

CME/CE Teleconference Workbook

CV Risk Management: What Recent Outcomes Trials Mean for Clinical Practice



Faculty

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Target Audience

Nurse practitioners

Physician assistants

Primary care physicians
are also welcome

Jointly presented by:



This activity is made possible by an unrestricted educational grant from Pfizer Inc.

ACCREDITATION INFORMATION



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To qualify for continuing education credit or contact hours, you must:

1. Read the workbook and listen to the entire teleconference.
2. Relate the content material to the learning objectives.
3. Answer the self-assessment questions and complete the evaluation form found online at www.practicingclinicians.com/tod/eval and submit. Physician assistants, nurse practitioners, and physicians must answer at least 7 of the 10 questions correctly to receive credit.

The estimated time to complete this activity is 1 hour.

Teleconference-on-Demand Series

Release date: March 3, 2006.

Expiration: March 3, 2007.

DISCLAIMER

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CME/CE Teleconference Workbook

CV Risk Management: What Recent Outcomes Trials Mean for Clinical Practice

OVERVIEW

This CME/CE teleconference series will focus on helping clinicians apply cardiovascular (CV) risk clinical trial data and CV risk guidelines to clinical practice. Faculty will review recent landmark trials in CV risk management and what their outcomes mean for real-world clinical practice. In addition, faculty will review JNC 7, the National Cholesterol Education Program 2004 update, American Diabetes Association guidelines, and other major guidelines involving CV risk, discuss key differences among these guidelines, and critique the evidence base supporting their recommendations.

Each 1-hour teleconference includes a short introduction, a 30- to 35-minute presentation, and a 15- to 20-minute question-and-answer session with a member of the faculty.

LEARNING OBJECTIVES

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CME/CE activity.

Upon completion of this activity, participants should be better able to:

- Explain the rationale for a global approach to CV risk management.
- Extrapolate data from recent clinical trials to select appropriate pharmacologic and nonpharmacologic treatment for CV risk factors in clinical practice.
- Apply current CV risk guidelines to clinical practice.

FACULTY

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FACULTY DISCLOSURE

As providers accredited by the Accreditation Council for Continuing Medical Education and the American Nurses Credentialing Center, it is the policy of The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a sponsor has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

Dr Blumenthal: *honoraria, speakers bureau:* AstraZeneca Pharmaceuticals LP, Kos Pharmaceuticals, Inc., Merck & Co., Inc, Pfizer Inc., Schering-Plough Corporation.

Dr Blank: *honoraria, speakers bureau:* Merck & Co, Inc., Pfizer Inc, Takeda Pharmaceutical Company Limited; *grant/research support:* sanofi-aventis Group, Kos Pharmaceuticals, Inc., Pfizer Inc.

Dr Foody: *consultant, honoraria:* Merck & Co., Inc., Pfizer Inc.

No speaker has indicated that his/her presentation will include information on off-label products.

CV Risk Management: What Recent Outcomes Trials Mean for Clinical Practice

A CV Risk Teleconference Series



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Slide 1

- ▶ The objectives of this teleconference series are to:
 - ▶ Explain the rationale for a global approach to cardiovascular (CV) risk.
 - ▶ Extrapolate data from recent clinical trials to select appropriate pharmacologic and nonpharmacologic treatment for CV risk factors in clinical practice.
 - ▶ Apply current CV risk guidelines to clinical practice.

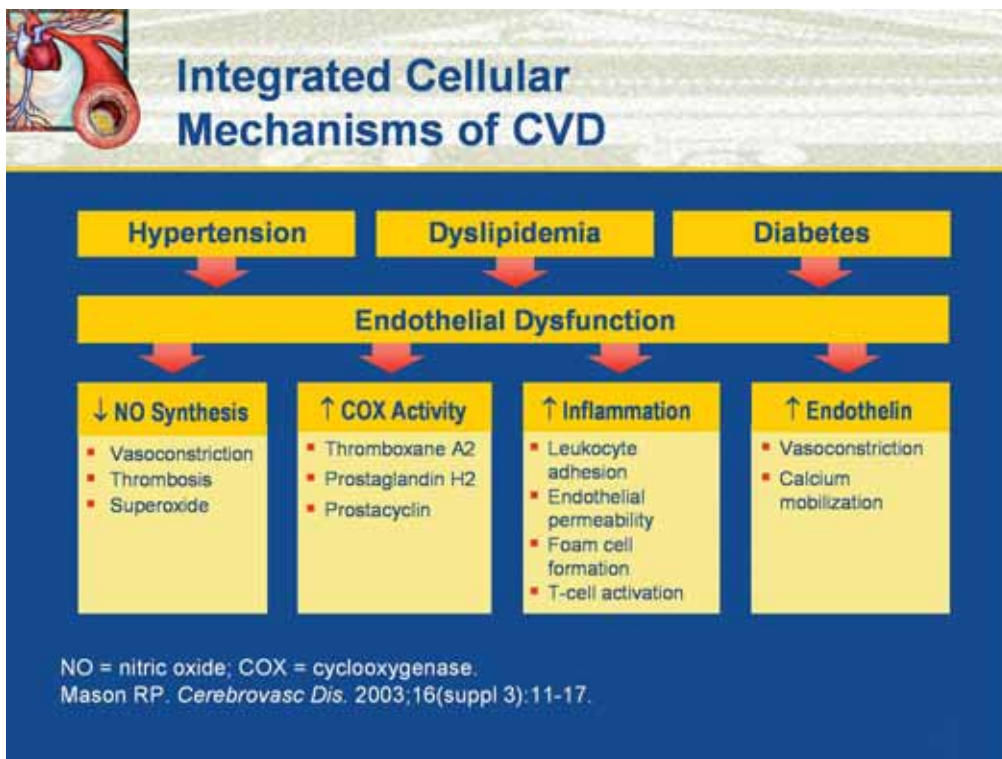


What Is the PCE?

- ▶ The **Practicing Clinicians Exchange (PCE)** is an innovative network of live educational activities and home study materials designed for NPs and PAs. This unique CME/CE format will provide NPs and PAs with educational opportunities built to meet real-world clinical needs
- ▶ The PCE's goal is to provide practicing clinicians with comprehensive CME/CE programs in a variety of therapeutic areas, with opportunities to earn multiple CME/CE credits

Slide 2

- ▶ The Practicing Clinicians Exchange (PCE) is a CME/CE initiative developed specifically for nurse practitioners (NPs) and physician assistants (PAs), although primary care physicians are also welcome to participate.
- ▶ This teleconference series has been integrated with a symposium series and home study workbook. For more information, visit www.practicingclinicians.com, the official PCE Web site.

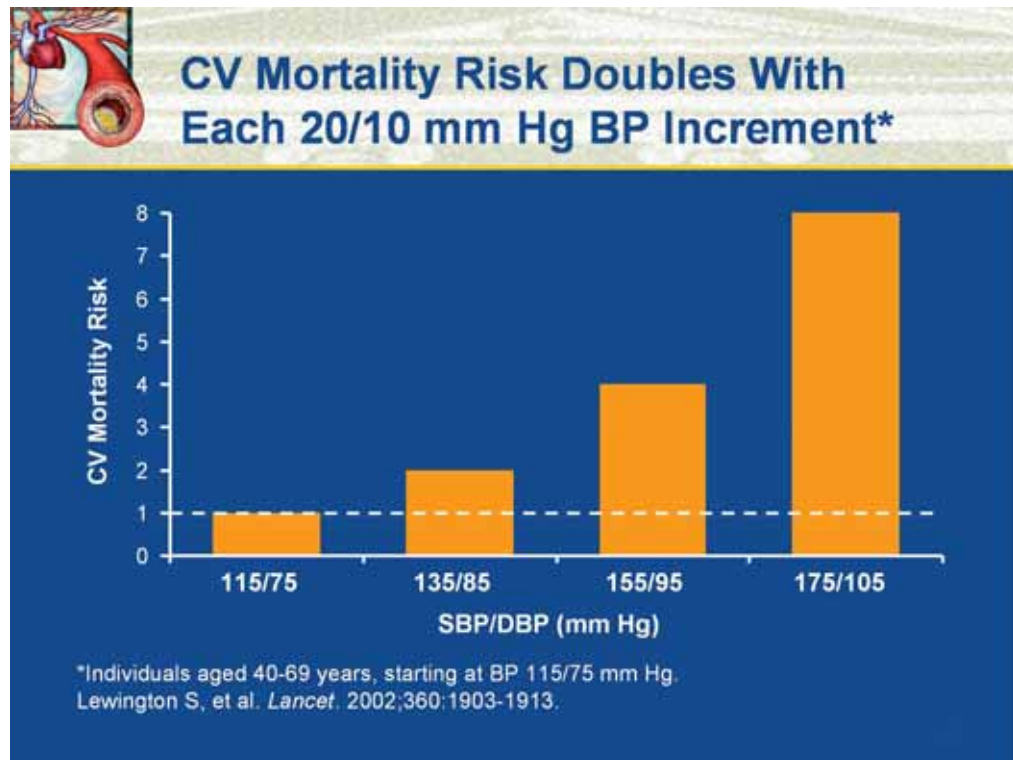


Slide 3

- ▶ Hypertension, dyslipidemia, and diabetes lead to the development of vascular disease through the common pathway of endothelial dysfunction.
- ▶ Endothelial dysfunction is associated with reduced nitric oxide (NO) synthesis, which leads to vasoconstriction, increased thrombosis, and increased production of cell-damaging superoxides. Endothelial damage increases activity of cyclooxygenases (COX), increasing production of thromboxane A2, prostaglandin H2, and prostacyclin, and affecting platelet/endothelial-cell interactions.
- ▶ Endothelial dysfunction also is associated with inflammation, leading to leukocyte adhesion, increased endothelial permeability, and migration of leukocytes into the adventitia with foam cell formation and activation of T cells. In addition, increased endothelin production leads to vasoconstriction and calcium mobilization.

