TYPE 2 DIABETES MELLITUS

UPDATES IN TREATMENT

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Disclosures

- I have no conflicts of interest to disclose

Objectives

- Gain a better appreciation of the importance of patient engagement
- Gain a better appreciation of how lifestyle choices may/may not effect outcomes
- Gain a better appreciation of how a patient's characteristics affect outcomes
- Gain a better understanding of how age affects A1C target
- Gain a better understanding of the effect non-insulin medications have on cardiovascular outcomes

Numbers

- World wide, approximately 347 million people have diabetes
  - 90% Type 2
  - May double by 2030
- In the US, 34 million adults have diabetes
  - About 10% of adults
    - Ranks 43 in the world in prevalence
  - 90-95% Type 2
  - Approximately 1 in 3 adults have pre-diabetes

Goals of Treatment

- Prevent or delay complications
- Maintain/Optimize quality of life

Prevent or delay complications

- Cardiovascular Disease is the leading cause of death and complications
- Young adults with DM2 lose about 15 years from the average life expectancy
- Developing DM2 between the ages of 18-44 may increase the risk of developing an MI by three times
- In 2014, 108,000 diabetic adults had lower extremity amputations
  - That's 5 out of every 1000 diabetic patients
  - African Americans are 4 times more likely to experience a diabetes related amputation
- Diabetes accounts for 44% of new cases of renal failure

Patient engagement

- Involving and encouraging patients in their own care to help improve health outcomes, drive better care, and achieve lower costs

Patient Engagement

- Lifestyle changes
  - Weight loss
  - Exercise
  - Diet/Nutrition
  - Smoking cessation
- Medication compliance
- Preventive exams

Exercise Example - cycling

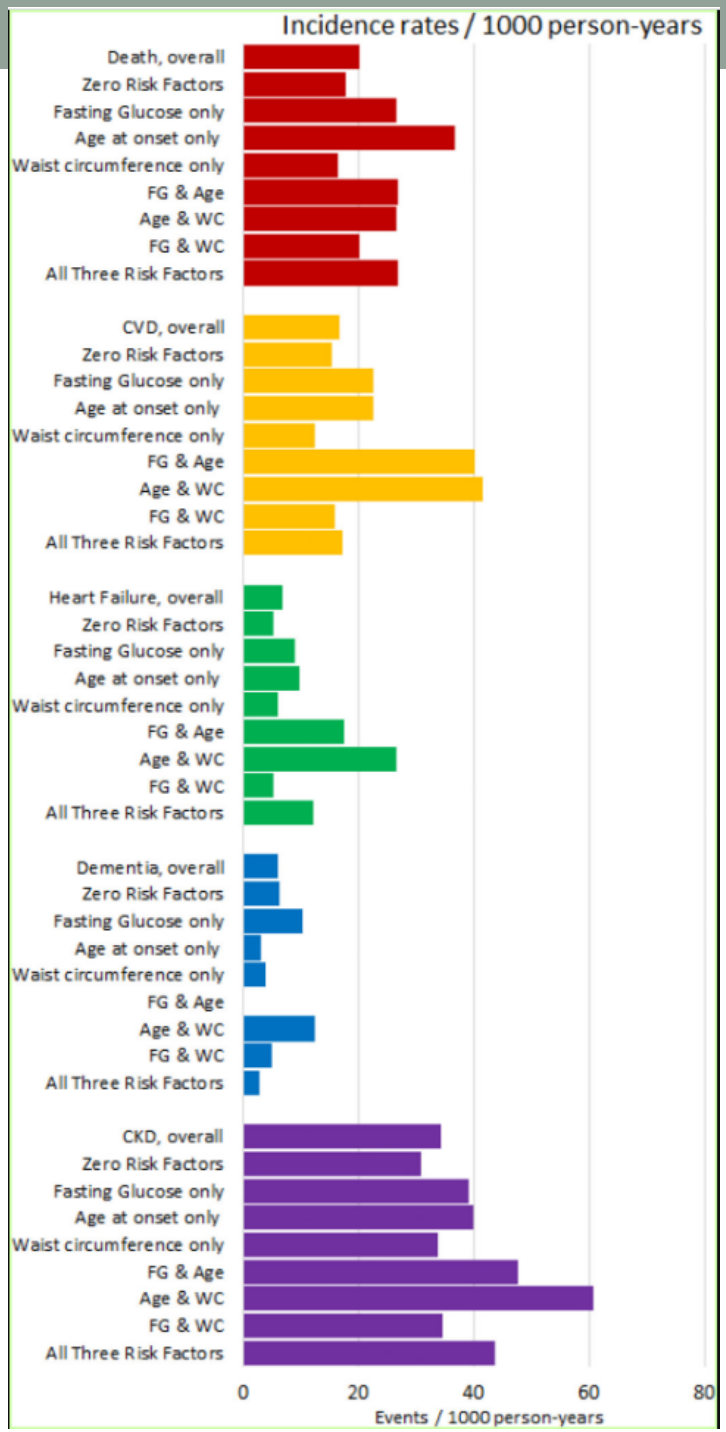
- Prospective Cohort Study by Dr Reid-Larsen
  - part of the European Prospective Investigation into Cancer and Nutrition Study
- 5000 DM patients
  - 38% cycled every week
  - Mean age 56, diabetes 8 years, 20% smokers, avg BMI 29
- Cycled 1 hour every week – 25% reduction in all cause mortality
- Cycled 2.5 – 5 hours per week – 31% reduction in all cause mortality
- Cycled > 5 hours per week – 24% reduction

