Type 2 Diabetes Update Overview for the Boards

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Disclosures:
- None

Learning Objectives
- Diabetes Prevention
  - Lifestyle, metformin, newer agents?
- Expanded diagnostic criteria for diabetes
  - Using HbA1c?
- What is the role for newer therapies?
  - Any role for TZDs?
  - GLP1 agonists and DPP-4 inhibitors
- What targets for Cardiovascular Risk Reduction?
  - Weight
  - BP
  - Lipids
  - Aspirin

Number of New Diabetes Cases in the US
1.7M new cases per year

Estimates of people aged 20 years or older with diagnosed and undiagnosed diabetes, by age group, United States, 2005-2008

Source: 2005-2008 National Health and Nutrition Examination Survey
Hyperglycemia?

- Maria is a 64-year old woman with a family history of type 2 diabetes. She is treated for hypertension with a beta-blocker and HCTZ. She has grade 2 obesity.
- A routine fasting glucose is 108 mg/dl ...

Diabetes Prevention

- There is a high rate of progression from pre-diabetes states to diabetes (40% over 6 yrs)
- Lifestyle modification is most effective (reduction in DM by 58%) and should comprise
  - 30 mins of exercise 5 times weekly
  - 7% weight loss
- Metformin has best efficacy in more overweight and younger patients
- Acarbose poorly tolerated but some efficacy
- Liraglutide looks promising
- No apparent role for nateglinide or valsartan for this purpose

Matching A1c and Glucose

| Tom’s A1c (6.6%) and fasting glucose (108 mg/dl) are discordant |
|---|---|---|
| A1c (%) | mg/dl | mmol/L |
| 6 | 126 | 7.0 |
| 7 | 154 | 8.6 |
| 8 | 183 | 10.2 |
| 9 | 212 | 11.8 |
| 10 | 240 | 13.4 |
| 11 | 269 | 14.9 |
| 12 | 298 | 16.5 |

Diagnosis of Diabetes

- Diabetes should be diagnosed when A1C is >=6.5%.
  - Diagnosis should be confirmed with a repeat A1C test except in symptomatic subjects with plasma glucose levels >200 mg/dl.
- Prevention efforts should target patients with A1c of between 5.7 and 6.5%
  - The risk for diabetes based on levels of glycemia is a continuum; therefore, there is no lower glycemic threshold at which risk clearly begins.
  - The categorical clinical states pre-diabetes, IFG, and IGT fail to capture the continuum of risk and will be phased out of use.
Maria is a 64-year old woman with a family history of type 2 diabetes. She is treated for hypertension with a beta-blocker and HCTZ. She has grade 2 obesity.

A routine fasting glucose is 108 mg/dl … what should you do next?

A Hemoglobin A1c is 6.6%

How should she be evaluated now?

What are her treatment targets?

**Evaluation after new diagnosis of diabetes**

- Evaluation for cause
  - Endocrinopathy
    - Thyroid, Cushing’s, acromegaly
  - Pancreatic disease
    - Chronic pancreatitis, pancreatic cancer
  - Hemochromatosis
- Evaluation for complications
  - HTN, hyperlipidemia
  - Renal (malb, cr)
  - Eye (retinal screen)
  - Neuropathy (exam)
- Evaluation of readiness to initiate lifestyle modification

**ADVANCE, ACCORD, VADT**

What have we learned?

- Glycemic goals must be individualized
- No evidence that a specific glucose-lowering regimen is better or worse
- CV benefit of lower glucose levels, if any, accrues over years
- Pts earlier in their disease appear derive benefit from tighter control
- Significant hypoglycemia may be associated with CV risk

**Current US Treatment of T2DM**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Meds</td>
<td>16%</td>
</tr>
<tr>
<td>Insulin Only</td>
<td>14%</td>
</tr>
<tr>
<td>Oral Meds Only</td>
<td>14%</td>
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<tr>
<td>Insulin + Oral</td>
<td>16%</td>
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**Comparative Efficacy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>A1c Reduction</th>
</tr>
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<tbody>
<tr>
<td>Sulfonylurea</td>
<td>1-2%</td>
</tr>
<tr>
<td>Metformin</td>
<td>1-2%</td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.5-1.5%</td>
</tr>
<tr>
<td>TZD</td>
<td>0.5-1%</td>
</tr>
<tr>
<td>DPP4 inhibitor (saxagliptin, sitagliptin)</td>
<td>0.5-1%</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitor</td>
<td>0.5-1%</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

