2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Risk

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Professor of Nursing, Nurse Practitioner
Rush University Medical Center
Table 1. Applying Classification of Recommendation and Level of Evidence

<table>
<thead>
<tr>
<th>LEVEL A</th>
<th>LEVEL B</th>
<th>LEVEL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple populations evaluated*</td>
<td>Limited populations evaluated*</td>
<td>Very limited populations evaluated*</td>
</tr>
<tr>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
<td>Only consensus opinion of experts, case studies, or standard of care</td>
</tr>
<tr>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td>Recommendation that procedure or treatment is useful/effective</td>
</tr>
<tr>
<td>Sufficient evidence from multiple randomized trials or meta-analyses</td>
<td>Evidence from single randomized trial or nonrandomized studies</td>
<td>Only expert opinion, case studies, or standard of care</td>
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<tr>
<td>Recommendation in favor of treatment or procedure being useful/effective</td>
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<td>Recommendation in favor of treatment or procedure being useful/effective</td>
</tr>
<tr>
<td>Some conflicting evidence from multiple randomized trials or meta-analyses</td>
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<td>Only diverging expert opinion, case studies, or standard of care</td>
</tr>
<tr>
<td>Recommendation’s usefulness/efficacy less well established</td>
<td>Recommendation’s usefulness/efficacy less well established</td>
<td>Recommendation’s usefulness/efficacy less well established</td>
</tr>
<tr>
<td>Greater conflicting evidence from multiple randomized trials or meta-analyses</td>
<td>Greater conflicting evidence from single randomized trial or nonrandomized studies</td>
<td>Only diverging expert opinion, case studies, or standard of care</td>
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</tbody>
</table>

**CLASS I**
 Benefit >> Risk
 Procedure/Treatment SHOULD be performed/administered

**CLASS IIa**
 Benefit >> Risk
 Additional studies with focused objectives needed
 IT IS REASONABLE to perform procedure/administer treatment

**CLASS IIb**
 Benefit ≥ Risk
 Additional studies with broad objectives needed; additional registry data would be helpful
 Procedure/Treatment MAY BE CONSIDERED

**CLASS III**
 No Benefit or CLASS III Harm

<table>
<thead>
<tr>
<th>Procedure/Test</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>COR III: No benefit</td>
<td>Harmful</td>
</tr>
<tr>
<td>COR III: Helpful</td>
<td>to Patients</td>
</tr>
<tr>
<td>COR III: No Proven Benefit</td>
<td></td>
</tr>
</tbody>
</table>

**CLASS III**
 No Benefit or CLASS III Harm

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<tr>
<th>Procedure/Test</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>COR III: No benefit</td>
<td>Helpful</td>
</tr>
<tr>
<td>COR III: Excess Cost w/o Benefit or Harmful</td>
<td></td>
</tr>
</tbody>
</table>

**LEVEL A**
 Multiple populations evaluated*
 Data derived from multiple randomized clinical trials or meta-analyses

**LEVEL B**
 Limited populations evaluated*
 Data derived from a single randomized trial or nonrandomized studies

**LEVEL C**
 Very limited populations evaluated*
 Only consensus opinion of experts, case studies, or standard of care
### Table 1a. NHLBI Grading the Strength of Recommendations

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strength of Recommendation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><strong>Strong recommendation</strong>&lt;br&gt;There is high certainty based on evidence that the net benefit† is substantial.</td>
</tr>
<tr>
<td>B</td>
<td><strong>Moderate recommendation</strong>&lt;br&gt;There is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate.</td>
</tr>
<tr>
<td>C</td>
<td><strong>Weak recommendation</strong>&lt;br&gt;There is at least moderate certainty based on evidence that there is a small net benefit.</td>
</tr>
<tr>
<td>D</td>
<td><strong>Recommendation against</strong>&lt;br&gt;There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.</td>
</tr>
<tr>
<td>E</td>
<td><strong>Expert opinion</strong> (“There is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends.”)&lt;br&gt;Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Work Group thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.</td>
</tr>
<tr>
<td>N</td>
<td><strong>No recommendation for or against</strong> (“There is insufficient evidence or evidence is unclear or conflicting.”)&lt;br&gt;Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Work Group thought no recommendation should be made. Further research is recommended in this area.</td>
</tr>
<tr>
<td>Type of Evidence</td>
<td>Quality Rating*</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Well-designed, well-executed† RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes. MAs of such studies. Highly certain about the estimate of effect. Further research is unlikely to change our confidence in the estimate of effect.</td>
<td>High</td>
</tr>
</tbody>
</table>
| RCTs with minor limitations‡ affecting confidence in, or applicability of, the results. Well-designed, well-executed nonrandomized controlled studies§ and well-designed, well-executed observational studies|| Moderate
| MAs of such studies. Moderately certain about the estimate of effect. Further research may have an impact on our confidence in the estimate of effect and may change the estimate. | Low             |
| RCTs with major limitations. Nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results. Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). Physiological studies in humans. MAs of such studies. Low certainty about the estimate of effect. Further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate. | Low |
What’s New in the Guideline?

