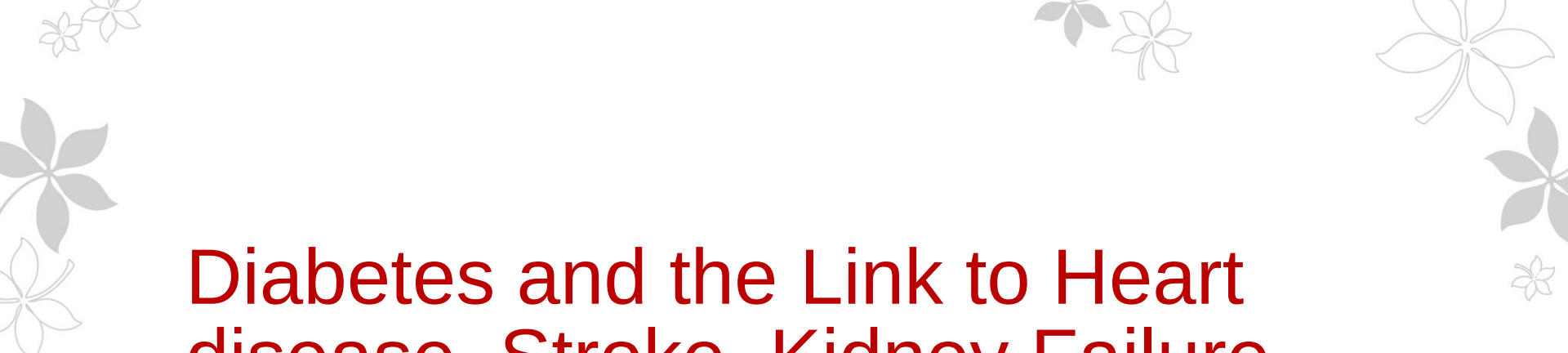




Diabetes and the Link to Heart disease, Stroke, Kidney Failure and other Complications

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Disclosures

- I serve on advisory boards or perform consulting activities with Eli Lilly, Dexcom
- I have served as an investigator for clinical trials sponsored or funded by Eli Lilly, Novo Nordisk, Sanofi, Viacyte, Abbott, and Dexcom



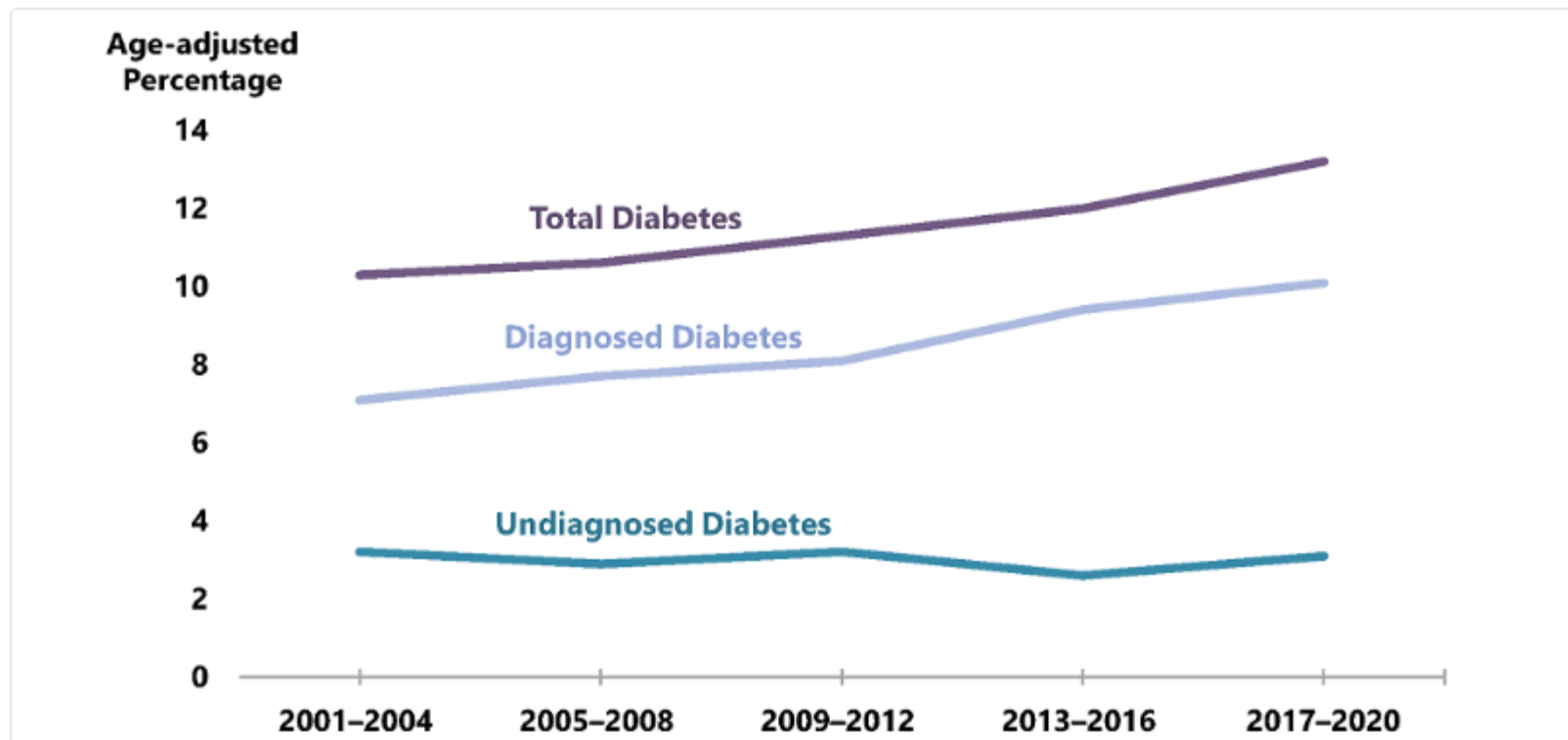
What is Diabetes?

- Diabetes is a group of diseases characterized by high blood glucose levels that result from defects in the body's ability to produce and/or use insulin.



Trends in Diabetes

Figure 1. Trends in age-adjusted prevalence of diagnosed diabetes, undiagnosed diabetes, and total diabetes among adults aged 18 years or older, United States, 2001–2020.

