Modern Trends in Diabetes Care
Diabetes Update 2013

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Disclosure

- In accordance with policies of the Accreditation Council for Continuing Medical Education (ACCME) and the Accreditation Council for Pharmacy Education (ACPE), University of Kentucky UK HealthCare CECentral (UKHCCEC), neither I nor my spouse have any relevant financial relationships during the past 12 months with commercial interests to disclose.
Need/Practice Gap & Supporting Resources

• Updates to diabetes standards of care each year
• New oral and injectable drugs for treatment of diabetes introduced to market or in development
• New studies/clinical trials influencing management of diabetes
Objectives

• Review the pathophysiology of diabetes and current treatment options.

• Summarize the 2013 revisions to the American Diabetes Association (ADA) Standards of Medical Care in Diabetes.

• Discuss the ADA/European Association for the Study of Diabetes (EASD)’s new, more individualized treatment guidelines for patients with diabetes.

• Discuss recent clinical trials that may influence diabetes management and care.

• Evaluate new products and medications to improve diabetes control.
Expected Outcome

• This CE should serve as an overview of these updates in diabetes care
Diabetes in the US

- 25.8 million in US-diabetes (8.3%)
  - 1/3 undiagnosed
- 79 million in US-prediabetes (35%)

Diabetes in the US

1994

2005

Age-Standardized Prevalence of Diabetes Diagnoses per 100 Adult Population by State (www.cdc.gov/diabetes/statistics/prev/state)
Impact of Uncontrolled Diabetes Mellitus

• 7th leading cause of death
• Leading cause of new cases of blindness in ages 20-74
• Leading cause of end-stage renal disease
• Most frequent cause of non-traumatic limb amputations
• 2-4 times more likely to have heart disease or a stroke
  • Heart disease is leading cause of diabetes-related deaths
• Total economic cost
  • 1997 $98 billion
  • 2002 $132 billion
  • 2007 $174 billion

CDC @ www.cdc.gov Accessed 2/11; National Diabetes Fact Sheet 2011
2012 Diabetes Costs

• $245 Billion
  • Not including:
    • Burden associated with undiagnosed diabetes
    • Pain and Suffering
    • Resources from care provided by nonpaid caregivers
  • $176 billion direct medical costs
  • $69 billion reduced productivity

• 41% increase from 2007 estimate

• Medical expenditures 2.3x higher in persons with diabetes
Diabetes in Kentucky
Diabetes in Kentucky

• 9th in nation for adults with diabetes (9.9%)
• 7% of adult Kentuckians have been diagnosed with pre-diabetes
• 6th leading cause of death
• Highest prevalence in Eastern KY
• #4 in nation for sedentary lifestyle
• #10 in nation for obesity
Pathophysiology

• Type 2 DM is characterized by:
  • Peripheral insulin resistance
  • Impaired regulation of hepatic glucose production
  • Declining β-cell function, eventually leading to β-cell failure.

• Initial deficit in insulin secretion and relative insulin deficiency in association with peripheral insulin resistance
Pathophysiology

• Insulin resistance
  • obesity or an increase in intraabdominal adipose tissue associated with insulin resistance

• Impaired hepatic glucose regulation
  • Liver overproduces and underutilizes glucose

• ß-cell function
  • Initially: impairment in 1st phase of insulin secretion
  • Later in disease course: impairment in 2nd phase of insulin release
  • Autoimmune destruction in small subset of patients
What is the goal blood pressure in a patient with diabetes?

1. <140/90
2. <130/80
3. <140/80
4. <120/80
What immunizations are recommended for patients with diabetes?

1. Influenza vaccine annually
2. Pneumococcal once before age 65, once after 65 (5 years apart)
3. Hepatitis B for all 19-59 years of age (Possible Hepatitis B for those >60 years old if at risk)
4. All of the above
ADA Standards of Care

• American Diabetes Association: Clinical Practice Recommendations 2013
  • www.diabetes.org
  • *Diabetes Care* 2013, Volume 26, Supplement 1
Standards of Care-Summary

• A1c goal < 7%; test every 3-6 months (point of care acceptable)
  • May target even lower A1c goals for some individuals without significant hypoglycemia
    • Short duration of diabetes, long life expectancy, no significant CVD

• Blood pressure goal <140/80; test at every visit
  • Preferred agents ACEI or ARBs
Standards of Care-Summary

• Cholesterol-test annually
  – Total cholesterol <200 mg/dL
  – LDL <100 mg/dL, <70 option for overt CVD
  – TG < 150 mg/dL
  – HDL > 40 men; >50 women; preferably >60
    • Statin use regardless of lipid levels
      – Overt CVD
      – Without CVD, > 40 AND have one or more CVD risk factor

• Microalbuminuria-test annually

• Serum creatinine-test annually (to estimate GFR)
Standards of Care-Summary

• Dilated eye exam-test annually
• Foot exam
  – Visual exam every visit
  – Sensory exam annually
• Influenza vaccine annually; pneumococcal once before age 65, once after 65 (5 years apart); Hepatitis B for all 19-59 years of age (Possible Hepatitis B for those >60 years old if at risk)
• Individualized MNT by dietitian
• DSME when diagnosed and prn thereafter
Standards of Care-Summary

• Aspirin 75-162 mg/day as primary prevention for increased CV risk
  • Men >50 years old, Women >60 years old AND
  • One additional risk factor
    - Family history of CVD
    - Dyslipidemia
    - HTN
    - Albuminuria
    - Smoking
Standards of Medical Care
Glycemic Goals of Therapy