• Focus on ASCVD risk reduction: 4 statin benefit groups
  – Goal is to reduce ASCVD events in secondary and primary prevention
  – High-intensity and moderate-intensity statin use

• A new perspective on LDL-C and/or non-HDL-C treatment goals
  – No evidence to support LDL-C and/or non-HDL-C treatment targets
  – Appropriate intensity of statin therapy should be used to reduce ASCVD risk in those *most likely to benefit*

What’s New in the Guideline?

• Global risk assessment for primary prevention
  – Use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both black and white men and women
    http://tools.cardiosource.org/ASCVD-Risk-Estimator/

• Safety recommendations
  – Used RCTs to identify important safety considerations of statins and provides expert guidance on management of adverse effects

• Role of biomarkers and noninvasive tests
  – Treatment decisions in selected individuals who are not in the 4 statin benefit groups may be informed by other factors
Lifestyle as the Foundation for Risk Reduction

*Guideline on Lifestyle Management*

- A critical component of health promotion and ASCVD risk reduction
  - Heart-healthy diet
  - Regular exercise
  - Avoidance of tobacco products
  - Maintenance of a healthy weight

4 Statin Benefit Groups

1. Individuals with *clinical* ASCVD, defined as the inclusion criteria for secondary prevention statin RCTs
   - Acute coronary syndromes
   - History of MI
   - Stable or unstable angina
   - Coronary or other arterial revascularization
   - Stroke or TIA
   - PAD
4 Statin Benefit Groups

2. Individuals with primary elevations of LDL-C ≥ 190 mg/dL

3. Individuals with diabetes aged 40-75 years with LDL-C 70-189 mg/dL and without clinical ASCVD

4. Individuals without ASCVD or diabetes with LDL-C 70-189 mg/dL and estimated 10-year ASCVD risk ≥ 7.5% (estimated using the Pooled Cohort Equations)
Use of Statins

• Statins have an acceptable margin of safety when used in properly selected individuals and appropriately monitored.

• Statin therapy recommended for secondary and primary prevention of ASCVD

• Based on RCTs, statins reduce morbidity and mortality associated with ASCVD

• Cost-effective: many statins are now generic
Figure 2. Major recommendations for statin therapy for ASCVD prevention

**ASCVD Statin Benefit Groups**
Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.

- Adults age >21 y and a candidate for statin therapy
  - Yes → Clinical ASCVD
  - No

**Clinical ASCVD**

- Yes → Age ≤75 y
  - Yes → High-intensity statin
    (Moderate-intensity statin if not candidate for high-intensity statin)
  - No → Age >75 y OR if not candidate for high-intensity statin
    Moderate-intensity statin
- No

**LDL-C ≥190 mg/dL**

- Yes → High-intensity statin
  (Moderate-intensity statin if not candidate for high-intensity statin)
- No

**Diabetes**
Type 1 or 2
Age 40-75 y

- Yes → Moderate-intensity statin
- No → Estimated 10-y ASCVD risk ≥7.5%*
  High-intensity statin

**Estimate 10-y ASCVD Risk with Pooled Cohort Equations**

- Yes → Moderate-to-high intensity statin
- No → ASCVD prevention benefit of statin therapy may be less clear in other groups

In selected individuals, consider additional factors influencing ASCVD risk and potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment.

Treat to Target was Abandoned

• Current trial data does not indicate what the target should be.
  – No data from clinical trials on the magnitude of additional ASCVD risk reduction achieved with one target lower than another
  – Potential for adverse effects of multidrug therapy that might be needed to achieve a specific goal
More on LDL-C and Non-HDL-C Goals

• RCT evidence shows that ASCVD events are reduced by using the maximum tolerated statin intensity in those groups shown to benefit.

• In secondary prevention, evidence supports high-intensity statin therapy to maximally lower LDL-C.

• No RCTs titrated drug therapy to specific LDL-C and non-HDL-C goals to improve ASCVD outcomes.

• In AIM-HIGH, the additional reduction in non-HDL-C with niacin DID NOT further reduce ASCVD risk in individuals treated to LDL-C levels of 40-80 mg/dL.
Primary Prevention

• Use the new Pooled Cohort Equations to estimate 10-year ASCVD risk.