Medication Compliance vs Complexity of Medication Regimen

- Comprehensive review of 76 studies
- Mean adherence 79% w/once daily dosing
- Mean adherence 51% w/4 times daily dosing
- 814,456 patients filled 4.1 chronic meds
- 23.3% of the medications included in the study had potential interaction
- More than half of the medications were used to treat comorbidities

Multi-Ethnic Study of Atherosclerosis

- 1597 men/women w/DM ages 45-84
- Free from clinical CVD at initial exam beginning 2000-2002
- Four racial/ethnic groups
  - Non-Hispanic White 38%
  - African American 28%
  - Hispanic 22%
  - Chinese Americans 12%
- Diabetes Data (38% did not meet any of the below thresholds)
  - Diabetes Onset (≤ age 45)
  - Fasting Glucose (glucose ≥ 140)
  - Waist circumference (women ≥ 105cm and men ≥ 110cm – about 43”)
- Six Communities – MD, IL, NC, CA, NY, MN
- Five Follow Up Exams – 2004, 2005, 2007, 2011, 2018


Incidence rates / 1000 person-years
Death, overall
Zero Risk Factors
Fasting Glucose only
Age at onset only
Waist circumference only
FG & Age
Age & WC
FG & WC
All Three Risk Factors
CVD, overall
Zero Risk Factors
Fasting Glucose only
Age at onset only
Waist circumference only
FG & Age
Age & WC
FG & WC
All Three Risk Factors
Heart Failure, overall
Zero Risk Factors
Fasting Glucose only
Age at onset only
Waist circumference only
FG & Age
Age & WC
FG & WC
All Three Risk Factors
Dementia, overall
Zero Risk Factors
Fasting Glucose only
Age at onset only
Waist circumference only
FG & Age
Age & WC
FG & WC
All Three Risk Factors
CKD, overall
Zero Risk Factors
Fasting Glucose only
Age at onset only
Waist circumference only
FG & Age
Age & WC
FG & WC
All Three Risk Factors
0
20
40
60
80
Events / 1000 person-years

Multi-Ethnic Study of Atherosclerosis – Relevance?

- Younger patients with pre-diabetes – delaying the onset may decrease the risk
- Waist circumference – encourage to lose weight and consider meds that could assist with weight loss

Weight/BMI/Weight Loss

- Meta-analysis suggests lower all-cause or cardiovascular mortality risk for overweight or obese individuals compared to normal weight individuals with MD2 (obesity paradox)
- Longitudinal observational studies looking at obesity and diabetes related complications have shown inconsistent/mixed results – limited data
  - Look AHEAD trial looked at intensive lifestyle intervention for weight loss – did not reduce the 10 year CVD risk
    - Post hoc analysis indicated that a weight loss of ≥10% might reduce the risk
  - ADDITION-Cambridge study observed that a ≥5% weight loss decreases 10 year CVD risk
- EPIC-Potsdam Study

EPIC-Potsdam Study

- Enrolled 27,548 healthy patients between 1994-1998 followed to 2009
- Intent was to study the role of diet on chronic disease
- 1083 participants developed DM
- Median age 60.4
- Pre-diagnosis BMI increased the risk of vascular complications
  - Increased 1.17 times for every 5 kg/in^2 higher BMI
- After diagnosis, BMI loss of > 1% per year was associated with lower total vascular complications
  - Predominantly microvascular complications such as neuropathy and kidney disease
  - No change in macrovascular complications; MI and stroke

Lifestyle is Very Important but What About Cardiovascular Risk?

