

Hypertension Guidelines and Lipid Control: Clinical Implementation of New Guidelines

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Disclosures

No Disclosures



Objectives

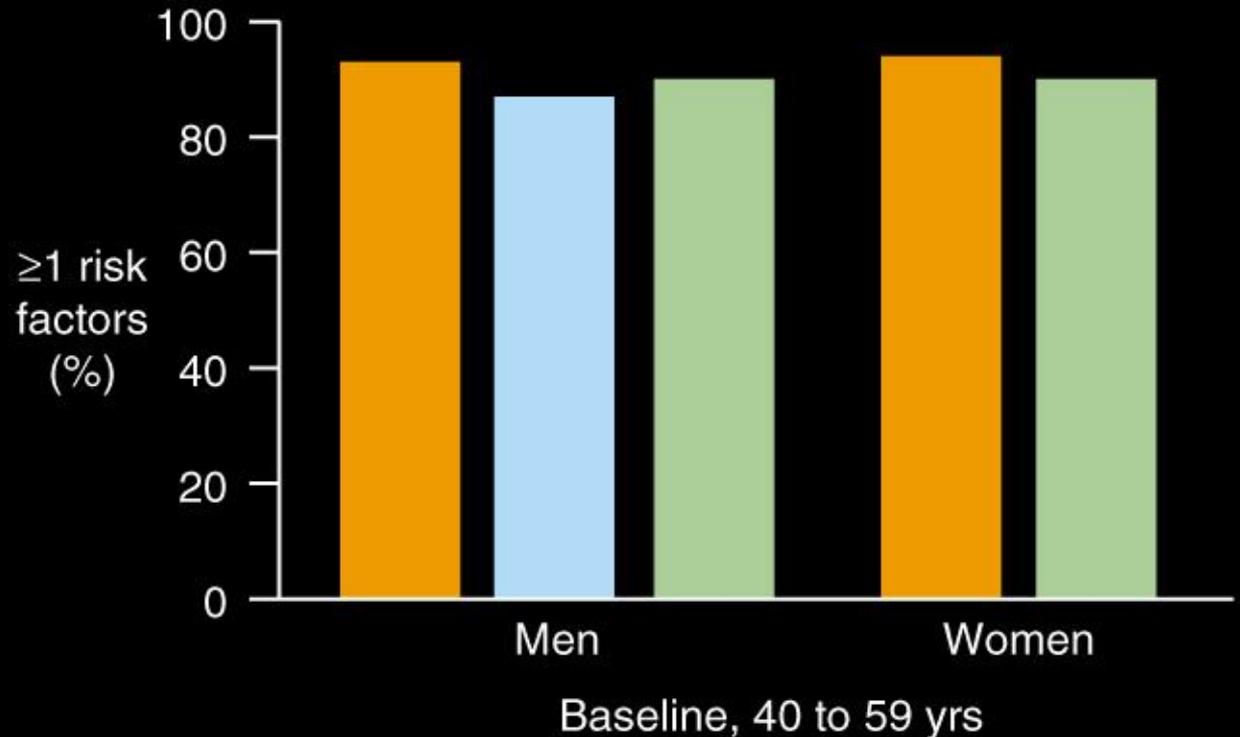
- To review 2013 ACC/AHA Guidelines on the treatment of blood cholesterol
- To review the JNC 8 report on the 2014 guideline for management of hypertension in adults
- To discuss key changes and some of the controversies in comparison to previous guidelines
- To present clinical scenarios regarding above guideline updates to assist with implementation into your everyday practice

4 Traditional risk factors precede >80% of CHD events

3 Prospective studies, ~384,000 subjects, 21–30 yr follow-up

Chicago Heart Assoc Detection Project MRFIT Framingham Heart Study

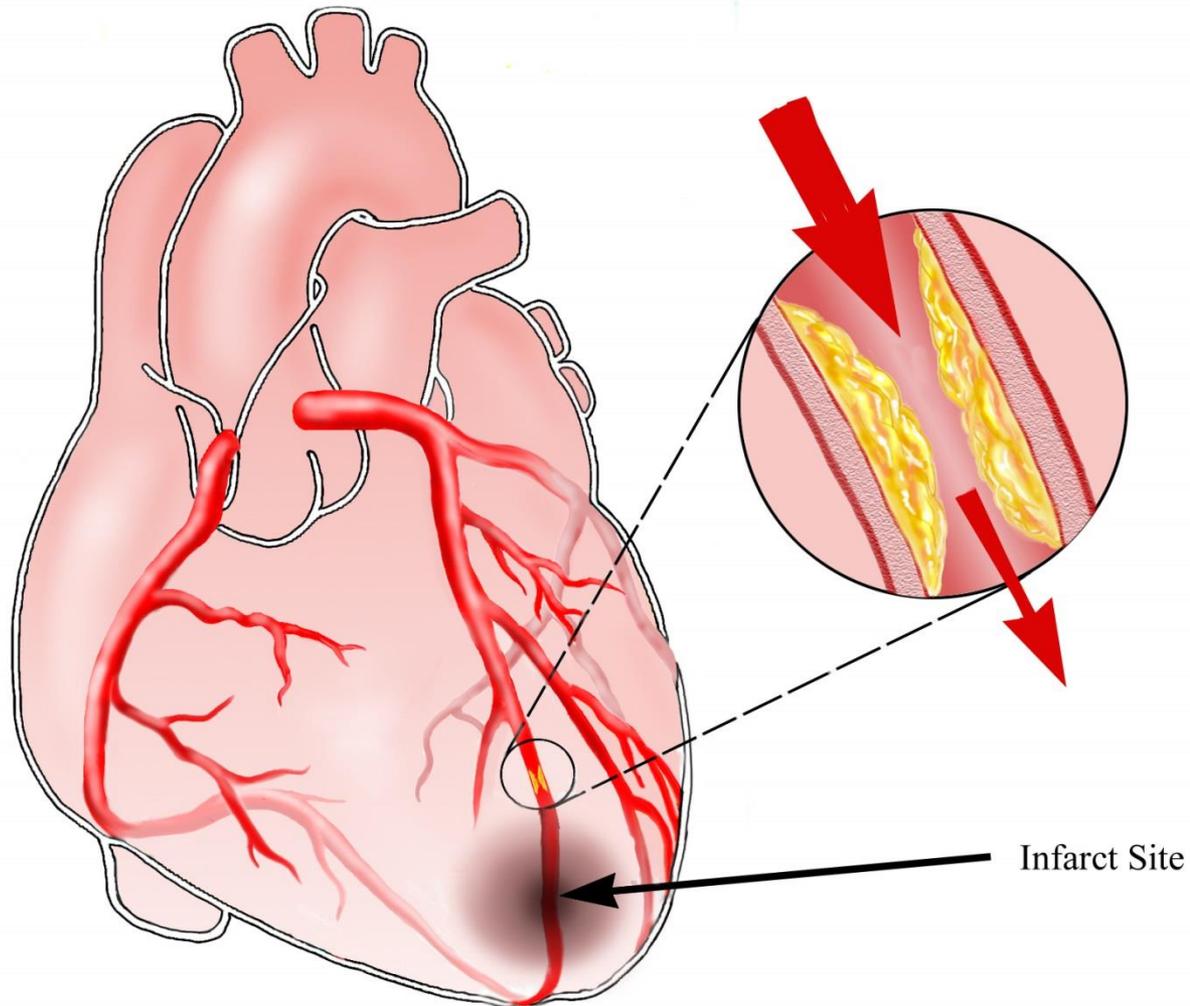
CHD mortality



Risk factors:

- Hyperlipidemia (Total-C \geq 240 mg/dL)
- Hypertension (BP \geq 140/90 mm Hg)
- Diabetes
- Cigarette smoking

Myocardial Infarction



The “Cath Lab”



Coronary Angiogram

Dye is injected into the coronary arteries



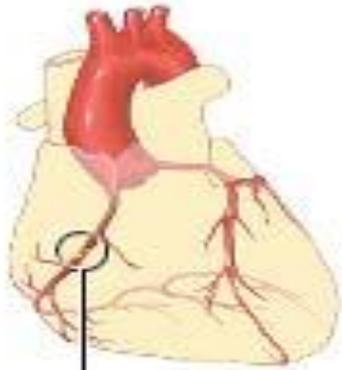
Coronary artery
blockage site

X-ray image

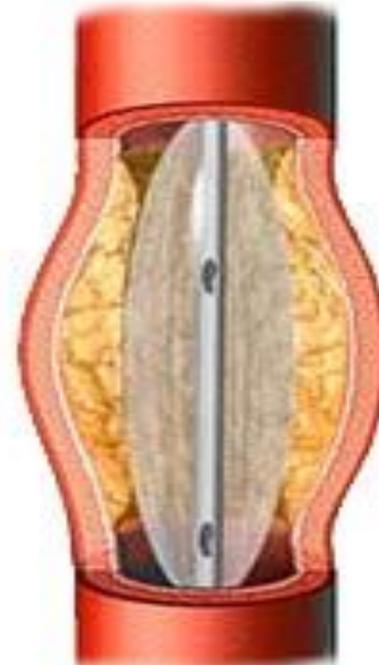
RCA Blockage



Angioplasty



A balloon-tipped tube is inserted in coronary artery



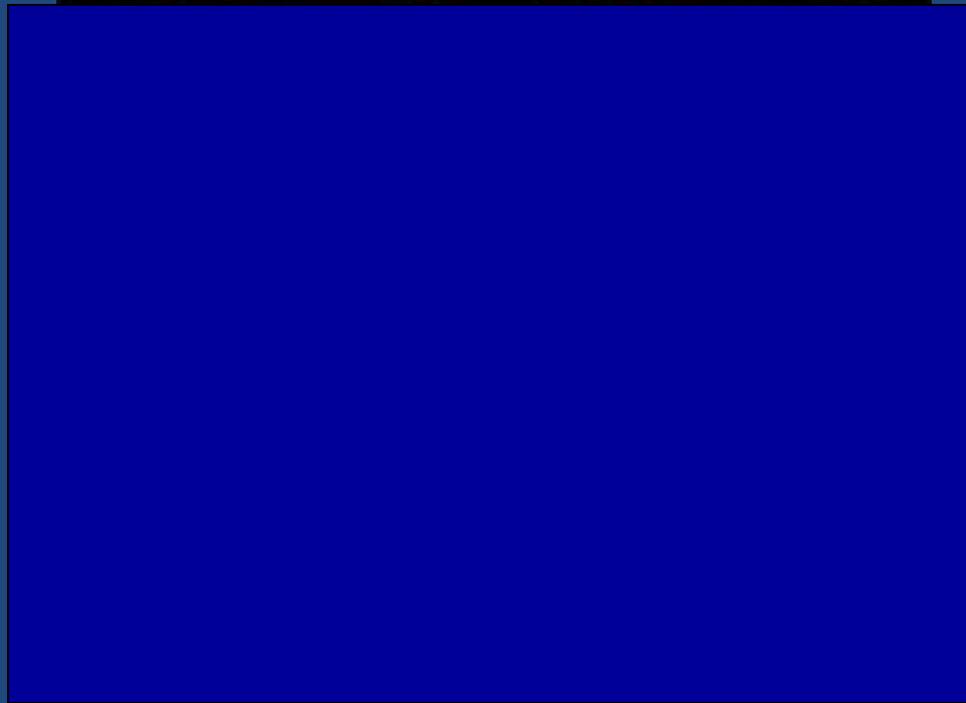
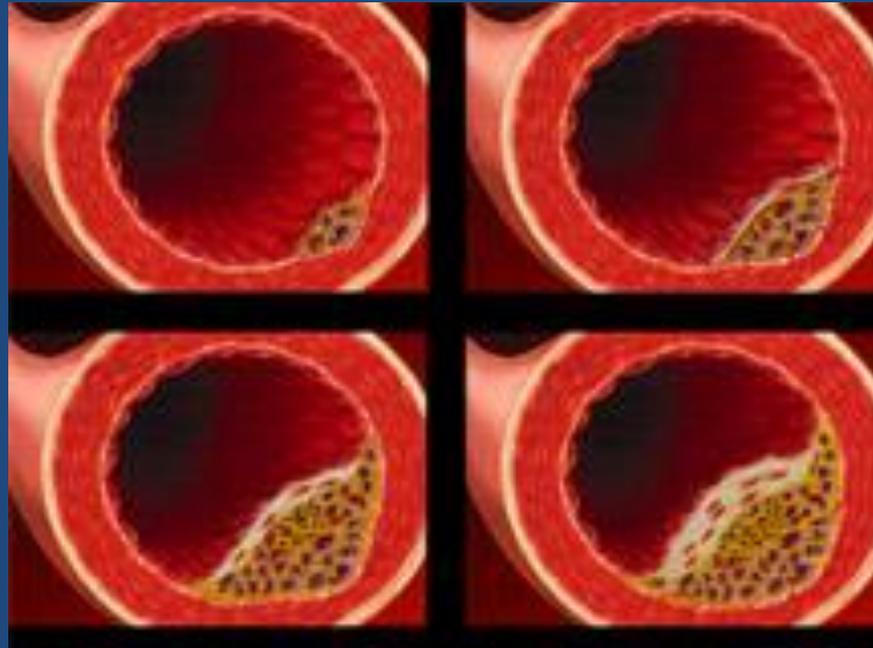
Balloon is expanded several times

