Monday, June 5, 2016
12:00-1:00PM

Type 2 Diabetes: Medical Management & Patients-Centered Lifestyle Modification Support – AAFP Chapter Lecture Series

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DISCLOSURE: Neither Dr. Ziemkowski nor any member of his immediate family has a financial relationship or interest with any proprietary entity producing health care goods or services. The content of his material(s)/presentation(s) in this CME activity will not include discussion of unapproved or investigational uses of products or devices.

LEARNING OBJECTIVES:
At the conclusion of this presentation, the participant should be able to:

1) Utilize the American Diabetes Association general recommendations for anti-hyperglycemic therapy in T2DM.

2) Apply shared decision making models to develop comprehensive lifestyle modification plans that are tailored for each patient's unique characteristics and health profiles, including cultural considerations and dietary preferences.

3) Assess and re-assess patients' individual profiles and preferences as treatment plans develop and evolve.
Type 2 Diabetes: Medication Management & Patient-Centered Lifestyle Modification Support

Peter Ziemkowski, MD, FAAFP
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The content of my material/presentation in this CME activity will include discussion of unapproved or investigational uses of products or devices as indicated: 

Metformin: It's use for prevention of progression of prediabetes to overt diabetes will be discussed.
Peter Ziemkowski, MD, FAAFP

Associate Professor, Department of Family and Community Medicine, Western Michigan University, Homer Stryker MD School of Medicine, Kalamazoo;

Dr. Ziemkowski is a graduate of the University of Illinois College of Medicine at Chicago. He completed his residency in family medicine at Michigan State University, Kalamazoo Center for Medical Studies, Kalamazoo, and an internship in emergency medicine at the University of Michigan, Ann Arbor, and St. Joseph Hospital. Dr. Ziemkowski practices family medicine in southwest Michigan, where he is on the faculty of the Western Michigan University Homer Stryker MD School of Medicine's Family Medicine Residency Program and serves as associate dean for Student Affairs. He has been teaching for 19 years, maintains a blog for residents at kzoofm.blogspot.com, and uses technology to help educate patients on healthy lifestyles. Dr. Ziemkowski's clinical interests include the care of metabolic conditions associated with cardiovascular risk, such as hypertension, hyperlipidemia, diabetes mellitus, and obesity. He believes that primary prevention of these diseases and their complications will deliver the greatest benefit to the greatest number of patients.
Learning Objectives

1. Utilize the American Diabetes Association general recommendations for anti-hyperglycemic therapy in T2DM.

2. Apply shared decision-making models to develop comprehensive lifestyle modification plans that are tailored for each patient's unique characteristics and health profiles, including cultural considerations and dietary preferences.

3. Assess and re-assess patients' individual profiles and preferences as treatment plans develop and evolve.
Prevalence

Diabetes
• 29.1 million US citizens
  – 9.3% of U.S. population
• Diagnosed: 21 million
• Undiagnosed: 8.1 million

Increase of 3.3 million people over 2010!

Prediabetes
• 86 million US Adults
  – 37% of U.S. population
  – 51% of those 65 years or older!

Number of People 20 Years or Older With Diagnosed and Undiagnosed Diabetes, by Age Group, United States, 2012 (percentage)

Racial and Ethnic Differences in Diagnosed Diabetes in People Aged 20 years or Older, United States, 2010-2012

<table>
<thead>
<tr>
<th>Racial/Ethnic Group</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>American Indians/Alaskan Natives</td>
<td>15.9%</td>
</tr>
<tr>
<td>Non-Hispanic Blacks</td>
<td>13.2%</td>
</tr>
<tr>
<td>Hispanics</td>
<td>12.8%</td>
</tr>
<tr>
<td>Asian Americans</td>
<td>9.0%</td>
</tr>
<tr>
<td>Non-Hispanic Whites</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

Diabetes

Every 24 Hours…

• 4658 new cases of diabetes are diagnosed.

• 200 nontraumatic lower limb amputations are performed.

• 136 people begin treatment for end-stage renal disease.

• 641 people die of diabetes, or diabetes is a contributing cause of death
  – The seventh leading cause of death overall!

Every 5 Minutes…

• 16 new cases of diabetes diagnosed.

• 2 people die of diabetes-related causes

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered</td>
</tr>
<tr>
<td>B</td>
<td>Supportive evidence from well-conducted cohort studies</td>
</tr>
<tr>
<td>C</td>
<td>Supportive evidence from poorly controlled or uncontrolled studies</td>
</tr>
<tr>
<td></td>
<td>Conflicting evidence with the weight of evidence supporting the recommendation</td>
</tr>
<tr>
<td>E</td>
<td>Expert consensus or clinical experience</td>
</tr>
</tbody>
</table>

Diagnosis of Diabetes Mellitus

1. FPG ≥126 mg/dL (7.0 mmol/L)
   - Fasting = no calories for at least 8 hours
2. 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L)
   - During oral glucose tolerance test (OGTT)
3. Hemoglobin A1C (A1C) ≥6.5%
4. Classic symptoms of hyperglycemia or hyperglycemic crisis, with a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)

- In absence of unequivocal hyperglycemia, criteria 1 through 3 should be confirmed by repeat testing.
- Only criteria 4 does not require repeat testing
- **NEW in 2016**: Changed the order to make it clear that no one test is preferred over another.
Types of Diabetes Mellitus

1. Type 1
   - ~5 to 10%

2. Type 2
   - ~90 to 95%

3. Gestational Diabetes Mellitus
   - ~7% all pregnancies, >200,000 cases/year

4. Other specific types
   - Monogenic syndromes (<5%), diseases of exocrine pancreas, drug/chemical induced
“New” Organization

1. Type 1 ($E10.--$)
   - Absolute insulin deficiency
     • Immune-mediated
     • Idiopathic

2. Type 2 ($E11.--$)
   - Insulin resistance + relative insulin deficiency
     • Most obese

3. Gestational ($O24.4$)

4. Other
   - Monogenic Diabetes Syndromes ($E13.--$)
     • Neonatal Diabetes ($P70.2$)
     • Maturity-onset diabetes of the young (MODY)
   - Diseases of the exocrine pancreas (Cystic fibrosis,...) ($E08.--$)
   - Drug or chemical induced (steroids,...) ($E09.--$)

Percentages approximate

Pre-Assessment Question

1. Prediabetes is defined as a fasting glucose in the range of 100-125 mg/dL, referred to as Impaired Fasting Glucose (IFG) or an A1C in the range of 5.7% to 6.4%, among other criteria.