- Lifestyle management is (and should be) emphasized throughout the disease process
  - Obesity
  - Diet
  - Physical inactivity
  - Dyslipidemia
  - Smoking cessation

Look AHEAD

- Randomized 5145 overweight or obese patients with DM2 – median f/u 9.6 years
- Intensive lifestyle intervention (intervention group) vs diabetes support and education (control group)
- Primary outcome was death from cardiovascular causes, non-fatal MI, non-fatal stroke, or hospitalization from angina

Winner Is?

- Weight loss
  - Intervention 8.6% vs 0.7% at year 1 and remained statistically significant
- A1C, physical fitness, waist circumference
  - Intervention had sustained statistical significance

Winner Is?

- Weight loss
  - Intervention 8.6% vs 0.7% at year 1 and remained statistically significant
- A1C, physical fitness, waist circumference
  - Intervention had sustained statistical significance
- **Primary outcome (cardiovascular)**
  - **403 intervention group vs 418 control**
  - **No statistical significance**

Lifestyle Plus Medications

- 315 patients with DM2 (2003 Study)
- Conventional treatment according to national guidelines vs intensive treatment with stepwise behavior modification and pharmacological therapy
  - Blood pressure
  - A1C
  - Lipid lowering therapy
  - Aspirin
- Reduced the risk of cardiovascular and microvascular events by about 50%

Preventive Measures

- National Health and Nutrition Examination Study (NHANES) data from 2011-2016
- 2,899 patients with diabetes > 1 year
- Assessed 5 outpatient services routinely recommended to prevent diabetic complications (categorized on number of times received in the past year; 1 – 4)
  - Routine physician exam
  - Assessment of A1C
  - Eye exam with pupil dilation (annually)
  - Foot exam
  - Assessment from a diabetes specialist (not an adopted guideline but typically depends on PCP's comfort level)
- Primary outcome was all-cause hospitalization within the past year

Results

- Hospitalization significantly more common in:
  - Older patients (61.8 vs 58.2 non-hospitalized)
  - Black Americans
  - Lower income levels (under $20,000)
  - Those who considered their health as “poor” or “fair”
- No significant difference in A1C, HTN
- Those who received a preventive foot exam were 33% less likely to be hospitalized within that year
- Those visiting a diabetes specialist were 44% less likely to be hospitalized within that year
- No other outpatient services displayed an independent association with hospitalization

Older Adults

- Up to 19% of adults age >65 have diabetes
  - Approximately half have pre-diabetes
- More than 25% of adults age ≥ 75 have diabetes
- Older adults are excluded from 2/3 of trials
- Poor glycemic control is associated with a decline in cognitive function and longer duration of diabetes with worsening cognitive functioning
- Hypoglycemia is responsible for 40% more hospitalizations than hyperglycemia
- Severe hypoglycemia has been linked to increased risk of dementia
  - Target goals should be modified to avoid hypoglycemia
- Treatment goals should be modified based on patient's clinical characteristics and life expectancy

