2019 Update on Recent Guideline Releases for Diabetes, Hypertension, and Dyslipidemia: Can We, Please, All Just Get on the Same Page?!  

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Disclosures  
Under guidelines established by the Accreditation Council for Pharmacy Education, disclosure must be made regarding financial relationships with commercial interests within the last 12 months.  

I, Jeremy Johnson, have no relevant financial relationships or affiliations with commercial interests to disclose.
Pharmacist Objectives

• At the completion of this activity, pharmacists will be able to:
  • Recognize inconsistencies between clinical practice guidelines released over the past 10-15 years
  • Identify clinical practice guideline updates for diabetes, hypertension, and dyslipidemia
  • Apply updates from new clinical practice guidelines to patient-care practices

Technician Objectives

• At the completion of this activity, pharmacy technicians will be able to:
  • Discuss pharmacology of medications for diabetes, hypertension and dyslipidemia and their therapeutic roles according to updated guidelines
  • Identify common adverse effects of medications for treatment of diabetes, hypertension and dyslipidemia
Overview

• Relevance of diabetes, hypertension, and dyslipidemia in modern ambulatory care practice
• Diabetes guideline updates and the impact of Cardiovascular Outcomes Trials (CVOTs) among antihyperglycemic agents
• History of hypertension and dyslipidemia guidelines
• Hypertension guideline updates
• Dyslipidemia guideline updates
• Implications for patient care

The DM Epidemic

• 30.3 million in US have DM
  • 9.4% of population
  • Only 23.1 million have been diagnosed
• ~95% have Type 2 DM

What is Coming
• 84.1 million in US have Prediabetes
  • 33.9% of US adults

Complications of DM

- Microvascular
  - Retinopathy
  - Nephropathy
  - Neuropathy

- Macrovascular
  - CVD
  - Stroke
  - Heart Failure (HF)

In 2014, 1.5 million hospitalizations in US among adults with diabetes due to CVD.
(70.4 per 1,000 patients with diabetes)


Cardiovascular Disease and DM

- ~65% of deaths are due to CVD

- Risk of death from ASCVD ↑ 2- to 4-fold
- Stroke risk ↑ 2- to 4-fold
- Heart failure ↑ 2- to 5-fold

CDC National Diabetes Fact Sheet. www.cdc.gov
CVD Risk Reduction in DM

- Statins
  - Ezetimibe
  - PCSK-9 inhibitors
- Aspirin
- ACE/ARB
- Antihyperglycemic agents

Do not use drugs that could increase CVD risk!

WHY THE SUDDEN INCREASE IN CARDIOVASCULAR OUTCOMES TRIALS
Among New Antihyperglycemic Agents
Rosiglitazone Controversy

- 2007 meta-analysis associated rosiglitazone with increased ischemic events
  - REMS on rosiglitazone
  - Mixed findings in other studies
  - Data determined “inconclusive”
- FDA lifted restricted prescribing program in December 2015

Conclusions:
“Rosiglitazone was associated with a significant increase in the risk of myocardial infarction (OR 1.43 (95% CI, 1.03 to 1.98; P=0.03) and with an increase in the risk of death from cardiovascular causes (OR 1.64; 95% CI, 0.98 to 2.74; P=0.06) that had borderline significance.”


FDA Response

- 2008 FDA mandate requiring RCT assessment of cardiovascular safety of all new antihyperglycemic agents
- Cardiovascular Outcomes Trials (CVOT)
  - Must demonstrate “non-inferiority” vs placebo for association with major adverse cardiovascular events (MACE)
  - Patients must be “high-risk”
  - Primary endpoint: “composite of cardiovascular death, nonfatal MI, and nonfatal stroke”
  - If shown non-inferior to placebo, may test for superiority

