2014 Guideline Update

Lipids
Stroke Prevention in Women
Management of Hypertension

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September 26, 2014

No Disclosures

Stone NJ, et al.
2013 ACC/AHA Blood Cholesterol 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

Scope of Guideline

- ***to reduce*** atherosclerotic cardiovascular disease(ASCVD)risk {RCTs,systematic analysis and metaanalysis of RCTs}.
- ASCVD – coronary heart disease(CHD),stroke,and peripheral arterial disease,all of presumed atherosclerotic origin.
- to **provide *strong evidence-based foundation.***
- only evidence from statin RCTs were used to develop guidelines.****
- Comprehensive approach to lipid management with relation to ASCVD reduction only, not for complex lipid disorders.

Basis of New Guidelines

- RCTs reviewed showed a consistent reduction in ASCVD events from Statins therapy in secondary and primary prevention, *no ASCVD event reduction in those with NYHA class II-IV HF or receiving maintenance hemodialysis.*
- Only *fixed doses of statins* with placebo or untreated controls, comparison of high dose with moderate intensity statins.
- No evaluation of the effect of titrated (dose adjusted) statin treatment to achieve prespecified LDL- C or non HDL-C goals.
- Use of niacin to additionally lower non HDL –C,once an LDL target was achieved, did not further reduce ASCVD outcomes.(AIM HIGH trial)
- The intensity of statin therapy is appropriate for those most likely to benefit.

Statin Intensity

HIGH INTENSITY THERAPY	MODERATE INTENSITY THERAPY	LOW INTENSITY THERAPY
Daily dose lowers LDL-C on average,by approximately ≥50%	Daily dose lowers LDL – C on average,by approximately 30-50%	Daily dose lowers LDL –C <30%
Atorvastatin (40) 80 mg	**Atorvastatin 10 *(20)* mg**	*Simvastatin 10 mg*
Rosuvastatin 20 *(40)* mg	**Rosuvastatin *(5)* 10 mg**	**Pravastatin 10-20 mg**
	Simvastatin 20-40 mg	**Lovastatin 20 mg**
	Pravastatin 40 *(80)* mg	*Fluvastatin 20-40 mg*
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg bid	
	Pitavastatin 2-4 mg	

4 Statin Benefit Groups

4 Statin Benefit Groups:

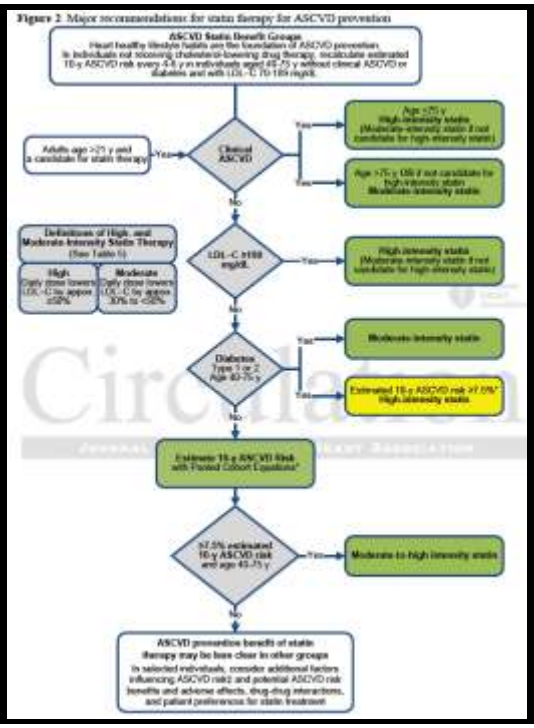
1. Individuals with clinical ASCVD
2. Individuals with primary elevations of LDL–C ≥190 mg/dL
3. Individuals 40 to 75 years of age with diabetes and LDL–C 70 to189 mg/dL without clinical ASCVD
4. Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL–C 70 to 189 mg/dL and have an estimated 10-year ASCVD risk of 7.5% or higher.

