Internal Medicine Update: Treating the Diabetic Patient

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Disclosures

• Promotional Speaker for Novo Nordisk
• Promotional Speaker for Medtronic
Objectives

- Discuss the 8 core defects in type 2 DM
- Review the Natural History of Diabetes
- Review Pharmacologic Therapy Used in Type 2 DM and current CVOT data and trials
- Use of Technology in Type 2 DM
  - Insulin pump/delivery devices
  - Continuous Glucose Monitoring
  - Web Based Programs
  - Smart Phone Apps
- Clinical Practice Guidelines
Statistics from the ADA

- **Prevalence**: In 2015, 30.3 million Americans, or 9.4% of the population, had diabetes.
  - Approximately 1.25 million American children and adults have type 1 diabetes.

- **Undiagnosed**: Of the 30.3 million adults with diabetes, 23.1 million were diagnosed, and 7.2 million were undiagnosed.

- **Prevalence in Seniors**: The percentage of Americans age 65 and older remains high, at 25.2%, or 12.0 million seniors (diagnosed and undiagnosed).

- **New Cases**: 1.5 million Americans are diagnosed with diabetes every year.

- **Prediabetes**: In 2015, 84.1 million Americans age 18 and older had prediabetes.

- **Deaths**: Diabetes remains the 7th leading cause of death in the United States in 2015, with 79,535 death certificates listing it as the underlying cause of death, and a total of 252,806 death certificates listing diabetes as an underlying or contributing cause of death.
Type 2 DM

• Banting lecture in 2009
• From the Triumvirate to the Octet
• Dr. Ralph Defronzo describes the core defects and the natural history of type 2 DM.
Ominous Octet

- Muscle
- Brain
- Liver
- Pancreas
  - Increased Glucagon
  - Decreased Insulin
- GI tract
- Kidney
- Adipose tissue
History of Diabetes

- 4-7 years before dx -> impaired glucose tolerance/insulin resistance/increased insulin secretion -> Fasting Bgs are normal to slightly elevated

- At diagnosis -> Beta cell failure, increased hepatic glucose production, insulin resistance, post prandial and fasting blood sugars are elevated.

- Early intervention is key!
Therapy

• Aimed at treating the 8 core defects
• HbA1c reduction
• Tolerability
• Safety profile
  • CVOT
• Affordable
Early Intervention is Key

• Diabetes Prevention Program – high risk patients randomized into 3 interventions
  • Lifestyle – weight loss, lower calorie, low fat diet, intensive counseling, exercise 150 minutes/week.
    • Reduced chance of developing DM by 58%, in patients age > 60, 71% reduction
  • Metformin – 850 mg BID
    • Reduced chance of developing DM by 31%
  • Placebo – routine counseling
    • 11%/year developed DM
AACE/ADA treatment guidelines

Glycemic Control Algorithm

**INDIVIDUALIZE GOALS**

**LIFESTYLE THERAPY** (Including Medically Assisted Weight Loss)

**MONOTHERAPY**

**DUAL THERAPY**

**TRIPLE THERAPY**

**SYMPTOMS**

NO

YES

**LEGEND**

- Add or intensify insulin
- Refer to Insulin Algorithm

**PROGRESSION OF DISEASE**

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* Order of medications represents a suggested hierarchy of usage length of text reflects strength of recommendation.
Treatment

Hyperglycemia in Type 2 Diabetes

- Neurotransmitter dysfunction
  - GLP-1 receptor agonists
  - Amylin
  - Bromocriptine

- Increased lipolysis and reduced glucose uptake
  - Thiazolidinediones

- Impaired insulin secretion
  - Sulfonylurea
  - Meglitinide
  - GLP-1 receptor agonists
  - DPP-4 inhibitors
  - Amylin

- Increased glucagon secretion
  - GLP-1 receptor agonists
  - DPP-4 inhibitors
  - Amylin

- Increased hepatic glucose production
  - Metformin
  - Insulin
  - Thiazolidinediones

- Decreased incretin effect
  - Metformin
  - α-Glucosidase inhibitors
  - Colesevelam

- Decreased glucose uptake
  - Metformin
  - Insulin
  - Thiazolidinediones

SGLT2-i
Metformin

- Biguanide
- Lowers hepatic glucose output
- GI side effects
- Caution with renal impairment
- Other benefits
- First Line therapy
Incretin based therapy

