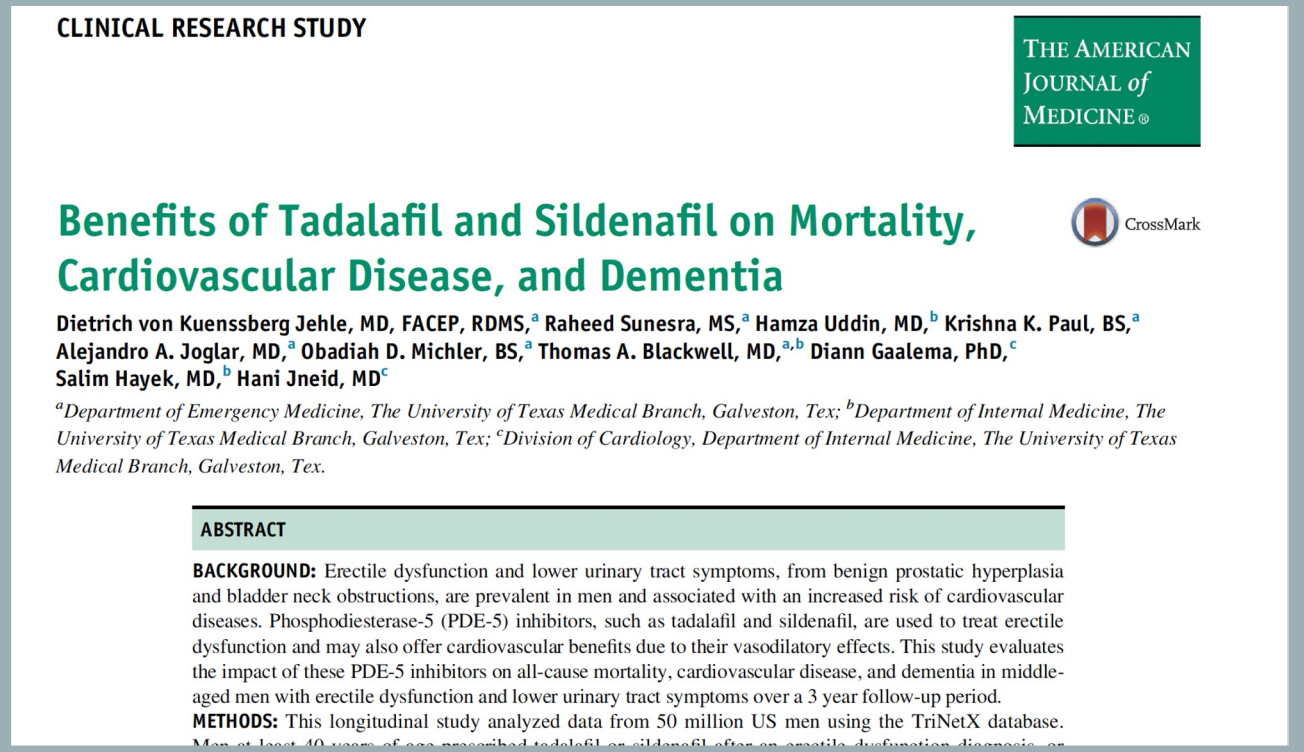
Robert A. Kloner MD, PhD[1,2] | Eric Stanek Pharm, D[3] | Karishma Desai PhD[4] | Christopher L. Crowe MPH[4] | Kathryn Paige Ball MPH[4] | Aaron Haynes BS[4] | Raymond C. Rosen PhD[5]

PDE5i Benefits: TriNetX Database Study

510,000 men >40 years (2004-2021)

Tadalafil + sildenafil use associated with:

- **All-cause mortality:** RR 0.66
- **Myocardial infarction:** RR 0.73
- **Stroke:** RR 0.66
- **VTE:** RR 0.79
- **Dementia:** RR 0.68



CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Benefits of Tadalafil and Sildenafil on Mortality, Cardiovascular Disease, and Dementia

Dietrich von Kuenssberg Jehle, MD, FACEP, RDMS,[a] Raheed Sunesra, MS,[a] Hamza Uddin, MD,[b] Krishna K. Paul, BS,[a] Alejandro A. Joglar, MD,[a] Obadiah D. Michler, BS,[a] Thomas A. Blackwell, MD,[a,b] Diann Gaalema, PhD,[c] Salim Hayek, MD,[b] Hani Jneid, MD[c]

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ABSTRACT

BACKGROUND: Erectile dysfunction and lower urinary tract symptoms, from benign prostatic hyperplasia and bladder neck obstructions, are prevalent in men and associated with an increased risk of cardiovascular diseases. Phosphodiesterase-5 (PDE-5) inhibitors, such as tadalafil and sildenafil, are used to treat erectile dysfunction and may also offer cardiovascular benefits due to their vasodilatory effects. This study evaluates the impact of these PDE-5 inhibitors on all-cause mortality, cardiovascular disease, and dementia in middle-aged men with erectile dysfunction and lower urinary tract symptoms over a 3 year follow-up period.

METHODS: This longitudinal study analyzed data from 50 million US men using the TriNetX database.

Tadalafil showed more significant benefits overall

Large Population Observational Study 2025

ED as a Fulcrum for Lifestyle Change

ARTICLE IN PRESS

MAYO CLINIC

MAYO CLINIC PROCEEDINGS

CLINICAL PRACTICE GUIDELINES

The Princeton IV Consensus Recommendations for the Management of Erectile Dysfunction and Cardiovascular Disease

Tobias S. Köhler, MD; Robert A. Kloner, MD, PhD; Raymond C. Rosen, PhD; Arthur L. Burnett, MD, MBA; Michael J. Blaha, MD; Peter Ganz, MD; Irwin Goldstein, MD; Noel N. Kim, PhD; Tom Lue, MD, ScD; Kevin T. McVary, MD; John P. Mulhall, MD, MSc; Sharon J. Parish, MD; Hossein Sadeghi-Nejad, MD; Richard Sadovsky, MD; Ira D. Sharlip, MD; and Martin Miner, MD

Abstract

The Princeton Consensus (Expert Panel) Conference is a multispecialty collaborative symposium dedicated to optimizing sexual function and preserving cardiovascular health. The Fourth Princeton

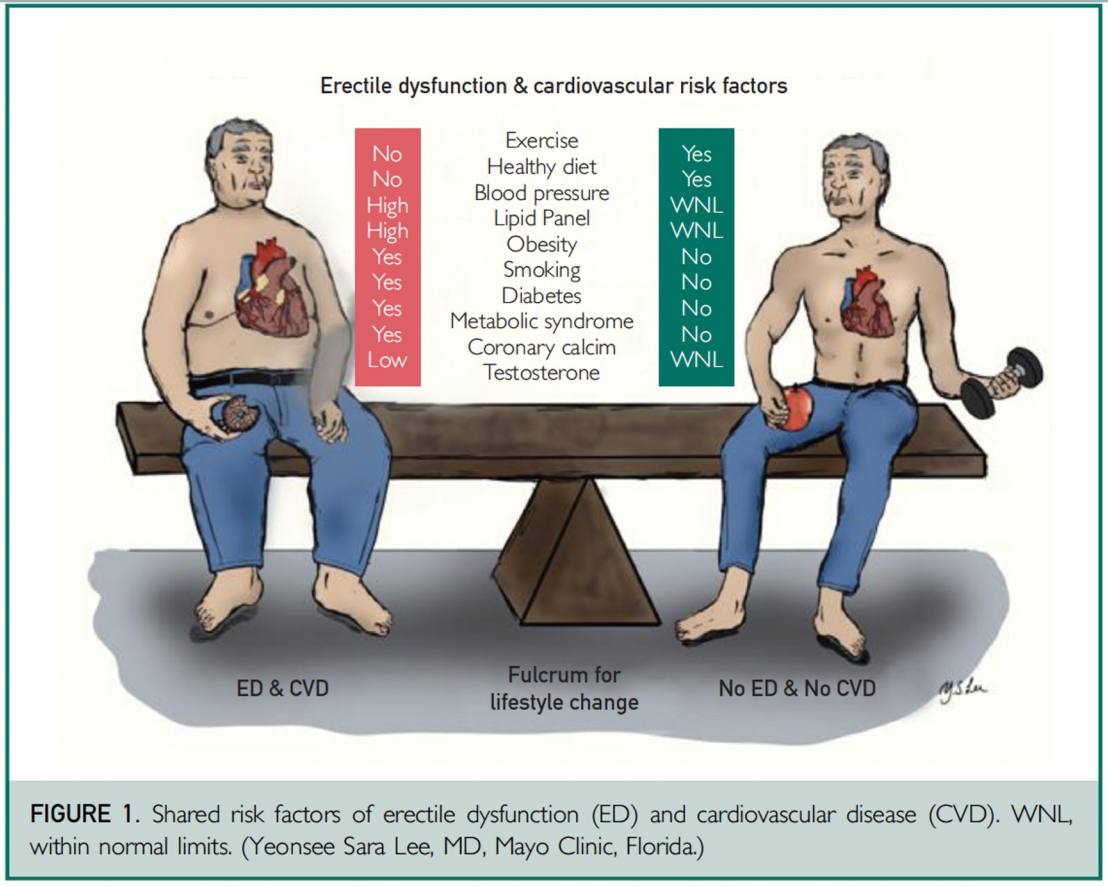


FIGURE 1. Shared risk factors of erectile dysfunction (ED) and cardiovascular disease (CVD). WNL, within normal limits. (Yeonsee Sara Lee, MD, Mayo Clinic, Florida.)