   Between these two measures, impaired fasting glucose is a better predictor of subsequent diabetes and cardiovascular disease than is a baseline A1C in the prediabetes range.

A. True
B. False
Prediabetes

Impaired Fasting Glucose (IFG) & Impaired Glucose Tolerance (IGT)

- **IFG** = FPG 100 to 125 mg/dL
- **IGT** = 2-hour plasma glucose 140 to 199 mg/dL (after 75 g challenge)
  - Risk factors for diabetes and cardiovascular disease
  - Strongly associated with
    - Obesity
      - Abdominal or visceral
    - Dyslipidemia
      - High triglyceride levels
      - And/or low high-density lipoprotein (HDL)
    - Hypertension

A1C

- **A1C** = 5.7% to 6.4%
  - Range 6.0% to 6.5%
    - 25% to 50% 5-year incidence of diabetes
    - Relative risk 20 x greater than at A1C = 5.0
  - Baseline A1C a stronger predictor of subsequent diabetes and cardiovascular diseases than fasting glucose

Testing for Type 2 DM in Adults

- Use informal assessment of risk factors or validated tool (B)
  - www.diabetes.org/are-you-at-risk
- All overweight adults with at least one risk factor. (B)
  - BMI ≥25 kg/m²
  - BMI ≥23 kg/m² in Asian Americans
- All patients starting at age 45 years (B)
- If normal, repeat at least every 3 years (C)

- All criteria considered equally appropriate (B)
  - Fasting Plasma Glucose
  - 2-hour plasma glucose (after 75-g glucose) OGTT
  - A1c
- Treat CV risk factors in patients with prediabetes. (B)
- Consider testing in overweight/obese children/adolescents with two or more additional risk factors. (E)

Risk Factors (any one)

- A1c ≥ 5.7%, IGT, IFG previously
- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity
  - African American
  - Latino
  - Native American
  - Asian American
  - Pacific Islander
- Women:
  - Polycystic ovary syndrome (PCOS) or h/o GDM

- Hypertension
  - (≥140/90 mm Hg / on therapy)
- Dyslipidemia
  - HDL <35 mg/dL
  - Triglyceride > 250 mg/dL
- H/o Cardiovascular Disease
- A1C ≥5.7%, IGT or IFG on previous testing
- Other clinical conditions associated with insulin resistance
  - Obesity
  - Acanthosis nigricans

Prevention/Delay of Type 2 DM

Patients with Prediabetes:

- Annual monitoring for progression (E)
- (A) referred to intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program (DPP) to achieve and maintain:
  - loss of 7% of body weight
  - Increase moderate-intensity physical activity (brisk-walking) to at least 150 minutes/week
- Technology tools, social networks, distance learning, DVD, mobile apps may be useful in lifestyle modification. (B)
- Based on cost-effectiveness, intervention programs should be covered by third-party payers (B)

- (A) Metformin for prevention (NOT FDA-APPROVED) should be considered, especially in:
  - BMI > 35 kg/m²
  - Age < 60 years
  - Women with prior gestational DM
  - Rising A1c despite lifestyle intervention
- B12 monitoring w/ long-term metformin (B)
- Screening/treatment of modifiable risk factors for CV disease (B)
- Diabetes self-management education and support (B)

Diabetes Prevention Program

Results

  - 3,234 participants, overweight, prediabetes
    - 45% from ethnic/racial minorities at increased risk
  - 4 groups
    - Lifestyle intervention:
      - 7% body weight loss
      - 150 minutes/week of exercise
    - Metformin 850 mg 2 times/day
    - Placebo
    - Troglitazone* (stopped due to risk of liver damage)

- 3-year risk of developing diabetes
  - Placebo = 28.9%
  - Metformin = 21.7%
  - Lifestyle intervention = 14.4%
- Lifestyle vs. Placebo (RRR = 58%)
  - Most effective in older adults (≥60 years)
    - reduced risk by 71%
  - RRR = 58%,
  - ARR = 14.5%, NNT = 6.9
- Metformin vs. Placebo
  - Most effective in young adults (25 to 44 years) with BMI ≥35 kg/m²
  - Least effective in middle age adults (>45 years)
    - Not significantly better than placebo in older adults (≥60 years)
  - RRR = 31%,
  - ARR = 7.2%, NNT = 13.9

Diabetes Prevention Program Outcomes Study

**Lifestyle Modification**
- Reduced development of DM vs. placebo
  - 34% (RRR)
  - 49% in those 60 years or older (RRR)
  - Delayed type 2 DM by ~4 years
- Reduced cardiovascular risk factors
- Reduced A1C and fasting glucose

**Metformin**
- Reduced development of DM vs. placebo
  - 18% (RRR)
  - Delayed type 2 DM by ~2 years
- Reduced A1C and fasting glucose

Mid-Point Q & A
Comprehensive Medical Evaluation and Assessment of Comorbidities

- Patient-centered communication style to optimize health outcomes/health-related quality of life. (B)
  - Active listening, patient preferences/beliefs.
  - Assess literacy, numeracy, potential barriers to care.
- Comprehensive Medical Evaluation (Initial)
  - Confirm and classify diabetes (B)
  - Detect complications/comorbid conditions (E)
  - Review previous treatment/risk factor control (E)
  - Begin patient engagement in management plan (B)
  - Develop continuing care plan (B)
- Immunizations
  - Routine age-related recommendations (C)
  - Annual influenza ≥ 6 months age (C)
  - Pneumonia vaccine: (C)
    - 2-64 y/o: PPSV23
    - ≥ 65 y/o: PCV13
      - (at least 1 yr after PPSV23)
      - (follow w/ 2nd PPSV23 – at least 1 yr later and 5 yrs after last PPSV23)
  - Hepatitis B, 3 doses:
    - Unvaccinated adults 19-59 y/o (C)
    - Consider in unvaccinated adults ≥ 60 y/o (C)
- Consider screening type 1 patients for autoimmune thyroid/celiac disease shortly after diagnosis. (E)
- People w/ cognitive impairment/dementia, treatment to avoid significant hypoglycemia (B)
Comprehensive Medical Evaluation and Assessment of Comorbidities