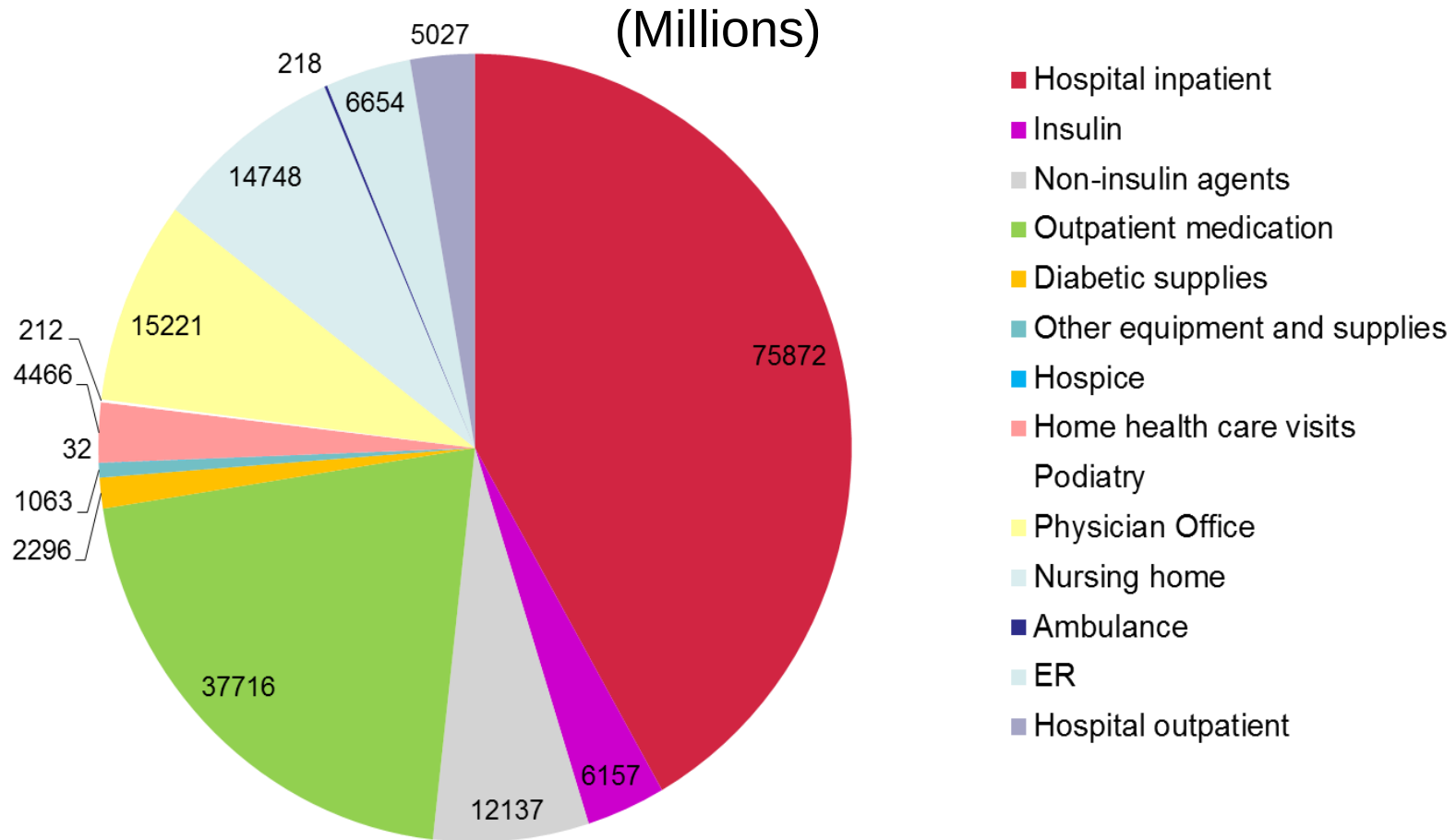


<https://www.cdc.gov/diabetes/data/statistics-report/diagnosed-undiagnosed-diabetes.html>



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Costs Due to Diabetes



\$176 billion (direct medical costs)

\$ 69 billion (reduced productivity)

\$245 BILLION (41% increase from 2007)

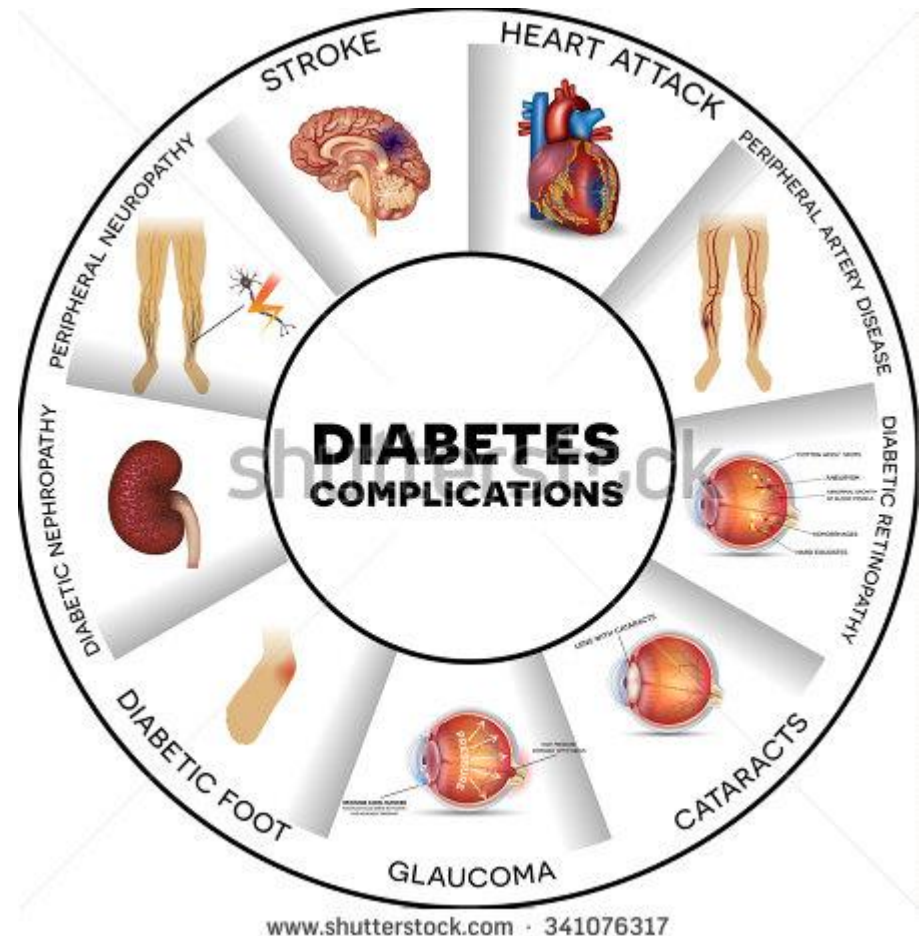
ADA. Diabetes Care 2013; 36:1033



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The Toll of Diabetes

- 7th leading cause of death in the U.S.
 - Heart attack and stroke account for 65% of deaths
- Leading cause of new blindness in adults
- Leading cause of kidney failure
- Leading cause of non-traumatic lower limb amputations



Heart Complications

AT THE **HEART** OF DIABETES

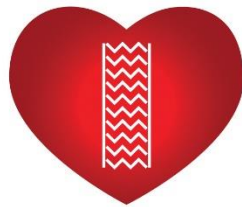
Diabetes & Heart Disease
By The #s

U.S. DIABETES PATIENTS HAVE:



2-3x

increased risk
for heart disease



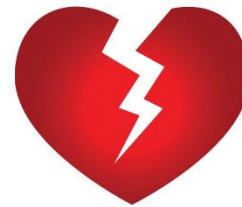
30%

of coronary stents
implanted in 2011



280,000

heart attacks
annually



2-4x

higher heart disease
morbidity and mortality rates



60%

chance of dying
from heart disease

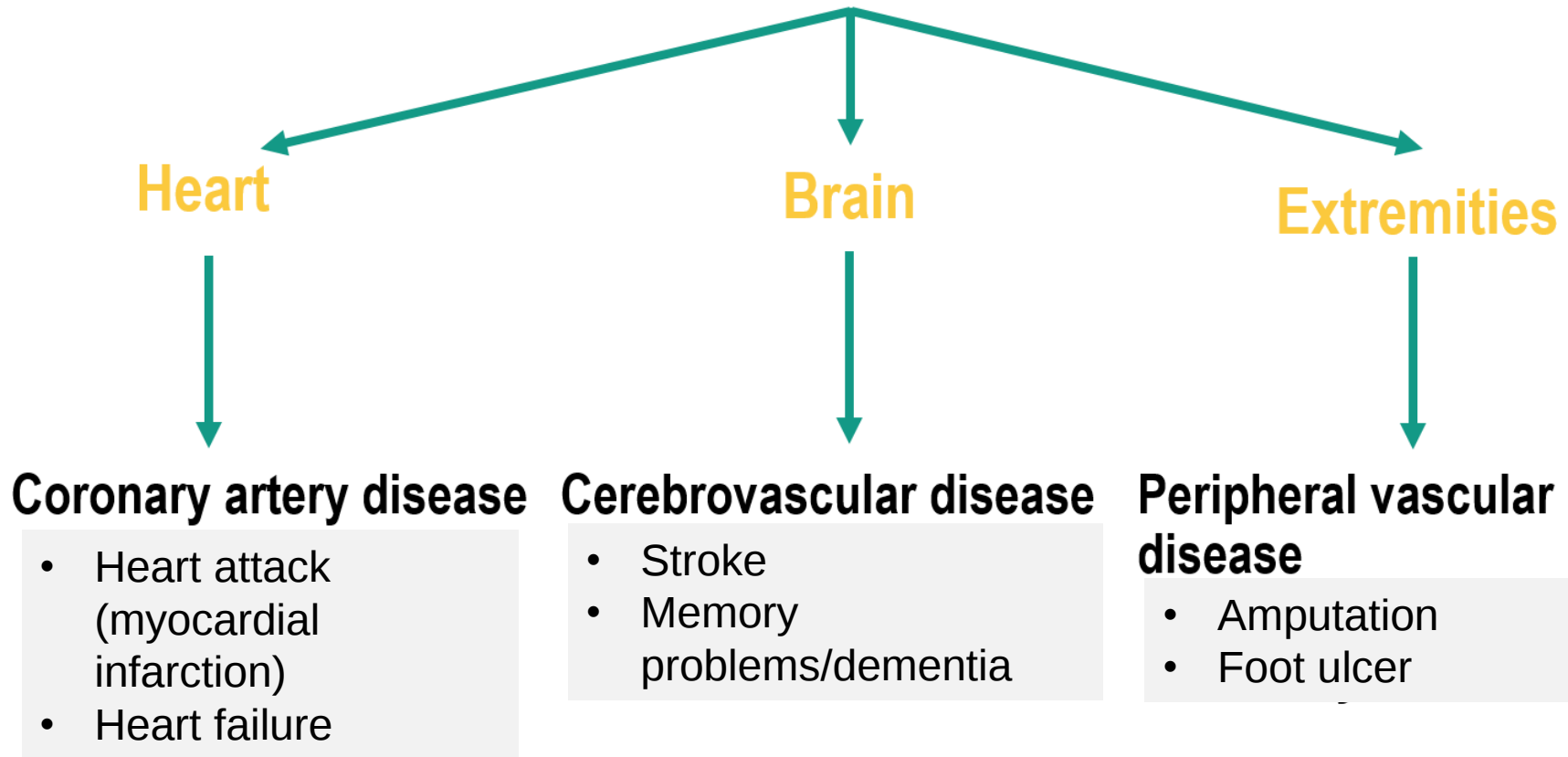
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Heart and Vascular Complications