Kholer T Mayo Proceed 2024

ED Screening: Current Evidence Gap

- **Agreement:** High ED prevalence in CVD-risk individuals
- **Agreement:** ED useful for CVD risk stratification
- **Gap:** ACC/AHA risk calculators don't include ED
- UK QRISK-3 includes ED (25% increased modified CV risk)
- CAC scoring discriminates risk levels

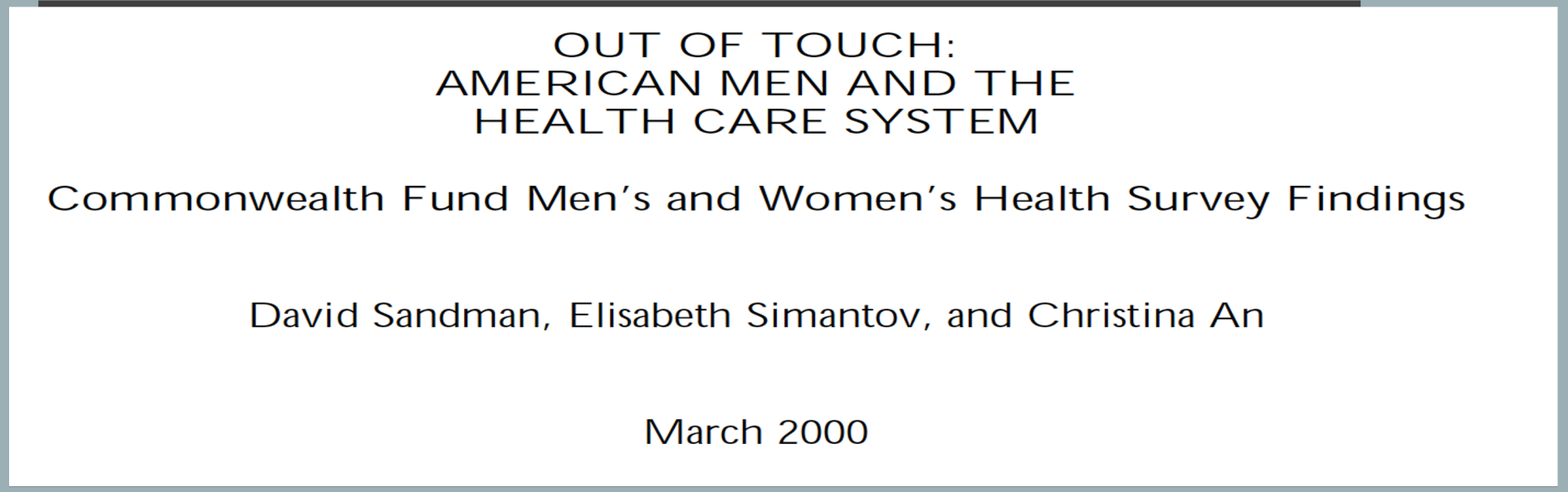
Role of PDE5i beyond ED? Beyond aspirin? GLP-1 agonists combined?

National Men's Health Initiative= Office of Men's Health: Why?

- **5-year shorter** life expectancy vs. women
- Higher mortality in 9/10 leading causes of death
- 44% have no annual physical exam
- 69% less healthcare utilization vs. women
- Few federal programs target men's health
- Economic burden: **$400 billion annually**
- **No Office of Men's Health or Office of Men's Health Research exists**

Why Do Men Die Earlier?

Brot A, et al. Am J Men's Health. 2011



- One in three men do not have a regular doctor
- More than half of men do not get regular screenings or other preventative care
- One in four men wait as long as possible to seek care or advice about a health problem

Commonwealth Study: Men's Health 2000

Men's Mental Health Crisis

- 6 million men experience depression annually
- **Only 25% seek treatment**
- **79% of suicides are men** (4x greater than women)
- 100 men die by suicide daily
- Substance abuse compounds crisis: 70% opioid overdoses

Depression & anxiety screening essential in men's health

CDC Suicide Data & Statistics 2025

Physical Fitness & Defense Readiness

- 31% of US men are obese
- **27% of men aged 18-25 ineligible for military service** due to obesity
- Declining fitness across demographics
- National security implications
- Health system failure in prevention

Obesity prevention is national priority

Rural & Underserved Men: Forgotten

- Limited access to care & specialists
- **2-7 year shorter** life expectancy than urban
- Higher rates: Obesity, substance abuse, smoking
- Proposed strategy: Men's Health Centers of Excellence/Barbershop Medicine Advocacy
- Data collaboration for policy & innovation
- Health literacy initiatives for behavior change

Testosterone: From Alchemy to Evidence

- **1935:** Synthesized from cholesterol; used for vitality
- **1940s:** Huggins/Hodges prostate cancer concern (dogma established)
- **Late 20th c.:** Viewed as performance/lifestyle drug; not utilized in urology or endocrinology
- **2014-15:** FDA added CV warning based on concerns

CV warning from the label

Old vs New Paradigm

OLD PARADIGM

- Testosterone as a carcinogen
- Testosterone as a cardiovascular risk factor
- Testosterone known mainly as a "lifestyle drug"

NEW PARADIGM

- Testosterone plays an important role across multiple organ systems throughout the body
- Testosterone deficiency negatively impacts health, reduces quality of life, and is associated with increased mortality risk
- Testosterone therapy offers multiple clinical benefits, such as improvements in diabetes, obesity, and bone mineral density

Testosterone: Natural Hormone Physiology

- Levels decline only modestly with age, but fall more
- rapidly with weight gain, diabetes, and other
- chronic health conditions
- The term "*age-related hypogonadism*" is
- misleading — aging alone has minimal impact on testosterone levels. Comorbidities, not age itself,
- are the main drivers of significant decline
- **Truth:** Comorbidities, not age, drive T decline

New Testosterone Paradigm

- Testosterone = Multi-organ system hormone, NOT lifestyle drug
- Deficiency negatively impacts health & increases mortality risk
- Therapy improves: Diabetes (T4DM), obesity, bone density
- TRAVERSE Trial (2023): 5,246 men; No ↑ MI, prostate cancer, or urinary symptoms
- **FDA removed boxed CV warning from label Feb. '25**

Testosterone therapy safe in appropriately selected men

Low Testosterone: A Common Problem Beyond Muscles & Sex

Prevalence: 5.6% of men aged 30-79; **Men >70:** 18.4%

Treatment gap: Only 5-20% receive therapy

- Symptomatic testosterone deficiency is underdiagnosed
- Routine screening not performed despite evidence
- Major public health gap

Traish A, et al. Steroids. 2014; Mulhall JP, et al. J Urol. 2018

Low Testosterone: Health Burden

- **CVD risk:** 1.17x
- **Bone fractures:** 1.50x
- **Diabetes:** 1.52x
- **Obesity:** 1.69x
- **Depression:** 1.86x
- **Male infertility:** 6x risk
- **Mortality:** 1.5-2x increased risk

Key point: T is reliable health marker

Therefore, why is it never measured?

De Silva A, et al. Lancet Diabetes Endocrinol. 2024

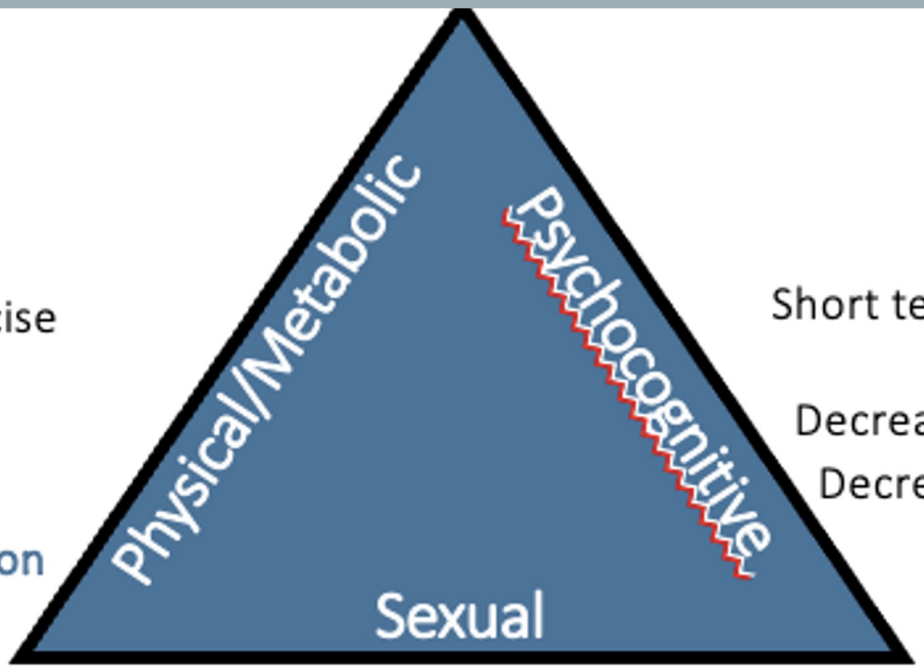
Testosterone: Regulatory Disconnect

- **FDA labeling:** Approved only for defined medical conditions (testes, pituitary, brain)
- **Professional guidelines:** AUA & Endocrine Society recommend for symptomatic men with low morning testosterone
- **Schedule III status:** T is only natural hormone classified as controlled substance
- Creates stigma & heightened safety concerns
- **Result:** Undertreatment despite evidence of safety & efficacy

FDA Labeling & Professional Guidelines Discrepancy

Symptoms/Signs of Testosterone Deficiency/

Low energy
Afternoon fatigue
Decreased strength
Decreased endurance
Decreased response to exercise
Fat gain (central obesity)
Sarcopenia
Bone density loss
Glycemic control dysregulation
Increased MACE risk



Irritability
Depression
Short term memory loss
Decreased focus
Decreased productivity
Decreased motivation

Erectile dysfunction
Low sex drive
Orgasm changes

The development of the symptoms/signs/consequences of TD is not due to the underlying cause, but rather the actual low T levels

Testosterone Treatment: Indications

- **Symptomatic men with documented low T** (typically <300 ng/dL morning level)
- Clinical symptoms + low labs = Treatment indication
- **FDA requires:** Specific medical condition (primary/secondary HG from testis, pituitary, hypothalamus)
- Professional guidelines: Age-related hypogonadism with sx + sy + low T warrants treatment
- =Functional hypogonadism: Requires comprehensive workup & optimization

