# Hypertension and Hyperlipidemia 2018: What's New in Treatment Guidelines and What Do We Do Now?

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## Disclosures

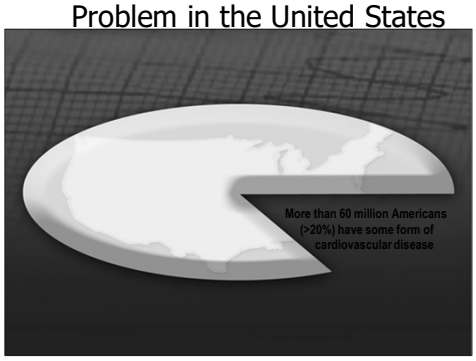
- Speaker Bureau: Sanofi-Pasteur, Merck, Pfizer, and Abbott
- Consultant: Pfizer, Sanofi-Pasteur, Merck, Arbor



## Objectives

- Upon completion of this lecture, the participant will be able to:
  - Identify complications associated with hypertension and hyperlipidemia
  - Discuss the revised JNC VII and AHA/ACC guidelines
  - Discuss nonpharmacologic and pharmacologic options for the treatment of hypertension and hyperlipidemia

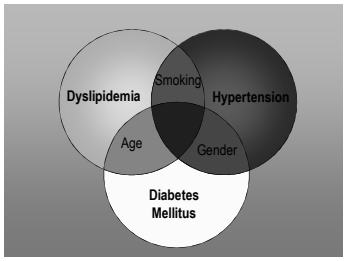
## CVD Is the Most Common Health Problem in the United States




Adapted from American Heart Association. *Heart Disease and Stroke Statistics – 2003 Update*. Dallas, Tex; 2002.



## Evolution in Understanding Cardiovascular Disease: Total Risk Perspective




**Cardiovascular Disease Is an Interplay of Risk Factors**

Kannel WB. *Am J Hypertens*. 2000;13:3S-10S; Poulter N. *Am J Hypertens*. 1999;12:92S-95S.



## Impact of Hypertension

- Hypertension is the most common condition seen in primary care
- **75 million** American adults (**29**%) have high blood pressure—that's 1 of every 3 adults
- 277,000 deaths annually in US due to hypertension[2]

[1]American Association of Clinical Endocrinologists Medical Guidelines For Clinical Practice for the Diagnosis and Treatment of Hypertension. Endocrine Practice, Vol 12 No. 2 March/April 2006
[2]National Center for Health Statistics. Health, United States, 2005, with Chartbook on the Health of Americans. Hyattsville, Maryland: 2004. Available at: http://www.cdc.gov/nchs/hus.htm

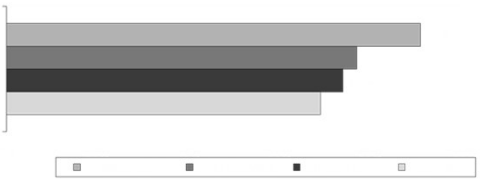
It is currently estimated that…

- For a 45 year old adult without hypertension, 40 year risk for developing is:
  - 93% African Americans
  - 92% Hispanics
  - 86% Whites
  - 84% Asians



## Hypertension Remains One of the Most Important Multipliers of CV Risk

BP >140/90 mm Hg is associated with:



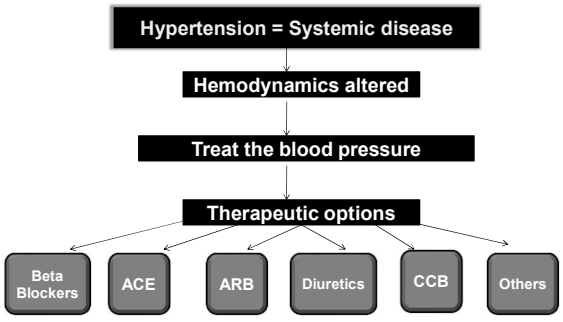
- 277,000 deaths in 2003

BP, blood pressure; CHF, congestive heart failure; MI, myocardial infarction.

Rosamond W et al. *Circulation*. 2007;115:1-103.

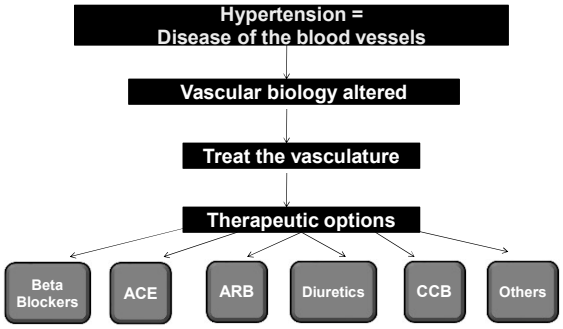


## Hypertension and Management: **Old** School




Adapted from Vascular Biology Working Group, University of Florida College of Medicine, Carl Pepine, MD, Director

## Hypertension and Management: **New** School




Adapted from Vascular Biology Working Group, University of Florida College of Medicine, Carl Pepine, MD, Director



## Case Study: MS

- 62 year old white female presents today for a complete PE
  - Feeling well without complaints
- Last visit in clinic 3 months ago
  - VS: 97.9, 84 bpm, 16 respirations/min, BP 142/94
  - BMI: 32
  - Eye: retinal examination normal
  - AAO, smiling, conversant
  - Carotids: 2+ bilaterally, no bruits
  - Heart: S1S2, RRR, no S3, S4, murmurs
  - PV: DPPT – 2+ bilaterally without edema



## Today:

- Diagnosis 3 months ago:
  - Obesity (E66.0)
  - Elevated blood pressure without diagnosis of hypertension (R03.0)

## Case Study: MS

- What did I do with her 3 months ago??
- Lifestyle recommendations were provided



## 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/ APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults



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**Best Proven Nonpharmacological Interventions for Prevention and Treatment of Hypertension***

| | Nonpharmacological Intervention | Dose | Approximate Impact on SBP | |
|---|---|---|---|---|
| | | | Hypertension | Normotension |
| Weight loss | Weight/body fat | Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight. | -5 mm Hg | -2/3 mm Hg |
| Healthy diet | DASH dietary pattern | Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat. | -11 mm Hg | -3 mm Hg |
| Reduced intake of dietary sodium | Dietary sodium | Optimal goal is <1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults. | -5/6 mm Hg | -2/3 mm Hg |
| Enhanced intake of dietary potassium | Dietary potassium | Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium. | -4/5 mm Hg | -2 mm Hg |

*Type, dose, and expected impact on BP in adults with a normal BP and with hypertension.
DASH indicates Dietary Approaches to Stop Hypertension; and SBP, systolic blood pressure.
Resources: Your Guide to Lowering Your Blood Pressure With DASH—How Do I Make the DASH?
Available at: https://www.nhlbi.nih.gov/health/resources/heart/hbp-dash-how-to.
Top 10 Dash Diet Tips. Available at: http://dashdiet.org/dash_diet_tips.asp

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**Best Proven Nonpharmacological Interventions for Prevention and Treatment of Hypertension* (cont.)**

| | Nonpharmacological Intervention | Dose | Approximate Impact on SBP | |
|---|---|---|---|---|
| | | | Hypertension | Normotension |
| Physical activity | Aerobic | ● 90–150 min/wk<br>● 65%–75% heart rate reserve | -5/8 mm Hg | -2/4 mm Hg |
| | Dynamic resistance | ● 90–150 min/wk<br>● 50%–80% 1 rep maximum<br>● 6 exercises, 3 sets/exercise, 10 repetitions/set | -4 mm Hg | -2 mm Hg |
| | Isometric resistance | ● 4 × 2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk<br>● 8–10 wk | -5 mm Hg | -4 mm Hg |
| Moderation in alcohol intake | Alcohol consumption | In individuals who drink alcohol, reduce alcohol† to:<br>● Men: ≤2 drinks daily<br>● Women: ≤1 drink daily | -4 mm Hg | -3 mm |

*Type, dose, and expected impact on BP in adults with a normal BP and with hypertension.
†In the United States, one "standard" drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).