Injury to Large Blood Vessels



Risk Factors for Heart and Vascular Disease

Modifiable

- Glucose
- Blood pressure
- Cholesterol
- Smoking
- High body mass index
- Kidney disease
- Social determinants of health/health equity

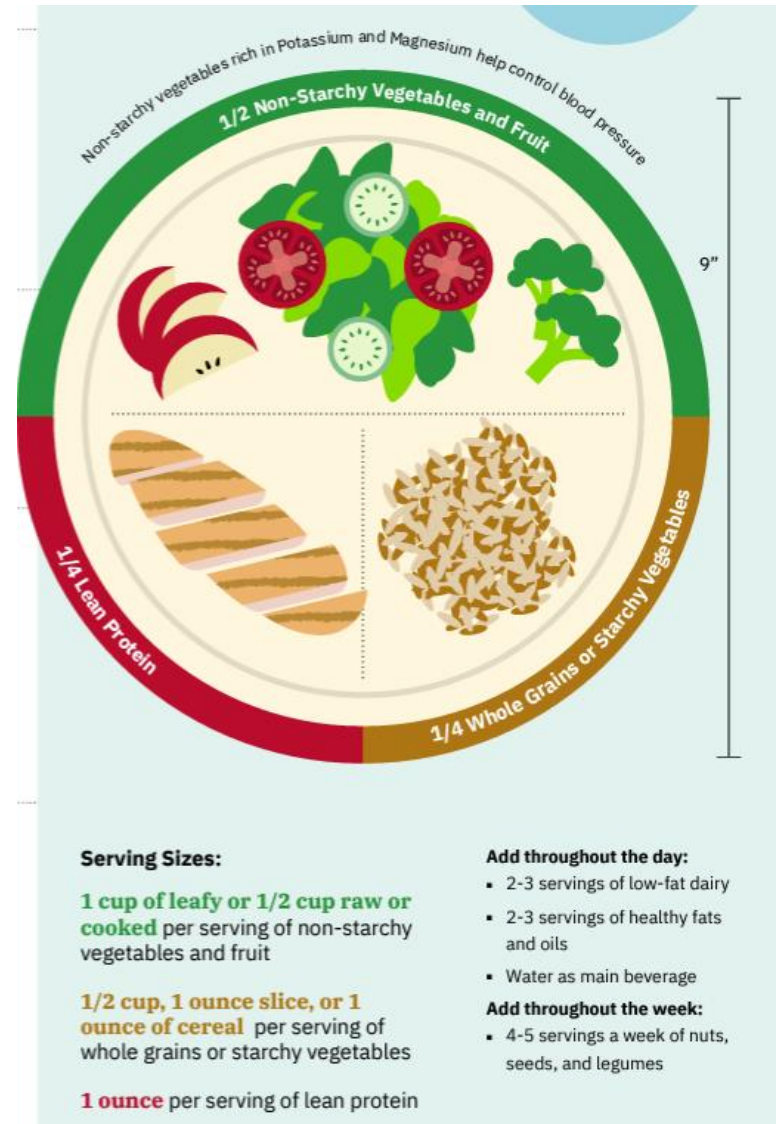
Not modifiable

- Sex assigned at birth
- Family history
- Age



Blood Pressure

- Measure at every visit
- Home BP monitoring
- Targets--individualized
 - 130/80: high risk (known cardiovascular disease)
 - 140/90: lower risk
- Lifestyle changes
 - DASH diet (reduced sodium, increased potassium)
 - Physical activity
 - Weight loss (if indicated)



Lipid (Cholesterol) Management

- Check lipids every 1-2 years
- Treatment-based approach, regardless of cholesterol levels
 - High dose statin for people with DM with known cardiovascular disease (CVD)
 - Moderate dose statin for people with DM 40-75 years of age without known CVD
 - Consider statin for others

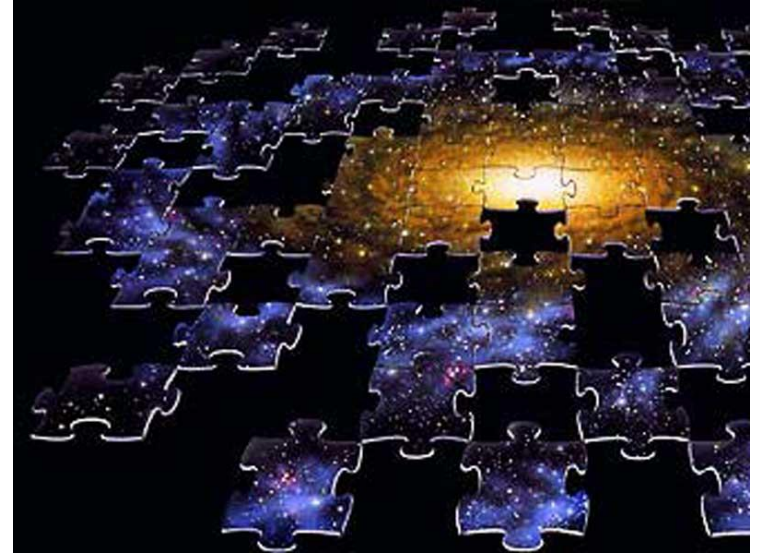


Glucose Lowering Medications

- Studies that demonstrate heart and vascular safety
 - DPP-4 inhibitors
 - Some GLP-1 receptor agonists
 - Insulins
- Studies that show a reduction in risk:
 - SGLT2 inhibitors: Empagliflozin, Canagliflozin, Dapagliflozin
 - Preferred for patients with heart failure or kidney disease
 - Some GLP-1 receptor agonists: Liraglutide, Semaglutide, Dulaglutide
 - These agents are preferred in patients with established CV disease



Does Glucose Control Protect the Heart?



- **Glucose control** prevents kidney damage, loss of vision, and amputations
- **Aggressive management of all risk factors is necessary to prevent heart disease**
 - Blood pressure
 - Cholesterol
 - Smoking
 - Diet/activity

Microvascular Complications

Injury to small blood vessels

Eye

- Retinopathy
- Cataract
- Glaucoma

Kidney (Nephropathy)

- Albuminuria
- Chronic kidney disease

Nerve

(Neuropathy)

