New Goals for Diabetes and Hypertension in the Very Elderly

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Objectives: Pharmacists

• Upon completion of this activity, pharmacists should be able to:
  1. Identify goals for the treatment of type 2 diabetes and hypertension in the very elderly population
  2. Given a very elderly patient with type 2 diabetes, recommend an appropriate individualized treatment
  3. Given a very elderly patient with hypertension, recommend an appropriate individualized treatment

Objectives: Pharmacy Technicians

• Upon completion of this activity, pharmacy technicians should be able to:
  1. Identify goals for the treatment of type 2 diabetes and hypertension in the very elderly population
  2. Given a very elderly patient with type 2 diabetes, identify potential treatment options
  3. Given a very elderly patient with hypertension, identify potential treatment options

Abbreviations

• A1C: Hemoglobin A1C
• ACC/AHA: American College of Cardiology Foundation/American Heart Association
• ACEIs: Angiotensin Converting Enzyme Inhibitors
• ACCORD: Action to Control Cardiovascular Risk in Diabetes Trial
• ACCOMPLISH: Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension
• ADA: American Diabetes Association
• ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
• AGS: American Geriatric Society
• ARBs: Angiotensin II Receptor Antagonists
• BP: Blood Pressure
• CAD: Coronary Artery Disease
• CV: Cardiovascular
• CVD: Cardiovascular Disease
• DPP-4: Dipeptidyl Peptidase-4
• EWPHE: European Working Party on High Blood Pressure in the Elderly
• GLP-1: Glucagon-Like Peptide-1 agonists
• HF: Heart Failure
• HYVET: Hypertension in the Very Elderly Trial
• LV: Left Ventricle
• MI: Myocardial infarction
• NICE: National Institute for Health and Clinical Excellence
• VADT: Veterans Affairs Diabetes Trial

Elderly versus Very Elderly

• Elderly (Older Adults) – ≥ 65 years of age
• VERY Elderly – ≥ 80 years of age

Disclosure

• I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.
Geriatric Management

Geriatric Facts

Prevalence of diabetes increases with age
- Peaks at 60 to 74 years of age

- From 1995-2004, the overall prevalence of type 2 diabetes in nursing home residents increased from 16 to 23%²
- Absolute risk for cardiovascular disease in older adults is much higher than younger adults³

Older Adults with Diabetes

“Common Geriatric Syndromes”

- Depression
- Cognitive impairment
- Urinary incontinence
- Injurious falls
- Persistent pains
- Risk of hypoglycemia
- Risk of hypotension
- Drug interactions

Increased Risk

Functional Disabilities

Goals of Therapy: Type 2 Diabetes

- Resolution of symptoms (fatigue, polyuria, polydipsia)
- Achieve euglycemia while avoiding hyperglycemia and hypoglycemia
- Prevent/manage microvascular and macrovascular complications
  - Keeping in mind the patient’s life expectancy

Glycemic Goals

- Individually tailored
  1. Comorbidities
  2. Functional status
  3. Life expectancy

California Healthcare Foundation/American Geriatrics Society 2003

- For older persons, target A1C should be individualized
  - Relatively healthy adults with good functional status
    - A1C goal: ≤ 7%
  - Frail older adults, persons with life expectancy of less than 5 years, and others in whom the risks outweigh the benefits of intensive glycemic control
    - A1C goal such as 8% is appropriate
ADA Diabetes Care 2013

- Goals similar to younger adults
  - Functional, cognitively intact, and significant life expectancy
  - Might be reasonably RELAXED for others → A1C goal ≤ 8%
  - History of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions...
  - Avoid hyperglycemia

ADA/AGS 2012 Consensus Report of Diabetes in Older Adults

...Food For Thought...

Is there a harm in lowering A1C to <6.5% in older adults with type 2 diabetes mellitus?

STOP

ACCORD Trial: Diabetes

- 10,251 patients with type 2 diabetes and established cardiovascular disease or at least 2 risk factors
  - Mean age: 62.2 years
  - Mean HbA1C: 8.3%
  - Mean BMI (kg/m²): 32
- Randomized, double-blind
  - Intensive glycemic control: target A1C <6%
  - Standard control target A1C of 7-7.9%
- Primary outcome:
  - First occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes

The trial was stopped early! The intensive glycemic control arm had an increased risk of death

Clinical Pearl: ACCORD Trial

Based on ACCORD...