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## Patient: MS

- 62 year old white female presents today for a complete PE
  - Feeling well without complaints
- Todays visit
  - VS: Pulse: 88 bpm, BP 160/96 mm/Hg
  - BMI: 32
  - Eye: retinal examination normal
  - AAO, smiling, conversant
  - Carotids: 2+ bilaterally, no bruits
  - Heart: S1S2, RRR, no S3, S4, murmurs
  - PV: DPPT – 2+ bilaterally without edema

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# Do We Have a Diagnosis of Hypertension?

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## Diagnosis

- 2 readings; separated apart
  - Use the average of 2 or more readings obtained on 2 or more occasions to estimate the individuals BP
- Patient should not ingest caffeine or smoke for 30 minutes before readings
- Patient should sit for 5 minutes with arm at heart level before blood pressure is checked



## Additional Recommendations

- Out of the office and self-monitoring of BP are recommended to confirm the diagnosis and for titration of BP-lowering medications
- For adults with untreated systolic BP of > 130 but < 160 or diastolic BP > 80 but < 100 mm Hg, it is reasonable to screen for white count hypertension using ABPM or HBPM prior to diagnosis



**Corresponding Values of SBP/DBP for Clinic, HBPM, Daytime, Nighttime, and 24-Hour ABPM Measurements**

| Clinic | HBPM | Daytime ABPM | Nighttime ABPM | 24-Hour ABPM |
|---|---|---|---|---|
| 120/80 | 120/80 | 120/80 | 100/65 | 115/75 |
| 130/80 | 130/80 | 130/80 | 110/65 | 125/75 |
| 140/90 | 135/85 | 135/85 | 120/70 | 130/80 |
| 160/100 | 145/90 | 145/90 | 140/85 | 145/90 |

ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; DBP diastolic blood pressure; HBPM, home blood pressure monitoring; and SBP, systolic blood pressure.

**Categories of BP in Adults***

| BP Category | SBP | | DBP |
|---|---|---|---|
| **Normal** | <120 mm Hg | and | <80 mm Hg |
| **Elevated** | 120–129 mm Hg | and | <80 mm Hg |
| **Hypertension** | | | |
| Stage 1 | 130–139 mm Hg | or | 80–89 mm Hg |
| Stage 2 | ≥140 mm Hg | or | ≥90 mm Hg |

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.



## Case Study: MS

- ≥ 60 years of age
- 2 readings confirm diagnosis
- Benign Essential Hypertension
  - Stage 2



**Basic and Optional Laboratory Tests for Primary Hypertension**

| | |
|---|---|
| **Basic testing** | Fasting blood glucose* |
| | Complete blood count |
| | Lipid profile |
| | Serum creatinine with eGFR* |
| | Serum sodium, potassium, calcium* |
| | Thyroid-stimulating hormone |
| | Urinalysis |
| | Electrocardiogram |
| **Optional testing** | Echocardiogram |
| | Uric acid |
| | Urinary albumin to creatinine ratio |

*May be included in a comprehensive metabolic panel.
eGFR indicates estimated glomerular filtration rate.

# Treatment of Hypertension



## Benefits of Lowering Blood Pressure

Average Percent Reduction

CVA: 35% - 40%
MI: 20% - 25%
CHF: 50%

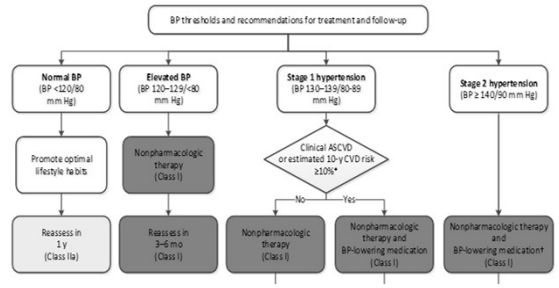
The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, And Treatment of High Blood Pressure, *http://jama.ama-assn.org/cgi/content/full/289.19.2560v1*. Assessed 5-1-08



## Case Study: MS

- How should she be treated?

**Blood Pressure (BP) Thresholds and Recommendations for Treatment and Follow-Up (continued on next slide)**

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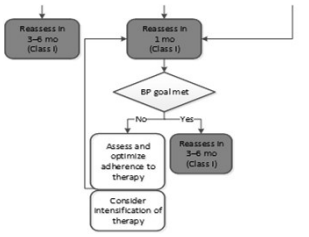


Colors correspond to Class of Recommendation in Table 1.
*Using the ACC/AHA Pooled Cohort Equations. Note that patients with DM or CKD are automatically placed in the high-risk category. For initiation of RAS inhibitor or diuretic therapy, assess blood tests for electrolytes and renal function 2 to 4 weeks after initiating therapy.
†Consider initiation of pharmacological therapy for stage 2 hypertension with 2 antihypertensive agents of different classes. Patients with stage 2 hypertension and BP ≥160/100 mm Hg should be promptly treated, carefully monitored, and subject to upward medication dose adjustment as necessary to control BP. Reassessment includes BP measurement, detection of orthostatic hypotension in selected patients (e.g., older or with postural symptoms), identification of white coat hypertension or a white coat effect, documentation of adherence, monitoring of the response to therapy, reinforcement of the importance of adherence, reinforcement of the importance of treatment, and assistance with treatment to achieve BP target.

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## Treatment and Follow-up Recommendations

- Elevated blood pressure or Stage 1 hypertension with low CVD risk
  - Repeat BP after 3-6 months of nonpharmacologic therapy
- Stage 1 Hypertension and high ASCVD risk (> 10%, 10-year risk)
  - Nonpharmacologic and pharmacologic therapy out of the gate
  - Recheck in 1 month

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## Treatment and Follow-up Recommendations

- Stage 2:
  - Nonpharmacologic and 2 anti-hypertensives out of the gate
  - F/u in 1 month
- SBP $\geq$ 160 or DBP $\geq$ 100 mm Hg
  - Initiate nonpharmacologic and 2 anti-hypertensives out of the gate
  - Careful monitoring; within days



## Pharmacologic Treatments



## Recommendations for Treatment

- Stage 1 hypertension
  - ACE, ARB, CCB, Thiazides
- Stage 2 hypertension
  - Two first line medications
- CKD
  - ACE or usual first line medications
- Blacks
  - Thiazides and CCB are preferred

## Choice of Initial Medication

| COR | LOE | Recommendation for Choice of Initial Medication |
|---|---|---|
| I | A$^{SR}$ | For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs. |

SR indicates systematic review.