NOT the whole story



The start



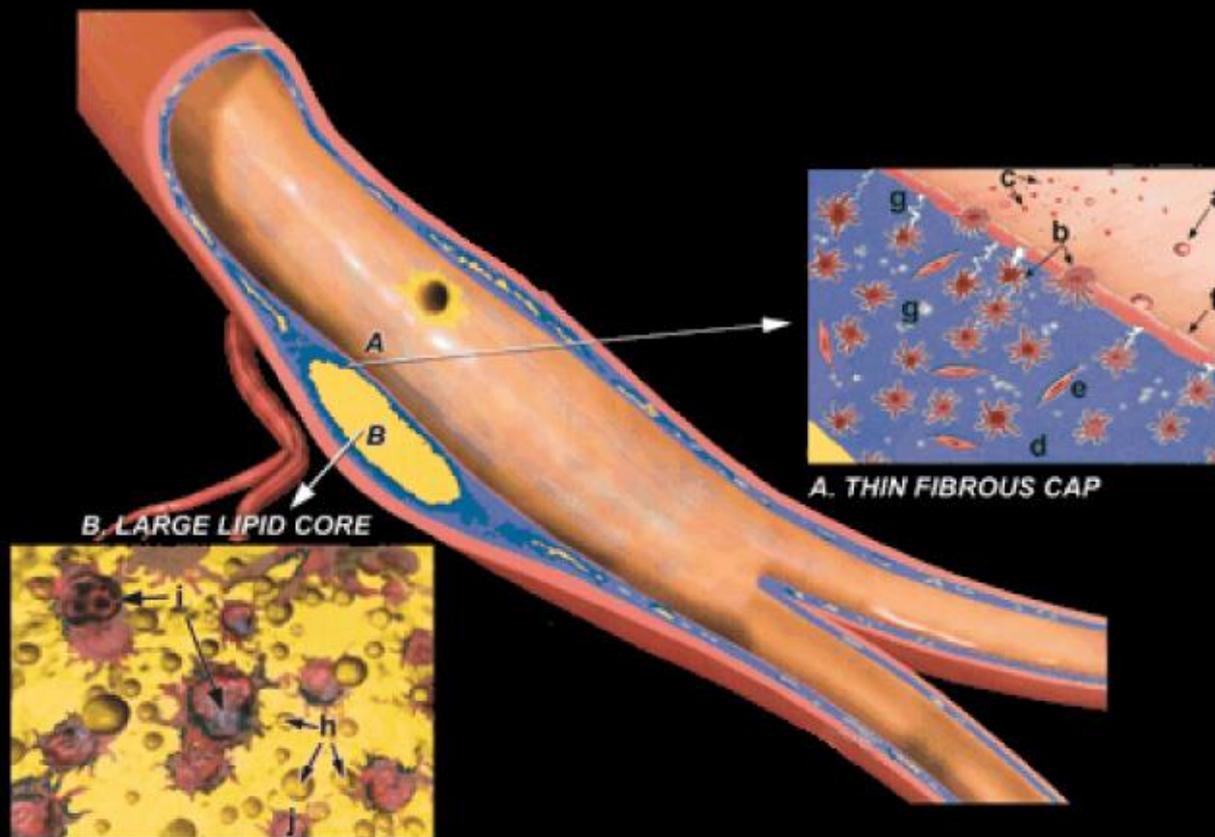


Coronary Artery



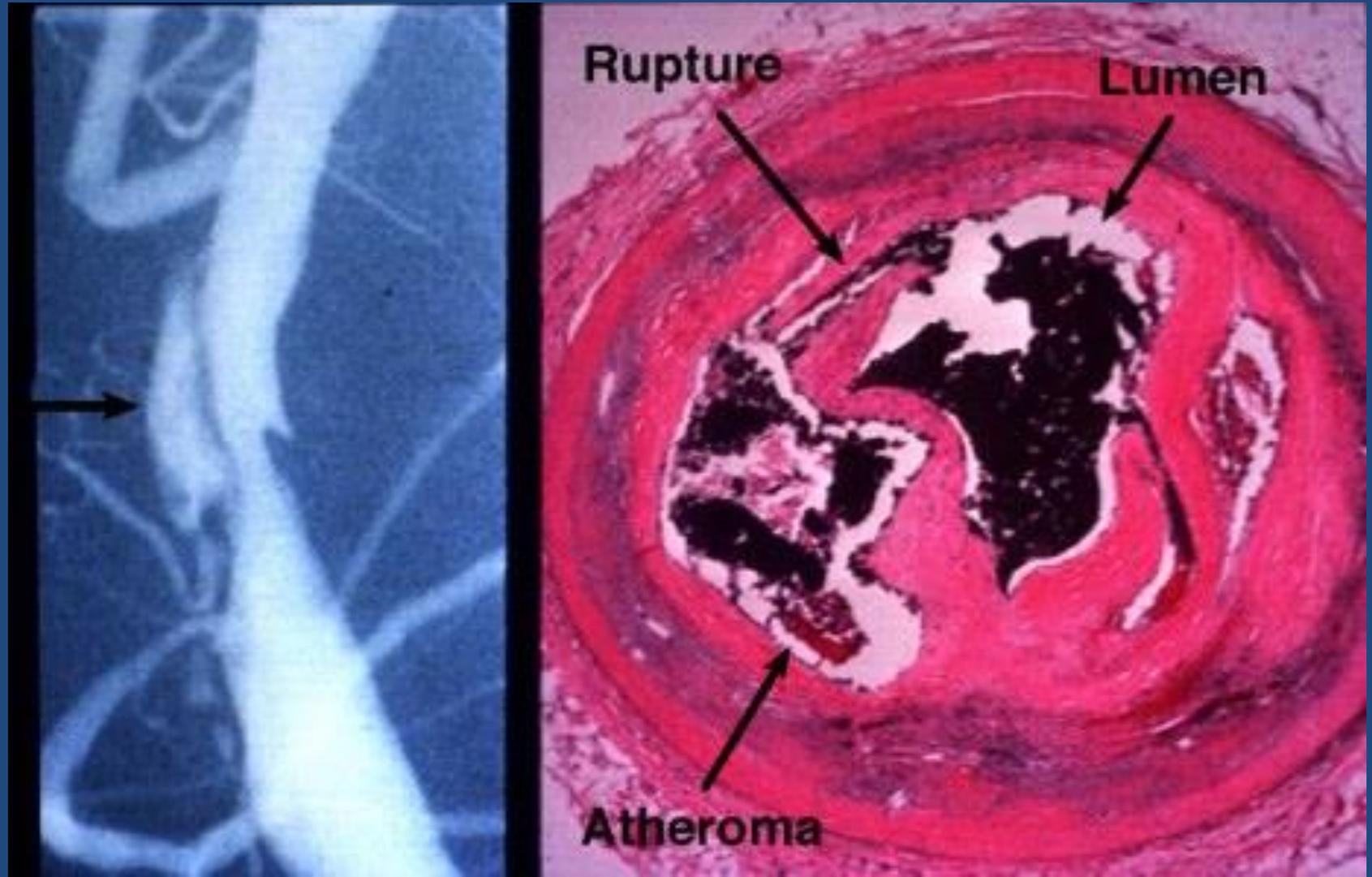
Note: all the fat

Most common type of vulnerable plaque



- Thin fibrous cap
- ↓ Smooth muscle cells
- ↑ Macrophage infiltration
- Large lipid core with little luminal narrowing

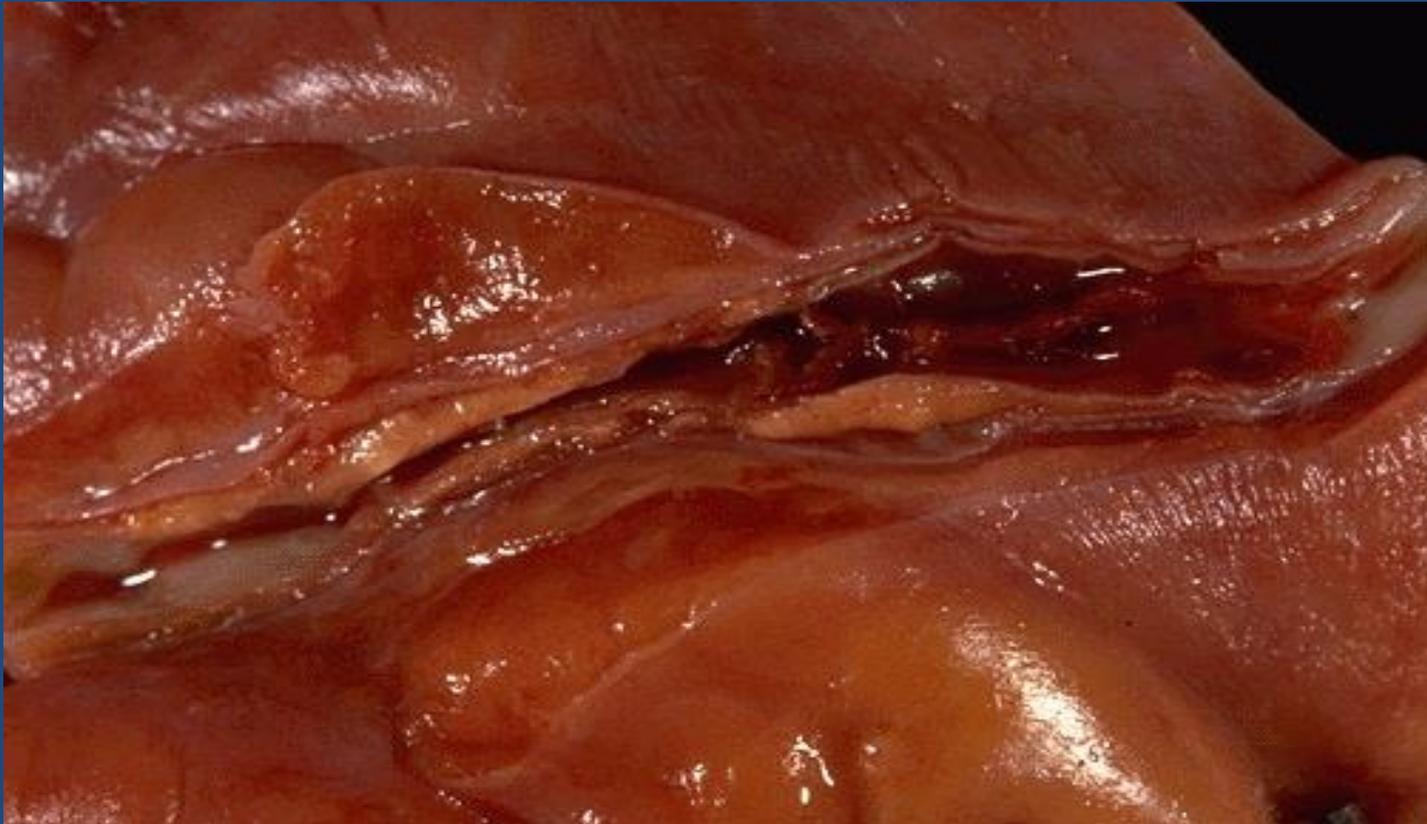
Pathophysiology



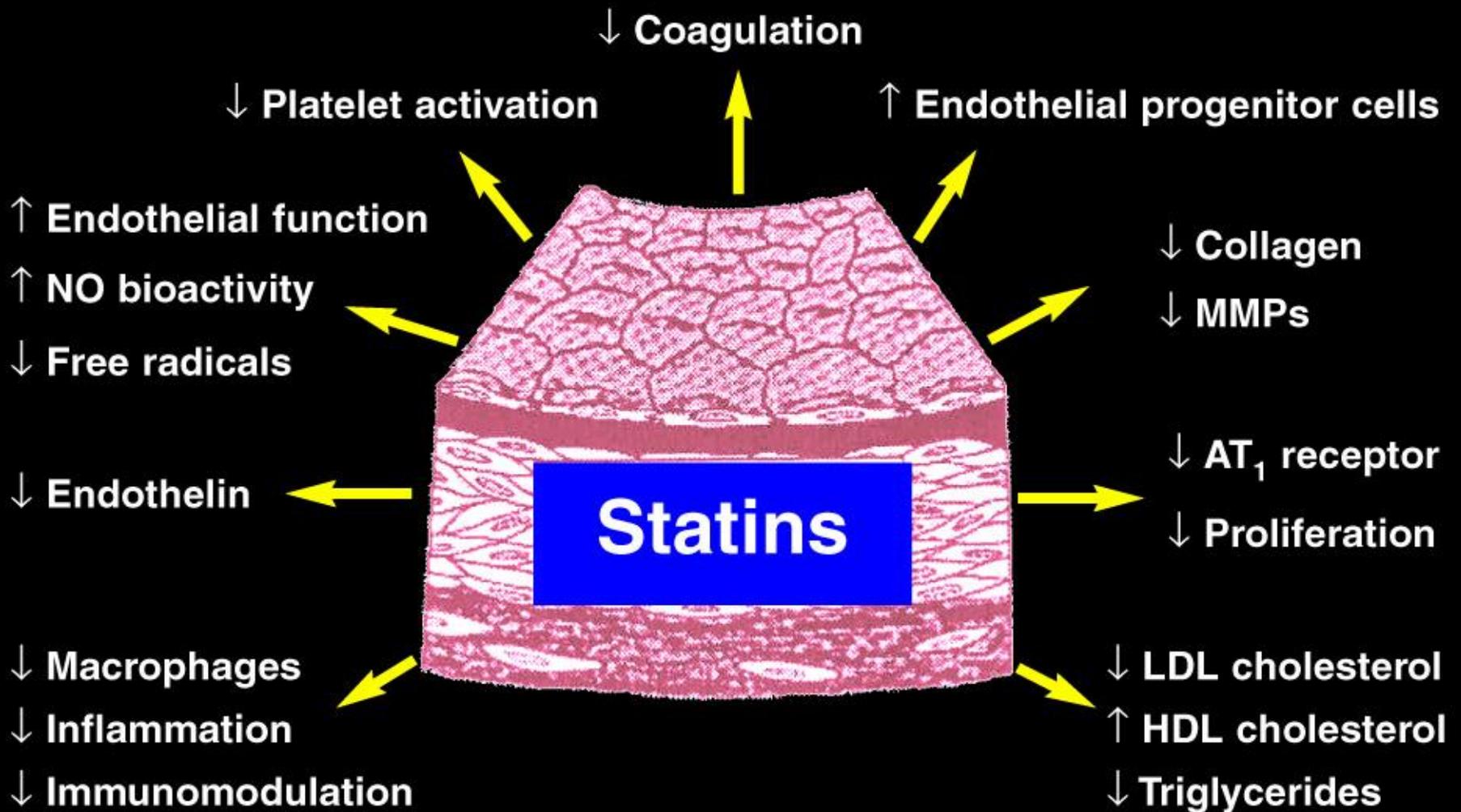
Formation of Blood Clot



Complete Blockage



Pleiotropic effects of statins on the vessel wall

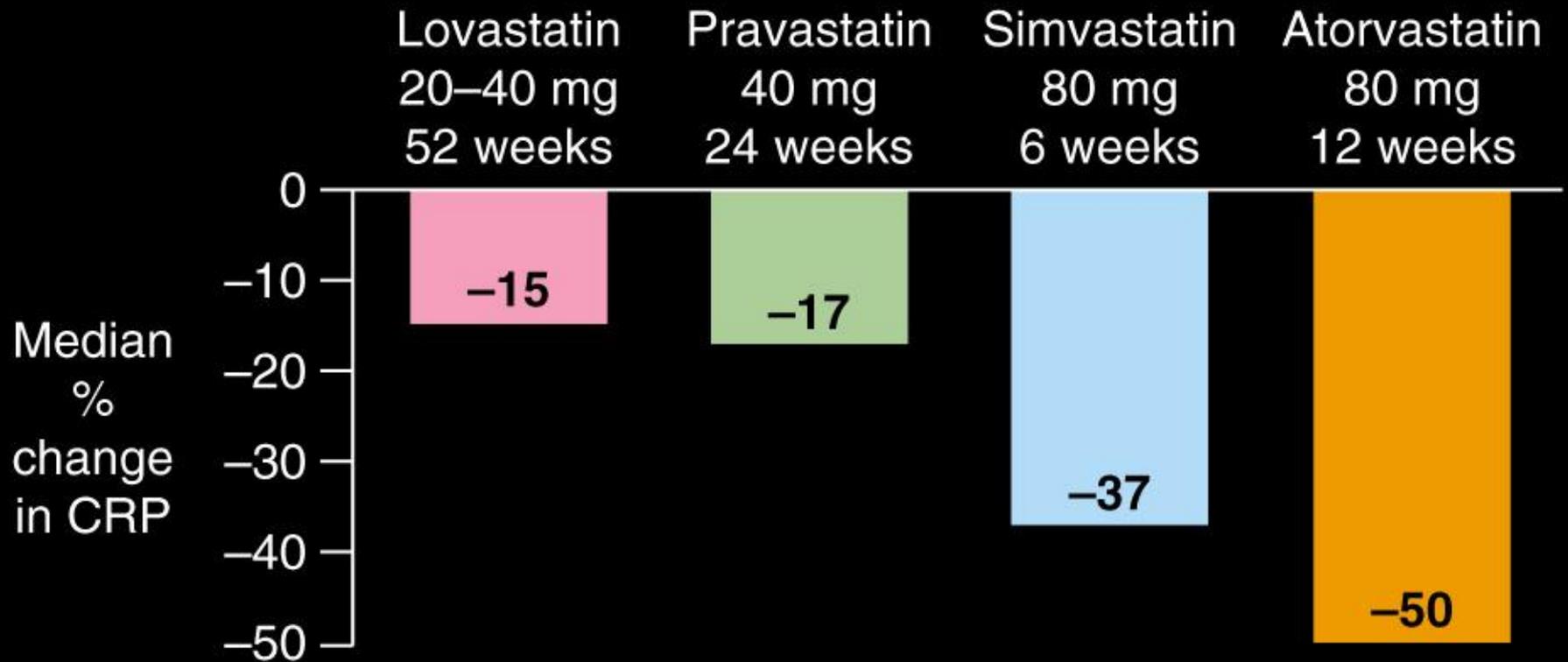


MMPs = matrix metalloproteinases

Wassmann S, Nickenig G. *Endothelium*. 2003;10:23-33.

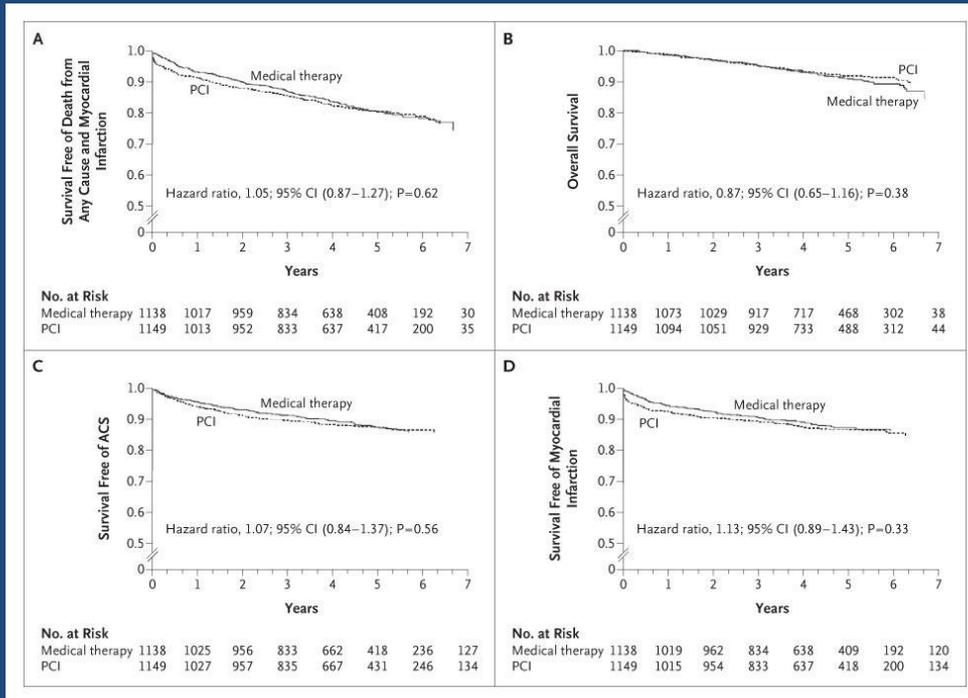
Statins reduce C-reactive protein

Median change in placebo-controlled trials with hypercholesterolemic patients



Ridker PM et al. *N Engl J Med.* 2001;344:1959-65.
Albert MA et al. *JAMA.* 2001;286:64-70.
Bays HE et al. *Am J Cardiol.* 2002;90:942-6.
Ballantyne CM et al. *Circulation.* 2003;107:2409-15.

