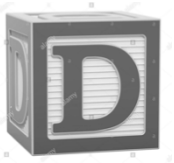
# Current Treatment of Diabetes



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## Disclosures

- **I have spoken for, consulted for, or been paid honorarium by the following:**

**Bausch & Lomb, Optos, ZeaVision, VSP, Risk Medical Solutions, Regeneron, Zeiss, Genentech, American Diabetes Association, EyeNuk, AI Optics**

- **These associations did not unduly influence the content of this presentation or my patient care recommendations**

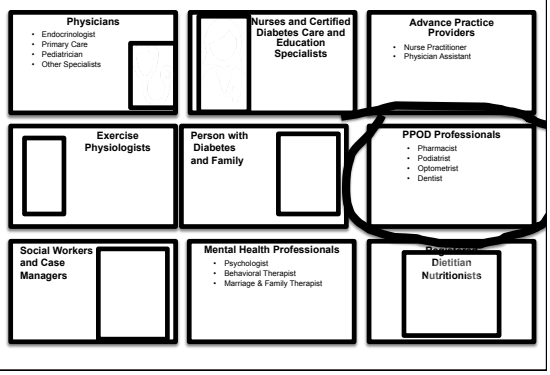
## What Is Being Treated?

- **Hyperglycemia**
- **Hypertension**
- **Dyslipidemia**
- **Macrovascular Complications**
- **Microvascular Complications**

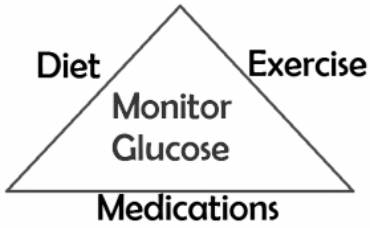
PREVENTION

- **Prediabetes – prevent conversion to T2DM**

## The Multidisciplinary Diabetes Care Team




## The Treatment Triangle




**Patient Education** | **Psychosocial Support**

## When Might Patients Test Their Glucose?

- **Fasting:** (answers the question "are my dietary choices and/or medication regimen working while I sleep?") [large impact on mean glucose and A1c]
- **Pre-prandially:** (answers the question of "how much I should eat now? And how effective is my drug/ exercise regimen?")
- **2 hours post-prandially:** (answers the question "what foods do and don't allow me to maintain good BS control?" AND correlates reasonably well with A1**c** **)**
- **When patients feel unwell**

## Real World Testing: SMBG/A1c

- Most patients with T2DM perform self-monitoring of blood glucose < 1X/day
- ADA Guidelines call for at least daily SMBG if patients use hypoglycemic medications
- Multiple studies show that SMBG has minimal impact on HbA1c in T2DM
- Guidelines recommend quarterly HbA1c for T1DM or sub-optimal control in T2DM
- Biannual HbA1c for well-controlled T2DM
- Analysis of 115K+ patients showed 51% received physician-ordered HbA1c at inappropriate intervals
  - 21% requested too soon (younger/healthier/men)
  - 30% requested too infrequently (sicker/older/women)

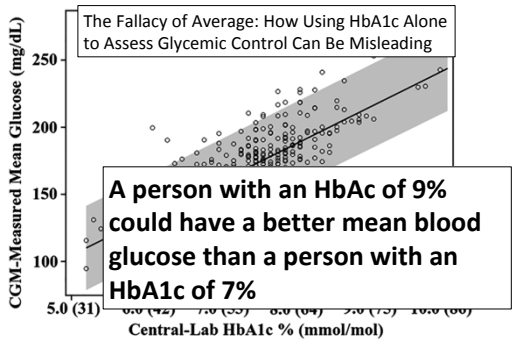
Diabetes Care 2020 Jan; 43 (Supplement 1): S77-S88. Clin Chem 2012 May;58(5):906-15.

## Continuous Glucose Monitoring (CGM)

- **Continuous glucose monitoring systems (CGM) render fingerstick spot glucose testing irrelevant except for purposes of calibration**
- **These systems are becoming increasingly popular amongst all DM patients (especially on insulin Tx)**
  - **40% of T1DM**
  - **≈9% of T2DM**
- **Allow real-time alerts for high and low blood glucose and calculation of glucose time-in-range**
  - **Predict DR & DKD independently of A1c**
- **Helps correct deficiencies of A1c**

Sensors (Basel). 2019 Feb; 19(4): 800.

**Plot of CGM-measured mean glucose concentration vs. laboratory-measured HbA1c.**




Roy W. Beck et al. Dia Care 2017;40:994-999

## Measured A1c versus CGM-derived A1c (AKA GMI or glucose management indicator)

1,000+ patients from U Wash Endocrine Clinic wearing CGM

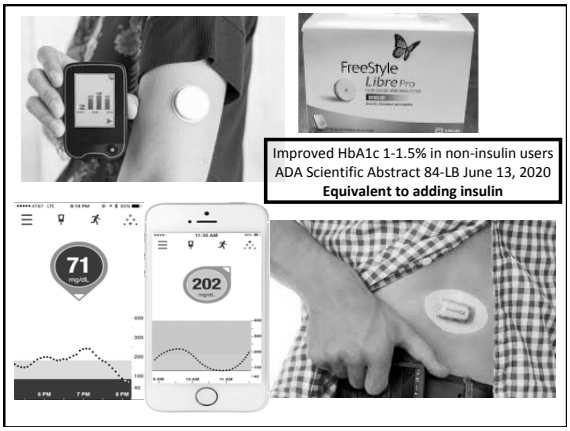
- Measured and calculated A1c differed by > 0.5% in 64% of patients
- Measured and calculated A1c differed by > 1.0% in 22% of patients
- ***"Our gold standard ain't so golden"***
  - Personal correspondence with Irl B. Hirsch, MD, FACE
  - Clinical Director of UW Endocrinology
  - 2017 Endocrine Society Laureate

HbA1c and Glucose Management Indicator Discordance: A Real-World Analysis. Diabetes Technol Ther. 2020 Dec 1.

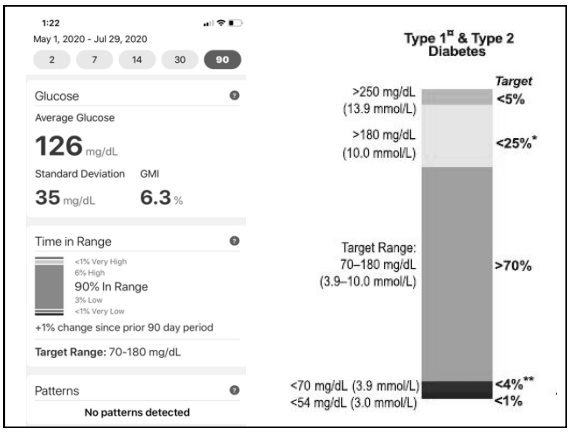
## Benefits of Glucose Time-In-Range

- TIR refers to the percentage of the day a patient's blood glucose is 70-180 mg/dl
- For any given TIR, there is WIDE variability in HbA1c (e.g. TIR = 60%, HbA1c range = 7-12%)
  - 1441 participants from the DCCT
  - 3262 T2DM patients in China
- **A 10% decrease in TIR increases DR risk 64% and risk of microalbuminuria 40%** ($p < 0.001$)
- **→ INDEPENDENT of HbA1c**

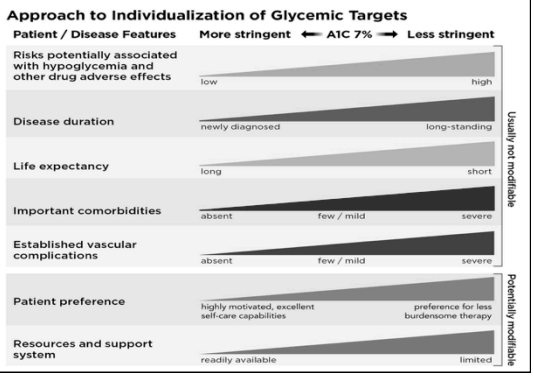
Diabetes Care. 2019 Mar;42(3):400-405 Diabetes Care 2018 Nov; 41(11): 2370-2376
J Diabetes Sci Technol. 2019 Jul;13(4):614-626.




