Management of Diabetes Mellitus: Should We Change Our Algorithm?

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Disclosure
No relevant financial relationships

Presentation Outline
- Updates in prevention of complications (other than glycemic control)
- Controversies in glycemic control
- Updates/controversies with diabetes medications

Screening for Diabetes 2016
- BMI ≥25 (or ≥23 in Asian Americans) plus other risk factors
  - Inactivity
  - Low HDL or high TG
  - First degree relative
  - PCOS
  - High-risk ethnicity
  - Acanthosis nigricans
  - Gestational DM
  - Hx CVD
  - HTN
- Age 45
- Repeat Q3 years

ADA Diabetes Care, 2016
Management of Diabetes

**USPSTF Screening for Diabetes 2015**
- Screen as part of cardiovascular risk assessment in adults 40 - 70 who are overweight or obese

**Diagnosis of Diabetes 2016**
- A1C ≥ 6.5%
- FPG ≥ 126 mg/dl (7.0 mmol/L)
- 2-h plasma glucose ≥ 200 during OGTT
- Symptoms and random plasma glucose ≥ 200 mg/dl (11.1 mmol/L)
- Need two separate measurements

**Diagnosis of Pre-Diabetes 2016**
- A1C 5.7 – 6.4%
- FPG 100 - 125 mg/dl (5.6mmol/L - 6.9 mmol/L)
- 2-h plasma glucose 140 mg/dl – 199 mg/dl during OGTT (7.8mmol/L – 11.0 mmol/L)

**2016 Practice Guidelines: ASA**
- Use in all patients with DM and CVD
- ASA: For primary prevention - only use in those at increased CV risk (10 year risk >10%).
  - Typically men over 50, women over 60 with other risk factors.
2016 Practice Guidelines: HTN and Tobacco

- BP: Goal < 140 and <90
  - But not <130 (no evidence) and not <70 (higher mortality)
  - Still prefer ACEI or ARB

- Don’t forget tobacco.
  - Recommend against e-cigarettes

2016 Practice Guidelines: Lipids

- Mostly consistent with ACC/AHA
  - CVD: High intensity statin
  - 40-75: moderate or high intensity statin

- Differences with ACC/AHA
  - <40 with other risks: consider statin
  - >75: consider statin

2016 Practice Guidelines: Bariatric Surgery

- Bariatric Surgery may be considered for adults with BMI > 35 and type 2 DM, especially if diabetes and comorbidities are difficult to control with lifestyle and meds

- Although small trials have shown glycemic benefit with BMI 30-35 and DM, there is currently insufficient evidence to recommend surgery

Case 1

74 year old woman with type 2 diabetes, hypertension, coronary heart disease (s/p MI in 2010), GERD, and osteoarthritis.

Meds: Metformin, glipizide, aspirin, lisinopril, metoprolol, atorvastatin, omeprazole, tylenol, topical diclofenac

Exam: BP 132/80, BMI 29 kg/m²
  Normal exam
Management of Diabetes

Case 1

Her glycemic goal should be:

A. HbA1c <6.5%
B. HbA1c <7.0%
C. HbA1c <7.5%
D. HbA1c <8.0%
E. HbA1c <9.0%

Glycemic Control Update

- 3 important newer trials
  - ADVANCE
  - ACCORD
  - VA Diabetes Trial

ACCORD Trial

- NIH RCT in DM 2, 10,251 patients, known CVD or risk factors, mean A1c 8.1%
  - Intensive vs. standard BP (120 v. 140)
  - Lipid control (statins v. statins + fibrates)
  - Normalization v. standard BS control (A1c 6 v. 7-7.9)
  - Outcomes: CV events. Also microvascular events, quality of life, others