COURAGE TRIAL: Med Treatment vs PCI



- Randomized trial, 2287 patients with coronary artery disease and evidence of ischemia were assigned to receive optimal medical therapy with or without percutaneous coronary intervention (PCI)
- At a median of 4.6 years, the rates of death and myocardial infarction were 19.0% in the PCI group and 18.5% in the medical-therapy group
- The PCI group had lower rates of angina and repeat revascularization
- As an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy

Boden WE et al. N Engl J Med 2007;356:1503-1516



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From: **Effect of Intensive Compared With Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis: A Randomized Controlled Trial**

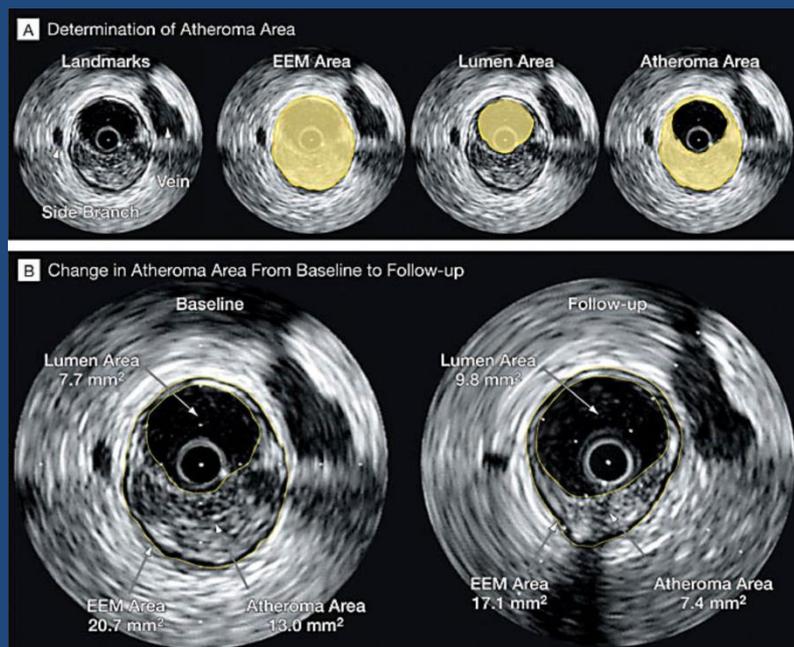


Figure Legend:

A, Atheroma area is calculated by subtracting the lumen area from the area of the external elastic membrane (EEM). B, Patient randomized to 80 mg of atorvastatin. There is substantial reduction in atheroma area (from 13.0 to 7.4 mm²). A lesser increase in lumen area is noted (from 7.7 to 9.8 mm²). See video.

- RCT of patients with CHD to intensive lipid therapy with atorvastatin 80 mg/day vs moderate therapy with pravastatin 40 mg/day.
- Measured plaque volume with coronary IVUS at baseline and after 18 months of therapy
- Primary end-point demonstrated reduced progression of atheroma volume with atorvastatin (-0.4 vs 2.7%)

Case 1

- A 45 year old male with history of smoking presents to your office for routine evaluation. He is asymptomatic. He smokes two pack per day. He reports pain in his calves with walking up inclines.
- On exam his BMI 31, blood pressure is 152/75 and Heart rate is 72. His exam is normal with the exception of an auscultated femoral bruit.
- His yearly lab work demonstrates a glucose of 122, HBA1C of 6.2, Tot cholesterol of 200 mg/dl, TG 165 mg/dl, and HDL 28 mg/dl, LDL 139 mg/dl

Case 1 Continued:

In regard to the patient's lipid abnormalities, the best initial treatment strategy for this patient is:

- A. Lifestyle modifications
- B. Niaspan
- C. Atorvastatin 80 mg daily
- D. Pravachol 20 mg daily

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

by Neil J. Stone, Jennifer G. Robinson, Alice H. Lichtenstein, C. Noel Bairey Merz, Conrad B. Blum, Robert H. Eckel, Anne C. Goldberg, David Gordon, Daniel Levy, Donald M. Lloyd-Jones, Patrick McBride, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Karol Watson, and Peter W. F. Wilson

Circulation
Volume 129(25 suppl 2):S1-S45
June 24, 2014



Key Elements of Guideline

- Expert panel components of 16 members including PCPs, cardiologists, endocrinologists, and experts in clinical lipidology
- ASCVD includes coronary heart disease, stroke, and peripheral arterial disease all of which presumed atherosclerotic origin
- Focus for guidelines was based on predominantly randomized controlled treatment trials

New Perspective on LDL-C and non HDL – C Treatment goals

Identifies four STATIN treatment benefit groups to reduce ASCVD for primary and secondary prevention

1. Clinical ASCVD (hx ACS, MI, UA, angina, coronary or vascular revascularization, CVA, PAD)
2. Family history and primary elevation of LDL-c > 190mg/dl
3. Type 2 DM aged 40-75 with LDL 70-189 mg/dl
4. Without clinical ASCVD or DM and LDL – C 70-189 mg/dl and estimated 10 year risk > 7.5%

New Perspective on LDL-C and non HDL – C Treatment goals

- No recommendations for targets for treatment goal based on review of RCT
- Focus on use of appropriate intensity of statin therapy based on age and indication for statin therapy
- Non statin therapies including niacin, fibrates, and zetia are not recommended as adjunctive therapies as they do not provide adequate risk reduction to support risk of adverse effects

Statin Benefit Groups

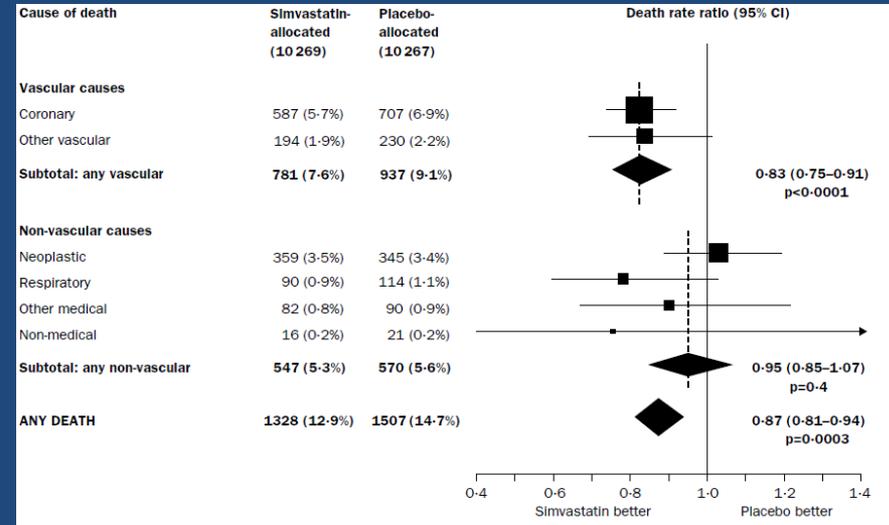
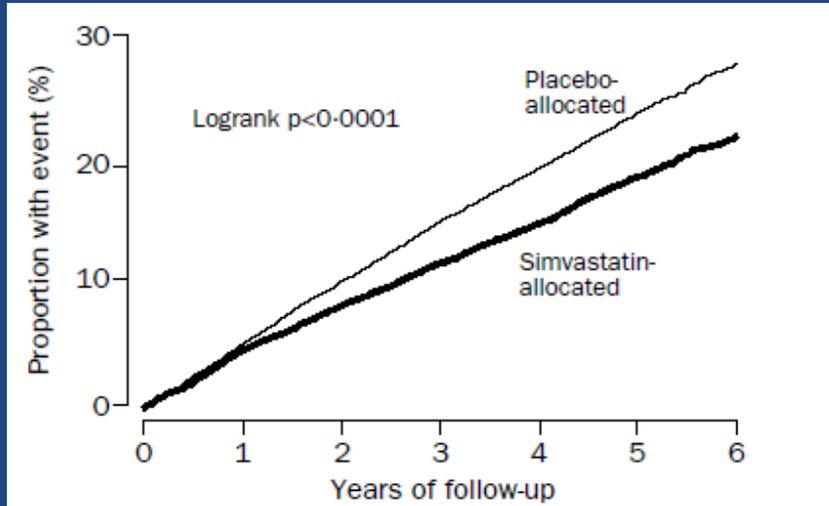
Statin Treatment: Group 1

- Group 1 Clinical ASCVD. Age less than 75
- Defined by inclusion criteria for secondary prevention trials
- Includes patients with history of ACS, MI, unstable or stable angina, coronary or arterial revascularization, stroke, TIA, or peripheral arterial disease thought to be atherosclerotic in origin
- Focus is on high dose statin therapy
- No evidence for incremental improvement in outcomes with add on therapy in AIM-High, Accord, and Arbiter 6
- Patient's greater than age 75 with clinical ASCVD suggest weighing risk reduction benefits, potential for adverse events, drug-drug interactions, and patient preferences when initiating moderate or high intensity statin therapy. Reasonable to continue if tolerating without issues. Class IIA (E)

Don't Forget: Lifestyle Modifications

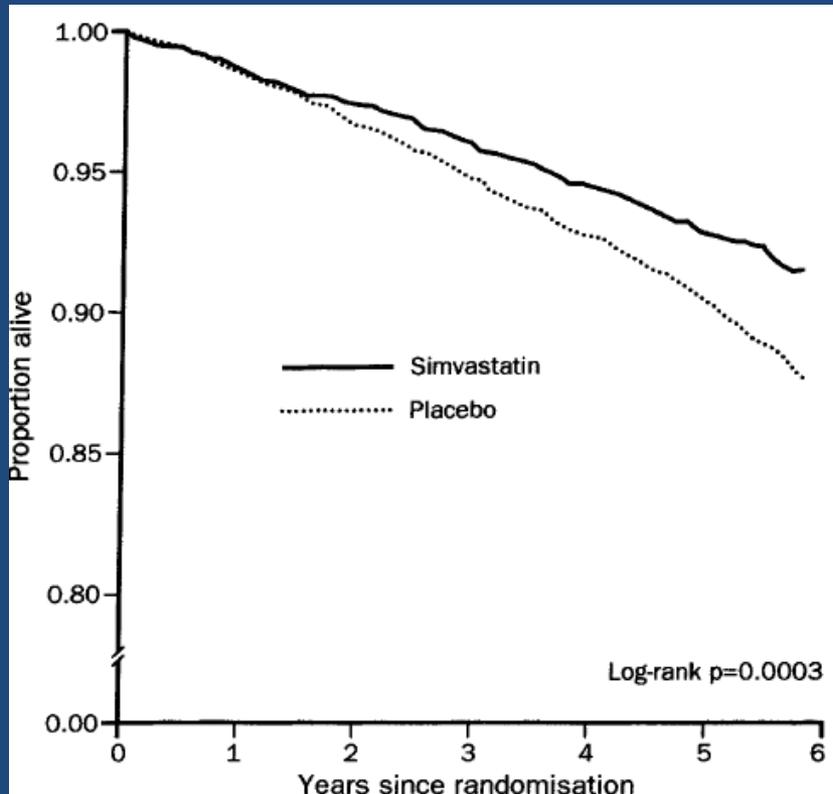
- Lifestyle Heart Study 1991: Small study in patients with established CAD randomized to vegetarian diet. Found significant improvement in lipids, reduction in obstructive lesions (from 61.1 to 55.8 percent diameter stenosis in lesions with more than a 50 percent stenosis) versus an increase in the control group (from 61.7 to 64.4 percent), and angina frequency and intensity.
- LYON Heart Study in 1996 found 28% relative risk reduction in CV death and non-fatal MI in 605 patients with established CAD randomized to mediteranean diet.
- Lee et al. found 30 and 45% risk reduction in all cause mortality and CV mortality with running as little as 5-10 minute per day at speed of 6 mph

Heart Protection Study



- 20,536 patients randomly assigned to simvastatin 40 mg daily vs placebo
- Entry criteria included history of CV disease (Coronary, CVA, PAD), DM, or treated HTN.
- Findings: 13% reduction in all cause mortality. 24% reduction in major CV events (19.8 vs 25.2%), and 25% reduction in first event rate for CVA (4.3 vs 5.7%)
- No increased risk of non vascular causes of death
- Percent reduction in events found regardless of baseline LDL cholesterol

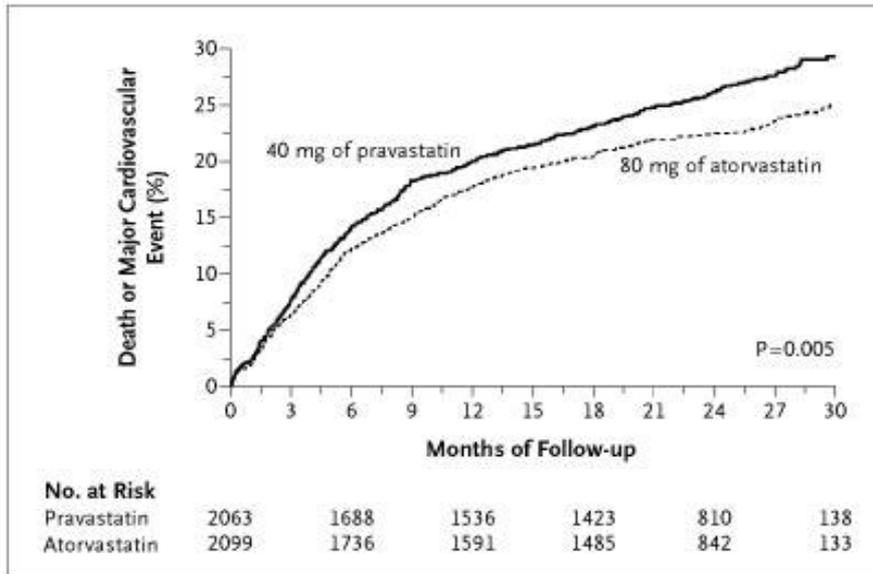
4S Trial – Scandinavian Simvastatin Survival Study



- 4444 patients with established CHD (angina or prior MI) and baseline tot chol 221-309 mg/dl
- Randomly assigned to simvastatin 20 or 40mg vs placebo
- Simvastatin treated group had reduction of mortality after 5 years (8 vs 12%)
- Major coronary events 19% vs 28% simv vs placebo
- 42% risk reduction in CHD deaths

Prove IT – TIMI 22 Trial: ACS patients randomized to Atorvastatin 80 mg vs Pravastatin 40 mg

- Randomly assigned 4162 patients hospitalized within 10 days from ACS with baseline total cholesterol greater than 240 mg/dl not on therapy or 200 mg/dl if on lipid
- At 2 years there was 16% RR in risk for reaching primary combined endpoint of all cause mortality, MI, UA requiring hospitalization, and coronary revasc > 30 days



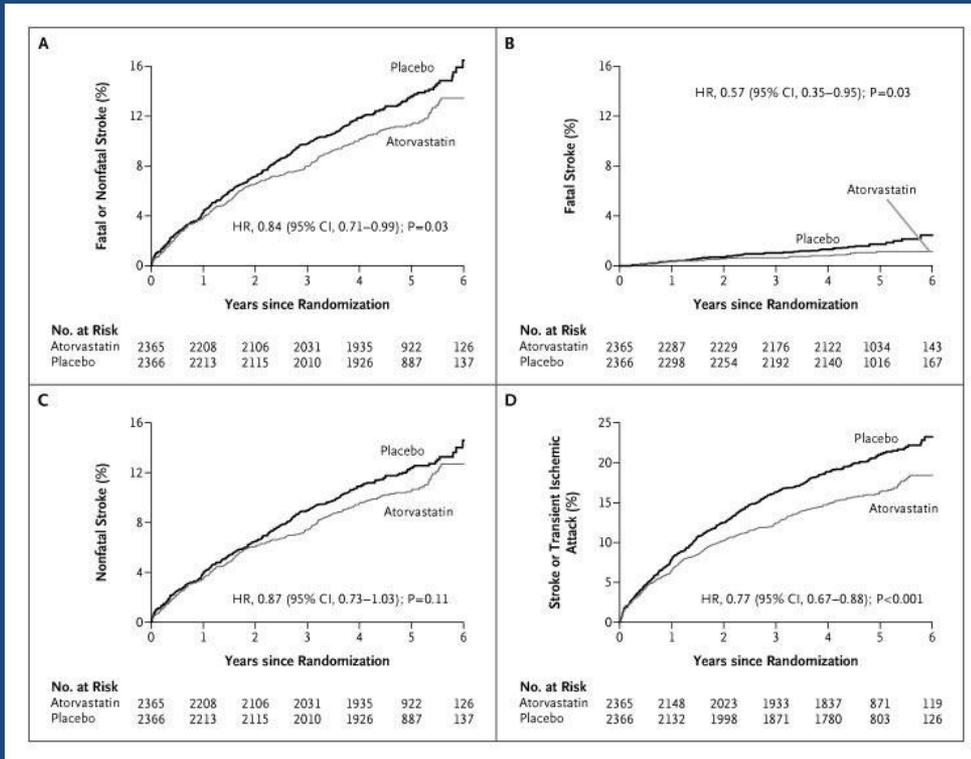
Cannon CP et al. N Engl J Med 2004;350:1495-1504.



