AMBULATORY UPDATE:
SUPPORTIVE CARE IN CANCER PATIENTS

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Learning objectives

• Compare and contrast mechanism of action, side effect profile, and contraindications of various medications used in the treatment of hypertension, dyslipidemia, and diabetes mellitus with focus on newer agents

• Apply current hypertension, dyslipidemia, and diabetes mellitus treatment standards/guidelines to clinical practice

• Develop complete pharmacotherapeutic plans related to primary care disease states for patients using evidence-based medicine
Role of primary care in management of cancer patients

- New models of care and targeted drugs are allowing more opportunities for general practitioners and pharmacists to deliver oncology services to patients to enhance outcomes
- Call for more integration of care across disciplines
Hypertension background

- One-third of adults (~80 million people) in the United States have hypertension (HTN)
- Costs associated w/HTN > $46 billion in 2011
- ~54% of those with HTN are adequately controlled
- Most common condition encountered by primary care providers in clinical practice
- High prevalence of HTN in the U.S. is being driven by ↑ age of population and growing number of obese individuals
- Controversy regarding blood pressure targets

Updates in HTN therapy

• What are the appropriate targets for blood pressure control?

• Paucity of evidence led to JNC 8 recommendation for target BP of <150/90 mmHg for patients ≥ 60 years of age

• Recommendation for target of <140/90 mmHg for younger patients based on expert opinion
JNC 8 key recommendations

• **Patients aged ≥ 60 years**- initiate therapy if SBP ≥ 150 mmHg OR DBP ≥ 90 mmHg and treat to <150/90 mmHg (if well tolerated <140 mmHg is acceptable)

• **Patients < 60 years**- initiate therapy if SBP ≥ 140 mmHg and treat to < 140 OR initiate therapy if DBP ≥ 90 mmHg to a goal <90 mmHg

• **Nonblack initial therapy**- thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)

• **Black initial therapy**- thiazide or CCB

• **Patients ≥ 18 years w/CKD and SBP ≥ 140 mmHg or DBP ≥ 90 mmHg**- goal <140/90 mmHg

ASH/ISH clinical practice guidelines

- Most recommendations are consistent with other guidelines (e.g. JNC 8)
- Choice of medications can also be influenced by other conditions
  - *Diabetes mellitus*
  - *Chronic kidney disease*
  - *Coronary artery disease*
  - *Stroke history*
  - *Heart failure*
  - Pregnancy

# ASH/ISH clinical practice guidelines

**HTN plus other conditions**

<table>
<thead>
<tr>
<th>Patient type</th>
<th>First drug</th>
<th>Add 2(^{nd}) drug</th>
<th>If 3(^{rd}) drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN and DM</td>
<td>ACEI or ARB (if black, CCB or thiazide)</td>
<td>CCB or thiazide</td>
<td>Alternative 2(^{nd}) drug</td>
</tr>
<tr>
<td>HTN and CKD</td>
<td>ACEI or ARB</td>
<td>CCB or thiazide</td>
<td>Alternative 2(^{nd}) drug</td>
</tr>
<tr>
<td>HTN and CAD</td>
<td>BB+ ACEI or ARB</td>
<td>CCB or thiazide</td>
<td>Alternative 2(^{nd}) drug</td>
</tr>
<tr>
<td>HTN and stroke history</td>
<td>ACEI or ARB</td>
<td>CCB or thiazide</td>
<td>Alternative 2(^{nd}) drug</td>
</tr>
<tr>
<td>HTN and HF</td>
<td><em><strong>patients with systolic dysfunction should receive ACEI or ARB + BB + diuretic + spironolactone</strong></em></td>
<td><em><strong>if needed, DHP-CCB can be added for HTN control</strong></em></td>
<td></td>
</tr>
</tbody>
</table>