# CARDIOVASCULAR OUTCOMES TRIALS (CVOT) SINCE 2008 FDA MANDATE

DPP-4 Inhibitors, GLP-1 Receptor Agonists, SGLT2 Inhibitors

## CVOT Trials

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Trial</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Saxagliptin</td>
<td>SAVOR TIMI-53</td>
<td>2013</td>
</tr>
<tr>
<td></td>
<td>Alogliptin</td>
<td>EXAMINE</td>
<td>2013</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
<td>TECOS</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>CAROLINA</td>
<td>2018</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>CARMELINA</td>
<td>2018</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>Lixisenatide</td>
<td>ELIXA</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>Liraglutide</td>
<td>LEADER</td>
<td>2016</td>
</tr>
<tr>
<td></td>
<td>Semaglutide</td>
<td>SUSTAIN-6</td>
<td>2016</td>
</tr>
<tr>
<td></td>
<td>Exenatide</td>
<td>EXSCEL</td>
<td>2017</td>
</tr>
<tr>
<td></td>
<td>Dulaglutide</td>
<td>REWIND</td>
<td>2018</td>
</tr>
<tr>
<td>SGLT2 Inhibitors</td>
<td>Empagliflozin</td>
<td>EMPA-REG</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>Canagliflozin</td>
<td>CANVAS Program</td>
<td>2017</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin</td>
<td>DECLARE TIMI-58</td>
<td>2019</td>
</tr>
<tr>
<td></td>
<td>Ertugliflozin</td>
<td>VERTIS CV</td>
<td>2020</td>
</tr>
</tbody>
</table>

**DPP-4 Inhibitors:**
- Non-Inferior
- Not Superior

**GLP-1 Agonists:**
- Non-Inferior
- Mixed findings for Superiority

**SGLT2 Inhibitors:**
- Non-Inferior
- Superior
GLP-1 Receptor Agonists

- Glucagon-Like Peptide-1 Receptor Agonists
- Injectable: twice daily, once daily, or once weekly
- AE: Nausea, pancreatitis, thyroid tumors (animal studies—avoid if history or family history)
- Titrate doses gradually to reduce/avoid nausea

GLP-1 RA CVOT: LEADER

- Liraglutide 1.8 mg vs placebo
  - n=9340 with type 2 DM and high CV risk
- Non-inferiority/superiority study
- Primary outcome: composite of CV death, nonfatal MI, nonfatal stroke
  - 13% vs 14.9%; HR 0.87, 95%CI 0.78-0.97; p<0.001 for non-inferiority
  - Superiority demonstrated as well; p=0.01

LEADER: results

- Death from any cause was driven to statistical significance by Death from cardiovascular causes.
- Cardiovascular safety as well as benefit
- Very positive findings

GLP-1 RA CVOTs

- Cardiovascular safety shown for each GLP-1 RA studied
- Cardiovascular benefit shown for liraglutide
  - Possible trend for semaglutide and exenatide LAR

SGLT2 Inhibitors

- Sodium-Glucose Cotransporter 2 Inhibitors
- Oral
- AE: genital mycotic infections, UTI, increased urination, decreased eGFR, hypovolemia, hypotension, hyperkalemia, ketoacidosis
- Monitoring: renal function, blood pressure, potassium
SGLT2 Inhibitor CVOT: EMPA-REG OUTCOME

- Empagliflozin 10 mg or 25 mg daily vs placebo
  - n=7020 patients with type 2 diabetes and CVD
- Non-inferiority/superiority study
- Primary Outcome: composite of CV death, nonfatal MI, or nonfatal stroke
  - 10.5% vs 12.1%; HR 0.86, 95%CI 0.74-0.99; p<0.001 for non-inferiority
  - \( p=0.04 \) for superiority (cardiovascular benefit)

Zinman B. N Engl J Med. 2015;373:2117-2128

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (N=2333)</th>
<th>Empagliflozin (N=4687)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome$^a$</td>
<td>282 (12.1)</td>
<td>43.9</td>
<td>490 (10.5)</td>
<td>37.4</td>
</tr>
<tr>
<td>Noninferiority</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superiority</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome$^a$</td>
<td>333 (14.3)</td>
<td>52.5</td>
<td>599 (12.8)</td>
<td>46.4</td>
</tr>
<tr>
<td>Noninferiority</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superiority</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>194 (8.3)</td>
<td>28.6</td>
<td>269 (5.7)</td>
<td>19.4</td>
</tr>
<tr>
<td>From any cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From cardiovascular causes</td>
<td>137 (5.9)</td>
<td>20.2</td>
<td>172 (3.7)</td>
<td>12.4</td>
</tr>
</tbody>
</table>