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## Follow-Up After Initiating Antihypertensive Drug Therapy

| COR | LOE | Recommendation for Follow-Up After Initiating Antihypertensive Drug Therapy |
|---|---|---|
| I | B-R | Adults initiating a new or adjusted drug regimen for hypertension should have a follow-up evaluation of adherence and response to treatment at monthly intervals until control is achieved. |

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## Racial and Ethnic Differences in Treatment

| COR | LOE | Recommendations for Race and Ethnicity |
|---|---|---|
| I | B-R | 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. |
| I | C-LD | 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. |

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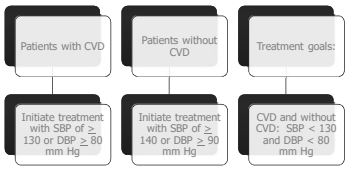
Important






**BP Treatment Threshold and the Use of CVD Risk Estimation to Guide Drug Treatment of Hypertension**

| COR | LOE | Recommendations for BP Treatment Threshold and Use of Risk Estimation* to Guide Drug Treatment of Hypertension |
|---|---|---|
| I | SBP: A<br>DBP: C-EO | Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher, and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP 130 mm Hg or higher or an average DBP 80 mm Hg or higher. |
| I | C-LD | Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher. |

*ACC/AHA Pooled Cohort Equations (http://tools.acc.org/ASCVD-Risk-Estimator/) to estimate 10-year risk of atherosclerotic CVD.

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**2017 Hypertension Guideline**

**Hypertension in Patients With Comorbidities**

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## Diabetes Mellitus

| COR | LOE | Recommendations for Treatment of Hypertension in Patients With DM |
|---|---|---|
| I | SBP: B-R[SR] | 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. |
| | DBP: C-EO | |
| I | A[SR] | 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. |
| IIb | B-NR | In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria. |

SR indicates systematic review.

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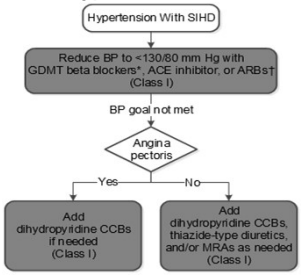
## Management of Hypertension in Patients With SIHD




Colors correspond to Class of Recommendation in Table 1.
*GDMT beta blockers for BP control or relief of angina include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Avoid beta blockers with intrinsic sympathomimetic activity. The beta blocker atenolol should not be used because it is less effective than placebo in reducing cardiovascular events.
†If needed for BP control.
•ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; GDMT, guideline-directed management and therapy; and SIHD, stable ischemic heart disease.

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## Heart Failure

| COR | LOE | Recommendation for Prevention of HF in Adults With Hypertension |
|---|---|---|
| I | SBP: B-R | In adults at increased risk of HF, the optimal BP in those with hypertension should be less than 130/80 mm Hg. |
| | DBP: C-EO | |

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## Heart Failure With Reduced Ejection Fraction

| COR | LOE | Recommendations for Treatment of Hypertension in Patients With HF*r*EF |
|---|---|---|
| I | C-EO | Adults with HF*r*EF and hypertension should be prescribed GDMT titrated to attain a BP of less than 130/80 mm Hg. |
| III: No Benefit | B-R | Nondihydropyridine CCBs are not recommended in the treatment of hypertension in adults with HF*r*EF. |

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## Heart Failure With Preserved Ejection Fraction

| COR | LOE | Recommendations for Treatment of Hypertension in Patients With HF*p*EF |
|---|---|---|
| I | C-EO | In adults with HF*p*EF who present with symptoms of volume overload, diuretics should be prescribed to control hypertension. |
| I | C-LD | Adults with HF*p*EF 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. |

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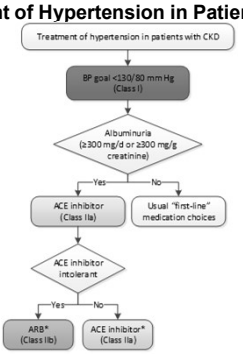
## Management of Hypertension in Patients With CKD




•Colors correspond to Class of Recommendation in Table 1.

•*CKD stage 3 or higher or stage 1 or 2 with albuminuria ≥300 mg/d or ≥300 mg/g creatinine.

•ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP blood pressure; and CKD, chronic kidney disease.

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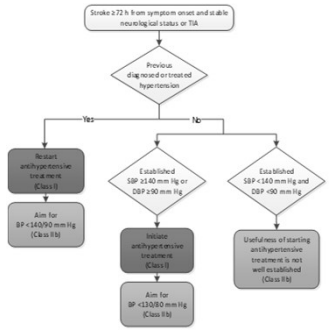
**Management of Hypertension in Patients With a Previous History of Stroke (Secondary Stroke Prevention)**

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Colors correspond to Class of Recommendation in Table 1. DBP indicates diastolic blood pressure; SBP, systolic blood pressure; and TIA, transient ischemic attack.

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## Thiazide Diuretics

- Dosing:
  - Start @ 12.5 mg of HCTZ
  - Increase to 25 mg at 6 weeks
- Benefits
  - 55% reduction in CHF
  - 37% reduction in CVA
  - 27% reduction in cardiac events
- If not adequately controlled, add additional agents



## Chlorthalidone

- Making a come back into thiazide arena; preferred in 2017 guidelines
- Dosage: 25 mg once daily
- May increase dosage to 100 mg once daily
- Chlorthalidone and thiazide diuretics
  - May be associated with a 21% decrease in fracture risk compared with lisinopril and amlodipine[1]

[1]Joshua I. Barzilay, MD et al. **Association of 3 Different Antihypertensive Medications With Hip and Pelvic Fracture Risk in Older Adults: Secondary Analysis of a Randomized Clinical Trial**. *JAMA Internal Medicine*, November 2016 DOI: 10.1001/jamainternmed.2016.6821

## Decreased Efficacy

- When GFR decreases below 30 mL/min, thiazide diuretics are likely ineffective
- Consider changing to loop diuretic at that time



## Diuretic Precautions

- Electrolyte imbalances
- Syncope/presyncope when combined with ACE/ARB
- Hemoconcentration
- Decrease in urate excretion
- Worsening of insulin resistance at higher doses
- Fatigue

**Product inserts accessed 04-20-2008**

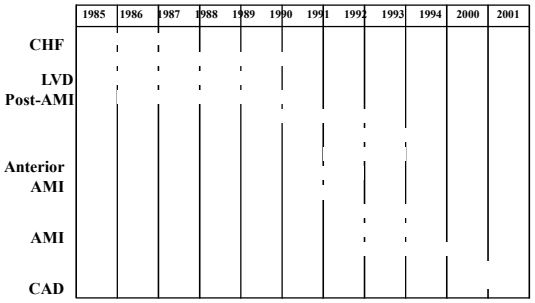


## Angiotensin Converting Enzyme (ACE) Inhibitors

- Increased nitrous oxide at vessel for vasodilatation
- Improved glucose disposal
- Reduction in LV geometry changes
- Reduction in inflammation
- Stabilization of fibrous cap of lipid lesion
- Decreased proteinuria
- Improves endothelial function
- Reduced mortality in patients with CHF
- Decreases post-MI mortality

Sato Atsuhisa, Pleiotropic effects of angiotensin-converting enzyme inhibitors; differentiation Among ace inhibitors may lead to further organ protection. Abstr 21st *Sci Meet Int Soc Hypertens* 2006, 423(2006)