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SPARCL TRIAL

- In this five-year placebo-controlled trial involving patients who had a recent stroke or transient ischemic attack and baseline low-density lipoprotein cholesterol levels of 100 to 190 mg per deciliter (3 to 5 mmol per liter), atorvastatin (80 mg daily) resulted in an absolute reduction in nonfatal or fatal stroke of 2.2 percent and of major cardiovascular events of 3.5 percent
- In patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke



The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. *N Engl J Med* 2006;355:549-559



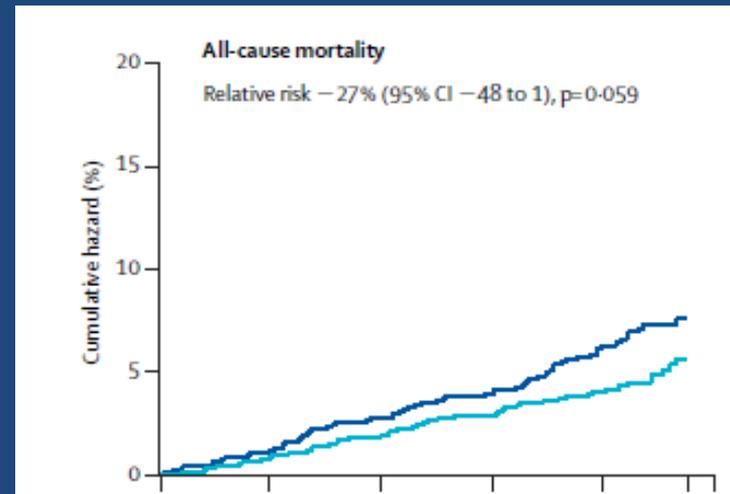
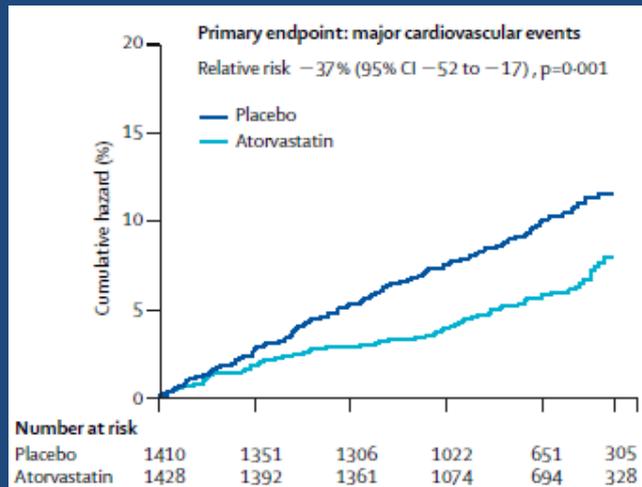
Group 2

- Primary elevations in LDL cholesterol greater than 190 mg/dl
- Initial treatment strategy high dose statin therapy
- Goal at least 50% decrease in LDL levels
- Given difficulty to control lipid abnormalities, add on therapy can be considered

Group 3 - Diabetics

- Individuals 40-75 with type 2 diabetes with LDL 70-189 mg/dl
- Moderate intensity therapy age 40-75 (Class IA(A))
- High intensity statin therapy with DM with 10 years ASCVD risk > 7.5% - Class IIA (E)
- Patients less than 40 or greater than 75 weigh the benefits, risk for adverse events, drug-drug interactions, and patient preference – Class IIA (E)

CARDS TRIAL – Type 2 DM



- 2838 diabetic patients with serum LDL < 160 mg/d, fasting TG < 600, and at least one following (retinopathy, albuminuria, smoking, or HTN) randomized to atorvastatin 10 mg daily vs placebo
- 37% reduction in CV events in the atorvastatin group vs placebo
- Rate of coronary heart disease events reduced by 36%, coronary revascularization 31%, stroke by 48%, and death by 27%

Case 2

55 year old male with hypertension and history of smoking. His medications include Lisinopril/HCTZ 20/25 mg daily. He is asymptomatic. His BP during the office visit is 148/70 with a pulse of 78. His BMI is 31 and his exam is otherwise normal. His lipids demonstrate a total cholesterol of 180 mg/dl, HDL 32 mg/dl, TG 157 mg/dl, and LDL cholesterol of 117 mg/dl.

Case 2 - Continued

The most appropriate therapy in terms of the patient's lipid abnormalities in addition to lifestyle modifications is:

- A. Atorvastatin 40 mg daily
- B. Niacin 2gm daily
- C. Fibrate therapy
- D. No medical intervention required at this stage

Group 4 – Primary Prevention

- Without clinical ASCVD or DM and LDL – C 70-189 mg/dl and estimated 10 year risk > 7.5% should be treated with moderate to high intensity statin therapy.
Class IE

Case 2 - Continued

- ASCVD Risk estimator (gender male, age 55, tot cholesterol 180 mg/dl, HDL cholesterol 32 mg/dl, SBP 148, HTN on treatment, No DM, and + smoking)
- 10 years ASCVD risk 19.8%
- Lifetime ASCD risk 69%
- 3.6 % with optimal Risk Factor modification
- 10 year risk without smoking is 10.9%

Global Risk Assessment For Primary Prevention

1. Suggest use of new pooled cohort equations to estimate 10 year ASCVD in both white and black men and women.

Risk Factor
Sex
Age
Race
Total Cholesterol
HDL-Cholesterol
Systolic Blood Pressure
Treatment for High Blood Pressure
Diabetes
Smoker

Your 10-Year ASCVD Risk (%)
10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)
Your Lifetime ASCVD Risk* (%)
Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (shown above in column E)

Global Risk Assessment For Primary Prevention

- Class IA recommendation to initiate moderate to high intensity statin therapy for adults age 40-75 with 10 year ASCVD risk $> 7.5\%$
- Class IIA, Reasonable to offer treatment with moderate intensity statin in adults age 40-75 with 10 ASCVD risk of 5-7.5%
- No recommendations on initiation or discontinuation of statins on patients with class II-IV NYHA HF or on hemodialysis

Case 3

- 50 year old male with presents to the office after his brother passes away suddenly after suffering an acute anterior wall myocardial infarction. He has no prior history of diabetes, hypertension, or smoking. He exercises regularly and is asymptomatic.
- His exam is normal and includes a BP of 130/76. His ECG is normal.
- His lab work demonstrates a normal fasting glucose. His lipid profile demonstrates a total cholesterol of 180 mg/dl, HDL cholesterol 45 mg/dl, triglycerides of 132 mg/dl, and LDL cholesterol 109 mg/dl. 10 year ASCVD risk is 3.4%

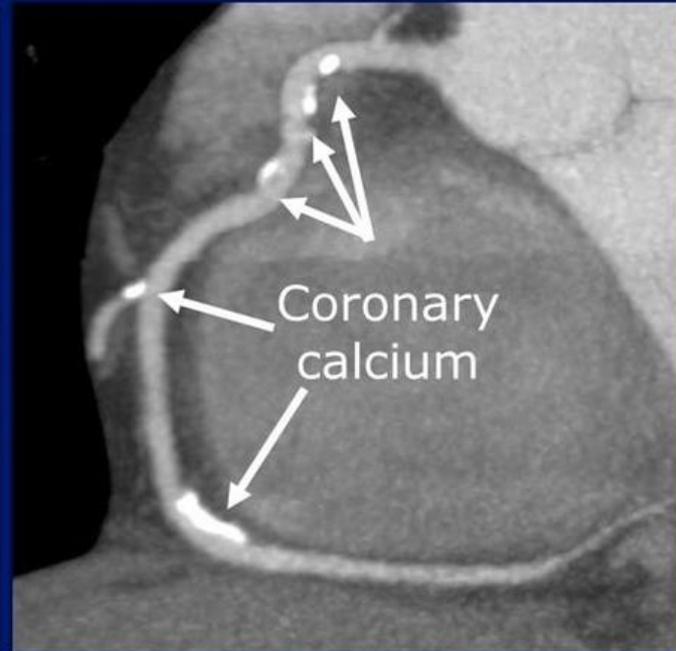
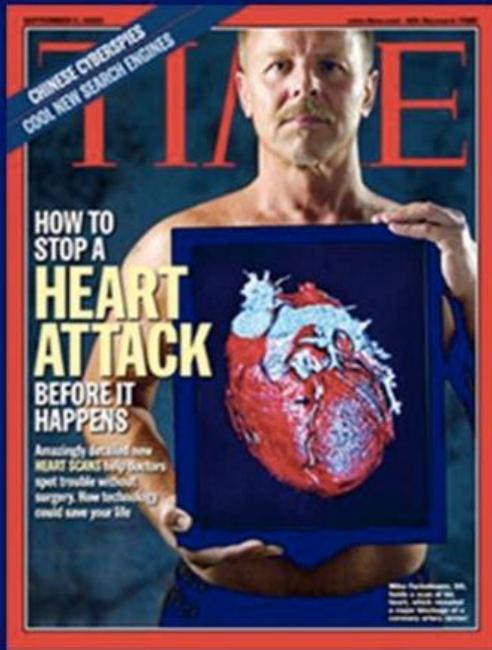
Case 3 - continued

The most appropriate treatment for the patient would be to:

- A. Initiate moderate intensity statin therapy
- B. Refer for a treadmill stress test for risk stratification
- C. Refer for CT calcium score
- D. Reassure patient. Encourage ongoing lifestyle modifications. No further medical intervention or testing indicated at this stage

Case 3 - Answer

Early detection of calcified cholesterol plaques in the coronary arteries allows timely initiation of preventive medical therapies that stop the disease on its track.



Coronary Calcium score = 600

Is Lower Better



Table IV.2-4. Management of LDL Cholesterol in Persons Beginning with 10-year Risk Assessment

10-Year Risk	LDL Goal	LDL Level at Which to Initiate TLC	LDL Level at Which to Consider Drug Therapy (After TLC)
>20%	<100 mg/dL	≥100 mg/dL	See CHD and CHD risk equivalent
10-20%	<130 mg/dL	≥130 mg/dL	≥130 mg/dL
<10%:			
Multiple (2+) risk factors	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
0-1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL*

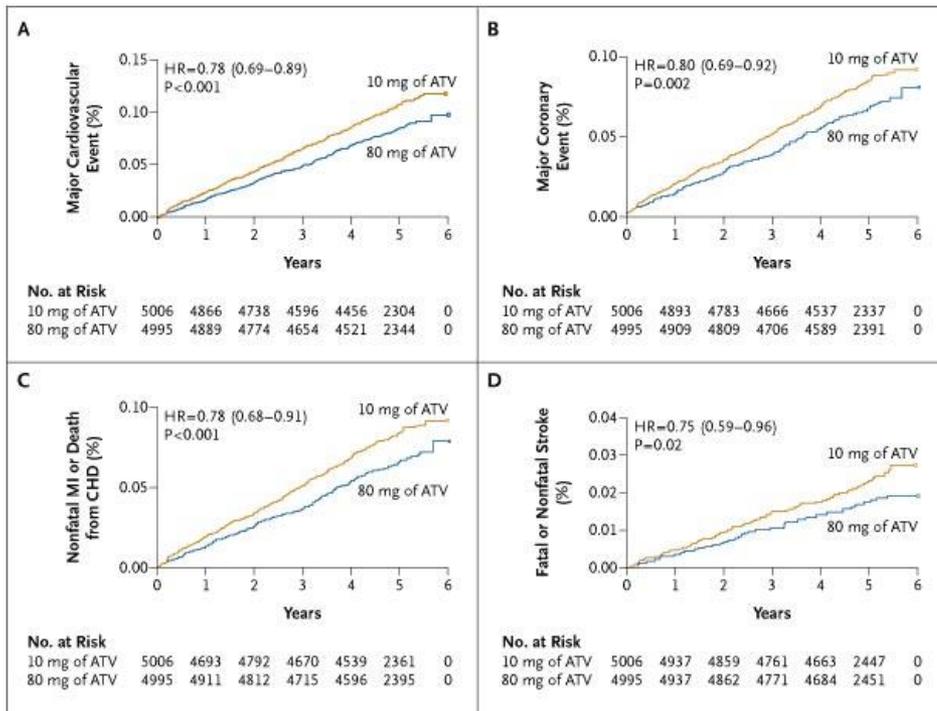
* Drug therapy optional for LDL-C 160-189 mg/dL (after dietary therapy).



ATP III. Third Report of the National Cholesterol Education Program

TNT Trial: Stable coronary heart disease randomized to atorvastatin 10 mg vs 80 daily

Primary End-point major CV event (death from CHD, non-fatal MI, resuscitation after cardiac arrest, or CVA



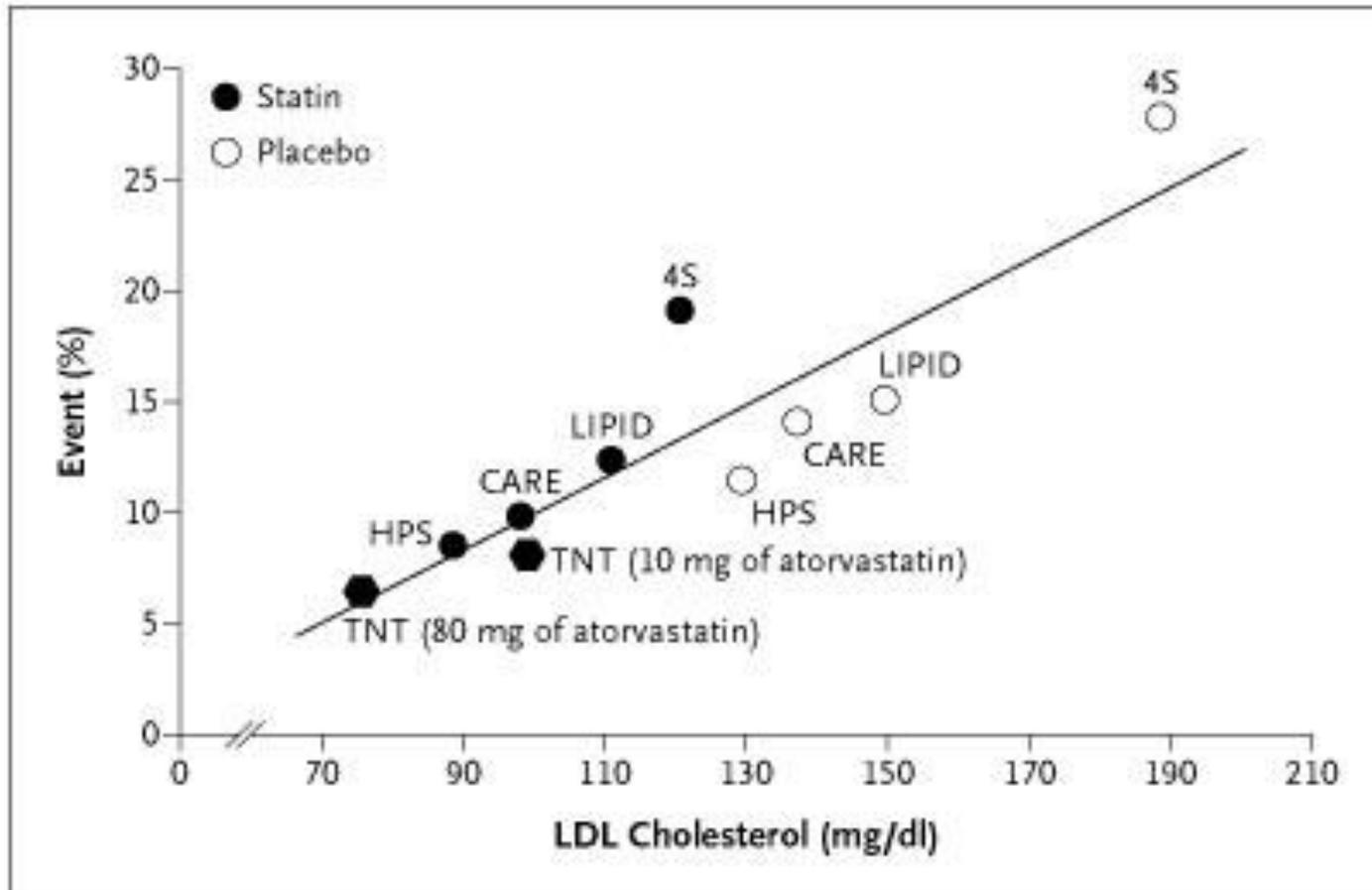
- 10,001 patients
- Baseline LDL 130-250 mg/dl
- Target LDL low dose < 100 and high dose < 75 mg/dl
- LDL cholesterol lower in high group (77 versus 101 mg/dl)
- 22% reduction in CV events (8.7% vs 10.9%)
- No significant reduction in all cause mortality
- No increase in myalgias
- Slight increase in LFTS 1.2 vs 0.2%