Khera et al. Mayo Proceed

2016AUA & Endocrine Society Treatment Guidelines

Testosterone Therapy: Benefits & Efficacy

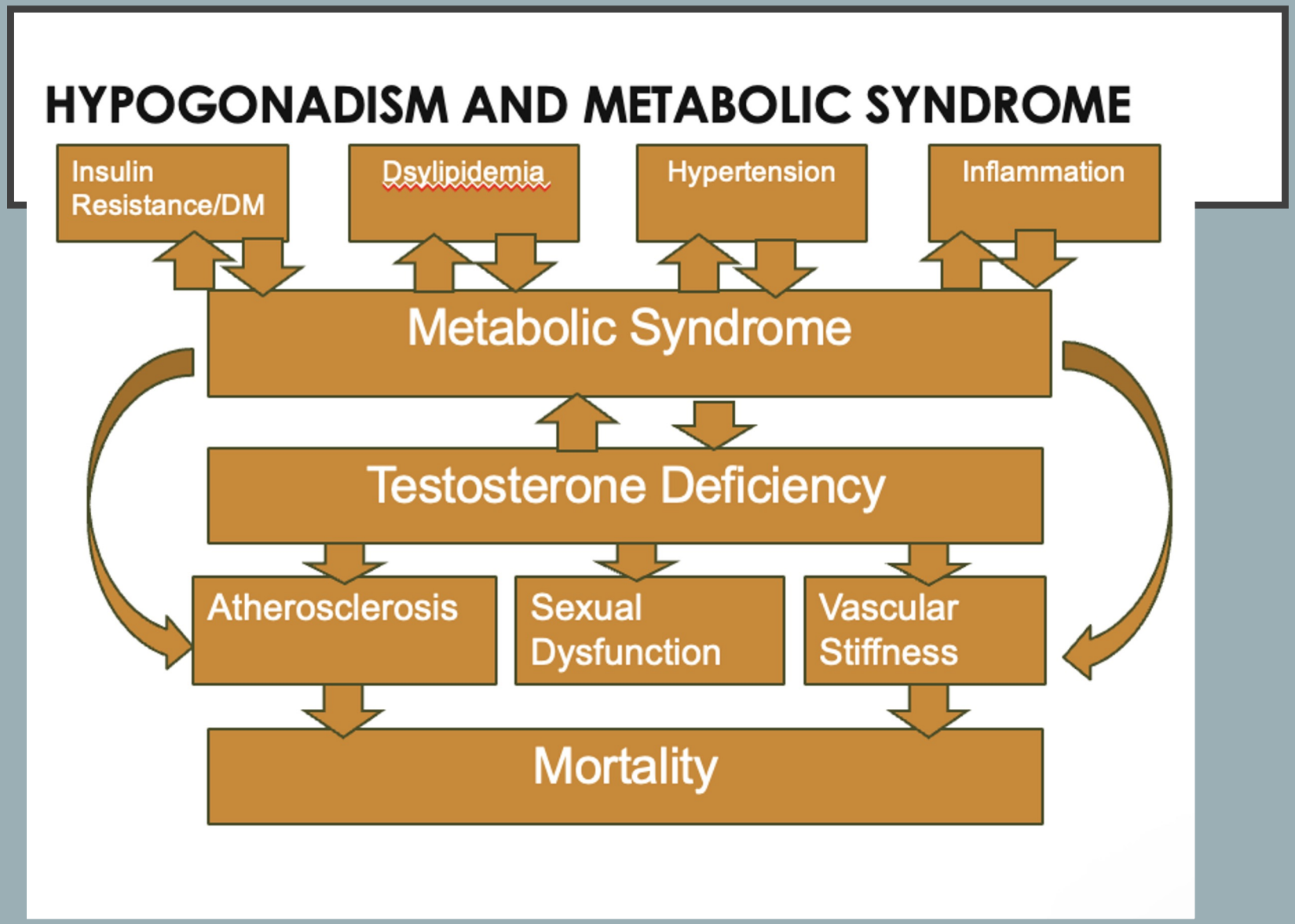
- The diagnosis of functional (age-related) hypogonadism should prompt thorough assessment & optimization of general health including: LH; FSH; A1c; Lipid panel; Baseline PSA

TTh should be offered to men with "age-related" hypogonadism with low levels & sx & sy

- **Key message:** Address lifestyle first or concomitantly (weight loss, comorbidity control)

Individualized approach, not monotherapy

Low T Increases CV Risk; TTh Does Not !!



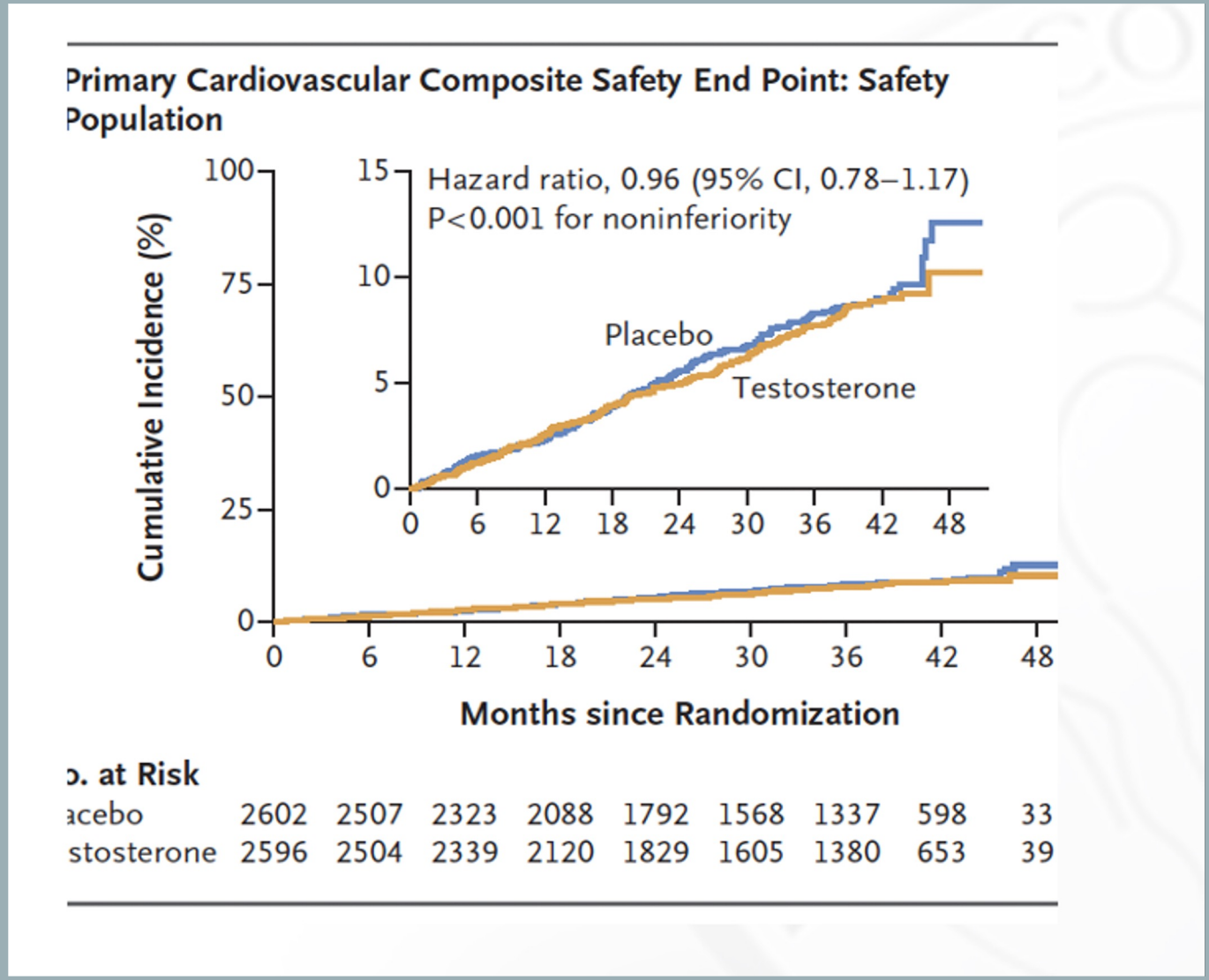
TRAVERSE Trial: CV Safety of T Therapy

Double-blind RCT: 5,200 men (45-80 yo) with hypogonadism & high CV risk

No increase in MACE vs. placebo

Slightly higher: VTE, arrhythmias, kidney injury, bone fractures (not attributed to TTh)

- Median follow-up: 33 months
- Exonerates testosterone for CV safety
- FDA removed black-boxed warning post-TRAVERSE



Lincoff TRAVERSE Trial. NEJM. 2023

T4DM Trial: T + Lifestyle for Diabetes 2021 Lancet

RCT: 1,007 men (50-74 yo) with obesity, new/at-risk T2DM: low T Prediabetes or DM

Testosterone + Lifestyle vs. Placebo + Lifestyle

41% reduction in T2DM prevalence

13% more men reversed diabetes

- 2-year follow-up
- Demonstrates synergy: T therapy + lifestyle

T Trials: Effects of Testosterone Treatment in Older Men Snyder 2016 NEJM

- RCT T gel vs placebo 790 men ≥65 years
- Modest but **clinically significant benefits of testosterone gel on sexual function, mood, anemia, bone density, and some measures of physical function**, but no improvement in vitality/energy.
- Not powered for safety but no increase in CVS events with TTh.