## ACE Inhibitor Trials




Latini, et al. *Curr Perspect*, 1995;92:3132-7



## ACE Inhibitors Precautions

- Hyperkalemia
- Increase in creatinine
- May improve insulin sensitivity
- Decrease in serum Na+ may result in syncope and dizziness when used with diuretics
- Angioedema
- Cough

**Product inserts accessed 04-20-2009**



## Angiotensin Receptor Blockers

## Angiotension Receptor Blockers (ARB's)

- Utilized since April 1995
- Blocks uptake at receptor site
- Angiotension II produced in locations other than in the lungs
- BP decreased by reducing vascular tone and enhancing NA+ and water clearance



## Metabolic Effects of ARB's

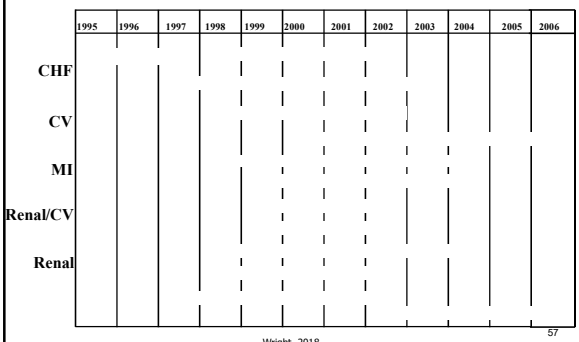
- Angiotensin II Receptor Blockers

- Metabolically neutral
- No impact on lipids
- No impact on insulin
- No impact on K+
- Lowers uric acid levels
- Minimal side effect profile

**Product Inserts accessed 04-20-2009**



## ARB Trials



## ACE vs ARB
## ONTARGET Trial

| | |
|---|---|
| | **1. Assess the effects of ACE VS ARB in terms of efficacy**<br>**2. Assess if the combination ACE & ARB was superior** |
| Results: | Telmisartan was found to be "noninferior" to ramipril in patients with vascular disease or high risk diabetes |
| | Combination of these two agents was associated with more adverse events without an increase in benefit. |

Yusuf, S, Teo KK, Pogue, J et al for the ONTARGET investigators. Telmisartan, ramipril, or both in patients At high risk for vascular events *N Engl J Med* 2008;358:1547-1559.

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## Calcium Channel Blockers

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## Calcium Channel Blockers

- Effectively treat systolic hypertension
- May be superior to other antihypertensives for stroke prevention
- Effective in patients with:
  - Comorbid conditions (Raynauds, migraine)[1]
- Particularly effective in
  - Elderly and African American's[2]

1. Materson BJ, Reda DJ, eta l. Single drug therapy for hypertension in men. A comparison of six Antihypertensive agents with placebo. N Engl J Med. 1993;328:914-921.
2. Tuomilehto J, Rastenyte D, et al. Effects of calcium channel blockade in older patients with Diabetes and hypertension. N Engl J med. 1999;340:677-684.

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## The Calcium Blockers

**Dihydropyridines**

- Studies of DPH's effects on proteinuria have produced conflicting results
- NKF recommends that in patients who have diabetes and kidney disease, DPH's should only be used in combination with and ACE or ARB

Thornley-Brown D, et al for the African American Study of Kidney Disease and Hypertension Study Group. Differing effects of antihypertensive drugs on the incidence Of Diabetes mellitus among patients with hypertensive kidney disease. *Arch Intern Med*. 2006;166(7):797-805.

**Nondihydropyridines**

- Regression of proteinuria
- Combination of Verapamil + ACE, reduction in proteinuria can be greater than achievable with verapamil alone.
- NKF now recommends adding a NDH to treat hypertension with an ACE inhibitor or an ARB to slow the progression of kidney disease.

National Kidney Foundation. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004; 43(suppl 1):S1-S290.



## What About Other Antihypertensives? When Do You Use?



## Update

- AHA/ACC: highlighted beta-blockers, renin-angiotensin-aldosterone system blockers, and thiazide diuretics as the mainstays of drug treatment for patients with CAD

http://www.pm360online.com/ahaacc-updates-hypertension-guidelines-for-cad-patients/ accessed 05-27-2015

## Beta blockers

- More cardioselective beta blockers are preferred
  - Bisoprolol and metoprolol succinate
  - Carvedilol (alpha and beta receptor activity) preferred in HFrEF
- Not first line unless CAD or HFrEF
- Should not be abruptly discontinued



## Alpha Blockers



## Alpha Blockers

- End in azosin
- Block postsynaptic Alpha$_1$ Receptors
- Results in vasodilatation and can cause orthostatic hypotension
- Relatively inexpensive
- Additive agent for older men to decrease BPH symptomatology
- Add-on agent only
- Should never be used as monotherapy due to increased risk of stroke and CHF

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, And Treatment of High Blood Pressure. *http://jama.ama-assn.org/cgi/content/full/289.19.2560v1*. Assessed 5-1-08

## Centrally Acting Blockers



## Centrally Acting Agents

- Stimulates central alpha$_2$ receptors which results in:
  - Inhibiting efferent sympathetic activity
- Additive agents
- Should be used last line
  - Examples: Clonidine (catapress, catapress TTS); methyldopa
- Caution: sedation, orthostatic hypotension



## Aldosterone Agonists

## Aldosterone Antagonists

- Spironolactone (Aldactone)
- HCTZ / spironolactone (Aldactazide)
- Eplerenone (Inspra)



## Aldosterone Antagonists

- May be recommended in the following individuals:
  - Post MI
  - NYHA Class III or IV
  - Ejection fraction of < 35%
  - Serum creatinine of < 2.5 mg/dl
  - K+ < 5.0 mmol/L

Mardi Gomberg-Maitland, Baran DA, Fuster, V. Treatment of Congestive Heart Failure Guidelines for the Primary Care Physician and Heart Failure Specialist. *Arch Intern Med* 2001;161:324-352et al. ACC/AHA 2005 Chronic Heart Failure Guideline Update. *JACC*.2005; 46:1116-43.



## Aldosterone Antagonists

- Spironolactone or eplerenone is preferred in treatment of primary aldosteronism and in resistant hypertension

# Precautions

- Must monitor electrolytes
- Must obtain baseline renal function
- Should discontinue the $K^+$ supplement
- Should limit to use in severe heart failure and post MI patients

Clavell, Alfredo L. Common Mistakes made in the Treatment of Congestive Heart Failure. Success with Failure: New Strategies for Evaluation and Treatment of CHF. Whistler BC, Canada 8-2000.



# Direct Renin Inhibitor

Renin is the enzyme at the beginning of the RAAS, one of the key regulating centers for blood pressure. Blocking this enzyme can decrease the downstream impact of the RAAS system.

Suppression of the RAAS has been shown to treat hypertension and reduce target organ damage.



# Direct Renin Inhibition Inhibits the Entire Renin System[1-4]

| Class | PRA | Ang I | Ang II |
|---|---|---|---|
| ACEI | ↑ | ↑ | ↓ |
| ARB | ↑ | ↑ | ↑ |
| Direct Renin Inhibitor (DRI) | ↓ | ↓ | ↓ |

Increased peptide levels have not been shown to overcome the blood pressure–lowering effect of these agents.
ACEI, angiotensin-converting enzyme inhibitor; Ang, angiotensin; ARB, angiotensin receptor blocker; PRA, plasma renin activity.