Individuals in the last group can be identified by using the Pooled Cohort Equations for ASCVD risk prediction developed by the Risk Assessment Work Group. Lifestyle counseling should occur at the initial and follow-up visits as the foundation for statin therapy and may improve the overall risk factor profile

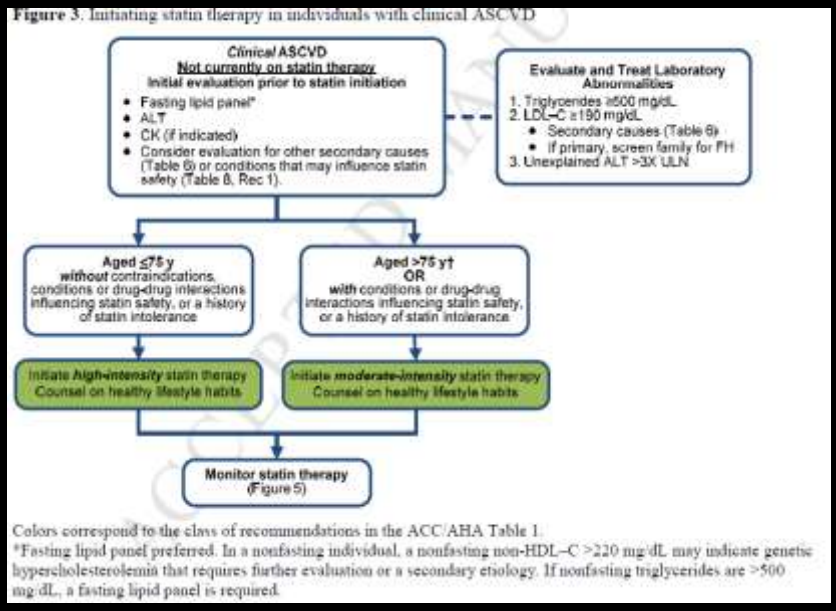
Statin Treatment Targets

(There are no targets)

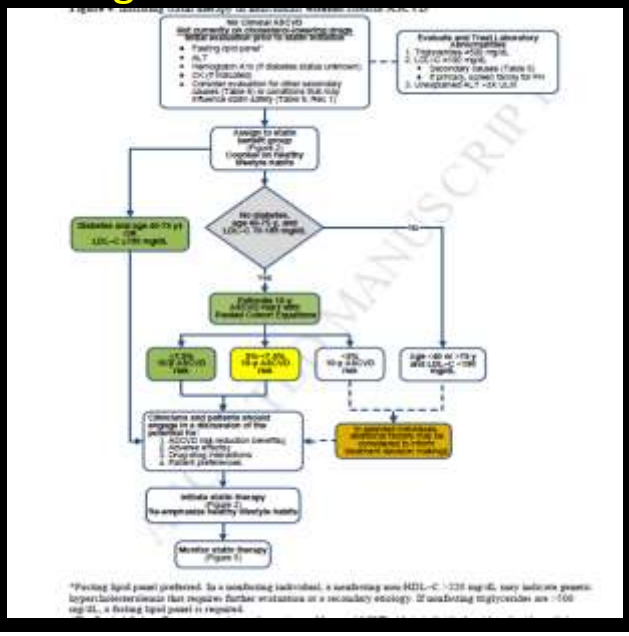
Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Treatment Targets				
1. The panel makes no recommendations for or against specific LDL–C or non-HDL–C targets for the primary or secondary prevention of ASCVD.	N (No recommendation)	1-4	N/A	N/A



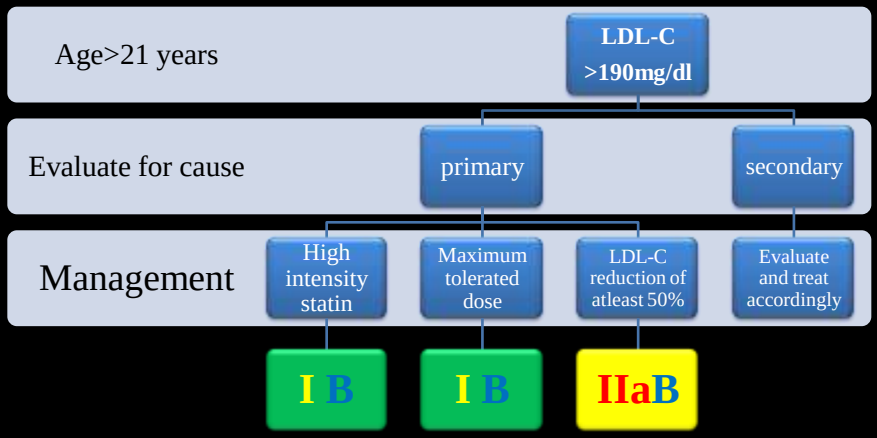
Initiating Statin Therapy: Clinical ASCVD