Zinman B. N Engl J Med. 2015;373:2117-2128
SGLT2 Inhibitor CVOT: CANVAS

- Canagliflozin 100 mg or 300 mg vs placebo
  - n=10,142 patients with type 2 DM; 2/3 high risk for CVD
- Non-inferiority/superiority study
- Primary Outcome: composite CV death, nonfatal MI, or nonfatal stroke
  - 26.9 vs 31.5 participants per 1000 patient years; HR 0.86, 95%CI 0.75-0.97; p<0.01 for non-inferiority
  - \( p=0.02 \) for superiority (cardiovascular benefit)
SGLT2 Inhibitor CVOT: CANVAS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (N=5795)</th>
<th>Placebo (N=4347)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7.1</td>
<td>8.4</td>
<td>0.90 (0.71–1.13)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>11.2</td>
<td>12.6</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>7.9</td>
<td>9.6</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>118.7</td>
<td>131.1</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>16.3</td>
<td>20.8</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73 (0.67–0.79)</td>
</tr>
<tr>
<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td>0.60 (0.47–0.77)</td>
</tr>
</tbody>
</table>


SGLT2 Inhibitor CVOT: CANVAS

A Death from Cardiovascular Causes, Nonfatal Myocardial Infarction, or Nonfatal Stroke

Hazard ratio, 0.86 (95% CI, 0.75–0.97) P<0.001 for noninferiority P=0.02 for superiority

SGLT2 Inhibitor CVOTs

- Empagliflozin and canagliflozin both show
  - Cardiovascular safety
  - Cardiovascular benefit
- Empagliflozin showed “all cause mortality reduction” without reduction in MI or Stroke
  - Mechanism unknown
- Positive renal outcomes
- Improved Heart Failure outcomes

AMERICAN DIABETES ASSOCIATION (ADA) GUIDELINES

Evolution of the Type 2 Diabetes Treatment Algorithm
Impact of CVOTs

- ADA 2018 Standards of Medical Care in Diabetes
- Updated Type 2 Diabetes Treatment Algorithm
- When beginning Dual Therapy:

![Dual Therapy Diagram]

ADA. Diabetes Care. 2018;41(suppl 1):S1-159

Impact of CVOTs

- ADA 2018 Standards of Medical Care in Diabetes
- Updated Type 2 Diabetes Treatment Algorithm
- Dual Therapy considerations:

![Dual Therapy Table]

ADA. Diabetes Care. 2018;41(suppl 1):S1-159
Considerations

- Work to reduce CVD risk among patients with Type 2 DM
- Consider liraglutide, empagliflozin, or canagliflozin as a 2nd line agent after metformin in high risk patients with ASCVD
- Discuss pros and cons of each drug with patients
  - Shared-decision making
    - Injection vs oral
    - Weight loss, AE, costs
    - A1c-lowering potential
- Use other agents to reduce CVD risk
DM Case 1

60 yo male was recently diagnosed with T2DM and HFrEF, in addition to his HTN and Stage 2 CKD. He is currently using metformin 1000 mg BID along with improved diet and exercise, but based on his recent A1c of 8.2% and SMBG, his PCP will add a new medication. All other standards have been addressed. What evidence-based treatment would you recommend?

A. saxagliptin  
B. empagliflozin  
C. liraglutide  
D. glipizide

DM Case 2

Based on the drug chosen in the previous case, which set of adverse effects or monitoring parameters must be addressed?

A. Pancreatitis, worsened heart failure  
B. Genitourinary fungal infections, DKA  
C. Thyroid cancer, nausea  
D. Hypoglycemia, weight gain
HYPERTENSION AND DYSLIPIDEMIA

The Evolution of the Guidelines

National Heart Lung and Blood Institute (NHLBI)

Hypertension
- Joint National Committee 1977
- JNC-7 (2003)

Dyslipidemia (ASCVD)
- National Cholesterol Education Program: Adult Treatment Panel 1985
- ATP-3 2001, then updated 2004

Then…
National Heart Lung and Blood Institute (NHLBI)

Hypertension
- JNC-8 Committee to join ACC/AHA
- Published in JAMA instead
  - 2014 HTN Guideline ("JNC-8")

Dyslipidemia (ASCVD)
- ATP-4 Committee to join ACC/AHA
- 2013 ACC/AHA Lipid (ASCVD) Guideline
  - Controversial due to New Philosophy
    - LDL goals changed to Statin Intensity
- 2014 National Lipid Association
- 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies
- 2016 US Preventive Task Force
- 2017 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies

Then...