- Peripheral
- Autonomic

Blindness

Kidney failure

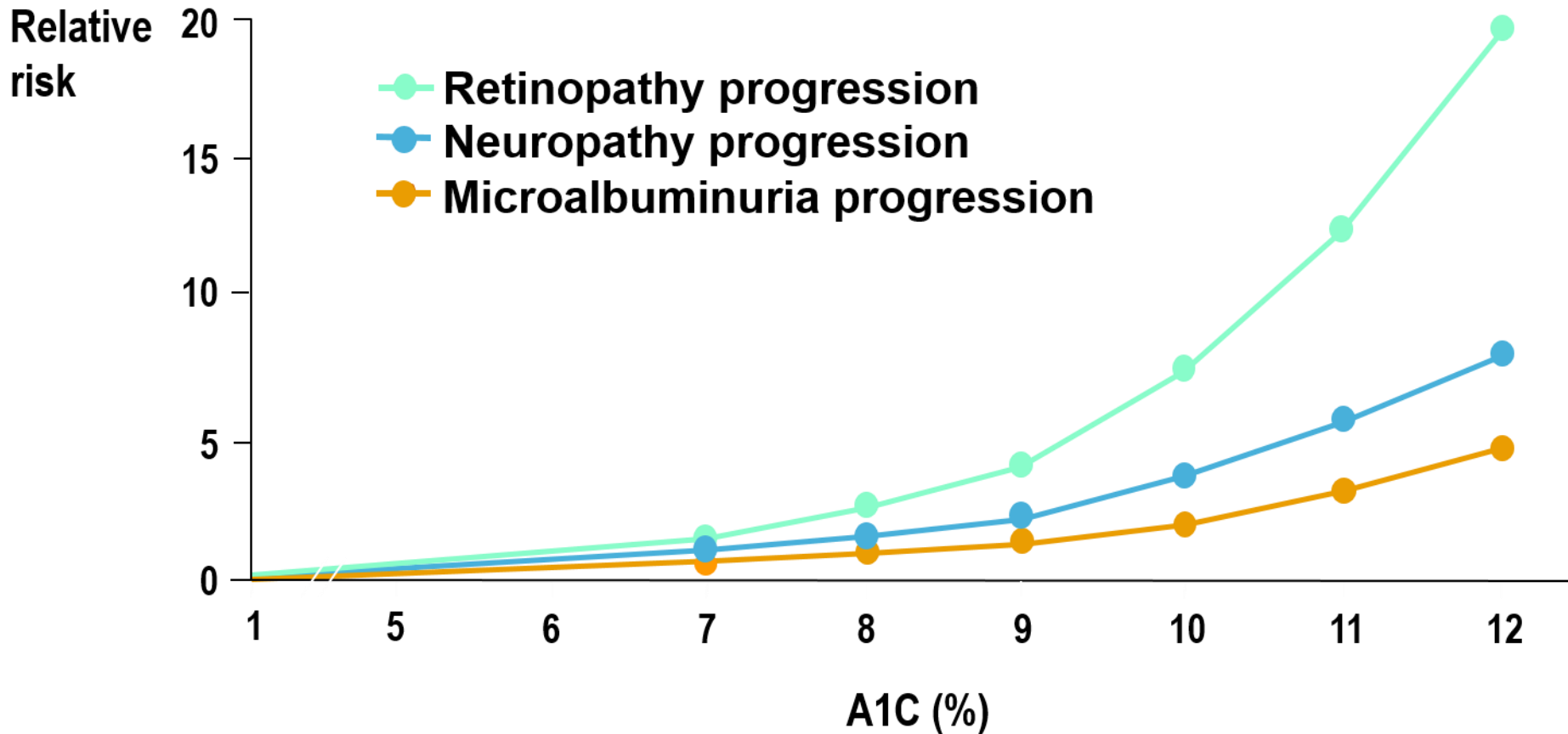
**Amputation
Foot ulcer**

Death or disability



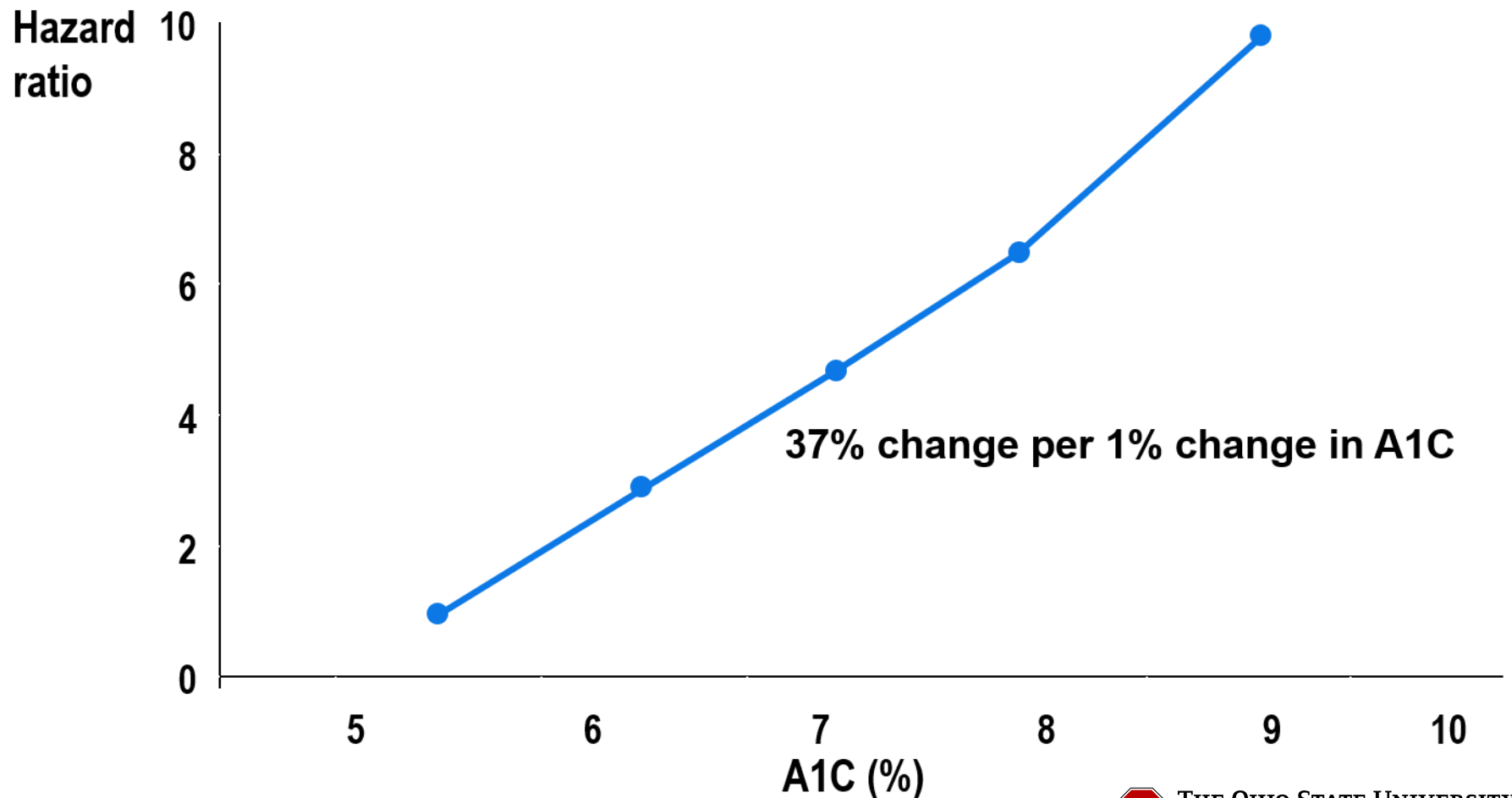
Risk of Microvascular Complications vs A1C in Type 1 Diabetes

Results From the Diabetes Control & Complications Trial



Risk of Microvascular Events vs A1C in Type 2 Diabetes

Results From the United Kingdom Prospective Diabetes Study



Post-Trial Follow-up of UKPDS and DCCT: *Metabolic Memory*

- A continued reduction in risk for complications and emergent risk reductions for heart disease and all-cause mortality were observed during long-term follow-up after the end of the studies.

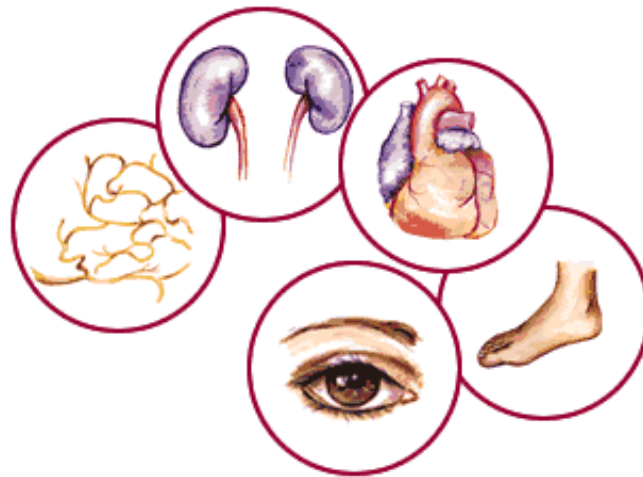


"The Persistence of Memory", Dali, 1931



Mechanisms for Microvascular Complications

- Direct toxic effect of glucose
- Genetics
- Co-morbidities (eg. High blood pressure)
- Social determinants of health and health equity

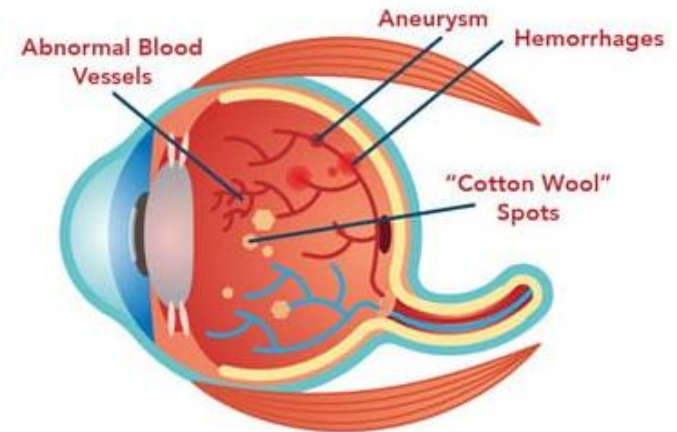


Modifiable Risk Factors for Complications

	Nephropathy	Neuropathy	Retinopathy	Cardiovascular
Glucose	✓	✓	✓	?
Blood Pressure	✓		✓	✓
Lipids	?		?	✓
Smoking	✓	✓	✓	✓



Eye Disease (Retinopathy)



- Screening:
 - Yearly dilated eye exam
 - Before or in first trimester of pregnancy and every trimester
- Prevention: Optimize A1c, blood pressure, cholesterol
- Treatment
 - Early stage is reversible
 - Can slow progression
 - High risk: measures to prevent or treat vision loss
 - Laser surgery
 - Injections of Vascular endothelial growth factor (VEGF) therapy