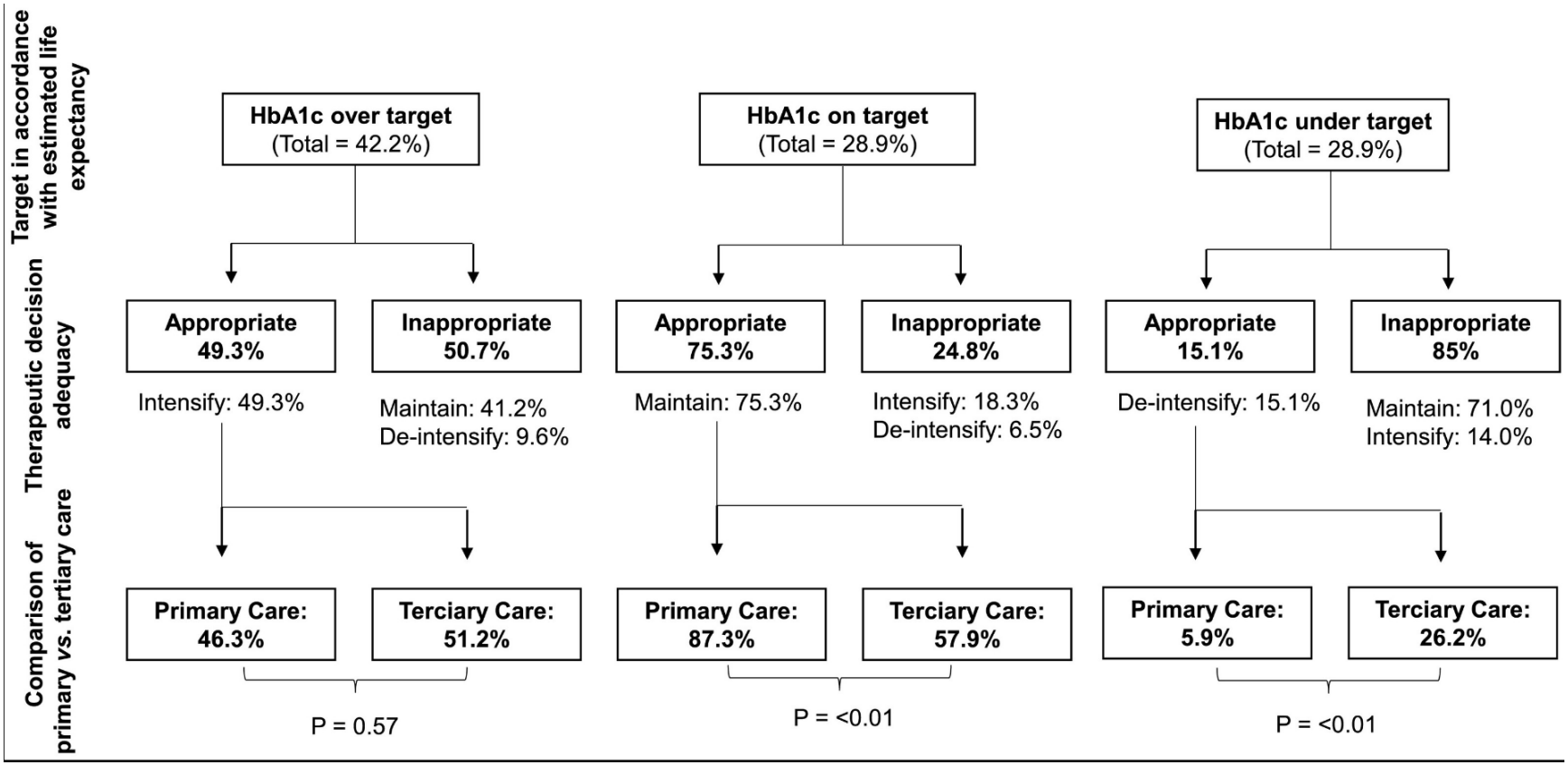
A1C Target Goals for Older Adults

7 - 7.5%	• Healthy, few chronic illnesses • Longer life expectancy
< 8%	• Multiple coexisting illnesses • Intermediate remaining life expectancy
< 8.5%	• Very complex, poor health • Limited remaining life expectancy

Older Adults with Diabetes

- Multicenter, cross-sectional study to evaluate the adequacy of treatment decisions in older adults (>65)
- Older adults with diabetes who received endocrinology care at university center (162 patients) or at a primary care health center (160 patients)
- Followed for at least one year with and at least two consultations
- Target goals set at
  - Between 7 – 7.5% if estimated life expectancy > 10 years
  - Between 7.5-8% if estimated life expectancy 5 – 10 years
  - Between 8-8.5% if estimated life expectancy < 5 years
- Primary outcome was the adequacy of the treatment decision
  - Optimizing the treatment by increasing or adding meds
  - De-intensifying the treatment by reducing dose or withdrawing meds

Results


Target in accordance with estimated life expectancy
Therapeutic decision adequacy
Comparison of primary vs. tertiary care
HbA1c over target
(Total = 42.2%)
HbA1c on target
(Total = 28.9%)
HbA1c under target
(Total = 28.9%)
Appropriate
49.3%
Inappropriate
50.7%
Appropriate
75.3%
Inappropriate
24.8%
Appropriate
15.1%
Inappropriate
85%
Intensify: 49.3%
Maintain: 41.2%
De-intensify: 9.6%
Maintain: 75.3%
Intensify: 18.3%
De-intensify: 6.5%
De-intensify: 15.1%
Maintain: 71.0%
Intensify: 14.0%
Primary Care:
46.3%
Terciary Care:
51.2%
Primary Care:
87.3%
Terciary Care:
57.9%
Primary Care:
5.9%
Terciary Care:
26.2%
P = 0.57
P = <0.01
P = <0.01

Intensive vs Conservative Goals in Older DM Patients

- 108,620 patients ≥ 75 with DM
- Intensive control A1C < 7
- Conservative control A1C 7.1 – 8.5
- High risk meds/agents were insulin and/or SU
  - 21.6% intensive control on high risk agents
  - 39.5% intensive control on low risk agents
  - 23.7% conservative control on high risk agents
  - 15.2% conservative control on low risk agents
- Primary Outcomes
  - Diabetes-related ED visit, hospitalization, all-cause mortality within 30 days of index date (first A1C result after enrollment in study)

Intensive vs Conservative Goals in Older DM Patients

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- Intensive control A1C < 7
- Conservative control A1C 7.1 – 8.5
- High risk meds/agents were insulin and/or SU
- Primary Outcomes
  - Diabetes-related ED visit, hospitalization, all-cause mortality within 30 days of index date (first A1C result after enrollment in study)
- Almost 50% increase in primary outcomes for intensive control w/high risk meds vs conservative control w/low risk meds
- Significant increase with intensive control vs conservative control both w/high risk meds

"Resistance training is just as important as cardio. Train yourself to resist chocolate, pastries, fried foods, beer, pizza...."