ACCORD trial

<table>
<thead>
<tr>
<th></th>
<th>Intensive n=5,128</th>
<th>Standard n=5,123</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c achieved:</td>
<td>6.5%</td>
<td>7.5%</td>
<td>-</td>
</tr>
<tr>
<td>1* outcome:</td>
<td>352</td>
<td>371</td>
<td>0.90 (0.78-1.04)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>5.0%</td>
<td>3.1%</td>
<td>1.22 (1.01-1.46)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>2.6%</td>
<td>1.8%</td>
<td>1.35 (1.04-1.76)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>10.5%</td>
<td>3.5%</td>
<td>-</td>
</tr>
<tr>
<td>Wt. gain&gt;10 kg</td>
<td>27.8%</td>
<td>14.1%</td>
<td>-</td>
</tr>
</tbody>
</table>
Management of Diabetes

**ACCORD Trial**

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>Intensive</td>
<td>↓</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td>Deaths</td>
<td>203</td>
<td>257</td>
<td></td>
</tr>
<tr>
<td>11/1000/y</td>
<td>14/1000/y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number Needed to Harm: 333

February 2008 (after 3.5 years): NIH stops this arm of study

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**Glycemic Control Summary**

- No consistent evidence that tight glycemic control reduces risk of CVD in DM 2
- Possible subgroups with benefit:
  - shorter diabetes duration, no CVD
- Strong evidence of decrease in microvascular disease outcomes with more intensive glucose control
- More hypoglycemia and weight gain with more intensive regimens

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**Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials**

- **UKPDS**: ↓, ←, ↓, ←
- **DCCT / EDIC**: ↓, ←, ↓, ←
- **ACCORD**: ↓, ←, ↑
- **ADVANCE**: ↓, ←, ←
- **VADT**: ↓, ←, ←

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**2016 ADA Practice Guidelines: Glucose Control**

- Goal A1C ≤7 for most
- Goal A1C <6.5 for some: short duration, long life expectancy, and no CVD
- Goal less stringent (<8) for history of hypoglycemia, limited life expectancy, advanced micro or macrovascular complications, extensive comorbid conditions, and longstanding DM. The general goal (<7) is difficult to attain is such patients
Glycemic Control in Older Adults

- For majority of adults older than 65, the harms of HgA1c <7.5 or >9 are likely to outweigh the benefits.

- Optimal targets depend on patient factors, meds, life expectancy, and patient preferences.

- For example: if only need metformin, lower target may be preferred; if need insulin or finger sticks a higher target may be preferred.


2016 AACE Practice Guidelines: Glucose Control

- A1C ≤6.5 is optimal if it can be achieved in a safe and affordable manner.

- Higher targets (>6.5) may be appropriate for certain individuals (patients with concurrent serious illness and risk of hypoglycemia) and may change over time

Case 1

Her glycemic goal should be:

1. HbA1c <6.5%
2. HbA1c <7.0%
3. HbA1c <7.5%
4. HbA1c <8.0%
5. HbA1c <9.0%
Case 2: 48 yo woman with DM, BMI 33, on diet and exercise and max dose metformin. HbA1C is now 8.5. Your next best step is:

A. Continue current therapy
B. Begin a sulfonylurea
C. Begin pioglitizone
D. Begin NPH insulin or long-acting insulin analogue
E. Begin exenatide (Byetta™), liraglutide (Victoza™), sitagliptin (Januvia™), saxagliptin (Onglyza™)
F. Begin canagliflozin (Invokana™), dapaglifozin (Farxiga™), empaglifozin (Jardiance™)

Metformin

- Lowers A1C 1.5-2%
- Weight loss (0-2 kg)
- Lowers triglyceride and LDL; increases HDL
- No hypoglycemia
- No self monitoring
- Inexpensive
- Disadvantages: GI side effects, decreased B12 absorption, (very low) risk of lactic acidosis

Thiazolidinediones (TZD)

- Lowers A1C 0.4-1.5%
- No hypoglycemia when used alone
- Other risks: osteoporosis, bladder cancer with pioglitazone, weight gain edema
- FDA lifted restrictions on rosiglitazone in November 2013
- No hypoglycemia
- No self monitoring
- Preference for pioglitazone
Oral Agent “Failure”
Why does this occur?