References

- Borghi C. Interactions between hypercholesterolemia and hypertension: implications for therapy. *Curr Opin Nephrol Hypertens.* 2002;11:489-496.
- Giannattasio C, Mancia G. Arterial distensibility in humans: modulating mechanisms, alterations in diseases and effects of treatment. *J Hypertens.* 2002;20:1889-1899.
- John S, Schmieder RE. Potential mechanisms of impaired endothelial function in arterial hypertension and hypercholesterolemia. *Curr Hypertens Rep.* 2003;5:199-207.
- Mason RP. Atheroprotective effects of long-acting dihydropyridine-type calcium channel blockers: evidence from clinical trials and basic scientific research. *Cerebrovasc Dis.* 2003;16(suppl 3):11-17.
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Slide 4

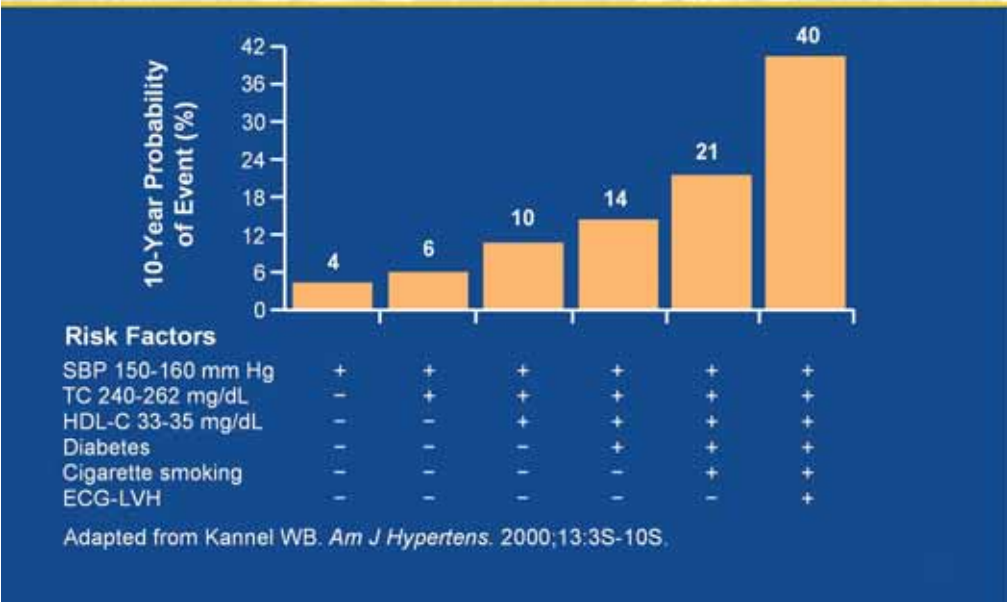
- ▶ In a meta-analysis conducted by Lewington and colleagues, the relationship between blood pressure (BP) and vascular mortality was assessed in 1 million adults, aged 40 to 69 years, with no previous vascular disease, who were enrolled in 61 prospective observational studies of BP and mortality.
- ▶ During the 12.7 million person-years of observation, there were 56,000 vascular deaths, 34,000 deaths from ischemic heart disease, and 10,000 deaths attributed to other vascular causes.
- ▶ As shown in this slide, an increased risk for cardiovascular disease (CVD) began at a BP of 115/75 mm Hg and increased significantly for each increment of 20 mm Hg usual systolic blood pressure (SBP) and 10 mm Hg usual diastolic blood pressure (DBP).

Reference

Lewington S, Clarke R, Qizilbash N, Peto R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-1913.



Risk of CHD in Mild Hypertension by Intensity of Associated Risk Factors

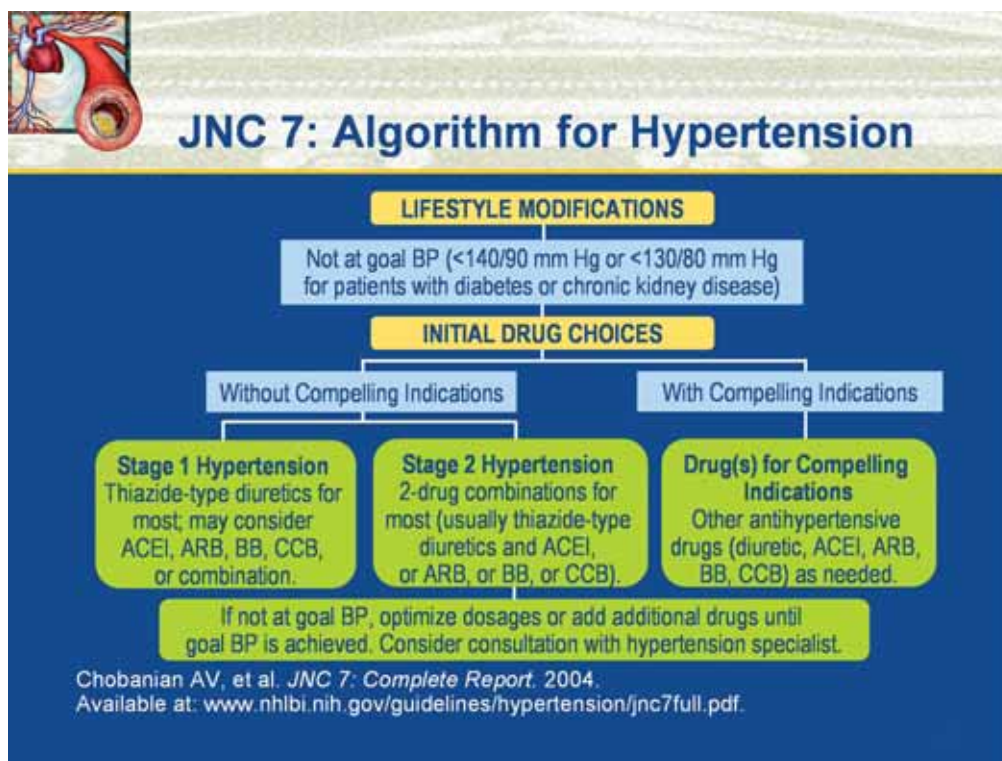


Slide 5

- ▶ The risk of CHD in patients with hypertension—particularly elevated SBP—is a significant predictor of death from coronary heart disease (CHD). Risk for CHD is exacerbated by the intensity of associated risk factors (eg, elevated total cholesterol [TC], low high-density lipoprotein cholesterol [HDL-C], diabetes, cigarette smoking, and left ventricular hypertrophy).
- ▶ Each additional CHD risk factor or CHD risk equivalent, whatever its degree, can increase the overall 10-year risk of coronary death in both men and women.
- ▶ In addition to these risk factors shown above, obesity, physical inactivity, and elevated low-density lipoprotein cholesterol (LDL-C) increase the overall risk for CHD in patients with mild hypertension.

Reference

Kannel WB. Risk stratification in hypertension: new insights from the Framingham Study. *Am J Hypertens.* 2000;13:3S-10S.



Slide 6

- ▶ The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) provides 4 categories for BP (not shown).
 - ▶ Blood pressures <120/80 mm Hg are considered normal.
 - ▶ Patients with prehypertension, a new category in the JNC 7 guidelines, have BPs of 120-139/80-89 mm Hg.
 - ▶ Overt hypertension is subcategorized into stage 1 (140-159/90-99 mm Hg) and stage 2 ($\geq 160/\geq 100$ mm Hg).
- ▶ Recent clinical trials have shown that most patients require ≥ 2 antihypertensive agents to achieve goal BP (<140/90 mm Hg, or <130/80 mm Hg for patients with diabetes or chronic kidney disease).
- ▶ This slide shows the JNC 7 algorithm for the treatment of hypertension. Treatment choices are driven by BP level, comorbid conditions, and compelling indications.
- ▶ In patients with stage 1 hypertension but without compelling indications, a thiazide-type diuretic—either alone or in combination with another class—is recommended as initial therapy. A drug from a different class should be added if the first drug is insufficient to achieve goal BP.
- ▶ In patients with stage 2 hypertension but without compelling indications, combination therapy with 2 drugs from different classes is indicated. These combinations generally consist of a thiazide-type diuretic plus an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), β -blocker (BB), or calcium channel blocker (CCB).
- ▶ Compelling indications are discussed on the next slide.

Reference

Chobanian AV, Bakris GL, Black HR, et al, for the National High Blood Pressure Education Program Coordinating Committee. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Complete Report*. Bethesda, Md: National Heart, Lung, and Blood Institute; 2004. NIH Publication No. 04-5230. Available at: www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf.



JNC 7: Compelling Indications for Antihypertensive Drug Classes

Compelling Indication	Recommended Drugs					
	Diuretic	BB	ACEI	ARB	CCB	Aldo ANT
Heart failure	•	•	•	•		•
Post MI		•	•			•
High coronary disease risk	•	•	•		•	
Diabetes	•	•	•	•	•	
Chronic kidney disease			•	•		
Recurrent stroke prevention	•		•			

Aldo ANT = aldosterone antagonist.

Chobanian AV, et al. *JNC 7: Complete Report*. 2004.

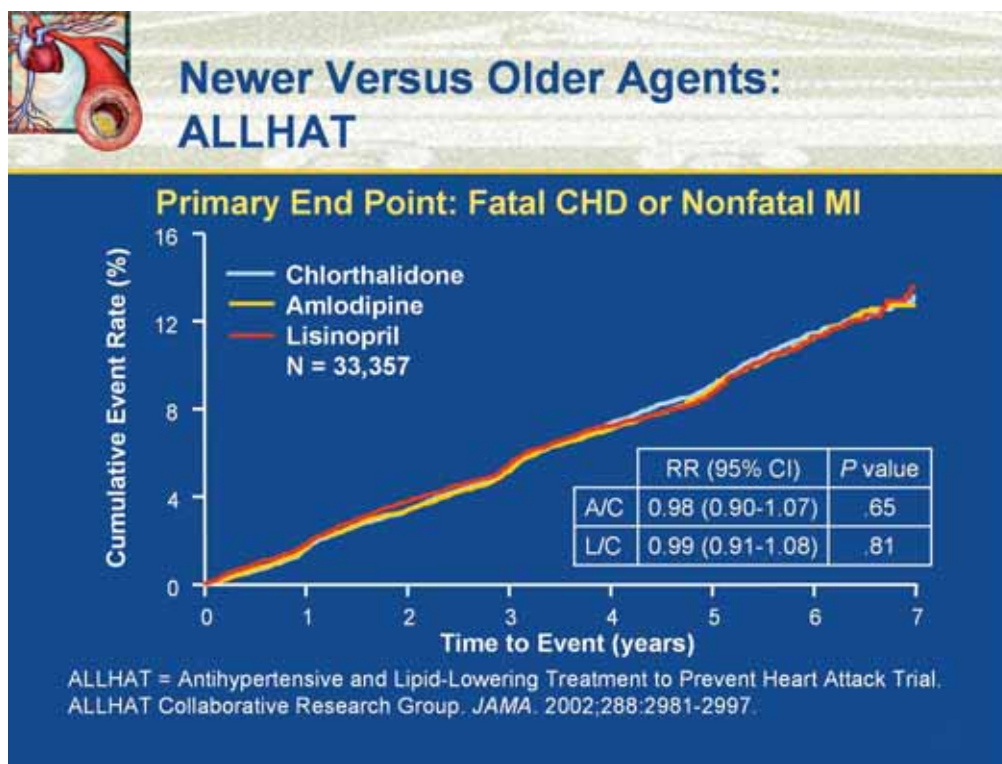
Available at: www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf.