DM Meds Effect on Cardiac Outcomes

- Metformin
- Insulin
- SU
- TZD
- DPP4i
- SGLT2i
- GLP-1RA

Metformin

- United Kingdom Prospective Diabetes Study (UKPDS)
- Significant risk reduction
  - MI 39%
  - Diabetes related death 42%
- Meta-analysis of 10 articles reporting on 13 trials
  - Total of 2079 patients
  - Uncertainty whether metformin reduces the risk of cardiovascular disease in DM2 patients
  - Mainly due to absence of evidence

Insulin

- UKPDS
  - No increased risk of MI or diabetes related death was observed
- ORIGIN Trial
  - 12,573 patients
  - Cardiovascular risk factors
  - Pre-diabetes or DM2
  - Insulin glargine or standard care (SU/metformin) or placebo
  - Glargine had neutral effect on cardiovascular outcomes
  - Increased hypoglycemia and modest weight gain

Sulfonylureas

- Tolbutamide – first generation sulfonylurea
  - Increased risk of cardiovascular disease
  - Prompted classwide warning of risk
- UKPDS
  - No increased risk of MI or diabetes related death
  - Glyburide or Chlorpropamide
- Meta-analysis of trials involving 2nd-3rd generation SU
  - 47 RCTs involving 37,650 patients
  - Glipizide, Glyburide, Glimeperide
  - SU not associated with increased risk for all-cause mortality, cardiovascular mortality, MI, or stroke

Pioglitazone

- Placebo controlled trial of DM2 patients with macrovascular disease
  - Non-significant 10% reduction in risk of primary end-point events
  - Reduced the risk of
    - Death from any cause (14%)
    - Non-fatal MI (12%)
    - Stroke (11%)
- Estimated benefit may be offset by increase risk of heart failure

DPP-4 Inhibitors

- Non-inferior compared with placebo in cardiovascular outcome trials
- Exception is Saxagliptin
  - Significantly increased risk of hospitalization for heart failure

SGLT2

- EMPA-REG
  - Empagliflozin, Cardiovascular Outcomes and Mortality in DM2
  - Significantly reduced the risk of combined cardiovascular outcomes of CV death, MI, and non-fatal stroke as well as reduced hospitalization for HF
  - Reduced secondary renal endpoints(reduced risk of doubling of Cr, ESRD, or death from ESRD by 39%)
- CANVAS
  - Canagliflozin Cardiovascular Assessment Study
  - Significantly reduced the risk of combined cardiovascular outcomes of CV death, MI, and non-fatal stroke as well as reduced hospitalization for HF
  - Reduced secondary renal endpoints(reduced risk of doubling of Cr, ESRD, or death from ESRD by 40%)
  - Increased risk of amputation
- CREDENCE
  - Canagliflozin and Renal End points in Diabetes with Established Nephropathy Clinical Evaluation
  - Stopped early due to showing a 32% reduction for development of ESRD over control
- DECLARE-TIMI
  - Dapagliflozin Effect on Cardiovascular Events Thrombolysis in Myocardial Infarction
  - Dapagliflozin reduced a composite of CV death and heart failure hospitalizations
  - Did not significantly lower the combined risk of CV death, non-fatal MI, and stroke

DAPA-HF Trial

- ADA 2020 Virtual Scientific Sessions in June ; Dr Inzucchi
- “Effect of Dapagliflozin on the incidence of diabetes: A prespecified exploratory analysis from DAPA-HF”
  - Phase 3 placebo controlled international study
  - 4774 patients with average age of 66 followed for approximately 18 months
    - 2605 were not diabetic
- Risk of worsening HF or death from cardiovascular causes was lower with dapagliflozin
- Reduced new-onset DM by 32% (4.9% vs 7.1% of patients)
  - Additional analysis, those that did develop DM during the trial experienced a 70% increase in mortality