Hypertension
ACC/AHA 2017

Whelton PK, et al.
2017 High Blood Pressure Clinical Practice Guideline


A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

- Very similar to JNC-7, but updated
- Stronger evidence than “JNC-8”
BP Staging

Definition of HTN

![BP Staging Diagram]


Approach to Treatment

![Approach to Treatment Diagram]

# Lifestyle Modifications

## BP Thresholds for and Goals of Pharmacological Therapy in Patients With Hypertension According to Clinical Conditions

<table>
<thead>
<tr>
<th>Clinical Condition(s)</th>
<th>BP Threshold, mm Hg</th>
<th>BP Goal, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical CVD or 10-year ASCVD risk ≥10%</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>No clinical CVD and 10-year ASCVD risk &lt;10%</td>
<td>≥140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)</td>
<td>≥130 (SBP)</td>
<td>&lt;130 (SBP)</td>
</tr>
<tr>
<td><strong>Specific comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic kidney disease after renal transplantation</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Heart failure</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Stable ischemic heart disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Secondary stroke prevention</td>
<td>≥140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Secondary stroke prevention (lacunar)</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
</tbody>
</table>
Principles of Therapy

- Choice of Initial Medication (First-line)
  - Thiazide diuretic, CCB, ACEi, or ARB
- Monotherapy if Stage 1 HTN
- Start 2 first-line agents if Stage 2 HTN
- Follow up MONTHLY until controlled

- Considerations if Comorbidities →

Stable Ischemic Heart Disease

Post MI or angina: Think BB or ACEi

Heart Failure

### 9.2.1. Heart Failure With Reduced Ejection Fraction

**Recommendations for Treatment of Hypertension in Patients With HF/HFpEF**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-E0</td>
<td>1. Adults with HF/hypertension should be prescribed GDMT (2) titrated to attain a BP of less than 130/80 mm Hg.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>2. Non-hypertensive CCBs are not recommended in the treatment of hypertension in adults with HF/HFpEF [1].</td>
</tr>
</tbody>
</table>

**ACEi**, **BB**

### 9.2.2. Heart Failure With Preserved Ejection Fraction

**Recommendations for Treatment of Hypertension in Patients With HFpEF**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-E0</td>
<td>1. In adults with HFpEF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension.</td>
</tr>
<tr>
<td>I</td>
<td>C-LD</td>
<td>2. Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta blockers titrated to attain SBP of less than 130 mm Hg (1-4).</td>
</tr>
</tbody>
</table>

**ACEi** before ARB

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**Figure 6. Management of Hypertension in Patients With CKD**

- BP goal <130/80 mm Hg (Class I)
- Alumina = (≥300 mg/dL or ≥3.0 mg/dL creatinine)
- ACE inhibitor (Class IIa)
- Thiazide CCB ACEi ARB
- ARB (Class II)
- ACE inhibitor (Class IIa)

**CKD**

*NEW*

**CKD: Think ACEi before ARB**

Colors correspond to Class of Recommendation in Table 1.

*CKD stage 1 or higher or stage 1 or 2 with albuminuria ≥300 mg/dL or ≥3.0 mg/dL creatinine
ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; and CKD, chronic kidney disease.
Secondary Stroke Prevention

9.4.3. Secondary Stroke Prevention

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>1. Adults with previously treated hypertension who experience a stroke or transient ischemic attack (TIA) should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events (1-3).</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>2. For adults who experience a stroke or TIA, treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic plus ACE inhibitor, is useful (1, 3-5).</td>
</tr>
</tbody>
</table>

Post Stroke: Think thiazide and ACEi


Diabetes

9.6. Diabetes Mellitus

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-HR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. In adults with DM and hypertension, antihypertensive drug treatment should be initiated at a BP of 130/80 mm Hg or higher with a treatment goal of less than 130/80 mm Hg (1-8).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DEP: C-EO</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>AHR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective (1, 9, 10).</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria (11, 12).</td>
<td></td>
</tr>
</tbody>
</table>

NEW: Any of the initial 4 may be started ACEi or ARB are only “mandated” if albuminuria

## Racial and Ethnic Differences in Treatment

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations for Race and Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.</td>
</tr>
<tr>
<td>I</td>
<td>C-LD</td>
<td>Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension.</td>
</tr>
</tbody>
</table>

HF or CKD override race  
Race overrides DM

---

## HTN Case 1

- 60 yo African American male with diabetes and CKD with albuminuria. Select the most appropriate initial drug therapy for this patient.