SPRINT*

- *Systolic Blood Pressure Intervention Trial
- Randomized, open-label evaluating intensive versus standard blood pressure in nondiabetic adults > 50 years of age
- Primary composite outcome of myocardial infarction (MI), other acute coronary syndrome (ACS), heart failure (HF), or death from cardiovascular (CV) causes
- 9361 patients at high risk for cardiovascular events randomly assigned to standard (< 140 mmHg) versus aggressive (< 120 mmHg) control
- Mean BP in standard group 134.6 mmHg versus 121.5 mmHg in intensive group
- Stopped early after mean follow-up of 3.26 years with aggressive control favored
# SPRINT primary and secondary outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intensive treatment, n (%) (n=4678)</th>
<th>Standard Treatment, n (%) (n=4683)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
<th>NNT over 3.26 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>243 (5.2)</td>
<td>319 (6.8)</td>
<td>0.75 (0.64-0.89)</td>
<td>&lt;0.001</td>
<td>61</td>
</tr>
<tr>
<td>HF</td>
<td>62 (1.3)</td>
<td>100 (2.1)</td>
<td>0.62 (0.45-0.84)</td>
<td>0.002</td>
<td>125</td>
</tr>
<tr>
<td>CV mortality</td>
<td>37 (0.8)</td>
<td>65 (1.4)</td>
<td>0.57 (0.38-0.85)</td>
<td>0.005</td>
<td>172</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>155 (3.3)</td>
<td>210 (4.5)</td>
<td>0.73 (0.60-0.90)</td>
<td>0.003</td>
<td>90</td>
</tr>
<tr>
<td>MI</td>
<td>97 (2.1)</td>
<td>116 (2.5)</td>
<td>0.83 (0.64-1.09)</td>
<td>0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke</td>
<td>62 (1.3)</td>
<td>70 (1.5)</td>
<td>0.89 (0.63-1.25)</td>
<td>0.50</td>
<td>NS</td>
</tr>
</tbody>
</table>

SPRINT

- Hypotension, acute worsening of renal function, syncope, and electrolyte disturbances more frequently seen in aggressively managed group
- 28% of SPRINT participants were ≥ 75 years of age
- How feasible is such an aggressive BP target clinically?

Medications/substances which may cause resistant HTN

- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Sympathomimetics
  - Decongestants
  - Stimulants
- Cocaine, amphetamines
- Recent caffeine or alcohol intake
- Oral hormonal contraceptives
- Adrenal steroid hormones
- Erythropoietin
- Natural licorice
- Cyclosporine, tacrolimus
- Herbal products
  - Ma huang
  - Bitter orange
Choosing pharmacotherapy

- Think evidence-based medicine
- Remember ease of administration/dosing
- Consider co-morbid conditions and compelling indications (e.g. past medical history, renal and hepatic function, electrolytes, allergies, etc.)
- Check co-prescribed medications and assess for drug interactions
- Take cost/patient’s prescription drug insurance formulary into consideration (many $4 generic medication formularies available at retail pharmacies)
Antihypertensive classes

• Diuretics
  – Thiazides
  – Loops
  – Potassium-sparing aldosterone antagonists (AAs)
• β-blockers (BBs)
• Calcium channel blockers (CCBs)
  – Dihydropyridine (DHP-CCB)
  – Non-dihydropyridine (NDHP-CCB)
• Angiotensin-converting enzyme inhibitors (ACEIs)
• Angiotensin receptor blockers (ARBs)
• Renin inhibitor
• α₁-blockers
• Direct vasodilators
• Central α₂-agonists
• Peripheral sympathetic inhibitors
REFRACTORY HTN: INCREASE MONOTHERAPY OR SWITCH TO COMBINATION THERAPY?
A 63-year-old African-American female presents to the clinical pharmacist practitioner for primary care management. Past medical history is significant for hypertension and major depressive disorder. Self-reported current medications include amlodipine 10 mg PO daily, lisinopril 40 mg PO daily, and citalopram 40 mg PO daily. She reports NKDA. Vitals today in clinic include a blood pressure of 162/92 mmHg (166/92 mmHg recheck), pulse 64 beats/minute, weight 88 kg, and respiratory rate 16 breaths/min. Most recent basic metabolic panel shows Na+ =136 mmol/L, K+ =3.5 mmol/L, and Scr =1.1 mg/dL. Upon further review of the patient’s electronic medical record, past blood pressures have been 172/90 mmHg and 166/88 mmHg, respectively. What would be the most reasonable medication to add next to her current antihypertensive regimen?

- a. Losartan 25 mg PO daily
- b. Spironolactone 25 mg PO daily
- c. Chlorthalidone 25 mg PO daily
- d. Metoprolol XL 25 mg PO daily
Diabetes mellitus (DM) background

• A group of chronic metabolic disorders characterized by hyperglycemia that may result in long-term microvascular and neuropathic complications
• Complications contribute to leading causes of new cases of blindness, end-stage renal disease, and nontraumatic lower limb amputations
• Macrovascular complications are also associated with DM
  – Coronary artery disease
  – Peripheral vascular disease
  – Stroke

Epidemiology and etiology

- DM affects almost 30 million people in the United States
- Total financial impact ~ $245 billion in 2012
- DM is characterized by complete lack of insulin, a relative lack of insulin, or insulin resistance
- ↑ prevalence of DM is influenced by lifestyle, ethnicity, and age
Classification of diabetes mellitus