Slide 7

- ▶ Patients with prehypertension or hypertension who have compelling indications (specific high-risk conditions) require therapy with specific antihypertensive agents (eg, ACE inhibitors, ARBs, β -blockers, CCBs). Compelling indications include heart failure (HF), post-myocardial infarction (MI) status, high CHD risk, diabetes, chronic kidney disease, and prevention of recurrent stroke.
- ▶ The selection of agents for patients with these high-risk conditions are based on favorable outcome data from clinical trials.
- ▶ Other management considerations include medications already being taken by the patient, tolerability, and desired BP targets.

Reference

Chobanian AV, Bakris GL, Black HR, et al, for the National High Blood Pressure Education Program Coordinating Committee. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Complete Report*. Bethesda, Md: National Heart, Lung, and Blood Institute; 2004. NIH Publication No. 04-5230. Available at: www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf.

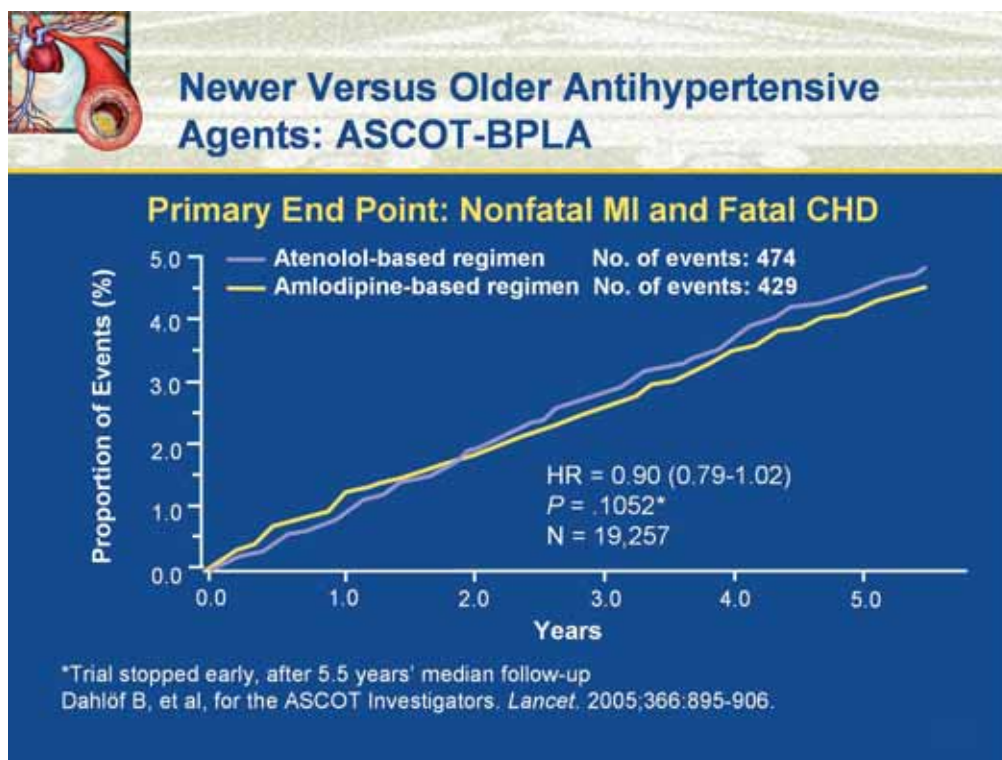


Slide 8

- ▶ The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a randomized, double-blind, active-controlled clinical trial conducted between 1994 and 2002. The study enrolled 33,357 patients aged ≥ 55 years who had hypertension and ≥ 1 additional risk factor for CHD. Patients were randomized to the thiazide diuretic chlorthalidone, the CCB amlodipine, or the ACE inhibitor lisinopril and followed for ~ 4 to 8 years.
- ▶ This slide shows the result for the primary end point, the composite of fatal CHD or nonfatal MI. No significant difference in these rates between amlodipine (6-year rate, 11.3%) and chlorthalidone (6-year rate, 11.5%) was observed. Relative risk for amlodipine versus chlorthalidone was 0.98 (95% CI, 0.90-1.07).
- ▶ Similarly, no significant difference in these rates between lisinopril (6-year rate, 11.4%) and chlorthalidone was observed. Relative risk for lisinopril versus chlorthalidone was 0.99 (95% CI, 0.91-1.08).
- ▶ Secondary outcomes were similar for chlorthalidone and amlodipine, except for a higher 6-year rate of HF with amlodipine (7.7% vs 10.2%, respectively).
- ▶ For chlorthalidone versus lisinopril, higher rates of combined CVD (30.9% vs 33%), stroke (5.6% vs 6.3%), and HF (7.7% vs 8.7%) were observed in the lisinopril group.

Reference

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. 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;288:2981-2997.

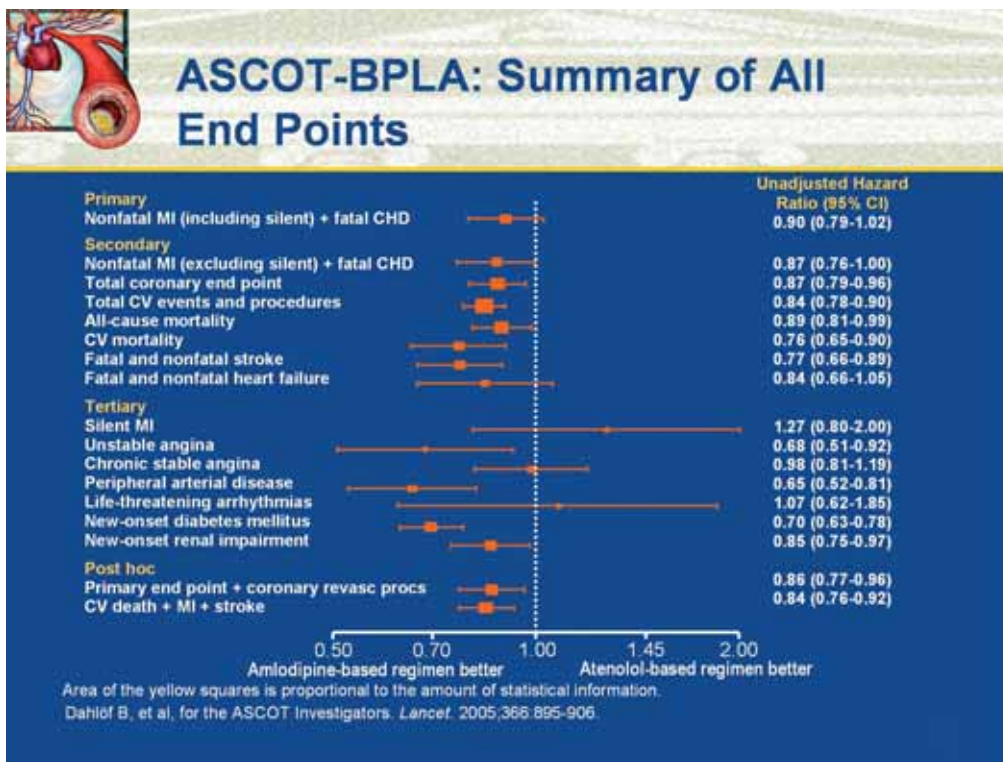


Slide 10

- ▶ The blood pressure-lowering arm of the ASCOT trial (ASCOT-BPLA) was terminated early after a median follow-up of 5.5 years because patients allocated to the atenolol-based regimen had significantly higher mortality as well as worse outcomes on several other secondary end points.
- ▶ Because the study was powered for 1150 individuals to have primary end point events and only 903 events had occurred by the last follow-up date because of early termination, ASCOT-BPLA was underpowered for the primary end point.
- ▶ A 10% reduction in the risk of the composite primary end point of nonfatal MI (including silent MI) plus fatal CHD was observed in patients taking the amlodipine-based regimen ($P = .1052$).
- ▶ Fewer patients in the amlodipine arm experienced fatal or nonfatal stroke ($P = .0003$), CV events or procedures ($P < .0001$), or death from any cause ($P < .025$; not significant in relation to the prespecified P -value for significance of .01). In addition, the development of diabetes was significantly lower in the amlodipine arm than in the atenolol arm ($P < .0001$).

Reference

Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895-906.

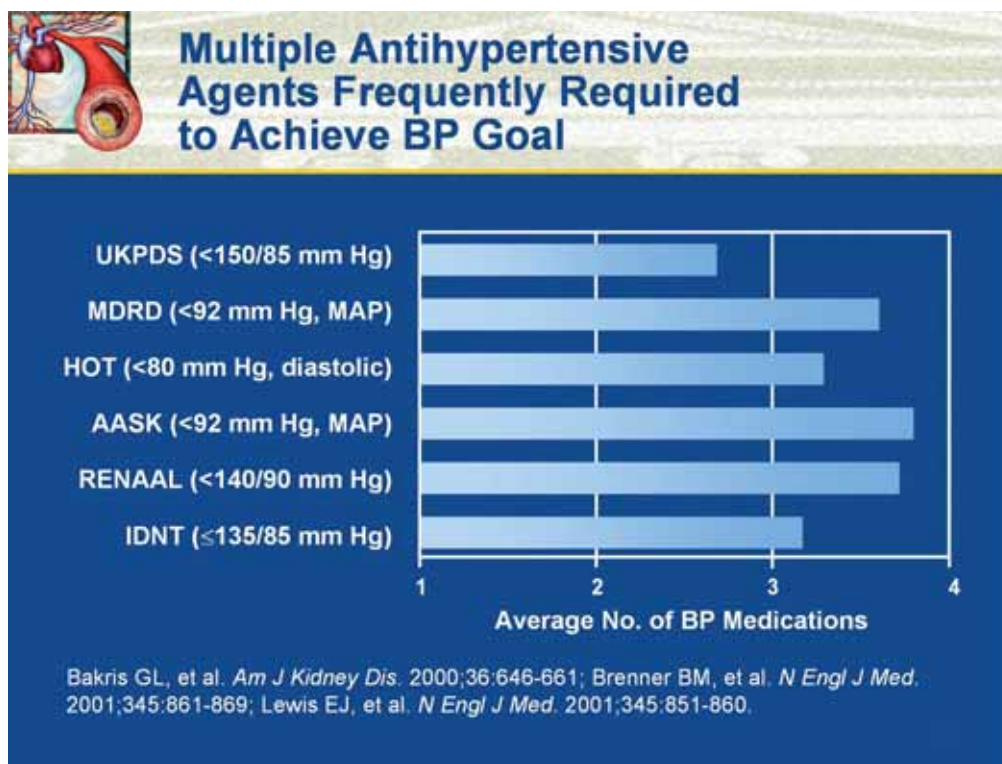


Slide 11

- ▶ This slide summarizes all primary, secondary, tertiary, and post-hoc end points assessed in ASCOT-BPLA.
- ▶ Although the difference in the primary end point between the amlodipine and atenolol arms was not significant due to early termination of ASCOT-BPLA, risk reductions favored the amlodipine-based regimen for the majority of prespecified secondary and tertiary end points, as well as for post-hoc end points consisting of:
 - ▶ The composite of the primary end point and coronary revascularization procedures
 - ▶ The composite of CV death, MI, and stroke.
- ▶ The ASCOT investigators believe these results will have implications for the choice of newer antihypertensive regimens in the majority of patients with hypertension and will most likely influence future guidelines.