Heart Failure

- Approximately 50% of patients with DM2 may develop heart failure
- EMPA-REG
  - Empagliflozin, Cardiovascular Outcomes and Mortality in DM2
  - 35% reduction in hospitalization for HF vs placebo
- CREDENCE
  - Canagliflozin and Renal End points in Diabetes with Established Nephropathy Clinical Evaluation
  - 39% reduction in hospitalization for heart failure and 31% reduction in composite of cardiovascular death or hospitalization for heart failure
- DECLARE-TIMI
  - Dapagliflozin Effect on Cardiovascular Events Thrombolysis in Myocardial Infarction
  - 35% reduction in hospitalization for HF vs placebo
- Studies show benefit in preventing hospitalization for heart failure
  - Suggest, but do not prove, may be beneficial in established heart failure

SGLT-2

- Up to 40% of the US adult population have some form of kidney disease
- MACE
  - Empagliflozin Yes
  - Canagliflozin Yes
  - Dapagliflozin Neutral
- HF
  - Empagliflozin Yes
  - Canagliflozin Yes
  - Dapagliflozin Yes
- CKD
  - Empagliflozin Yes
  - Canagliflozin Yes
  - Dapagliflozin Yes

GLP-1 Receptor Agonists

- LEADER – Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
  - 9340 patients
    - 81% established CVD
    - 24.7% ≥ stage 3 CKD
    - Both 15.8%
  - Deaths from cardiovascular causes were significantly reduced
  - Rates of non-fatal MI, non-fatal stroke, and hospitalization for HF lower but non-significant
- SUSTAIN-6 – Semaglutide in Subjects With Type 2 Diabetes
  - 2735 patients
    - 83% had established CVD, CKD, or both
  - Deaths from cardiovascular causes was consistent with the LEADER trial
  - Rates of non-fatal MI, non-fatal stroke was significantly lower

Oral Semaglutide

- 3183 patients
- Objective was to rule out an 80% excess cardiovascular risk compared to placebo
- 84.7% 50 years or older with CVD or CKD
- Death from cardiovascular causes
  - 0.9% (Oral Semaglutide) vs 1.9% (Placebo)
- Non-fatal MI
  - 2.3% vs 1.9%
- Non-fatal stroke
  - 0.8% vs 1.0%
- Death from any cause
  - 1.4% vs 2.8%
- Cardiovascular risk was non-inferior to placebo
- Shorter duration, fewer patients, less events may suggest cardiovascular effect is independent of route of administration