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial plasma glucose</td>
<td>&lt;100 mg/dL</td>
<td>70-130 mg/dL</td>
</tr>
<tr>
<td>Postprandial plasma glucose</td>
<td>&lt;140 mg/dL</td>
<td>&lt;180 mg/dL</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>4-6%</td>
<td>&lt;7%*</td>
</tr>
</tbody>
</table>

Note: Normal = nondiabetic; goals = diabetic
*General goal for all persons; may be more aggressive in some individuals

Diagnosis

- FPG ≥ 126 mg/dL (no caloric intake for at least 8 hours) - Preferred test*
- 2-hour postprandial glucose ≥ 200 mg/dL during an oral glucose tolerance test (OGTT)*
- A1C ≥ 6.5%*
- Presence of symptoms (polyuria, polydypsia, and unexplained weight loss) plus a casual glucose concentration ≥ 200 mg/dL (casual – any time of day regardless of last meal)
- *All must be confirmed on a subsequent day
Who should be tested?

- All persons >45 years of age, and repeated every 3 years, if normal
  - Those with prediabetes should be tested yearly
- Adults of any age if overweight or obese and one or more additional risk factor(s) present
- Persons who are symptomatic
- Children and Adolescents
  - Overweight
    - 2 or more additional risk factors
Risk Factors for Type 2 DM

- Family history
- Overweight (BMI ≥ 25 kg/m²)
- Physical inactivity
- Race/ethnicity (e.g., African-Americans, Hispanic-Americans, Native Americans, Asian-Americans, and Pacific Islanders)
- History of CVD
- Polycystic ovary syndrome
- Previously identified IFG or IGT or A1C ≥ 5.7%
- Hypertension (>140/90 mmHg in adults)
- HDL cholesterol < 35 mg/dl and/or a triglyceride level > 250 mg/dl
- History of GDM or delivery of a baby weighing >9 lbs
- Other clinical conditions associated with insulin resistance
b1  Note attached to page has unfinished statement:  (e.g. severe obesity)
bh67000, 9/27/2010
Recent Significant Updates

• Standards of Care 2010
  – Revisions to diagnostic criteria
    • A1C
  – Section previously titled “Diagnosis of pre-diabetes” has been renamed “Categories of increased risk for diabetes”
    • A1C range of 5.7-6.4% included (in addition to IFG and IGT)
  – Major revisions to “Diabetes Self-Management Education” section
  – Significant revisions to “Antiplatelet agents” section
  – Major revisions to “Diabetes care in the hospital” section
Recent Significant Updates

– Standards of Care 2011
  – Revisions to “Detection and diagnosis of GDM” section
    • Changes in the diagnosis and testing
  – “Hypertension/Blood Pressure Control” revised to reflect importance of individualization of goals
  – “Children and Adolescents” revised to remove lower limits on A1C and includes individualization
Recent Significant Updates

- Standards of Care 2012
  - Therapy for Type 2 Diabetes was revised to include more specific recommendations for starting and advancing pharmacotherapy for hyperglycemia
  - New table listing properties of noninsulin therapies for type 2 diabetes added
Standards of Care 2013 Revisions

• Major Implications
  • May improve insurance coverage for testing supplies
  • Reduce the number of patients needing medications for hypertension
  • Increase hepatitis B vaccination rates
2013 Revisions

• Section II.C. Screening for Type 1 Diabetes has been revised to include more specific recommendations
  • Consider referring relatives of type 1 patients for antibody testing for risk assessment
  • Couple testing with:
    • Education about diabetes development and symptoms
    • Patient follow-up in clinical trials that are looking at interventions to slow beta cell loss
  • May allow for earlier identification of type 1 and lessen presentation with ketoacidosis
2013 Revisions

• Section IV. Prevention/Delay of Type 2 Diabetes has been revised to reflect the importance of screening for and treating other cardiovascular risk factors.
  • Added section to emphasize the importance of screening for (and treatment of) other cardiovascular risk factors (obesity, hypertension, and dyslipidemia) to help reduce cardiometabolic risk in individuals at high risk for developing type 2 diabetes.
• All individuals who are overweight or obese should be intensively counseled to lose weight and to exercise.

• Lifestyle modification therapy emphasizing modest weight loss (7% of body weight) and moderate-intensity physical activity such as walking 150 minutes/week is the treatment of choice for patients with IFG or IGT or A1C of 5.7%-6.4%

• Medication use (see next slide)
ADA 2013 Standards of Care

- **Metformin** may be considered in patients with IFG, IGT, or an A1C of 5.7-6.4%, *especially* for those:
  - <60 yo
  - BMI >35 kg/m²
  - Women with prior GDM
2013 Revisions

• Section V.C.a. Glucose Monitoring has been revised to highlight the need for patients on intensive insulin regimens to do frequent self-monitoring of blood glucose.
  • Previous recommendations:
    • Test three or more times/day
    • Often misinterpreted that people should only measure three times/day, thus affecting the number of strips covered by insurance
  • New recommendations:
    • Blood sugar monitoring should be individualized
    • Frequent self-monitoring of blood glucose for patients on intensive insulin regimens
    • Education for patients using less intensive treatment on interpretation of results and utility of SMBG for self-management of their disease
2013 Revisions

• Section V.D. Pharmacological and Overall Approaches to Treatment has been revised to add a section with more specific recommendations for insulin therapy in type 1 diabetes.
  • Metformin still preferred first-line pharmacological agent for type 2 BUT significant changes in treatment guidelines focusing on a more patient-centered approach and individualization of treatment
  • To be discussed in next section
2013 Revisions

• Section V.F. Diabetes Self-Management Education (DSME) and Support (DSMS) has been revised to be consistent with the newly revised National Standards for Diabetes Self-Management Education and Support.
American Diabetes Association Standards of Medical Care and DSME

• DSME and DSMS when their diabetes is diagnosed and as needed thereafter.