Snyder NEJM Ttrials 2016

T4DM Trial. Lancet Endocrinology. 2021

Prostate Cancer & Testosterone: Myth vs. Reality

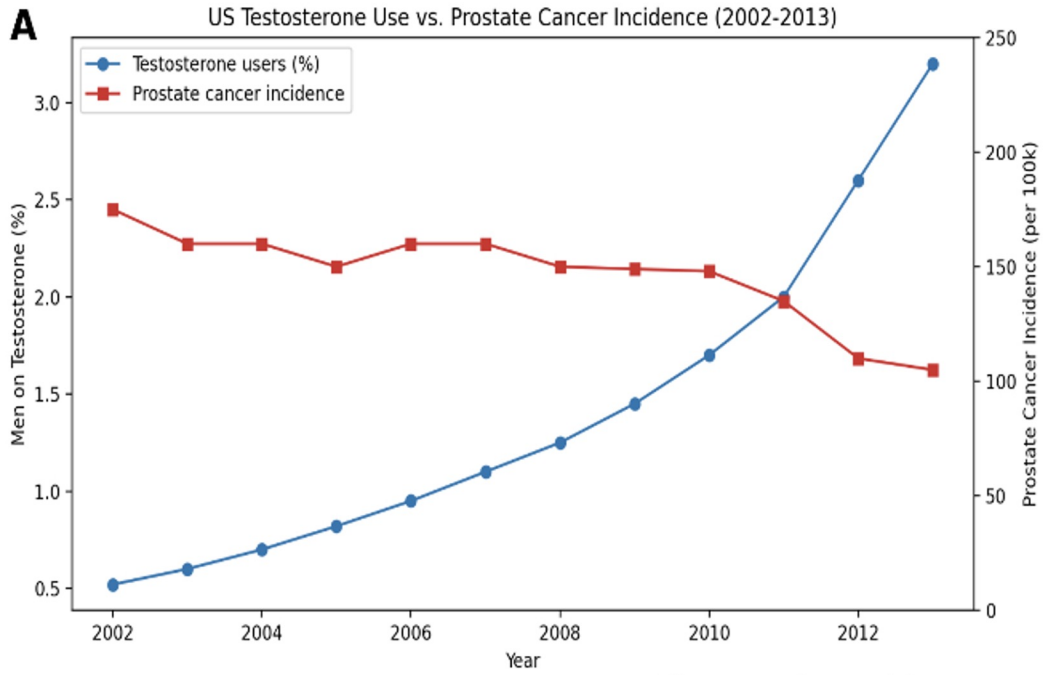
Modern evidence uniformly shows T does NOT cause or promote prostate cancer

- **FDA label (unchanged since 1970s):** Contraindication & warning
- **Evidence:** Endogenous T does NOT increase PCa risk
- **RCTs:** PCa rates identical in T vs. placebo arms
- No PCa increase despite 6-fold ↑ in T use (2002-2013)
- Men on T with prior PCa: No increased recurrence/progression
- **Conclusion:** Prostate warnings contradict evidence; should be removed

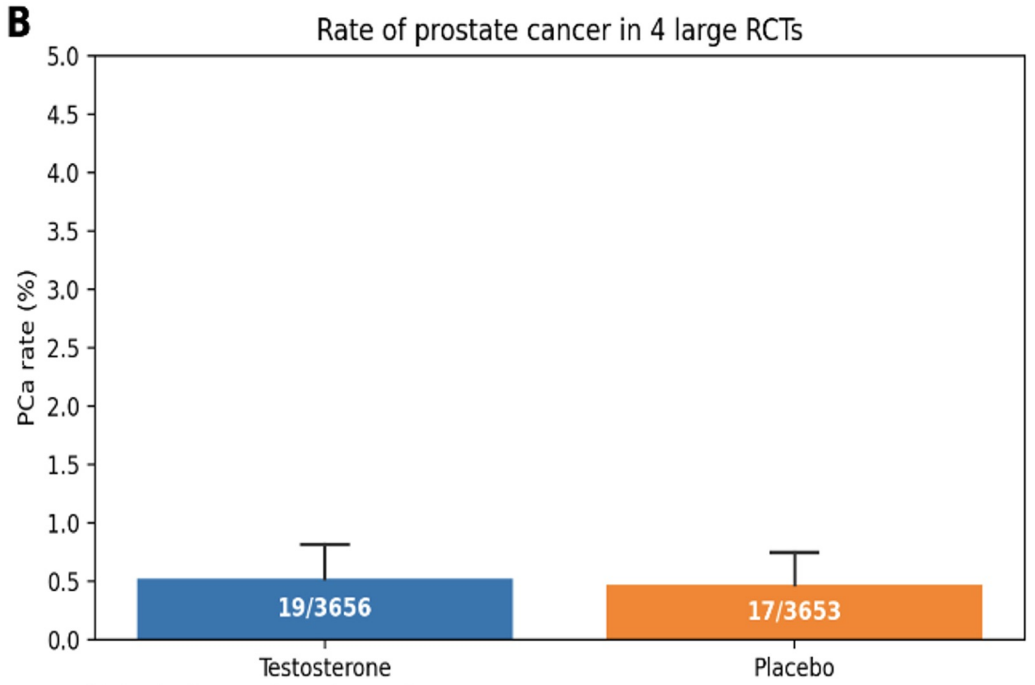
Morgentaler A, et al.; Bhasin S, et al. JAMANetwork 2023

Prostate warnings are contradicted by the evidence

No PCa increase despite 6-fold increase in T usage 2002-2013



RCTs: PCa rates identical in T and placebo arms



Figures from Morgentaler and Traish, submitted

Conclusions T Def:

- Testosterone deficiency adversely affects a man's health, quality of life and risk of mortality
- Large randomized controlled trials and observational studies demonstrate the safety and multiple clinical benefits of testosterone therapy
- Current FDA prostate warnings are not supported by contemporary evidence and should be removed
- Testosterone should not be treated as a controlled substance; its current scheduling creates unnecessary barriers
- Men who have signs and symptoms of testosterone deficiency along with documented low levels may be candidates for treatment, regardless of the cause
- There is no scientific basis for excluding age-related hypogonadism from treatment eligibility

THANK YOU

QUESTIONS?

Medicines, Old and New: 2026 Therapeutic Updates in Heart Failure

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Disclosures

- No disclosures

Objectives

1. Review current medication recommendations for the spectrum of heart failure
2. Discuss newly expanded evidence for digoxin in heart failure (DIGIT-HF trial)
3. Identify patients with heart failure that may benefit from addition of GLP-1 receptor agonist therapy (STEP-HFpEF-DM and STEP-HFpEF trials)
4. Identify patients with heart failure that may benefit from finerenone therapy (FINEARTS-HF trial)
5. Explore novel therapies for specific cardiomyopathies, including mavacamten in hypertrophic cardiomyopathy and tafamidis in transthyretin cardiac amyloidosis

Heart Failure

- Complex clinical syndrome resulting from structural or functional cardiac abnormality
- Leads to impaired ventricular filling (diastolic) or contraction (systolic)
- Results in reduced cardiac output
- Cardinal symptoms include dyspnea, fatigue, and fluid retention

Epidemiology and Clinical Impact

- More than 6 million adults in the United States affected
- Prevalence expected to increase due to aging population
- Leading cause of hospitalization among adults > 65 yrs
- High morbidity, mortality, and healthcare costs

Etiology

Ischemic heart disease

Prior myocardial infarction

Chronic coronary disease

Hypertension, long-standing

Valvular heart disease

Arrhythmias

e.g. Atrial fibrillation

Table 4. Classification of HF by LVEF

Type of HF According to LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤40%
HFimpEF (HF with improved EF)	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%–49% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	LVEF ≥50% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

ACC/AHA guideline for mgmt. of HF 2022

Guideline-Directed Heart Failure (GDMT) Medications (ACC/AHA and ESC)

	HFrEF EF ≤ 40%	HFmrEF EF 41-49%	HFpEF EF ≥ 50%
ARNI ACEi ARB	✅	✅	✅ ARB or ARNI
SGLT2-inhibitor	✅	✅	✅
Beta Blocker	✅	✅	❌
Mineralocorticoid Receptor Antagonist (MRAs)	✅	✅	✅
Digoxin	*If symptomatic despite GDMT*	❌	❌

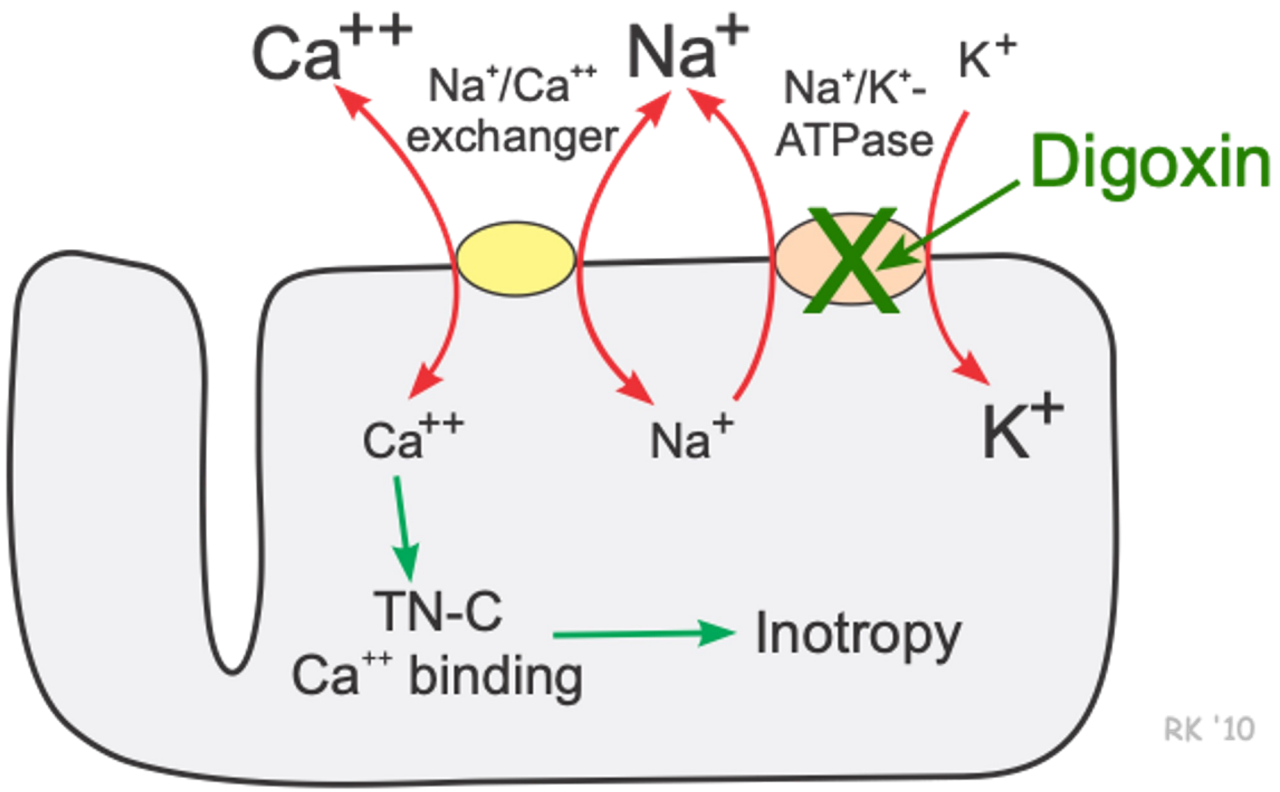
Digoxin

DIGIT-HF, NEJM 2025

Historical Use of Digoxin in Heart Failure

- Derived from the foxglove plant (*Digitalis purpurea*)
- Became a cornerstone therapy for heart failure during 19th–20th century
- The DIG Trial (1997) demonstrated:
  - Reduced heart failure hospitalizations
  - No significant mortality benefit
- Use declined with emergence of modern GDMT (e.g. ARB, BB)
- Now typically considered adjunct therapy for:
  - Symptomatic HFrEF despite optimal therapy
  - Rate control in atrial fibrillation with heart failure