- Type 1 diabetes mellitus (T1DM)
- Type 2 diabetes mellitus (T2DM)
- Latent autoimmune diabetes in adults (LADA)
- Gestational diabetes (GDM)
- Diabetes due to other causes
Key points regarding most recent practice recommendations

• Recommendations/guidelines are less prescriptive as previous recommendations
• Wide array of pharmacologic agents are now available for the treatment of T2DM
• Important to use a multidisciplinary, collaborative, patient-centered approach in the treatment of DM
• Meeting goals of therapy, side effect profile, contraindications, comorbidities, and cost of medications must be considered on a patient-by-patient basis

Diabetes types

• Type 1 DM is usually diagnosed by age 30 years and is marked by autoimmune destruction of pancreatic β-cells

• Type 2 DM affects ~90-95% of all diagnosed cases of DM and is progressive in development
  – Combination of insulin deficiency, insulin resistance, and other hormonal irregularities
  – Majority of those with T2DM are overweight

• Gestational diabetes
What about Diabetes “1.5”? 

• **Latent autoimmune diabetes in adults** (LADA), slow-onset type 1, or type 1.5 DM, is a form of autoimmune T1DM that occurs in individuals older than the usual age of T1DM onset

• Patients often are mistakenly thought to have T2DM because the person is older and may respond initially to treatment with oral blood glucose-lowering agents

• Patients do not have insulin resistance, but antibodies are present in the blood that are known to destroy pancreatic β cells

• **C-peptide**, a surrogate marker for insulin secretion, may be used to establish or verify a diagnosis of T1DM
### Clinical presentation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T1DM</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual age of onset</td>
<td>Childhood or adolescence</td>
<td>Adult</td>
</tr>
<tr>
<td>Speed of onset</td>
<td>Abrupt</td>
<td>Gradual</td>
</tr>
<tr>
<td>Family history</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Body type</td>
<td>Thin</td>
<td>Obese or history of obesity</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>No</td>
<td>Often</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Present</td>
<td>Rare</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Polyuria, polydipsia, polyphagia, rapid weight loss</td>
<td>Asymptomatic (well...)</td>
</tr>
<tr>
<td>Ketones at diagnosis</td>
<td>Present</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Acute complications</td>
<td>Diabetic ketoacidosis (DKA)</td>
<td>Rare</td>
</tr>
<tr>
<td>Microvascular complications at diagnosis</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Macrovascular complications at or before diagnosis</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

### Diagnostic criteria and categories for DM

<table>
<thead>
<tr>
<th></th>
<th>DM</th>
<th>Prediabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C, %</td>
<td>≥ 6.5</td>
<td>5.7-6.4</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>≥ 126</td>
<td>100-125</td>
</tr>
<tr>
<td>2-h glucose, mg/dL</td>
<td>≥ 200</td>
<td>140-199</td>
</tr>
<tr>
<td>Random glucose in patients with classic symptoms of DM, mg/dL</td>
<td>≥ 200</td>
<td>N/A</td>
</tr>
</tbody>
</table>

# Current recommendations for CVD risk factor management in T2DM

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relevant statement or guidelines</th>
<th>Specific recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition</td>
<td>“Nutrition Therapy Recommendations for the Management of Adults with Diabetes”</td>
<td>↓ energy intake Carbohydrate monitoring Salt restriction</td>
</tr>
<tr>
<td>Obesity</td>
<td>“2013 AHA/ACC/TOS Guideline for Management of Overweight and Obesity in Adults”</td>
<td>Lifestyle changes can produce a 3-5% weight loss Bariatric surgery for some</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>“Management of Hyperglycemia in T2DM: A Patient-Centered Approach”</td>
<td>Target A1Cs are patient-specific</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>“JNC 8” “Standards of Medical Care in Diabetes-2015”</td>
<td>Most individuals with DM target &lt;140/90 mmHg Consider ACEI or ARB</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>“2013 ACC/AHA Guideline on Treatment of Blood Cholesterol”</td>
<td>Consider those patients with DM aged 40-75 years as well as ASCVD ≥ 7.5% for statin use</td>
</tr>
</tbody>
</table>
## Goals of therapy