Patients with type 2 diabetes and high risk of cardiovascular disease:

- A1C target of 7.0 – 7.9% (median of 7.5%)
ADVANCE Trial

- 11,140 patients type 2 diabetes, aged ≥ 55 years with additional risk factor for vascular event, any level of BP, and any level of glucose control with no immediate indication for insulin
  - Mean age: 66 years
  - Mean HbA1C: 7.5%
  - Mean BMI (kg/m²): 28

- Randomized, factorial
  1. Intensive glucose lowering (A1C target of ≤ 6.5% and include gliclazide MR) and routine BP lowering (perindopril/indapamide combination)
  2. Standard glucose therapy and routine BP lowering
  3. Intensive glucose lowering and placebo
  4. Standard glucose therapy and placebo

- Primary composite outcome:
  - Macrovascular (myocardial infarction, stroke, or cardiovascular death) and microvascular (retinopathy or nephropathy) events

Clinical Pearl: ADVANCE Trial

- Pursuing a A1C of 6.5%

  **Beneficial in reducing microvascular events, especially nephropathy BUT caution for severe hypoglycemia and hospitalization**

A1C and Functional Decline

- Longitudinal cohort study
  - 367 participants
  - Mean age: 80 years
  - Community-dwelling, nursing home-eligible individuals with diabetes mellitus

- Outcomes
  - Functional decline or death at 2 years (primary predictor was A1C)

- Results
  - 73% experienced death or functional decline during the study
  - After 2 years
    - Higher A1C was associated with less functional decline or death (P = 0.006)
    - A1C of 8.0% - 8.9% was associated with a lower likelihood of functional decline or death than A1C of 7.0% - 7.9% (relative risk = 0.88, 95% CI= 0.79 - 0.99)

- Conclusion
  - In community-dwelling, fall-eligible individuals with diabetes mellitus, A1C of 8.0% to 8.9% is associated with better functional outcomes at 2 years than A1C of 7.0% to 7.9%

Pharmacotherapy Principle...
Pharmacologic Options

Initiation of Therapy

- Metformin usually first line if no contraindications exist

- A1C goal not achieved on noninsulin monotherapy over 3–6 months
  - Add a second oral agent, a GLP-1 receptor agonist, or insulin

Biguanide

- Metformin (Glucophage®, Glucophage XR®, Glumetza®, Fortamet®, Riomet®)
- Lowers A1C by 1–2%
  - Primarily reduces FPG
  - Reduces weight
- Dose
  - 500 mg PO QID or 1 g PO BID
  - Renal impairment adjust dose
  - Max dose: 2500 mg/d but maximal clinical dose 2 g/day
  - Use dose not recommended in elderly

Advantages:
- Low risk of hypoglycemia
- Low cost

Caution:
- Risk of lactic acidosis
  - Required renal function
  - Contar/lucre
  - Hold prior to procedures using contrast dye
  - Weight neutral
  - Gastrointestinal side effects and Vitamin B12 deficiency

Contraindications:
- Concomitantly to use of insulin
- Diabetic ketoacidosis

Sulfonylureas

- Lowers A1C by 1-2%
  - Reduces fasting and postprandial blood glucose

Use short-acting sulfonylureas
- i.e., Glipizide (Glucotrol®, Glucotrol XL®)
  - 5–20 mg/day given as BID

Advantages:
- Works quickly
- Low cost

Caution:
- Hypoglycemia more common in long-acting formulations
  - Glyburide
  - Glimepiride

Contraindications:
- Type 1 diabetes mellitus
- Diabetic ketoacidosis

Meglinides

- Lowers A1C by 0.5–1%
  - Reduces postprandial blood glucose

- Short-acting
  - Repaglinide (Prandin®): 0.5–1 mg before meals
  - Nateglinide (Starlix®): 120 mg before meals

Advantages:
- Rapid onset of action
- Less hypoglycemia and weight gain than sulfonylureas

Caution:
- Modest weight gain
- Hypoglycemia less than sulfonylureas
- Dosing frequency
- Costly
- Gemfibrozil interaction with nateglinide

Contraindications:
- Diabetic ketoacidosis
- Type 1 diabetes mellitus

α-Glucosidase Inhibitors

- Lowers A1C by 0.5–1%
  - Reduces postprandial blood glucose

Acarbose (Precose®):
- 25 mg with first bite of meal; titrate to TID

Miglitol (Glytarp®):
- 25 mg with first bite of meal; titrate to TID

Advantages:
- Low risk of hypoglycemia

Caution:
- Flatulence and diarrhea
- Dosing frequency
- Costly
- Rare elevation in liver function test
- Weight neutral
- Not widely tested in elderly

Contraindication:
- CrCl < 25 mL/min or SCr > 2 mg/dL
- Inflammatory bowel disease or intestinal obstruction
- Cerebrovascular Accident
Thiazolidinediones

- Considered in some patients:
  - Lower initial A1C values
  - Specific contraindications to metformin, sulfonylureas
  - Unable/unwilling to take insulin
- Lowers A1C by 0.8-1.5%
- Mixed blood glucose lowering
- Pioglitazone (Actos®): 15-45 mg/day
  - Increased risk of bladder cancer
  - Fluid retention and bone loss with pioglitazone
- Rosiglitazone (Avandia®): Increased risk of cardiovascular events