Eye Disease: Excuses

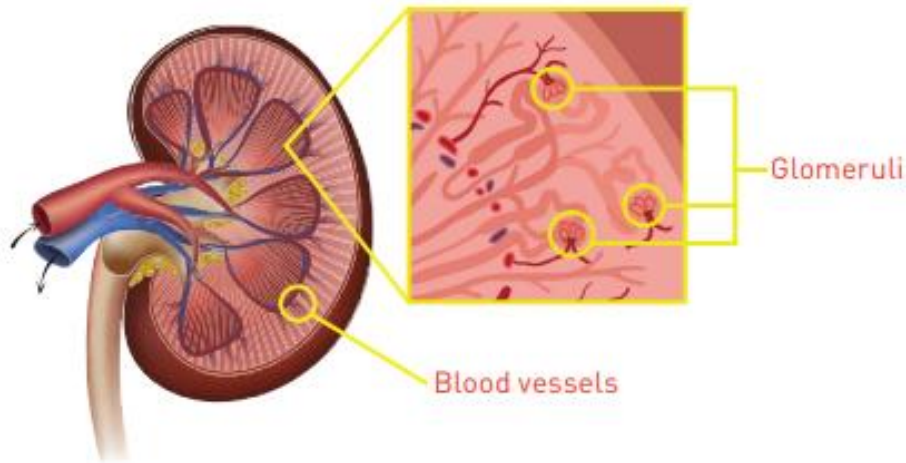
- *I can see fine*
- *I cannot afford any more medical expenses*
- *I am worried the exam will be painful or uncomfortable.*
- *I am afraid the doctor will find something wrong with my eyes.*
- *I just saw an eye doctor who gave me a prescription for new glasses. My eyes must be fine*

Once you have the appointment...

- Discuss the results. After your exam, ask the eye doctor to send the results to your primary care physician and/or endocrinologist.

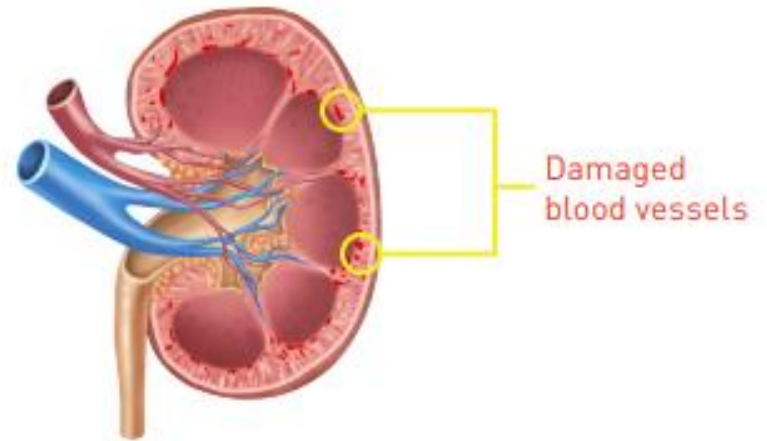


Kidney disease (Nephropathy)



Healthy kidney

Tiny blood vessels (glomeruli) filter and remove waste from the blood

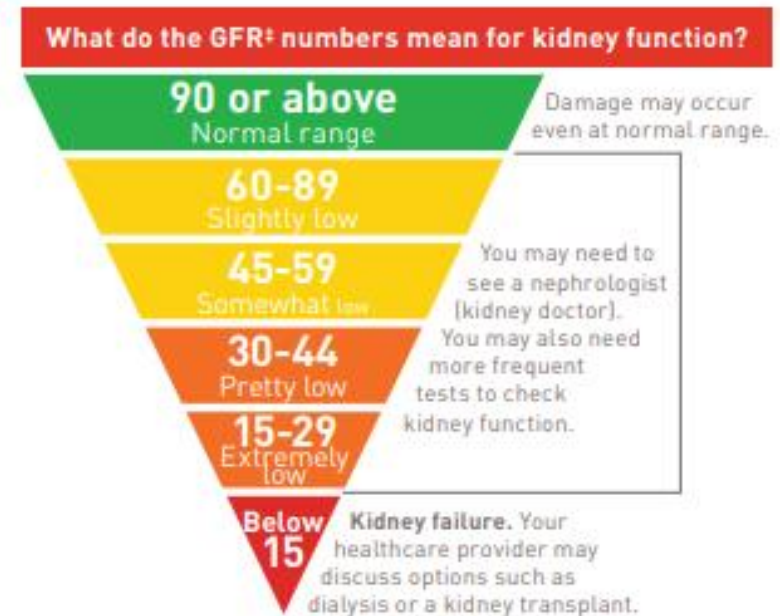


Diabetes and kidney disease

High blood sugar damages blood vessels that filter the kidneys

Kidney Tests

	Normal Result	
Urine protein (microalbumin)	Below 30 mg	Earliest sign of kidney disease
Serum creatinine	Men: <1.4 mg/dl Women: <1.2 mg/dl	Can occur with or without elevated urine protein

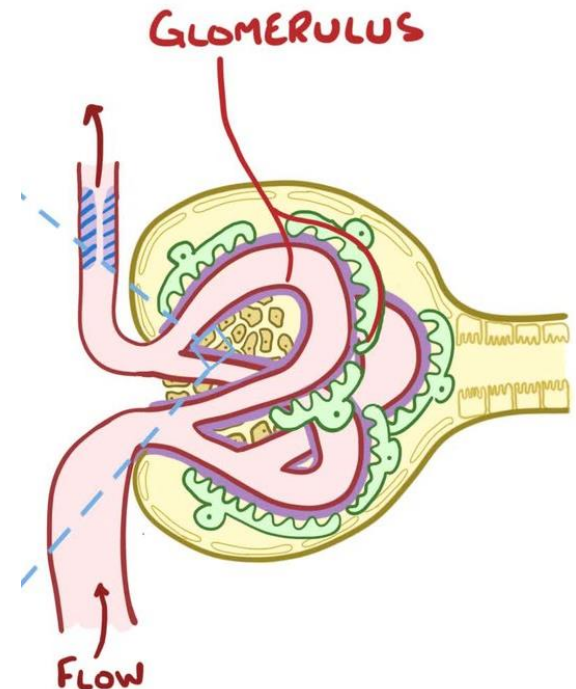


What is GFR?

- GFR: glomerular filtration rate, calculated from the serum creatinine level
- The GFR tells us how well your kidneys are working.

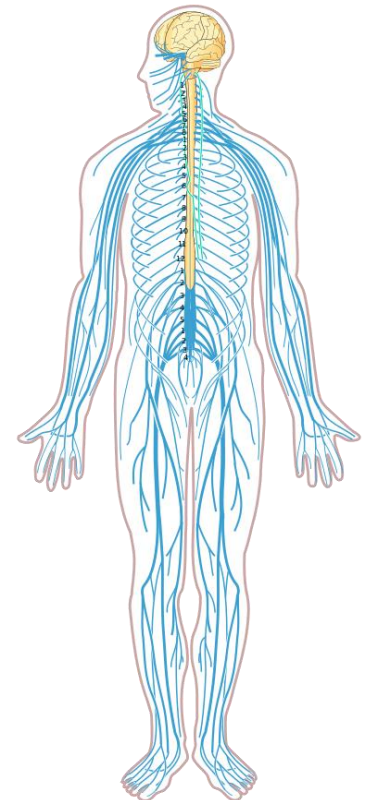
Kidney disease (Nephropathy)

- Screening
 - Annual urine albumin (may be reversible)
 - Blood creatinine (usually irreversible)
- Prevention: lower glucose, blood pressure
- Treatment
 - Lower glucose levels
 - Optimize blood pressure <140/90 mmHg, consider 130/80 mmHg
 - ACE-inhibitor or Angiotensin receptor blocker (ARB)
 - Consider SGLT2 inhibitor (high evidence)
 - Avoid /adjust dose of certain medications



Nerve Disease (neuropathy)

- Can affect any nerve in the body
- Most common is the long nerves: Peripheral Sensory Polyneuropathy (PSPN)
- Assessment
 - Up to 50% of PSPN is asymptomatic
 - Symptoms: numbness, tingling, burning
 - Annual foot exams
 - Diagnosis of exclusion
- Management
 - Foot care/precautions
 - Treat pain



Foot care

- Check your feet every day
- Wash feet (do not soak) daily. Apply lotion but avoid spaces between your toes
- Wear shoes and socks or slippers at all times (check shoes for foreign objects prior to wearing)
- Shoes should fit well
- Trim nails straight across
- Do not remove corns or calluses on your own
- Avoid extreme temperatures: heating pads, electric blankets, space heaters, hot water
- Keep feet dry in cold/rain