• Effective self-management and quality of life are the key components of DSME and should be measured and monitored as part of care.

• DSME should address psychosocial issues, since emotional well-being is associated with positive diabetes outcomes.

• Because DSME can result in cost-savings and improved outcomes, DSME should be adequately reimbursed by third-party payers.
DSME/DSMS

• On-going processes of facilitating the knowledge, skill, and ability necessary for diabetes self-care

• Overall objectives to support:
  • Informed decision making
  • Self-care behaviors
  • Problem solving
  • Active collaboration with health care team to improve clinical outcomes, health status, and quality of life in a cost-effective manner
2013 Revisions

• Section V.K. Hypoglycemia has been revised to emphasize the need to assess hypoglycemia and cognitive function when indicated.

• Recommendations:
  • Hypoglycemic episodes assessed at every encounter for those at risk
  • Treatment: Rule of 15
  • Glucagon Rx for all at significant risk of severe hypoglycemia
  • Hypoglycemia unawareness/severe episode should trigger re-evaluation of treatment regimen
  • Insulin treated patients with hypoglycemia unawareness/severe episodes should raise glycemic targets for at least several weeks to partial reverse hypoglycemia unawareness and reduce risk of future episodes
  • Ongoing assessment of cognitive function
2013 Revisions

• Section V.M. Immunization has been updated to include the new Centers for Disease Control and Prevention (CDC) recommendations for hepatitis B vaccination for people with diabetes.
  • Administer hepatitis B vaccination to unvaccinated adults with diabetes who are aged 19 through 59 years
  • Possible Hepatitis B for those >60 years old if at risk
2013 Revisions

- Section VI.A.1. Hypertension/Blood Pressure Control has been revised to suggest that the systolic blood pressure goal for many people with diabetes and hypertension should be <140 mmHg, but that lower systolic targets (such as <130 mmHg) may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden.

- Hypertension/Blood Pressure Control
  - Previous goal <130/80
  - Revised goal <140/80
    - Lower systolic targets (<130 mmHG) recommended for certain individuals (i.e. younger patients).
  - Potential for reduced number of medications taken
  - Treatment of HTN still important
2013 Revisions

• Section VI.A.2. Dyslipidemia/Lipid Management and Table 10 have been revised to emphasize the importance of statin therapy over particular LDL cholesterol goals in high-risk patients.
  • Dyslipidemia/Lipid Management
    • Previous standards recommended combination therapy when targets were not reached on maximally tolerated doses of statins.
    • New standards revised to state that combination therapy has been shown not to provide additional cardiovascular benefit above statin therapy alone and is generally not recommended.
2013 Revisions

- Section VI.B. Nephropathy Screening and Treatment and Table 11 have been revised to highlight increased urinary albumin excretion over the terms micro- and macroalbuminuria, other than when discussion of past studies requires the distinction.

Table 11-Definitions of abnormalities in albumin excretion

<table>
<thead>
<tr>
<th>Category</th>
<th>Spot Collection (mg/mg creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>30</td>
</tr>
<tr>
<td>Increased urinary albumin excretion*</td>
<td>≥30</td>
</tr>
</tbody>
</table>

*Historically, ratios between 30 and 299 have been called microalbuminuria and those 300 or greater have been called macroalbuminuria (or clinical albuminuria).
2013 Revisions

- Section VI.C. Retinopathy Screening and Treatment has been revised to include anti–vascular endothelial growth factor therapy for diabetic macular edema.
- Section IX.A. Diabetes Care in the Hospital has been revised to include a recommendation to consider obtaining an A1C in patients with risk factors for undiagnosed diabetes who exhibit hyperglycemia in the hospital.
2013 Revisions

• The position statement “Diagnosis and Classification of Diabetes Mellitus” has been revised slightly to add newer information about monogenic forms of diabetes.
  • Classification
    • Type 1: β-cell destruction (usually leading to absolute insulin deficiency)
    • Type 2: progressive insulin secretory defect on the background of increased insulin resistance
    • Gestational: diabetes diagnosed during pregnancy that is not clearly overt diabetes
    • Other specific types of diabetes due to other causes
      • Genetic defect in β-cell function
      • Genetic defect in insulin action
      • Diseases of the exocrine pancreas (cystic fibrosis)
      • Drug- or chemical-induced (HIV/AIDS treatment or after organ transplant)
Consensus statement from the American Diabetes Association and the American Geriatrics Society

• Randomized controlled trials for treatment and treatment targets often exclude older adults (aged 65 and older)

• Highest prevalence of diabetes in this age-group

• Treatment goals for older adults with type 2 diabetes should take into account patient characteristics/health status and life expectancy
  • A1c goals <7.5% to < 8.5%
  • blood pressure goals <140/80 to < 150/90
  • FBS goals of 90-130 to 100-180
Consensus Report to Address Key Questions

1. What is the epidemiology and pathogenesis of diabetes in older adults?
2. What is the evidence for preventing and treating diabetes and its common co-morbidities in older adults?
3. What current guidelines exist for treating diabetes in older adults?
4. What issues need to be considered in individualizing treatment recommendations for older adults?
5. What are consensus recommendations for treating older adults with or at risk for diabetes?
6. How can gaps in the evidence best be filled?
Pharmacological Approaches to Treatment
Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care, V27, Number 1, December 2009, 4-16
Healthy eating, weight control, increased physical activity

Initial drug monotherapy
- Efficacy (↓ HbA₁c)
- Hypoglycemia
- Weight
- Side effects
- Costs