• Guideline is “patient centered”
  – Potential for risk reduction benefit, adverse effects, and drug-drug interactions, along with patient preferences, must be considered before statins are prescribed for the primary prevention of ASCVD.
Shared Decision Making (SDM) When Appropriate

- Engage in a clinician–patient discussion before initiating statin therapy, especially for primary prevention in patients with lower ASCVD risk.
- The cholesterol guidelines recommend not only the risk calculation, but also the clinician–patient review of the risk and the decision to take a statin.
Shared Decision Making (SDM) When Appropriate

- Age is a major contributor to the ASCVD risk calculation.
- A 65-year-old man and a 71-year-old woman with optimal risk factors have a >7.5% 10-year risk.
- Clinical judgment, statin safety issues, and consideration of patient preferences inform the treatment plan.
- Prescription of a statin is not automatic.
- Treatment plan is a comprehensive approach to risk reduction that begins with the use of the ASCVD risk calculator and incorporates addressing of the modifiable risk factors.
10-year ASCVD risk of 7.5% or higher

- These individuals can be identified by using the new Pooled Cohort Equations for ASCVD risk prediction, developed by the Risk Assessment Work Group.
- Stroke now included in ASCVD risk assessment, in addition to myocardial infarction (MI)
- Separate equations for nonwhite populations
Role of Biomarkers and Noninvasive Tests

• In select individuals who are not in 1 of 4 statin benefit groups, and for whom the decision to initiate statin therapy is unclear, additional factors may be used to inform treatment decisions.

• Factors include:
  – LDL-C ≥ 160 mg/dL
  – Family history of premature ASCVD
  – Hs-CRP ≥ 2 mg/L
  – CAC score ≥ 300 Agatston units or 75th percentile for age, sex, and ethnicity
  – ABI < 0.9
  – Elevated lifetime risk of ASCVD
Intensity of Statin Therapy

- High-intensity statin therapy is defined as a daily dose that lowers LDL-C by $\geq 50\%$
- Moderate-intensity statin therapy lowers LDL-C by 30% to <50\%.
Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL−C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL−C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL−C on average, by &lt;30%</td>
</tr>
<tr>
<td><strong>Atorvastatin (40†)–80 mg Rosuvastatin 20 (40) mg</strong></td>
<td><strong>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</strong></td>
<td><strong>Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg</strong></td>
</tr>
</tbody>
</table>

Figure 3. Initiating statin therapy in individuals with clinical ASCVD

**Clinical ASCVD**
- Not currently on statin therapy
  - Initial evaluation prior to statin initiation
    - Fasting lipid panel*
    - ALT
    - CK (if indicated)
    - Consider evaluation for other secondary causes (Table 6) or conditions that may influence statin safety (Table 8, Rec 1).

**Evaluate and Treat Laboratory Abnormalities**
1. Triglycerides ≥500 mg/dL
2. LDL–C ≥190 mg/dL
   - Secondary causes (Table 6)
   - If primary, screen family for FH
3. Unexplained ALT >3X ULN

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**Aged ≤75 y without** contraindications, conditions or drug-drug interactions influencing statin safety, or a history of statin intolerance
- Initiate **high-intensity** statin therapy
- Counsel on healthy lifestyle habits

**Aged >75 y† or with** conditions or drug-drug interactions influencing statin safety, or a history of statin intolerance
- Initiate **moderate-intensity** statin therapy
- Counsel on healthy lifestyle habits

**Monitor statin therapy**
(Figure 5)

<table>
<thead>
<tr>
<th>Secondary Cause</th>
<th>Elevated LDL–C</th>
<th>Elevated Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Saturated or <em>trans</em> fats, weight gain, anorexia</td>
<td>Weight gain, very low-fat diets, high intake of refined carbohydrates, excessive alcohol intake</td>
</tr>
<tr>
<td>Drugs</td>
<td>Diuretics, cyclosporine, glucocorticoids, amiodarone</td>
<td>Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid</td>
</tr>
<tr>
<td>Diseases</td>
<td>Biliary obstruction, nephrotic syndrome</td>
<td>Nephrotic syndrome, chronic renal failure, lipodystrophies</td>
</tr>
<tr>
<td>Disorders and altered states of metabolism</td>
<td>Hypothyroidism, obesity, pregnancy*</td>
<td>Diabetes (poorly controlled), hypothyroidism, obesity; pregnancy*</td>
</tr>
</tbody>
</table>

*Cholesterol and triglycerides rise progressively throughout pregnancy (81); treatment with statins, niacin, and ezetimibe are contraindicated during pregnancy and lactation.