Digoxin Mechanism of Action



https://cvpharmacology.com/cardiostimulatory/digitalis

Key Clinical Considerations

- Narrow therapeutic index
  - Trough 0.5-0.9 mg/dL for heart failure
  - Trough < 1.2 mg/dL for atrial fibrillation
- Monitor:
  - Renal function
  - Electrolytes (especially potassium)
  - Serum digoxin levels
- Watch for toxicity: GI symptoms, visual disturbances, arrhythmias

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2025 VOL. 393 NO. 12

Digitoxin in Patients with Heart Failure and Reduced Ejection Fraction

U. Bavendiek,[1] A. Großhennig,[2] J. Schwab,[3,4] D. Berliner,[1] A. Rieth,[5] L.S. Maier,[6] T. Gaspar,[7,8] N.H. Thomas,[2] X. Liu,[2] S. Schallhorn,[1] E. Angelini,[1] S. Soltani,[1] F. Rathje,[1] M.-A. Sandu,[1] W. Geller,[1] R. Hambrecht,[9] M. Zdravkovic,[10] S. Philipp,[11] D. Kosevic,[12] G. Nickenig,[13] D. Scheiber,[14] S. Winkler,[15] P.M. Becher,[16-18] P. Lurz,[19] M. Hülsmann,[20] S. Wiesner,[2] C. Schröder,[21] B. Neuhaus,[22] A. Seltmann,[22] H. von der Leyen,[23,24] C. Veltmann,[1,25] S. Störk,[26,27] M. Böhm,[28] A. Koch,[2] and J. Bauersachs,[1] for the DIGIT-HF Study Group*

DIGIT-HF Study Group. N Engl J Med. 2025 Sep 25;393(12):1155-1165.

DIGIT-HF: Revisiting Cardiac Glycosides in Modern Heart Failure

Background

- Cardiac glycosides such as Digoxin and Digitoxin have historically been used for symptom relief in heart failure
- Older trials (DIG Trial) showed:
  - ↓ heart failure hospitalizations
  - No clear mortality benefit
- With modern GDMT, the role of cardiac glycosides became uncertain

Purpose of DIGIT-HF

- Evaluate whether digitoxin added to modern HF therapy improves outcomes in patients with HFrEF

DIGIT-HF Study Group. N Engl J Med. 2025 Sep 25;393(12):1155-1165.

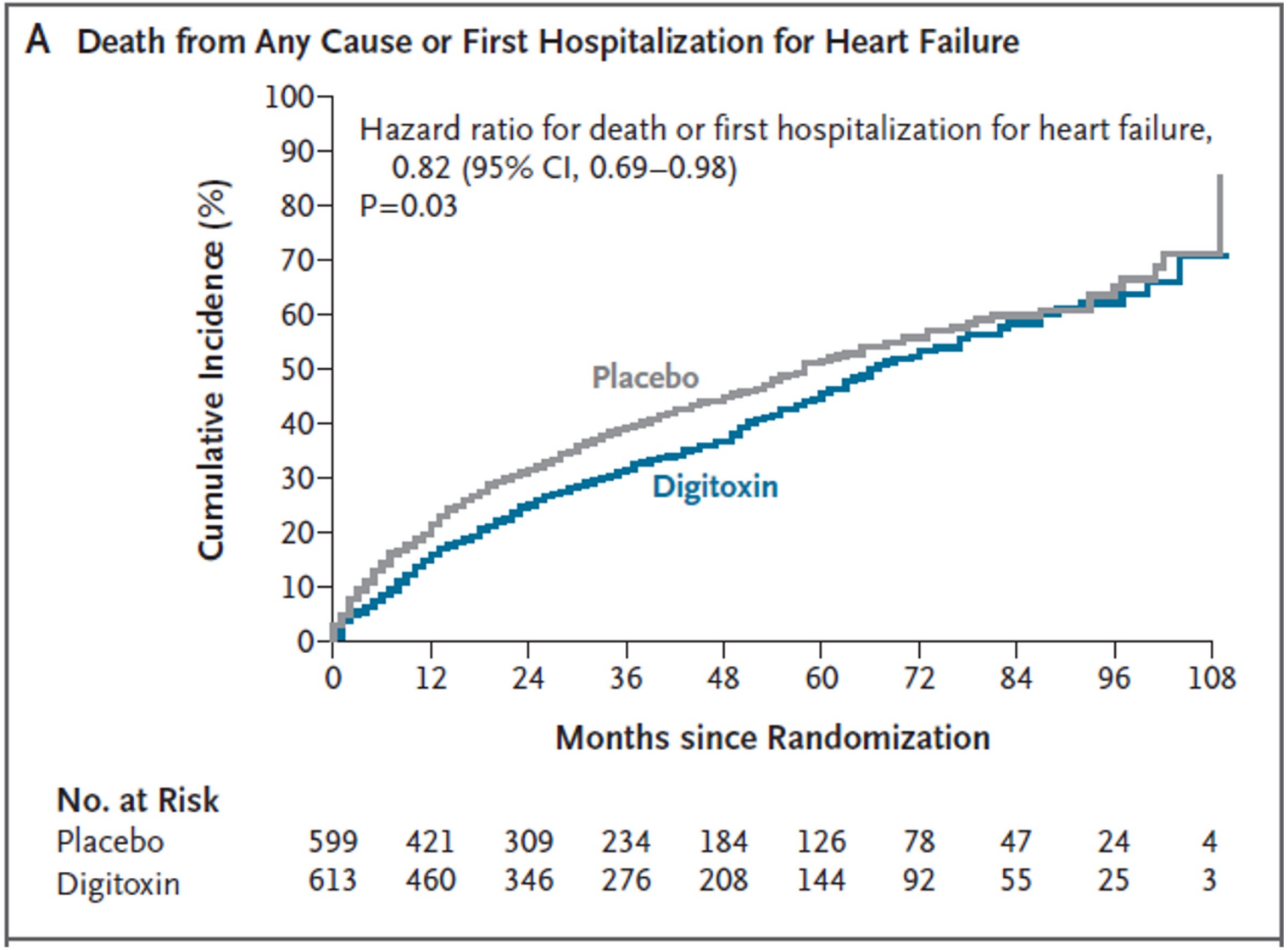
DIGIT-HF: Trial Design

Design	Randomized, double-blind, placebo-controlled trial
Population	N=1,212 patients with symptomatic HFrEF (mean EF ≈ 29%) Inclusion: • LVEF ≤40% with NYHA III–IV • OR LVEF ≤30% with NYHA II
Intervention	• Digitoxin added to standard HF therapy • Starting dose: 0.07 mg daily, titrated to target serum levels
Primary Outcome	Composite of all-cause death and hospitalization for worsening HF
Follow-up	Median 36 months

DIGIT-HF Study Group. N Engl J Med. 2025 Sep 25;393(12):1155-1165.

DIGIT-HF: Results

Primary Outcome: 39.5% digitoxin vs 44.1% placebo (HR 0.82, p=0.03)



DIGIT-HF Study Group. N Engl J Med. 2025 Sep 25;393(12):1155-1165.

Comparing Landmark Cardiac Glycoside Trials

Feature	**DIG Trial (1997)**	**DIGIT-HF Trial (2025)**
Drug studied	Digoxin	Digitoxin
HF treatment era	Pre-modern therapy (limited ACE inhibitor & beta-blocker use)	Modern guideline-directed therapy
Population	~6,800 patients with HFrEF	~1,200 patients with symptomatic HFrEF
Primary outcome	Mortality	Death + HF hospitalization
Main result	No mortality benefit	Modest improvement in composite outcome
Clinical impact	Reduced HF hospitalizations	Suggests possible benefit when added to modern HF therapy

DIGIT-HF: Implications for Clinical Practice

Digitoxin may be considered adjunct therapy in symptomatic HFrEF despite optimal GDMT

Consider use in patients with HFrEF and:

- Atrial fibrillation
- Higher heart rates
- Low blood pressure

Important caveats

- Trial smaller than planned → limited statistical power
- Findings cannot be directly extrapolated to digoxin

GLP-1 Agonists

STEP-HFpEF-DM and STEP-HFpEF trials

Background: Cardiovascular Safety of Antidiabetic Medications

Patients with Type 2 Diabetes have a 2-4x higher risk of cardiovascular disease, including:

- Myocardial Infarction
- Stroke
- Heart Failure

Historically, diabetes medications were approved based primarily on glycemic control (A1c reduction) rather than cardiovascular outcomes