Improved HbA1c 1-1.5% in non-insulin users
ADA Scientific Abstract 84-LB June 13, 2020
**Equivalent to adding insulin**




## Glucose Targets are Individualized




## Management Goals for Adults: A1C and TIR

| Individualized A1C | | Time in Range* | |
|---|---|---|---|
| Most nonpregnant adults | <7.0% | Most nonpregnant adults: | >70% |
| Those who can without undue risk: | <6.5% | Older or high-risk adults | >50% |
| Seniors, those with complications & comorbidities: | <8.0% | Pregnancy, type 1 diabetes | >70% |
| Pregnant women | <6 to <7% | Pregnancy, type 2 or gestational diabetes | ?** |

* Expressed as percentage of CGM readings.
** Not yet determined; more research is needed.

American Diabetes Association. Diabetes Care 2020;43(Suppl. 1): S66–S76
American Diabetes Association. Diabetes Care 2020;43(Suppl. 1): S183–S192
Battelino T, Danne T, Bergenstal RM, et al. Diabetes Care 2019;42: 1593–1603

## Medical Nutrition Therapy


- MNT
- The foundation for the management & prevention of diabetes
- "the application of evidenced based nutritional recommendations using an individualized, coordinated team effort including the patient"

*Diabetes Care 2008; 31: S61-S78*

## Goals of MNT in those with diabetes

- Normal or as near normal as possible glucose, lipids and blood pressure
- Prevent or slow down the rate of development of chronic complications
- Address individual nutrition needs (personal/cultural preferences and willingness to change)
- Maintain pleasure of eating by only limiting food choices when indicated by scientific evidence

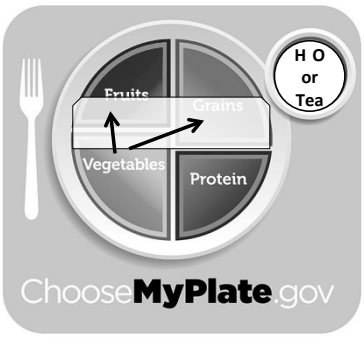
ADA Position Statement: Nutrition Recommendations and Interventions for Diabetes. Diabetes Care 2008.

Monday, July 14, 14

## General Dietary Recommendations

- Energy-restricted low-fat or low- carb diet
- Increased dietary fiber (>20g/d)
- Eliminate trans fats; reduce saturated fat to 7-9% of calories (≤ 15 g sat fat per ADA)
- 150 minutes moderate intensity exercise/week if no contraindications
- 5-7% weight loss in obese pts
- Smoking avoidance
- Sodium intake < 2300 mg/day

*American Diabetes Association*
*American Association of Clinical Endocrinology*

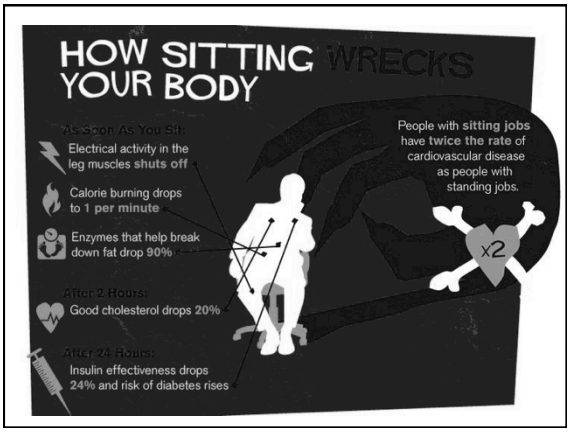


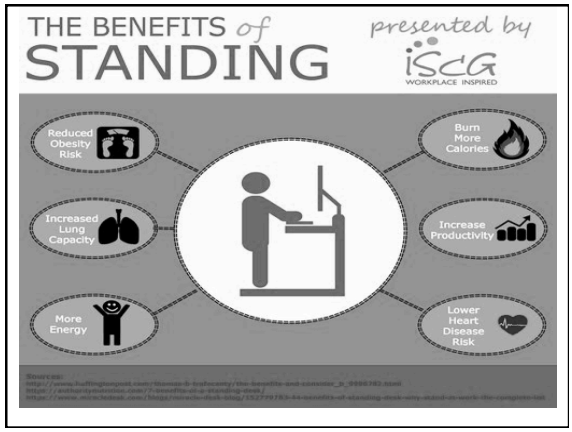

## Benefits of Exercise for People with Diabetes

- Promotes overall health
- Improves blood glucose control and insulin sensitivity
  - Can help ↓glucose levels
- Reduces cardiovascular risk
- Facilitates weight loss (& weight maintenance)
- Enhances well-being
- Can help prevent or delay type 2 diabetes
- Prevents bone & muscle loss (osteopenia/sarcopenia)

- **Daily exercise with no more than 2 consecutive days off**
- **Aerobic, HIIT, strength training balance, flexibility activities**
- **Sedentary time < 30 minutes continuous**
- **1 hour continuous moderate intensity exercise for younger patients if no contraindications**

Colberg SR, Sigal RJ, Yardley JE, et al. Diabetes Care 2016;39:2065–2079




## A Simple Strategy for Motivational Interviewing

- Ask patients to write down your recommendations (more likely to remember)
- Ask patients the one thing they would like to improve upon – enter that in the chart (get 'buy-in')
- Ask patients about that one thing at follow-up (a big or small step is better than no step at all)

**MEMORY**
**BUY-IN**
**ACCOUNTABILITY**

## Diabetes Self-Management Education

- The American Diabetes Association recommends that all people with diabetes be referred for diabetes education and support at four critical times:
  - At diagnosis
  - Annually for assessment of education, nutrition, and emotional needs
  - When new complicating factors influence self-management → **DR**
  - When transitions in care occur

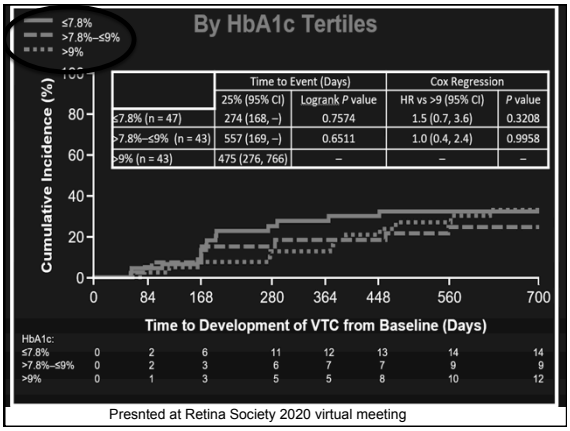
Strawbridge LM, Lloyd JT, Meadow A, Riley GF, Howell BL. Health Educ Behav 2015;42:530–538
Li R, Shrestha SS, Lipman R, Burrows NR, Kolb LE, Rutledge S; Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 2014;63:1045–1049
Powers MA, Bardsley J, Cypress M, et al. Diabetes Care 2015;38:1372–1382

**Yet, <10% of people newly diagnosed with diabetes use these services, and access and utilization remain low for all people with diabetes.**