Reference

Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895-906.



Slide 12

- ▶ To achieve adequate BP lowering, the majority of patients require multiple antihypertensive medications.
- ▶ Bakris and colleagues reviewed clinical trials in which patients with either diabetes or renal impairment were randomized to 2 BP reduction targets. Among these trials were the United Kingdom Prospective Diabetes Study (UKPDS), Modification of Diet in Renal Disease (MDRD), Hypertension Optimal Treatment (HOT), and the African American Study of Kidney Disease (AASK). The authors demonstrated that patients assigned to the lower BP target required an average of 3.2 daily antihypertensive medications to achieve goal.
- ▶ As shown in the graph, patients in 2 other studies (RENAAL and IDNT) required >3 nonstudy medications to achieve BP goals.
- ▶ These data further emphasize the importance of using multiple antihypertensive agents in the treatment of high-risk patients with hypertension.

References

- Bakris GL, Williams M, Dworkin L, et al, for the National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis.* 2000;36:646-661.
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- Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens.* 2002;4:393-404.
- Lewis EJ, Hunsicker LG, Clarke WR, et al, for the Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345:851-860.



National Cholesterol Education Program (NCEP) Management Guidelines

- ▶ Obtain a fasting lipid profile in all patients. For those who have had an MI, obtain a fasting lipid profile within 24 hours of admission
- ▶ Start therapeutic lifestyle changes in all patients, including:
 - ▶ Reduced intakes of saturated fats (<7% of total calories) and cholesterol (<200 mg/d)
 - ▶ Increased physical activity
 - ▶ Weight reduction
 - ▶ Add plant stanols/sterols (2 g/d) and viscous fiber (10-25 g/d) to enhance LDL-C lowering

NCEP ATP III. 2002. NIH Publication No. 02-5215. Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/>.

Slide 13

- ▶ According to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines, a fasting lipoprotein profile (TC, LDL-C, HDL-C, and triglycerides [TG]) should be obtained in all patients aged ≥ 20 years once every 5 years. Among those who have had an MI, a fasting lipid profile should be obtained within 24 hours of admission.
- ▶ Therapeutic lifestyle changes (TLC) should be instituted in all patients with above-optimal LDL-C levels. TLC consists of reducing intake of saturated fat to <7% of total calories, lowering cholesterol intake to <200 mg/d, increasing physical activity, controlling weight, and adding plant stanols/sterols and viscous fiber to enhance LDL-C lowering.

Reference

National Cholesterol Education Program. *Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Full Report*. Bethesda, Md: National Heart, Lung, and Blood Institute; 2002. NIH Publication No. 02-5215. Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/>.



NCEP Management Guidelines (cont'd)

- ▶ For primary and secondary prevention, use statins first-line to achieve LDL-C goal
- ▶ If patient remains above LDL-C goal, intensify statin therapy—and add a second LDL-C-lowering agent, if needed
- ▶ If TG ≥ 150 mg/dL or HDL-C < 40 mg/dL:
 - ▶ Emphasize weight management, physical activity, smoking cessation
- ▶ If TG 200-499 mg/dL after initiation of LDL-C-lowering therapy:
 - ▶ Calculate non-HDL-C as secondary target
 - ▶ Consider adding nicotinic acid or a fibrate
- ▶ If TG ≥ 500 mg/dL
 - ▶ Very low-fat diet, weight reduction, increased physical activity
 - ▶ Consider treating with nicotinic acid or a fibrate before LDL-C-lowering therapy

NCEP ATP III. 2002. NIH Publication No. 02-5215. Available at:
<http://www.nhlbi.nih.gov/guidelines/cholesterol/>.

Slide 14

- ▶ The NCEP ATP III guidelines recommend statin therapy for most patients with elevated LDL-C levels.
- ▶ Among patients who remain above LDL-C goal despite an initial trial of a statin, the first step is to intensify statin therapy. An LDL-C-lowering agent from a second class (eg, a bile acid sequestrant or nicotinic acid) may be added, if needed.
- ▶ In patients with elevated TG (≥ 150 mg/dL) or low HDL-C (< 40 mg/dL), weight management, physical activity, and smoking cessation should be recommended.
- ▶ If TG level remains between 200 and 499 mg/dL in patients taking LDL-C-lowering therapy, the level of non-HDL cholesterol (defined as TC minus HDL-C) should be determined and used as a secondary target of therapy. The goal for non-HDL cholesterol should be set at 30 mg/dL higher than that for LDL-C. Nicotinic acid or a fibrate may be added to statin therapy, if used with caution, to achieve the non-HDL cholesterol goal.
- ▶ In patients with TG > 500 mg/dL, a very low-fat diet, weight reduction, and increased physical activity are recommended. Patients are usually treated with fibrates or nicotinic acid first; after TG levels have been lowered, attention should turn to LDL-C-lowering therapy.

Reference

National Cholesterol Education Program. *Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Full Report*. Bethesda, Md: National Heart, Lung, and Blood Institute; 2002. NIH Publication No. 02-5215. Available at:
<http://www.nhlbi.nih.gov/guidelines/cholesterol/>.



NCEP Guidelines Recognize Interaction Among Risk Factors and Risk Equivalents

Risk Factors

- ▶ Cigarette smoking
- ▶ BP \geq 140/90 mm Hg (or taking antihypertensive medication)
- ▶ Low HDL-C ($<$ 40 mg/dL)
- ▶ Family history of premature CHD
 - ▶ $<$ 55 years in first-degree male relative
 - ▶ $<$ 65 years in first-degree female relative
- ▶ Age
 - ▶ Men \geq 45 years
 - ▶ Women \geq 55 years

Risk Equivalents

- ▶ Diabetes
- ▶ Other clinical atherosclerotic disease
 - ▶ Peripheral arterial disease
 - ▶ Abdominal aortic aneurysm
 - ▶ Carotid artery disease
- ▶ \geq 2 risk factors with 10-year risk for hard CHD $>$ 20%, based on Framingham risk assessment

Grundy SM, et al. *Circulation*. 2004;110:227-239; NCEP ATP III. 2002. NIH Publication No. 02-5215. Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/>.

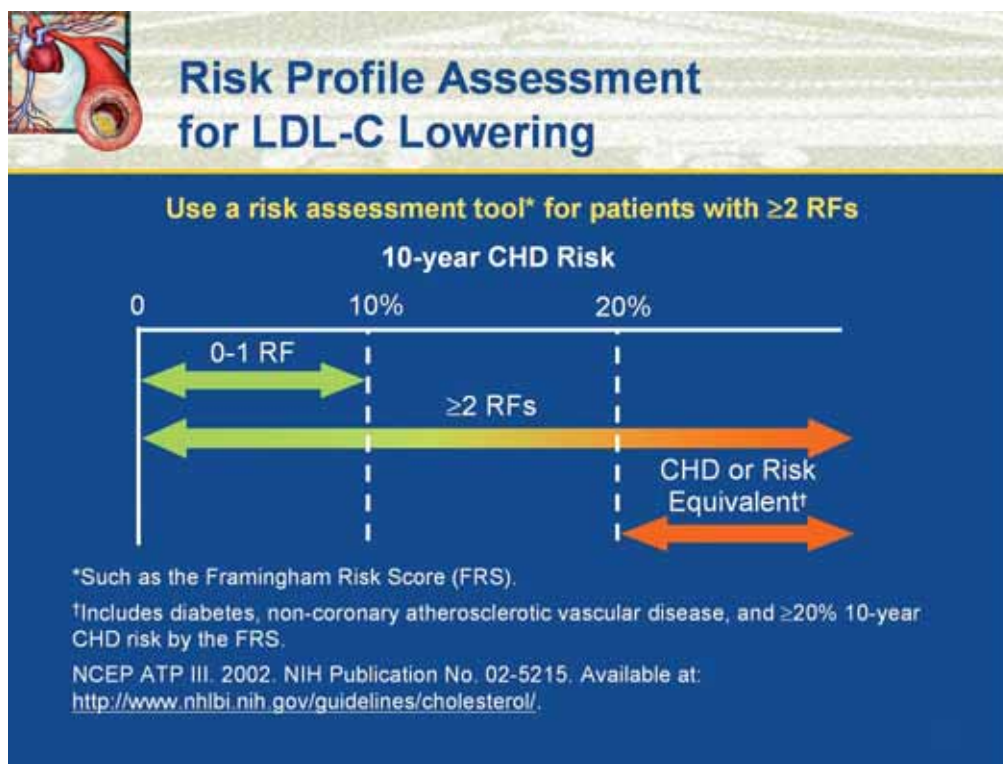
Slide 15

- ▶ The NCEP ATP III guidelines recognize the additive and synergistic interactions between risk factors for CHD and lipid levels.
- ▶ Major CHD risk factors that modify LDL-C goals include cigarette smoking, elevated BP or the need for antihypertensive medication, low HDL-C, family history of premature CHD, and age.
- ▶ Patients with a CHD risk equivalent carry a 10-year risk of major coronary events equal to that of a patient with established CHD ($>$ 20%). CHD risk equivalents include: peripheral artery disease, abdominal aortic aneurysm, and symptomatic carotid artery disease; diabetes (ATP III regards diabetes as a CHD risk equivalent because of its frequent association with multiple risk factors and the high mortality among patients with diabetes following MI); and multiple risk factors conferring a 10-year risk of CHD $>$ 20% based on Framingham risk assessment.