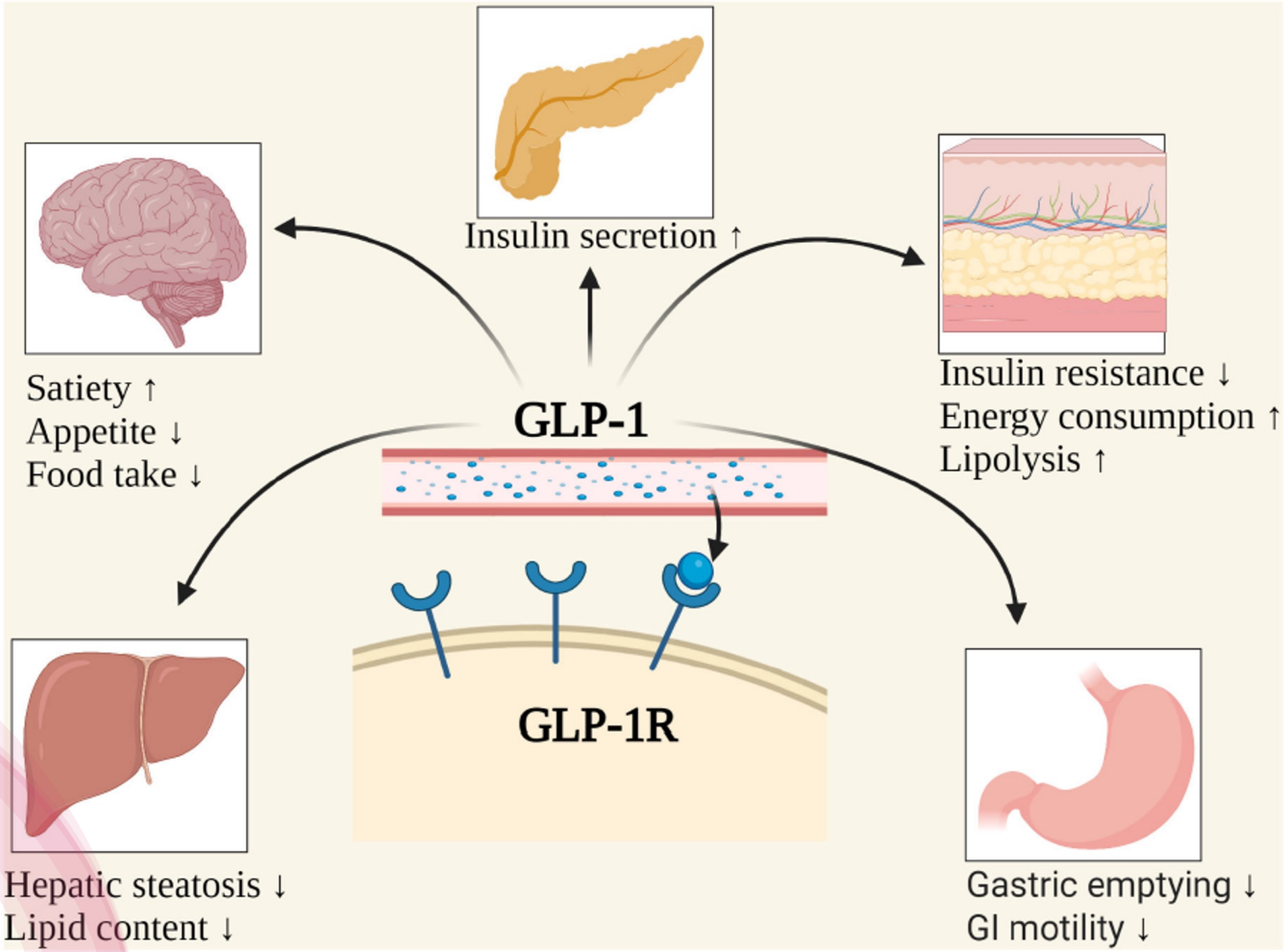
Key Turning Point

- Concern for CV risk with **Rosiglitazone** after a large meta-analysis suggested increased risk of MI
- In 2008 FDA issued requirements for all diabetes meds coming to market; trials must include:
  - ✓ Cardiovascular safety evaluation
  - ✓ Large cardiovascular outcome trials (CVOTs)
  - ✓ Assessment of major adverse cardiovascular events (MACE)
- Since the FDA guidance, studies have shown that diabetes medications provide **cardiovascular benefit**, including:
  - Empagliflozin (EMPA-REG OUTCOME)
  - Liraglutide (LEADER)
  - Semaglutide (SUSTAIN-6)

GLP-1 Agonists

- Glucagon-Like Peptide-1 is an **incretin hormone** released from the intestine after meals that helps regulate glucose and metabolism
- Medications such as **Semaglutide**, **Liraglutide**, and **Dulaglutide** mimic this hormone

GLP-1 Agonist Mechanism of Action



Wang JY, et al. Front Endocrinol (Lausanne). 2023 Feb 1;14:1085799.

Why GLP-1 Receptor Agonists May Benefit Patients with Heart Failure

- Patients with Heart Failure, particularly HFpEF, may have metabolic comorbidities such as:
  - Obesity
  - Type 2 Diabetes
  - Systemic inflammation and insulin resistance
- These factors contribute to worsening HF symptoms and functional limitation

ORIGINAL ARTICLE

Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

M.N. Kosiborod, M.C. Petrie, B.A. Borlaug, J. Butler, M.J. Davies, G.K. Hovingh, D.W. Kitzman, D.V. Møller, M.B. Treppendahl, S. Verma, T.J. Jensen, K. Liisberg, M.L. Lindegaard, W. Abhayaratna, F.Z. Ahmed, T. Ben-Gal, V. Chopra, J.A. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovský, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. van der Meer, D. Von Lewinski, D. Wolf, and S.J. Shah, for the STEP-HFpEF DM Trial Committees and Investigators*

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Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C Petrie, for the STEP-HFpEF Trial Committees and Investigators*

STEP-HFpEF Trial Committees and Investigators. N Engl J Med. 2023 Sep 21;389(12):1069-1084.
STEP-HFpEF DM Trial Committees and Investigators. N Engl J Med. 2024 Apr 18;390(15):1394-1407.

STEP-HFpEF Trials

	STEP-HFpEF	STEP-HFpEF-DM
Design	Randomized, double-blind, placebo-controlled trial	
Population	N=529 patients • BMI ≥30 kg/m² • NYHA class II–IV symptoms • Elevated natriuretic peptides • **No diabetes**	N=616 • BMI ≥30 kg/m² • NYHA class II–IV symptoms • Elevated natriuretic peptides • **With diabetes**
Intervention	Weekly **Semaglutide 2.4 mg** vs placebo	
Primary Outcome	1. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score 2. Percent body weight change	
Follow-up	Duration 52 weeks	

STEP-HFpEF Trial Committees and Investigators. N Engl J Med. 2023 Sep 21;389(12):1069-1084.
STEP-HFpEF DM Trial Committees and Investigators. N Engl J Med. 2024 Apr 18;390(15):1394-1407.

STEP-HFpEF and STEP-HFpEF-DM Trial Results

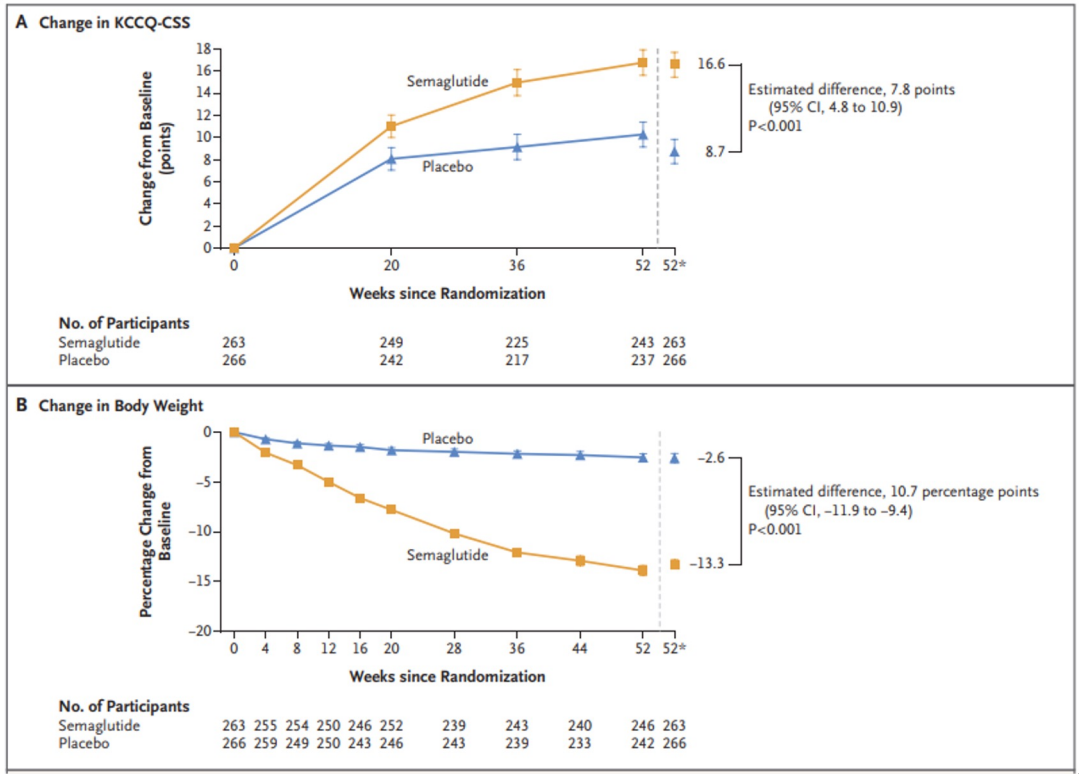
Semaglutide vs placebo:

	STEP-HFpEF	**STEP-HFpEF-DM**
Outcome	N=529 patients	N=616 patients
KCCQ	+16.6 vs +8.7 p<0.001	+13.7 vs +6.4 p<0.001
Body weight change	−13.3% vs −2.6% p<0.001	−9.8% vs −3.4% p<0.001
6-minute walk distance	+21.5 m vs +1.2 m p<0.01	+12.7 m vs −1.6 m p<0.05
NT-proBNP change	−20.9% vs −5.3% p<0.05	−18.3% vs −4.3% p<0.05