## Metabolic Memory

- Patients with tight glucose control within 1-8 years of Dx are significantly less likely to develop severe DR despite worsening glucose control over time
- Patients with poor glucose control within 1-8 years of Dx are significantly more likely to devlop severe DR despite improved glucose control over time
- **Tight glucose control is worthless for protection against PDR/CI-DME once NPDR becomes moderately severe or severe (post-hoc analysis of the PANORAMA trial)**

Kowluru RA. Diabetic retinopathy, metabolic memory and epigenetic modifications. Vision Res. 2017 Oct;139:30-38.
JAMA Ophthalmol. 2021 Sep 1;139(9):946-955.




| | Time to Event (Days) | | Cox Regression | |
|---|---|---|---|---|
| | 25% (95% CI) | Logrank *P* value | HR vs >9 (95% CI) | *P* value |
| ≤7.8% (n = 47) | 274 (168, –) | 0.7574 | 1.5 (0.7, 3.6) | 0.3208 |
| >7.8%–≤9% (n = 43) | 557 (169, –) | 0.6511 | 1.0 (0.4, 2.4) | 0.9958 |
| >9% (n = 43) | 475 (276, 766) | – | – | – |

Presnted at Retina Society 2020 virtual meeting

- What Optometrists Should Know About

## Diabetes Medications

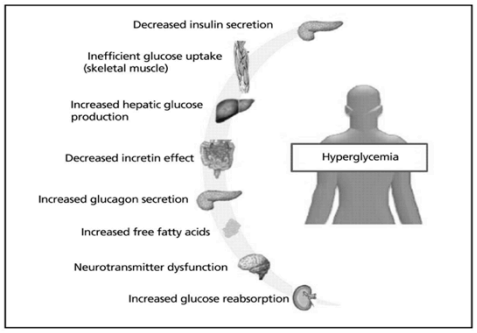
## Reasons To Know & Understand Your Patients' Diabetes Meds

- **They affect eye health and vision**
- **It allows us to more effectively counsel patients with diabetes**
- **It allows us to critically assess the diabetes treatment plan**
- **It allows us to better participate on the diabetes care team**

**Each 1 point drop in HbA1c lowers Risk of DR Progression by 37%-60%**

Stratton IM et al. *BMJ*. 2000;321:405-412.

## OMINOUS OCTET **in Type 2 Diabetes Mellitus**




DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus [Banting Lecture]. Diabetes. 2009;58(4):773-795[2]

## KEY POINT

Hyperglycemia aggravates all of the metabolic abnormalities of DM

Improving blood glucose control improves multiple metabolic abnormalities asociated with DM

## Typical Medication Regimen T1DM

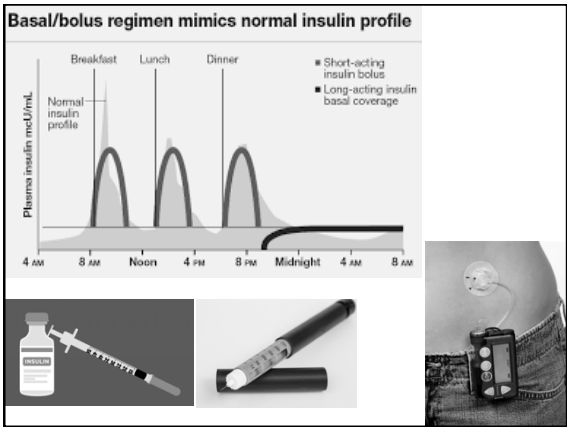
- **Insulin**: basal (background) to compensate for hepatic gluconeogenesis and glycolysis (liver & muscle) → e.g. Lantus, Levemir, NPH

**+**

- **Insulin**: prandial (meal time) to compensate for glucose in food/drink → e.g. Humalog, Novolog, Apidra, Humulin R

**OR**

- **Insulin Pump**: slow drip basal insulin combined with prandial insulin bolus with food/ drink




## Typical Medication Regimen

- **T2DM**
  - **Metformin – multiple effects** **+**
  - **OTHER glucose lowering agents PRN**

**+**

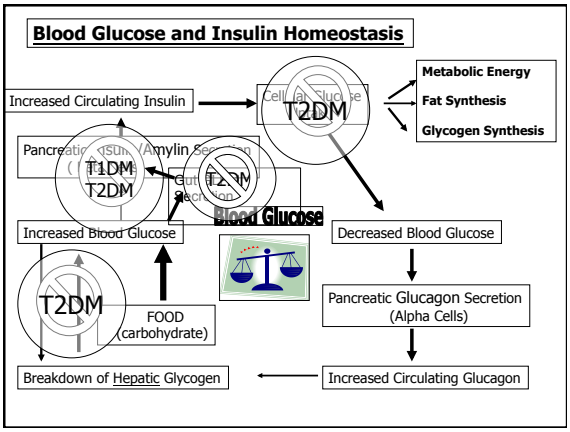
- **ACEI or ARB**: lower BP & renoprotective

**+**

- **Statin**: inflammatory dyslipidemia

**+**

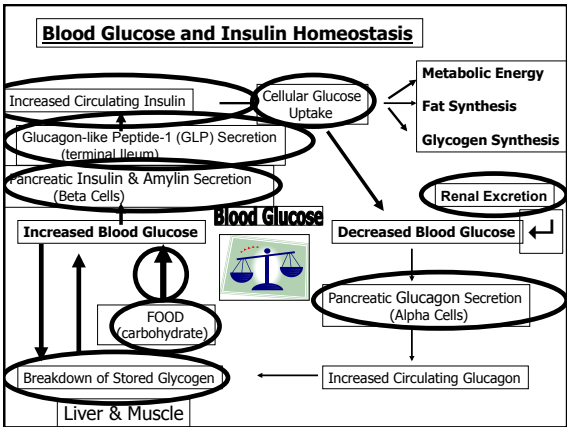
- **Aspirin**: reduce platelet adhesion to MI/ stroke risk




## How Blood Sugar Meds Work

- Increase insulin or insulin production
- Make cells more sensitive to insulin
- Prevent the liver from making glucose
- Slow digestion of sugars
- Increase gut hormones that lower glucose levels by several mechanisms
- Promote renal clearance of sugar via urine

**Let's look at our targets…..**



## Insulin

Required in T1DM

- Allows glucose transport across cell membranes of insulin sensitive tissues (esp. skeletal muscle & liver)
- Classified by onset and duration of action: rapid acting (Humalog™, Novolog™), short acting (Humulin R™), intermediate (NPH), long acting (Lantus™, Levemir™)
- Problems: hypoglycemia, weight gain, pharmacokinetics, hyperinsulinemia, localized rxns

Being used frequently in T2DM

## Insulin - Pearls

- Many patients fear insulin due to (mis)perceptions of disease severity and fear of pain/needles
- Much evidence that early use of insulin in T2DM delays β cell failure
- Insulin can lower HbA1c "indefinitely"
- Patients on insulin may have a dose-dependent increased risk for DR and cancer – upregulates VEGF

*Front Physiol*. 2017;8:204

## Insulin Secretagogues

- Stimulate insulin secretion by functioning pancreatic β cells (not for T1DM)
- Categorized as sulfonylureas {SFU] (Micronase™, Glucotrol™, Amaryl™) & non-SFU glinides (Prandin™, Starlix™)
- Cheap
- Problems: weight gain, hypoglycemia, hyperinsulinemia, increased CV risk,
- Inceased cancer risk but < insulin

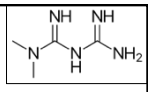
J Clin Endocrinol Metab. 2012 Jul;97(7):E1170-5.