1. Johnston CI. *Blood Press Suppl*. 2000;1:9(suppl 1):9-13.
2. Widdop RE et al. *Hypertension*. 2002;40:516-520.
3. Fabiani ME et al. *Angiotensin II Receptor Antagonists*. 2001:263-278.
4. Lin C et al. *Am Heart J*. 1996;131:1021-1034.

## Warning re: Aliskiren

- Do not combine with ACE or ARB
- Avoid use of aliskiren and valsartan (Valturna)
- Warning followed after early termination of the ALTITUDE trial
  - Offered no benefit and was associated with an increased risk of CVA's



## 2017 Hypertension Guideline

**Special Patient Groups**



## Pregnancy

| COR | LOE | Recommendations for Treatment of Hypertension in Pregnancy |
|---|---|---|
| I | C-LD | Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy. |
| III: Harm | C-LD | Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors. |

## Age-Related Issues

| COR | LOE | Recommendations for Treatment of Hypertension in Older Persons |
|---|---|---|
| I | A | Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community-dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher. |
| IIa | C-EO | For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. |

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## 2017 Hypertension Guideline

### Other Considerations

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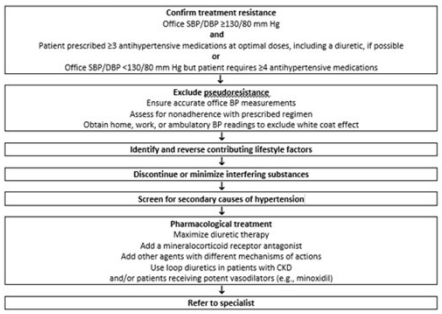
## Resistant Hypertension: Diagnosis, Evaluation, and Treatment

**Figure 10. Resistant Hypertension: Diagnosis, Evaluation, and Treatment**




BP indicates blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs; and SBP, systolic blood pressure.
Adapted with permission from Calhoun et al.

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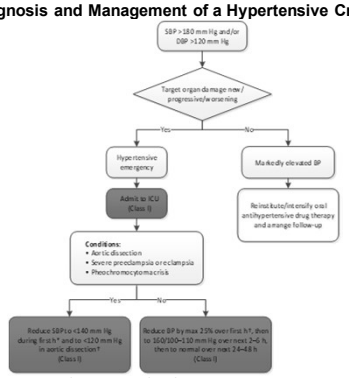
## Diagnosis and Management of a Hypertensive Crisis




Colors correspond to Class of Recommendation in Table 1.
*Use drug(s) specified in Table 19.
†If other comorbidities are present, use drug specified in Table 20.
BP indicates blood pressure; DBP, diastolic blood pressure; ICU, intensive care unit; and SBP, systolic blood pressure.

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## Hypertensive Urgency vs. Emergency

- Urgency
  - BP ≥ 180/120
  - No TOD
  - Often asymptomatic but may have headache, SOB
  - Adjust oral medications and f/u within 1 –few days
- Emergency
  - BP ≥ 180/120
  - + TOD
  - IV medication indicated
  - Goal: reduce mean arterial pressure by 25% in 1 hour
  - Monitored in ICU

http://www.consultant360.com/articles/acute-hypertension-hypertensive-urgency-and-hypertensive-emergency accessed 12-01-2016



## Patients Undergoing Surgical Procedures

| COR | LOE | Recommendations for Treatment of Hypertension in Patients Undergoing Surgical Procedures |
|---|---|---|
| | | **Preoperative** |
| I | B-NR | In patients with hypertension undergoing major surgery who have been on beta blockers chronically, beta blockers should be continued. |
| IIa | C-EO | In patients with hypertension undergoing planned elective major surgery, it is reasonable to continue medical therapy for hypertension until surgery. |
| IIb | B-NR | In patients with hypertension undergoing major surgery, discontinuation of ACE inhibitors or ARBs perioperatively may be considered. |

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**Patients Undergoing Surgical Procedures (cont.)**

| COR | LOE | Recommendations for Treatment of Hypertension in Patients Undergoing Surgical Procedures |
|---|---|---|
| | | **Preoperative** |
| IIb | C-LD | In patients with planned elective major surgery and SBP of 180 mm Hg or higher or DBP of 110 mm Hg or higher, deferring surgery may be considered. |
| III: Harm | B-NR | For patients undergoing surgery, abrupt preoperative discontinuation of beta blockers or clonidine is potentially harmful. |
| III: Harm | B-NR | Beta blockers should not be started on the day of surgery in beta blocker–naïve patients. |
| | | **Intraoperative** |
| I | C-EO | Patients with intraoperative hypertension should be managed with intravenous medications until such time as oral medications can be resumed. |

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# Combination Therapy

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**Choice of Initial Monotherapy Versus Initial Combination Drug Therapy**

| COR | LOE | Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy* |
|---|---|---|
| I | C-EO | Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target. |
| IIa | C-EO | Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target. |

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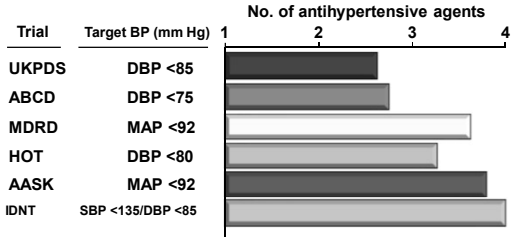
## Multiple Antihypertensive Agents Are Needed to Achieve Target BP




DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

Bakris GL et al. *Am J Kidney Dis*. 2000;36:646-661.
Lewis EJ et al. *N Engl J Med*. 2001;345:851-860.



## Sprint Trial

- Compares standard hypertensive treatment vs. intensive treatment
- 9300+ patients
- Goal:
  - Standard < 140 mm/Hg
  - Intensive < 120 mm/Hg
- Primary end point: MI, CVA, CHF, Death
- Stopped early at 3.26 years
  - 1.65%/year vs. 2.19%/year
  - All cause mortality decreased as well

http://www.nejm.org/doi/full/10.1056/NEJMoa1511939 accessed 02-10-2016



## Medication Adherence

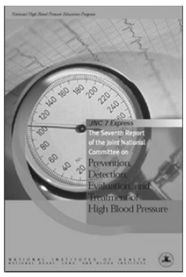
- Significant problem in United States
- Factors which affect adherence rates
  - Uninsured
  - Cost of medication
  - Multiple pills vs. one combine medication
  - Number of pharmacy visits
  - Patients who do not monitor

Hypertension is More than a Number!



## Target Organ Damage

- Heart
  - LVH, Angina, CHF, MI
- Brain
  - Stroke or TIA
  - Dementia
- Chronic Kidney Disease
- Peripheral Vascular Disease
- Retinopathy




*JAMA*. 2003:289:2560-2577.



## Hypertensive Urgency vs. Emergency

- Urgency
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- Emergency
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  - IV medication indicated
  - Goal: reduce mean arterial pressure by 25% in 1 hour
  - Monitored in ICU

http://www.consultant360.com/articles/acute-hypertension-hypertensive-urgency-and-hypertensive-emergency accessed 12-01-2016

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

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

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CVD, cardiovascular disease; and SBP, systolic blood pressure.

# Hyperlipidemia

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## 2013 ACC/AHA Guideline

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

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

***Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease***

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.