A. Thiazide or CCB  
B. Thiazide, CCB, ACEi, or ARB  
C. ACEi  
D. BB
HTN Case 2

• 60 yo African American male with diabetes and HF. Select the most appropriate initial drug therapy for this patient.

A. Thiazide or CCB
B. Thiazide, CCB, ACEi, or ARB
C. ACEi
D. BB

HTN Case 3

• 60 yo African American male with diabetes. Select the most appropriate initial drug therapy for this patient.

A. Thiazide or CCB
B. Thiazide, CCB, ACEi, or ARB
C. ACEi
D. BB
Hyperlipidemia
(ASCVD)

NCEP
ATP 3
Released: 2001
Updated: 2004
NCEP ATP III Guidelines

Step 1
Determine lipoprotein levels—obtain complete lipoprotein profile after 9- to 12-hour fast.

<table>
<thead>
<tr>
<th>LDL Cholesterol - Primary Target of Therapy</th>
<th>Optimal</th>
<th>Near optimal/above optimal</th>
<th>Borderline high</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100-129</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>130-159</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>160-189</td>
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</tr>
<tr>
<td>≥ 190</td>
<td></td>
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</tr>
</tbody>
</table>

“LDL is the major atherogenic lipoprotein and has long been identified by NCEP as the primary target of cholesterol-lowering therapy”

“This focus on LDL has been strongly validated by recent clinical trials, which show the efficacy of LDL-lowering therapy for reducing risk for CHD”


NCEP ATP III Guidelines

Treatment of elevated triglycerides (≥150 mg/dL)

- Primary aim of therapy is to reach LDL goal
- Intensify weight management
- Increase physical activity
- If triglycerides are ≥200 mg/dL after LDL goal is reached, set secondary goal for non-HDL cholesterol (total – HDL) 30 mg/dL higher than LDL goal.

If triglycerides ≥500 mg/dL, first lower triglycerides to prevent pancreatitis:
- very low-fat diet (<15% of calories from fat)
- weight management and physical activity
- fibrate or nicotinic acid
- when triglycerides <500 mg/dL, turn to LDL-lowering therapy.

### LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal (mg/dL)</th>
<th>LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC) (mg/dL)</th>
<th>LDL Level at Which to Consider Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD Risk Equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 (optional &lt;70)</td>
<td>≥100</td>
<td>≥100 (&lt;100: consider drug options)</td>
</tr>
<tr>
<td>2+ Risk Factors (10-year risk ≤20%)</td>
<td>&lt;130</td>
<td>≥130</td>
<td>10-year risk 10–20%: ≥130 (100-129: consider drug options)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10-year risk &lt;10%: ≥160</td>
</tr>
<tr>
<td>0–1 Risk Factor</td>
<td>&lt;160</td>
<td>≥160</td>
<td>≥190 (160-189: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

Grundy SM. Circulation. 110:227-39;2004

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### Not good enough?

- “Half of all myocardial infarctions and strokes occur despite apparently healthy men and women with LDL levels below currently recommended thresholds for treatment”
- “Even with adequate LDL lowering, many patients on statin therapy have significant CVD risk”

Findings

• “unable to find evidence to support titrating statins to a target LDL or non-HDL goal”

• “extensive evidence that appropriate statin intensity should be used to reduce ASCVD risk”

• “use of non-statins to additionally lower non-HDL once LDL goal achieved, DID NOT further reduce ASCVD outcomes”
Findings

• Non-statin therapies in general have not demonstrated significant ASCVD event reduction.
• Lifestyle modifications remain a critical component of health promotion and ASCVD risk reduction
• Identification of 4 statin benefit groups to focus on ASCVD risk reduction
Intensity of Statin Therapy

- Expected LDL-lowering:
  - High-intensity $\geq 50\%$
  - Moderate-intensity 30 to $<50\%$
  - Low-intensity $<30\%$

- High-intensity reduces ASCVD risk more
- However, moderate- or low-intensity still provides protection, just not as much as high-intensity