LaRosa, J. et al. N Engl J Med 2005;352:1425-1435



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TNT Trial Slide: Event Rates Plotted against LDL Cholesterol Levels during Statin Therapy in Secondary-Prevention Studies

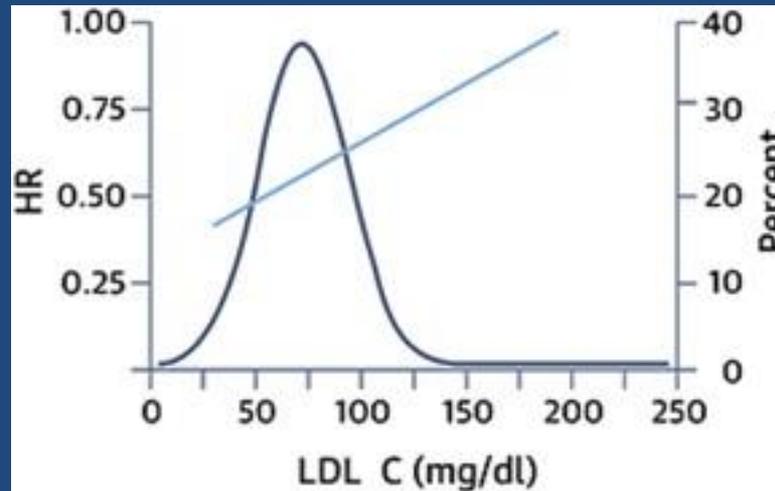


LaRosa, J. et al. N Engl J Med 2005;352:1425-1435



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Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events : A Meta-Analysis of Statin Trials



Central Illustration On-Statin LDL-C Levels and Risk for Major Cardiovascular Events Distribution of achieved on-statin LDL-C levels (dark blue curve ; right y -axis) and the risk of major cardiovascular events (light blue line ; left y -axis). The x...

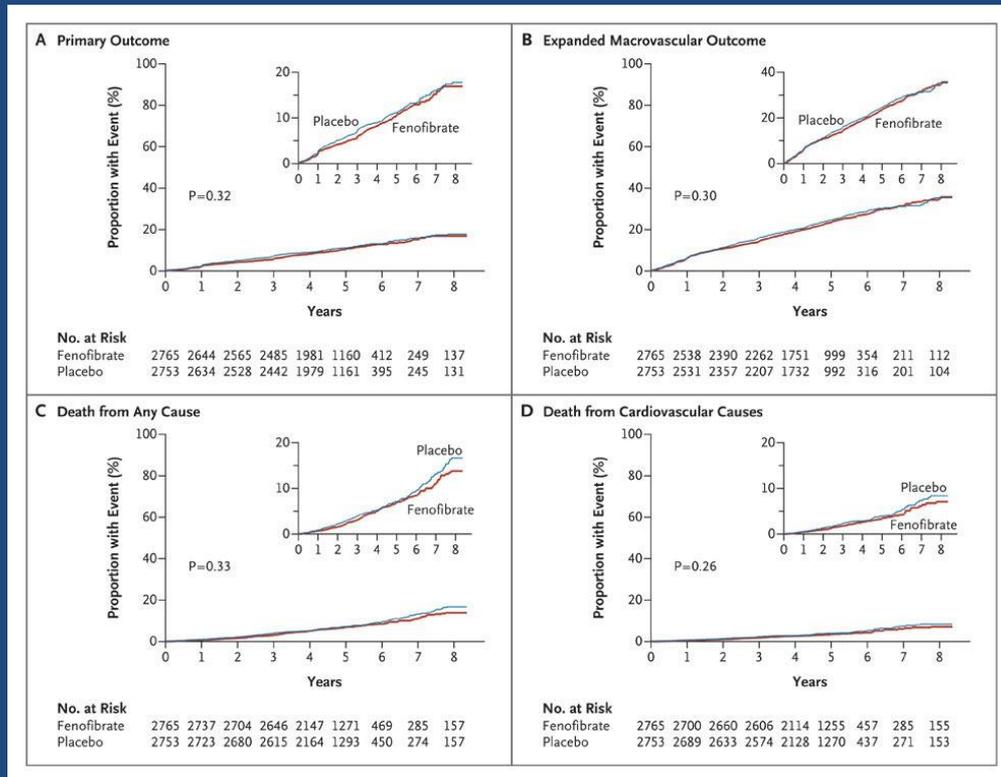
S. Matthijs Boekholdt , G. Kees Hovingh , Samia Mora , Benoit J. Arsenault , Pierre Amarenco , Terje R. Pedersen , ...

Journal of the American College of Cardiology, Volume 64, Issue 5, 2014, 485 - 494

What about the other drug classes



ACCORD Lipid Trial: Type 2 DM randomized to fenofibrate Vs Placebo



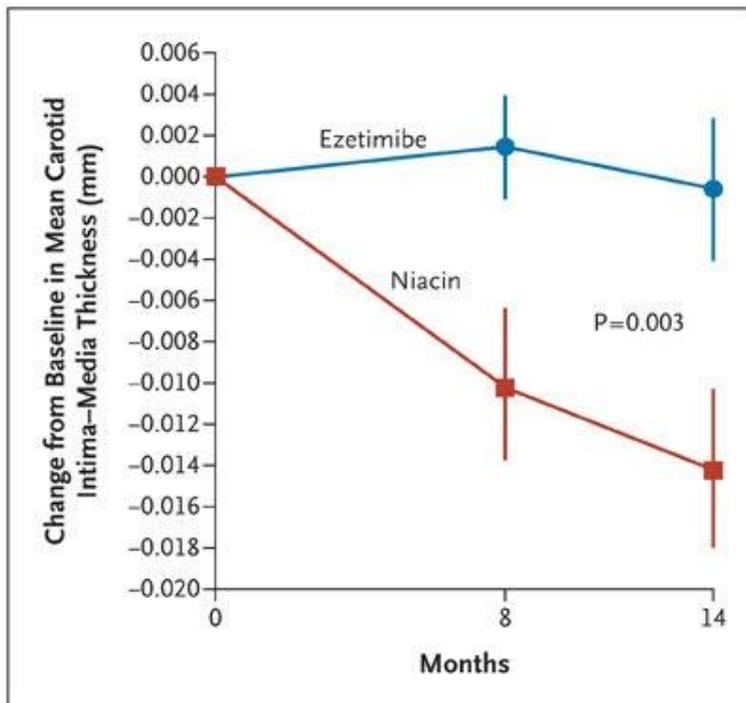
- 5518 patients with type 2 DM and clinical or subclinical CVD
- All patients treated with simvastatin
- No significant difference in primary endpoint time to major CV event (nonfatal MI, non-fatal CVA, or death from CV cause)
- No significant difference in any components of primary endpoint or death

The ACCORD Study Group. N Engl J Med 2010;362:1563-1574



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ARBITER 6 Changes in the Mean Carotid Intima-Media Thickness over the 14-Month Study Period, According to Treatment Group



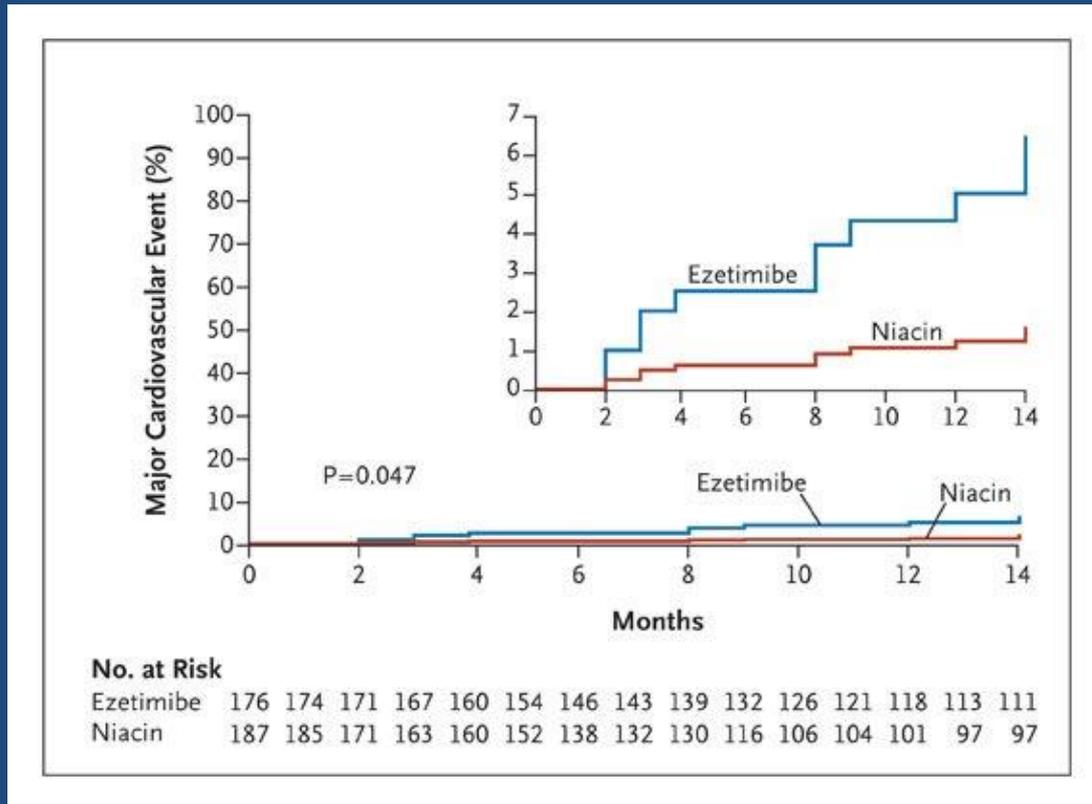
- 208 patients with CHD or CHD risk equivalent on statin therapy
- Randomized to Niacin 2 gm vs ezetimibe 10 mg
- Niacin reduced CIMT at both 8 and 14 months compared to ezetimibe

Taylor AJ et al. N Engl J Med 2009;361:2113-2122



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Kaplan-Meier Estimates of the Incidence of a Major Cardiovascular Event among the 363 Study Patients, According to Treatment Group



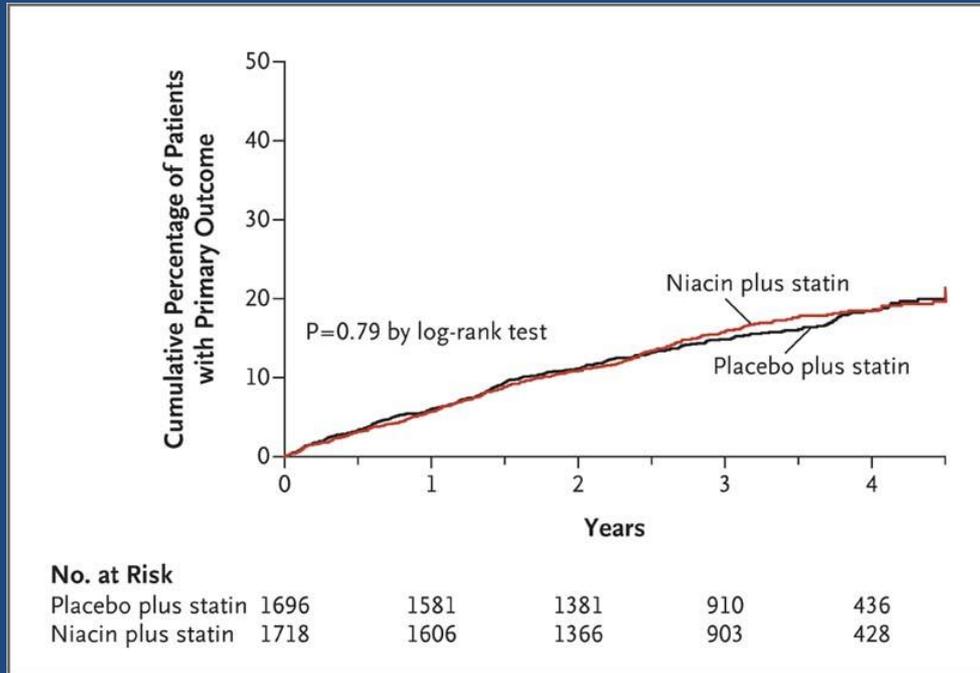
- Fewer composite CV events seen with niacin compared to ezetimibe group
- More patients with niacin withdrew secondary to side effects (17 vs 3)
- The use of extended-release niacin causes a significant regression of carotid intima-media thickness when combined with a statin

Taylor AJ et al. N Engl J Med 2009;361:2113-2122



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AIM- HIGH Study



- Patients with established cardiovascular disease randomized to niacin vs placebo
- All on statin. LDL at baseline < 70 mg/dl
- The addition of niacin to intensive statin therapy provided no additional clinical benefit over a period of 3 years, despite favorable changes in TG and HDL levels

The AIM-HIGH Investigators. N Engl J Med 2011;365:2255-2267



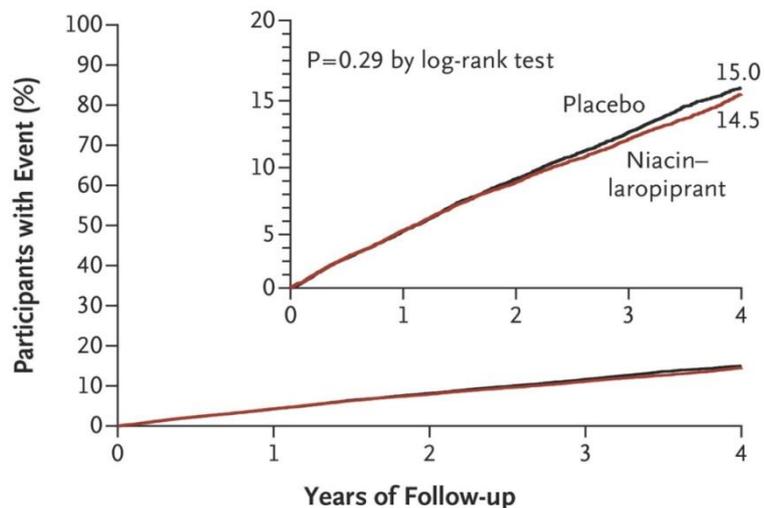
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Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients

The HPS2-THRIVE Collaborative Group*

- 25,673 pts with established vascular disease(78.4% CAD, 31.4% CVA, 12.5% PVD, 32% DM, 36% metabolic syndrome) randomized to niaspan 2gm/lapiporant 40 mg vs placebo
- Run in phase to achieve optimal LDL with simvastatin 40 mg with addition of zetia if not at goal
- Average LDL cholesterol at baseline 63 mg/dl
- Primary outcome time to first vascular event (non fatal MI, death from CV cause, CVA, arterial revascularization)

HPS2 – Thrive Trial – Niaspan/laropirant vs placebo in high risk vascular patients



No. at Risk

Niacin-laropirant	12,838	12,232	11,517	7672	4978
Placebo	12,835	12,247	11,523	7643	5036
Benefit per 1000 participants assigned to niacin-laropirant		0±3	3±3	5±5	5±7

- No significant difference found in primary end point (13.2% vs 13.7%; P = 0.29)
- Increased incidence of DM and worsening DM control
- Increased risk for adverse events including GI, musculoskeletal, infection, bleeding

The HPS2-THRIVE Collaborative Group. N Engl J Med 2014;371:203-212.