- In patients w/ HIV (E)
  - screen for DM & prediabetes with fasting glucose
    - Every 6-12 months before starting antiretroviral tx
    - Every 3 months after starting or changing antiretroviral tx
  - If initial screen normal, recheck every year
  - If prediabetes detected, recheck every 3-6 months

- Anxiety disorders, consider screening:(B)
  - If anxiety/worries (about complications, insulin injections, medications, hypoglycemia) interfere w/ self-management.
  - In those w/ fear, dread, irrational thoughts, avoidance or excessive repetitive behaviors, social withdrawal.

- Depression screening
  - Annually in patients w/ DM, especially if h/o depression. (B)
  - Consider at complication diagnosis/significant change in medical status. (B)
Comprehensive Medical Evaluation and Assessment of Comorbidities

- **Disordered Eating**
  - Consider reevaluation of treatment for those with symptoms of disordered eating behavior, an eating disorder, or disrupted patterns of eating. (B)
  - Consider screening for disordered/disrupted eating when hyperglycemia and weight loss are unexplained (based on self-reports of behavior related to medications, meal plan, and physical activity). Review treatment plan for effects on hunger/caloric intake. (B)

- **Serious Mental Illness**
  - Annually screen for prediabetes/DM in those on atypical antipsychotics. (B)
  - If second-generation antipsychotic prescribed for adolescents/adults with DM, carefully monitor for changes in weight, glycemic control, cholesterol level. (C)
  - Incorporate monitoring of DM self-care into treatment goals in people w/ DM and serious mental illness (B)
Lifestyle Management

- Diabetes self-management education (DSME) and support (DSMS)
  - Recommended in all people with DM, to facilitate knowledge, skills and ability necessary at diagnosis and thereafter (B)
  - Measure/monitor health status, quality of life as part of routine care (C)
  - Should be patient-centered, respectful, responsive to preference, needs and values (A)
  - Focused on prevention in prediabetes (B)
  - Can improve outcomes/reduce cost (B)
  - Should be third-party reimbursed (E)
- Medical Nutrition Therapy
  - (see reference)

- Physical Activity
  - Children: (C)
    - ≥ 60 mins/day moderate/vigorous aerobic + muscle/bone strengthening ≥ 3 days/week.
  - Adults w/ type 1 (C) and type 2 DM (B):
    - > 150 mins/week moderate intensity over ≥ 3 days with no more than 2 consecutive days without activity.
    - Resistance training 2-3 sessions/week on non-consecutive days.
  - Decrease sedentary behavioral in all.
  - Interrupt prolonged sitting every 30 mins for blood glucose benefits in type 2 (C)
  - Flexibility/balance 2-3 x/week in older adults w/ DM. may consider yoga/tai chi (C)
Lifestyle Management

• Smoking Cessation: Tobacco & e-Cigarettes
  – Advise all patients not to use cigarettes, other tobacco products (A) or e-cigarettes. (E)
  – Include smoking cessation counseling/treatment as a routine part of diabetes care (B)

• Diabetes Distress
  – Routinely monitor for diabetes distress, particularly when treatment targets not met and/or at onset of diabetes complications.

• Psychosocial Assessment and Care
  – Psychosocial care should be integrated with a collaborative, patient-centered approach with goal of optimizing outcomes and health-related quality of life. (A)
  – Psychosocial screening/follow-up: attitudes about illness, expectations of management/outcomes, affect/mood, quality of life, resources (financial, social, emotional), and psychiatric history. (E)
  – Consider assessment for diabetes distress, depression, anxiety, disordered eating, cognitive capacities at diagnosis and periodically (B)
  – Consider screening older adults ≥ 65 for cognitive function/depression screening/treatment (A)
FDA-Approved Diabetes Medications

**Insulin / Insulin Releasers**

- Secretagogues
  - Sulfonylureas
  - Meglitinides ("glinides")
- Analogs (Insulin)
  - Rapid/Short/Intermediate/Long-acting
  - Inhaled (-unavailable?)

**Euglycemics**

- Insulin Sensitizers
  - Biguanides, Thiazolidinediones (TZDs)
- SGLT2 Inhibitors
- α-glucosidase inhibitors
- GLP-1 analogs (subcutaneous)
- DPP4-inhibitors (oral)
- Amylin analogs
- Others
  - Dopamine-receptor agonists
  - Bile acid sequestrants
Sulfonylureas

- **1st Generation**
  - chlorpropamide
    - *Diabinese*
  - tolbutamide
    - *Orinase*
  - tolazamide
    - *Tolinase*

- **2nd Generation**
  - glimepiride
    - *Amaryl*
  - glyburide
    - *Diabeta*, *Glycron*, *Glynase*
  - glipizide
    - *Glucotrol*

- Stimulate insulin secretion
  - Expected A1C reduction = 1-2%

- Advantages
  - Rapid onset of action

- Disadvantages
  - Hypoglycemia
  - Weight gain (~ 2kg)
  - Poor maintenance of glucose targets

* No longer marketed under brand name.

Meglitinides (“Glinides”)

- Repaglinide  
  - Prandin
- Nateglinide  
  - Starlix

- Stimulate insulin secretion
  - Very similar to sulfonylureas
  - Expected A1C reduction = 0.5-1.5%

- Advantages
  - Rapid onset of action / short duration

- Disadvantages
  - Short duration (mealtime dosing)
  - Hypoglycemia
2. Which of the following medication classes can, on average, achieve the greatest decrease in A1C alone?