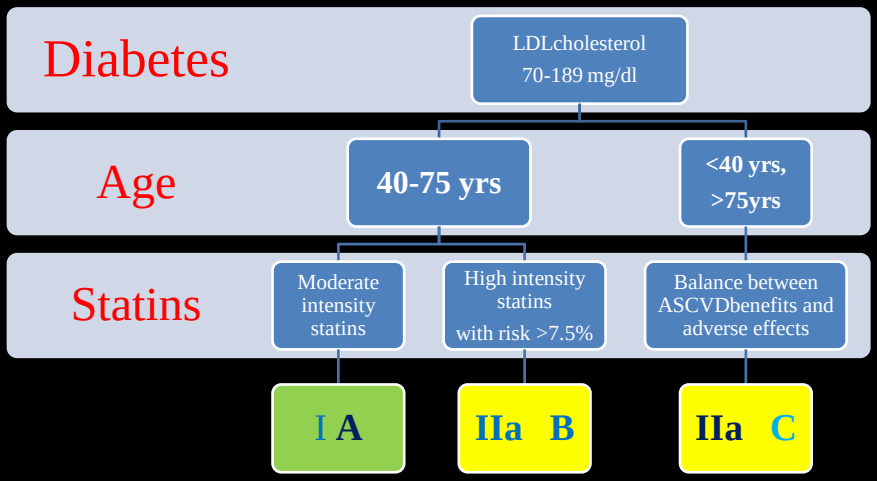
Initiating Statins: No clinical ASCVD



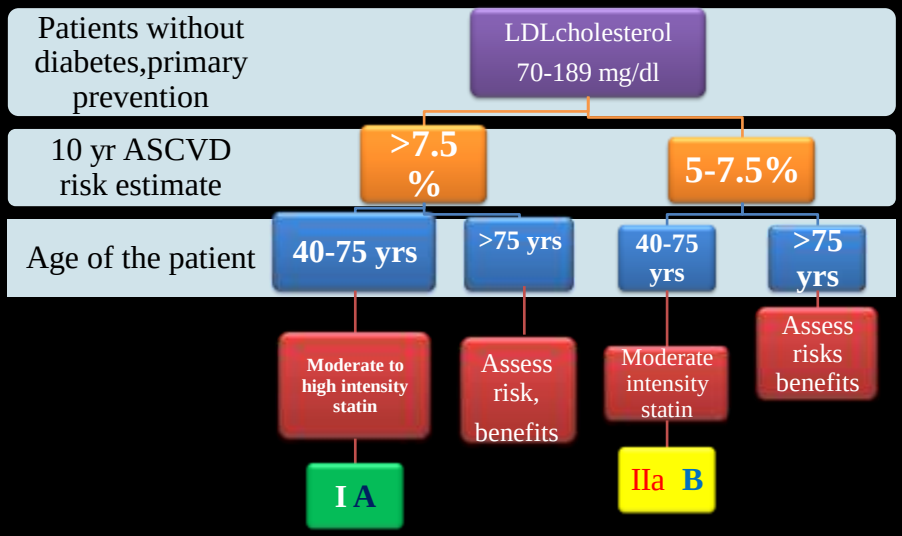
Primary prevention: LDL>190mg/dl

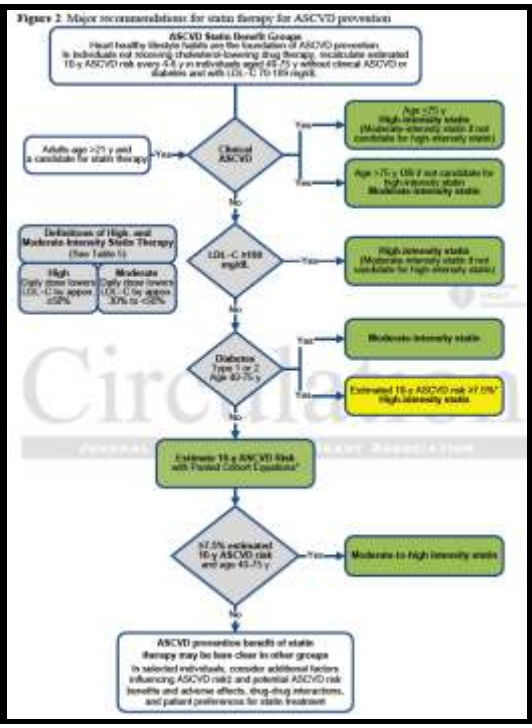


Primary prevention: with diabetes



Primary Prevention: No Diabetes. LDL 70-189





Monitoring Statin Therapy

Stone NJ, et al.
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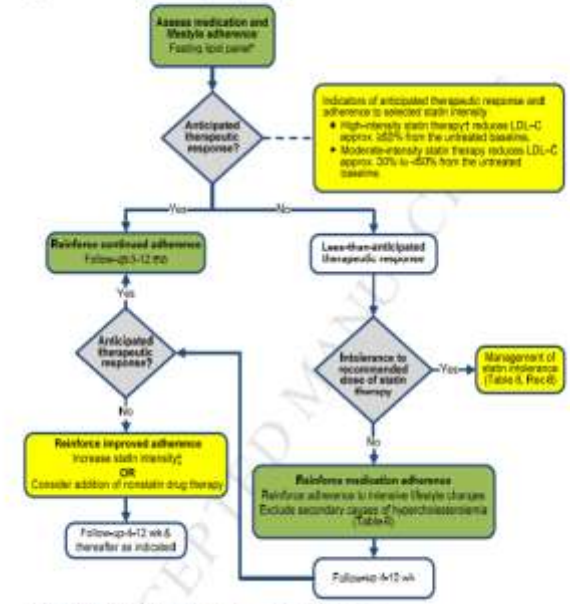
Figure 5. Statin Therapy: Monitoring therapeutic response and adherence



Pooled Cohort Risk Assessment Equations

Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event

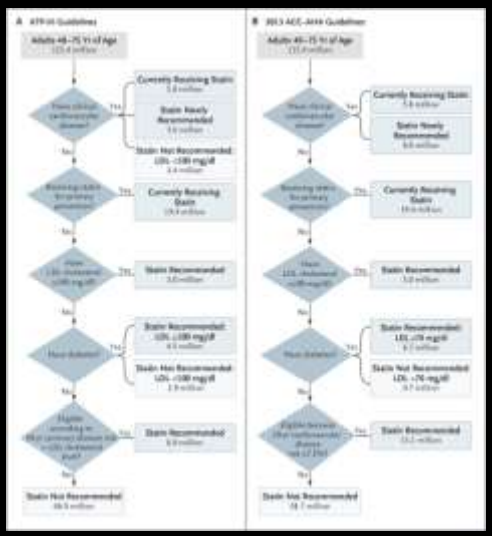
Risk Factors for ASCVD

Gender	Male / Female	Systolic BP	mmHg
Age	years	Receiving treatment for high blood pressure (if SBP > 120 mmHg)	No / Yes
Race	White or other	Diabetes	No / Yes
Total Cholesterol	mg/dL	Smoker	No / Yes
HDL Cholesterol	mg/dL		

Reset | Calculate

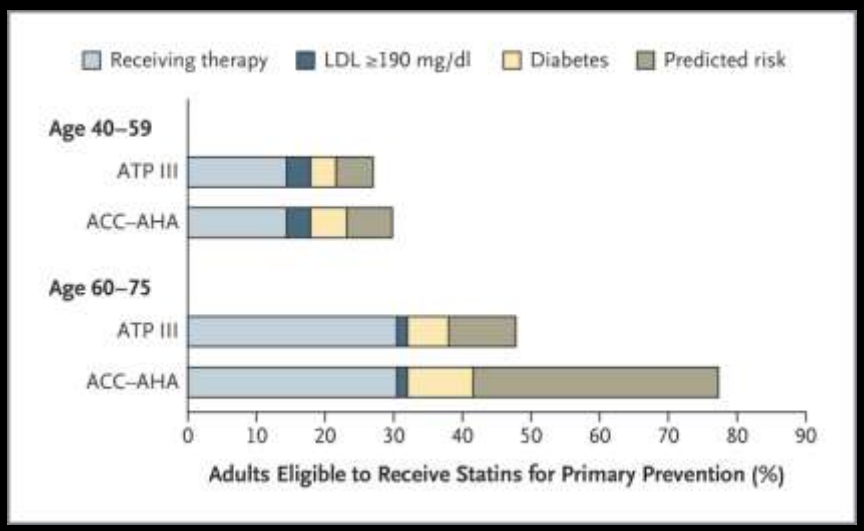
US units

Extrapolation of the NHANES Sample to All U.S. Adults, According to Two Guidelines for the Management of Cholesterol.