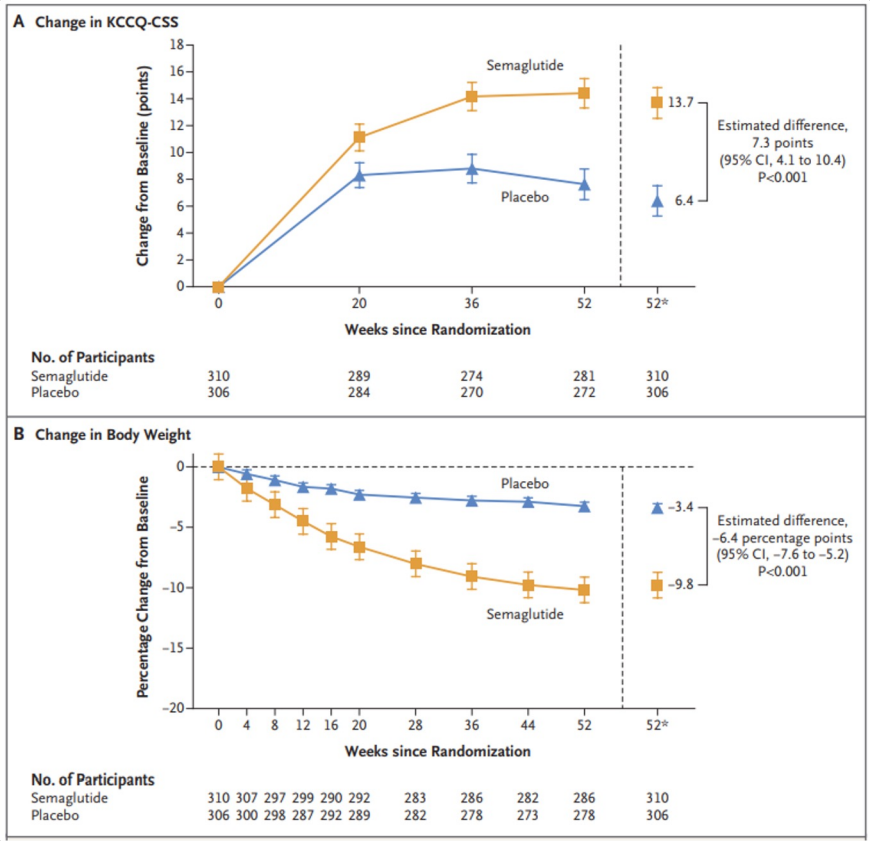
STEP-HFpEF Trial Committees and Investigators. N Engl J Med. 2023 Sep 21;389(12):1069-1084.
STEP-HFpEF DM Trial Committees and Investigators. N Engl J Med. 2024 Apr 18;390(15):1394-1407.

STEP-HFpEF Trial Results

STEP-HFpEF



STEP-HFpEF-DM



STEP-HFpEF Trial Committees and Investigators. N Engl J Med. 2023 Sep 21;389(12):1069-1084.
STEP-HFpEF DM Trial Committees and Investigators. N Engl J Med. 2024 Apr 18;390(15):1394-1407.

Which HF Patients May Benefit?

- HFpEF
- Central obesity
- Insulin resistance
- Systemic inflammation
- Reduced exercise tolerance

Finerenone

FINEARTS-HF Trial

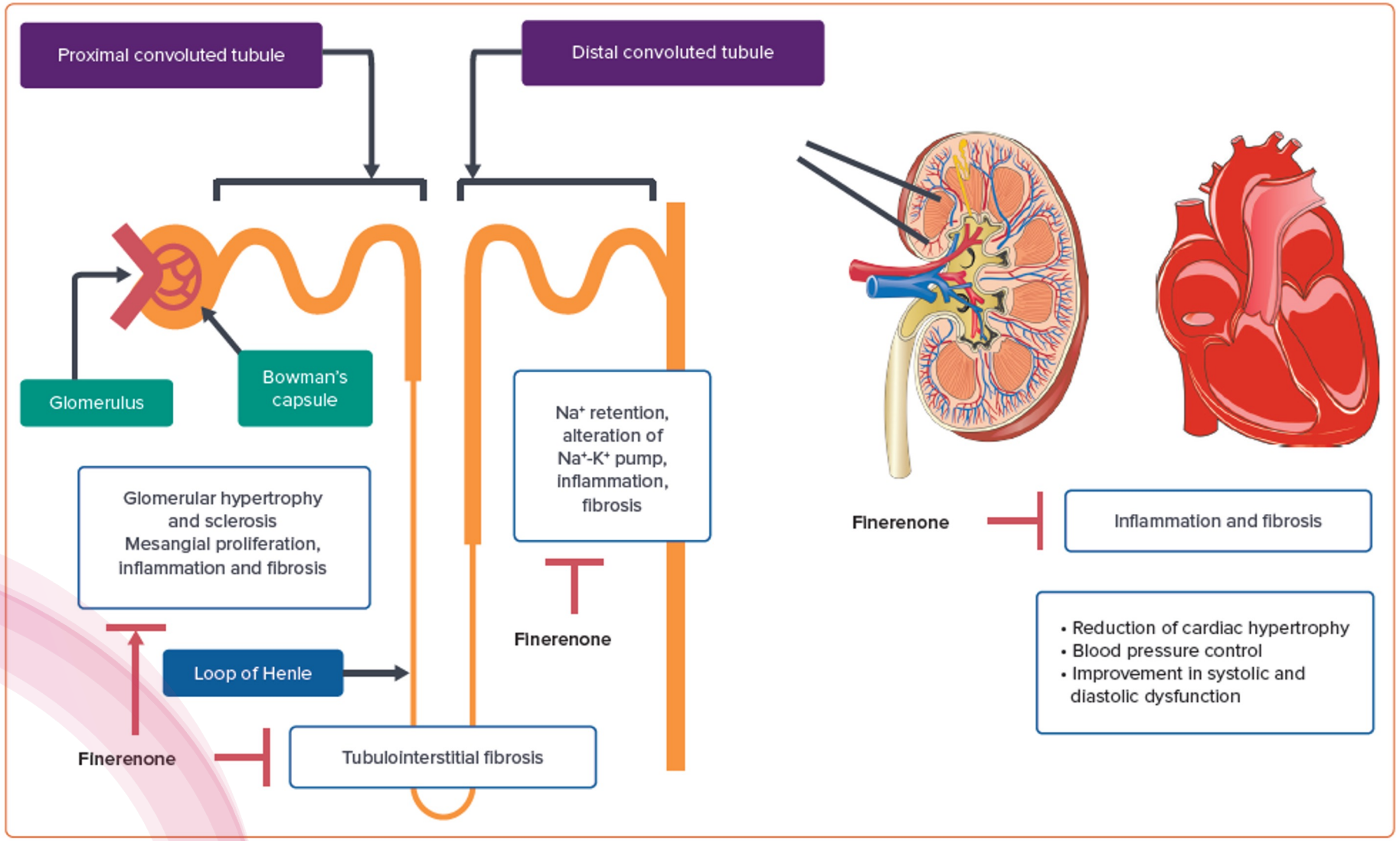
Mineralocorticoid Receptor Antagonists (MRAs) in HF

- HF and CKD patients have elevated aldosterone, which promotes:
  - Fibrosis
  - Inflammation
  - Cardiac remodeling
- MRAs improve survival & reduce HF hospitalization in HFrEF (RALES, EPHESUS, EMPHASIS-HF) and HFpEF (TOPCAT)
- Safety: monitor potassium & renal function; spironolactone may cause gynecomastia

Finerenone: Next-Generation MRA

- Traditional MRAs (spironolactone, eplerenone) are effective but limited by hyperkalemia and renal dysfunction
- Finerenone is a non-steroidal MRA with:
  - Greater selectivity
  - Lower risk of gynecomastia
  - Potentially safer in patients with CKD

Finerenone Mechanism of Action



Cardiac Failure Review 2024;10:e19.

Finerenone Trials

Trial	Population	Intervention	Key Findings
FIDELIO-DKD	CKD + T2DM	Finerenone vs placebo	↓ composite of CKD progression and CV events
FIGARO-DKD	CKD + T2DM	Finerenone vs placebo	↓ CV death or HF hospitalization
FINE-HF (planned/ongoing)	*HFrEF ± CKD*	*Finerenone*	*Expected to evaluate **direct HF outcomes***

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Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

S.D. Solomon, J.J.V. McMurray, M. Vaduganathan, B. Claggett, P.S. Jhund, A.S. Desai, A.D. Henderson, C.S.P. Lam, B. Pitt, M. Senni, S.J. Shah, A.A. Voors, F. Zannad, I.Z. Abidin, M.A. Alcocer-Gamba, J.J. Atherton, J. Bauersachs, M. Chang-Sheng, C.-E. Chiang, O. Chioncel, V. Chopra, J. Comin-Colet, G. Filippatos, C. Fonseca, G. Gajos, S. Goland, E. Goncalvesova, S. Kang, T. Katova, M.N. Kosiborod, G. Latkovskis, A.P.-W. Lee, G.C.M. Linssen, G. Llamas-Esperón, V. Mareev, F.A. Martinez, V. Melenovský, B. Merkely, S. Nodari, M.C. Petrie, C.I. Saldarriaga, J.F.K. Saraiva, N. Sato, M. Schou, K. Sharma, R. Troughton, J.A. Udell, H. Ukkonen, O. Vardeny, S. Verma, D. von Lewinski, L. Voronkov, M.B. Yilmaz, S. Zieroth, J. Lay-Flurrie, I. van Gameren, F. Amarante, P. Kolkhof, and P. Viswanathan, for the FINEARTS-HF Committees and Investigators*

FINEARTS-HF Committees and Investigators. N Engl J Med. 2024 Oct 24;391(16):1475-1485

FINEARTS-HF: Trial Design

Design	Randomized, double-blind, placebo-controlled trial
Population	N=6,001 adults (mean age ~72) • NYHA class II–IV HF • **LVEF ≥40%** • elevated natriuretic peptides • structural heart disease
Intervention	• Finerenone (titrated 10–40 mg daily based on kidney function) vs placebo, added to guideline-directed therapy
Primary Outcome	Composite of cardiovascular (CV) death and total worsening HF events (first/recurrent HF hospitalization or urgent HF visits)
Follow-up	Median 2.6 years

FINEARTS-HF Committees and Investigators. N Engl J Med. 2024 Oct 24;391(16):1475-1485

FINEARTS-HF Results

Outcome	**Finerenone (N=3003)**	**Placebo (N=2998)**	**Finerenone vs Placebo**
Primary: Total worsening HF events + CV death	1083 events 14.9 events/100 patient-yr	1283 events 17.7 events/100 patient-yr	Rate ratio 0.84 (95% CI 0.74–0.95), **p=0.007**
Total worsening HF events	842	1024	Rate ratio 0.82 (95% CI 0.71–0.94), **p=0.006**
CV death	242 (8.1%)	260 (8.7%)	HR 0.93 (95% CI 0.78–1.11), **not significant**

FINEARTS-HF Committees and Investigators. N Engl J Med. 2024 Oct 24;391(16):1475-1485.