Wright, 2018 96

## Major Recommendations

97

## Treatment Options



## What's New?

| | |
|---|---|
| 1 | *Focus on ASCVD Risk Reduction: 4 statin benefit groups*<br>• Based on a comprehensive set of data from RCTs that identified 4 statin benefit groups which focus efforts to reduce ASCVD events in secondary and primary prevention.<br>• Identifies high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention. |
| 2 | *A New Perspective on LDL–C and/or Non-HDL–C Treatment Goals*<br>• The Expert Panel was unable to find RCT evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets.<br>• The appropriate intensity of statin therapy should be used to reduce ASCVD risk in *those most likely to benefit.*<br>• Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD. |

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.

## What's New?

| | |
|---|---|
| 3 | *Global Risk Assessment for Primary Prevention*<br>• This guideline recommends use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women.<br>• By more accurately identifying higher risk individuals for statin therapy, the guideline focuses statin therapy on *those most likely to benefit*.<br>• It also indicates, based on RCT data, those high-risk groups that may not benefit.<br>• Before initiating statin therapy, this guideline recommends a discussion by clinician and patients. |

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.



## What's New?

| | |
|---|---|
| 4 | *Safety Recommendations*<br>• This guideline used RCTs to identify important safety considerations in individuals receiving treatment of blood cholesterol to reduce ASCVD risk.<br>• Using RCTs to determine statin adverse effects facilitates understanding of the net benefit from statin therapy.<br>• Provides expert guidance on management of statin-associated adverse effects, including muscle symptoms. |
| 5 | *Role of Biomarkers and Noninvasive Tests*<br>• Treatment decisions in selected individuals who are not included in the 4 statin benefit groups may be informed by other factors as recommended by the Risk Assessment Work Group guideline. |

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.



## Major Recommendations

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.

## Four Major Statin Benefit Groups

- Those with clinical ASCVD
- Those with primary elevations of LDL–C ≥190 mg/dL
- Those with diabetes aged 40 to 75 years with LDL– C 70 to 189 mg/dL and without clinical ASCVD
- And…those without clinical ASCVD or diabetes with LDL–C 70 to189 mg/dL and estimated 10-year ASCVD risk ≥7.5%



## Let's Start with Clinical ASCVD

- Definition:
  - Acute coronary syndromes
  - History of MI
  - Stable or unstable angina
  - Coronary or other arterial revascularization
  - Stroke or TIA
  - Peripheral arterial disease presumed to be of atherosclerotic origin

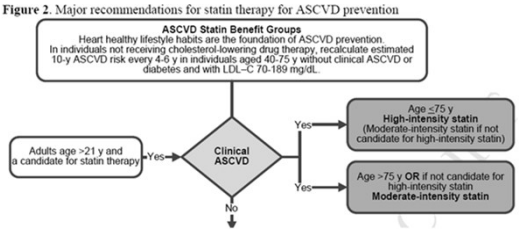
Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.



## Let's Start with Clinical ASCVD

- What to do….

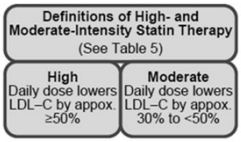
**Figure 2**. Major recommendations for statin therapy for ASCVD prevention




Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.

## High and Moderate Intensity Statins

- Definitions:




Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.



## High, Moderate and Low- Intensity Statins

- Let's operationalize:

**Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)***

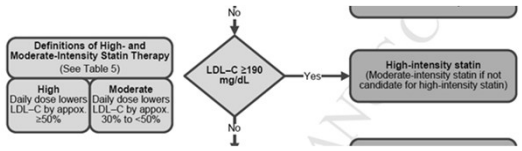
| High-Intensity Statin Therapy | Moderate-Intensity Statin Therapy | Low-Intensity Statin Therapy |
|---|---|---|
| Daily dose lowers LDL–C on average, by approximately ≥50% | Daily dose lowers LDL–C on average, by approximately 30% to <50% | Daily dose lowers LDL–C on average, by <30% |
| **Atorvastatin (40†)–80 mg**<br>**Rosuvastatin 20** *(40)* **mg** | **Atorvastatin 10** *(20)* **mg**<br>**Rosuvastatin** *(5)* **10 mg**<br>**Simvastatin 20–40 mg‡**<br>**Pravastatin 40** *(80)* **mg**<br>**Lovastatin 40 mg**<br>*Fluvastatin XL 80 mg*<br>**Fluvastatin 40 mg bid**<br>*Pitavastatin 2–4 mg* | *Simvastatin 10 mg*<br>**Pravastatin 10–20 mg**<br>**Lovastatin 20 mg**<br>*Fluvastatin 20–40 mg*<br>*Pitavastatin 1 mg* |

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.



## LDL-C ≥ 190 mg/dL

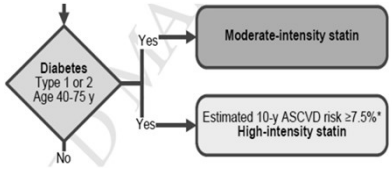
- If yes….high intensity statin:




Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.

## Diabetes Aged 40 - 75 years with LDL– C 70 to 189 mg/dL and without clinical ASCVD

- What to do:




Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.



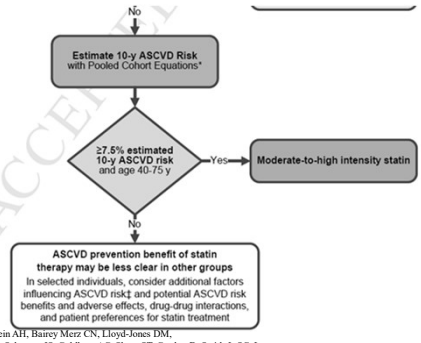
## So How Do You Calculate 10-Y ASCVD Risk?

- Tools available to calculate risk:
  - http://my.americanheart.org/cvriskcalculator
  - http://www.cardiosource.org/science-andquality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.



## Last Statin Benefit Group




Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.

## HMG CoA Reductase Inhibitors

- Action
  - Inhibit the HMG CoA reductase enzyme
  - Enzyme is essential for the synthesis of cholesterol
  - Also increases the uptake of LDL by the liver
  - Additional properties:
    - Smooth muscle cell proliferation, platelet aggregation and deposition, fibrinogen, endothelial vasodilation and blood viscosity are also affected by the statins



## Statins: LDL Lowering at Various Doses From Package Inserts

| | | | | |
|---|---|---|---|---|
| Lova *Mevacor®* | | 20 mg=29% | 40 mg=31% | 80 mg=48% |
| Prava *Pravachol®* | 10 mg=19% | 20 mg=29% | 40 mg=34% | 80 mg=48% |
| Simva *Zocor®* | 10 mg=28% | 20 mg=35% | 40 mg=40% | 80 mg=48% |
| Fluva *Lescol®* | | 20 mg=17% | 40 mg=23% | 80 mg=33% |
| Atorva *Lipitor®* | 10 mg=38% | 20 mg=46% | 40 mg=51% | 80 mg=54% |
| Rosuva *Crestor®* | 5 mg=43% | 10 mg=50% | 20 mg=53% | 40 mg=62% |
| Pitava *Livalo®* | | 1 mg=30% | 2 mg=36% | 4 mg=45% |



## Recent Landmark Coronary Prevention Studies

## Statins

- Recent study
  - Analysis of 20 years of data, researchers assessed the benefits of statin use on cardiovascular outcomes and all-cause mortality risk among men with various levels of LDL-C cholesterol
    - **STATINS REDUCE CHD RISK BY 27%**

http://www.consultant360.com/exclusives/statins-reduce-chd-risk-27 accessed 09-14-2017



## Important Information

- Statins may increase risk of diabetes
  - Studies now confirm this in both men and women
  - A meta-analysis of 13 trials, > 90,000 patients, found that statin use increases the overall absolute risk of developing diabetes mellitus by 0.39% over four years
- Statins may be administered to children age 7 and up with markedly elevated LDL's unresponsive to traditional therapy
- No longer need to monitor liver enzymes on scheduled basis; clinician judgement

http://www.aafp.org/afp/2017/0115/p78.html



## CK Measurement

- Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy.