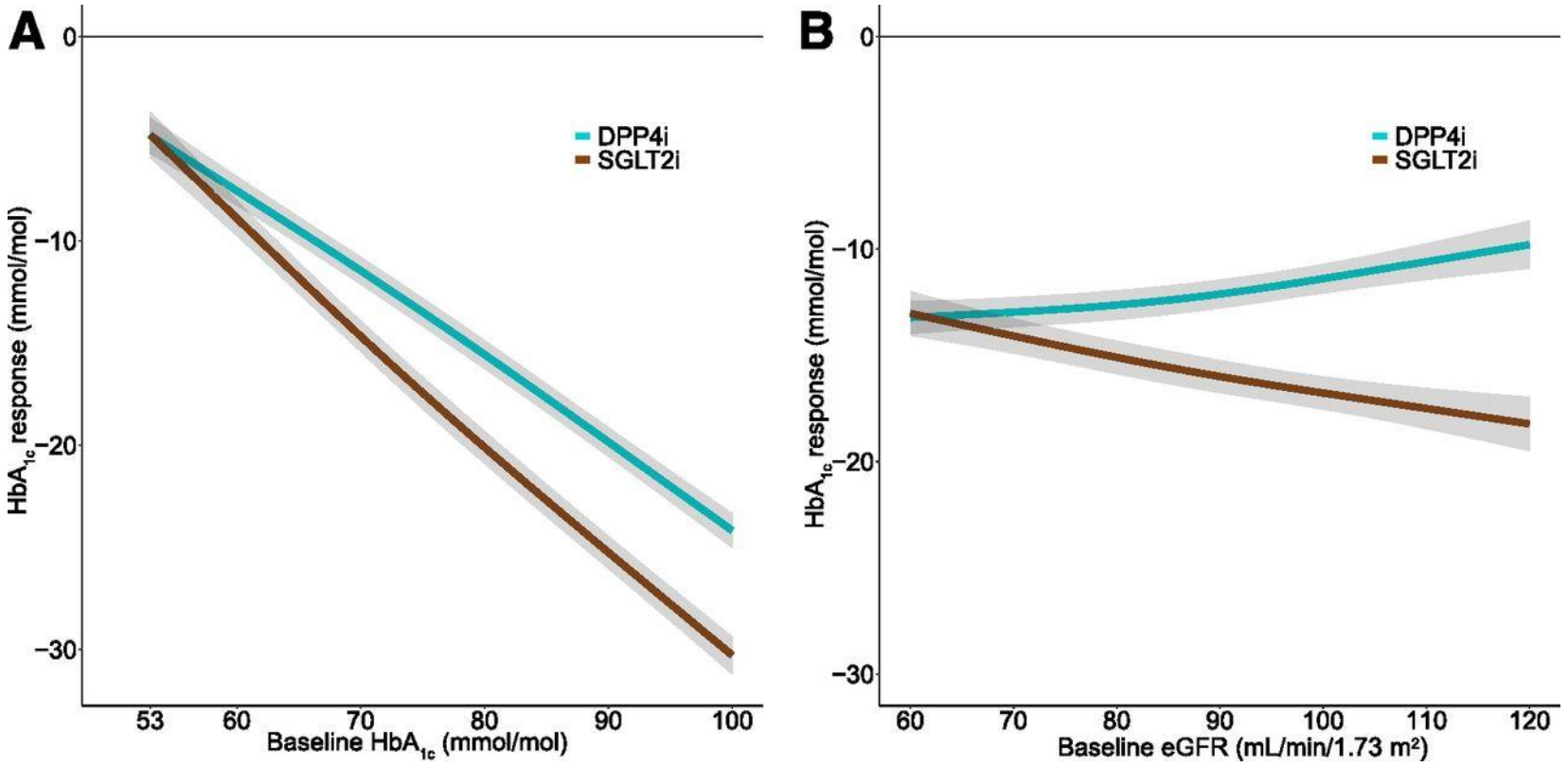
GLP-1RA vs SGLT2

- Meta-analysis by T.A. Zilniker et al reviewed data from eight trials and 77,242 patients
  - 42,920 (55.6%) in GLP-1RA trials and 34,322 (44.4%) in SGLT2 trials
  - Both reduced the risk of MACE by 14% in patients with known ASCVD
    - Neither reduced the risk of MACE in patients without established ASCVD
  - SGLT2 reduced the relative risk of hospitalization for HF by 31%
    - GLP-1RA had a non-significant 7% relative risk reduction
  - SGLT2 showed relative risk reduction of 45% for the composite of reductions in eGFR, ESKD, and death due to renal causes
    - GLP-1RA reduced microalbuminuria but excluding microalbuminuria had a non-significant relative reduction of 8%