Statin Intensity Categories and Drugs

<table>
<thead>
<tr>
<th>High-intensity</th>
<th>Moderate-intensity</th>
<th>Low-intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
<td>Pravastatin 10-20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20-40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
<td>Fluvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4 mg</td>
<td></td>
</tr>
</tbody>
</table>
Summary of Lipid Guideline Differences

ATP 3

• Focus on LDL goals
• Use statins or any lipid-lowering drugs to attain goal

2013 ACC/AHA

• Focus on statin intensity
• Use statins almost exclusively

Dyslipidemia Guidelines

• ATP-4 Committee to join ACC/AHA
• 2013 ACC/AHA Lipid (ASCVD) Guideline
  • Controversial due to New Philosophy
    • LDL goals changed to Statin Intensity
• 2014 National Lipid Association
• 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies
• 2016 US Preventive Task Force
• 2017 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies
2018 ACC/AHA Blood Cholesterol Guidelines

2018
AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA
Guideline on the Management of Blood Cholesterol
A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

WRITING COMMITTEE MEMBERS
Scott M. Grundy, MD, PhD, FAHA, Chair*
Neil J. Stone, MD, FACC, FAHA, Vice Chair*

What's New in the 2018 Cholesterol Guideline?

- Top 10 take-home messages
- New drugs were added to secondary prevention recommendations as a result of outcome data from clinical trials
  - Threshold of 70 mg/dL added for very high risk patients
  - Goal is not a number but rather a percent LDL-C reduction
- In primary prevention, consider presence of ASCVD risk enhancers to incorporate in clinician-patient risk discussion
- Communicate lifetime risk estimation in young adults

Grundy SM, Stone NJ, ACC/AHA. J Am Coll Cardiol. 2018,
https://doi.org/10.1016/j.jacc.2018.11.003
Beyond Statins -- Getting LDL to Goal

- In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL to consider the addition of nonstatins to statin therapy
- Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions
  - If LDL-C level remains ≥ 70 mg/dL on maximally tolerated statin, reasonable to add ezetimibe
  - If LDL-C level remains ≥ 70 mg/dL on maximally tolerated statin + ezetimibe, reasonable to add PCSK9 inhibitor

Risk-Enhancing Factors for Primary Prevention*

<table>
<thead>
<tr>
<th>Family history of premature ASCVD</th>
<th>Chronic kidney disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, age &lt; 55 years</td>
<td>eGFR 15-59 ml/min/1.73 m² with or without albuminuria</td>
</tr>
<tr>
<td>Females, age &lt; 65 years</td>
<td>Not treated with dialysis or transplant</td>
</tr>
<tr>
<td>Primary hypercholesteremia*</td>
<td>Chronic inflammatory conditions</td>
</tr>
<tr>
<td>LDL-C 160-189 mg/dL (4.1-4.8 mmol/L)</td>
<td>Psoriasis, rheumatoid arthritis, HIV/AIDS</td>
</tr>
<tr>
<td>Non-HDL-C 190-219 mg/dL (4.9-5.6 mmol/L)</td>
<td>High-risk race/ethnicities</td>
</tr>
<tr>
<td>Metabolic syndrome (total: 3)</td>
<td>South Asian</td>
</tr>
<tr>
<td>Increased waist circumference</td>
<td>Lipid/Biomarkers</td>
</tr>
<tr>
<td>Triglycerides &gt; 150 mg/dL</td>
<td>hS-CRP ≥ 2.0 mg/L</td>
</tr>
<tr>
<td>Low HDL-C (&lt; 40 mg/dL [men], &lt; 50 mg/dL [women])</td>
<td>Lp(a) ≥ 50 mg/dL (≥ 125 nmol/L)</td>
</tr>
<tr>
<td>Elevated BP</td>
<td>apoB ≥ 130 mg/dL</td>
</tr>
<tr>
<td>Elevated glucose</td>
<td>ABI &lt; 0.9</td>
</tr>
<tr>
<td>Conditions specific to women</td>
<td>Presence of risk-enhancing factors may affect the threshold for nonstatin intensification.</td>
</tr>
<tr>
<td>Premature menopause (before age 40 years)</td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td></td>
</tr>
</tbody>
</table>

*No established ASCVD or diabetes. Optimally, 3 determinations.
Secondary Prevention