## Insulin Secretagogues - Pearls

- Contraindicated in hepatic/renal insufficiency
- 5-10% failure per year (β cell burnout)
- Lower HbA1c 1-1.5% at max dosage

Insulin and Secretagogues Can Cause Serious Hypoglycemia (Blood Sugar < 70 mg/dl)
- Confusion, tremor, sweating
- Develops in minutes

## Metformin (a 'biguanide')




- Decreases hepatic gluconeogenesis & may improve insulin sensitivity
  - Phenformin & Buformin removed from market due to toxicity (lactic acidosis)
- Problems: gastric distress (30%), CI in renal insufficiency, rare lactic acidosis
- Metformin lowered the risk of major CV events by 40% in obese type 2s (UKPDS) compared to those on SFUs

## Metformin Pearls

- First line agent for type 2 diabetes:
  - ↓A1c 1-1.5%
  - Weight neutral
  - XR version (generic) ↓GI side effects in 80%
- Cheap, Effective, Cardioprotective
- Multiple mechanisms of action ("pleiotropic")
  - Reduces hepatic glucose release
  - Improves hepatic and peripheral insulin sensitivity
  - Increases butyrate producing gut bacteria that improve blood glucose
  - Appears to decrease cancer risk and cancer mortality

## Butyrate in T2DM

- **Introduction of butyrate-producing flora in insulin resistant patients improves insulin sensitivity in the short term**

**Gastroenterol October 2012; 143(4): 913–916.e7**

- **Metformin treatment induces dramatic increases in butyrate-producing Clostridium species and Akermansia mucinaphila**

Appl. Environ. Microbiol. **October 2014** vol. 80 no. 19 **5935-5943**

## Surprising Metformin Fact

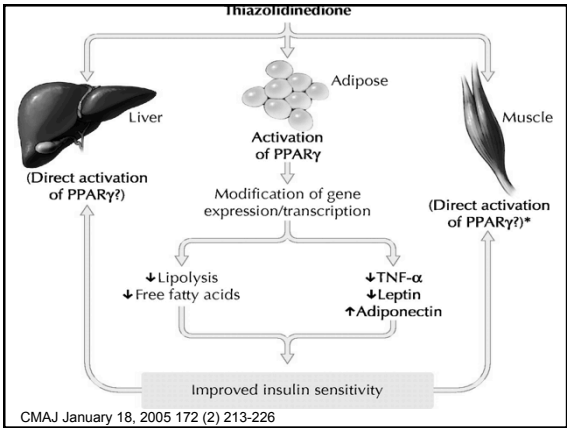
- **33-50% of non-insulin diabetes medications are NOT being prescribed with metformin**
- **Counter to Clinical Practice Guideline recommendations of AACE, ADA, AAFP to use metformin as first-line agent with all other agents being ADDITIVE**

*Hampp, C. et al. "Use of Antidiabetic Drugs in the U.S., 2003-2012" Diabetes Care. 2014; 38: 8p*

## Thiazolidinediones (aka TZDs or Glitazones)

- **Improve peripheral insulin sensitivity in liver, fat cells, muscle**
- **Two Agents: Actos™ & Avandia™**
  - **pioglitazone & rosiglitazone**
- **Don't cause hypoglycemia**
- **Problems: edema (including CME), weight gain, possible hepatotoxicity, increased risk of CHF and bladder cancer (pioglitazone)**
- **Combat hyperinsulinemia**
- **Lower A1c about 1-1.5%**

**Third Line Agents**

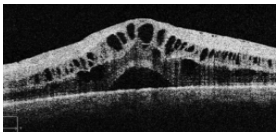


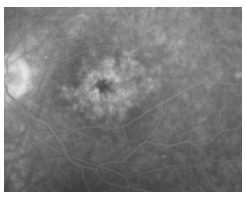

CMAJ January 18, 2005 172 (2) 213-226

## TZDs Increase Risk of CME in Pts on Insulin >> No insulin

- Especially at higher doses
- Especially if pre-existing DME

Arch Intern Med. 2012 Jul 9;172(13):1005-11.

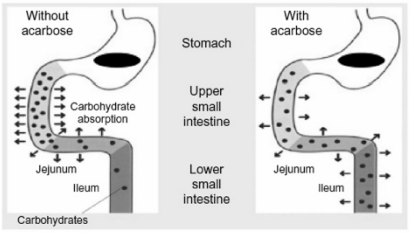




## Starch Blockers (α-Glucosidase or amylase Inhibitors)

- Block intestinal absorption of carbs
- Agents: Precose™ (acarbose) & Glyset™ (miglitol)
- Lower post-prandial blood sugars
- Problems: GI distress (flatulence and diarrhea)
- Affect on HbA1c < 1%

## Starch Blockers prevent GI absorption of Carbs



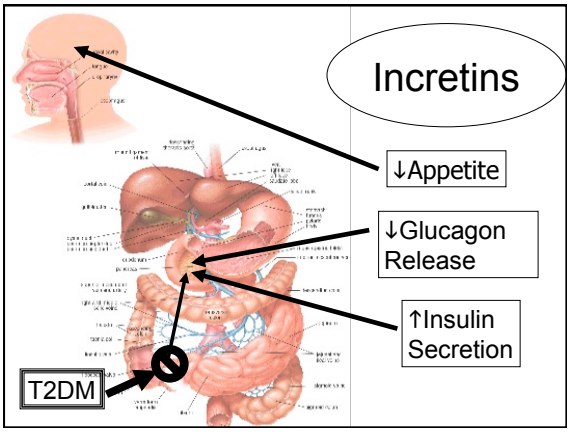

**Pre-prandial vinegar reduces post-prandial glucose roughly 30 mg/dl in multiple, small trials in humans**

J Evid Based Integr Med. 2018 Jan-Dec;23:2156587217753004

## Incretin Mimetics ("-tides")

- The "incretin effect" refers to the fact that CHO passing through the gut produces more insulin response than an equivalent amount of IV glucose
- GLP-1 (glucagon like peptide 1) is an incretin hormone secreted by the L cells of the terminal ileum
- GLP-1 increases insulin secretion, decreases glucagon secretion, and reduces appetite

**First Drug: Byetta™ exenatide**




## GLP-1 Drugs and CVD Risk

- **Victoza** (liraglutide) cut CV events 13%/CV death 22% in patients with established CVD N Engl J Med. 2016 Jul 28;375(4):311-22
- **Trulicity** (dulaglutide) 'significantly' cut MACE (11-13%) in patients with & without established CVD
  REWIND Trial – J Clin Endocrinol Metab 2021, February 4
- **Semaglutide** (Ozempic) reduced MACE 28% in retrospective analysis Diabetes 2018 Jul; 67(Supplement 1)
- Pioneer-2 study: **oral semaglutide** - 1.3% decrease in A1c at 52 wks – MACE reduced 21% over 16 mos ($p < 0.001$) and CV death by 51%

American Diabetes Association 2018 Scientific Sessions. June 25, 2018; Orlando, Florida. Abstract 2-LB.
NEJM 2019; 381:841-51

## Incretins (GLP-1 analogs) - Pearls

- Byetta™ & Bydureon™ (exenatide); Victoza™ (liraglutide), Trulicity™ (dulaglutide), Ozempic™ (semaglutide) → oral version (Rybelsus™)
  - Lower HbA1c 0.7-2%
  - Injected
  - Significant weight loss (9-15+ lbs.)