A. A thiazolidinedione (e.g. pioglitazone)
B. An SGLT-2i (e.g. canagliflozin)
C. A biguanide (e.g. metformin)
D. A DPP-4i (e.g. sitagliptin)
E. A meglitinide (e.g. repaglinide)
Mrs. M is a 66-year-old female with a long-standing diagnosis of type 2 diabetes. She has used metformin at a dose of 1000 mg twice daily for 8 years, adding insulin glargine to her regimen 3 years ago. Under your direction, she has titrated the insulin glargine to 40 units at bedtime daily. You have followed Mrs. M closely since her renal function began to worsen 2 years ago. On her recent lab work, you noticed that she now has CKD 3a since her eGFR is now at 40.
Pre-Assessment Question – Case #1

3. What is the most immediate medication course of action, given the finding of worsening renal function in this patient?

A. Stop metformin immediately, adding an SGLT-2 inhibitor to compensate.
B. Decrease her insulin glargine to compensate for lack of renal clearance.
C. Add a DPP-4 inhibitor to improve renal function.
D. Continue metformin at current dose; continuing to closely monitor renal function.
E. Change insulin glargine to rapid-acting insulin three times daily.
Insulin Sensitizers

• Biguanides
  – Metformin
    • Glucophage, Glucophage XR, Fortamet, Glumetza, Riomet – liquid

• TZDs
  – Pioglitazone
    • Actos
  – Rosiglitazone
    • Avandia
Biguanides = Metformin

- Decrease hepatic glucose output
  - Expected A1C reduction = 1-2%
  - Weight neutral, Low risk of hypoglycemia
  - Nausea, diarrhea
- Long-term use associated with B12 deficiency
  - Recommend "periodic monitoring"

### Metformin dosing and use

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>eGFR</th>
<th>Metformin dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>60-&lt;90</td>
<td>2550 mg</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>45-&lt;60</td>
<td>2000 mg</td>
<td>Monitor renal function closely, avoid if unstable</td>
</tr>
<tr>
<td>3b</td>
<td>30-&lt;45</td>
<td>1000 mg</td>
<td>Don’t start metformin, monitor closely, stop if unstable</td>
</tr>
<tr>
<td>4</td>
<td>&lt;30</td>
<td>-</td>
<td>DO NOT USE</td>
</tr>
</tbody>
</table>


* NOT TESTED IN A CLINICAL TRIAL, NOT FROM FDA REVIEW
TZDs

• Sensitize muscle/fat/liver to insulin
  – Expected A1C reduction = 0.5-1.4%
  – Weight gain, fluid retention (CHF)
• Rosiglitazone access restrictions lifted Nov 2013

• NEW 2016:
  – Pioglitazone associated with higher risk of bladder cancer (again).
    • (not Rosiglitazone)
    • 63% increase risk
      – Worse w/ increased dose/duration

Mrs. M has remained on metformin and insulin glargine for several more months, with no further significant reduction in her renal function. She continues to have good AM fasting blood sugars averaging around 110 mg/dL. Despite this, her A1c is above goal at 8.2%, and she has noticed that her fasting blood sugars before lunch and dinner are now much higher, averaging 190 mg/dL. She would like to continue to maintain good blood sugar control.
Pre-Assessment Question – Case #2

4. What is the best medication change at this time?

A. Increase her insulin glargine by at least 50% to better control pre-meal blood sugar.
B. Add a GLP-1 (daily or weekly) to achieve a better blood sugar control at least risk of hypoglycemia.
C. Add pre-meal insulin to reduce overall risk of hypoglycemia.
D. Stop metformin because it is likely causing hyperglycemia as a response to metabolic acidosis.
E. Change insulin glargine to rapid-acting insulin three times daily.
Incretins / Incretin Mediators

- **GLP-1 Receptor Agonist = (Incretin mimetics)**
  - Exenatide
    - *Byetta, Bydureon*
  - Liraglutide*
    - *Victoza*
  - Albiglutide
    - *Tanzeum*
  - Dulaglutide
    - *Trulicity*

- **DPP-4 inhibitors = (Incretin enhancers)**
  - Sitagliptin
    - *Januvia*
  - Saxagliptin
    - *Onglyza*
  - Linagliptin
    - *Tradjenta*
  - Alogliptin
    - *Nesina*
Incretins

- Intestinal hormones
  - Glucagon-like peptide 1 (GLP-1)
  - Gastric Inhibitory Peptide (GIP)
- Stimulated by eating
  - \( \uparrow \) insulin/\( \downarrow \) glucagon
    - Release insulin in glucose-dependent manner
- Slowed gastric emptying
  - (?) decreased food intake
- Result
  - Lower blood glucose
  - Slowed appearance in circulation

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www.deo.ucsf.edu
GLP-1-RA (Incretin Mimetics)

• Long-lasting analog of GLP-1
  – Expected A1C reduction = 0.5-1.5%

• Advantages
  – Lowers postprandial glucose
  – Weight loss ~ 2-3 kg/6 months
    • (Liraglutide 3 mg daily (Saxenda) FDA-approved for weight loss)
  – Weekly forms (exenatide ER, albiglutide, duraglutide)

• Disadvantages
  – Require subcutaneous injection
  – GI side effects – nausea/vomiting/diarrhea

• Since 2008: all DM drugs must pass CVOT: Cardiovascular Outcome Trials:
  • In LEADER trial:
    – Liraglutide v. Placebo v. Standard Care
    – Composite Outcome: MI, Stroke, CV Death
      • 13% Liraglutide group
      • 14.9% Placebo group
      • = 13% RRR -or- 1.9% ARR
    – NNT – prevent 1 event (composite) / 3 yrs = 66
    – NNT-prevent 1 death / 3yrs = 98
GLP-1-RA/Insulin combinations