Autonomic Neuropathy

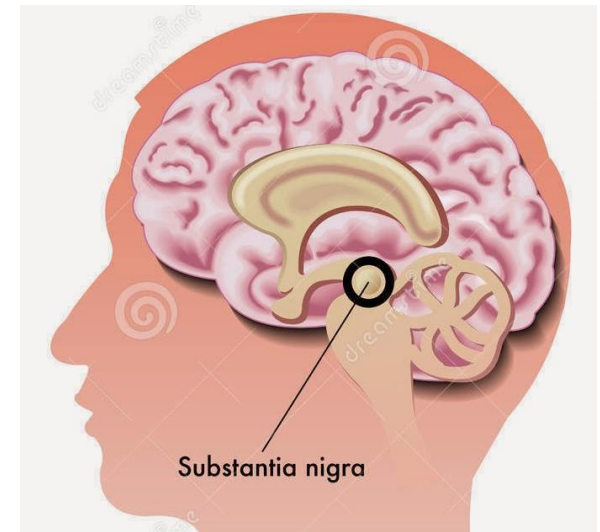
- Affects the nerves that control the organs
- Typically occurs many years after onset of diabetes
- Usually other complications are present

	Comment
Heart	Dizziness Heart racing
Stomach	Nausea, vomiting Bloating post-meal
Intestine	Constipation Diarrhea
Bladder	Incontinence, difficulty emptying the bladder
Sexual dysfunction	Can be early



Parkinson's Disease (PD)

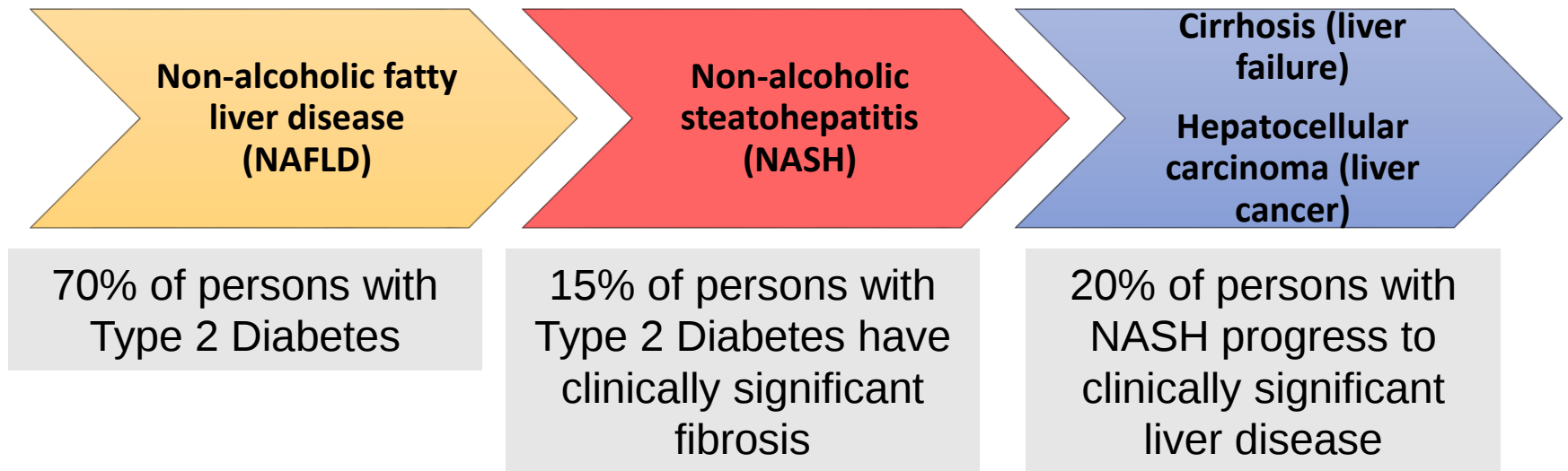
- Damage to the substantia nigra¹
 - tremor, stiffness or rigidity, slowness of movement
 - sleep problems, constipation, anxiety, depression, and fatigue
- Diabetes: 30% higher chance of developing PD, faster progression²
 - Why?
 - Shared genetic cause?
 - Diabetes may accelerate damage of PD
 - role of insulin resistance
 - Does treatment of diabetes help?
 - unknown—possible GLP-1 receptor agonists^{3,4}



1. www.apdaparkinson.org
2. Komici et al. J Parkinsons Dis. 2021;11(4):1585-1596.
3. Mulvaney et al. Cochrane Database Syst Rev. 2020;7(7):CD012990.
4. Wang et al. Int J Environ Res Public Health. 2020;17(13):4805.

Non-Alcoholic Liver Disease Epidemic

- Screening for high-risk groups:
 - Body mass index (BMI) >35
 - Type 2 diabetes >10 years, >age 50
 - Elevated liver function tests
- Treatment:
 - Weight loss
 - Medications: pioglitazone, GLP-1 based therapies
 - Identify/treat end stage disease



DM and Mental health

- Depression
 - Depression is associated with ↑risk of DM and vice versa
 - Co-treatment as part of multi-disciplinary team improves glucose control and self-care
- Anxiety
 - Compounded by injections, not meeting glucose goals, complications
 - Fear related to hypoglycemia → avoidance
- Diabetes distress: negative psychological reaction related to emotional burden and worries about managing a complicated, demanding chronic disease
 - Linked to ↑A1c, self care
 - Diabetes self-management education and support (DSMES) effective
- Other mental health disorders also associated with diabetes and glucose levels: schizophrenia, obsessive compulsive disorder, eating disorders

Language

Use language that is

- neutral, nonjudgmental, and based on facts, actions or biology
- Free from stigma, respectful, inclusive, imparts hope
- Person-centered
- Fosters collaboration

Avoid	Use instead
Diabetic	Person with diabetes
Test	Monitor
Control	Manage
Suffering from diabetes	Living with diabetes
Good/bad/poor glycemic control	A1c, A1c level, glycemic goal
Compliance or adherence	Medication-taking
Obese, morbidly obese	Weight, BMI
Refuse	Decline

Supporting Mental Health



- Eat right: fruits, veggies, whole grains



- Reduce coffee, soda, and alcohol



- Be more active: improves mood, energy, sleep



- Sleep well



- Reach out/Find support



- Get involved



- Sometimes counseling or medication are needed



Autoimmune conditions associated with Type 1 diabetes

- Thyroid: screen at diagnosis and periodically thereafter
- Celiac disease: screen adults with stomach symptoms, osteoporosis, vitamin d deficiency, iron deficiency
- Other
 - Pernicious anemia (B12 deficiency)
 - Autoimmune hepatitis (liver disease)
 - Primary adrenal insufficiency (low cortisol/stress hormone)
 - Dermatomyositis
 - Myasthenia gravis
 - Multiple sclerosis
 - Vitiligo

Other Common Conditions in Persons with Diabetes

	Comment
Cancer	Colon, liver, uterus, bladder, pancreas
Pancreatitis	DM increases risk of pancreatitis and vice versa
Osteoporosis	Increase risk in T1D and T2D Use caution with pioglitazone, SGLT2i
Hearing loss	
Obstructive sleep apnea	85% of people with T2D + BMI >30 ¹ Treatment improves quality of life and blood pressure
Periodontal (gum) disease	↑risk/severity in persons with DM ^{2,3} Treatment may improve glucose control

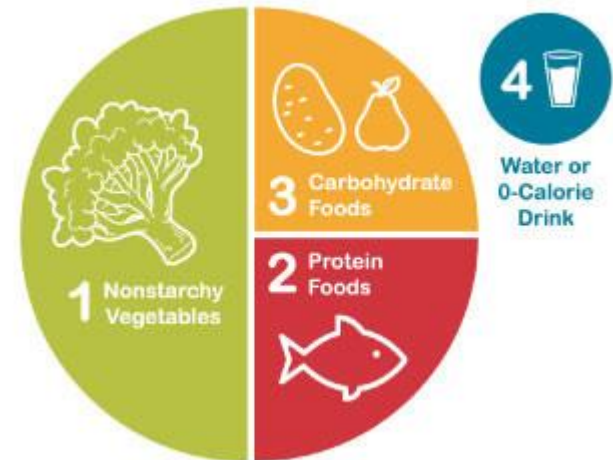
1. ADA. Diabetes Care 2021 Jan; 44(Supplement 1): S40-S52
2. Foster et al. Diabetes Care. 2009):1017-9.
3. Bibbins-Domingo et al. USPSTF. JAMA 2017;317;407-14.
4. Shaw et al. Diabetes Res Clin Pract 2008;81:2-12

What should I eat?