<table>
<thead>
<tr>
<th>Area</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glycemia</strong></td>
<td></td>
</tr>
<tr>
<td>A1C</td>
<td>&lt; 7% (0.07; 53 mmol/mol Hgb) • Possible &lt;6.5% or &lt;8% depending on patient</td>
</tr>
<tr>
<td></td>
<td>Evaluate every 3 months until in goal; then every 6 months</td>
</tr>
<tr>
<td>eAG</td>
<td>&lt; 154 mg/dL (8.6 mmol/L)</td>
</tr>
<tr>
<td>Preprandial plasma glucose</td>
<td>80–130 mg/dL (4.4–7.2 mmol/L)</td>
</tr>
<tr>
<td>Peak postprandial plasma glucose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt; 180 mg/dL (10.0 mmol/L)</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>&lt; 140/90 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Evaluate at every visit</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evaluate at diagnosis and/or age 40, then every 1-2 years thereafter</td>
</tr>
<tr>
<td><strong>Monitoring for Complications</strong></td>
<td></td>
</tr>
<tr>
<td>Eyes</td>
<td>Dilated eye exam yearly</td>
</tr>
<tr>
<td>Feet</td>
<td>Feet should be examined at every visit</td>
</tr>
<tr>
<td>Urinary microalbumin</td>
<td>Yearly</td>
</tr>
</tbody>
</table>

Glycemic recommendations for nonpregnant adults with DM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>&lt;6.5%, &lt;7%, &lt;8% (depending on patient)</td>
</tr>
<tr>
<td>Preprandial capillary plasma glucose</td>
<td>80-130 mg/dL</td>
</tr>
<tr>
<td>Peak postprandial capillary plasma glucose</td>
<td>&lt;180 mg/dL</td>
</tr>
</tbody>
</table>

Available antidiabetic agents

- Metformin
- Alpha-glucosidase inhibitors (AG-is)
- Sulfonylureas/meglitinides (glinides) (SUs/GLNs)
- Thiazolidinediones (“glitazones”, TZDs)
- Dipeptidyl-peptidase (DPP)-IV inhibitors (“gliptins”)
- Glucagon-like peptide (GLP)-1 receptor agonists (“tides”)
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors (“flozins”)
- Miscellaneous agents
- Insulins (intravenous, subcutaneous, inhaled)
Mechanisms/sites of action of medications

Metformin:
- ↑ Glucose uptake
- ↓ Gluconeogenesis
- ↓ Glucagon secretion
- ↑ Gluconeogenesis

TZDs:
- ↑ Glucose uptake
- ↑ Insulin sensitivity

Meglitinides, Sulphonylureas:
- ↑ Insulin release
- ↓ Glucagon secretion
- ↑ Insulin secretion

DPP-4i, GLP-1RA:
- ↓ Glucagon secretion
- ↑ Insulin secretion

TZDs:
- ↑ Glucose uptake

GLP-1RA:
- ↓ Gastric emptying
- ↑ GLP-1

DPP-4i:
- ↑ GLP-1

Metformin:
- ↑ GLP-1
- ↓ Glucose absorption

SGLT-2i:
- ↑ Renal glucose excretion
Dipeptidyl-peptidase (DPP)- IV inhibitors

- Sitagliptin, saxagliptin, linagliptin, alogliptin
- MOA-↓ DPP-IV activity, ↑ insulin secretion (glucose-dependent), ↓ glucagon secretion (glucose-dependent)
- Average A1C reduction of ~0.5%-0.9%
- Advantages
  - No hypoglycemia, well tolerated
- Disadvantages
  - Modest ↓ A1C
  - ? Pancreatitis
- Higher cost

Glucagon-like peptide (GLP)-1 receptor agonists

- Exenatide, exenatide (extended-release), liraglutide, albiglutide, dulaglutide
- MOA: ↑ insulin secretion (glucose-dependent), ↓ glucagon secretion (glucose-dependent), slows gastric emptying
- Average A1C reduction of ~0.8%-2%
- Advantages
  - No hypoglycemia
  - Weight reduction
- Disadvantages
  - GI side effects, ? acute pancreatitis, ? thyroid cancer
- High cost

## Comparison of GLP-1 RAs

<table>
<thead>
<tr>
<th></th>
<th>Albiglutide</th>
<th>Exenatide ER</th>
<th>Exenatide</th>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>30 mg SC weekly; can ↑ to 50 mg SC weekly</td>
<td>2 mg SC once weekly</td>
<td>5 mcg SC BID; can ↑ to 10 mcg BID after one month</td>
<td>0.6 mg SC daily X 1 week; 1.2 mg daily then ↑ to 1.8 mg weekly</td>
</tr>
<tr>
<td><strong>Efficacy (↓ A1C)</strong></td>
<td>~1%</td>
<td>~1.3%</td>
<td>~1%</td>
<td>~1.5%</td>
</tr>
<tr>
<td><strong>Monthly cost</strong></td>
<td>$325</td>
<td>~$450</td>
<td>~$450</td>
<td>~$400-600</td>
</tr>
<tr>
<td><strong>Nausea incidence</strong></td>
<td>11%</td>
<td>14%</td>
<td>30%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>Thyroid T-cell tumors</strong></td>
<td>“Black Box” Warning</td>
<td>“Black Box” Warning</td>
<td>GLP-1 RAs have been associated with C-cell tumors in rodents</td>
<td>“Black Box” Warning</td>
</tr>
</tbody>
</table>