• NEW in November 2016:
• GLP-1 / Ultra-long insulin combinations
  – Insulin degludec/liraglutide (*Xultophy*)
    • (*Tresiba + Victoza*)
  – Insulin glargine/lixisenatide (*Soliqua*)
    • (*Lantus + Adlyxin*)
• Compare to basal or basal+prandial insulin
  – Expected A1c reduction = 1.2-1.8%
  – Less hypoglycemia
DPP-4 Inhibitors (Incretin enhancers)

- Inhibit Dipeptidyl peptidase 4
  - The enzyme that breaks down GLP-1
  - Expected A1C reduction = 0.5-1.0%
  - Weight neutral, well tolerated
  - Do not cause hypoglycemia (as monotherapy)
  - Increase in upper respiratory infections noted

- FDA Warnings:
  - 2015: Risk of severe joint pain with all DPP-4s
  - 2016: Increased risk of heart failure with saxagliptin or alogliptin (and combinations including either)

- CVOT: No significant difference vs. placebo
SGLT2 Inhibitors

- Canagliflozin
  - Invokana
- Empagliflozin
  - Jardiance
- Dapagliflozin
  - Farxiga

- Reduces reabsorption of glucose in kidneys, increases urinary glucose excretion
  - Expected A1C reduction = ~0.5-1.0%
- Insulin Independent!
  - Effective in all stages of Diabetes
SGLT2 Inhibitors

• Advantages
  – Once daily dosing.
  – Weight loss
    • ~ 2 kg over 6-12 months

• Disadvantages
  – Require renal dosing!
  – Adverse reactions
    • Dehydration
    • Genital yeast infection
    • Nasopharyngitis
    • Urinary tract infections
    • Increased LDL-C
    • Bladder cancer

• FDA Warnings:
  – 2016: strengthened existing warnings of Acute Kidney Injury for Canagliflozin & Dapagliflozin
  – 2015: DKA in Type 2 patients with al SGLT2i
SGLT2 Inhibitors

• CVOT:
• In EMPA-REG Outcome trial:
  – Empagliflozin v. Placebo v. Standard Care
  – Composite Outcome: MI, Stroke, CV Death
    • 10.5% Empagliflozin group
    • 12.1% Placebo group
    • = 14% RRR -or- 1.6% ARR
  – NNT – prevent 1 event (composite) / 3 yrs = 61
  – NNT-prevent 1 death / 3yrs = 39

• NOTE: Cannot directly compare Cardiovascular Outcome Trials for different medications head-to-head!
  – They are all done in different patient populations
  – Different inclusion/exclusion
  – Different baseline A1c, medications, …
α-glucosidase inhibitors

• Delay carbohydrate digestion in proximal small intestine
  – Expected A1C reduction = 0.5-0.8%

• Advantages
  – Lower postprandial glucose

• Disadvantages
  – GI side effects – flatulence/diarrhea
    • 25-45% of patients discontinue due to side effects

Amylin

- AKA Islet Amyloid Polypeptide (IAPP)
- Co-secreted with Insulin
- Binds to brain receptors
  - Inhibits glucagon
  - Delays gastric emptying
  - Promotes satiety
- Amylin analogue
  - Pramlintide
  - Only non-insulin drug approved for Type 1 DM

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Pramlinitide

- Synthetic analog of Amylin
  - Expected A1C reduction = 0.5-0.7%

- Advantages
  - Approved for Type 1 and Type 2 Diabetes

- Disadvantages
  - Only approved for use along with insulin
    - Risk of serious hypoglycemia (reduce insulin 50%)
  - Requires subcutaneous injection with meals
  - GI side effect – nausea (~30% of patients)

Other Drugs

• Dopamine Receptor Agonist
  – Quick-release Bromocriptine
    • Mechanism unknown
    • Expected A1C reduction = ~0.5%
    • Advantages
      – Minimal risk of hypoglycemia
    • Disadvantages
      – GI adverse effect - nausea

• Bile-acid sequestrants
  – Colesevelam
    • Mechanism unknown
    • Expected A1C reduction = ~0.5%
    • Advantages
      – Also reduces LDL cholesterol
      – Works in GI tract, not systemically absorbed
    • Disadvantages
      – Raises triglycerides

<table>
<thead>
<tr>
<th>Category</th>
<th>Class</th>
<th>A1C decrease</th>
<th>Drugs</th>
<th>Relative Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitizer</td>
<td>Biguanides</td>
<td>1.0-2.0%</td>
<td>metformin</td>
<td>$ (generic)</td>
</tr>
<tr>
<td></td>
<td>TZDs</td>
<td>0.5-1.4%</td>
<td>pioglitazone, rosiglitazone</td>
<td>$$$$</td>
</tr>
<tr>
<td>Secretagogue</td>
<td>Sulfonylureas</td>
<td>1.0-2.0%</td>
<td>(various)</td>
<td>$ (generic)</td>
</tr>
<tr>
<td></td>
<td>Metaglutinides</td>
<td>0.5-1.5%</td>
<td>repaglinide, netaglinide</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>GLP-1 analog</td>
<td>0.5-1.5%</td>
<td>exenatide, liraglutide</td>
<td>$$$$</td>
</tr>
<tr>
<td></td>
<td>DPP4 inhibitor</td>
<td>0.5-0.8%</td>
<td>sitagliptin, saxagliptin, linagliptin</td>
<td>$$$$</td>
</tr>
<tr>
<td>Others</td>
<td>α-glucosidase inhibitor</td>
<td>0.5-0.8%</td>
<td>miglitol, acarbose</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>Amylin analog</td>
<td>0.5-1.0%</td>
<td>pramlintide</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>Dopamine agonist</td>
<td>~0.5%</td>
<td>bromocriptine</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>Bile acid sequestrant</td>
<td>~0.5%</td>
<td>colesevelam</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td>SGLT2 Inhibitor</td>
<td>~0.5-1.0%</td>
<td>canagliflozin, dapagliflozin</td>
<td>$$$$</td>
</tr>
</tbody>
</table>
Insulin / Analogs

• Most effective at glycemic control
  – Expected A1C reduction = 1.5-3.5%
    • able to lower any A1C to near goal