Oral Medications

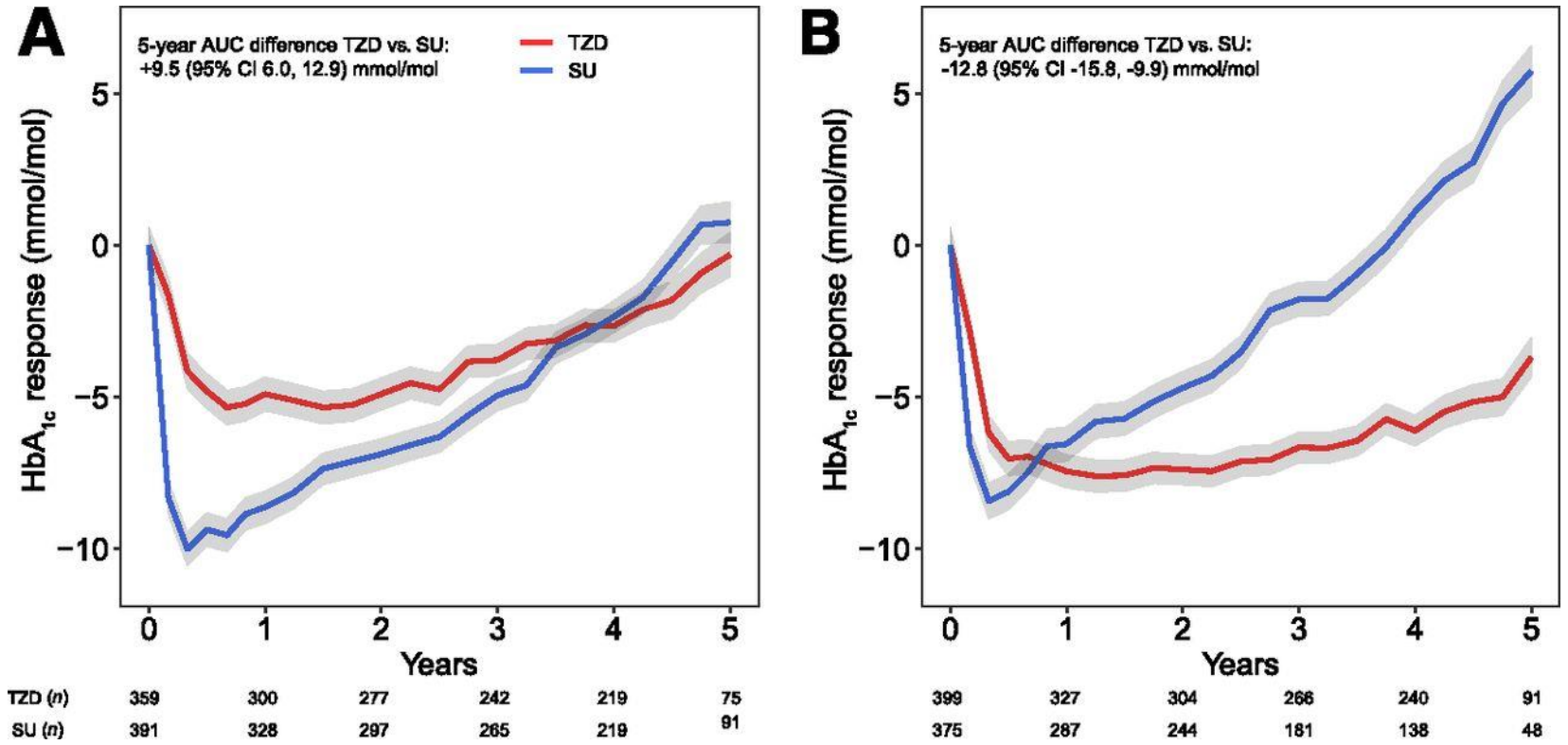
Class/Drug	Decrease in A1C	Mechanism	Common Adverse Effects	Benefits and Considerations
Sulfonylureas	Up to 2%	Stimulate Pancreas to release insulin	Hypoglycemia Weight gain	High rate of secondary failure Low cost
Metformin	Up to 2%	Inhibits hepatic glucose production, increase glucose uptake, alters gut microbiota	Nausea, diarrhea, B12 def, rare lactic acidosis	Considered first-line, weight neutral/loss Low risk hypoglycemia Low cost
Pioglitazone	Up to 1.5%	Decreased insulin resistance	Weight gain, edema, contraindicated in heart failure	Low risk hypoglycemia, durability, low cost
DPP-4i	Up to 1%	Inhibit enzyme that breaks down incretins	Nausea, diarrhea, possible pancreatitis, rare severe joint pain	Weight neutral, low risk hypoglycemia, high cost
SGLT2i	Up to 1%	Block reabsorption of glucose from urine	Increased urination, volume depletion, AKI, warning amputation, rare Fournier's gangrene	Weight loss, reduced blood pressure, benefit in CKD, high cost

Associations between baseline HbA1c and baseline eGFR (Chronic Kidney Disease Epidemiology Collaboration formula) and HbA1c response at 6 months (baseline HbA1c minus 6-month HbA1c) with SGLT2i and DPP-4i treatment in U.K. primary care data (Clinical Practice Research Datalink) (n = 20,965).



John M. Dennis Diabetes 2020;69:2075-2085

Five-year glycemic response (change from baseline in HbA1c) with TZD and SU treatment in males without obesity (BMI <30) (A) and females with obesity (BMI ≥30) (B) subgroups in 1,232 participants in the ADOPT clinical trial (21).



John M. Dennis Diabetes 2020;69:2075-2085

Different Effects Depending on Race?

- 6 GLP1RA Trials analyzed
  - 4195 Asians and 37530 Whites
  - MACE benefits significantly better in Asians than in whites
- 5 SGLT2 Trials analyzed
  - 3980 Asians and 29007 Whites
  - 3 Trials found no significant reduction in MACE in Asians but possible low statistical power and underrepresentation of Asians
  - 2 Trials found potentially better in HF

Future

- Newer Medications
- SGLT1-2 inhibitor
- Longer acting insulin
- Trimaster Study results in May(ish)
- CKD
- Race, Gender, Physical Characteristics may affect medication effectiveness
- More secondary results from previous trial reviews
  - Non-alcoholic Steatohepatitis, etc

Summary

- Cardiovascular disease is the leading cause of death and complications
- Patient engagement is important
- Take pre-diabetes seriously
- Lifestyle plus medications may reduce events up to 50%
- Individualize the A1C Target for the patient
- Metformin is still considered first line
- SGLT2i and GLP-1RA appear to have good effects but expensive and may not be needed in all DM2 patients

"I try to eat healthy. I never sprinkle salt on ice cream, I only eat decaffeinated pizza and my beer is 100% fat free."

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