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Are Statins Safe?

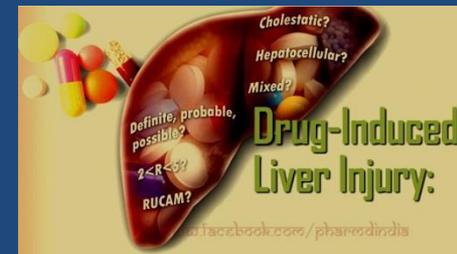
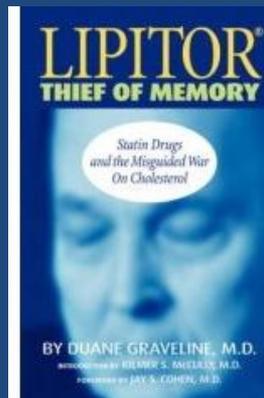
IS THE BENEFIT
REALLY WORTH
THE RISK?



The **DANGERS** of **STATIN DRUGS**



statin



Safety Considerations

- Baseline measurement of ALT suggested however serial evaluation not required unless concern for hepatotoxicity
- CK should not be routinely measured unless patients at increased risk for adverse muscle events, history of statin intolerance, muscle disease, or concomitant drug therapy that increases risk
- Evaluate for diabetes based on diabetes screening guidelines. 0.1 occurrence per 100 patients treated
- Exercise increased caution in dosing in patients greater than 75 and on concomitant therapy that can effect drug metabolism

Cholesterol Therapy Take Home Points

- Focus is on 4 groups that will benefit from statin therapy
- Treatments with statin based on intensity therapy and titration of dose not required to achieve prespecified LDL targets
- Add on therapy not suggested with alternative cholesterol drug classes

Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD;
Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH;
Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS;
Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD;
Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

James PA, et al., JAMA 2014; 311 (5); 507-20

JNC 8 – Questions guiding Evidence Review

tions are made reflecting these questions. These questions address thresholds and goals for pharmacologic treatment of hypertension and whether particular antihypertensive drugs or drug classes improve important health outcomes compared with other drug classes.

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

Evidence Review - Outcomes

ment effects. Studies were included in the evidence review only if they reported the effects of the studied interventions on any of these important health outcomes:

- Overall mortality, cardiovascular disease (CVD)-related mortality, CKD-related mortality
- Myocardial infarction, heart failure, hospitalization for heart failure, stroke
- Coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement), other revascularization (includes carotid, renal, and lower extremity revascularization)
- End-stage renal disease (ESRD) (ie, kidney failure resulting in dialysis or transplantation), doubling of creatinine level, halving of glomerular filtration rate (GFR).

The panel limited its evidence review to RCTs because they are less subject to bias than other study designs and represent the gold standard for determining efficacy and effectiveness.⁶ The studies

Case 4

- 65 year old male presents for his yearly OV. He has a past history of borderline hypertension but is not medical therapy. His BP at home ranges from 135-150/70-80 with an average BP of 145/78.
- In the office his blood pressure is 148/74. His exam is normal.
- ECG in the office is normal without LVH.
- Lab work is unremarkable and includes normal renal function, fasting glucose, and the absence of urine protein.

Case 4: Continued

What is most appropriate treatment for the patient in regard to his blood pressure:

- A. Chlorthalidone
- B. Lisinopril
- C. Terazosin
- D. Continued observation without initiation of medical therapy

JNC Recommendation 1: Age > 60 BP Target less than 150/90

Recommendation 1

In the general population aged 60 years or older, initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP) of 150 mm Hg or higher or diastolic blood pressure (DBP) of 90 mm Hg or higher and treat to a goal SBP lower than 150 mm Hg and goal DBP lower than 90 mm Hg.

Strong Recommendation - Grade A

Corollary Recommendation

In the general population aged 60 years or older, if pharmacologic treatment for high BP results in lower achieved SBP (for example, <140 mm Hg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted.

Expert Opinion - Grade E

SYST EUR Trial - Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension

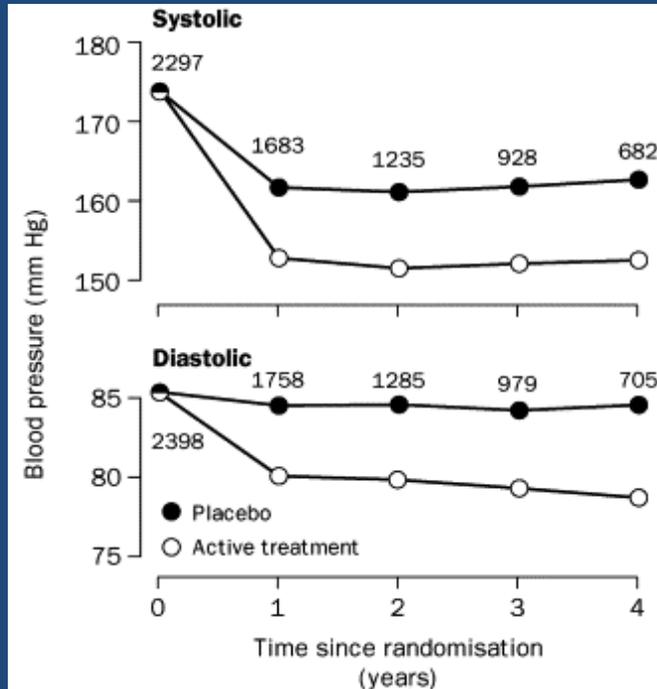
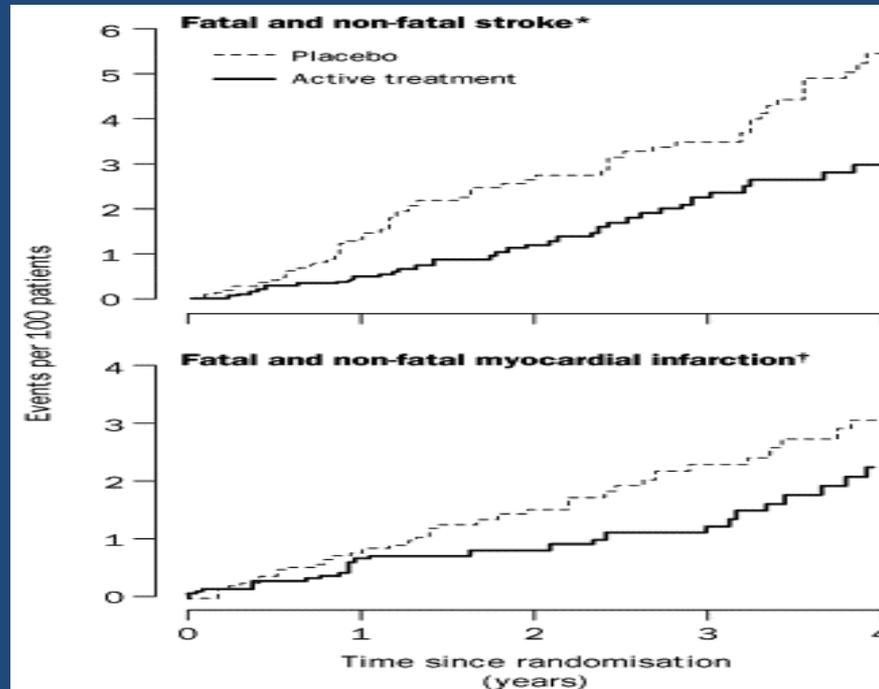


Figure 3 Average sitting systolic and diastolic blood pressure at randomisation and during follow-up

- European Trial
- 4695 patients randomized to treatment for BP with nitrendipine vs placebo
- Add on therapy allowed after with enalapril and HCTZ
- Baseline SBP at least 160 sitting and 140 standing, Diastolic BP ≤ 95 mmHg
- Primary end point fatal and non-fatal CVA

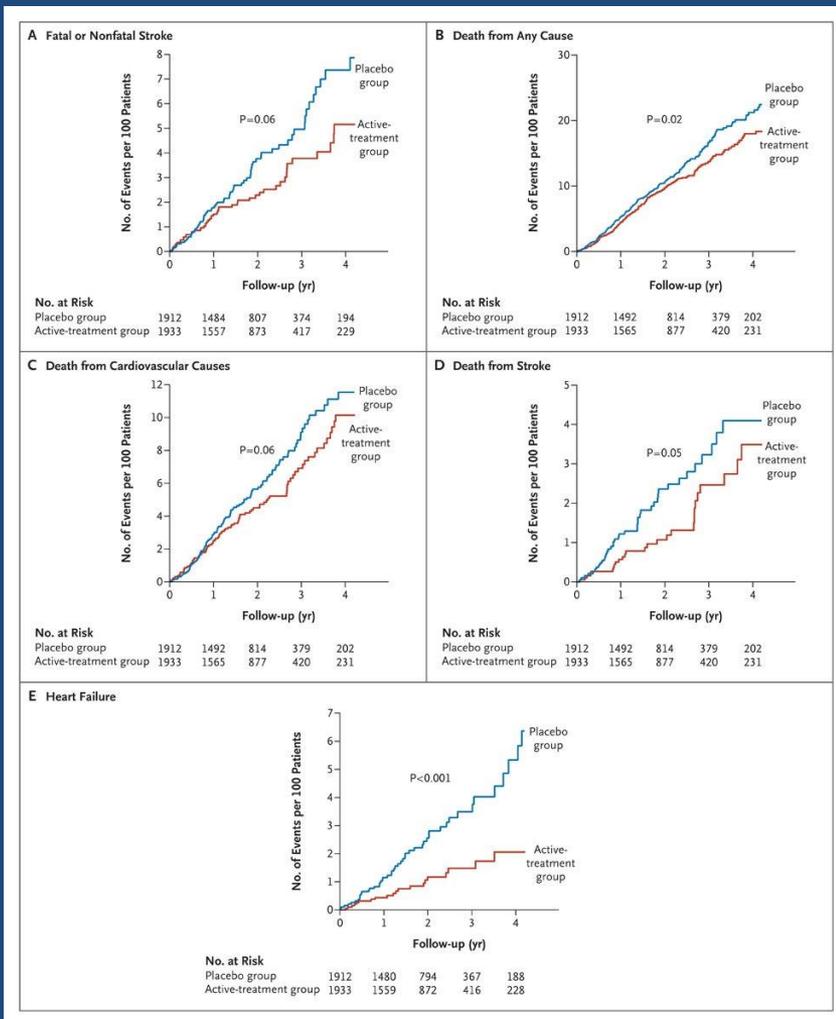
Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension



- 34% reduction in all cerebrovascular events
- 31% reduction in non-fatal and fatal CV events

Figure 4 Cumulative rates of fatal and non-fatal stroke and myocardial infarction by treatment group * p=0.003. †p=0.12.

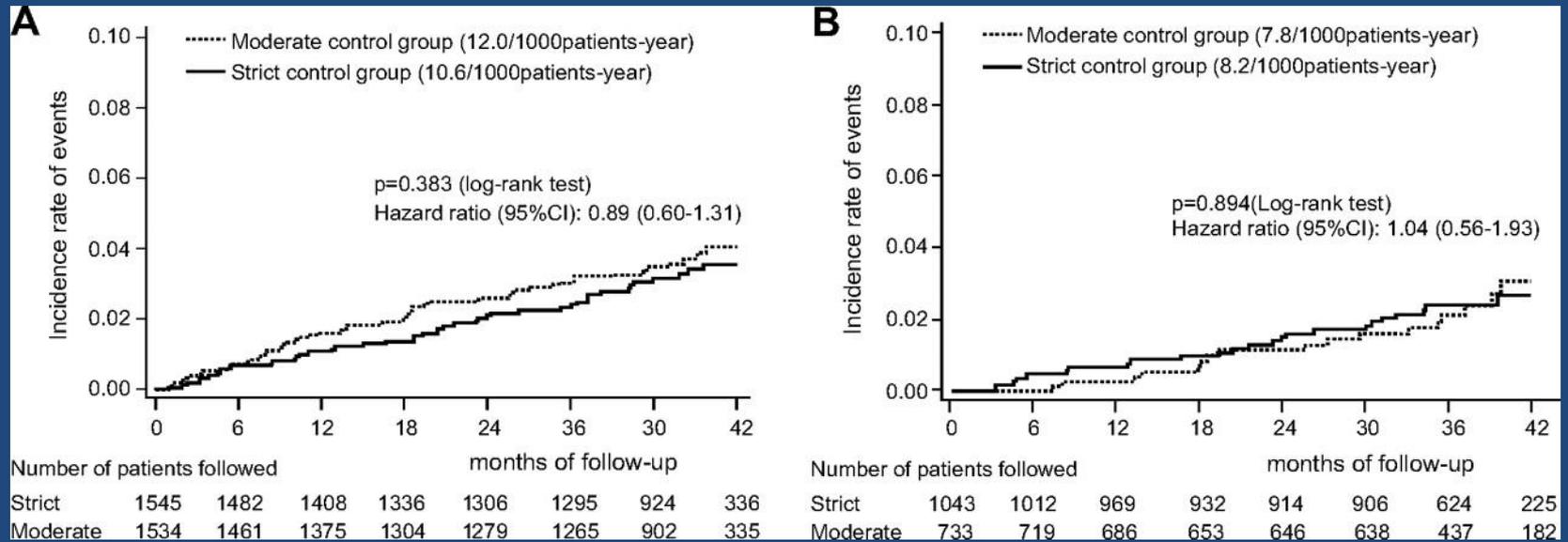
HYVET Trial – Treatment of HTN in patients greater than 80 years old



➤ RCT of elderly patients > 80 YO with SBP > 160 Pts randomized to treatment with diuretic indapamide vs placebo with addition of ACE-I perindopril to achieve SBP < 150 mmHg.

- 30% RR in fatal/nonfatal CVA
- 21% RR in all cause mortality
- 64% RR in heart failure

VALISH Trial



- RCT of 3260 patients aged 70-84 with isolated systolic HTN 160-199 randomized to strict (< 140) vs moderate BP control (140-149).
- Valsartan initial drug with add on therapy allowed to achieve predefined target
- No significant difference found in primary composite endpoint

JNC 8 Recommendations for Systolic and Diastolic BP in patients younger than 60

- In general population younger than 60 years old initiate pharmacologic **therapy for diastolic BP higher than 90 mmHg with goals to lower to less than 90 mmHg** (strong recommendation)
- In general population younger than 60, initiate pharmacologic therapy for **SBP > 140 with goal to lower to less than 140 mmHg** (Recommendation based on expert opinion)

JNC 8 – Age < 60

Systolic and Diastolic BP targets

- Diastolic BP old news from trials 1970/80s
- Limited RCT data for systolic BP target.
Recommendation based on expert opinion
- Diastolic BP trials often additionally achieved SBP < 140 mmHg
- Attempted to keep treatment algorithm simple by same targets for the different groups
- Insufficient evidence to justify lower treatment targets

Recommendation 4: CKD BP Target to < 140/90

Recommendation 4

In the population aged 18 years or older with CKD, initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher or DBP of 90 mm Hg or higher and treat to goal SBP of lower than 140 mm Hg and goal DBP lower than 90 mm Hg.