- The most effective diet is the one that *you* can continue long-term
- Very low-carb diets
 - Improved sugars
 - But may also increase LDL cholesterol (the bad stuff)
 - Use with caution if you are taking an SGLT2 inhibitor

Heart healthy diet

1. Portion control
2. Do not skip meals
3. Plenty of fruits and vegetables.
4. Whole-grain, brown rice/pasta
5. Eat fish, especially oily fish (salmon, tuna)
6. Limit saturated fat: butter, shortening, lard
7. Avoid *trans* fats (partially hydrogenated).
8. Choose lean meats and skinless poultry.
6. Choose low-fat dairy products.
7. Limit beverages and foods with added sugars.
8. Limit sodium—use herbs, lemon juice



Diabetes plate method

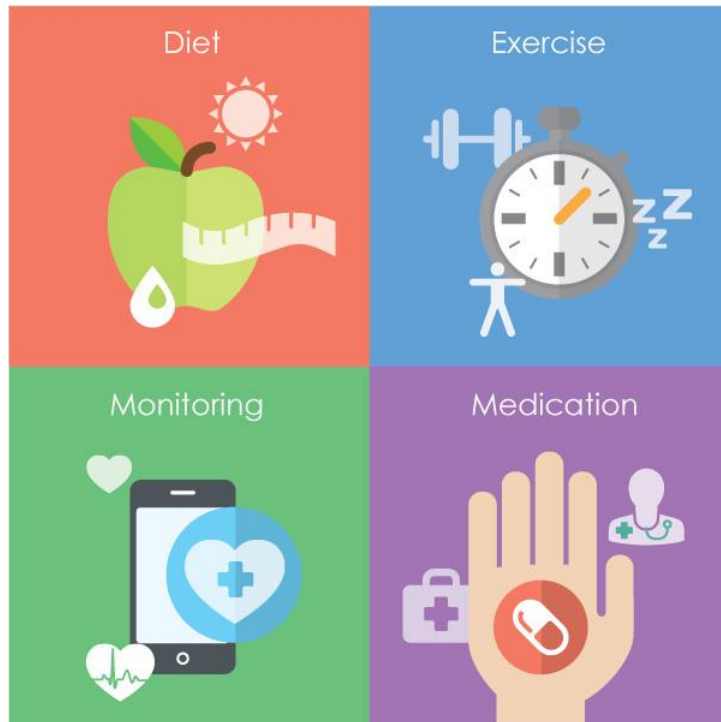
Exercise

- 150 min. of moderate to vigorous aerobic activity/week
- Resistance exercise 2-3x/week
- Flexibility and balance training 2-3x/week for older adults (including yoga/tai chi)
- Important for keeping weight off
- Benefit in reducing sugars



But I already know what I need to do...

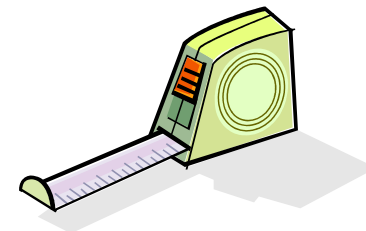
Take control of diabetes with diabetes self-management education



- Is this a good sugar?
- What do I do if I'm high?
- What do I do if I'm low?
- What should I do if I'm sick?
- Should I eat that?
- How do I take this medicine?
- What kind of exercise can I do?
- How can I prevent complications?
- And many more...



Measuring Glucose levels



Health status	A1c	Fasting/pre-meal	Peak Postmeal	Bed
General Population				
Healthy*	7.0	80-130	180	*
Older Adults				
Healthy	7.5	90-130	*	90-150
Intermediate	8.0	90-150		100-180
Poor	8.5	100-180		110--200

***Goals should be individualized**

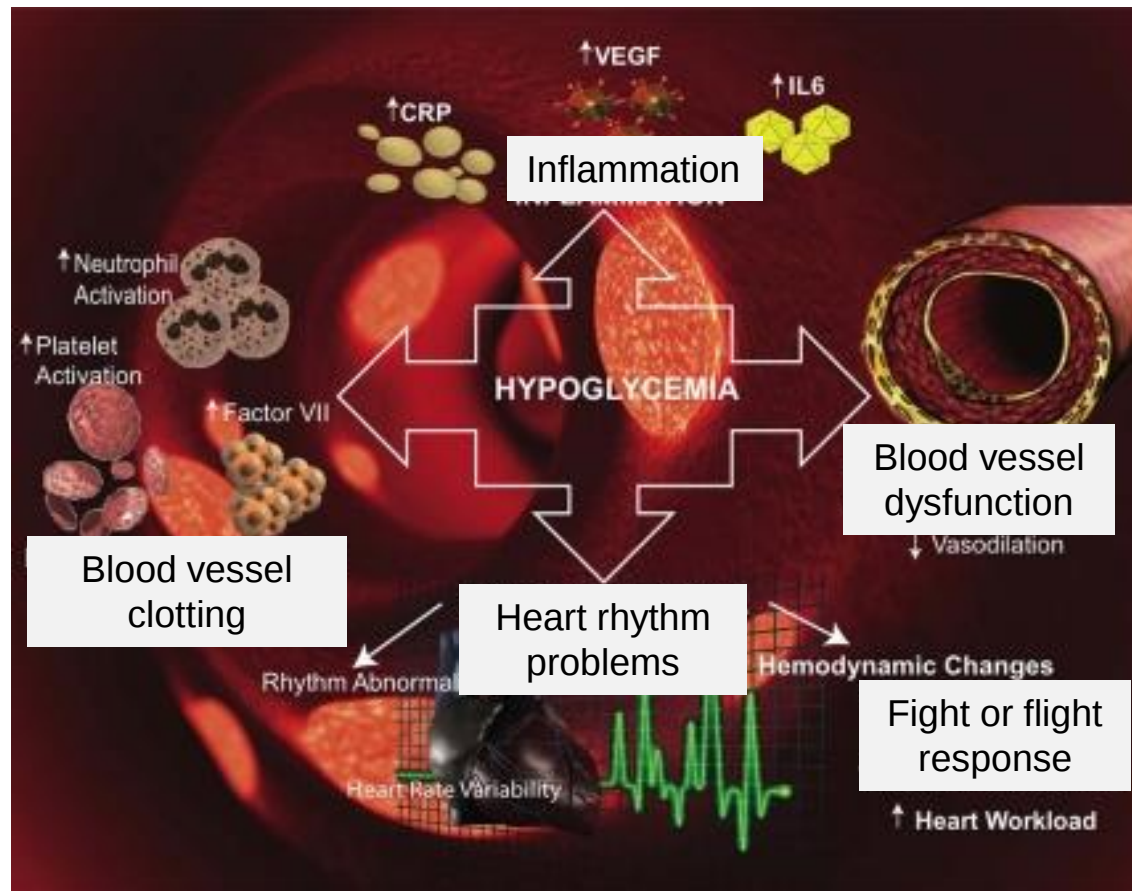
Frequency of glucose monitoring depends on your medication plan.

- Insulin: 3+ times per day or Continuous glucose monitoring
- No insulin: 1+ times per day.

But it only improves glucose control if you use the information!

Is hypoglycemia harmful?

Up to 4x increased risk of mortality



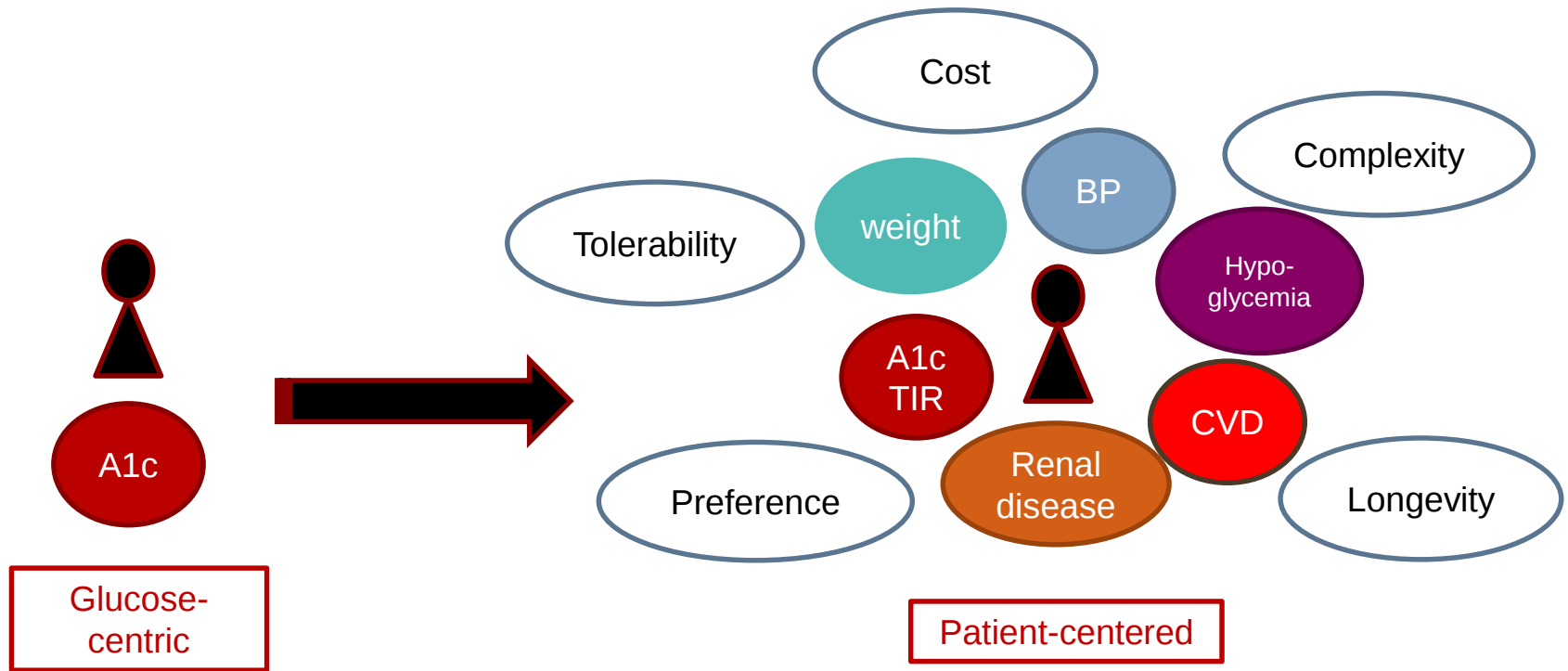
Pistrosch and Hanefeld. Curr Diab Rep 2015;15:117