Statin Safety Recommendations

• Use moderate-intensity statin therapy in patients who are predisposed to statin-associated adverse effects.
  – Multiple or serious comorbidities, including impaired renal or hepatic function
  – History of previous statin intolerance or muscle disorders
  – Unexplained ALT elevations > 3 times ULN
  – Concomitant use of drugs affecting statin metabolism
  – > 75 years of age
  – History of hemorrhagic stroke
  – Asian ancestry

• CK should not be routinely measured, although it is reasonable to measure baseline CK in persons at increased risk for adverse muscle events
Statin Safety Recommendations

• During statin therapy, it is reasonable to measure CK for muscle symptoms (pain, stiffness, cramping, weakness)
• Baseline ALT should be performed before initiating statin therapy
• During statin therapy, it is reasonable to measure ALT if symptoms suggest hepatotoxicity (unusual fatigue, weakness, loss of appetite, abdominal pain, dark urine, jaundice)
• Decreasing the statin dose may be considered with 2 consecutive LDL-C levels < 40 mg/dL
• It may be harmful to initiate simvastatin at 80 mg daily or increase the dose to 80 mg daily
Statin Safety Recommendations

• Individuals on statin therapy should be evaluated for new onset DM.
  – Those who develop DM should be counseled on a heart-healthy diet, physical activity, healthy body weight, stopping tobacco use. Statin therapy should be continued to reduce their risk of ASCVD events.

• Use caution in individuals > 75 years of age, persons taking concomitant meds that alter drug metabolism, taking multiple drugs, taking drugs for conditions that required complex medication regimens (transplant patients or patients with HIV). Review prescribing information before initiating any cholesterol-lowering drug.
Monitoring Statin Therapy

- A baseline lipid panel should be obtained followed by a second lipid panel 4 to 12 weeks after initiation of statin therapy to determine patient’s adherence.
- Thereafter, assessments should be every 3 to 12 months as clinically indicated.
- LDL-C levels and per cent reduction are to be used only to assess response to therapy and adherence.
Insufficient Response to Statin Therapy

- In persons with a less-than-anticipated response to statin therapy or are intolerant to the recommended intensity of statin therapy:
  - Reinforce adherence to medication and lifestyle changes
  - Exclude secondary causes of hyperlipidemia
  - Investigate statin intolerance
- In persons at high ASCVD risk receiving the maximum tolerated statin who have a less-than-anticipated therapeutic response, addition of a nonstatin LDL lowering agent may be considered if the benefits outweigh the potential for adverse effects
  - Individuals with clinical ASCVD < 75 years of age
  - Individuals with baseline LDL-C ≥ 190 mg/dL
  - Individuals 40 to 75 years of age with diabetes
Synopsis of the Guideline

1. Adherence to a healthy lifestyle
2. Statins therapy for four groups
3. Safe use of statins
4. Shared Decision Making (SDM) when appropriate
5. Estimation of 10-year ASCVD risk
6. Intensity of statin therapy
7. No specific target LDL-C or non–HDL-C goals
8. Regularly monitor patients for adherence

Adapted from Stone NJ Ann Intern Med. Published online 28 Jan 28 2014
Blood Pressure Guidelines

By

JNC 8 Panel
Background

• JNC I 1976

• JNC 7 2003

• JNC 8 Organized in 2008
  – Review submitted 06/2013
Background

• Submitted for review to 16 federal agencies and 20 individual reviewers

• NHLBI subsequently decided AHA/ACC should make future guidelines

• Panel members submitted guidelines to JAMA for review
  – No official organization sponsorship
Methodology

• JNC 7
  – Followed methods of prior JNC committees
  – Literature review by expert committee
  – Evidence from all study designs evaluated
    • RCT and observational
  – Comprehensive overview of HTN management
    (measurement techniques, resistant hypertension, etc)
Methodology

• JNC 8
  – Based on 2011 Institute of Medicine guidelines recommendations\(^1\)
  – Systematic review of RCTs only
    • No meta-analyses of RCTs or observational data
  – Focused on 3 “highest ranked” questions for BP management
    • Nine recommendations

\(^1\)Graham R et al. National Academies 2011
Guideline Questions

1) Does initiating antihypertensive treatment at specific BP thresholds improve health outcomes?

2) Does treatment with antihypertensive therapy to a specific BP goal improved health outcomes?