Two-drug combinations
- Efficacy (↓ HbA₁c)
- Hypoglycemia
- Weight
- Major side effect(s)
- Costs

Three-drug combinations

More complex insulin strategies

If needed to reach individualized HbA₁c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin +</th>
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<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
</table>
| Sulfonlurea
  - High
  - Moderate risk
  - Gain
  - Hypoglycemia
  - Low |
| Thiazolidinedione
  - High
  - Low risk
  - Gain
  - Edema, HF, Fx's
  - High |
| DPP-4 Inhibitor
  - Intermediate
  - Low risk
  - Neutral
  - Rare
  - High |
| GLP-1 receptor agonist
  - High
  - Low risk
  - Loss
  - GI
  - High |
| Insulin (usually basal)
  - Highest
  - High risk
  - Gain
  - Hypoglycemia
  - Variable |

If needed to reach individualized HbA₁c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):

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| GLP-1 receptor agonist
  - High
  - Low risk
  - Loss
  - GI
  - High |
| Insulin (usually basal)
  - Highest
  - High risk
  - Gain
  - Hypoglycemia
  - Variable |

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:

Insulin
  - (multiple daily doses)
AACE/ACE DIABETES ALGORITHM FOR GLYCEMIC CONTROL

A1C 6.5 - 7.5%**

Monotherapy

MET** DPP4 1 GLP-1 TZD 2 AGI 3

2 - 3 Mths**

Dual Therapy

MET + GLP-1 or DPP4 1

TZD 2

Glinide or SU 6

Colesvelam

AGI 3

2 - 3 Mths**

Triple Therapy

MET + GLP-1 or DPP4 1

TZD 2

Glinide or SU 6,7

2 - 3 Mths**

A1C > 9.0%

Under Treatment

MET + GLP-1 or DPP4 1

± SU 7

± TZD 2

GLP-1 or DPP4 1

± Other Agent(s) 5

INSULIN

May not be appropriate for all patients

** For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered

* If A1C goal not achieved safely

1 Preferred initial agent

2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)

3 GLP-1 or PPG if PPG or GLP-1

4 If PPG

5 Low-dose secretagogue recommended

a) Discontinue insulin secretagogue with multidose insulin

b) Can use pramlintide with prandial insulin

7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4

8 If a C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution

9 If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered

Available at www.aace.com/pub

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Glycemic Control Algorithm

Lifestyle Modification
(Including Medically Assisted Weight Loss)

Entry A1c < 7.5%

Entry A1c ≥ 7.5%

Entry A1c > 9.0%

Monotherapy*
- Metformin
- GLP-1 RA
- DPP-4-i
- SGLT-2
- TZD
- SUagliptin

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

Dual Therapy*
- GLP-1 RA
- DPP-4-i
- SGLT-2
- TZD
- SGLT-2
- Basal Insulin
- Basal Insulin
- Basal + GLP-1 RA
- Basal + DPP-4-i
- Basal + SGLT-2
- Basal + TZD
- SUagliptin

If not at goal in 3 months proceed to triple therapy

Triple Therapy*
- GLP-1 RA
- DPP-4-i
- SGLT-2
- TZD
- SGLT-2
- Basal Insulin
- Basal Insulin
- Basal + GLP-1 RA
- Basal + DPP-4-i
- Basal + SGLT-2
- Basal + TZD
- SUagliptin

If not at goal in 3 months proceed to or intensify insulin therapy

Progression of Disease

Legend

ADD OR INTENSIFY INSULIN

No Symptoms

Symptoms

Dual Therapy

Triple Therapy

Insulin + Other Agents

### Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th>HYPO</th>
<th>MET</th>
<th>DPP-4i</th>
<th>GLP-1 RA</th>
<th>TZD</th>
<th>AGI</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>SU</th>
<th>GLI</th>
<th>INSULIN</th>
<th>SGLT-2</th>
<th>PRAML</th>
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<tbody>
<tr>
<td>Neutral</td>
<td>Neutral</td>
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<td>Neutral</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>WEIGHT</th>
<th>Slight Loss</th>
<th>Loss</th>
<th>Gain</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Gain</th>
<th>Gain</th>
<th>Loss</th>
<th>Loss</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>RENAL/GU</th>
<th>Contra-Indicated Stage 3b,4,5</th>
<th>Dose Adjustment May be Necessary (Except Linagliptin)</th>
<th>Branched Chain Length May Be Indicated</th>
<th>CRI &lt; 30</th>
<th>May Worsen Fluid Retention</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Neutral</th>
<th>More Hypo Risk</th>
<th>More Hypo Risk &amp; Fluid Retention</th>
<th>Infections</th>
<th>Neutral</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1Sx</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>CHF</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>CVD</td>
<td>Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Bone Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>?</td>
<td>Bone Loss</td>
</tr>
</tbody>
</table>

**Legend:**
- **Green:** Few adverse events or possible benefits
- **Yellow:** Use with caution
- **Red:** Likelihood of adverse effects

An A1C target of 6-6.5% would be appropriate for a patient with which of the following characteristics?

1. Less motivated
2. Excellent self-care capacities
3. Long-standing disease duration
4. Severe comorbidities
In addition to lifestyle changes, ______________ should be the initial therapy for patients with diabetes.