Pencina MJ et al. N Engl J Med 2014;370:1422-1431

Percent of U.S. Adults Who Would Be Eligible for Statin Therapy for Primary Prevention, According to Set of Guidelines and Age Group.



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Concerns

- Conflicts of Interest of the Panel
- Overestimation of risk by the pooled cohort calculator

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AHA/ASA Guideline

Guidelines for the Prevention of Stroke in Women

A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association Council on Stroke

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists

American Heart Association | American Stroke Association

Guideline Purpose

The aim of this statement is to summarize data on stroke risk factors that are unique to, and more common in women than men, and to expand upon the data provided in prior stroke guidelines and cardiovascular prevention guidelines for women.

Sex-Specific Risk Factors

Risk Factor	Sex-specific Risk	Stronger prevalence in women	Similar prevalence in men and women
Pregnancy	X		
Pre-eclampsia	X		
Gestational diabetes	X		
Oral contraceptive use	X		
Postmenopausal hormone use	X		
Changes in hormonal status	X		
Migraine with aura		X	
Atrial fibrillation		X	
Diabetes		X	

Sex-Specific Risk Factors- continued

Risk Factor	Sex-specific Risk	Stronger prevalence in women	Similar prevalence in men and women
Hypertension		X	
Physical inactivity			X
Age			X
Prior cardiovascular disease			X
Obesity			X
Diet			X
Smoking			X
Metabolic syndrome			X
Depression		X	
Psychosocial stress		X	

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Epidemiology of Stroke in Women

Women are disproportionally affected:

- Women have a higher lifetime risk
- 3.8 million women vs. 3 million in men
- 5th leading cause of death for men, the 3rd for women
- 53.5% of the estimated 795,000 new or recurrent strokes occur in women annually

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Vascular Stroke Risk

- Hypertension (HTN):
  - Is the most modifiable RF in both men and women
  - Is the major RF for women and first stroke
  - Is higher in post-menopausal years or >55 years of age
  - Is prevalent in about 78% of women (diagnosed and undiagnosed)
  - Is present in about 75% of women over the age of 60

HTN Summary and Gaps

- Further study needed regarding hormone related BP management
- BP management guidelines should be followed
  - AHA/ASA Guidelines for the Primary Prevention of Stroke, the ESH/ESC Guidelines and JNC-7

Pregnancy and Stroke

- Increased risk during pregnancy (especially 3rd trimester) and postpartum period

  Due to:

  venous stasis edema

  hypercoagulable states

  Stroke occurs in 34/100,000 deliveries

-
- Stroke in non-pregnant aggregate 21/100,000

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Pregnancy Complications and Long-Term Stroke Risk

- Research has suggested that complications during pregnancy (preeclampsia, gestational diabetes and HTN caused by pregnancy) are associated with a higher risk for future CV disease that expands beyond the childbearing years compared to women without these disorders

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Cerebral Venous Thrombosis (CVT)

- Stroke type caused by a thrombus formed in the venous sinuses.
  - Presents primarily with a complaint of headache
  - CVT accounts for 0.5-1% of all strokes
  - Incidence higher in women compared to men
  - Overall lower mortality and better functional outcomes than other stroke subtypes

CVT Risk Factors

- Female predominance
  - Hormonal factors
  - Contraceptives
  - Pregnancy
- Thrombophilia link
  - Antithrombin III, protein C, protein S deficiency, factor V Leiden