References

Grundy SM, Cleeman JI, Merz CNB, et al, for the Coordinating Committee of the National Cholesterol Education Program. NCEP Report. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004;110:227-239.

National Cholesterol Education Program. *Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Full Report*. Bethesda, Md: National Heart, Lung, and Blood Institute; 2002. NIH Publication No. 02-5215. Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/>.



Slide 16

- ▶ Risk assessment in patients without established CHD or CHD risk equivalents and with ≥ 2 risk factors can be determined using a 2-step procedure:
 - ▶ Patients with established CHD or CHD risk equivalents have a $>20\%$ 10-year risk for CHD events.
 - ▶ In patients without CHD or CHD risk equivalents, assess the number of risk factors. Patients with 0 or 1 risk factor for CHD generally have a $<10\%$ 10-year risk for CHD and are usually in the lowest-risk category. In patients with 2 or more risk factors, determine 10-year risk for CHD using Framingham scoring.
 - Patients with ≥ 2 risk factors and whose 10-year risk is $>20\%$ require intensive treatment.
 - Patients with ≥ 2 risk factors and whose 10-year risk is 10% to 20% may require less intensive treatment.

References

- Grundy SM, Cleeman JJ, Merz CNB, et al, for the Coordinating Committee of the National Cholesterol Education Program. NCEP Report. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004;110:227-239.
- National Cholesterol Education Program. *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III) Full Report*. Bethesda, Md: National Heart, Lung, and Blood Institute; 2002. NIH Publication No. 02-5215. Available at: <http://www.nhlbi.nih.gov/guidelines/cholesterol/>.



NCEP ATP III LDL-C Goals and Cut-points for Drug Therapy

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy
High and very high risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)	≥100 mg/dL	≥100 mg/dL (<100 mg/dL: consider drug options)
Moderately high risk: 2+ risk factors (10-year risk 10% to 20%)	<130 mg/dL (optional goal: <100 mg/dL)	≥130 mg/dL	≥130 mg/dL (100-129 mg/dL: consider drug options)
Moderate risk: 2+ risk factors (10-year risk <10%)	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0-1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL- lowering drug optional)

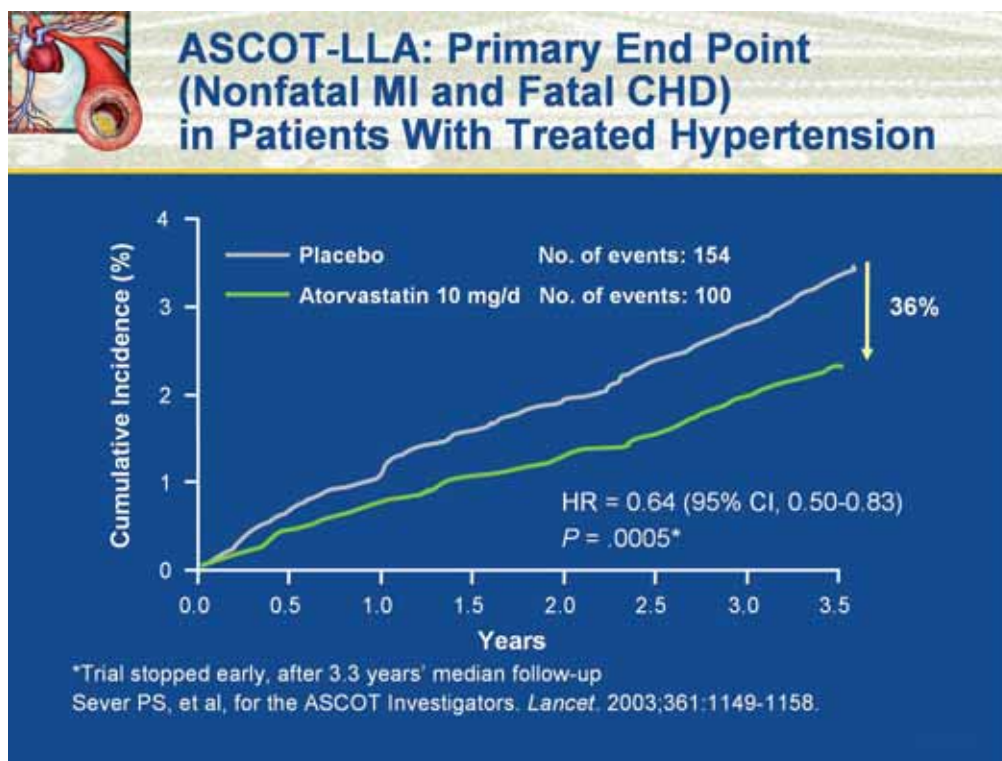
Grundy SM, et al. *Circulation*. 2004;110:227-239.

Slide 17

- ▶ The 2004 NCEP Report identified a new subset of *very high-risk* patients and recommends a therapeutic option of treating them to a LDL-C goal of <70 mg/dL. This recommendation includes patients who are already at a level of <100 mg/dL. TLC should be initiated in all patients at high and very high risk when LDL-C levels exceed 100 mg/dL.
- ▶ The 2004 NCEP Report also identified a new subset of patients at *moderately high risk*, who have multiple (≥ 2) risk factors and a 10-year CHD risk of 10% to 20%. The LDL-C goal for this category remains at a level of <130 mg/dL; however, the current NCEP Report provides a therapeutic option to set a lower LDL-C goal of <100 mg/dL.
- ▶ The NCEP Report advises that the intensity of lipid-lowering therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

Reference

Grundy SM, Cleeman JI, Merz CNB, et al, for the Coordinating Committee of the National Cholesterol Education Program. NCEP Report. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004;110:227-239.



Slide 18

- ▶ One of the key clinical trials that led to revision of the NCEP ATP III guidelines outlined in the previous slide was ASCOT-LLA.
- ▶ As noted previously, the ASCOT trial enrolled patients with mild to moderate risk for a CV event. These patients had hypertension and ≥ 3 other CHD risk factors (but no pre-existing CHD). Patients with baseline TC concentrations of ≤ 251 mg/dL were randomly assigned to the addition of atorvastatin 10 mg/d or placebo.
- ▶ The primary outcome in ASCOT was the combined end point of nonfatal MI and fatal CHD. This primary end point was significantly reduced by 36% in the atorvastatin group ($P < .0005$), and this effect seemed to emerge early.
- ▶ The lipid-lowering arm of ASCOT was stopped about 1.7 years early, after a median follow-up of 3.3 years, following the Data Safety Monitoring Committee recommendation, which was based on the highly significant reduction in the primary end point of CHD events with atorvastatin compared with placebo and a reduction in the incidence of stroke. At this time, 100 primary events (nonfatal MI and fatal CHD) had occurred in the atorvastatin group and 154 in the placebo group (hazard ratio, 0.64 [95% CI, 0.50-0.83]; $P = .0005$). The mean

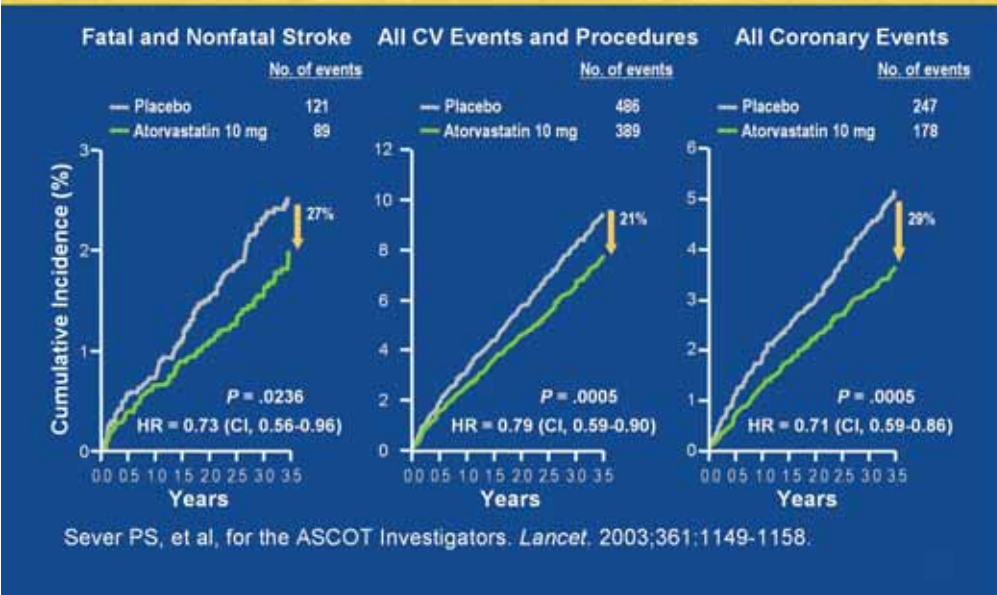
LDL-C at the time of trial termination was 90 mg/dL in the atorvastatin group and 126 mg/dL in the placebo group.

Reference

Sever PS, Dahlöf B, Poulter NR, et al, for the ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149-1158.