DPP-4 Inhibitors

- Lowers A1C levels by 0.6-0.8%
- Moderately effective
- Reduces primarily postprandial glucose

- Advantages:
  - Low risk of hypoglycemia
  - Well tolerated

- Caution:
  - Limited experience, cost
  - Fluid retention, congestive heart failure, MI and fractures risk
  - Rare hepatotoxicity
  - Weight gain

- Contraindications:
  - Class III or IV heart failure
  - Hepatic disease

GLP-1 Agonists

- Lowers A1C levels by 0.6-1.4%
  - Primarily postprandial with increased levels overnight
- Administered subcutaneously
  - Exenatide (Byetta®): 5 mg SC QD, may titrate to 10 mg
  - Exenatide ER extended release 20mg
  - Liraglutide (Victoza®): 0.6 mg SC QD, may titrate up to 1.8 mg SC QD/day

- Advantages:
  - Low risk of hypoglycemia
  - No priming required

- Caution:
  - Associated with significant weight loss
  - Nausea, vomiting, diarrhea
  - Subcutaneous injections
  - Costly
  - Foot monitoring
    - Acute pancreatitis
    - Determination of renal function

- Contraindications:
  - Avoid in CrCl < 30 mL/min
  - Gastritis, pancreatitis
  - Rosiglitazone: History of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2

Insulin

- Risk of hypoglycemia carefully considered
- Evaluate patient’s physical and cognitive abilities
- If needed, use long acting or intermediate insulin
  - When GFR < 50 mL/min, less insulin is needed

Preventing Complications

- Individualized screening for diabetes complications
  - Pay attention to complications leading to functional impairment
- Cardiovascular risk factors should be treated with considerations
  1. Time frame of benefit
  2. Individual

Microvascular Complications

- Retinopathy
  - Complete eye exam at time of diagnosis and yearly
  - If normal, may consider every 2-3 years
- Nephropathy
  - Annual testing for increased urinary albumin excretion
- Foot
  - Diabetic neuropathy prevalence increases with age
  - Examine at every visit
Cardiovascular Risk Reduction

- Smoking Cessation
- Dyslipidemia
  - Recommends statin except in those with very limited life expectancy
  - LDL goal: < 100 mg/dL
  - CVD
    - Optimal LDL goal: 70-80 mg/dL
    - Similar risk reduction in CVD events to younger adults
- Aspirin
  - AGS: secondary prevention
  - ADA: men > 50, women > 60 years of age with at least 1 additional risk factor
  - Daily low-dose aspirin
- Hypertension
  - Beneficial in all

ADA/AGS 2012 Consensus Report of Diabetes in Older Adults

...Food For Thought...

What about patients without diabetes?

Hypertension in the Very Elderly Trial (HYVET)

- 3,845 patients ≥ 80 years with hypertension
- Randomized, double blind
  - Placebo OR indapamide (sustained release, 1.5 mg) +/- perindopril (2 or 4 mg)
  - Target blood pressure of 150/80 mmHg
- Endpoints
  - Primary: Stroke (fatal and non-fatal)
  - Secondary: Death from any cause, death from cardiovascular causes, death from cardiac causes, and death from stroke
- Stopped early

In very elderly patients...
- BP treatment significantly reduces the risks of death from stroke and death from any cause
ACCF/AHA 2011 Expert Consensus

• Goals for hypertension in the elderly

  – Uncomplicated hypertension
    • Goal: < 140/90 mmHg
  
  – Target **systolic** blood pressure: < 140 mmHg
    • ≥ 80 years of age, may accept 140-145 mmHg

ACCF/AHA 2011 Expert Consensus

• Initial therapy
  – Start at the lowest dose and gradually increase to max tolerated dose
  
  – If...
    • Response is inadequate after reaching full dose, add a second drug
      • No diuretic initially, consider using as the second drug
      • Still inadequate – add a third drug
    • No therapeutic response or significant adverse effects, substitute
    • BP is > 20/10 mm Hg above goal, initiate with 2 antihypertensive drugs
  
    • Before adding new drugs, examine reasons for inadequate response

Pharmacologic Options

Diuretics

• Thiazide diuretics are recommended for initial therapy
  • Hydrochlorothiazide
  • Chlorthalidone
  
    • Caution:
      • Sodium and water depletion may cause orthostatic hypotension
      • Hypokalemia, hypomagnesemia, hypernatremia – increase arrhythmias
      • Hyperuricemia, glucose intolerance, dyslipidemia
  
  – Others
    • Sulfonamide diuretic
      • ie. indapamide
    • Loop diuretics
      • ie. furosemide, bumetanide, torsemide
    • Mineralcorticoid antagonists
      • ie. spironolactone, eplerenone
    • Epithelial sodium transport channel antagonists
      • ie. amiloride, triamterene