3) Are there differences in benefit/harm between antihypertensive drugs or drug classes on specific health outcomes?
# Level of Evidence

## Size of Treatment Effect

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Level</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Benefit &gt;&gt; Risk</td>
<td>A</td>
<td>Procedure/Treatment SHOULD be performed/ administered</td>
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<td>Benefit &gt;&gt; Risk</td>
<td>B</td>
<td>Additional studies with focused objectives needed; IT IS REASONABLE to perform procedure/administer treatment</td>
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<td>Class IIb</td>
<td>Benefit &gt; Risk</td>
<td>C</td>
<td>Additional studies with broad objectives needed; additional registry data would be helpful. Procedure/Treatment MAY BE CONSIDERED</td>
</tr>
<tr>
<td>Class III</td>
<td>Risk &gt; Benefit</td>
<td>D</td>
<td>Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL</td>
</tr>
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### Estimate of Certainty (Precision) of Treatment Effect

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<td>Limited populations evaluated*</td>
<td>Recommendation in favor of treatment or procedure being useful/effective</td>
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<tr>
<td>Level C</td>
<td>Very limited populations evaluated*</td>
<td>Recommendation in favor of treatment or procedure being useful/effective</td>
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*Denotes the number of randomized trials or meta-analyses.
### Strength of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong Recommendation</td>
</tr>
<tr>
<td></td>
<td>There is high certainty based on evidence that the net benefit(^a) is substantial.</td>
</tr>
<tr>
<td>B</td>
<td>Moderate Recommendation</td>
</tr>
<tr>
<td></td>
<td>There is moderate certainty based on evidence that the net benefit is moderate to substantial or there is high certainty that the net benefit is moderate.</td>
</tr>
<tr>
<td>C</td>
<td>Weak Recommendation</td>
</tr>
<tr>
<td></td>
<td>There is at least moderate certainty based on evidence that there is a small net benefit.</td>
</tr>
<tr>
<td>D</td>
<td>Recommendation against</td>
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<tr>
<td></td>
<td>There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.</td>
</tr>
<tr>
<td>E</td>
<td>Expert Opinion</td>
</tr>
<tr>
<td></td>
<td>(“There is insufficient evidence or evidence is unclear or conflicting, but this is what the committee recommends.”)</td>
</tr>
<tr>
<td></td>
<td>Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the committee thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.</td>
</tr>
<tr>
<td>N</td>
<td>No Recommendation for or against</td>
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James, PA et al. JAMA 2014
# Quality of Evidence

<table>
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<tr>
<th>Type of Evidence</th>
<th>Quality Rating¹</th>
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<td>Well-designed, well-executed RCTs that adequately represent populations to which</td>
<td>High</td>
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<tr>
<td>Well-conducted meta-analyses of such studies</td>
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<td></td>
</tr>
<tr>
<td>change our confidence in the estimate of effect.</td>
<td></td>
</tr>
<tr>
<td>RCTs with minor limitations affecting confidence in, or applicability of, the</td>
<td>Moderate</td>
</tr>
<tr>
<td>results</td>
<td></td>
</tr>
<tr>
<td>Well-designed, well-executed non-randomized controlled studies and well-designed,</td>
<td></td>
</tr>
<tr>
<td>well-executed observational studies</td>
<td></td>
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<tr>
<td>Well-conducted meta-analyses of such studies</td>
<td></td>
</tr>
<tr>
<td>Moderately certain about the estimate of effect; further research may have an</td>
<td></td>
</tr>
<tr>
<td>impact on our confidence in the estimate of effect and may change the estimate</td>
<td></td>
</tr>
<tr>
<td>RCTs with major limitations</td>
<td>Low</td>
</tr>
<tr>
<td>Non-randomized controlled studies and observational studies with major</td>
<td></td>
</tr>
<tr>
<td>limitations affecting confidence in, or applicability of, the results</td>
<td></td>
</tr>
<tr>
<td>Uncontrolled clinical observations without an appropriate comparison group (eg,</td>
<td></td>
</tr>
<tr>
<td>case series, case reports)</td>
<td></td>
</tr>
<tr>
<td>Physiological studies in humans</td>
<td></td>
</tr>
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<td>Meta-analyses of such studies</td>
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<tr>
<td>the estimate.</td>
<td></td>
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James, PA et al. JAMA 2014
JNC 8 Algorithm

General population (no diabetes or CKD)

- **Age ≥60 years**
  - Blood pressure goal
    - SBP <150 mm Hg
    - DBP <90 mm Hg
  - Nonblack
    - Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination.
  - Black
    - Initiate thiazide-type diuretic or CCB, alone or in combination.

- **Age <60 years**
  - Blood pressure goal
    - SBP <140 mm Hg
    - DBP <90 mm Hg
  - All ages
    - Diabetes present
      - No CKD
        - Blood pressure goal
          - SBP <140 mm Hg
          - DBP <90 mm Hg
        - All races
          - Initiate ACEI or ARB, alone or in combination with other drug class.
    - Diabetes present
      - Yes
        - Blood pressure goal
          - SBP <140 mm Hg
          - DBP <90 mm Hg
        - All races
          - Initiate ACEI or ARB, alone or in combination with other drug class.