Clinical ASCVD

ASCVD not at very high-risk^

Healthy Lifestyle

Age ≤75 y

High-intensity statin (Goal: LDL-C ≤50%)
(Class I)

If high-intensity statin not tolerated, use moderate-intensity statin (Class I)

Age >75 y

If on maximal statin therapy and LDL-C ≥70 mg/dL (1.8 mmol/L), adding ezetimibe may be reasonable (Class IIa)

Initiation of moderate- or high-intensity statin is reasonable (Class IIa)

Continuation of high-intensity statin is reasonable (Class IIa)

If on maximal statin and LDL-C ≥70 mg/dL (1.8 mmol/L), adding ezetimibe is reasonable (Class IIa)

If on maximal statin and LDL-C ≥70 mg/dL (1.8 mmol/L), adding ezetimibe is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)

If PCSK9-I is considered, add ezetimibe to maximal statin before adding PCSK9-I (Class I)

If on clinically judged maximal LDL-C lowering therapy and LDL-C ≥70 mg/dL (1.8 mmol/L), or non-HDL-C ≥100 mg/dL (2.6 mmol/L), adding PCSK9-I is reasonable (Class IIa)

Very high-risk^

ASCVD

Dashed arrow indicates RCT-supported efficacy, but is less cost effective


Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

Age 0-19 y

Lifestyle to prevent or reduce ASCVD risk

Diagnosis of familial hyperlipidemia is a state

Age 20-39 y

Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk

Consider statin if family history predominate ASCVD and LDL-C ≥190 mg/dL (5.0 mmol/L)

Age 40-75 y

LDL-C ≥70 mg/dL (1.8 mmol/L), or non-HDL-C ≥100 mg/dL (2.6 mmol/L)

10-year ASCVD risk percent begins risk discussion

LDL-C ≥190 mg/dL (5.0 mmol/L)

No risk assessment; high-intensity statin
(Class I)

Diabetes mellitus and age 40-75 y

Moderate-intensity statin
(Class I)

Diabetes mellitus and age 40-75 y

Risk assessment to consider high-intensity statin
(Class Ia)

Age >75 y

Clinical assessment; risk discussion

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (e.g., rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)
- Lipid/lipoprotein
- Persistently elevated triglycerides ≥275 mg/dL (≥3.0 mmol/L)

In selected individuals if measured:
- hsCRP ≥3.0 mg/L
- Lp(a) level ≥50 mg/dL or ≥125 mg/dL
- apoB 100 mg/dL
- Ankle-brachial index (ABI) <0.9

Risk discussion:
Emphasize lifestyle to reduce risk factors (Class I)

Risk discussion:
If risk enhancers present, then risk discussion regarding moderate-intensity statin therapy (Class IIb)

Risk discussion:
If risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)

Risk discussion:
If risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 50% (Class I)

Risk discussion:
Consider initial statin to reduce LDL-C ≤50%
(Class I)

If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lower risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

Monitoring and Follow up

Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

• Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline.

• In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).

Lipid Case 1

• 62 yo female with a hx of MI, but considered to be only high risk and not “very high risk”. What is the goal for her LDL?

A. LDL < 100
B. LDL < 70
C. 50% reduction of LDL
D. 30-49% reduction of LDL
Lipid Case 2

• 62 yo female with a hx of MI, but considered to be only high risk and not “very high risk”. She has not tolerated atorvastatin and cannot tolerate rosuvastatin 40 mg. After 4-12 weeks on rosuvastatin 20 mg daily without adverse effects, her LDL has dropped ~45% and is 85 mg/dL. What is the most appropriate next step in her therapy?

A. No additional therapy is needed
B. Add ezetimibe
C. Add alirocumab
D. Add niacin

Summary

• The diabetes guidelines have more of a focus on ASCVD risk reduction
• The hypertension guidelines have tighter goals and thresholds
• The lipid guidelines combine both former philosophies to use appropriate statin intensities and achieve particular goal reductions.
2019 Update on Recent Guideline Releases for Diabetes, Hypertension, and Dyslipidemia: Can We, Please, All Just Get on the Same Page?!

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Ambulatory Care Pharmacist, OSU Internal Medicine

2019 OSHP Annual Meeting
OSU Center for Health Sciences. Tulsa, OK
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