Class I Recommendations: Cerebral Venous Thrombus

Class I Recommendations	Class, (LOE)
In patients with suspected CVT, routine blood studies consisting of a complete blood count, chemistry panel, prothrombin time, and activated partial thromboplastin time should be performed.	Class I,LOE C
Screening for potential prothrombotic conditions that may predispose a person to CVT (eg, use of contraceptives, underlying inflammatory disease, infectious process) is recommended in the initial clinical assessment.	Class I,LOE C
For women with CVT during pregnancy, low molecular weight heparin (LMWH) is full anticoagulant doses should be continued throughout pregnancy, and LMWH or vitamin K antagonist with a target INR of 2.0 to 3.0 should be continued for at least 6 weeks postpartum (for a total minimum duration of therapy of 6 months).	Class I,LOE C

Oral Contraceptives (OCs)

- Stroke risk with low dose OCs users is about 1.4 to 2.0 times that of non-OC users
- Stroke risk is low but increases with age
- Other contraception: (need future evaluation of stroke risk)
  - Transderm patch
  - Vaginal ring
  - Intrauterine devices (IUDs)

Subgroups at Higher Risk of Stroke with Oral Contraceptives (OCs)

- Older women
- Smoke cigarettes
- Have hypertension
- Diabetes
- Obesity
- Hypercholesterolemia
- Prothrombotic mutations

Class I Recommendations: Oral Contraceptives

Class I Recommendations	Class, (LOE)
Measurement of blood pressure prior to initiation of hormonal contraception is recommended.	Class I, LOE B

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Recommendations: Menopause and Postmenopausal Hormone Therapy

Class III Recommendations	Class, (LOE)
Hormone therapy (conjugated equine estrogen) with or without medroxyprogesterone) should not be used for primary or secondary prevention of stroke in postmenopausal women.	Class III LOE A
Selective estrogen receptor modulators, such as raloxifene, tamoxifen, or tibolone, should not be used for primary prevention of stroke.	Class III LOE A

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Migraine with Aura

- Defined as a typical migraine headache with the addition of:
  - -homonymous visual disturbance
  - -unilateral paresthesia's
  - -numbness
  - -unilateral weakness
  - -aphasia or unclassified speech disturbance

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Migraine with Aura

- Migraine alone:
  - aggregate prevalence about 18.5%
  - Women four times more likely over men
- Migraine plus aura:
  - Prevalence approximately 4.4%
  - results in a 2.5% increase in ischemic stroke risk
  - Stroke risk increases with oral contraceptive use

Migraine with Aura

Migraine with Aura:

- Increases stroke risk with frequency
- Is associated with risk of IS and ICH in women especially under the age of 55 years (but risk is low)
- May be included in future risk profiles
- Is linked with milder strokes and TIA's

Recommendations: Migraine with Aura

Class IIb Recommendations	Class, (LOE)
Because there is an association between higher migraine frequency and stroke risk, treatments to reduce migraine frequency might be reasonable, through evidence is lacking that this treatment reduces the risk of first stroke.	Class IIb LOE C
Class IIa Recommendations	**Class, (LOE)**
Due to the increased stroke risk seen in women with migraine headaches with aura and smoking, it is reasonable to strongly recommend smoking cessation in women with migraine headaches and aura.	Class IIa LOE B

Obesity

- Obesity:
  - Is a risk factor for stroke (after considering other risk factors such as age, physical activity, smoking, alcohol consumption, diabetes and HTN
  - Epidemic may counter other advances made in smoking cessation, HTN and dyslipidemia awareness in the US
  - Is highly prevalent in non-hispanic black women

Metabolic Syndrome (MetSD)

- Affects 1/3 of the US population
- Stroke events in women (30% vs 4%) over men with Met SD
- Characterized as:
  - Abdominal adiposity
  - Dyslipidemia
  - Hypertension
  - Insulin resistance

Lifestyle

- Adherence to healthy lifestyle behaviors has shown to decrease stroke incidence in women.
- Lifestyle behaviors include:
  - Healthy diet
  - Physical activity
  - Moderate alcohol intake
  - Abstinence from smoking
  - Healthy BMI

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Recommendations: Obesity, Metabolic Syndrome and Lifestyle

Class I Recommendations	Class, (LOE)
A healthy lifestyle consisting of regular physical activity, moderate alcohol consumption (< 1drink per day for non-pregnant women), abstention from cigarette smoking, a diet rich in fruit, vegetables, grains, nuts, olive oil and low saturated fat is recommended for primary stroke prevention in women with cardiovascular risk factors.	Class I, LOE B
Lifestyle interventions focusing on diet and exercise are recommended for Primary stroke prevention among individuals at high risk for stroke	Class I, LOE B