ASCOT-LLA: Secondary End Points

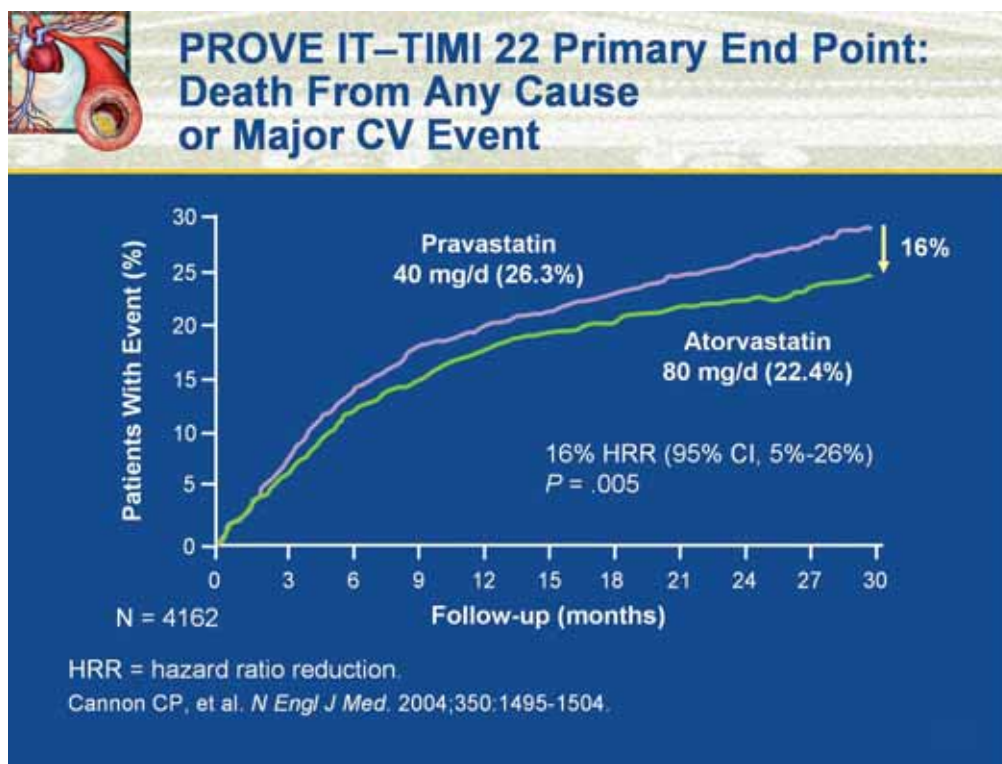


Slide 19

- ▶ Analysis of the secondary end points in ASCOT-LLA showed that reductions occurred in the atorvastatin group compared with the placebo group for:
 - ▶ Fatal and nonfatal stroke: 27% reduction ($P = .0236$; not significant in relation to the prespecified P -value for significance of .01).
 - ▶ All CV events and procedures: 21% reduction ($P = .0005$).
 - ▶ All coronary events: 29% reduction ($P = .0005$).
- ▶ According to the ASCOT investigators, if ASCOT-LLA had not been stopped early and had continued for an average follow-up of 5 years as originally planned, the reduction in fatal and nonfatal CHD events may have approached the 50% level, which based on observational studies is what could be expected from a 1.0 mmol/L (39 mg/dL) reduction in serum cholesterol. Further, the investigators noted that the benefits of statin treatment in ASCOT-LLA were additional to those of good BP control.

Reference

Sever PS, Dahlöf B, Poulter NR, et al, for the ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149-1158.



Slide 20

- ▶ The amended NCEP ATP III guidelines were also based, in part, on results of the Pravastatin or Atorvastatin Evaluation and Infection-Thrombolysis in Myocardial Infarction 22 (PROVE-IT) study, which was designed to determine whether intensive LDL-C lowering with statin therapy in high-risk patients would reduce major coronary events, including mortality, more than standard LDL-C lowering.
- ▶ Patients in the PROVE-IT study had been hospitalized for an acute coronary syndrome within 10 days of the index event. Those in the intensive lipid-lowering-therapy arm received atorvastatin 80 mg/d. In these patients, the median on-treatment LDL-C level was 62 mg/dL. Patients in the moderate lipid-lowering-therapy arm received pravastatin 40 mg/d. The median on-treatment LDL-C level in this group was 95 mg/dL.
- ▶ This graph depicts the Kaplan-Meier event rates for the primary end point (death from any cause or a major CV event). At 2 years, the event rate for the pravastatin group was 26.3%, and the rate for the atorvastatin group was 22.4%. This difference represented a 16% reduction in the risk for major CV events in favor of atorvastatin (95% CI, 5%-26%; $P = .005$).
- ▶ Another trial—the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study—compared the impact of pravastatin 40 mg/d with that of atorvastatin 80 mg/d on coronary disease progression. Following 18 months of treatment, atheroma volume demonstrated no significant change from baseline among patients receiving atorvastatin 80 mg/d ($-0.4%$, $P = .98$) but showed significant progression from baseline among patients receiving pravastatin 40 mg/d ($+2.7%$, $P = .001$). The change in atheroma volume differed significantly between the 2 groups ($P = .02$).

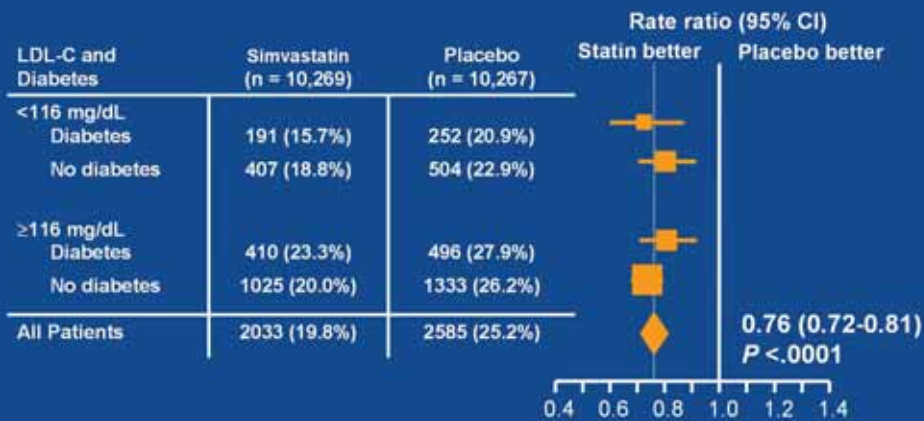
References

Cannon CP, Braunwald E, McCabe CH, et al, for the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350:1495-1504.

Nissen SE, Tuzcu FM, Schoenhagen P, et al for the REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA.* 2004;291:1071-1080.



HPS: First Major Vascular Event by LDL-C and Prior Diabetes



HPS Collaborative Group. *Lancet*. 2003;361:2005-2016.

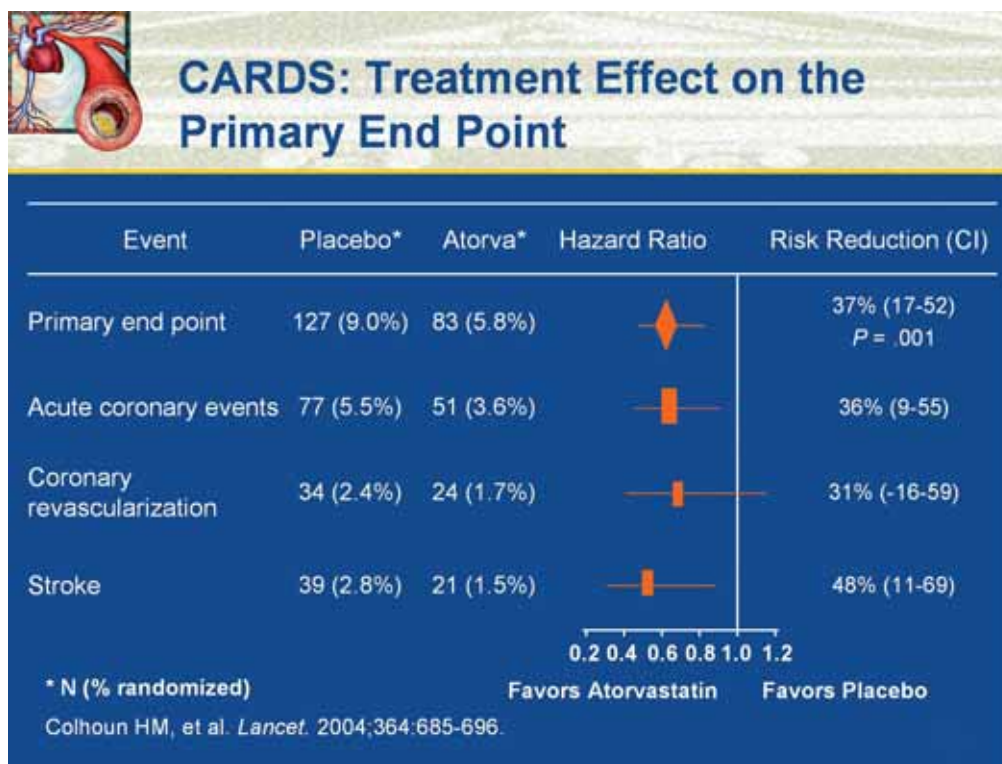
Slide 21

- ▶ The Heart Protection Study (HPS) was another key clinical trial used to develop the revised NCEP ATP III guidelines for lipid-lowering therapy.
- ▶ HPS enrolled 20,536 patients with coronary disease, other occlusive arterial disease, or diabetes. Patients were randomized to therapy with either placebo or simvastatin 40 mg/d and followed for 5 years. The primary end point was total mortality for the overall analysis and fatal or nonfatal vascular events for the subcategory analysis.
- ▶ In the overall patient population, all-cause mortality was 14.7% in patients who received placebo, compared with 12.9% among patients who received simvastatin 40 mg/d ($P = .0003$).
- ▶ Results of a further analysis of the diabetes cohort in HPS are shown in this slide. Regardless of baseline cholesterol levels (<116 mg/dL vs ≥ 116 mg/dL), use of the simvastatin regimen led to similar proportional reductions in the risk of a first major vascular event, both in patients with diabetes and those without. This finding suggests that statin therapy benefits patients with diabetes even if they do not have pre-existing CVD or a high level of LDL-C.

References

Collins R, Armitage J, Parish S, et al, for the Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361:2005-2016.

Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.