Diabetes or CKD present

- Blood pressure goal
  - SBP <140 mm Hg
  - DBP <90 mm Hg
  - All ages
    - CKD present with or without diabetes
      - Blood pressure goal
        - SBP <140 mm Hg
        - DBP <90 mm Hg
      - All races
        - Initiate ACEI or ARB, alone or in combination with other drug class.
JNC 8 Algorithm

James, PA et al. JAMA 2014
Select a drug treatment titration strategy
A. Maximize first medication before adding second or
B. Add second medication before reaching maximum dose of first medication or
C. Start with 2 medication classes separately or as fixed-dose combination.
Recommendations at a Glance

When do the guidelines recommend starting medication?

If you are younger than 60 years
- Systolic 140 mm Hg or higher
- Diastolic 90 mm Hg or higher

If you are 60 years or older
- Systolic 150 mm Hg or higher
- Diastolic 90 mm Hg or higher

If you have chronic kidney disease or diabetes at any age
- Systolic 140 mm Hg or higher
- Diastolic 90 mm Hg or higher

Jin, J. JAMA 2014
“The Minority View”

• 5/17 panel members strongly disagreed with the age specific recommendation

1) Increased target -> reduction in antihypertensive intensity on a population level

2) Higher SBP goal may reverse current decline in CVD mortality, especially stroke

3) Insufficient evidence to support change

Wright et al. Annals of Internal Medicine 2014
“The Minority View”

- Age 60 vs. 80 for different SBP treatment goals

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Population</th>
<th>Goal BP, mm Hg</th>
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</tr>
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<tbody>
<tr>
<td>2014 Hypertension</td>
<td>General ≥60 y</td>
<td>&lt;150/90</td>
<td>Nonblack: thiazide-type diuretic, ACEI, ARB, or CCB; black: thiazide-type diuretic or CCB</td>
</tr>
<tr>
<td>guideline</td>
<td>General &lt;60 y</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
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<tr>
<td></td>
<td>CKD</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>ESH/ESC 2013</td>
<td>General nonelderly</td>
<td>&lt;140/90</td>
<td>Diuretic, β-blocker, CCB, ACEI, or ARB</td>
</tr>
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<td>27</td>
<td>General elderly &lt;80 y</td>
<td>&lt;150/90</td>
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<td></td>
<td>General ≥80 y</td>
<td>&lt;150/90</td>
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<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;140/85</td>
<td>ACEI or ARB</td>
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<tr>
<td></td>
<td>CKD no proteinuria</td>
<td>&lt;140/90</td>
<td>ACEI or ARB</td>
</tr>
<tr>
<td></td>
<td>CKD + proteinuria</td>
<td>&lt;130/90</td>
<td></td>
</tr>
<tr>
<td>CHEP 2013</td>
<td>General &lt;80 y</td>
<td>&lt;140/90</td>
<td>Thiazide, β-blocker (age &lt;60y), ACEI (nonblack), or ARB</td>
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<td>38</td>
<td>General ≥80 y</td>
<td>&lt;150/90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>&lt;130/80</td>
<td>ACEI or ARB with additional CVD risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACEI, ARB, thiazide, or DHPCCB without additional CVD risk</td>
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<td>ADA 2013</td>
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<td>ACEI or ARB</td>
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<td>39</td>
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<td>ACEI or ARB</td>
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<td>KDIGO 2012</td>
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<tr>
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<td>CKD + proteinuria</td>
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<td>NICE 2011</td>
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<td>&lt;55 y: ACEI or ARB</td>
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<td>41</td>
<td>General ≥80 y</td>
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<td>≥55 y or black: CCB</td>
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<td>ISHIB 2010</td>
<td>Black, lower risk</td>
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<td>Diuretic or CCB</td>
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<tr>
<td>42</td>
<td>Target organ damage or CVD risk</td>
<td>&lt;130/80</td>
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</tr>
</tbody>
</table>

Wright et al. Annals of Internal Medicine 2014
Age 60 vs. 80 for different SBP treatment goals

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<td></td>
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</table>

Wright et al. Annals of Internal Medicine 2014
“The Minority View”

“...we concluded that the evidence for increasing a blood pressure target in high-risk populations should be at least as strong as the evidence required to decrease the recommended blood pressure target”

Wright et al. Annals of Internal Medicine 2014
A Caveat for the Old Old

• A SBP goal of < 150 mmHg for frail persons aged ≥ 80 years is reasonable since they are at higher risk for treatment-related adverse effects
Controlling Hypertension in Adults\(^1\)

Systolic 140–159 or diastolic 90–99 (Stage 1 hypertension)
- Lifestyle modifications as a trial
- Consider adding thiazide

Recheck and review readings in 3 months\(^*\)

Systolic >160 or diastolic >100 (Stage 2 hypertension)
- Two drugs preferred:
  - Lifestyle modifications and
  - Thiazide and ACEI, ARB, or CCB
  - Or consider ACEI and CCB

Recheck and review readings in 2–4 weeks\(^*\)

No

BP at goal?