1. metformin
2. sulfonylurea/glinide
3. pioglitazone
4. DPP-4
5. insulin
6. Any of the above may be used
Patient Characteristics for More Stringent Therapy (Target A1C 6-6.5%):

- Highly motivated
- Adherent
- Excellent self-care capacities
- Low potential risk of hypoglycemia and other adverse effects
- Newly diagnosed
- Long life expectancy
- No important comorbidities
- No established vascular complications
- Have readily available resources & support system

Patient Characteristics for Less Stringent Therapy (Target 7.5-8%):

- Less motivated
- Non-adherent
- Poor self-care capabilities
- High risk for hypoglycemia related adverse effects & other adverse effects
- Long-standing disease duration
- Short life expectancy
- Severe comorbidities
- Severe established vascular complications
- Limited resources &/or support system

Approach to management of hyperglycemia:

<table>
<thead>
<tr>
<th>Factor</th>
<th>More stringent</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient attitude and expected treatment efforts</td>
<td>Highly motivated, adherent, excellent self-care capacities</td>
<td>Less motivated, non-adherent, poor self-care capacities</td>
</tr>
<tr>
<td>Risks potentially associated with hypoglycemia, other adverse events</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Few/mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Few/mild</td>
</tr>
<tr>
<td>Resources, support system</td>
<td>Readily available</td>
<td>Limited</td>
</tr>
<tr>
<td>Medication Class</td>
<td>MOA</td>
<td>Cause Hypoglycemia?</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Biguanides</td>
<td>↓ Hepatic glucose production</td>
<td>No</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>↑ Insulin secretion</td>
<td>Yes</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>↑ insulin secretion</td>
<td>Yes</td>
</tr>
<tr>
<td>TZDs</td>
<td>↑ Insulin sensitivity</td>
<td>No</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Slows intestinal carbohydrate digestion/absorption</td>
<td>No</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Unknown ? ↓ Hepatic glucose production ? ↑Incretin Levels</td>
<td>No</td>
</tr>
<tr>
<td>Dopamine-2 agonists</td>
<td>Modulates hypothalamic regulation of metabolism ↑ Insulin sensitivity</td>
<td>No</td>
</tr>
<tr>
<td>Injectable GLP-1 receptor agonists</td>
<td>↑ Insulin secretion ↓Glucagon secretion Slows gastric emptying ↑ Satiety</td>
<td>No</td>
</tr>
<tr>
<td>Amylin mimetics</td>
<td>↓ Glucagon secretion Slows gastric emptying ↑ Satiety</td>
<td>Yes</td>
</tr>
<tr>
<td>DPP-4</td>
<td>↑ Insulin secretion ↓ Glucagon secretion</td>
<td>No</td>
</tr>
</tbody>
</table>
Implementation Strategies

• Initial Therapy
  • Lifestyle changes
  • Metformin
    • May use sulfonylurea/glinide, pioglitazone, or DPP-4 inhibitor if Metformin cannot be used
    • HbA$_{1c}$ ≥ 9% = combination of two noninsulin agents or insulin itself
Implementation Strategies

• Dual Combination Therapy
  • Initiate when goal A1c not achieved after 3 months
    • Second oral agent
    • GLP-1 agonist
    • Basal insulin
    • Typically, any second agent will lower HbA$_{1c}$ levels an additional $\sim 1\%$
    • No single best agent
      • Must consider specific patient characteristics
Implementation Strategies

• Triple Combination Therapy
  • Initiate when goal A1c not achieved after 3 months
    • Third noninsulin agent
    • Insulin
      • Most patients require the use of insulin therapy
      • HbA1c levels ≥ 8.5%
Non-insulin regimens

Basal insulin only (usually with oral agents)

Basal insulin + 1 (mealtimes) rapid-acting insulin injection

Pre-mixed insulin twice daily

Basal insulin + ≥2 (mealtimes) rapid-acting insulin injections

Number of injections

1
Low

2
Mod.

3+
High

Regimen complexity

More flexible

Less flexible

Flexibility
KEY POINTS FOR INSULIN THERAPY

• Typical beginning basal dose is 0.1-0.2 units/kg/day

• Beginning basal dose for severe hyperglycemia is 0.3-0.4 units/kg/day

• Increase dose by 1-2 units (or 5-10% in those already on higher doses) to the daily dose once or twice weekly if the fasting glucose levels are above the patient’s targeted range

• As reaching the target becomes nearer, adjust dose more modestly and less frequently
KEY POINTS FOR INSULIN THERAPY (cont.)

• If a hypoglycemic event occurs, decrease the dose
• If postprandial glucose readings become >180mg/dL consider adding prandial insulin
• Add prandial insulin first to the meal with the largest carbohydrate content
• Add prandial insulin to subsequent meals (*largest carb content to smallest*) as needed
• Consider premixed insulin if the patient eats regularly and is in need of a more simple regimen than basal/bolus dosing
• Individualization of therapy is key!
Significant Clinical Trials
EUREXA

• Open-label study
• 1029 adults
  • A1c 6.5% to 9.0%
  • Taking metformin randomized to add
    • Exenetide (5-10 μg twice daily) or
    • Glimepiride (titrated to max daily dose)
• Four years of follow-up
• Primary Endpoint: Treatment Failure
  • A1c level >9% after 3 months of treatment, or
  • A1c level >7% at two consecutive readings after 6 months of treatment

EUREXA findings

• Significantly fewer exenatide recipients than glimepiride recipients had treatment failure (41% vs. 54%).

• Significantly more exenatide recipients than glimepiride recipients reached a target A1c level of <7% (44% vs. 31%).

• Patients in exenatide group LOST a mean of 3.3 kg vs. a mean weight GAIN of 1.2 kg in the glimepiride group.

• Significantly more hypoglycemia in patients taking glimepiride.