Finerenone: Takeaways

- Consider for patients with HFpEF/HFmrEF, especially with CKD and/or T2DM
- Primary benefit: reduces HF morbidity and hospitalizations
- Monitoring: baseline and periodic serum K^+ and eGFR
- Can be used alongside standard HF therapies including SGLT2 inhibitors
- Offers a non-steroidal MRA option with potentially lower risk of hormonal side effects

Novel Cardiomyopathy Treatments

Mavacamten for hypertrophic cardiomyopathy and tafamidis for transthyretin cardiac amyloidosis

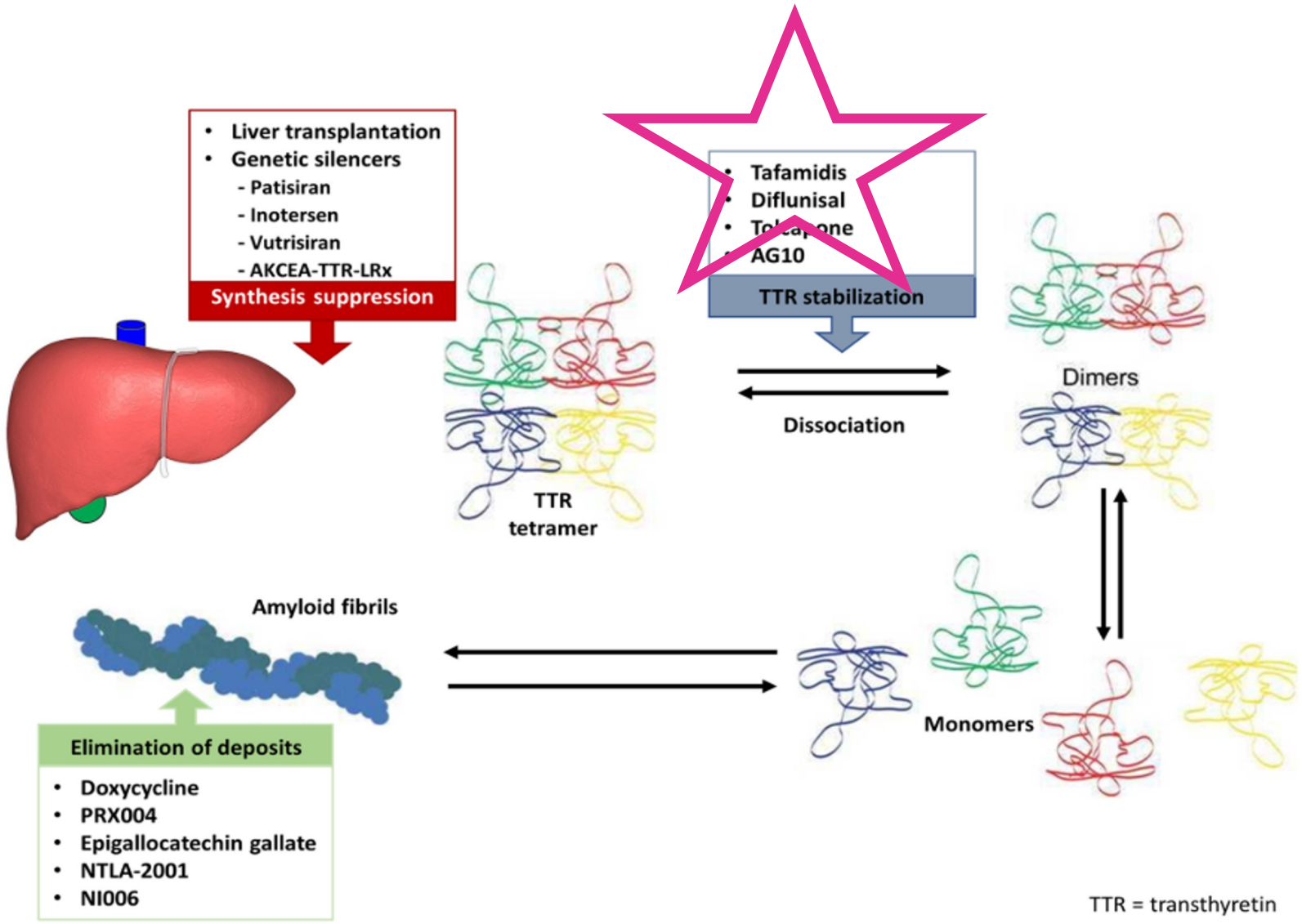
Transthyretin Amyloid Cardiomyopathy (ATTR-CM)

- Progressive infiltrative cardiomyopathy caused by deposition of misfolded transthyretin (TTR) amyloid in the myocardium
- Leads to stiff ventricles, diastolic dysfunction, and HFpEF-like symptoms

Clinical Features

- HF symptoms: dyspnea, fatigue, exercise intolerance
- Signs: concentric LV hypertrophy, preserved EF, restrictive filling
- Conduction disease, arrhythmias
- Extracardiac manifestations: carpal tunnel, neuropathy, autonomic dysfunction

Tafamadis: Mechanism of Action



Yadav JD, et al. Ann Pharmacother. 2021 Dec;55(12):1502-1514.

Tafamadis Clinical Outcomes

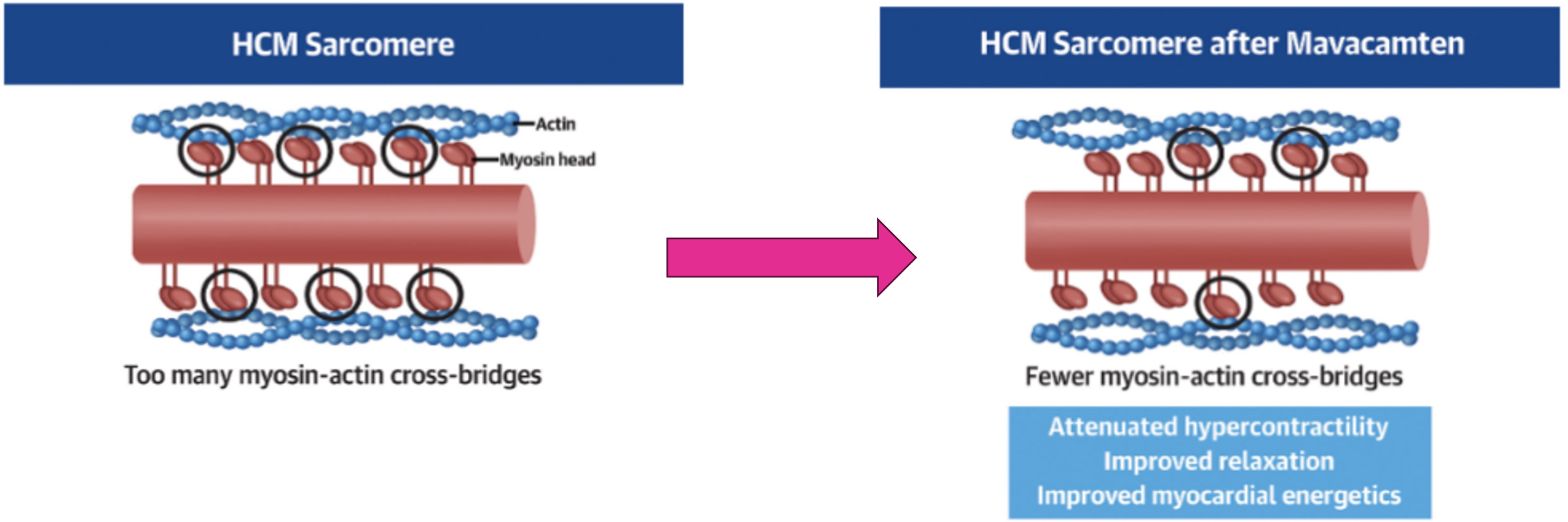
ATTR-ACT Trial: Key Points

- N=441 patients with transthyretin amyloid cardiomyopathy (ATTR-CM)
- Intervention: Tafamidis 20 mg or 80 mg daily vs placebo for 30 months
- Results:
  - ↓ All-cause mortality: 29.5% vs 42.9% (tafamidis vs placebo)
  - ↓ CV hospitalizations: 0.48 vs 0.70 events/patient-year
- Safety: Well tolerated; adverse events similar to placebo

Hypertrophic Cardiomyopathy (HCM)

- Genetic cardiac disorder characterized by left ventricular hypertrophy (LVH) without secondary cause
- Often involves asymmetric septal hypertrophy
  - Leads to **diastolic dysfunction, LVOT obstruction, arrhythmias**
- Disease-modifying therapy: **Mavacamten** for obstructive HCM

Mavacamten Mechanism of Action



Hegde SM, et al. J Am Coll Cardiol. 2021 Dec 21;78(25):2518-2532.

Mavacamten Clinical Outcomes

Key Trials: EXPLORER-HCM and VALOR-HCM

Improves symptoms and exercise tolerance

- Improved 6-minute walk test, KCCQ score, and NYHA class

Reduces heart outflow blockage (LVOT obstruction)

- Significant improvement in resting and peak pressure gradients
- Most patients had ≥50% improvement in obstruction

Helps reduce HF symptoms and hospitalizations

Generally safe and well tolerated

- Mild side effects: dizziness, fatigue, fainting

Medicines, Old and New: 2026 Therapeutic Updates in Heart Failure

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