- Changing HbA1c goals
- Compliance, side effects
- Wrong diagnosis (LADA—latent autoimmune diabetes in adults 10%)
- Stress, diabetogenic medications
- Postprandial hyperglycemia
- Natural progression of the disease

Natural History of Type 2 Diabetes

Insulin

Introduction of insulin
- Bedtime
- Intermediate/Long-acting insulins
  - NPH, glargine, levemir
  - 10 units
- Self-monitoring of blood glucose (hypoglycemia education)
**When to go to > 1 shot per day**

- HgA1c >7
- Glucose in AM at goal but glucose before dinner >140

**Options**

- Add premeal lispro/aspart
- Add bid premixed insulin – 70/30, 75/25

**Questions**

- Continue metformin
- ? Sulfonylurea, ? Thiazolidinedione (mostly not)

**Function of Insulin in Regimens**

- Basal insulin
- Meal coverage (carbohydrates)
- Correction of high blood sugar

**INCRETINS**

Gut factors that promote insulin secretion in response to nutrients

Major incretins: GLP-1, CCK, GIP

**Oral Glucose Promotes More Insulin Release than IV Glucose - Indicating a Role for Incretins**
Management of Diabetes

Incretin Drugs

GLP Agonists
- Exenatide (2005/2012)
- Liraglutide (2010)
- Dulaglutide (2014)
- Albiglutide (2014)
- Taspoglutide
- Lixisenatide
- Semaglutide

DPP IV Inhibitors
- Sitagliptin (2006)
- Saxagliptin (2009)
- Alogliptin (2013)
- Linagliptin (2011)
- Vildagliptin
- Dutagliptin
- Metaglipitin
- Gemiglipitin

A1C (%) Effect (change from baseline)

<table>
<thead>
<tr>
<th></th>
<th>Placebo BID</th>
<th>5 mcg exenatide BID</th>
<th>10 mcg exenatide BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>0.1</td>
<td>-0.4</td>
<td>-0.8</td>
</tr>
<tr>
<td>SFU</td>
<td>0.1</td>
<td>-0.5</td>
<td>-0.9</td>
</tr>
<tr>
<td>MET+SFU</td>
<td>0.2</td>
<td>-0.6</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

Changes in A1C from baseline vs placebo statistically significant

Weight (change from baseline) & Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Placebo BID</th>
<th>5 mcg exenatide BID</th>
<th>10 mcg exenatide BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>-1.4</td>
<td>-3.1</td>
<td>-4.2</td>
</tr>
<tr>
<td>SFU</td>
<td>3.3</td>
<td>14.4</td>
<td>35.7</td>
</tr>
<tr>
<td>MET + SFU</td>
<td>1.26</td>
<td>19.2</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Hypoglycemia (%)
- MET
- SFU
- MET + SFU

Open-label extension study to 90 weeks: persistence in weight loss and ↓A1C
Side Effects

GI
- Nausea (44% vs 18% with placebo); incidence lessens over time; 3% dropout rate due to nausea
- Vomiting (13% vs 4%)
- Diarrhea (13% vs 6%)

Headache (9% vs 6%)
Hypoglycemia (see previous slide)

Improvements in HbA1c With Initial Co-administration of Sitagliptin and Metformin

<table>
<thead>
<tr>
<th></th>
<th>Mean Baseline HbA1c = 8.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1091</td>
</tr>
<tr>
<td>Placebo</td>
<td>+0.8</td>
</tr>
<tr>
<td>Sita 100 mg QD</td>
<td>+1.0</td>
</tr>
<tr>
<td>Met 500 mg BID</td>
<td>+1.3</td>
</tr>
<tr>
<td>Sita 50 mg BID + Met 500 mg BID</td>
<td>+1.6</td>
</tr>
<tr>
<td>Sita 50 mg BID + Met 1000 mg BID</td>
<td>+2.1</td>
</tr>
</tbody>
</table>

* Placebo-subtracted LS mean change from baseline at Week 24.
Sita=sitagliptin; Met=metformin.
Aschner P, et al. Oral presentation at the EASD 42nd Annual Meeting; 14-17 September 2006; Copenhagen.