Slide 22

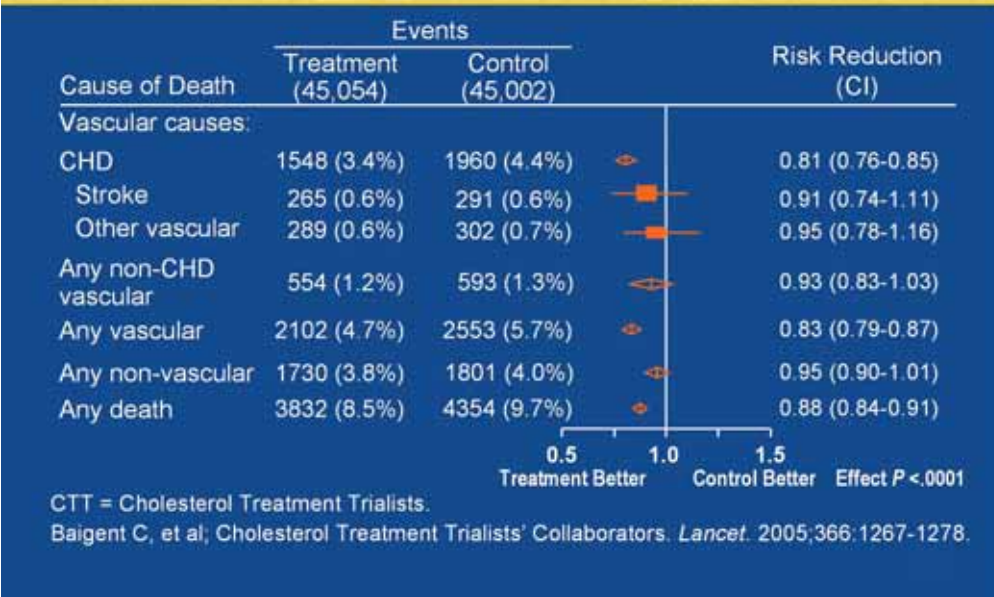
- ▶ The Collaborative Atorvastatin Diabetes Study (CARDS) further extends and confirms the results of other major end point studies. Although many previous end point studies included patients with diabetes, CARDS was the first to examine the impact of lipid-lowering therapy with a statin in patients with diabetes without a previous history of CVD and with normal baseline levels of LDL-C.
- ▶ The study enrolled 2838 patients with type 2 diabetes with no documented evidence of CVD, LDL-C <160 mg/dL, and normal TC levels who also had at least 1 of the following: retinopathy, albuminuria, current smoking, or hypertension.
- ▶ Patients were randomized to therapy with placebo or to atorvastatin 10 mg/d. The primary end point was time to first occurrence of a composite of acute CHD, coronary revascularization, or stroke.
- ▶ The trial was terminated after 3.9 years (2 years earlier than expected) because the prespecified stopping rule was exceeded. In the overall patient population, there was a 37% reduction in risk for the primary end point in patients who received atorvastatin (P = .001).
- ▶ Risk for the secondary end points of acute coronary events, coronary revascularization, and stroke was also reduced, by 36%, 31%, and 48%, respectively.
- ▶ Together, these data demonstrate that lipid-lowering therapy with a statin results in a significant reduction in the risk for first CV events among patients with diabetes and normal pre-treatment lipid levels.

Reference

Colhoun HM, Betteridge DJ, Durrington PN, et al, for the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685-696.



CTT Meta-analysis: Cause-Specific Mortality per mmol/L LDL-C Reduction



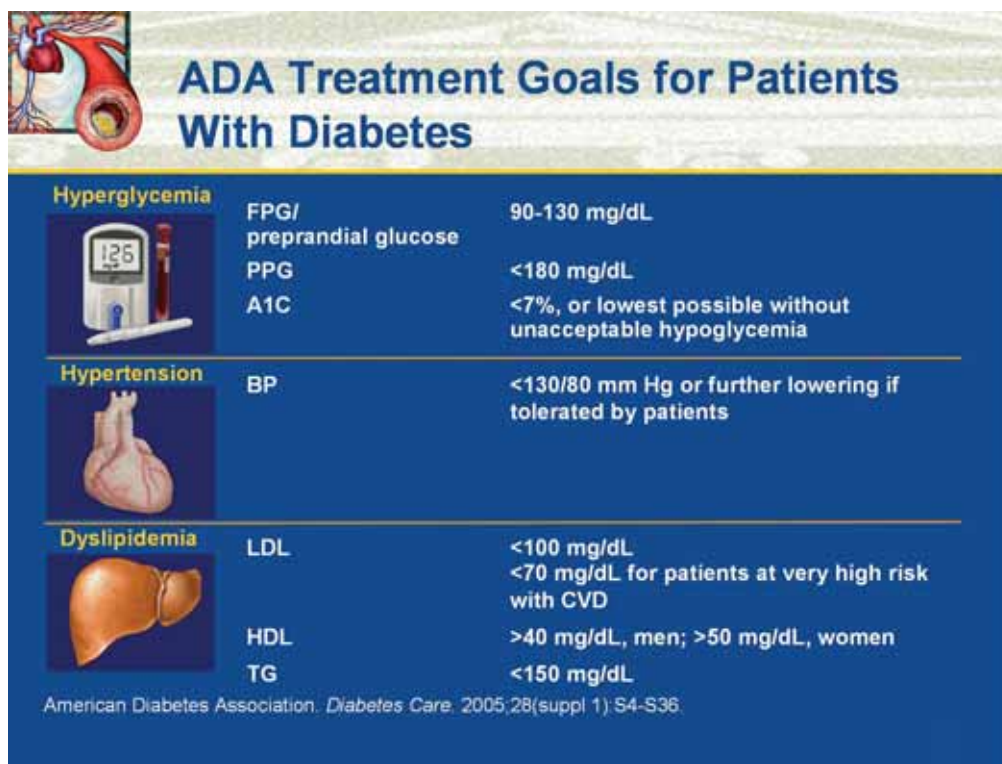
Slide 23

- ▶ In a meta-analysis of 14 randomized clinical trials of interventions that lower LDL-C, the Cholesterol Treatment Trialists' (CTT) Collaborators examined the impact of LDL-C lowering with a statin on clinical outcomes.
- ▶ Among the 90,056 patients enrolled in the studies included in this meta-analysis, there was a 12% proportional reduction in all-cause mortality for each mmol/L reduction in LDL-C levels (equivalent to a 39 mg/dL reduction in LDL-C) ($P < .0001$).
- ▶ This reduction reflected a highly significant 19% reduction in coronary mortality ($P < .0001$) and nonsignificant reductions in noncoronary vascular mortality and nonvascular mortality.
- ▶ LDL-C lowering was associated with significant reductions in MI or coronary death (23%; $P < .0001$), need for revascularization (24%; $P < .0001$), and fatal and nonfatal stroke (17%; $P < .0001$). Together, there was a 21% reduction in the risk for any major vascular event per mmol/L reduction in LDL-C level ($P < .0001$).

- ▶ These data indicate that statin therapy reduces the risk for major coronary events, coronary revascularization, and stroke by ~ 20% per mmol/L reduction in LDL-C level (or 20% per 39 mg/dL). This benefit was observed regardless of initial lipid profile or other presenting characteristics.

Reference

Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' Collaborators. Efficacy and safety of cholesterol lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267-1278.



The slide features a title 'ADA Treatment Goals for Patients With Diabetes' with an illustration of a heart and blood vessels. Below the title, there are three sections: 'Hyperglycemia' with a glucose meter icon, 'Hypertension' with a heart icon, and 'Dyslipidemia' with a liver icon. Each section lists specific goals for FPG/preprandial glucose, PPG, A1C, BP, LDL, HDL, and TG. At the bottom, it cites the American Diabetes Association, *Diabetes Care*, 2005;28(suppl 1):S4-S36.

Condition	Parameter	Goal
Hyperglycemia	FPG/preprandial glucose	90-130 mg/dL
	PPG	<180 mg/dL
	A1C	<7%, or lowest possible without unacceptable hypoglycemia
Hypertension	BP	<130/80 mm Hg or further lowering if tolerated by patients
Dyslipidemia	LDL	<100 mg/dL <70 mg/dL for patients at very high risk with CVD
	HDL	>40 mg/dL, men; >50 mg/dL, women
	TG	<150 mg/dL

American Diabetes Association. *Diabetes Care*. 2005;28(suppl 1):S4-S36.

Slide 24

- ▶ In view of the elevated risk for CV events and vascular morbidities in patients with diabetes, and the results of recent clinical trials, the ADA has developed stringent recommendations for the control of hyperglycemia, hypertension, and dyslipidemia in patients with diabetes.
- ▶ Glycemic control is fundamental to the management of diabetes. The ADA recommends that preprandial glucose be maintained between 90 and 130 mg/dL; postprandial glucose levels should not exceed 179 mg/dL, and hemoglobin A1C levels should be maintained below 7% or the lowest value achievable without unacceptable hypoglycemia. Because epidemiologic studies suggest that there is no lower limit of A1C levels below which further lowering does not reduce risk of complications, more stringent goals (ie, 6%) may be considered in some patients.
- ▶ Blood pressure levels should be maintained below 130/80 mm Hg. Further BP lowering is desirable if tolerated by the patient. The ADA notes that multiple-drug therapy is frequently required in patients with diabetes to achieve adequate BP lowering.
- ▶ A LDL-C of <100 mg/dL is the primary goal of lipid-lowering therapy in patients with diabetes, but the ADA recommends a goal of <70 mg/dL in patients with very high risk (eg, diabetes and established CVD). Lowering TG to <150 mg/dL and raising HDL-C to >40 mg/dL in men and >50 mg/dL in women are secondary goals of lipid-modifying therapy.

Reference

American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2005;28(suppl 1):S4-S36.



Established Modifiable CV Risk Factors in Type 2 Diabetes

UKPDS 23

Variables	P Value*
LDL-C, HDL-C, TG	<.0001
Hemoglobin A1C	.0003
SBP	.0032
Smoking, FPG	.016

Adjusted for age and sex in 2693 white patients with type 2 DM with dependent variable as time to first event.

*Significant for CAD (n = 280). P values are significance of risk factors after controlling for all other risk factors in model.

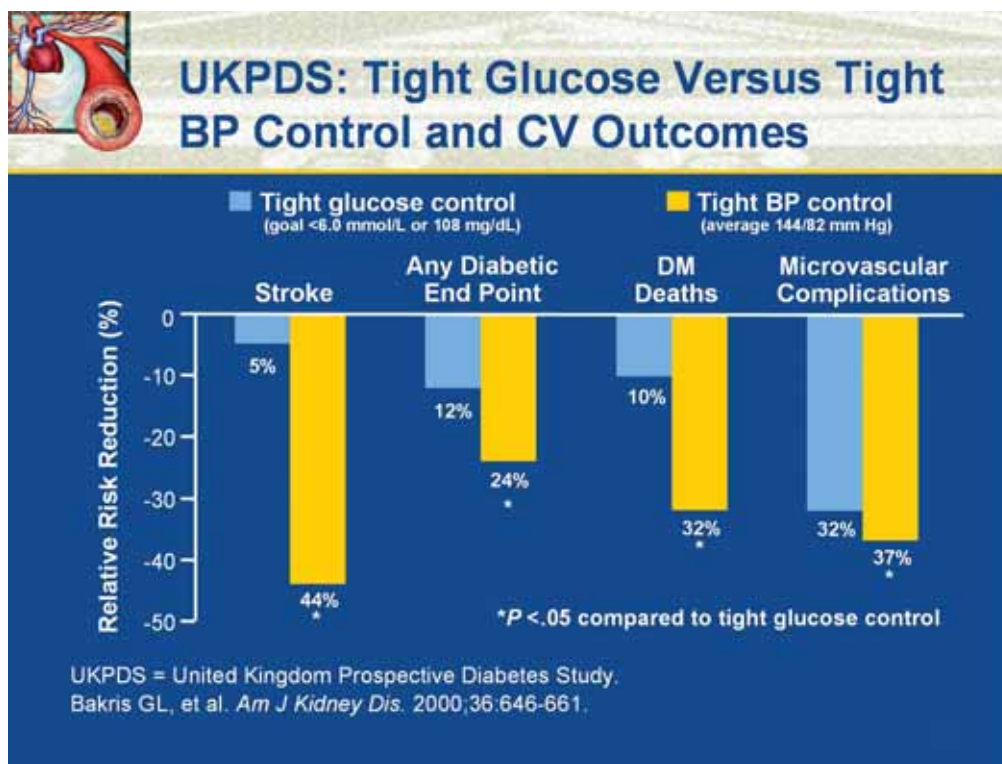
Turner RC, et al. *BMJ*. 1998;316:823-828.