**Expensive Nausea**

- DPP-IV inhibitors (-gliptins; Januvia™) are oral drugs that block inactivation of endogenous GLP-1
  - Weight neutral
  - Lower HbA1c about 0.7%

## Breaking News

ONCE-WEEKLY wegovy™ semaglutide injection 2.4 mg

- Semaglutide 2.4 mg weekly + lifestyle intervention (LI) used in patients with BMI ≥ 30 (or ≥ 27 with 1+ weight-related comorbidities) versus LI + placebo injection (n= 1961 without diabetes)
  - 2.4X FDA-approved dose in T2DM
  - Nausea/vomiting in 80%/40% of treatment vs control subjects
  - Mean weight loss = 33 lbs at 68 weeks
- 1/3 of subjects lost ≥ 55 lbs

N Engl J Med. 2021 Feb 10.

## But Wait…there's more!

- Tirzepatide is a dual GLP-1/GIP analog
  - GIP = glucose-dependent insulinotropic peptide (↑insulin secretion with higher blood glucose levels)
- SURPASS-2 Trial compared weekly tirzepatide versus semaglutide injection in T2DM
  - After 40 weeks, mean A1c reduction was 2.46 vs 1.86
  - 51% vs 20% achieved A1c < 5.7%
- Mean weight loss was 27.3 lbs vs 13.7 lb
- Approval likely this year

Press Release, Eli Lilly & Company, March 4, 2021

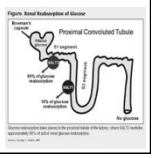
## SGLT2 Inhibitors – the -flozins

- Block reabsorption of glucose at the proximal renal tubule – facilitating urinary excretion of glucose when gluciose > 180 mg/dl
  - Invokana (canagliflozin); Farxiga (dapagliflozin); Jardiance (empagliflozin)
- Reduce hyperinsulinemia, BP, visceral fat, arterial stiffness, uric acid, TGs
- Dapagliflozin approved for CHF

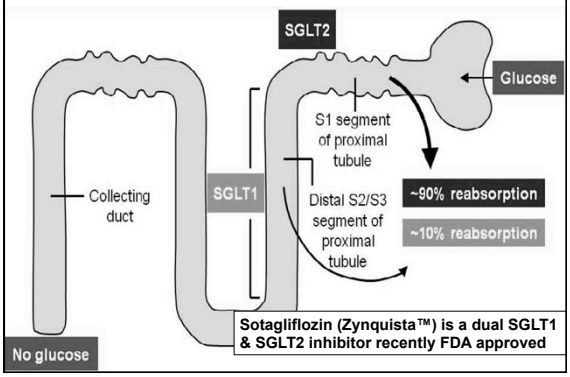
Postgrad Med. 2013 May;125(3):21-32.

**Adverse Events**: UTI, DKA, fracture
? ↑ amputation risk with Canagliflozin

**EXPENSIVE**




## SGLT2 Inhibitors ↑ Urinary Glucose Excretion




**Sotagliflozin (Zynquista™) is a dual SGLT1 & SGLT2 inhibitor recently FDA approved**

## CVD-Real Study (3-year data)

- 470,000 patients from 6 countries (Japan, Singapore, Canada, Israel, South Korea, Australia) – retrospective data analysis
- Use of any SGLT2 drug lowered risk of all-cause mortality by 49%, MI by 19%, stroke by 32%; HHF by 40% in subjects **with AND without CVD**
  - 2020 data show ↓ 50% ESRD or 50% decline in eGFR

Lancet Diabetes Endocrinol. 2020 Jan;8(1):27-35.

- **ADA guidelines now recommend SGLT2 as 2nd-line therapy for T2DM after metformin, especially if pre-existing CVD, especially CHF**

Journal of the American College of Cardiology Mar 2018

## SFUs versus GLP-1/SGLT2 Drugs

- **GLP-1 analogs (Victoza, Ozempic, Trulicity)**
  - **LEADER, SUSTAIN-6, REWIND trials**
- **SGLT2 inhibitors (Jardiance, Farxiga, Invokana)**
  - **EMPA-REG , CANVAS, DEPICT trials**
- **Meta-analysis shows reduced CV risk with any GLP-1/SGLT2 compared to older SFUs**

**Patients on older SFUs (glipizide/glyburide) were 42 to 45X more likely to have an MI/CVA/CV death**

**EASD 2015, Stockholm** → Diabetes Obes Metab. 2017 Mar;19(3):329-335.

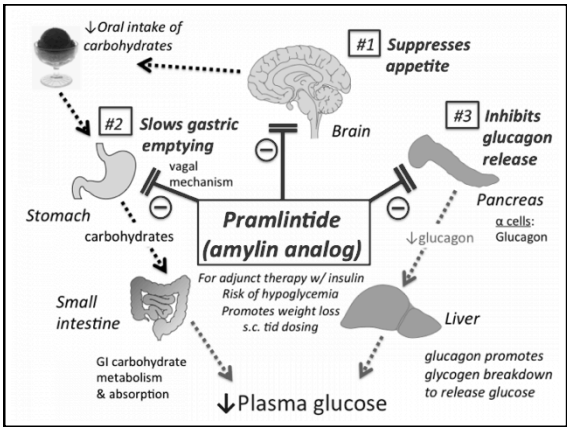
## Infrequently Used Blood Glucose Dtrugs Drugs with Legitimate Benefit

- Pramlintide (Symlin)
- Bromocriptine (Cycloset)
- Colesevelam (Welchol)

## Pramlintide (synthetic amylin): Simlyn™

- What is **pramlintide**?
  - Synthetic amylin, a peptide co-secreted with insulin by pancreatic beta cells
  - Amylin production ↓ as B cells decline in DM
  - FDA approved for use in both T1DM and T2DM → it is not widely used
    - Pamlinitde (Simlyn) lowers HbA1c 0.4 – 0.6%
    - serum amylin is reduced in Alzheimer's & diabetes
  - Rodent Alz Dis models show improved cognition & reduced B--amyloid deposits
  - Single human trial showed the same (n=8)

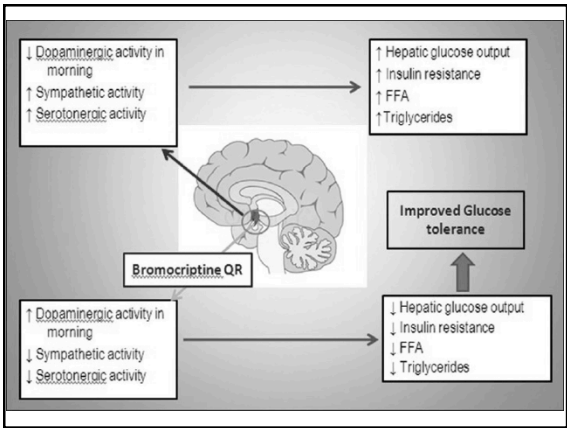
Alzheimers Dis. 2018;62(2):597-609.




## Cycloset™: Quick Release Bromocriptine

- Dopamine receptor agonist with multiple neuroendocrine effects
- CV outcomes trials in T2DM show a 50+% reduced risk of MI, stroke, CV death
- Lowers HbA1c ≈ 0.5%
- Expensive ($500+/month)
- Adverse effects: dizziness, headache, nausea,

Diabetes Care. 2010 Jul; 33(7): 1503–1508
J Am Heart Assoc. 2012 Oct;1(5):e002279
Postgrad Med. 2016 Nov;128(8):761-769.