EASIE Trial
(Evaluation of Insulin Glargine Versus Sitagliptin in Insulin-Naive Patients)

• Open-label trial
• 515 adults
  • A1c 7% to 11%
  • Taking metformin randomized to add
    • Once-daily insulin glargine titrated to a fasting glucose level of 72–99 mg/dL or
    • Sitagliptin 100 mg once daily
• 24 weeks

EASIE Trial Findings

• Significantly greater reduction in mean A1c in patients in insulin glargine group than patients in sitagliptin group (–1.7% vs. –1.1%)
• More patients who received insulin glargine reached the A1c target of 7% (68% vs. 42%).
• Slight increase in mean body weight of patients in the insulin glargine group and slight decrease in sitagliptin group
• Significantly more hypoglycemic events in insulin glargine group (4.2 vs. 0.5 per patient-year).

ORIGIN (Outcome Reduction With Initial Glargine Intervention)

• Treatment with insulin glargine:
  • Failed to reduce MI, stroke, and CV death (neutral effect)
  • Did prevent progression from IFG and IGT to diabetes

• ORIGIN -- Omega 3 Fatty Acid Trial
  • Double-blind study
  • Patients with Type 2 diabetes, IFG, or IGT
  • Treatment with 900mg of Omega 3 Fatty Acids compared to placebo
    • No reduction in CV events
    • No reduction in LDL, A1c, BP, or heart rate
    • Reduction in triglycerides (14.5 mg/dl)
GRACE (Glucose Reduction and Atherosclerosis Continuing Evaluation)

- 1,184 patients
  - ≥ 50 years old
  - pre-diabetes or recently diagnosed type 2 diabetes
  - High cardiovascular risk (hypertension, smokers, hyperlipidemia, adverse carotid ultrasound test)
- 6.2 years
- Failure of Omega 3 fatty acids (1-g/day) and insulin glargine to slow down the progression of carotid atherosclerosis in patients with pre-diabetes or recently diagnosed type 2 diabetes
- Similar incidence of cardiovascular death, nonfatal MI or nonfatal stroke in the glargine and standard care groups (sulfonylurea and metformin)

GRACE: Insulin Glargine Fails to Halt Atherosclerosis Progression article in 9/4/12 issue of Clinical Endocrinology Vol.7 No. 9 p.1,27
Look AHEAD
(Action for Health in Diabetes)

• 5,145 adults with diabetes and a body mass index >25 kg/m²
  • Randomly assigned to one of two groups:
    • Intensive lifestyle group (included individual sessions with a nutritionist and/or personal trainer, as well as group sessions and refresher courses)
    • General diabetes education and support (Control Arm)

• No difference in the rate of nonfatal MI, nonfatal stroke, death, or hospitalization for angina among patients in intervention arm
  • No benefit in cardiovascular outcomes

• Significant reductions in weight and improvements in physical-fitness levels among patients in intervention arm

NIH News October 19, 2012 edition
COMBO-DN trial

• Large multi-national trial
  • Comparing duloxetine and pregabalin

• Patients with painful diabetic neuropathy

• Conclusions
  • Duloxetine > pregabalin for pain relief
  • No difference in combination therapy with duloxetine and pregabalin vs. monotherapy with either agent alone
  • 1/3 of patients achieved pain reduction >50%
FREEDOM Trial  
(Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease)  

- Randomized Trial  
- 1,900 patients  
  - candidates for CABG (coronary artery bypass grafting) and PCI (percutaneous coronary intervention)  

- Results  
  - 5-year all cause mortality and non-fatal MI or stroke  
    - CABG group = 18.7 %  
    - PCI group = 26.6 %  
  - 5-year costs of CABG lower than PCI (initial cost of CABG higher)
SWAN study (Study of Women’s Health Across the Nation)

- 3,075 participants
  - 42 to 52 years of age at study entry
  - Completed questionnaires about hot flashes and night sweats

- Findings
  - Glucose levels and degree of insulin resistance rose as frequency of hot flashes rose.
  - Glucose levels were 33% higher in women who reported hot flashes 1 to 5 days per week than in those who reported no hot flashes
  - Glucose levels were 1.25% higher in women who reported hot flashes on 6 days or more per week

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints)

- Trial halted December 2011 due to increased risk of renal impairment, hyperkalemia, and hypotension when used in combination with ACE inhibitors and ARBs
  - In April 2012, FDA suggested that Tekturna should not be used in patients with diabetes who are receiving ARBs or ACEI
  - Avoid use of Tekturna with ARBs or ACEI in patients with moderate renal impairment (GFR <60 ml/min)
  - Valturna (aliskiren and valsartan combo) pulled from the market
SEARCH for Diabetes In Youth Study

- Registry started in 2000 and will continue until 2015
- Over 20,000 participants
- Five centers in US participating
- Findings so far
  - 21% increased incidence of type 2 diabetes and a 23% increased incidence of type 1 diabetes in people under 20 years old from 2001 to 2009
  - Signs of kidney damage, peripheral neuropathy, elevated triglyceride present
  - Elevations of blood glucose and lipids seen in youth that spent more time watching TV
New Approved Therapies
Which of the following statements is true regarding Bydureon (exenatide 2mg)?