• Advantages
  – Available in a range of onset/duration

• Disadvantages
  – Requires subcutaneous injection
  – Risk of hypoglycemia
Insulin / Analogs

- **Rapid-Acting**
  - Glulisine
    - Apidra
  - Lispro
    - Humalog
  - Aspart
    - NovoLog
  - Inhaled
    - Afrezza
- **Short-Acting**
  - Regular Human Insulin
    - Humulin R
    - Novolin R
  - Intermediate-Acting
    - NPH Human Insulin (Neutral Protamine Hagedorn)
      - Humulin N
      - Novolin N, Novolin NPH
      - Isophane insulin
  - Long-Acting
    - Glargine
      - Lantus (U100), Basaglar
      - Toujeo (U300) – pen only
    - Detemir
      - Levemir
  - Ultra-Long-Acting
    - Degludec (FDA-approved Oct 2015)
      - Tresiba (U100 & U200) – pen only

Inhaled Insulin

• New in 2016:
  – Doing poorly in market
  – (Sanofi dropped marketing, MannKind continuing)

• Human insulin
  – 4 mg (blue) &
  – 8 mg (green) cartridges
  – Rapid acting
    • Equivalent to lispro
  – Used with Basal insulin
  – Pregnancy class C

• Adverse effects
  – Hypoglycemia (!)
  – Cough (25%)

• Recommend spirometry in all patients
  – Baseline, after 6 months, & annually
    • Small decline in FEV1 in normal patients
  – Not recommended in smokers
  – Contraindicated in COPD/Chronic Lung Disease (asthma)
    • Bronchospasm risk
<table>
<thead>
<tr>
<th>Class</th>
<th>Preparation</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid</td>
<td>Lispro</td>
<td>5 – 15 minutes</td>
<td>1 – 2 hours</td>
<td>4 – 5 hours</td>
</tr>
<tr>
<td></td>
<td>Aspart</td>
<td>5 – 15 minutes</td>
<td>1 – 2 hours</td>
<td>4 – 5 hours</td>
</tr>
<tr>
<td></td>
<td>Glulisine</td>
<td>5 – 15 minutes</td>
<td>1 – 2 hours</td>
<td>4 – 5 hours</td>
</tr>
<tr>
<td></td>
<td>Inhaled (comparable to lispro)</td>
<td>~1 – 2 hours</td>
<td>~2.5 hours</td>
<td></td>
</tr>
<tr>
<td>Short</td>
<td>Regular Human</td>
<td>30 – 60 minutes</td>
<td>2 – 4 hours</td>
<td>8 – 10 hours</td>
</tr>
<tr>
<td>Intermediate</td>
<td>NPH</td>
<td>1 – 2 hours</td>
<td>4 – 8 hours</td>
<td>10 – 20 hours</td>
</tr>
<tr>
<td>Long</td>
<td>Detemir</td>
<td>1 – 2 hours</td>
<td>Flat</td>
<td>12 – 20 hours</td>
</tr>
<tr>
<td></td>
<td>Glargine</td>
<td>1 – 2 hours</td>
<td>Flat</td>
<td>20 – 24 hours</td>
</tr>
<tr>
<td>Ultra-long</td>
<td>Degludec</td>
<td>30 – 90 minutes</td>
<td>Flat</td>
<td>&gt; 24 hours (half-life 25 hours)</td>
</tr>
</tbody>
</table>

Glycemic Targets

- American Diabetes Association (ADA)
  - A1C < 7.0%
  - Preprandial
    - 80-130 mg/dL
  - Peak postprandial
    - < 180 mg/dL
    - (1-2 hours after starting meal)

- A1C testing
  - Twice a year in those meeting goals (E)
  - Quarterly in those not meeting goals (or with change in therapy) (E)
  - Use A1C point-of-care testing for timely changes (E)

Pre-Assessment Question

Mr. H is an 84-year-old male with long-standing DM type 2, h/o MI, and s/p CABG, with stage 2 CKD. He now returns with an A1C of 6.8%. He reports no significant symptoms but has had occasional AM fasting blood sugars down to mid-60s. On other mornings he notes blood sugars as high as 182 mg/dL. You take his blood sugar and it is currently 58 mg/dL.

5. What is the best approach to the continued care of this patient?
   A. No change to his medications, because his A1C is within the goal range, thereby reducing his risk of further cardiovascular complications.
   B. Change his medication regimen to prevent hypoglycemia, considering a new A1C goal possibly as high as 8.0%.
   C. Increase his medications to achieve an A1C goal of 6.5% in order to further reduce his risk of cardiovascular disease, because it is the diabetic complication associated with greatest mortality.
   D. Keep his A1C goal at 7.0% but consider a change to insulin to better control his glycemic swings.
   E. Ask him to perform fingerstick blood glucose checks 3 or 4 times daily to guide any medication changes.
A1C Goals – nonpregnant adults

- <7% most (A)
  - Reduces microvascular complications
- <6.5% if no hypoglycemia or adverse events (C)
  - Short duration of DM
  - Type 2 DM on lifestyle or metformin only
  - Long life expectancy
  - No significant CVD

- <8% or higher (B)
  - H/O severe hypoglycemia
  - Limited life expectancy
  - Advanced micro-macrovascular complications
  - Extensive comorbid conditions
  - Long-standing diabetes / difficult to control

Hypoglycemia

- Ask at-risk patients about hypoglycemia (symptomatic or asymptomatic) at each encounter. (C)
- Treat hypoglycemia (“Rule of 15s”) (E)
  - Glucose 15-20 g preferred
  - Any carbohydrate acceptable
  - Check blood sugar after 15 minutes
  - Repeat glucose 15-20 g if hypoglycemia persists
  - Once blood sugar normal, consume meal or snack

- Prescribe glucagon for those at risk of severe hypoglycemia. Instruct family members and caregivers in administration. (E)
- In those with severe hypoglycemia or unawareness:
  - Reevaluate treatment (E)
  - If insulin treated, raise glycemic goal for several weeks (to partially reverse hypoglycemia unawareness) and reduce risk of further episodes (A)
- If low/declining cognition, increased hypoglycemia vigilance by clinician, patient and caregivers (B)