GLP-1 agonists
- Injectable, 1-2 times daily, or weekly therapy
- Studies on oral therapy
- Pharmacologic doses of incretin mimetics
- Some CV data for liraglutide, (?) semaglutide
- Weight loss
- Safe for reduced renal function
- Concern for pancreatitis
- SE: nausea/myalgias

DPP4-inhibitors
- Oral therapy
- No CV benefits, but safe
- Raises native incretin levels from the GI tract by inhibiting breakdown
- Weight neutral
- Adjustments for renal function
- Myalgias
- Lower HbA1c reduction than GLP-1

Mechanism: increases insulin secretion by the beta cells and reduce glucagon secretion by the alpha cells in the pancreas
SGLT-2 inhibition

• Blocks the reabsorption of glucose in the kidney.
  • Threshold for glucose excretion 180 mg/dl, increased in DM to 220
  • Lowers to about 80-100 mg/dl
• SE
  • Mycotic infection
  • Caution with renal impairment, egfr > 45 or > 60
  • Warnings about amputation
• Benefits
  • HbA1c reduction
  • BP reduction
  • Weight loss
  • CV data
Thiazolidinedione

- PPAR-gamma receptor
- Improves insulin sensitivity
- Caution in cardiac patients
- Caution in liver dysfunction
Other Meds

• Colesevelam – mechanism unknown/GI tract?

• Dopamine Receptor Agonist – Short acting bromocriptine -> improves insulin sensitivity, works in the brain.

• Alpha – glucosidase inhibitor –slows carbohydrate breakdown in the GI tract
Sulfonylurea

- Long acting and short acting
- Increase insulin production by the beta cell (glucose independent mechanism)
- Last on treatment algorithm
- Not for use in the elderly!
- Hypoglycemia and weight gain.
- CV data suggests increased morbidity and mortality with use.
Combination therapy

- SGLT-Metformin
- DPP-4 – Metformin
- SGLT-2/DPP4 combination
- Metformin/TZD
- Metformin/SU
- TZD/DPP-4
- Insulin/GLP-1
Insulin

• Initiation with basal insulin

• Intensifying with bolus insulin: subcutaneous or inhaled
  • Set dose at meals vs carb counting calculating doses

• Needs high frequency of BG monitoring
History of Medications: My training and practice

- Fellowship 2004-2008
- Meta-analysis regarding cardiovascular safety by Dr. Nissen (cardiology)
- D/C of TZD use and introduction of DPP-4 inhibition/incretin based therapy
- Dr. Rasouli at the VA noted no CV data for new meds to compare vs TZD!
- FDA to institute CVOT to be sure meds were safe.
Meta Analysis

- Steve Nissen. MD cardiologist
- NEJM June 2007
- 42/116 clinical trials using rosiglitazone met criteria for analysis
- All occurrences of myocardial infarction and death from cardiovascular causes were tabulated
- Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.
CVOT

• ACCORD Trial

• Insulin – non-inferior

• SGLT-2 – Empa Reg, empagliflozin

• Devote – Liraglutide
ACCORD

• Action to Control Cardiovascular Risk in Diabetes

• Normal HbA1c < 6% vs 7-7.9% HbA1c to see if there was a reduction in the rate of CV events in established cv disease or equivalents

• Primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes

• Higher mortality in the intensive-therapy group led to a discontinuation of intensive therapy after a mean of 3.5 years of follow-up.
ACCORD data

• At 1 year, stable median glycated hemoglobin levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively.

• The primary outcome occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard-therapy group (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16)

• 257 patients in the intensive-therapy group died, as compared with 203 patients in the standard-therapy group (hazard ratio, 1.22; 95% CI, 1.01 to 1.46; P=0.04)
**ACCORD Results**

![Graph showing primary outcome](image)