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.

## According to Original Guideline, NO Longer Were We….

- Treating to a target LDL, HDL or triglycerides

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.



## 2016 ACC Update

- Statin intolerance
  - Temporary discontinuation of statin therapy
  - Lower dosing
  - Re-challenge preferably with 2-3 statins of differing metabolic pathways
  - Intermittent (1-3x weekly) dosing of long half-life statins

http://www.acc.org/latest-in-cardiology/ten-points-to-remember/2016/03/30/11/58/2016-acc-expert-consensus-decision-pathway-on-the-role-of-nonstatin



## Essentially….

- The following medications should be used for those who are completely statin intolerant
- Or….who have poor response to statins, despite maximal therapy and are in the highest risk groups (ASCVD, Diabetes, LDL-C $\geq$190 mg/dL)
  - If benefits outweigh risk and keeping in mind, no evidence to support risk reduction

Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, McBride P, Eckel RH, Schwartz JS, Goldberg AC, Shero ST, Gordon D, Smith Jr SC, Levy D, Watson K, Wilson PWF, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.11.002.

## Ezetimibe (Zetia): A Cholesterol Absorption Inhibitor

- Dosage: 10 mg once daily
- Efficacy: 18% reduction in LDL when used as monotherapy
  - When added to a statin – 25% reduction in LDL
  - 2016 Update: 1st non-statin option to be used or added if LDL not reduced by 50% or unable to take statin



## Combination Therapy

- Ezetimibe and simvastatin (Vytorin)
- Ezetimibe and atorvastatin (Liptruzet)
  - Dosages: 10/10, 10/20, 10/40
- Some studies support additional benefits from addition of ezetimibe in patients with ASCVD



## Bile Acid Sequestrants

- "Resins" (2nd option – 2016 ACC update)
- Indications: Hyperlipidemia; Particularly LDL
- Examples:
  - Cholestyramine (Questran)
  - Colestipol (Colestid)
  - Colesevelam HCL (Welchol)

## Bile Acid Sequestrants

- Side effects
  - –GI side effects are the most common
  - –Elders: may be at risk for a fecal impaction
  - –Decreased vitamin/medication absorption
  - –May also increase bleeding tendencies

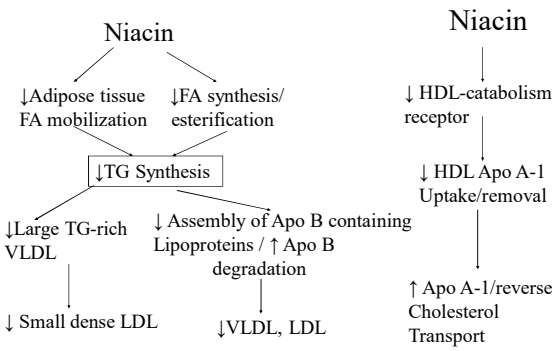


## Nicotinic Acid

- Examples
  - –Niacin (Immediate release)
  - –Niaspan (Extended release)
  - –INDICATION TO BE ADDED TO STATIN FOR HDL IMPROVEMENT AND TRIGLYCERIDE REDUCTION – REMOVED BY FDA



## Mechanism of Action of Niacin



## Not Everyone Deserves Niacin

- Recent information:
  - Individuals with heart disease and LDL < 70 mg/dL show no benefit from increasing HDL with niacin (AIM HIGH TRIAL)
  - High dose Niacin was added to simvastatin
  - Studied was concluded at 18 months when no benefit was seen; followed for 36 months
  - Despite raising HDL, no improved outcomes



## Another Study


- Recent information:
  - HPS2-THRIVE Trial
  - The addition of extended-release niacin–laropiprant to statin-based LDL cholesterol–lowering therapy did not significantly reduce the risk of major vascular events but did increase the risk of serious adverse events
  - Laropiprant has not cholesterol lowering effect and is used mainly to decrease flushing associated with niacin (prostaglandin receptor antagonist)

http://www.nejm.org/doi/full/10.1056/NEJMoa1300955 accessed 07-19-2014



## Fibric Acid Derivatives

- "Fibrates"
- Indications
  - Hypertriglyceridemia with a family history of atherosclerosis
- Examples
  - Gemfibrozil (Lopid)
  - Fenofibrate (Tricor)

## Fibric Acid Derivatives

- Mechanism of Action
  - Increase the clearance of VLDL from the plasma and therefore increase the secretion of cholesterol into bile
- Dosing
  - Gemfibrozil (Lopid): 600mg bid
  - Fenofibrate (Tricor, Antara):
    - 48 mg and 145 mg once daily
  - Fenofibric acid (Trilipix): 45mg and 135mg



## Fibric Acid Derivatives

- Results
  - Triglyceride reduction: 20-50%
  - HDL increase: 10-15%
  - LDL +/-
  - Limited data regarding long-term benefits of fibrate therapy
- Side effects
  - Generally well tolerated



## Significant FDA Warnings

- Combination of fibrate including fenofibric acid (Trilipix) in combination with statin
- Increased risks of rhabdomyolysis
- INDICATION TO BE ADDED TO STATIN REMOVED BY FDA

# Other Therapies



## Omega-3 Fatty Acids

- Omega-3 Fatty Acids (Lovaza, Vascepa)
- 1 gram capsules
- Dosages: 4 capsules daily
- Indications: reduce triglyceride levels in excess of 500 mg/dL
- Precautions: bleeding, anticoagulants
- Side effects: Burping



## Fish Oils

- AHA recommending 1 gram per day of fish oils for those with heart disease
- First prescription drug containing omega – 3 fatty acids (EPA and DHA)
- Lowers triglycerides as much as 45%
  - More concentrated (meaning they contain 3x more EPA and DHA than OTC products)

## One Regimen

- Flax Seed daily
  - Shown to reduce total cholesterol and LDL
  - No research to support lower morbidity and mortality
- Red Yeast Rice daily
  - Previously equivalent to approximately 10 mg of lovastatin (Mevacor)
  - No longer the case
  - No statin-like active ingredient



## Plant Stanols/Sterols

- Benecol, Right Start, Take Control
  - All spreadable "margarine" like products that have been shown to reduce LDL by approximately 15%
  - Can certainly be added to statin, niacin, fibrate or bile acid sequestrant
    - Dosage: 2 – 3 tbsp per day



## Super "Statins"

- PCSK9 Inhibitors
  - PCSK9 is a protein that promotes degradation of LDL receptor sites on the liver rendering less available to bind LDL
  - Monoclonal antibodies which inhibit PCSK9 enzyme resulting in more sites available on the liver
  - Less LDL in blood and more LDL on liver

## PCSK9 Inhibitors

- Indications:
  - Individuals at high risk for CVD (i.e. established CVD) on maximal doses of statins who need additional LDL reduction or who are unable to tolerate statins
  - Individuals with HeFH
    - (heterozygous familial hypercholesterolemia)