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Risk Stratification for Women with AF

CHADS2 Risk Stratification Tool	
CHF	1 POINT
HTN	1 POINT
AGE ≥ 75	1 POINT
DIABETES MELLITUS	1 POINT
PRIOR STROKE/TIA	2 POINTS

- Risk assessment of women for stroke should take into account age and sex-specific differences

STROKE RISK SCORE	
0 POINT	LOW RISK
1 POINT	MODERATE RISK
≥2 POINTS	HIGH RISK

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Risk Stratification for Women with AF - continued

- Female sex is an independent predictor of stroke in patients with AF.
- CHA2DS2-Vasc score is an extension of the CHADS2 adding extra points for female sex

CHA2DS2-VASc Risk Stratification Tool	
Female Sex	1 POINT
Hx MI, PAD, or AORTIC PLAQUE	1 POINT
AGE 65-74	1 POINT
AGE > 75	2 POINT
EJECTION FRACTION < 35	(pending presently under consideration)

53

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Depression and Psychosocial Stress

- Depression increases the risk of stroke on both men and women
- Psychlogical stress incurs a 30% higher risk of stroke
- Women should be assessed for depression and psychosocial stress since both are more common in women

Recommendation: Depression and Psychosocial Stress

- Further research is needed to determine the mechanisms underlying the association between depression and stroke as well as to test whether depression might contribute to a stroke risk prediction score in women.

Carotid Stenosis

- Gender differences:
  - Women have smaller caliber ICA's
  - Women have shorter stenotic segments
  - Carotid endarterectomy (CEA) is performed less often in women (36.4% vs.53.8% in men)
  - Being female is an independent predictor of not receiving a CEA

Medical and Surgical Management of Carotid Stenosis

- Women appeared to derive less benefit from surgery (comparing medical mgmt. to surgical)
- Benefits and risks of carotid procedures in women with high grade stenosis remain unanswered.

New Guidelines for Hypertension

with thanks to Jennifer L. Simon, Pharm.D. for use of some of her slides

- National Institute for Health and Clinical Excellence (NICE), 2011
- Kidney Disease: Improving Global Outcome (KDIGO), 2012
- European Society of Hypertension/European Society of Cardiology, (ESH/ESC), 2013
- American Diabetes Association (ADA), 2014
- American Society of Hypertension and the International Society of Hypertension (ASH/ISH), 2014
- Eighth Joint National Committee (JNC8), 2013

Previous (JNC7)Hypertension Algorithm Summary

- Blood pressure goals
  - General population: < 140/90 mmHg
  - Hypertension with diabetes: < 130/80 mmHg
- Preferred agents for General Population
  - First-line
    - Thiazide Diuretic : HCTZ
      - ALLHAT Trial
  - Second-line
    - ACE inhibitor: Enalapril
  - Third-line
    - Beta-blocker (BB): Atenolol
    - Calcium Channel Blocker (CCB): Amlodipine

Comparison of JNC Guidelines

JNC7

- Nonsystematic literature review and expert opinion
- Range of study designs
- No grading system for recommendations
- Recommendations:
  - Lifestyle modifications
  - Initial therapy for HTN
  - Compelling indications
  - Addressed secondary HTN and resistant HTN

JNC8

- Systematic review
- Randomized, controlled trials (RCT) only
- Graded recommendations
- Recommendations:
  - No specific lifestyle recommendations
  - Initial therapy for HTN
  - Racial, CKD, and diabetic subgroups addressed
  - Addressed three key questions

JNC8: Key Questions

- In adults with HTN, does initiating antihypertensive pharmacologic therapy at **specific BP thresholds** improve health outcomes?
- In adults with HTN, does treatment with antihypertensive pharmacologic therapy to a **specified BP goal** lead to improvements in health outcomes?
- In adults with HTN, do various **antihypertensive drugs** or drug classes differ in comparative benefits and harms on specific health outcomes?