## Comparison of GLP-1 RAs

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<thead>
<tr>
<th></th>
<th>Albiglutide</th>
<th>Exenatide ER</th>
<th>Exenatide</th>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pancreatitis</strong></td>
<td>Rare, but consider</td>
<td>Rare, but consider</td>
<td>Rare, but consider</td>
<td>Rare, but consider</td>
</tr>
<tr>
<td><strong>Use in renal impairment</strong></td>
<td>Use caution</td>
<td>Use caution</td>
<td>Use caution</td>
<td>Use caution</td>
</tr>
<tr>
<td><strong>Use in hepatic impairment</strong></td>
<td>Not expected to be of concern</td>
<td>Not expected to be of concern</td>
<td>Not expected to be of concern</td>
<td>Use caution</td>
</tr>
<tr>
<td><strong>Macrovascular outcomes</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Weight loss</strong></td>
<td>0.6 kg</td>
<td>2.3 kg</td>
<td>2.9 kg</td>
<td>2.5 kg</td>
</tr>
</tbody>
</table>

SGLT2 inhibitors

• Canagliflozin, dapagliflozin, empagliflozin
• MOA
  – Sodium-glucose co-transporter 2 (SGLT2) inhibitor thereby ↓ reabsorption of filtered glucose in proximal renal tubule
  – Lowers renal threshold for glucose
  – ↑ urinary glucose excretion, thus ↓ serum glucose
SGLT2 inhibitors

• Average A1C reduction of ~0.5%-0.9%

• Advantages
  – Rarely hypoglycemia
  – Some lowering of blood pressure
  – Weight loss of 0.7-3.5 kg is typical

• Disadvantages
  – ↑urinary tract and genital infections
  – Renal dose adjustment necessary
Comparison of SGLT2 inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>100-300 mg qday</td>
<td>5-10 mg qday</td>
<td>10-25 mg qday</td>
</tr>
<tr>
<td><strong>Efficacy (↓A1C)</strong></td>
<td>0.5-1%</td>
<td>0.5-1%</td>
<td>0.5-1%</td>
</tr>
<tr>
<td><strong>Monthly cost</strong></td>
<td>~$300</td>
<td>~$300</td>
<td>~$300</td>
</tr>
<tr>
<td><strong>Genital mycotic infections</strong></td>
<td>3% in circumcised men vs 11% in uncircumcised men, 10-15% women</td>
<td>7.6% in women vs 1.5% placebo and 2.7% in men vs 0.3% men placebo</td>
<td>1.6%-3.4% in men vs 0.4% placebo, 5.4%-6.4% in women vs 1.5% placebo</td>
</tr>
<tr>
<td><strong>Urinary tract infections</strong></td>
<td>4.3-5.3% vs 4% placebo</td>
<td>5% vs 3.7% placebo</td>
<td>7.6%-9.3% vs 7.6% placebo</td>
</tr>
<tr>
<td><strong>Bladder cancer</strong></td>
<td>No apparent ↑ risk</td>
<td>10/6045 (0.17%) vs 1/3512 (0.03%) placebo</td>
<td>Incidence low and comparable to placebo</td>
</tr>
</tbody>
</table>

## Comparison of SGLT2 inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in renal impairment</td>
<td>Discontinue if eGFR is consistently &lt;45 mL/min/1.73m², contraindicated in</td>
<td>Discontinue if eGFR falls below &lt;60 mL/min/1.73m², contraindicated in</td>
<td>Discontinue if eGFR is consistently &lt;45 mL/min/1.73m²; contraindicated in</td>
</tr>
<tr>
<td></td>
<td>eGFR &lt;30 mL/min/1.73m²</td>
<td>eGFR &lt;30 mL/min/1.73m²</td>
<td>eGFR &lt;45 mL/min/1.73m²</td>
</tr>
<tr>
<td>Use in hepatic impairment</td>
<td>Do not use in severe hepatic impairment</td>
<td>Has not been studied in severe hepatic impairment</td>
<td>AUC ↑75% and C&lt;sub&gt;max&lt;/sub&gt; ↑48% in severe impairment</td>
</tr>
<tr>
<td>Blood pressure decreases</td>
<td>SBP 3.7-5.4 mmHg vs. placebo</td>
<td>SBP 3-5 mmHg vs. placebo</td>
<td>SBP 2.6-3.4 mmHg vs. placebo</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1.9-2.9 kg</td>
<td>2-4 kg</td>
<td>2-3 kg</td>
</tr>
</tbody>
</table>
Cardiovascular Outcome Trials (CVOTs) with newer antidiabetic agents