**ADOPT study - monotherapy**

![Graph showing A1c reduction over years for different treatments](https://example.com/ADOPT.png)

**Source:** NEJM 2006; 355: 2427
TZDs in 2011

- Problems
  - Low efficacy
  - Weight gain
  - Heart failure (more diuretics)
  - Lipid changes (more statins)
  - Expense
- Concern for
  - CV risk
  - Bone loss
- Alternatives available

Sales Trends for Rosi- and Pioglitazone


DPP4 Inhibitors

- Possible benefits
  - Orally administered
  - Low risk of hypoglycemia
  - Low toxicity
  - No weight gain
  - May improve B-cell function
  - Can be combined with other oral agents
- Possible drawbacks
  - Similar or lower efficacy to metformin or a TZD
  - High cost
  - Unknown long term safety or efficacy
  - Awaiting FDA approval for ala- & vildagliptin

Metformin + Sitagliptin Combo


LEAD-6: Liraglutide vs. Exenatide

Lancet 2011; 24:375(B724):1447-56

Liraglutide vs. Sitagliptin

Lancet 2011; 24:375(B724):1447-56
Exenatide bid/Liraglutide qd

- Possible benefits
  - Combination therapy with sulfonylurea and/or metformin
  - Mild weight loss
  - Low risk of hypoglycemia

- Possible drawbacks
  - Mild-moderate efficacy on A1c
  - Injectable
  - Much less potent than insulin
  - High Cost
  - High rate of nausea
  - Possible pancreatitis?

Approximate comparative wholesale costs (1mo supply)

- Glipizide $14
- Metformin $36
- Nateglinide $154
- Sitagliptin $216
- Pioglitazone $279
- Liraglutide $306

Empowering our Patients: Treat to Target

- 756 overweight men and women with inadequate glycemic control (HbA1c >7.5%) on one or two oral agents
- continued prestudy oral agents and randomized between
  - Bedtime Glargine NPH once daily
  - Start with 10u nightly, adjust weekly seeking a target fasting plasma glucose (FPG) <or=100 mg/dl (5.5 mmol/l).
  - 24-weeks

Weight effects of diabetes therapies

Avoiding weight gain with diabetes meds

- Consider adding orlistat
- Avoid insulin + TZD combination
- When using SU, combine it with metformin
- When starting insulin
  - Continue metformin
  - Reinforce dietary restriction
  - Consider detemir (levemir) rather than glargine (lantus)

Targets for CV Risk Reduction

- Susie is an obese 48-year-old woman who has had type 2 diabetes and hypertension for 4 years.
- She works as a mortgage broker and keeps regular work and meal time hours. She is not physically active. She does not smoke.
- For diabetes she takes metformin 1000 mg twice daily, glipizide 10 mg twice daily and 25 units of insulin glargine at bedtime. She takes simvastatin 40 mg, lisinopril 40 mg.
- BMI is 34. BP is 128/76 mmHg; LDL is 84 mg/dl, TG is 180 and HDL is 30 mg/dl. Her A1C is 7.7%.
- Her fasting AM sugars have been consistently in the 100-150 range.
- What are your treatment priorities?
Look AHEAD Trial

- N= 5145 Type 2 DM with BMI >25
- Randomized to intensive lifestyle intervention vs. support/education
  - 39 vs. 3 meetings/52 weeks
  - Goals: 10% wt loss, 175 mins exercise pw

**Results**

<table>
<thead>
<tr>
<th></th>
<th>+Lifestyle</th>
<th>Support Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>-8.6%</td>
<td>-0.7%</td>
</tr>
<tr>
<td>Fitness</td>
<td>+20%</td>
<td>+6%</td>
</tr>
<tr>
<td>A1c reduction</td>
<td>-0.7%</td>
<td>-0.1%</td>
</tr>
<tr>
<td>SBP</td>
<td>-7 mmHg</td>
<td>-3 mmHg</td>
</tr>
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</table>

Diabetes Care 2007; 30: 1374

Orlistat in pts with Diabetes

- Greater weight loss
- Superior glycemic control


Liraglutide and weight loss over 20 weeks

- Mean wt loss (kg): 4.8  5.5  6.3  7.2  4.1

Lancet 2009; 374:1606

Physical Activity and Diet

- N= 593 dx of type 2 DM within 8 mo
- Randomized to monthly nurse support with diet or diet+pedometer, or control.