**Table 4. Primary and Secondary Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (N=5128)</th>
<th>Standard Therapy (N=5123)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients (%)</td>
<td>352 (6.9)</td>
<td>371 (7.2)</td>
<td>0.90 (0.78–1.04)</td>
<td>0.16</td>
</tr>
<tr>
<td>% per yr</td>
<td>2.11</td>
<td>2.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cause</td>
<td>257 (5.0)</td>
<td>203 (4.0)</td>
<td>1.14 (1.01–1.36)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cardiovascular causes</td>
<td>135 (2.6)</td>
<td>94 (1.8)</td>
<td>0.66 (0.56–0.80)</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>186 (3.6)</td>
<td>235 (4.6)</td>
<td>1.43 (1.06–1.91)</td>
<td>0.004</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>67 (1.3)</td>
<td>61 (1.2)</td>
<td>0.37 (0.23–0.57)</td>
<td>0.06</td>
</tr>
<tr>
<td>Fatal or nonfatal congestive heart failure</td>
<td>152 (3.0)</td>
<td>124 (2.4)</td>
<td>0.75 (0.53–1.08)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Causes of death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>257 (5.0)</td>
<td>203 (4.0)</td>
<td>1.14 (1.01–1.36)</td>
<td>0.04</td>
</tr>
<tr>
<td>Unexpected or presumed cardio-vascular disease</td>
<td>86 (1.7)</td>
<td>67 (1.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>19 (0.4)</td>
<td>13 (0.3)</td>
<td>0.72 (0.46–1.14)</td>
<td>0.24</td>
</tr>
<tr>
<td>Fatal congestive heart failure</td>
<td>23 (0.4)</td>
<td>16 (0.3)</td>
<td>0.12 (0.06–0.25)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fatal procedure†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For cardiovascular disease</td>
<td>10 (0.2)</td>
<td>3 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For noncardiovascular disease</td>
<td>1 (&lt;0.1)</td>
<td>3 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal arrhythmia†</td>
<td>4 (0.1)</td>
<td>10 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal stroke†</td>
<td>9 (0.2)</td>
<td>11 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other cardiovascular disease</td>
<td>8 (0.2)</td>
<td>10 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>65 (1.3)</td>
<td>63 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition other than cancer</td>
<td>50 (1.0)</td>
<td>35 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>7 (0.1)</td>
<td>11 (0.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The primary outcome was the first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes. Data within categories are not mutually exclusive, and patients who were classified as having more than one possible cause of death are listed in the relevant categories. Hazard ratios are for the intensive-therapy group as compared with the standard-therapy group.

† This condition was a component of the outcome of fatal cardiovascular disease.

‡ Additional details are provided in the Supplementary Appendix.
HbA1c lowering vs the treatment?

CV studies were to first prove medications were safe!
Is it the insulin?

ORIGIN: Outcome reduction with initial glargine intervention
NEJM 2012

- Secondary prevention
- Early DM
- Lantus vs standard of care

DEVOTE TRIAL (insulin degludec had similar CV safety profile with less hypoglycemia.)
Empa-REG

• Secondary prevention

• Empagliflozin 10 mg and 25 mg doses

• When added to standard of care therapy, (statin, BB, ACE/ARB, ASA) significant reduction in cv morbidity and mortality
Cardiovascular Outcomes and Death from Any Cause.
Number needed to treat

• 4s study 31 patients over 5.4 years to save 1 life (simvastatin)

• HOPE (ramapril) 49 patients over 5 years

• Empagliflozin 46 patients over 3.1 years
CVD-Real

• Multicenter trial with ALL SGLT-2s

• Data were collected via medical claims, primary care/hospital records and national registries from the US, Norway, Denmark, Sweden, Germany and the UK.

• Primary prevention

• In this large multinational study, treatment with SGLT-2i versus oGLDs was associated with a lower risk of HHF and death, suggesting that the benefits seen with empagliflozin in a randomized trial may be a class effect applicable to a broad population of T2D patients in real-world practice

• DeDECLARE data will be completed later this year
CVD-REAL

• Treatment with SGLT-2i versus oGLD was associated with a 39% relative risk reduction in HHF, a 51% reduction in all-cause death, and a 46% reduction in the HHF or death composite.

• Approximately 87% of patients did not have known cardiovascular disease, suggesting possible cardiovascular benefits for a broad population of T2D patients.