1. Administered twice daily
2. Patients can store at room temperature for up to 90 days
3. Must be administered with a full meal
4. Fixed dose for all patients
Bydureon (exenatide 2mg)

• Injectable GLP-1 agonist
• Once weekly exenatide
• On market since 2/2012
• Mechanism of Action
  • Enhances glucose dependent insulin secretion (increases synthesis & secretion), delays gastric emptying, and suppresses glucagon, reduces food intake
• Indications: As an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes
• Dose:
  • 2 mg SubQ once every 7 days at anytime, with or without meals
Bydureon Pearls

- Fixed dose for all patients
- Administer SQ in thigh, abdomen, or upper arm
- Only works in the presence of hyperglycemia
- Single dose vials that must be reconstituted and used immediately
- Store in refrigerator or at room temperature no more than 4 weeks if needed
Bydureon Pearls

• When compared to Byetta
  • Additional 0.7% decrease in A1C
  • Less nausea
  • Increased injection site reactions
  • Small asymptomatic injection site nodule

• Converting from Byetta to Bydureon
  • Administer the weekly dose the day after the daily dose is discontinued.
  • Patients may experience higher than normal blood glucose levels for approximately two weeks after conversion.
Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors

- Glucose filtered by the glomerulus, but completely reabsorbed
- Block SGLT2 transporter thus causing excessive glucose to remain in urine
SGLT2 Inhibitors

• Dapagliflozin: Rejected over concerns of breast and bladder cancer risks
• Canagliflozin (Invokana®): First drug in this class, approved March 2013
  • Concerns over increased risks for genitourinary infections
  • Long term data on impact on cardiovascular risk needed
SGLT2 Inhibitors

• Pros
  • A1C lowering ability
  • Weight loss
  • Minimal polyuria or compensatory hunger
  • Slight drop in systolic BP

• Cons
  • Hypoglycemia
  • Genital/Urinary infections
  • Drop in A1C = better outcomes?
Alogliptin (Nesina)

- DDP-IV inhibitor (Fourth in this class)
- Similar adverse effect profile
- Two Combination products
  - alogliptin + metformin (Kazano)
  - alogliptin + pioglitazone (Oseni)
- Projected to be available summer 2013
Ranibizumab (Lucentis)

- Dose: 0.3 mg once monthly intravitreal injection
- Anti-VEGF agent used to treat diabetic macular edema
  - Improvement in visual acuity (RIDE and RISE trials)
- Approved August 10, 2012
- Potential SE:
  - increased incidence in eye pain
  - vitreous floaters
  - retinal detachment
  - stroke

Tapentadol (Nucynta ER)

• Opioid agonist indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults

• Contraindications
  • Significant respiratory depression
  • Acute or severe bronchial asthma
  • Paralytic ileus
  • Hypersensitivity to tapentadol or to any other ingredients of the product
  • In patients who are receiving monoamine oxidase inhibitors (MAOIs) or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events
Tapentadol (Nucynta ER)

• Dosing:
  • Initial dose of tapentadol ER in patients not currently taking opioid analgesics is 50 mg twice a day.
    • Instruct patients to swallow tapentadol ER tablets whole.
  • Titrate patients to adequate analgesia with dose increases of 50 mg no more than twice daily every three days
  • Recommended maintenance dose is 100 mg to 250 mg twice daily, taken approximately every 12 hours
  • Maximum 24-hour dose is 500 mg
  • Gradually taper the dose when tapentadol ER is discontinued
  • Reduce the dose of tapentadol ER in patients with moderate hepatic impairment.
  • Tapentadol ER use in patients with severe renal impairment is not recommended.
Sensus Pain Management System

• NeuroMetrix, Inc.
• FDA Clearance in late November 2012
• System sends electrical pulses through the skin to stimulate nerves and thereby relieve chronic pain associated with diabetic neuropathy
Evidence of Weight Control and Diabetes Management

• **Catholic University of Rome (60 patients, 2 years)**
  - Target of A1c < 6.5% and FBS < 100 mg/dl
    - Conventional Treatment: 0% achieved
    - Gastric bypass: 75% achieved
    - Biliopancreatic diversion: 95% achieved

• **Cleveland Clinic (150 patients, 12 months)**
  - Target of A1c <6% and decrease in need for diabetes medicines
    - Medical therapy only: 12% achieved
    - Roux-en-Y gastric bypass: 42% achieved
    - Sleeve gastrectomy: 37% achieved

• **Swedish Obese Subjects (SOS) Trial (>3000 patients, 15 years)**
  - 111 of surgery patients developed type 2 diabetes
  - 392 of non-surgery patients developed type 2 diabetes

• 1999—Discovered that incretin levels were 5x higher in patients after undergoing gastric bypass
Gastric Bypass and Diabetes Remission

- Retrospective study
- 4,434 adults
  - uncontrolled or medication-controlled type 2 diabetes
  - had gastric bypass
- Within 5 years after surgery
  - 68.2 % had an initial complete diabetes remission
  - 35.1 % redeveloped diabetes
- Conclusion: Gastric bypass surgery is associated with durable remission of type 2 diabetes in many (but not all) severely obese adults with diabetes

A Multisite Study of Long-term Remission and Relapse of Type 2 Diabetes Mellitus Following Gastric Bypass Obesity Surgery January 2013, Volume 23, pp.93-102
Phentermine and topiramate (Qsymia)

• Used together with a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:
  • 30 kg/m² or greater (obese) or
  • 27 kg/m² or greater (overweight) in the presence of at least one weight-related medical condition such as high blood pressure, type 2 diabetes, or high cholesterol
Phentermine and topiramate (Qsymia) Dosage and Administration

• Take once daily in morning. (Avoid evening dose to prevent Insomnia)
• Recommended dose: Qsymia 3.75 mg/23 mg (phentermine 3.75 mg/topiramate 23 mg extended-release) daily for 14 days; then increase to 7.5 mg/46 mg daily.
• Discontinue or escalate dose if 3% weight loss is not achieved after 12 weeks on 7.5 mg/46 mg dose.
• Discontinue Qsymia if 5% weight loss is not achieved after 12 weeks on maximum daily dose of 15 mg/92 mg.
• Discontinue 15 mg/92 mg dose gradually to prevent possible seizure.
• Do not exceed 7.5 mg/46 mg dose for patients with moderate or severe renal impairment or patients with moderate hepatic impairment.