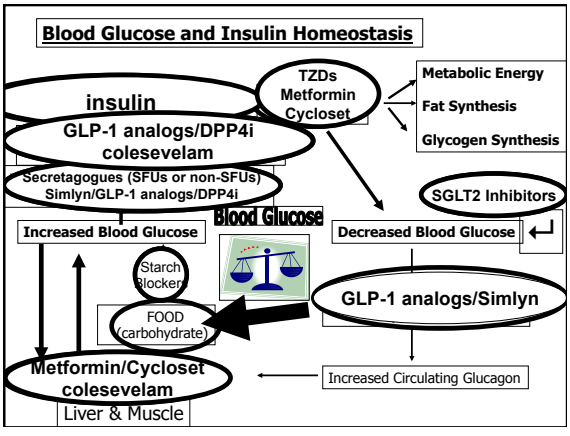



## Colesevelam (Welchol™)

- Bile acid sequestrant (BAS) that lowers LDL cholesterol ≈ 15%
- Lowers absolute HbA1c value about 0.5%
  - Reduces hepatic glucose production
  - Potentiates endogenous GLP-1

Clin Med Insights Endocrinol Diabetes. 2013; 6: 75–79.

- Adverse GI Effects: gas, nausea



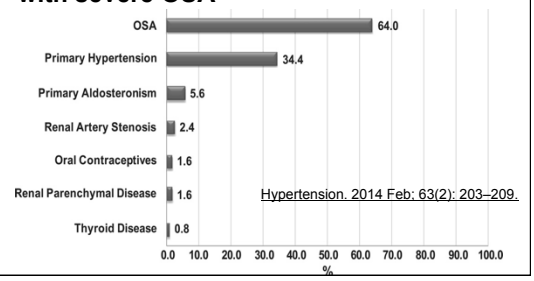
## Beyond Blood Glucose: BP & Lipids

- **Goal is to reduce atherosclerotic cardiovascular disease (ASCVD = coronary heart disease, cerebrovascular Dz, peripheral arterial disease) and heart failure (HF)**
- **Hypertension: A-B-C-D approach**
  - **ACE Inhibitors (-prils) or ARB drugs (-sartans): renoprotective (and appear to be retino-protective)**
  - **Beta-blockers**
  - **Calcium Channel Blockers**
  - **Low dose diuretics**
  - **For' 'Resistant HTN' on 3 meds → add an aldosterone antagonist (e.g. spironolactone)**

Diabetes Care 2019 Jan; 42(Supplement 1): S103-S123

## HTN and OSA

- **50% of hypertensive patients have OSA**
- **Drug-resistant HTN is highly associated with severe OSA**




Hypertension. 2014 Feb; 63(2): 203–209.

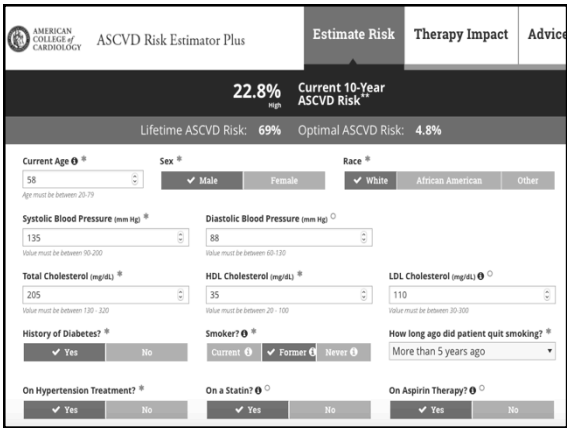
## ASCVD Risk Calculator

**Atherosclerotic Cardiovascular Disease**

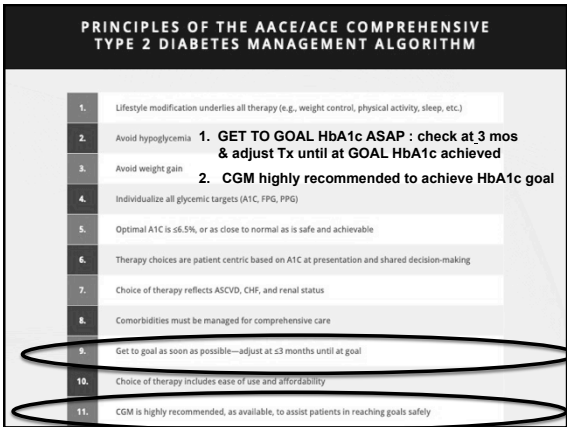
**http://tools.acc.org/ASCVD-Risk-Estimator-Plus**

- If 10-year ASCVD < 15% treat BP to < 140/90
- If 10-year ASCVD >15% treat BP to < 130/80
- If 10-year ASCVD > 20%, or known ASCVD, use *high-intensity statin* (rosuvistatin 20-40mg or atorvastatin 40-80mg)
- If > 40 years old without known ASCVD, consider *moderate intensity statin* (e.g. 10-20 mg atorvastatin)
- If known ASCVD & LDL-C ≥ 70 on maximum statin Tx, add ezetemibe or a PCSK9 inhibitor (Praluent/ Repatha)

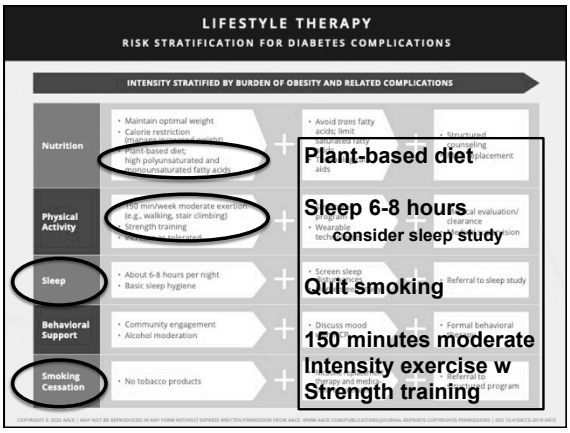
Diabetes Care 2019 Jan; 42(Supplement 1): S103-S123