Pharmacologic Therapy for Type 2

- **Monotherapy**
  - Metformin is preferred initial agent (A) (remember B12!)
  - Consider insulin in newly diagnosed
    - Symptomatic and/or markedly elevated glucose / A1C (E)
- **Dual Therapy**
  - A1C not at goal after 3 months on (non-insulin) monotherapy
    - Add second oral, GLP-1 RA, or basal insulin (A)
  - Use patient-centered approach to choice of agent. (E)
    - Consider efficacy, cost, side effects, weight, comorbidities, hypoglycemia risk, patient preference
  - For those not achieving glycemic goals **Insulin therapy should not be delayed** (B)
  - w/ long-standing suboptimally controlled type 2 DM and established ASCVD, consider empagliflozin or liraglutide. (B)

Antihyperglycemic Therapy in T2DM

American Diabetes Association Standards of Medical Care in Diabetes. Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74
Combination Injectable Therapy in T2DM

Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent
- Start: 10 U/day or 0.1-0.2 U/kg/day
- Adjust: 10-15% or 2-4 units once or twice weekly to reach FBG target
- For hypo: Determine and address cause; if no clear reason for hypo, dose by 4 units or 10-20%

If AIC not controlled, consider combination injectable therapy

Add 1 rapid-acting insulin injection before largest meal
- Start: 4 units, 0.1 U/kg, or 10% basal dose. If AIC >8%, consider basal by same amount
- Adjust: + dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

If AIC not controlled, advance to basal-bolus

Add GLP-1 RA
If not tolerated or AIC target not reached, change to 2 injection insulin regimen
- If goals not met, consider changing to alternative insulin regimen

Change to premixed insulin twice daily (before breakfast and supper)
- Start: Divide current basal dose into 1/3 AM, 1/6 PM or 1/6 AM, 1/6 PM
- Adjust: + dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

If AIC not controlled, advance to 3rd injection

Add ≥2 rapid-acting insulin injections before meals (basal-bolus)
- Start: 4 units, 0.1 U/kg, or 10% basal dose/meal. If AIC >9%, consider basal by same amount
- Adjust: + dose(s) by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

If goals not met, consider changing to alternative insulin regimen

Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)
- Start: Add additional injection before lunch
- Adjust: + doses by 1-2 units or 10-15% once or twice weekly to achieve SMBG target
- For hypo: Determine and address cause; if no clear reason for hypo, corresponding dose by 2-4 units or 10-20%

American Diabetes Association Standards of Medical Care in Diabetes. Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74
Pharmacologic Therapy for Type 2

- **Monotherapy**
  - Metformin
    - *Consider using eGFR ≥ 30 mL/min*
    - If contraindicated/not tolerated, then use 2nd line:
      - Avoid Sulfonylureas
        - hypoglycemia risk
      - DPP-4 inhibitors preferable

- **Combinations to avoid:**
  - DPP-4-i + GLP-1-RA
    - Affect same pathway
  - Multiple-dose insulin + Sulfonylurea (any Insulin Secretagogues)
    - Need implies significant β-cell dysfunction

# DM Goals in Elderly

<table>
<thead>
<tr>
<th>Health</th>
<th>Life Expectancy</th>
<th>A1C goal</th>
<th>Fasting or prandial goal (mg/dL)</th>
<th>Bedtime glucose goal (mg/dL)</th>
<th>Blood Pressure goal (mm/Hg)</th>
<th>Lipid Treatment (unless contraindicated/not tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (few chronic conditions, good cognition)</td>
<td>Longer</td>
<td>&lt;7.5%</td>
<td>90-130</td>
<td>90-150</td>
<td>&lt;140/90</td>
<td>Statin</td>
</tr>
<tr>
<td>Intermediate (multiple chronic conditions, mild-moderate cognitive impairment)</td>
<td>Intermediate</td>
<td>&lt;8.0%</td>
<td>90-150</td>
<td>100-180</td>
<td>&lt;140/90</td>
<td>Statin</td>
</tr>
<tr>
<td>Poor (long-term care, end-stage illness, moderate to severe cognitive impairment)</td>
<td>Limited</td>
<td>&lt;8.5%</td>
<td>100-180</td>
<td>110-200</td>
<td>&lt;150/90</td>
<td>Consider benefit (secondary prevention)</td>
</tr>
</tbody>
</table>

Mr. B is an obese white male with a BMI of 47 kg/m². He has had significant difficulty controlling his blood sugar despite triple oral therapy with metformin, exenatide (a GLP-1) and empagliflozin (an SGLT-2i).

6. The current ADA guidelines recommend consideration of which of the following treatments?

A. Change his GLP-1 agonist to liraglutide and increase dose to stimulate weight loss.
B. Consider bariatric surgery such as a Roux-en-Y gastric bypass.
C. Add an ultra-long-acting insulin to decrease appetite and cause weight loss.
D. Consider a DPP-4i since it should also stimulate weight loss.
E. Add acarbose to cause adverse effects of diarrhea and flatulence.
Obesity Management

- Calculate/document BMI at each visit (B)
- In those willing to lose weight:
  - Prescribe diet, physical activity, behavioral therapy to achieve 5% weight loss (A)
    - Use high-intensity (≥16 sessions in 6 months) interventions, focused on 500-750 kcal/day deficit (A)
    - Diets w/ same caloric restriction (different protein, carbohydrate, fat content) are equally effective (A)
    - If meeting short-term goals, refer to long-term (>1 year) comprehensive weight management programs (A)
  - In selected patients, consider >5% weight loss w/ short-term (3 month) very-low calorie diets (< 800 kcal/day) with trained providers and close medical monitoring (B)
- Pharmacotherapy
  - Consider effect on weight when choosing glucose-lowering meds (E)
  - Minimize meds associated w/ weight gain for comorbid conditions (E)
  - Consider weight loss medications for selected type 2 patients w/ BMI ≥ 27 kg/m² (A)
    - Discontinue meds if < 5% weight loss after 3 months or not tolerated (A)