Expert Opinion - Grade E

- Applies to age 18-70, GFR < 60 ml/min/1.73 m², or albuminuria > 30 mg of albumin /gram
- Insufficient data to support lower BP targets of < 130/80

Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial

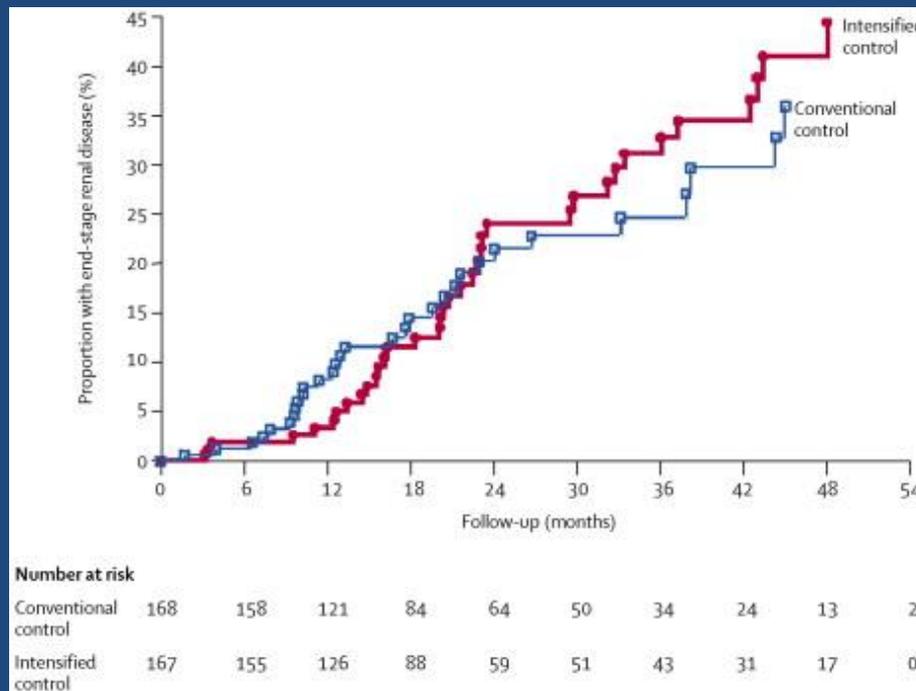


Figure 3 Proportion of patients with end-stage renal disease in each study arm

The Lancet, Volume 365, Issue 9463, 2005, 939 - 946

- 338 non diabetic pts with CKD randomized to target of DBP < 90 vs BP < 130/80
- Primary outcome time to ESRD
- All on background treatment of enalapril
- Intensified group added felodipine therapy
- Found no significant difference in primary outcome

Recommendation 8: CKD Med Classes

Recommendation 8

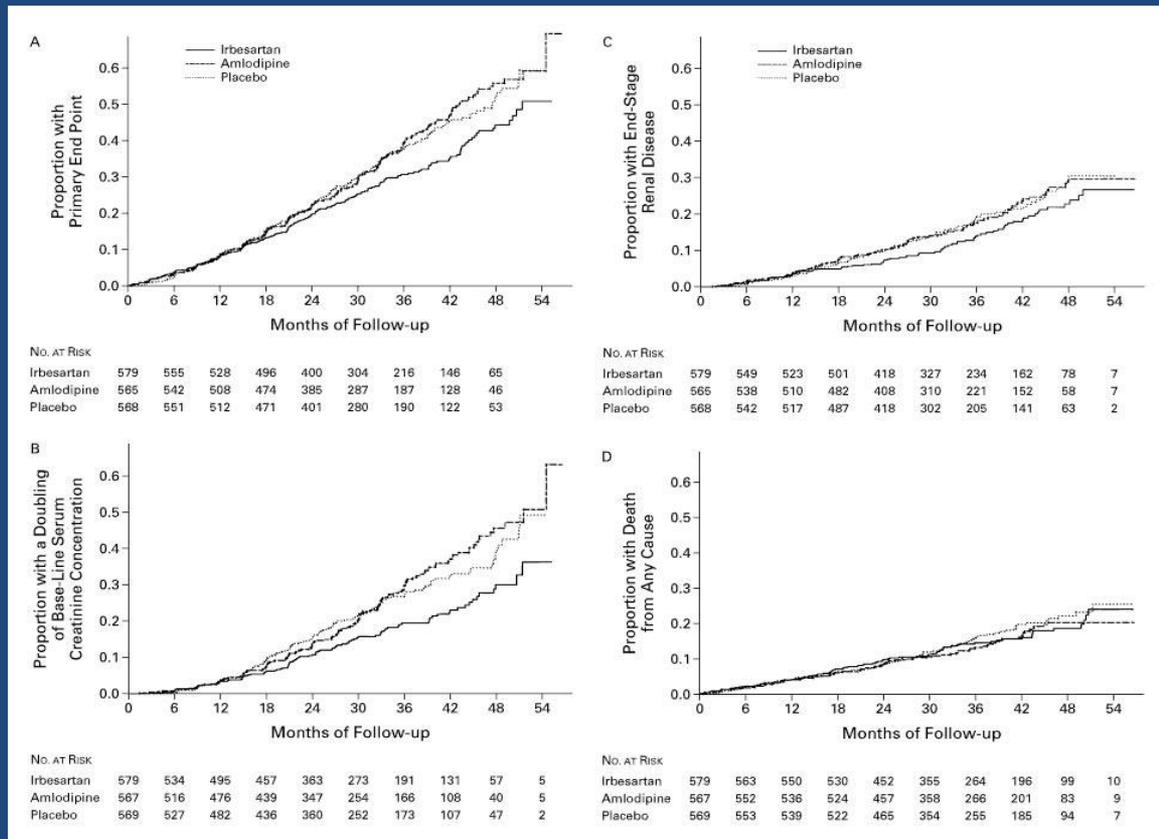
In the population aged 18 years or older with CKD and hypertension, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status.

Moderate Recommendation - Grade B

- Applies to patient with or without proteinuria
- ACE-I or ARB shown to improve kidney outcomes. No RCT for CV outcome
- In black patients with CKD, they suggest initial ACE-I or ARB. Without proteinuria, no clear recommendation of initial use of ACE-I vs CCB or diuretic
- Monitoring of electrolyte and renal function

James PA, et al., JAMA 2014; 311 (5); 507-20

Collaborative Study Group

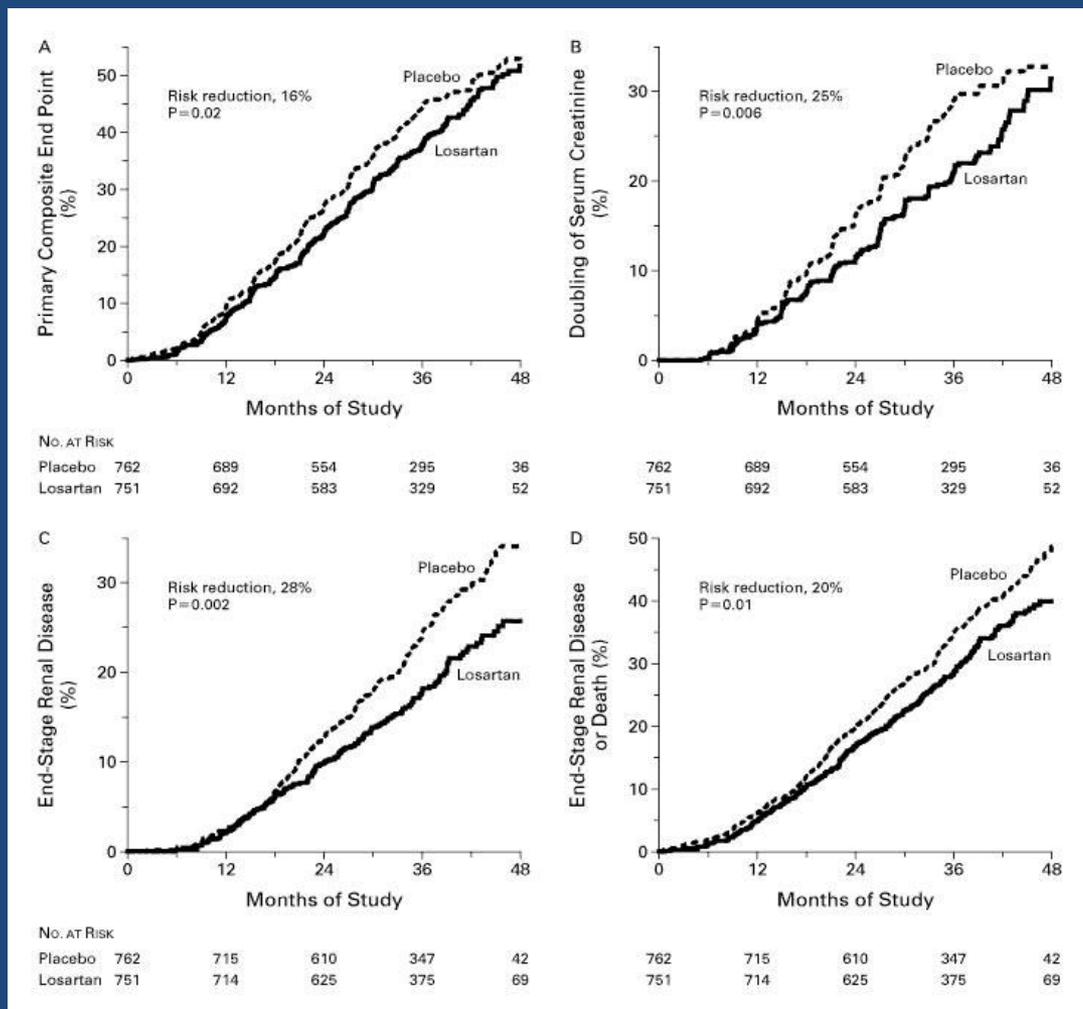


- RCT 1715 htn (BP > 135/85) pts with nephropathy (proteinuria, Cr 1-3) due to type 2 diabetes to rx with irbesartan, amlodipine, or placebo.
- The target blood pressure was less than 135/85 mm Hg
- Irbesartan had 20 percent RR reduction of combined endpoint (doubling CR, ESRD, mortality)
- 33% RR of doubling of serum creatinine concentration was 33 percent lower in the irbesartan group than in the placebo group and 37 percent lower in the irbesartan group than in the amlodipine group
- 23% RR reduction in development of ESRD compared to amlodipine or placebo
- No difference if BP between amlodipine and placebo
- No significant difference in total mortality of CV outcomes

Lewis EJ et al. N Engl J Med 2001;345:851-860.



RENAAL Study: Losartan Vs Placebo in Type 2 DM and Nephropathy



- 1513 patients with type 2 DM and nephropathy (urine albumin: urine Cr > 300 and Cr 1.3-3) randomized to losartan vs placebo
- BP at one year 146/78 losartan vs 150/80 placebo (p<.001). No significant difference in BP at end of study
- 16% RR with losartan in primary endpoint doubling serum Cr, ESRD, or mortality adjusting for BP difference
- 35% RR in level of proteinuria
- No significant difference in CV mortality

Brenner BM et al. N Engl J Med 2001;345:861-869.



The NEW ENGLAND
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Recommendation 5: Diabetics

Recommendation 5

In the population aged 18 years or older with diabetes, initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher or DBP of 90 mm Hg or higher and treat to a goal SBP of lower than 140 mm Hg and goal DBP lower than 90 mm Hg.

Expert Opinion - Grade E

- No RCT trials have shown that treatment to lower SBP goal compared to higher goal improves outcomes
- Consistent BP goal thought to improve implementation of guidelines

ACCORD Trial

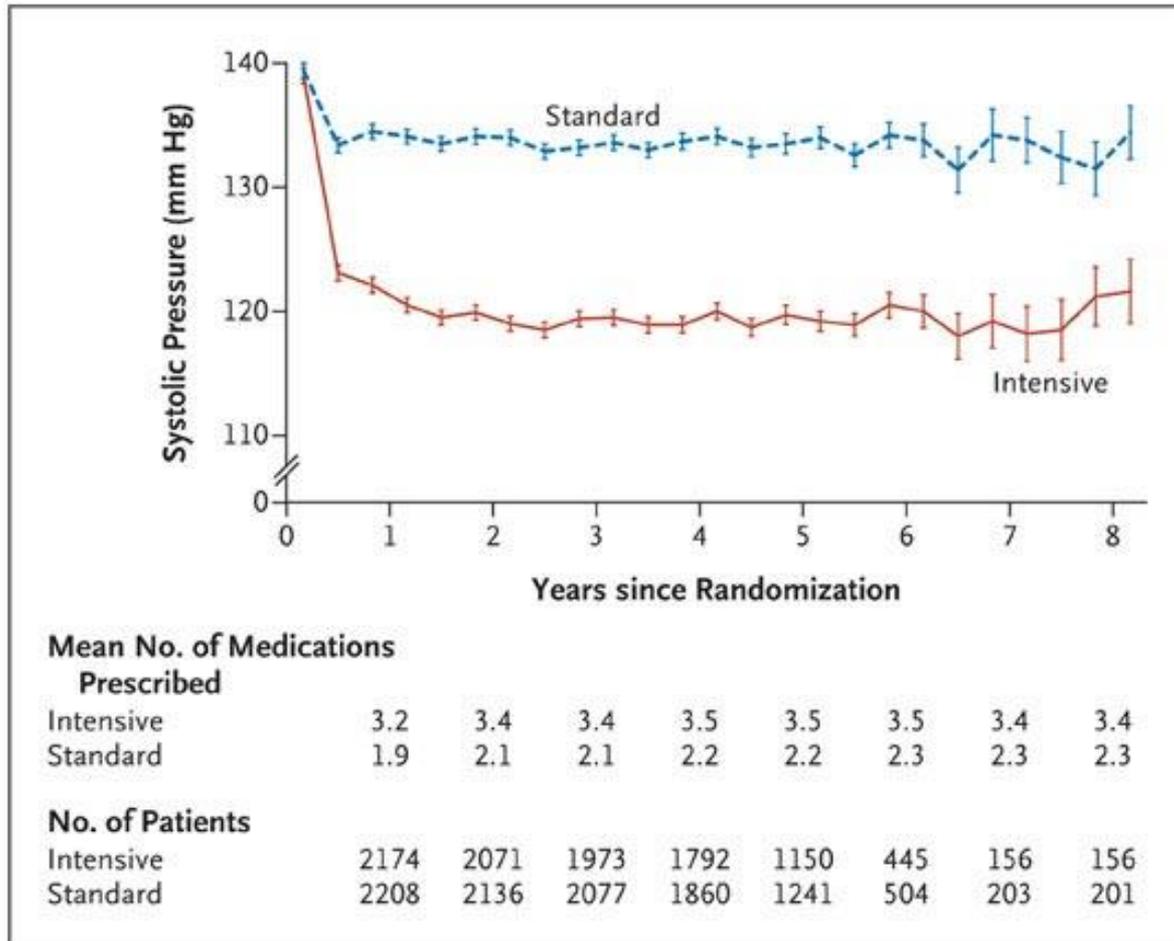
- In a randomized trial, 4733 patients with type 2 diabetes mellitus who were at high risk for cardiovascular events received treatment aimed at a target systolic blood pressure of less than 120 mm Hg or less than 140 mm Hg
- At a mean follow-up of 4.7 years, the rates of the primary end point (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) were not significantly different between the two trial groups
- In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events

The ACCORD Study Group. *N Engl J Med*
2010;362:1575-1585



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Mean Systolic Blood-Pressure Levels at Each Study Visit



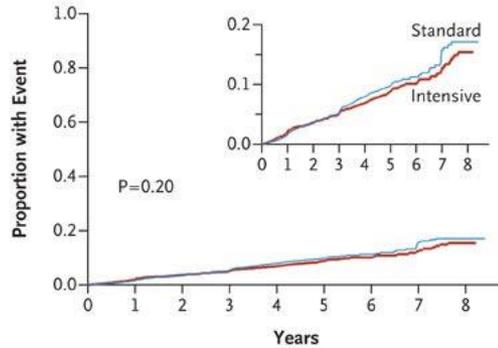
The ACCORD Study Group. *N Engl J Med* 2010;362:1575-1585



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Kaplan-Meier Analyses of Selected Outcomes

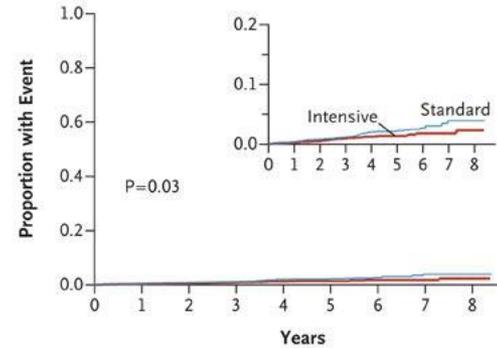
A Primary Outcome



No. at Risk

Intensive	2362	2273	2182	2117	1770	1080	298	175	80
Standard	2371	2274	2196	2120	1793	1127	358	195	108