• Since 2008, sponsors of ALL new antihyperglycemic drugs should demonstrate new therapy will not result in unacceptable ↑ in CV risk

• Newer agents have shown benefit in certain CV endpoints, although varying degrees of reduction
## Overview of basic characteristics of CVOTs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Status</th>
<th>Drug</th>
<th>Drug Class</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>N</th>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG</td>
<td>Completed</td>
<td>Empagliflozin</td>
<td>SGLT2-I</td>
<td>Empagliflozin 10 mg vs 25 mg vs placebo</td>
<td>CV death, MI, or stroke</td>
<td>7000</td>
<td>3.1</td>
</tr>
<tr>
<td>LEADER</td>
<td>Completed</td>
<td>Liraglutide</td>
<td>GLP-1 RA</td>
<td>Liraglutide vs placebo</td>
<td>CV death, MI, or stroke</td>
<td>9340</td>
<td>3.8</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>Completed</td>
<td>Semaglutide</td>
<td>GLP-1 RA</td>
<td>Semaglutide 0.5 mg vs semaglutide 1 mg vs placebo</td>
<td>CV death, MI, or stroke</td>
<td>3299</td>
<td>1.99</td>
</tr>
</tbody>
</table>

EMPA-REG results

<table>
<thead>
<tr>
<th>Cardiovascular endpoint</th>
<th>Hazard ratio (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>0.86 (0.74-0.99); 0.04</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.62 (0.49-0.77); &lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.87 (0.70-1.09); 0.23</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.18 (0.89-1.56); 0.26</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>0.99 (0.74-1.34); 0.97</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.65 (0.50-0.85); 0.002</td>
</tr>
</tbody>
</table>

## LEADER results

<table>
<thead>
<tr>
<th>Cardiovascular endpoint</th>
<th>Hazard ratio (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>0.87 (0.78-0.97); 0.01</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.78 (0.66-0.93); &lt;0.007</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.86 (0.73-1.00); 0.046</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.86 (0.71-1.06); 0.16</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>0.99 (0.76-1.26); 0.87</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.87 (0.73-1.05); 0.14</td>
</tr>
</tbody>
</table>

## SUSTAIN-6 results

<table>
<thead>
<tr>
<th>Cardiovascular endpoint</th>
<th>Hazard ratio (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>0.74 (0.58-0.95); &lt;0.001/0.02</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.98 (0.65-1.48); 0.92</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.74 (0.51-1.08); 0.12</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.61 (0.38-0.99); 0.04</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>0.82 (0.47-1.44); 0.49</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>1.11 (0.77-1.61); 0.57</td>
</tr>
</tbody>
</table>

WHERE ARE THE NEWER ANTIDIABETIC AGENTS PLACED INTO TREATMENT RECOMMENDATIONS?
A 48-year-old Hispanic female presents to her primary care provider for type 2 diabetes mellitus (T2DM) management. Past medical history is significant for T2DM and recurrent vaginal candidiasis. She reports NKDA. Current medications include Ortho Tri-Cyclen® 1 tab PO daily, metformin 1000 mg PO BID, and insulin degludec 32 units subq daily. She does not report any recent hypoglycemic episodes or hyperglycemic symptoms. She is currently performing self-monitoring of blood glucose BID, fasting and two hours after dinner. Fasting blood gluoses (FBGs) range from 78-146 mg/dL, with an average of 118 mg/dL. Scr is 0.8 mg/dL. Postprandial BGs range from 168-226 mg/dL, average of 196 mg/dL. Most recent POC A1C is 8.1%. What would be the most appropriate intervention to this patient’s diabetes management at this time?