## PCSK9 Inhibitors

- Two products currently available:
  - Evolocumab (Repatha)
  - Alirocumab (Praluent)
- Self-administered SC injections every 2 – 4 weeks
- Approximately 90% achieve LDL < 70 mg/dL



## Preliminary Outcome (Post-Hoc) Data

- Overall: 50% reduction in CV events by 12-18 months
- Cardiovascular events: patients given standard treatment vs. evolocumab (2.18% vs. 0.95%)
- Cardiovascular events: patients given alirocumab + statin vs. placebo vs. statin (48% decrease)

https://www.researchgate.net/publication/273786247_PCSK9_inhibitors_reduce_cardiovascular_events_preliminary_data_show accessed 12-01-2016

## Emerging Information

- These medications are safe to use long-term
- ACC– just updated ASCVD guidelines
  - Addition of non-statin therapies to maximally tolerated statin therapy is recommended to be considered among patients with clinical ASCVD when additional LDL lowering is desired
  - Addition of either ezetimibe or a PCSK9 inhibitor should also factor in patient preferences, costs, and route of administration in addition to percent of LDL lowering desired
  - For <25% of additional LDL lowering, ezetimibe may be preferred, while in patients who require >25% additional LDL lower, a PCSK9 inhibitor may be preferred

http://www.acc.org/latest-in-cardiology/ten-points-to-remember/2017/09/05/10/03/2017-focused-update-of-the-2016-acc-expert-consensus-nonstatin accessed 09-14-2017



## Just to Confuse Us…

- AACE released guidelines in 2017



American Association of Clinical Endocrinologists and American College of Endocrinology

**Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease**

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## ASCVD Risk Categories

- **Low risk:**
  - No risk factors
- **Moderate risk**:
  - 2 or fewer risk factors and a calculated 10-year risk of less than 10%
- **High risk:**
  - An ASCVD equivalent including diabetes or stage 3 or 4 CKD with no other risk factors, or individuals with 2 or more risk factors and a 10-year risk of 10%-20%
- **Very high risk**:
  - Established or recent hospitalization for ACS; coronary, carotid or peripheral vascular disease; diabetes or stage 3 or 4 CKD with 1 or more risk factors; a calculated 10-year risk greater than 20%; or HeFH
- **Extreme risk:**
  - Progressive ASCVD, including unstable angina that persists after achieving an LDL-C less than 70 mg/dL, or established clinical ASCVD with diabetes, stage 3 or 4 CKD, and/or HeFH, or in those with a history of premature ASCVD (<55 years of age for males or <65 years of age for females)
  - This category was added in this CPG based on clinical trial evidence and supported by meta-analyses that further lowering of LDL-C produces better outcomes in individuals with ACS. IMPROVE-IT demonstrated lower rates of cardiovascular events in those with ACS when LDL-C levels were lowered to 53 mg/dL combining ezetimibe with statins.

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CPG, clinical practice guideline; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial.

*AACE/ACE CPG.* 2017;epub ahead of print; Cannon, CP, et al. *N Engl J Med.* 2015;372(25):2387-239; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice.* 2017;23(4):479-497.

## Cholesterol Treatment Trialists' 2010: Efficacy of Intensive LDL-C Lowering in Patients With Low Baseline LDL-C

**Meta-analysis of randomized controlled trials of major vascular events (coronary death, myocardial infarction, coronary revascularization, and ischemic stroke) with at least 1,000 patients and ≥2 years of more vs. less intense statin dosage (N=169,138)**

**For each 39 mg/dL reduction in LDL-C:**

- Individuals with baseline LDL-C <77 mg/dL had a **29%** further reduction in major vascular events (*P*=0.007)
- Those with baseline LDL-C <70 mg/dL had a **37%** further reduction in major vascular events (*P*=0.004)

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

Cholesterol Treatment Trialists' Collaboration. *Lancet* 2010;376:1670-1681; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice.* 2017;23(4):479-497.

## Question: What are lipid treatment goals?

Recommendations associated with this question:

**R35.** Treatment goals for dyslipidemia should be personalized according to levels of risk **(Grade A; BEL 1)**.

**R36.** For individuals at **low risk** (i.e., with no risk factors), an LDL-C goal of less than 130 mg/dL is recommended **(Grade A; BEL 1)**.

**R37.** For individuals at **moderate risk** (i.e., with 2 or fewer risk factors and a calculated 10-year risk of less than 10%), an LDL-C goal of less than 100 mg/dL is recommended **(Grade A; BEL 1)**.

**R38.** For individuals at **high risk** (i.e., with an ASCVD equivalent including diabetes or stage 3 or 4 CKD with no other risk factors, or individuals with 2 or more risk factors and a 10-year risk of 10%-20%), an LDL-C goal of less than 100 mg/dL is recommended **(Grade A; BEL 1)**.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice.* 2017;23(4):479-497.

## Question: What are lipid treatment goals?

Recommendations associated with this question:

**R39.** For individuals at **very high risk** (i.e., with established or recent hospitalization for ACS; coronary, carotid or peripheral vascular disease; diabetes or stage 3 or 4 CKD with 1 or more risk factors; a calculated 10-year risk greater than 20%; or HeFH), an LDL-C goal of less than 70 mg/dL is recommended **(Grade A; BEL 1)**.

**R40.** For individuals at **extreme risk** (i.e., with progressive ASCVD, including unstable angina that persists after achieving an LDL-C less than 70 mg/dL, or established clinical ASCVD in individuals with diabetes, stage 3 or 4 CKD, and/or HeFH, or in individuals with a history of premature ASCVD (<55 years of age for males or <65 years of age for females), an LDL-C goal of less than 55 mg/dL is recommended **(Grade A; BEL 1)**.

**R41.** An LDL-C goal of <100 mg/dL is considered "acceptable" for children and adolescents, with 100 to 129 mg/dL considered "borderline" and 130 mg/dL or greater considered "high" (based on recommendations from the American Academy of Pediatrics) **(Grade D)**.

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HeFH. heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

## Lipid Goals for Individuals at Risk for ASCVD

| Lipid parameter | Goal (mg/dL) |
|---|---|
| TC | <200 |
| LDL-C | <130 (low risk)<br><100 (moderate risk)<br><100 (high risk)<br><70 (very high risk)<br><55 (extreme risk) |
| Non–HDL-C | 30 above LDL-C goal; 25 above LDL-C goal (extreme risk individuals) |
| TG | <150 |
| Apo B | <90 (individuals at high risk of ASCVD, including those with diabetes)<br><80 (individuals at very high risk with established ASCVD or diabetes plus ≥1 additional risk factor)<br><70 (individuals at extreme risk) |

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

AACE/ACE 2017;epub ahead of print; Baigent C, et al. Lancet. 2010;376:1670-1681; Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-494; Brunzell JD, et al. *Diabetes Care*. 2008;31:811-822; Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-2397; Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Ridker PM, *J Am Coll Cardiol*. 2005;45:1644-1648; Sever PS, et al. *Lancet*. 2003;361:1149-1158; Shepherd J, et al. *Lancet*. 2002;360:1623-1630; Weiner DE, et al. *J Am Soc Nephrol*. 2004;15(5):1307-1315.

Thank You For Your Time and Attention!

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