- Thiazide for most patients or ACEI, ARB, CCB, or combo
- If currently on BP med(s), titrate and/or add drug from different class

Recheck and review readings in 2–4 weeks\(^*\)

Yes

BP at goal?

- Encourage self-monitoring and adherence to meds
- Advise patient to alert office if he/she notes BP elevation or side effects
- Continue office visits as clinically appropriate

No

- Optimize dosage(s) or add medications
- Address adherence, advise on self-monitoring, and request readings from home and other settings
- Consider secondary causes

Consider referral to HTN specialist

*Recheck interval should be based on patient’s risk of adverse outcomes
This algorithm should not be used to counter the treating healthcare provider’s best clinical judgment.

Go AS et al., Hypertension 2013
Population Level Effect of Small Changes in Blood Pressure

- >50% of those with HTN are older than 60 in the US
- 51% treated to goal (JNC 7)
- Median SBP: treated 136mmHg, untreated 152mmHg
Blood Pressure and CVD Outcomes

- Prospective Studies Collaboration
- 61 observational studies
- 56,000 vascular deaths
- 12.7 million person year follow-up
Blood Pressure and CVD Outcomes

Lewington et al, Lancet 2002

Absolute risk (95% CI)

**Stroke**
- Age at risk:
  - 80-89 years
  - 70-79 years
  - 60-69 years
  - 50-59 years

Usual systolic blood pressure (mm Hg)

**IHD**
- Age at risk:
  - 80-89 years
  - 70-79 years
  - 60-69 years
  - 50-59 years
  - 40-49 years

Usual systolic blood pressure (mm Hg)
High Risk in Persons with the Higher Goal

• Age substantially increases risk for CV events.
  – No justification for different targets for patients older and younger than 60 years
• Risk range for white and AA men aged 60 years is 9% to 30%.
• Men aged ≥ 70 years with controlled SBP at 140 mmHg, even without CVD or DM, have a 10-year risk > 20%.
  – Based on absolute risk, using an age threshold of 60 years to define eligibility for less aggressive treatment lacks consistency.

Wright et al. Annals of Internal Medicine 2014
Insufficient Evidence for Differential HTN Treatment Benefit for Persons Older and Younger Than 60 Years

- HYVET and SHEP trials show that reducing SBP to ≈ 140 mmHg has substantial benefit without harm in older persons.
- Lack of benefit was shown in 2 Japanese trials that were underpowered (125 strokes and 67 CHD events combined).
  - Uncertain generalizability to other populations, e.g., African Americans
- Need stronger justification to recommend less aggressive target in high-risk populations

Wright et al. Annals of Internal Medicine 2014
• 4,733 participants with diabetes type 2

• Mean age 62, mean follow-up 5 years

• Clinical or subclinical CVD or ≥2 RF

• Primary outcome: nonfatal myocardial infarction, nonfatal stroke, or death from CVD
### ACCORD BP

![Graph showing systolic pressure over years since randomization for Intensive and Standard therapy groups.]

<table>
<thead>
<tr>
<th>Years since Randomization</th>
<th>Systolic Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive Therapy (N=2363)</td>
</tr>
<tr>
<td></td>
<td>134mmHg</td>
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</table>

### Table: Outcome Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (N=2363)</th>
<th>Standard Therapy (N=2371)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome*</td>
<td>208</td>
<td>237</td>
<td>0.88 (0.73–1.06)</td>
<td>0.20</td>
</tr>
<tr>
<td>Prespecified secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>126</td>
<td>146</td>
<td>0.87 (0.68–1.10)</td>
<td>0.25</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>36</td>
<td>62</td>
<td>0.59 (0.39–0.89)</td>
<td>0.01</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>34</td>
<td>55</td>
<td>0.63 (0.41–0.96)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Cushman, WC et al. NEJM 2010*
ACCORD BP