**Results**

<table>
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<tr>
<th></th>
<th>Diet+Exer</th>
<th>Diet</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c change</td>
<td>-0.04%</td>
<td>-0.09%</td>
<td>+0.11%</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.9</td>
<td>-0.6</td>
<td>-0.0</td>
</tr>
<tr>
<td>DM meds</td>
<td>42%</td>
<td>43%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Andrews; Lancet 2011; 378: 129

In one large trial an aggressive program of diet and exercise actually performed better than drug therapy in reducing serum glucose. A recent large randomized trial found the following reductions in HbA1c at 6 months [Andrews RC Lancet 2011;378(9786):129]:

-0.28% reduction with intensive dietary counseling
-0.33% reduction with intensive dietary counseling+exercise therapy
-no reduction in the control group.
Relative Weight Loss in Diabetes

- Intensive Lifestyle ~4-12% / 1yr
- Orlistat 120 mg tid ~3-6% / 1yr
- Sibutramine 15 mg daily ~3-5% / 1yr
- Metformin 1g bid ~1% / 1yr

New Drugs for Weight Loss
- Phentermine/topiramate (Qnexa™)
- Naltrexone/bupropion (Contrave™)

Types of Bariatric Surgery

- Adjustable Gastric Band
- Roux-en-Y Gastric Bypass
- Sleeve Gastrectomy
- Biliary Pancreatic Diversion

Effect of Bariatric Surgery in T2DM

- Estimated 24% reduction in mortality
- Remission rates for DM ~40/26/10% for roux/sleeve/banding
- ~5% reoperation rate over 10 yrs

Diabetes and Bariatric Surgery

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- Remission rates for DM ~40/26/10% for roux/sleeve/banding
- ~5% reoperation rate over 10 yrs

ADA Clinical Practice Recommendations 2012: Obesity

- Lifestyle change should be the primary approach to weight loss (A)
- At least 150 min/wk of moderate (50-70% MHR) exercise (A)
- and resistance training 3x/wk (A)
- Individual medical nutrition therapy should be provided (B)
- Saturated fat intake should be <7% of total calories (A)
- Trans-fats should be minimized (E)
- Insufficient evidence to recommend low-carb, glycemic-load or indexed diets.
- Bariatric surgery may be considered for adults with BMI >35 and type 2 diabetes, especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacologic therapy

Hypertension and Diabetes

- Present in 40-60% of patients with diabetes at diagnosis
- Pathogenesis
  - Hyperinsulinemia
  - Volume expansion
  - Increased arterial stiffness
  - Sleep apnea
- Control hypertension to prevent
  - Macrovascular disease
  - Renal disease
  - Retinopathy

Images: Walter Pories MD

Diabetes Care 2012 33:S4-S10

NEJM 2007; 357: 741

ACCORD – BP

- 4733 patients with type 2 diabetes randomly assigned to target SBP of <120 or <140 mmHg.
- Primary outcome: CV death, non-fatal MI, non-fatal stroke
- Mean follow-up 4.7 yrs.
- Results:
  - Achieved SBP separation (119 vs. 133)
  - Primary outcome 1.9 vs. 2.1% annual rate (P=0.20)
  - Stroke rate reduced from 0.53% to 0.32% per year (P=0.01)
  - Serious adverse events higher in intensive grp (3.3 vs. 1.3%, P<0.001)

ACCORD, NEJM March 14th 2011

Hypertension and Diabetes

- Initial therapy
  - Weight reduction
  - Increased consumption of fresh fruits, vegetables, and low-fat dairy products
  - Exercise
  - Sodium restriction
  - Avoidance of smoking
- Initiate antihypertensives immediately in pts with BP >140/90 or after 3 mo if BP not at goal (<130/80 mmHg)

Summary of Major Diabetes-Hypertension Studies: ALLHAT, ACCOMPLISH, UKPDS, HOT and HOPE

- Lower BP prolongs life
- Goal <130/80 mmHg
- First Line: ARB or ACEI
- Second Line: CCB, or Thiazides
- Third Line: B-blockers
- Most patients require combination therapy

ADA Clinical Practice Recommendations 2012

Hypertension

- Measure BP at every visit (C)
- Goal <130/80 mmHg (B)
- Behavioral therapy appropriate for up to 3 mo in pts with SBP between 80-89 mmHg (E)
- Multiple drug therapy usually required (B)
- Initial drug therapy of ACEI or ARB, then add thiazide (E); Monitor renal function and potassium levels
- In pregnancy target lower BP; avoid ACEI and ARB (E)
- Lower BP gradually in the elderly (E)
Aspirin Recommendations 2012