www.qsymia.com
lorcaserin hydrochloride (Belviq)

• Serotonin 2C receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:
  • 30 kg/m² or greater (obese) (1) or
  • 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition, (e.g., hypertension, dyslipidemia, type 2 diabetes)

• Dosage and Administration
  • One tablet of 10 mg twice daily
  • Discontinue if 5% weight loss is not achieved by week 12

• Adverse Events
  • Diabetic patients: hypoglycemia, headache, back pain, cough, and fatigue
Blood Glucose Meters

• First Glucose Meters in 1971
• 2012 = >75 different meters with multiple special features
Blood Glucose Monitors
A self-service kiosk at the point of retail to engage consumers to improve their health and promote customer loyalty.
Blood Glucose Log Apps for iPhone®

• Glooko.com
• Glucose Buddy
• ONSYNC
• Multiple others
iPhone® Apps for the Patient with Diabetes

- MyFitnessPal
- Calorie Counter mynetdiary
- Weight Watchers
- Healthy Grocery (Shopwell)
- Diabetes Health Mobile
- BP Monitor
- Diabetes Personal Calculator
- Diabetes Buddy
- Track 3
V-Go

- Disposable Insulin Delivery System
  - Lasts 24 hours
- Delivers
  - Insulin lispro or insulin aspart
  - A continuous preset basal rate of insulin over 24 hours
    - V-Go 20: 20 Units/24 hr
    - V-Go 30: 30 Units/24 hr
    - V-Go 40: 40 Units/24 hr
  - On-demand bolus dosing at mealtimes
    - Up to 36 Units in 2-unit increments

www.go-vgo.com
OmniPod Next Generation Insulin Management System

• Just received clearance from FDA in February 2013 and expect to transition everyone to new OmniPod over the next few months

• New Pod
  • 34% smaller, 25% lighter and 16% slimmer than older version, but still holds up to 200 units of insulin
  • Function that helps you verify that the cannula has deployed

• Personal Diabetes Manager (PDM) enhanced functionality
  • Screen now always shows details about your current insulin on board (IOB)
  • Communication distance between the PDM and Pod during regular use has increased up to 5 ft. (vs. 2 ft. with older version)

www.myomnipod.com
Up and Coming Diabetes Therapies
Insulin Under Investigation

• **LY2963016 – Eli Lilly**¹
  • Comparable to insulin glargine

• **LY2605541 – Eli Lilly**²
  • Novel basal insulin analog
  • IMAGINE Clinical Trials
    • Type 1: LY2605541 was associated with improvements in mean blood glucose and A1c compared to insulin glargine
    • Type 2:
      • LY2605541 resulted in comparable improvements in fasting glucose compared to insulin glargine
      • LY2605541 was associated with a 1.2 lb weight loss compared to weight gain with insulin glargine
    • Both Type 1 and Type 2:
      • LY2605541 was associated with increased overall hypoglycemia, but lower rates of nocturnal hypoglycemia as compared to insulin glargine
      • Increased ALT and AST and triglycerides with LY2605541 verses insulin glargine (but stayed WNL)
  • Phase III studies are underway to assess the efficacy and safety and further evaluate the clinical significance of changes in liver function tests and lipids

Insulin Under Investigation

- **Insulin degludec – Novo Nordisk**
  - November 2012: Federal Advisory Panel voted 8 to 4 in favor of licensing ultralongbasal insulin degludec for people with both type 1 and type 2 diabetes
  - As part of the provisional agreement, Novo Nordisk must conduct a rigorous postmarketing study to evaluate cardiovascular statement
GLP-1 Agonists under Investigation

- Albiglutide (Syncria) – GSK – once weekly
- Lixisenatide (Lyxumia) – Sanofi – once daily (Get Goal studies)
- Dulaglutide – Eli Lilly – AWARD 1-5 and REWIND studies being conducted (2013-2014) – once weekly
- VRS-859 – Diartis/Versartis Inc – once monthly
- NN9924 – Novo Nordisk – oral phase 1 trial
- ITCA 650 – Intarcia Therapeutics – continuous SQ for 3, 6, 12 months
- Others

Johnson, Tommy and Stacie-Marie Norman “Diabetes Update 2013”
DPP-4 Inhibitors under Investigation

- MK-3102 – Merck (once weekly DDP-4 inhibitor)
- PHX 1149/dutogliptin – Phenomix
- PF-734200/gosogliptin – Pfizer
- R-1579/carmegliptin – F Hoffman-LaRoche
- RO-0730699 - F Hoffman-LaRoche
- SSR-162369 – Sanofi
- BMS-686117 – BMS
- Others

Johnson, Tommy and Stacie-Marie Norman “Diabetes Update 2013”
PPAR-alpha/gamma agonists

• MOA: Bind and activate dual peroxisome proliferator-activated receptors, alpha and gamma
  • Alpha: target of fibrates, improve lipid profile
  • Gamma: target of TZDs, improve glycemic control

• Toxicities (cardiotoxicity, nephrotoxicity) have hindered this from making it to market

• Aleglitazar (in Phase III clinical trials)
“Glimins”

• Imeglimin
  • Phase IIa
  • MOA
    • indirectly activates AMPA-kinase at the mitochondrial level to decrease the phosphate ratio, ATP/ADP, thus inhibiting oxidative phosphorylations
  • Targets 3 key defects in T2DM:
    • Inhibits hepatic gluconeogenesis
    • Increases muscle glucose uptake (insulin-independent mechanism)
    • Restores normal insulin secretion through a glucose-dependent mechanism
Product Gallery
Questions