• The lower rates of HHF and death associated with SGLT-2i treatment appear likely class related as there was no significant heterogeneity across countries, despite geographic variations in the use of specific SGLT-2i (~76% canagliflozin in US and ~92% dapagliflozin in Europe.)
OTHER SGLT-2 inhibitor Trials

1. DECLARE TRIALS
   - Dapagliflozin
   - Primary outcome and secondary CV outcome arms.

2. Canvas TRIAL
   - Canagliflozin
   - WARNINGS ABOUT AMPUTATIONS
LEADER trial

• NEJM 2016

• Liraglutide daily GLP-1 therapy

• The major inclusion criteria
  • age of 50 years or more with at least one cardiovascular coexisting condition (coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage 3 or greater, or chronic heart failure of New York Heart Association class II or III)

  • age of 60 years or more with at least one cardiovascular risk factor, as determined by the investigator (microalbuminuria or proteinuria, hypertension and left ventricular hypertrophy, left ventricular systolic or diastolic dysfunction, or an ankle–brachial index [the ratio of the systolic blood pressure at the ankle to the systolic blood pressure in the arm] of less than 0.9)
Leader trial data
Further Trials?

• Consider the ethics of withholding medications in randomized placebo controlled trials.

• Non-inferiority studies with semaglutide show a CV risk reduction.
Technology In Type 2 DM
There’s an app for that!

• Insulin delivery devices

• Continuous Glucose monitoring

• Web based patient portals

• Smart phone apps
Insulin Pump Therapy

• Medtronic, Tandem and Omni Pod

• Program basal rates and calculations for meal boluses and corrections.
  • Requires carb counting and BG monitoring for success!
  • More diabetes education

• Mixed data on benefits vs cost.
  • Secondary Endpoints of reduced hypoglycemia, patient satisfaction and reduced insulin use are supported.
Insulin delivery Device

- Vgo – filled patch pump device with rapid acting insulin
  - “Basal” rate at 20, 30 or 40 units daily
  - Bolus doses in increments of 2 units for a total of additional 36 units/day (18 clicks)
Continuous Glucose Monitoring

• Dexcom
  • Sensor – wire under the skin that is changed every 7-10 days
  • Transmitter – “chip” that stores data
  • Receiver – device to view blood sugars
  • Real time CGM Data with alerts to receiver (smart phone, free-standing device or insulin pump)

• Freestyle Libre
  • Sensor – changed every 10-14 days
  • Reader – scans sensor to give blood sugar and trend.

Eversense is a new implantable sensor – 3 month use
Web Based Applications

• Glooko, Tidepool, Night Scout

• Allows patient to enter data in to a secure portal to send to physician for review.

• Can also enter meals, insulin doses, activity for interpretation
Phone Based Apps

• My Plate
• MyFitnessPal
• Fooducate
• Nutrition Info
• Wholesome

• Can use to track carbs, measure portion sizes, look up food nutrition information.
AACE/ADA HbA1c Guidelines

Glycemic Control Algorithm

**INDIVIDUALIZE GOALS**

**A1C ≤ 6.5%** For patients without concurrent serious illness and at low hypoglycemic risk

**A1C > 6.5%** For patients with concurrent serious illness and at risk for hypoglycemia

**LIFESTYLE THERAPY** (Including Medically Assisted Weight Loss)

**Entry A1C < 7.5%**
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Agi
- SU/GLN

**Entry A1C ≥ 7.5%**
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Agi
- SU/GLN

**Entry A1C > 9.0%**
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Agi
- SU/GLN

**MONOTHERAPY**

**DUAL THERAPY**

**TRIPLE THERAPY**

**Symptoms**

**No**
- DUAL Therapy
- OR
- TRIPLE Therapy

**Yes**
- INSULIN + Other Agents

**Progression of Disease**

**Legend**

- Few adverse events and/or possible benefits
- Use with caution

*Order of medications represents a suggested hierarchy of usage based on effectiveness and adverse effects.*
• **Guidance Statement 1:** Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.

• **Guidance Statement 2:** Clinicians should aim to achieve an HbA\(_1c\) level between 7% and 8% in most patients with type 2 diabetes.***

• **Guidance Statement 3:** Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA\(_1c\) levels less than 6.5%.***

• **Guidance Statement 4:** Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA\(_1c\) level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe chronic obstructive pulmonary disease or congestive heart failure) because the harms outweigh the benefits in this population.

* Evidence based on ACCORD, VDAT, ADVANCE and UKPDS – DPP-4 inhibitors, GLP-1 and SGLT-2i medications not available at the time of analysis.
Conclusion

• Ominous octet

• Early screening and early intervention is key

• Choosing medications to get patients to goal may include addressing comorbidities.

• Continuing to address comorbidities and reducing complications results in longer life expectancy

• Intensifying meds beyond oral therapy-> injectable therapy -> use of technology to safely improve control for best patient success

• Personalizing the care for the patient!