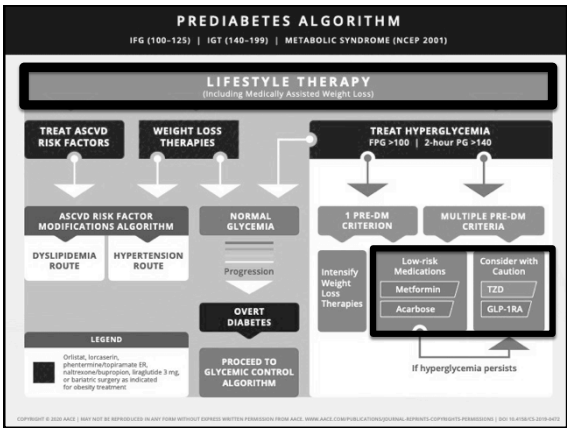


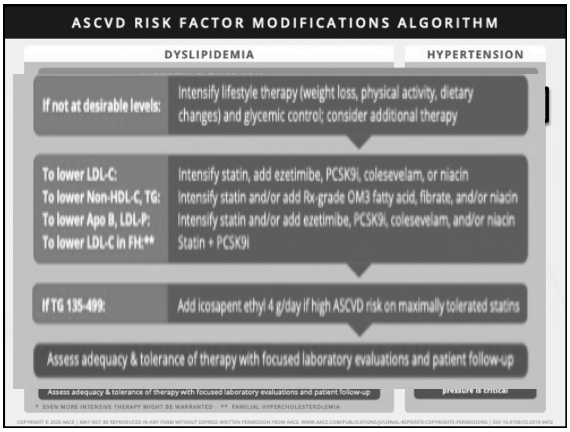

American Academy of Clinical Endocrinology 2021 Guidelines

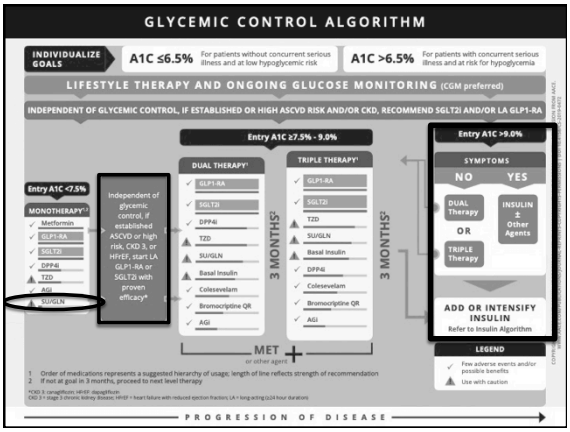


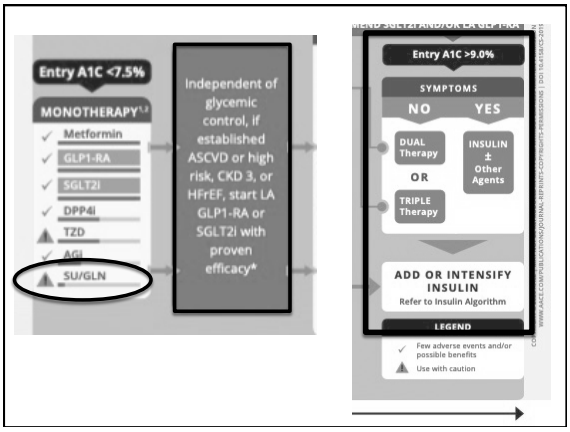

1. **GET TO GOAL HbA1c ASAP : check at 3 mos & adjust Tx until at GOAL HbA1c achieved**
2. **CGM highly recommended to achieve HbA1c goal**




## REAL WORLD DIABETES CONTROL

## ABCS 'Goals' per CDC

- **A1c; BP; Non-HDL-C; Smoking in US adults with self-reported diabetes**
  - Based on NHANES & BRFSS data
- 75.4% met A1c goal < 8.0%
- 70.4% met BP goal < 140/90 mm Hg
- 55.8% met lipid goal non-HDL-C < 130 mg/dl
- 86% were non-smokers
- Only 26.4% met all four goals

MMWR Morb Mortal Wkly Rep 2020;69:1665–1670.

## The Vast Majority of T2DM Patients Don't Achieve Metabolic Targets within 5 YEARS of DX!

***DISCOVER* Trial of 16K T2DM Subjects Worldwide: 38 Nations**

- After 5 years Dx with T2DM:
  - Mean A1c = 8.3% (Europe = 8.1%; US = 8.6%)
  - Mean Age at Dx = 51.6 years (EU = 61.9; US = 58.3)
  - **Only 17.6% with HbA1c ≤ 7% (18.7% EU; US = 17.1%)**
  - **Only 49.2% with HbA1c ≤ 8% (53.9% EU; 47.1% US)**
  - Microvasccular Dz = 18.9% CAD/Stroke = 12.9%
  - Metformin alone = 55.6% met + SFU = 20.9%
  - Metformin + DPP4 inhibitor (Januvia) = 23.5%

Diabetes Res Clin Pract. 2019;151:20-32.

## Diabetes Control Inertia

- MOST patients on mono- and dual therapy (e.g. metformin or metformin + 2nd-line agent) do NOT achieve glucose targets within 5 years
- 55.6% of PCPs displayed clinical inertia (not initiating intensified Tx based on sub-optimal HbA1c
- This significantly increases risk of DR/DR progression given harmful 'metabolic memory' shown in EDIC/UKPDS/ACCORD-Eye RCCT studies
- Can we do better?

Med Sci Monit. 2015; 21: 403–411.

## Triple Therapy in One Pill per Day: Glycemic Control & Cardioprotection

- **Qternmet XR**: metformin XR, saxagliptin (DPP4i) plus dapagliflozin (Farxiga) – FDA approval 05/2019 – fixed dose
  - Lowered HbAc1c ≤ 7% in 40% of patients with HbA1c > 8%
  - Mean HbA1c reduction = 1.5% @ week 24
  - Cardioprotection with metformin & dapagliflozin and renoprotection w dapagliflozin

  Diabetes Care. 2015;38(3):376-383
- **Trijardy XR**: metformin XR, linigliptin (DPP4 inhibitor) plus empagliflozin (Jardiance) – FDA approval 1/2020; four fixed dosages
  - Lowered A1c ≤ 7% in 60% of subjects @ week 24
  - Cardioprotection with metformin and empagliflozin
  - Weight loss and ↓ BP with empagliflozin
  - Reduced GI AEs with metformin XR c/w metformin

*Diabetes Care*. 2015;38(3):384-393.

## Efficacy of Glucose Lowering Agents

- **SINGLE Oral agents lower HbA1c by 1-2% at most**
- **Diet plus exercise lowers HbA1c by about 1%**
- **American Association of Clinical Endocrinology (AACE) guidelines strongly recommend an HbA1c ≤ 7% for most pts**
- **Selecting hypoglycemic agents to achieve the ADA/AACE targets for HbA1c ≤ 6.5/7%% is**

**3rd Grade Math**

## Case Example

- **54 yo with T2DM and HbA1c is 9.1% with mild NPDR and is "diet controlled"**
- **PCP started pt on glipizide – A1c Target ≤ 7%**
- **Had an MI at age 50**
- **What is likely outcome?**
- **What might the OD suggest?**

## Likely Outcome

- **A1c likely to drop to 8%**
  - **Is 8% ≤ 7% ??**
- **Diabetic Retinopathy likely to progress**
- **Patient's risk of having an MI, stroke or dying from these is HIGH**

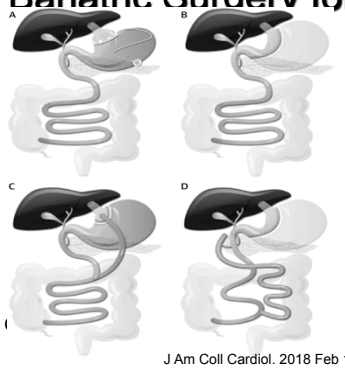
## Recommendations for Our Patient

- Talk to your PCP about discontinuing the SFU and starting metformin and either an SGLT2 inhibitor or GLP-1 analog
- Tell the patient all the SGLT2 companies have patient coupon cards


- Send a letter with your specific eye findings & recommendations to the PCP AND the patient's cardiologist
- Refer to endocrinology IF the patient returns without a better treatment regimen

## What About Bariatric/Metabolic Surgery?

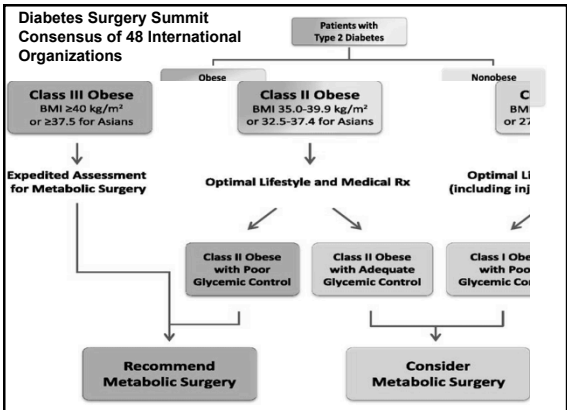
## Bariatric Surgery for DM




A. Adjustable Lap-Band
B. Gastric Sleeve
C. Gastric Bypass
D. Biliopancreatic Diversion +/- duodenal switch

Gastric Sleeve

J Am Coll Cardiol. 2018 Feb 13;71(6):670-687

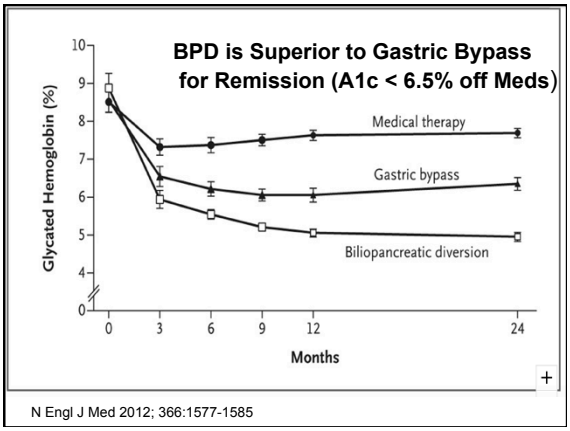



Diabetes Care 2016 Jun; 39(6): 861-877.