Cushman, WC et al. NEJM 2010

134mmHg
119mmHg

Years since Randomization

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (N = 2363)</th>
<th>Standard Therapy (N = 2371)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events</td>
<td>%/yr</td>
<td>no. of events</td>
<td>%/yr</td>
</tr>
<tr>
<td>Primary outcome*</td>
<td>208</td>
<td>1.87</td>
<td>237</td>
<td>2.09</td>
</tr>
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<tr>
<td>Any</td>
<td>36</td>
<td>0.32</td>
<td>62</td>
<td>0.53</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>34</td>
<td>0.30</td>
<td>55</td>
<td>0.47</td>
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<tr>
<td>Variable</td>
<td>Intensive Therapy (N=2362)</td>
<td>Standard Therapy (N=2371)</td>
<td>P Value</td>
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</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------------------------</td>
<td>---------------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events — no. (%)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Event attributed to blood-pressure medications</strong></td>
<td>77 (3.3)</td>
<td>30 (1.27)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>17 (0.7)</td>
<td>1 (0.04)</td>
<td>&lt;0.001</td>
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<tr>
<td>Syncope</td>
<td>12 (0.5)</td>
<td>5 (0.21)</td>
<td>0.10</td>
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<tr>
<td>Bradycardia or arrhythmia</td>
<td>12 (0.5)</td>
<td>3 (0.13)</td>
<td>0.02</td>
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<tr>
<td>Hyperkalemia</td>
<td>9 (0.4)</td>
<td>1 (0.04)</td>
<td>0.01</td>
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<tr>
<td>Angioedema</td>
<td>6 (0.3)</td>
<td>4 (0.17)</td>
<td>0.55</td>
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<tr>
<td>Renal failure</td>
<td>5 (0.2)</td>
<td>1 (0.04)</td>
<td>0.12</td>
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<tr>
<td>End-stage renal disease or need for dialysis</td>
<td>59 (2.5)</td>
<td>58 (2.4)</td>
<td>0.93</td>
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</tr>
<tr>
<td>Dizziness when standing</td>
<td>217/501 (44.3)</td>
<td>188/467 (40.3)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Estimated GFR &lt;30 ml/min/1.73 m²</td>
<td>99 (4.2)</td>
<td>52 (2.2)</td>
<td>&lt;0.001</td>
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</tbody>
</table>
### Lifestyle Modifications (LM)

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP Reduction (Range)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce weight</td>
<td>Maintain normal body weight (body mass index 18.5–24.9 kg/m²)</td>
<td>5–20 mm Hg/10 kg</td>
</tr>
<tr>
<td>Adopt DASH* eating plan</td>
<td>Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat</td>
<td>8–14 mm Hg</td>
</tr>
<tr>
<td>Lower sodium intake</td>
<td>a. Consume no more than 2,400 mg of sodium/day;</td>
<td>2–8 mm Hg</td>
</tr>
<tr>
<td></td>
<td>b. Further reduction of sodium intake to 1,500 mg/day is desirable since it is associated with even greater reduction in BP; and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c. Reduce intake by at least 1,000 mg/day since that will lower BP, even if the desired daily sodium intake is not achieved</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week)</td>
<td>4–9 mm Hg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men, and to no more than 1 drink per day in women and lighter weight persons</td>
<td>2–4 mm Hg</td>
</tr>
</tbody>
</table>

*DASH, dietary approaches to stop hypertension  
**The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals

Go AS et al., *Hypertension* 2013.
Decreasing your sodium intake: where is salt found in our diets?

- 5% added while cooking
- 6% added while eating
- 12% from natural sources
- 77% from processed and prepared foods
Treatment Recommendations: JNC 8

• In the general nonblack population, including those with DM, initial treatment should include a thiazide-type diuretic, CCB, ACEI, or ARB.
• In the general black population, including those with DM, initial treatment should include a thiazide-type diuretic or CCB.
• In pts ≥ 18 years with CKD and HTN, initial or add-on treatment should include ACEI or ARB to improve kidney outcomes.
Treatment Recommendations: JNC 8

- If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug. The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add a third drug.
- Do not use an ACEI and ARB in the same patient.
- Consider referral to a hypertension specialist for patients with difficult to control blood pressure.
Case Example

- 52-year-old Caucasian male
- History of hypertension; nonsmoker
- No known history of CAD; no symptoms of CAD
- Father had MI at age 55; mother has HTN
- BMI 29.5 kg/m²
- BP 160/88 mmHg (treated with lisinopril 10 mg)
- TC 210, HDL 33, TG 180, LDL 141, glucose 80
Pooled Cohort Risk Calculator

- Determines estimated 10-year risk for ASCVD events
- 10-year ASCVD risk: 11.5% vs 2.6% for male patient, same age, with optimal risk factors
- Lifetime ASCVD risk: 69% vs 5% for male with optimal risk factors
How would you manage this patient?
Primary Prevention with a 10-year ASCVD risk $\geq 7.5\%$

**Goals**

- Moderate-to-high intensity statin
- Weight reduction; heart-healthy diet
- Blood pressure control ($< 140/90$ mmHg)
  - *drug choices?*
  - *monitor in the office and at home*
- Regular physical activity program
What if this patient’s 10-year ASCVD risk was 7%?