Desouza et al. Diabetes Care 2010;33(6):1389-94



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A Shift in Treatment Paradigm



BP=blood pressure, TIR=time in range, % time between 70-180 mg/dl, CVD=cardiovascular disease



ADA Standards of Care 2022

Metformin or other agent based on
compelling indication and patient-
centered factors

Established cardiovascular or kidney disease

All patients

Lifestyle advice

Weight loss if overweight

- Caloric restriction
- Evidence-based weight loss programs
- Weight loss surgery
- Weight loss medication

Yes

No

If A1c above goal, consider compelling indications for treatment

Cardiovascular
disease

Heart failure/
kidney disease

GLP-1RA or
SGLT2i*

SGLT2i* preferred
GLP-1RA

Hypoglycemia

SGLT2i*
GLP-1RA
DPP-4i
TZD

Weight Gain

GLP-1RA
SGLT2i*

Cost

SFU
TZD

If A1c still above goal, add additional agent based upon compelling indications above

ASCVD=atherosclerotic cardiovascular disease, CKD=chronic kidney disease, GLP-1RA=glucagon-like peptide-1 receptor agonist, SGLT2i=sodium-glucose cotransporter-2 inhibitor, AGI=alpha-glucosidase inhibitor, SFU=sulfonylurea, TZD=thiazolidinedione

*if adequate kidney function



Durability of Therapies

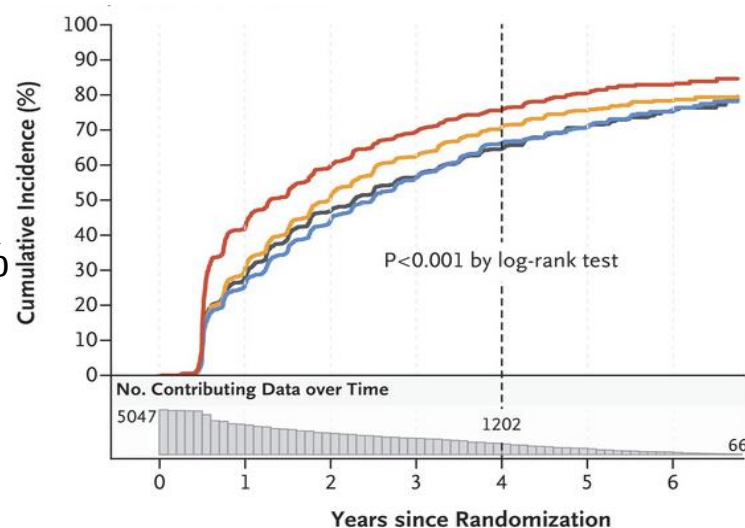
- NIH sponsored GRADE trial
- T2D <10 years on metformin, A1c 6.8-8.5%
- N=5047
- Randomly assigned to one of 4 therapies
- Follow-up 5.0 years
- Outcome: incidence of A1c $\geq 7\%$ (pt-yr)
 - Glargine: 26.5/100*[^]
 - Liraglutide: 26.1/100*[#]
 - Glimepiride: 30.4*^{*}
 - Sitagliptin: 38.1

*p<0.001 vs. sitagliptin

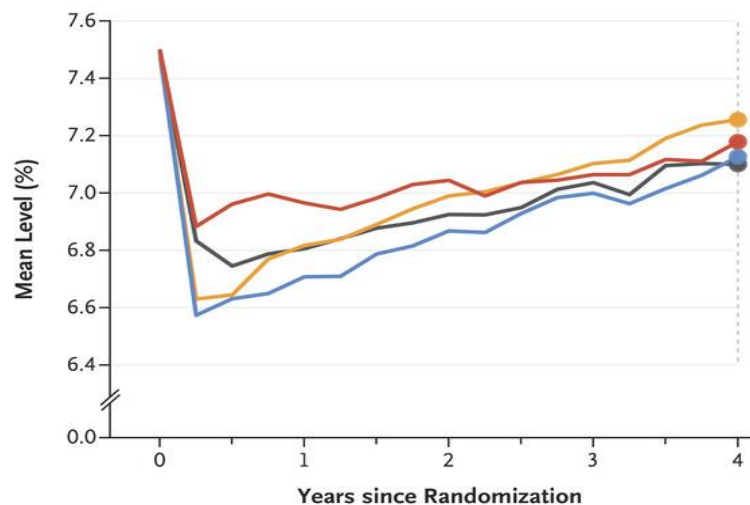
[^]p<0.05 vs. glimepiride

[#]p<0.01 vs. glimepiride

% with
A1c >7%



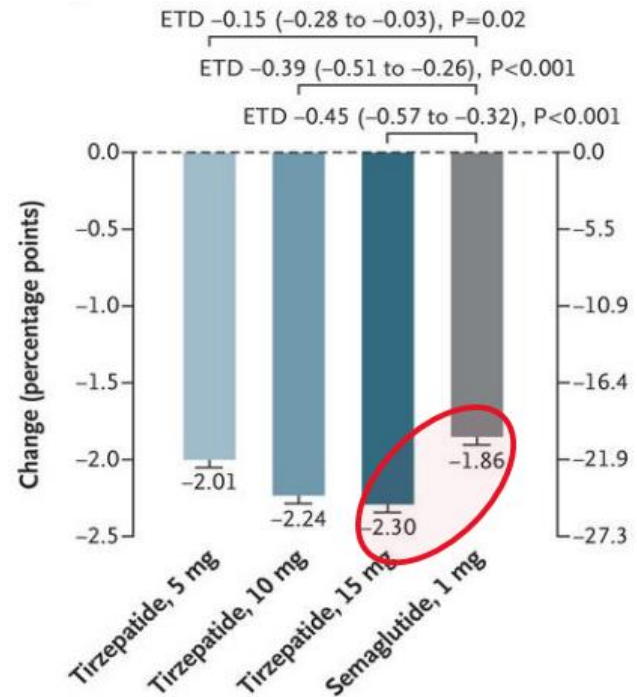
A1c
value



— Sitagliptin — Glimepiride — Liraglutide — Glargine

Tirzepatide

- GLP-1/GIP analogue
- Superior A1c/weight loss/QOL vs. semaglutide 1.0 mg
- Similar tolerability
- No comparisons with semaglutide 2 mg or higher
- No CV outcomes data (yet)



N=1878, 40 week RCT
Additional **5.5 kg** weight loss
vs. semaglutide

Taking Medications



- Take medications as directed
- Do not stop medications unless directed to do so
- If you have a side effect, let your provider know
- If you have difficulty affording or obtaining your medicine, let your provider know
- Track your medications using a pill box or app
- If you are prescribed a new medicine, ask whether it is safe to use with your other medications
- Keep a list of your medications with you
- Keep a list of past medications and any side effects



KEY TESTS/EXAMS

	Frequency
A1c or continuous glucose monitor (CGM) derived value - GMI=glucose management indicator→A1c estimated from CGM - TIR=time in range→% of time spent between 70-180 mg/dl	Quarterly if not at goal Twice yearly if meeting goal
Dilated eye exam	Yearly
Foot exam	Yearly (at risk foot more often)
Lipid (Cholesterol)	1-2 years
Urine Microalbumin	Yearly
Serum creatinine	Yearly
Blood pressure	Each visit
Weight	Each visit
Family planning	Each visit
Vaccines	varies

Conclusions

- Diabetes places a substantial burden on health
- Lifestyle changes, as part of a multi-pronged approach, can prevent or delay DM and prevent complications
- Glucose lowering therapy should be individualized and goal-directed