NICE Clinical Guidelines 2011
Beta-Blockers

- Indicated for hypertensive patients with certain comorbidities
  - CAD, HF, certain arrhythmias, migraine headaches, senile tremor

- Caution
  - Earlier beta-blockers: depression, sexual dysfunction, dyslipidemia, glucose intolerance

Calcium Channel Blockers

- Useful in patients with...
  - Increasing arterial stiffness
  - Decreased vascular compliance
  - Diastolic dysfunction
  - Certain cardiovascular conditions
    - Angina
    - Supraventricular arrhythmias

- Dihydropyridines
  - Felodipine, amiodipine, nifedipine, nicardipine

- Non-dihydropyridines
  - Verapamil, diltiazem

Caution

- Dihydropyridines:
  - Avoid short-acting rapid-release
  - Venlafaxine
  - IE: urticaria, Rash, angioedema

- Non-dihydropyridines:
  - Can precipitate heart block / underlying conduction defects
  - Avoid nifedipine, verapamil, diltiazem in LV systolic dysfunction

Renin-Angiotensin System

- ACEIs
  - Reduce morbidity and mortality in HF
  - Reduce systolic function post-MI
  - Retard progression of diastolic renal disease

- Caution:
  - Hypotension
  - Chronic dry cough
  - Renal failure
  - Hyperkalemia
  - Rarely:
    - Angioedema
    - Rash
    - Neutropenia
    - Agranulocytosis

- ARBs
  - Considered first line in elderly with diabetes mellitus
  - Alternative to ACEIs in hypertension and HF

- Direct Renin Inhibitors
  - Aliskiren
    - Major side effect: mild diarrhea
  - No data with eGFR < 30 mL/min/1.73 m²

Combination Therapy: ACCOMPLISH Trial

- 11,506 patients with hypertension and at high risk for cardiovascular events
  - Mean age: 68.4 years
  - 60.4% of the patients had diabetes
  - Mean BMI: 31 kg/m²

- Randomized, double-blind
  - Benazepril plus amiodipine OR
  - Benazepril plus hydrochlorothiazide

- Primary composite end point:
  - Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization

ACCOMPLISH Trial: Results

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Mean Age (years)</th>
<th>Mean BMI (kg/m²)</th>
<th>CV Events</th>
<th>CV Mortality</th>
</tr>
</thead>
<tbody>
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<td>Benazepril + Amlodipine</td>
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</tbody>
</table>

Clinical Pearl: ACCOMPLISH Trial

In high-risk patients with hypertension
- Benazepril + amiodipine is superior in reducing the risk of CV events and of death

Based on the ACCOMPLISH trial...

Combination of Benazepril + Amlodipine is superior to Benazepril + Hydrochlorothiazide in reducing morbidity and mortality
Meet Your Patient: GP

• GP is an 85 year old African American male who presents to your MTM clinic...

Meet Your Patient: GP

• Past Medical History:
  – Hypertension
  – Hyperlipidemia
  – Diabetes
  – Benign prostatic hyperplasia
  – Gastroesophageal reflux disease
  – Mild dementia
  – Osteoarthritis
• Allergies: No Know Drug Allergies
• Family History:
  – Father: Deceased – Diabetes, Hypertension;
  – Mother: Deceased – Hypothyroidism
• Social History:
  – Smokes 5-6 cigarettes/day; No intentions to quit
• Medications:
  – Amlodipine 5 mg PO QDAY
  – Metoprolol Tartrate 50 mg PO QDAY
  – Enalapril Maleate 20 mg PO QDAY
  – Simvastatin 40 mg PO QHS
  – Metformin 1000 mg PO BID
  – Glyburide 5 mg PO BID
  – Doxazosin 8 mg PO QHS
  – Omeprazole 20 mg PO QOD
  – Naproxen 200 mg PO PRN

Meet Your Patient: GP

• Vitals:
  – Temp 98.2 F
  – Ht: 62 in
  – Wt: 154.6 lbs
  – BMI: 28 kg/m²
  – BP: 162/80 mm Hg
  – RR: 18
  – LDL: 92 TG: 78 HDL: 42
  – Chem-8 142 106 22
    4.4 26.6 1.7
  – Hemoglobin: 9.8 mg/dL

Meet Your Patient: GP

• What are his drug-related problems?
• What is the patient’s A1C goal based on ADA? Based on ADA/AGS 2012 Consensus Report?
• What is the patient’s BP goal based on ADA/AGS 2012 Consensus Report?
  – If he did not have type 2 diabetes, what would be his BP goal based on ACCF/AHA 2011 Consensus Report?

Clinical Pearl: R.E.L.A.X

...with the very elderly

Type 2 Diabetes Mellitus  Blood Pressure

Thank You!
Key References

Diabetes

Hypertension