- a. Continue metformin 1000 mg PO BID and insulin degludec 32 units SUBQ daily and add dulaglutide 0.75 mg SUBQ weekly.
- b. Continue metformin 1000 mg PO BID and increase insulin degludec to 40 units SUBQ daily.
- c. Continue metformin 1000 mg PO BID, insulin degludec 32 units SUBQ daily, and add sitagliptin 100 mg PO daily.
- d. Continue metformin 1000 mg PO BID, insulin degludec 32 units SUBQ daily, and add canagliflozin 100 mg PO daily.
A 57-year-old Caucasian male presents to a family medicine physician assistant to establish care. Past medical history is significant for hypertension and type 2 diabetes mellitus. Self-reported current medications include aspirin 81 mg PO daily, glipizide XL 10 mg PO daily, metformin 500 mg PO BID, and pravastatin 80 mg PO daily. He reports being fatigued “all of the time”, is frequently thirsty, and is “always in the bathroom.” He reports that his glucometer broke a few months ago and therefore he has not been performing self-monitoring of blood glucose. POC A1C today in clinic is >14% and random BG is 352 mg/dL. eGFR ~ 48 mL/min/1.73m2. Weight is 92 kg. What would be the most appropriate intervention to the patient’s antidiabetic regimen at this time?

• a. Continue glipizide XL 10 mg PO daily, titrate metformin to 1000 mg PO BID, and start insulin glargine 10 units subq daily.
• b. Discontinue glipizide XL 10 mg PO daily, titrate metformin to 1000 mg PO BID, and start insulin detemir at 18 units subq daily.
• c. Continue glipizide XL 10 mg PO daily, discontinue metformin, and start insulin glargine at 18 units subq daily.
• d. Discontinue glipizide XL 10 mg PO daily, titrate metformin to 1000 mg PO BID, start insulin detemir at 20 units subq daily, and insulin aspart 6 units subq before each meal.
Hyperlipidemia background

• Cardiovascular disease (CVD) is still one of the most common age-related sources of morbidity and mortality in the world
• Statins are still the preferred treatment with ezetimibe being a second-line agent
• Pro-protein convertase subtilisin kexin 9 (PSCK9) inhibitors are a novel class in treatment of hyperlipidemia
Antihyperlipidemic agents

• ***Statins (i.e. HMG CoA-reductase inhibitors)
• Fibric acid derivatives (FADs)
• Bile acid sequestrants (BASs)
• Nicotinic acid (i.e. niacin)
• Ezetimibe
• Fish oil (omega-3 fatty acids)
• Proprotein convertase subtilisin/kexin-type 9 (PCSK9) inhibitors

PCSK9 inhibitors

- Alirocumab (Praluent®); evolocumab (Repatha™)
- Indicated as *adjunct to diet and maximally tolerated statin therapy* for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol (LDL-C)

PCSK9 inhibitors MOA

• A human monoclonal antibody that binds to PCSK9
• PCSK9 binds to the low-density lipoprotein receptors (LDLR) on hepatocyte surfaces to promote LDLR degradation within the liver
• LDLR is the primary receptor that clears circulating LDL; therefore, the ↓ in LDLR levels by PCSK9 results in ↑ blood levels of LDL-C
• By inhibiting the binding of PCSK9 to LDLR, PCSK9 inhibitors ↑ the number of LDLRs available to clear LDL, thereby ↓ LDL-C levels

PCSK9 inhibitors

• Demonstrated an additional 50-60% lowering in LDL in clinical trials
• Administered subq either Q2weeks or monthly with option of increasing to higher dose
• Recheck LDL in 4-8 weeks
• Nasopharyngitis, diarrhea, fatigue, headache, and injection site reactions were most commonly reported adverse events
• EXPENSIVE

Updated guidelines

• 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults released in November 2013
• In combination with 3 other recently released guidelines, intended to replace NCEP ATP III
• Created critical questions and conclusions based on evidence
Four statin benefit groups

• Individuals with clinical ASCVD
• Individuals with primary elevations of LDL-C ≥ 190 mg/dL
• Individuals 40-75 years of age with diabetes with LDL-C 70-189 mg/dL
• Individuals without clinical ASCVD or diabetes who are 40-75 years of age with LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk of ≥ 7.5%
New guideline and ASCVD risk calculator

• Rather than LDL-C or non-HDL-C targets, new guideline uses intensity of statin therapy as the goal of treatment
• Use of pooled cohort equations to estimate 10-year ASCVD risk in both white and black men and women who do not have clinical ASCVD
New perspective on treatment goals

• Expert panel unable to find RCT evidence to support continued use of LDL-C and/or non-HDL-C treatment goals
• Intensity of statin use should be to ↓ ASCVD risk in those most likely to benefit
• Nonstatin therapies do not provide acceptable risk reduction compared to adverse event profiles