Metabolic Surgery

- **Recommended** to treat type 2 DM in appropriate surgical candidates (A)
  - w/ BMI ≥ 40 kg/m² regardless of glycemic control
  - adults w/ BMI = 35-39 when inadequately controlled despite lifestyle and optimal medical therapy
- **Considered** w/ BMI 30-34.9 if inadequately controlled despite optimal medical control by oral or injectable medications (B)

- Should be performed in high-volume centers (C)
- Metabolic surgery patients:
  - Require long-term lifestyle support (C)
  - Before surgery should receive comprehensive mental health assessment (B)
  - Surgery postponed w/ h/o alcohol/substance abuse, significant depression, suicidal ideation, other mental health conditions until addressed (E)
  - After surgery, assess need for ongoing mental health services (C)

7. Mr. H. is a 67-year-old Middle Eastern male who was diagnosed with Diabetes several years ago and has had his medication titrated to where he is currently controlled on extended-release glipizide 20 mg. While he usually sees your partner, he came to urgently to see you last week with complaints of episodes of feeling lightheaded, dizzy and clammy. He took his blood sugar when this happened and found it to be 58 mg/dL. He remembers having symptoms like this last summer, but they were not so severe. He does not remember any such episodes last fall or winter.
On further questioning, it turns out that Mr. H. has been fasting during daylight hours for the month Ramadan during these times. He has continued to take his glipizide in the morning.

7. Which simple intervention may help eliminate his hypoglycemic episodes, yet maintain control?
   A. Stop glipizide until Ramadan ends.
   B. Change to a glinide medication taken twice daily.
   C. Forbid Mr. H from participating in the Ramadan fast.
   D. Take glipizide with the evening meal.
Treatment during fasting

- **Ramadan**
  - Holy month of fasting practiced by most Muslims
  - ~ 30 days, fasting during daylight hours.
  - Two daily meals
    - Suhur – meal before dawn
    - Iftar – meal after sunset
  - Ill individuals are exempted from fasting
    - 79% type 2 diabetics fast anyway

Treatment during fasting

- **High Risk**
  - Severe/recurrent hypoglycemia/unawareness
  - Poor glycemic control
  - Ketoacidosis/hyperosmolar coma in last 3 months
  - Acute illness, Intense physical labor
  - Pregnant
  - Advanced macrovascular complications, renal disease, dialysis, cognitive dysfunction

- **Moderate Risk**
  - Well controlled; Treated with short-acting insulin secretagogues, sulfonylureas, insulin +/- oral

- **Low Risk**
  - Well controlled/healthy; Treated with diet alone, metformin, DPP-4 inhibitor, TZD

Ramadan-Medication Adjustment

• Diet-controlled
  – Split calories over two meals
  – Complex carbs (pre-dawn)
  – Simple carbs (sunset)
  – Avoid high fat/sugar foods
  – Adequate fluid intake non-fasting hours

• Orals:
  – DPP4i, ‘glinides,’ TZD at mealtime without adjustment
  – Metformin
    • 1/3 dose pre-dawn
    • 2/3 dose sunset
    • - or – ER at sunset
  – Sulfonylurea
    • Once daily at sunset
    • Twice daily, reduce pre-dawn

1. Prediabetes is defined as a fasting glucose in the range of 100-125 mg/dL, referred to as Impaired Fasting Glucose (IFG) or an A1C in the range of 5.7% to 6.4%, among other criteria. Between these two measures, impaired fasting glucose is a better predictor of subsequent diabetes and cardiovascular disease than is a baseline A1C in the prediabetes range.

A. True
B. False
Post-Assessment Question

2. Which of the following medication classes can, on average, achieve the greatest decrease in A1C alone?

A. A thiazolidinedione (e.g. pioglitazone)
B. An SGLT-2i (e.g. canagliflozin)
C. A biguanide (e.g. metformin)
D. A DPP-4i (e.g. sitagliptin)
E. A meglitinide (e.g. repaglinide)
Case #1

Mrs. M is a 66-year-old female with a long-standing diagnosis of type 2 diabetes. She has used metformin at a dose of 1000 mg twice daily for 8 years, adding insulin glargine to her regimen 3 years ago. Under your direction, she has titrated the insulin glargine to 40 units at bedtime daily. You have followed Mrs. M closely since her renal function began to worsen 2 years ago. On her recent lab work, you noticed that she now has CKD 3a since her eGFR is now at 40.
Post-Assessment Question – Case #1

3. What is the most immediate medication course of action given the finding of worsening renal function in this patient?

A. Stop metformin immediately, adding an SGLT-2 inhibitor to compensate.
B. Decrease her insulin glargine to compensate for lack of renal clearance.
C. Add a DPP-4 inhibitor to improve renal function.
D. Continue metformin at current dose, continuing to closely monitor renal function.
E. Change insulin glargine to rapid-acting insulin three times daily.
Case #2 (Continued)

Mrs. M has remained on metformin and insulin glargine for several more months, with no further significant reduction in her renal function. She continues to have good AM fasting blood sugars averaging around 110 mg/dL. Despite this, her A1c is above goal at 8.2%, and she has noticed that her fasting blood sugars before lunch and dinner are now much higher, averaging 190 mg/dL. She would like to continue to maintain good blood sugar control.
Post-Assessment Question – Case #2

4. What is the best medication change at this time?

A. Increase her insulin glargine by at least 50% to better control pre-meal blood sugar.

B. Add a GLP-1 (daily or weekly) to achieve a better blood sugar control at least risk of hypoglycemia.

C. Add pre-meal insulin to reduce overall risk of hypoglycemia.

D. Stop metformin because it is likely causing hyperglycemia as a response to metabolic acidosis.

E. Change insulin glargine to rapid-acting insulin three times daily.
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Questions
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• Blog: kzooofm.blogspot.com
• Twitter: @pziemkowsk
References


References

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References


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