## Surgery is Effective…especially if done ≤ 5 years after DM diagnosis

- STAMPEDE 3-year study shows far superior A1c results than intensive medical therapy (IMT) - mean BMI = 36.7
  - 38% of gastric by-pass pts had A1c < 6% and 94% were off insulin at year 3
  - 25% and 92% of gastric sleeve pts
  - 5% and 45% with IMT (DM Meds + 1500 Kcal + 175 min moderate intensity exercise + 5% weight loss goal)

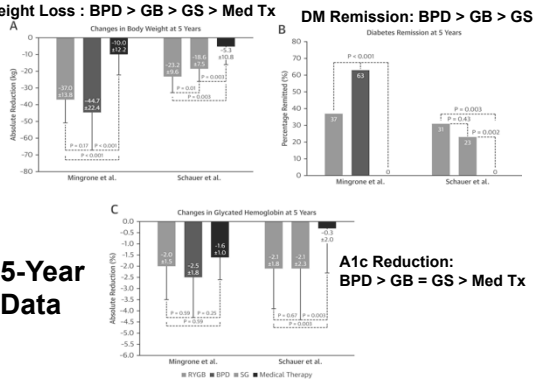
Bariatric surgery versus intensive medical therapy for diabetes -- 3-year outcomes, NEJM 2014




N Engl J Med 2012; 366:1577-1585

**Weight Loss : BPD > GB > GS > Med Tx**

**DM Remission: BPD > GB > GS**




**5-Year Data**

**A1c Reduction: BPD > GB = GS > Med Tx**

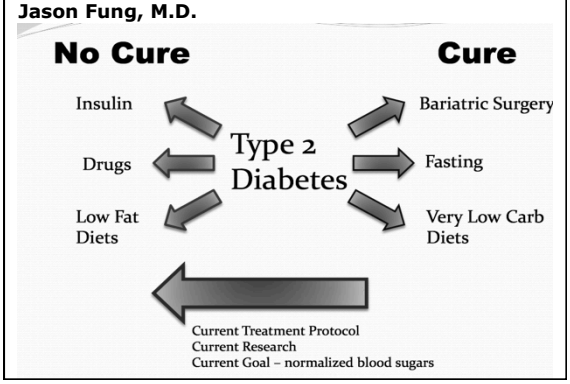
## Duodenal Ablation/Mucosal Resurfacing

- Hydrothermal ablation of duodenal mucosa (DMR) disrupts absorption of nutrients, including glucose
- Lowers HbA1c about 0.9% & weight about 5.5 lbs
- Less invasive than traditional bariatric surgeries
- FDA approval in May 2021 after INSPIRE trial showed 53% of T2DM subjects on insulin could D/C insulin at 18 mos with single DMR procedure + GLP-1 therapy

Gut. 2020 Feb;69(2):295-303. Gastrointest Endosc 2021 Jul;94(1):111-120.e3.

## Another Approach to T2DM

**Jason Fung, M.D.**




## Case Study - Patient PK

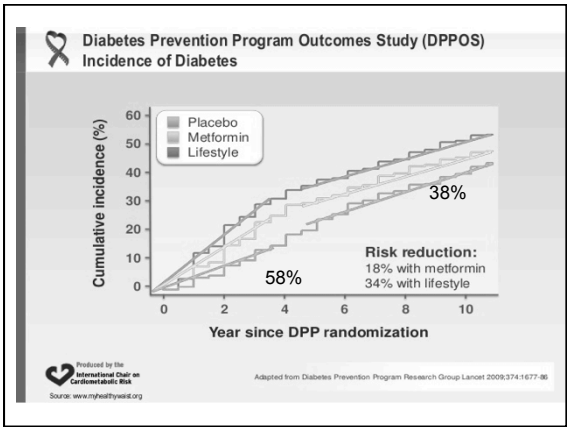
- 52 yo male - T2DM x 2 years – no DR
- Metformin + Januvia® (sitagliptin)
- A1c 6.6% at Dx, lowered on meds but now 7.4% and placed on insulin (Lantus®) QHS
- BMI 38 at Dx and now 40 kg/m$^2$
- We discussed options, including alternate daily fasting (ADF) combined with Paleo-type low carb diet on 'feeding days'

## PK 6 months later

- 35 lbs weight loss (BMI = 30 Kg/m$^2$)
- A1c now 5.4% and has discontinued insulin and Januvia
- PK reports increased energy, libido and clearer thinking
- *"This was the best thing I've ever done"*

## Preventing Diabetes in High-Risk Patients

- The Diabetes Prevention Program (DPP) conducted at 13 US centers showed that "lifestyle modification" (walking 30 minutes each day, five days each week) lowered the risk of developing T2DM in those with prediabetes or previous GDM by 58% over a three year period (38% @ 10 yrs)
- Metformin worked best if patients were heavier (BMI > 35), younger (< 60 yo) or had a Hx of GDM




## Early Time-Restricted Feeding (eTRF)

- Identical diets x 5 weeks with feeding window 7AM-3 PM versus 7 AM-7PM
  - 8 males with Pre-DM (mean BMI – 32.2)
- NO weight loss BUT significant reductions in:
  - Post-prandial insulin & insulin resistance
  - Blood Pressure (11/10 mm!), appetite, and oxidative stress

Cell Metab. 2018 Jun 5;27(6):1212-1221.e3.

## *'Disease Overwhelmus'*

- Many patients feel overwhelmed by their diagnosis, complexity of multifaceted treatment, and magnitude of information (misinformation)


## Quick Assessment

- **On a 5-Point Scale, rate how you're doing with your diabetes:**
  - **I am** feeling overwhelmed by the demands of living with diabetes. 1 2 3 4 5
  - I am feeling that I am often failing with my diabetes regimen. 1 2 3 4 5
- Higher scores suggest a need for stress reduction techniques/professional counseling, diabetes education, or BOTH

Ann Fam Med. May 2008; 6(3): 246–252.

## Battle Plan for ODs

- Refer patients to another provider if A1c > 10%
- Refer if A1c > 9% on two visits
- Refer if patient is < 60 yo and on glyburide/ glipizide as monotherapy for blood sugar control
- Recommend patients with known CVD or HF ask about GLP-1 agents or SGLT2 inhibitors
- Recommend healthy lifestyle habits
  - Exercise, more plant foods, adequate sleep, stress reduction

## Preventing Eye Disease

- Optimize metabolic control soon after diagnosis
  - Metabolic Memory is very important
- Nutraceutical Intervention?
- Diabetes Visual Function Supplement Study (DiVFuSS) showed a multi-component supplement significantly improves visual function, lipids, neuropathy symptoms & reduces inflammation
  - Totally prevented DR in an animal model

OPEN ACCESS

The Diabetes Visual Function Supplement Study (*DiVFuSS*)

A Paul Chous,[1] Stuart P Richer,[2] Jeffry D Gerson,[3] Reru A Kowluru[4]

Br J Ophthalmol. 2016 Feb;100(2):227-34

**Thank You GWCO!**

Questions?

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