- Ezetimibe
- Niacin
- Fibrate

Use clopidogrel instead if aspirin intolerant

Combine with clopidogrel in year after ACS (B)

Aspirin 75-162 mg indicated in diabetes patients if
- Known CVD (A)
- Men age > 50 or women age >60 + 1 CV risk factor
  (CV FHx, HTN, smoking, lipids, malb) (C)
- Combine with clopidogrel in year after ACS (B)
- Use clopidogrel instead if aspirin intolerant

Non-Statin Lipid Management

- Fibrates
  - Disappointing ACCORD- and FIELD-trial results
  - Fenofibrate+statin has lower risk of rhabdo than gemfibrozil+statin
  - Small risk of LFT and CK elevations
- Niacin
  - Most effective at increasing HDL
  - Induces hyperglycemia at high doses
  - Flushing less problematic with extended release
- Ezetimibe
  - Lowers LDL but no effect on carotid atheroma.
  - Can be combined with statins, fenofibrate or both

Lipid Control

- Test lipid panel at least annually (E)
- Lifestyle modification improves lipid profile (A)
- Statin if DM+CVD or DM + age >40 + 1 risk factor regardless of LDL
- LDL
  - Goal LDL <100 mg/dl (A)
  - Goal LDL of <70 mg/dl is option with overt CVD (B)
  - 30-40% LDL reduction regardless of LDL level (A)
- Consider
  - Increase HDL to >40 mg/dl or >50 mg/dl for men
  - Lower triglyceride to <150 mg/dl (C)
- Avoid statins in pregnancy (E)

Outcome: Early termination of trial for benefit at 3.9 yrs.
- 37% ↓ major CV event
- 45% ↓ stroke
- 27% ↓ death (NS)

ACCORD - Lipids

- 5518 patients with type 2 diabetes on simvastatin randomized between fenofibrate or placebo
- Primary outcome: CV death, non-fatal MI, non-fatal stroke
- Mean follow-up of 4.7 yrs
- Results:
  - Achieved TG and HDL separation
  - Event rate 2.2% and 2.4% FF and PBO grps (P=0.33)
  - Possible benefit when TG high (>204) and HDL low (<34) (P=0.06)

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Lower triglyceride to <150 mg/dl (C)

Increase HDL to >40 mg/dl or >50 mg/dl for men

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ACCORD, NEJM March 14th 2011

Acute coronary event, stroke, or revascularization.

ACCORD- and FIELD-trial results

Disappointing ACCORD- and FIELD-trial results

Bonilha et al. Circ. 2006; 113: 1065-72

ACCORD, NEJM March 14th 2011

Influenza
- annually to all

Pneumococcal vaccine
- All patients
  - Revaccinate once if >5 yrs since last vaccine and
  - patient is >65 yrs old OR
  - CKD/nephrotic OR
  - post-transplant/immunocompromised

Heptatitis B
- Ages 19-59
  - >60 at discretion

ADA Clinical Practice
Recommendations 2012: Immunization

ADA Clinical Practice
Recommendations 2012

ADA Clinical Practice
Recommendations 2012

ACA 2012, Diabetes Care

CARDS Study

2838 patients with diabetes at one CV risk factor; mean LDL of 161 mg/dl

Intervention: 10 mg atorvastatin vs. placebo.

Endpoint: acute coronary event, stroke, or revascularization.

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- Her fasting AM sugars have been consistently in the 100-150 range.
- What are your treatment priorities?

Clinical Inertia

- Only 66% of patients with A1c > 8% who saw their physician more than once had an intervention within 6 months.
- Only 6% of patients normalized spontaneously.
- Factors associated with Intervention
  - A1c level
  - Target organ disease
  - White ethnicity
  - Female patient
  - Younger age
- Reasons for Inertia
  - "at or near goal"
  - "transient"
  - "competing demands"
  - "unfamiliarity with patient"

Summary

- A1c is a useful diagnostic test for diabetes; threshold 6.5%.
- Though more than 80% of patients with diabetes will die from cardiovascular disease, very tight glucose control is not clearly associated with major CV risk reductions.
- Glucose control is clearly associated with protection from microvascular disease; The HbA1c target remains <7%.
- Different drugs have varying cost, hypoglycemia risk, ease of use, adverse events, and A1c reduction capacity.
- Important to be proactive with cardiovascular protection
  - BP control critical (consider spironolactone)
  - Statins important
- Empower and educate patients