High, moderate, and low-intensity statin therapy

<table>
<thead>
<tr>
<th>High-intensity</th>
<th>Moderate-intensity</th>
<th>Low-intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose ↓ LDL-C on average, ≥ 50%</td>
<td>Daily dose ↓ LDL-C on average, ~30-&lt;50%</td>
<td>Daily dose ↓ LDL-C on average, &lt; 30%</td>
</tr>
<tr>
<td>Atorvastatin (40)-80 mg Rosuvastatin (20) 40 mg</td>
<td>Atorvastatin 10 (20 mg) Rosuvastatin (5) 10 mg Simvastatin 20-40 mg Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg</td>
<td>Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

Stone et al. Circulation 2013;00:000-000.
PATIENT POPULATIONS ADDRESSED: 4 STATIN BENEFIT GROUPS

- Adults ≥21 years of age with clinical ASCVD, on statin for secondary prevention
- Adults ≥21 years of age with baseline LDL-C ≥190 mg/dL (not due to secondary modifiable causes), on statin for primary prevention
- Adults aged 40-75 years without clinical ASCVD but with diabetes and baseline LDL-C 70-189 mg/dL, on statin for primary prevention
- Adults aged 40-75 years without clinical ASCVD or diabetes, with baseline LDL-C 70-189 mg/dL and an estimated 10-year risk for ASCVD of ≥7.5%, on statin for primary prevention

FACTORS TO CONSIDER
- Adherence and lifestyle
- Statin intolerance
- Control of other risk factors
- Clinician-patient discussion regarding potential benefits, potential harms, and patient preferences regarding addition of non-statin medications
- Percentage LDL-C reduction (may consider absolute LDL-C level achieved)
- Monitoring of response to therapy, adherence, and lifestyle

OPTIONAL INTERVENTIONS TO CONSIDER
- Referral to lipid specialist and registered dietitian nutritionist
- Ezetimibe
- Bile acid sequestrants
- PCSK9 inhibitors
- Mipomersen, lomitapide, LDL apheresis may be considered by lipid specialist for patients with familial hypercholesterolemia

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, LDL = low-density lipoprotein, LDL-C = low-density lipoprotein cholesterol, PCSK9 = proprotein convertase subtilisin/kexin 9.

Patients ≥21 Years of Age with Stable Clinical ASCVD without Comorbidities, on Statin for Secondary Prevention

Patients ≥21 Years of Age with Clinical ASCVD with Comorbidities, on Statin for Secondary Prevention

Patients ≥21 Years of Age with Clinical ASCVD and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin for Secondary Prevention

Patients ≥21 Years of Age without Clinical ASCVD and with Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin for Primary Prevention

Patients Aged 40-75 years without Clinical ASCVD and with Diabetes and Baseline LDL-C 70-189 mg/dL, on Statin for Primary Prevention

Patients Aged 40-75 years without Clinical ASCVD or Diabetes, with LDL-C 70-189 mg/dL and 10-Year ASCVD Risk ≥7.5%, on Statin for Primary Prevention

A 69-year-old African-American female presents to her regularly scheduled diabetes group visit. Past medical history is significant for hypertension, type 2 diabetes mellitus, and dyslipidemia. She does not report any alcohol, tobacco, or illicit drug use. Current medications include HCTZ 25 mg PO daily, felodipine ER 10 mg PO daily, aspirin 81 mg PO daily, metformin 1000 mg PO BID, insulin detemir 42 units subq daily, and a daily multivitamin. She reports shortness of breath with enalapril. She reports no hypoglycemic episodes or hyperglycemic symptoms. Vital signs and most recent labs include blood pressure 152/76 mmHg, pulse 86 beats/min, TCHOL = 276 mg/dL, LDL = 196 mg/dL, HDL = 46 mg/dL, and TG = 172 mg/dL. Most recent POC A1C is 6.8%. She has been hesitant to start a statin, but is amenable today. What is her estimated 10-year risk of primary atherosclerotic cardiovascular disease (ASCVD) and what would be the most appropriate statin and dose to initiate?

- a. 42.4%; simvastatin 40 mg PO daily
- b. 6.9%; atorvastatin 80 mg PO daily
- c. 42.4%; rosuvastatin 40 mg PO daily
- d. 6.9%; rosuvastatin 20 mg PO daily
Conclusions

• Imperative for clinicians in all patient care specialties to be knowledgeable in primary care disease states
• Communication is extremely important among providers to optimize patient care outcomes
• Variety of new medications are available for use in primary care
AMBULATORY UPDATE:
SUPPORTIVE CARE IN CANCER PATIENTS

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August 5, 2017