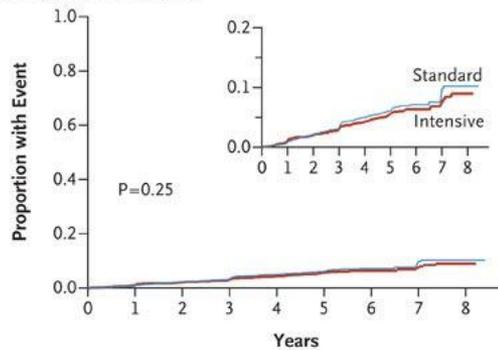
B Nonfatal Stroke



No. at Risk

Intensive	2362	2291	2223	2174	1841	1128	313	186	88
Standard	2371	2287	2235	2186	1879	1196	382	215	114

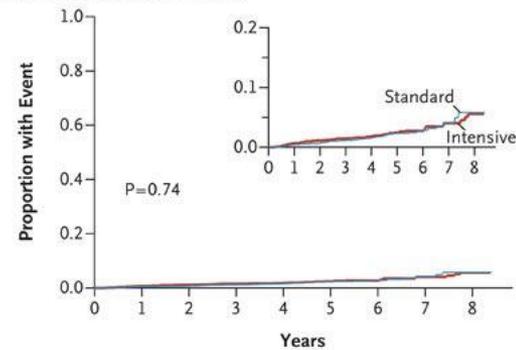
C Nonfatal Myocardial Infarction



No. at Risk

Intensive	2362	2278	2190	2133	1787	1087	299	177	82
Standard	2371	2278	2208	2141	1818	1145	365	201	112

D Death from Cardiovascular Disease



No. at Risk

Intensive	2362	2304	2252	2201	1870	1143	317	188	91
Standard	2371	2313	2268	2218	1922	1220	393	221	118

The ACCORD Study Group. N Engl J Med 2010;362:1575-1585



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Case 5

45 year old white male is seen in the office with new onset hypertension. His BP in the office is 166/96 with a HR of 82. All of the following are suggested first line agents for the patient's BP EXCEPT

- A. Lisinopril
- B. Chlorthalidone
- C. Losartan
- D. Atenolol

Recommendation 6: Med Classes

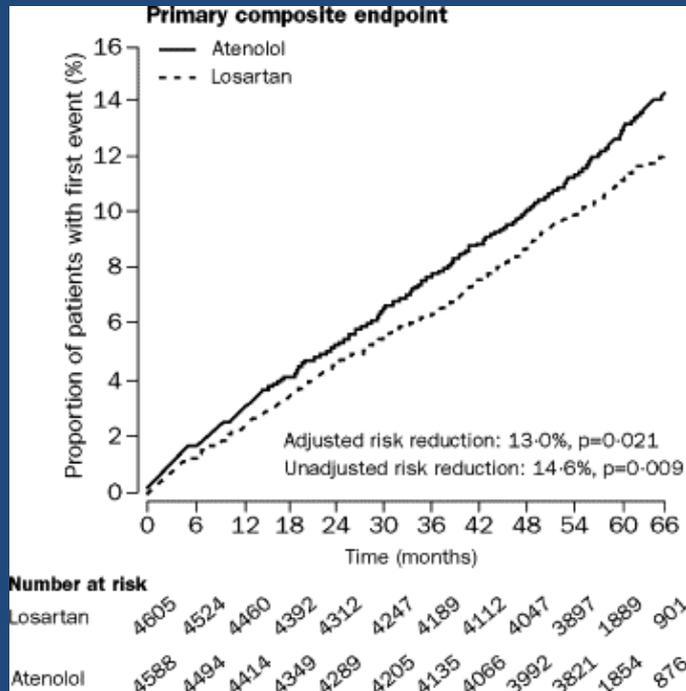
Recommendation 6

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB).

Moderate Recommendation - Grade B

- Only 4 drug classes recommended
- Emphasize BP control is the key to reduce mortality, CV, cerebrovascular, and kidney issues. No suggestion of one agent over another
- Acknowledge thiazide diuretic over CCB or ACE-I and ACE-I over CCB has shown benefit in HF outcomes
- Beta-blockers not recommended as initial treatment
- Alpha blockers not recommended as first line
- Suggest add on therapy to be chosen initially from one of the initial 4 drug classes
- Guidelines do not reflect patient's with CAD or CHF as they did not include these populations in their review

LIFE Trial



- RCT of 9193 pts randomized to atenolol vs losartan
- 13% risk reduction in CV morbidity and mortality

Björn Dahlöf , Richard B Devereux , Sverre E Kjeldsen , Stevo Julius , Gareth Beevers , Ulf de Faire , Frej Fyhrq...

Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol

The Lancet, Volume 359, Issue 9311, 2002, 995 - 1003

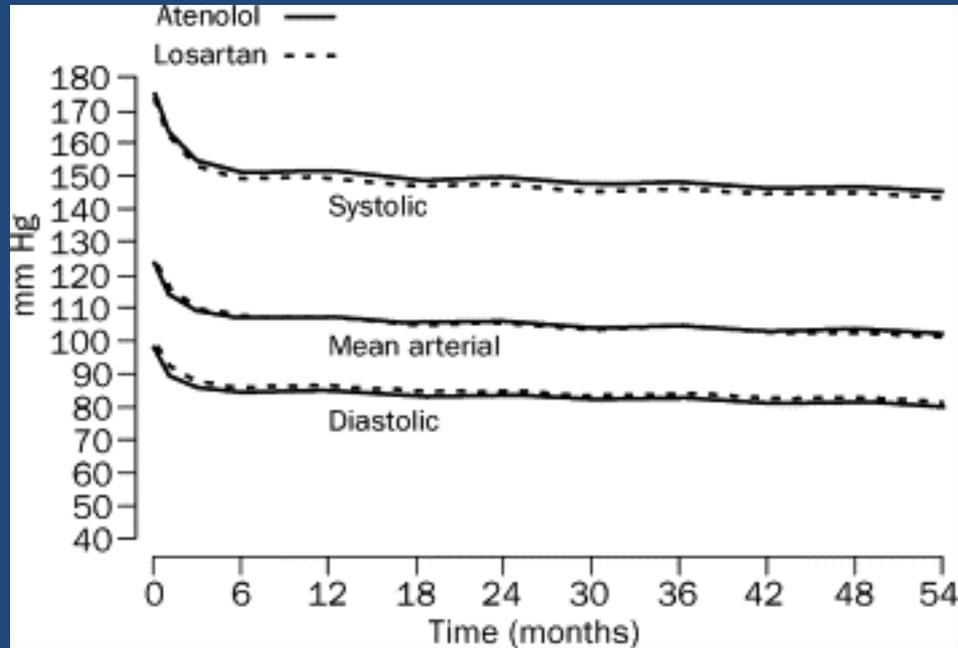


Figure 3 Blood pressure during follow-up

Björn Dahlöf , Richard B Devereux , Sverre E Kjeldsen , Stevo Julius , Gareth Beevers , Ulf de Faire , Frej Fyhrq...

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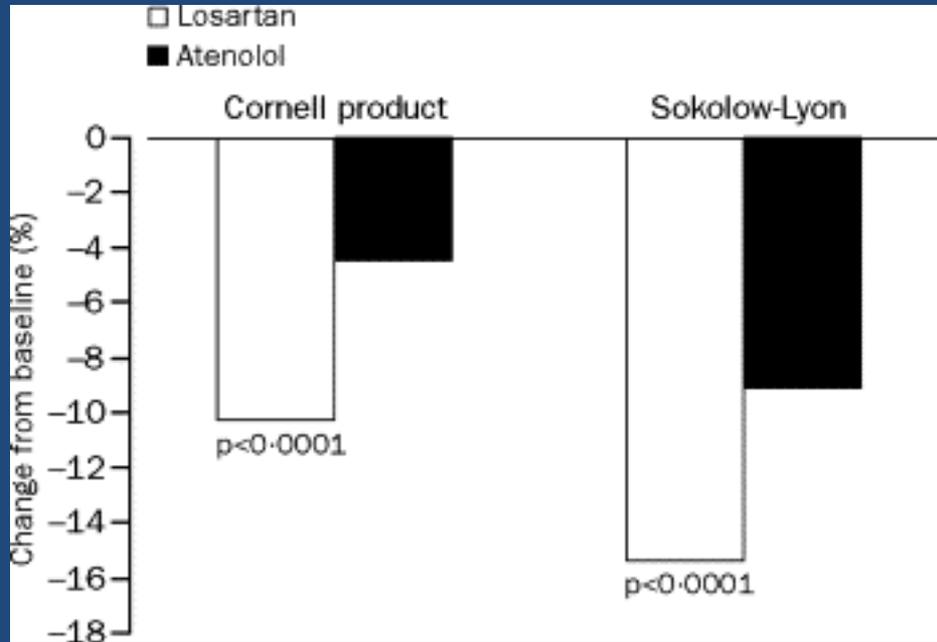


Figure 7 Change in Cornell voltage-duration product and Sokolow-Lyon from baseline p is for between-group differences.

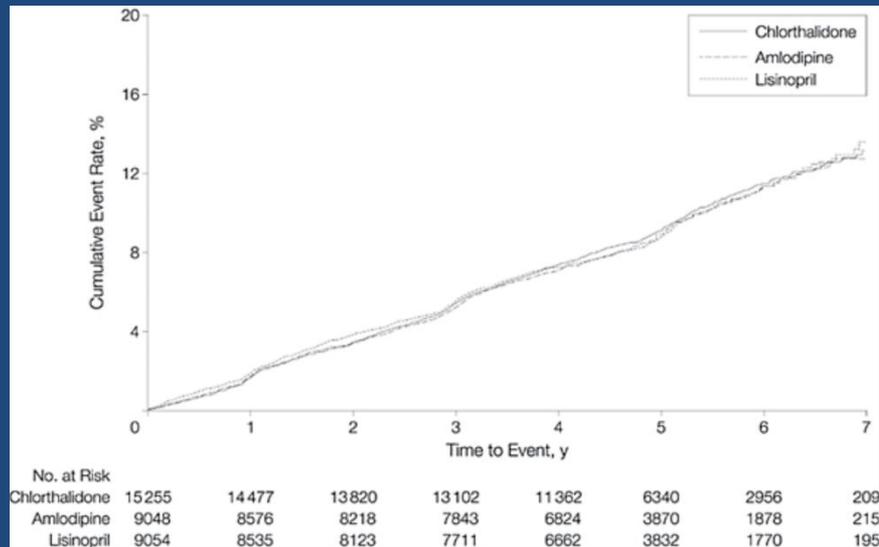
Björn Dahlöf , Richard B Devereux , Sverre E Kjeldsen , Stevo Julius , Gareth Beevers , Ulf de Faire , Frej Fyhrq...

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From: **Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)**

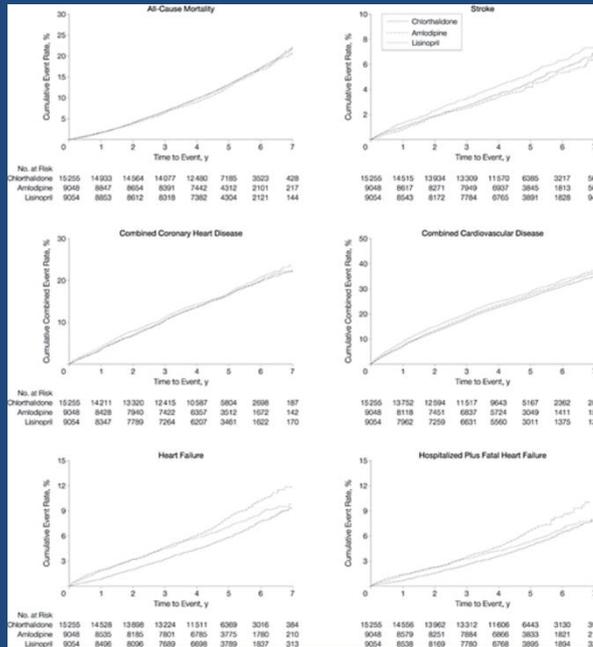
JAMA. 2002;288(23):2981-2997. doi:10.1001/jama.288.23.2981



- 33,357 pts > 55 with one CV RF
- RCT chlorthalidone vs amlodipine vs lisinopril
- No significant difference in primary combined endpoint of fatal CHD or non fatal MI

No significant difference was observed for amlodipine (relative risk[RR], 0.98; 95% confidence interval [CI], 0.90-1.07; P =.65) or lisinopril (RR, 0.99; 95% CI, 0.91-1.08; P =.81) vs chlorthalidone with a mean follow-up of 4.9 years.

From: Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)



- Secondary analysis showed amlodipine higher rate of HF
- Secondary analysis chlorthalidone vs lisinopril lower event rate for combined CVD, CVA, and HF

Recommendation 7: AA Med Choice

Recommendation 7

In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.

For general black population: Moderate Recommendation - Grade B

For black patients with diabetes: Weak Recommendation - Grade C

- ALLHAT Trial: Prespecified subgroup analysis.
- Chlorthalidone had improved outcome compared to lisinopril for CVA, HF, and combined CV outcomes.
- ACE-I compared to CCB had a 51% increased risk for CVA.
- CCB amlodipine had no difference compared to chlorthalidone in CVA, CHD, combined CV, kidney outcomes, or total mortality
- ACE-I vs CCB not studied as initial med not studied in blacks with diabetes.
- Does not apply if CKD. See Recommendation 8

Recommendation 9: Adjustment of therapy to goal

- Objective to attain and maintain goal BP
- Titration of therapy suggested by maximizing dose of initial drug and adding on second drug preferentially from ACE I/ARB, Calcium channel blocker, or thiazide diuretic first
- Do not use ACE I and ARB in same patient
- If require more than 3 drugs ok to use BP drugs from other classes and give consideration for referral to hypertensive specialist

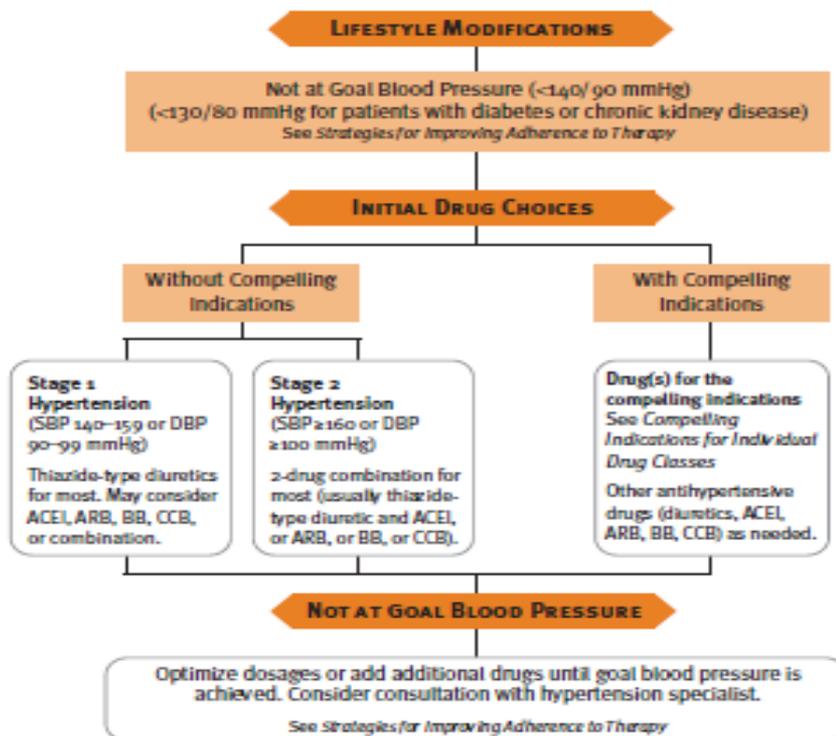
JNC 7 Versus JNC 8

TREATMENT

PRINCIPLES OF HYPERTENSION TREATMENT

- Treat to BP <140/90 mmHg or BP <130/80 mmHg in patients with diabetes or chronic kidney disease.
- Majority of patients will require two medications to reach goal.

ALGORITHM FOR TREATMENT OF HYPERTENSION



- Simplified Targets for treatment
- Beta-blocker no longer included as first line options
- More limited scope of compelling indications recommendations for specific drug classes

Take Home Points – JNC 8 new BP guidelines

- Treatment targets. $< 140/90$ (age < 60 , DM, CKD)
- BP target $< 150/90$ if > 60 years old
- Start with ACE-I, ARB, thiazide diuretic, CCB in non-black population
- Start with CCB and thiazide diuretic in black population
- CKD BP regimen should include an ACE I or ARB

Clinical Judgment

- “ Guidelines attempt to define practices that meet the needs of patients in most circumstances and are not a replacement for clinical judgment. The ultimate decision about care of a particular patient must be made by the healthcare provider and patient in light of the circumstances presented by the patient. As a result, situation may arise in which deviations from these guidelines may be appropriate.”

Questions