JNC8: Strength of Recommendation

Grade	Strength of Recommendation
A	**Strong**: High certainty net benefit is substantial
B	**Moderate** • Moderate certainty net benefit is moderate to substantial, or • High certainty that net benefit is moderate
C	**Weak**: At least moderate certainty of small net benefit
E	**Expert Opinion** • Insufficient evidence, or • Evidence is unclear or conflicting • Further research is recommended in this area

Recommendations for General Population Age < 60 Years

JNC 7

- BP Goal < 140/90 mmHg

JNC8

- SBP Goal < 140 mmHg
  - Grade E
- DBP Goal < 90 mmHg
  - Ages 30-59 years (Grade A)
  - Ages 18-29 years (Grade E)

Evidence for JNC8

- HDFP Trial
- Hypertension-Stroke Cooperative Trial
- MRC Trial
- ANBP Trial
- VA Cooperative Trial

Recommendations for General Population Age ≥ 60 Years

JNC 7

- BP Goal < 140/90 mmHg

(No age recommendations)

JNC8

- BP Goal < 150/90 mmHg
  - Rated Grade A

Evidence for JNC8

- HYVET Trial
- SHEP Trial
- JATOS Trial
- VALISH Trial

Recommendations for General Non-black Population (Including DM)

JNC 7

- First-line: Thiazide diuretics (no racial distinction made)

JNC8

- First-line
  - Thiazide diuretics
  - CCB
  - ACE inhibitor
  - ARB
- Grade B

Evidence for JNC8

- ALLHAT Trial
  - BP control more important than medication used
  - Alpha blockers not recommended first-line
- LIFE Study
  - Beta-blockers not recommended first-line
- Insufficient evidence to recommend other classes

Recommendations for General Black Population (Including DM)

JNC 7

- First-line: Thiazide diuretics (no racial distinction made)

JNC8

- Initial treatment for black population (Grade B) with DM (Grade C)
  - Thiazide diuretics
  - CCB

ALLHAT Trial

- Pre-specified subgroup analysis
- Thiazide more effective in improving CV outcomes compared to ACEi in black patient subgroup
  - 51% higher rate of stroke (RR 1.51; 95% CI 1.22-1.86) with use of ACEi as initial therapy in black patients (compared to CCB)
- 46% of patients in subgroup analysis had DM

Recommendations for General Population Age ≥ 18 with CKD

JNC 7

- Goal BP: < 130/80 mmHg
- First-line agent: ACEi or ARB

JNC8

- Goal BP: < 140/90 mmHg
  - Grade E
- Initial or add-on treatment: ACEi or ARB
  - Grade B
  - Regardless of race or DM status

Evidence for JNC8

- AASK Trial
- MDRD Trial
  - Potential benefit of goal <130/80 for patients with proteinuria (>3g/24 hours)
- REIN-2 Trial
- No trials showed goal <130/80 mmHg significantly lowered kidney or CV end points compared to 140/90

Summary of JNC8

BP Goal

- Age ≥ 60 years: < 150/90
  - Grade A
- General population: <140/90
  - Grade E (Grade A: DBP, age 30-59)
- Hypertension & DM: <140/90
  - Grade E
- Hypertension & CKD: <140/90
  - Grade E

Preferred Agent

- General population
  - Thiazide, CCB, ACEi, ARB (Grade B)
- Black population
  - CCB or Thiazide (Grade B)
    - Grade C for black patients with DM
- DM
  - Thiazide, CCB, ACEi, ARB (Grade B)
- CKD
  - ACEi or ARB (Grade B)

Recommendations for General Population Age ≥ 18 with DM

JNC 7

- Goal BP: < 130/80 mmHg

JNC8

- Goal BP: < 140/90 mmHg
  - Grade E

Evidence for JNC8

- ACCORD-BP Trial
  - No difference in outcomes with SBP < 140 vs. SBP < 120
- No good or fair quality trials to support DBP < 80

JNC8: Treatment Strategies

(Grade E)

- If goal BP not met after 1 month of treatment:
  - Increase dose of initial drug, or
  - Add a second drug (Thiazide, CCB, ACEi, or ARB)
- If goal BP not met with 2 medications:
  - Add and titrate a third medication (Thiazide, CCB, ACEi, or ARB)
  - Do not use ACE and ARB together
- Other classes may be used in the following scenarios:
  - Goal BP not met with 3 medications
  - Contraindication to thiazide, ACE/ARB, or CCB