Two Newer Studies of DPP-4 Meds

- **Saxagliptin not inferior (nor superior) to placebo for CV outcomes.**
  - But statistically significant increase in CHF admissions
  - A1C 0.2% lower

- **Sitagliptin not inferior (nor superior) to placebo for CV outcomes.**
  - No increase in CHF
  - A1C 0.3% lower

Scirica, NEJM 2013; Green, NEJM 2015

Sitagliptin – Adverse Reactions

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sitagliptin</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>n = 443</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>23 (5.2)</td>
</tr>
<tr>
<td>+ pioglitazone</td>
<td>n = 175</td>
</tr>
<tr>
<td>Upper resp. infection</td>
<td>11 (6.3)</td>
</tr>
</tbody>
</table>

Small increase in neutrophil count
No nausea or vomiting
No weight loss
Management of Diabetes

SGLT2 Inhibitors
Sodium-glucose cotransporter 2 Inhibitors

- Inhibit glucose reabsorption in renal proximal tubule (Canagliflozin, Dapagliflozin, Empagliflozin)
- Potential advantages
  - Weight loss (2.5-4kg), low risk of hypoglycemia, reduced BP, lowers A1C about 1%
- Potential disadvantages
  - Polyuria, electrolyte disorders, UTI, fungal genital infections, syncope, increased Cr, expensive

Empagliflozin, CV Outcomes, and Mortality

- RCT 7020 patients, high risk CV disease, 3.1 years
- Minimal changes in A1C (0.24% lower)
- Reduced combined CV outcome (10.5% vs. 12.1%) and reduced CV (3.7% vs. 5.9%) and all cause mortality (5.7% vs. 8.3%)
  - No difference in stroke or MI
  - No difference when secondary outcomes (unstable angina) included
  - Increased genital infections

LEADER Trial (Liraglutide)


Natural History of Type 2 Diabetes

Insulin Resistance

Incretins/Others?

Thiazolidinedione? - Biguanide

Lifestyle

SU

Insulin

Post-meal Glucose

Fasting Glucose

Insulin Level

Relative Function (%)

Beta-cell failure

Years of Diabetes

0 5 10 15 20 25 30

-10 -5 0 5 10 15 20 25 30

0 50 100 150 200 250 300 350

0 50 100 150 200 250 300 350
Pharmacological Therapy for Type 2 Diabetes

- Metformin is the preferred agent

- In patients with new DM2, marked symptoms, or marked BS or A1C, consider initiating insulin (with or without other agents).

- If monotherapy not to goal, add second oral agent, GLP-1 agonist, or basal insulin

A patient-centered approach should guide selection: efficacy, cost, side effects, weight, comorbidities, hypoglycemia, and patient preference.

- Insulin therapy is eventually indicated for many patients with DM2

<table>
<thead>
<tr>
<th>A1C</th>
<th>Cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1-2%</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>1-2%</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>0.5-1.5%</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>0.5-0.8%</td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.5-1.5%</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>0.5-1.5%</td>
</tr>
<tr>
<td>Acarbose</td>
<td>0.5-0.8%</td>
</tr>
<tr>
<td>Test strips</td>
<td>0.4% (?)</td>
</tr>
<tr>
<td>Glargine 45 U</td>
<td></td>
</tr>
<tr>
<td>YMCA</td>
<td></td>
</tr>
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ADA Diabetes Care, 2016
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Conclusions

- Tight glycemic control not effective in lowering total mortality or CV mortality (but is effective at preventing microvascular complications)
- Many newer diabetes agents available, all with some side effects and higher costs...few with hard outcome data. (But hard outcome data coming...)

Conclusions

- Glucose control may be more important early in diabetes
- Good BP, lipid control, smoking cessation, and aspirin use is important throughout the course of diabetes

Conclusions

The best way to treat DM in the long term...

...is to not develop it in the first place.