Slide 25

- ▶ Using data from the UKPDS 23, Turner and colleagues evaluated baseline risk factors for coronary artery disease (CAD) in patients with type 2 diabetes.
- ▶ Coronary artery disease was significantly associated with high LDL-C and TG, low HDL-C, hemoglobin A1C levels, SBP, fasting plasma glucose concentration, and a history of smoking.
- ▶ Of these risk factors, LDL-C, HDL-C, and TG levels were most strongly associated with risk for CAD. The estimated hazard ratio for the upper LDL-C tertile versus the lowest LDL-C tertile was 2.26; for HDL-C the risk for the highest versus the lowest tertiles was 0.55.

Reference

Turner RC, Millns H, Neil HAW, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS: 23). *BMJ*. 1998;316:823-828.



Slide 26

- ▶ Although glucose management is an important part of the management of type 2 diabetes, BP control has a greater impact on CV outcomes.
- ▶ In a retrospective analysis of data from the UKPDS, Bakris and colleagues compared the effect of tight glucose control (goal <108 mg/dL) and tight BP control (average of 144/82 mm Hg) on stroke, any diabetic end point, deaths related to diabetes, and microvascular complications.
- ▶ Across all end points examined, BP reductions contributed to a significantly greater extent to the relative reduction of CV events than did glucose control.

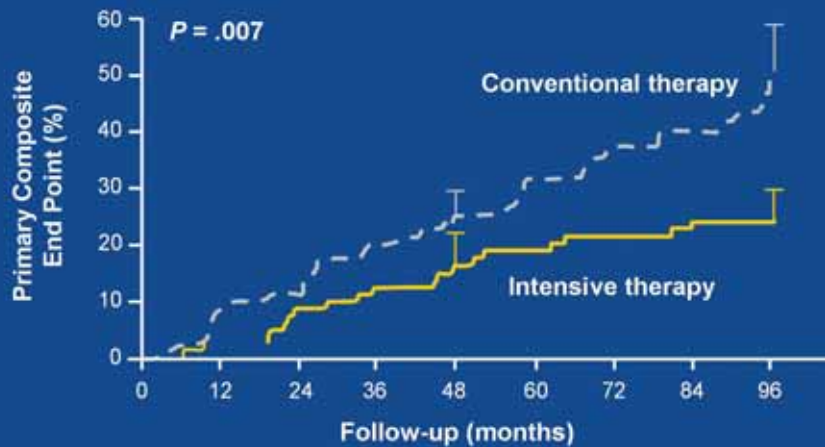
References

Bakris GL, Williams M, Dworkin L, et al, for the National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis.* 2000;36:646-661.

UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ.* 1998;317:703-713.



Steno-2 Study: Kaplan-Meier Estimates of Composite End Point



Gaede P, et al. *N Engl J Med*. 2003;348:383-393.


Slide 27

- ▶ The Steno-2 study compared intensive therapy (consisting of stepwise implementation of behavior modification and pharmacologic therapy targeted at hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, plus aspirin) with standard therapy in patients with type 2 diabetes and microalbuminuria.
- ▶ The primary end point in the Steno-2 study was a composite of death from CV causes, nonfatal MI, coronary artery bypass grafting, percutaneous coronary intervention, nonfatal stroke, amputation as a result of ischemia, or vascular surgery for peripheral atherosclerotic disease.
- ▶ At 7.8 years, 1 or more CV events had occurred in 44% of the patients in the conventional therapy group compared with only 24% of those in the intensive therapy group. Patients receiving intensive therapy also had a significantly lower risk of nephropathy, retinopathy, and autonomic neuropathy.
- ▶ This graph shows that the time-to-first-event curves for the primary composite end point continued to diverge during follow-up. The unadjusted hazard ratio for the intensive therapy group compared with the conventional therapy group was 0.47 (95% CI, 0.24-0.73; $P = .007$).

- ▶ The Steno-2 study results suggest that a long-term, intensified intervention program designed to modify multiple CVD risk factors in patients with type 2 diabetes and microalbuminuria may reduce the risk of CVD and microvascular events by ~ 50%. Continued divergence in the rates of the primary end point imply that continued therapy for longer intervals might yield an even better prognosis.

Reference

Gaede P, Vedel P, Larsen N, Jensen GVH, Parving H-H, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383-393.



FIELD: Primary Outcome

End Point	Placebo (n = 4900) n (%)	Fenofibrate (n = 4895) n (%)	HR (95% CI)	P Value
CHD death/ nonfatal MI	288 (6)	256 (5)	0.89 (0.75-1.05)	.16
CHD death	93 (2)	110 (2)	1.19 (0.90-1.57)	.22
Nonfatal MI	207 (4)	158 (3)	0.76 (0.62-0.94)	.010

FIELD = Fenofibrate Intervention and Event Lowering in Diabetes.
FIELD Study Investigators. *Lancet*. 2005;366:1849-1861.

Slide 28

- ▶ Both the ADA and the NCEP ATP III guidelines recommend TG-lowering therapy as a secondary target of lipid-lowering treatment.
- ▶ Treatment with fenofibrate yields moderate reductions in LDL-C, moderate increases in HDL-C, and substantial reductions in plasma TG.
- ▶ The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study examined the effects of long-term fenofibrate therapy on CVD events in 9795 patients with diabetes. The primary end point was the composite of CHD death and nonfatal MI.
- ▶ Over a median of 5 years of follow-up, fenofibrate resulted in an 11% reduction in the risk for the primary composite end point ($P = \text{NS}$). There was no significant difference between fenofibrate and placebo for the secondary end point of CHD death ($P = .22$). However, patients who received fenofibrate had a 23% reduced risk for nonfatal MI compared with those who received placebo ($P = .010$).
- ▶ The authors suggest that a higher rate of statin therapy initiation among patients who received placebo might have masked a moderately larger treatment benefit associated with fenofibrate.

Reference

FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366:1849-1861.



Definition of the Metabolic Syndrome (ATP III): 2005 Update

Risk factor*	Categorical Cut-points
↑ Waist circumference	≥102 cm (≥40 in) in men† ≥88 cm (≥35 in) in women†
↑ TG	≥150 mg/dL (or drug treatment for)
↓ HDL-C	<40 mg/dL in men (or drug treatment for) <50 mg/dL in women (or drug treatment for)
↑ BP	≥130 mm Hg SBP or ≥85 mm Hg DBP (or drug treatment for)
↑ Fasting glucose	≥100 mg/dL (or drug treatment for)

*Presence of 3 or more of these factors identifies the metabolic syndrome.
†A lower threshold can be used for patients especially prone to insulin resistance, particularly Asian Americans.
Grundy SM, et al. *Circulation*. 2005;112:2735-2752.
NOTE: The ADA recently issued a statement calling for a critical appraisal of the metabolic syndrome. Kahn R, et al. *Diabetologia*. 2005;48:1684-1699.

Slide 29

- ▶ The term *metabolic syndrome* refers to a clustering of specific CVD risk factors whose underlying pathology is thought to be related to insulin resistance. The presence of 3 or more of the risk factors shown above identifies the metabolic syndrome.
- ▶ Changes from the 2001 definition include:
 - ▶ Adjustment of waist circumference to a lower threshold in patients especially likely to have insulin resistance (eg, Asian Americans)
 - ▶ Including drug treatment for TG, HDL-C, BP, and elevated glucose in the definition
 - ▶ Reducing the threshold for fasting glucose from ≥110 mg/dL to ≥100 mg/dL.
- ▶ Although a number of organizations consider the metabolic syndrome a clinically useful tool, the ADA and the European Association for the Study of Diabetes (EASD) have concluded that it currently does not warrant designation as a syndrome. Until further research is performed, the ADA and EASD recommend that clinicians evaluate and treat all CV risk factors regardless of whether patients meet the criteria shown above.

References

- Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;112:2735-2752.
- Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2005;48:1684-1699.



Management of the Metabolic Syndrome: 2005 Update

- ▶ Weight reduction
- ▶ Increased physical activity
- ▶ Modification of atherogenic diet
- ▶ Drug therapy for dyslipidemia
- ▶ Drug therapy for hypertension
- ▶ Aspirin or clopidogrel for prothrombotic state
- ▶ Lifestyle changes to lower serum glucose (if diabetes has developed, drug therapy may also be needed to reduce A1C to ADA goal of <7%)

Grundy SM, et al. *Circulation*. 2005;112:2735-2752.

Slide 30

- ▶ Recommendations for clinical management of the metabolic syndrome include:
 - ▶ Weight reduction and increased physical activity, with a goal of a 7% to 10% reduction in body weight during the first year of therapy with continued weight loss to achieve a body mass index (BMI) of ≤ 25 kg/m²
 - ▶ Diet modification to reduce intake of saturated fat, trans fats, and cholesterol
 - ▶ Lifestyle changes and drug therapy for dyslipidemia in accordance with NCEP ATP III guidelines. The primary target of lipid-lowering therapy is LDL-C
 - ▶ Lifestyle changes and/or drug therapy for patients with BP $\geq 140/90$ mm Hg
 - ▶ Aspirin or clopidogrel to correct a prothrombotic state
 - ▶ Lifestyle changes to lower serum glucose. If diabetes has developed, drug therapy may be indicated to maintain or reduce hemoglobin A1C levels to the ADA goal of <7%.

Reference

Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;112:2735-2752.

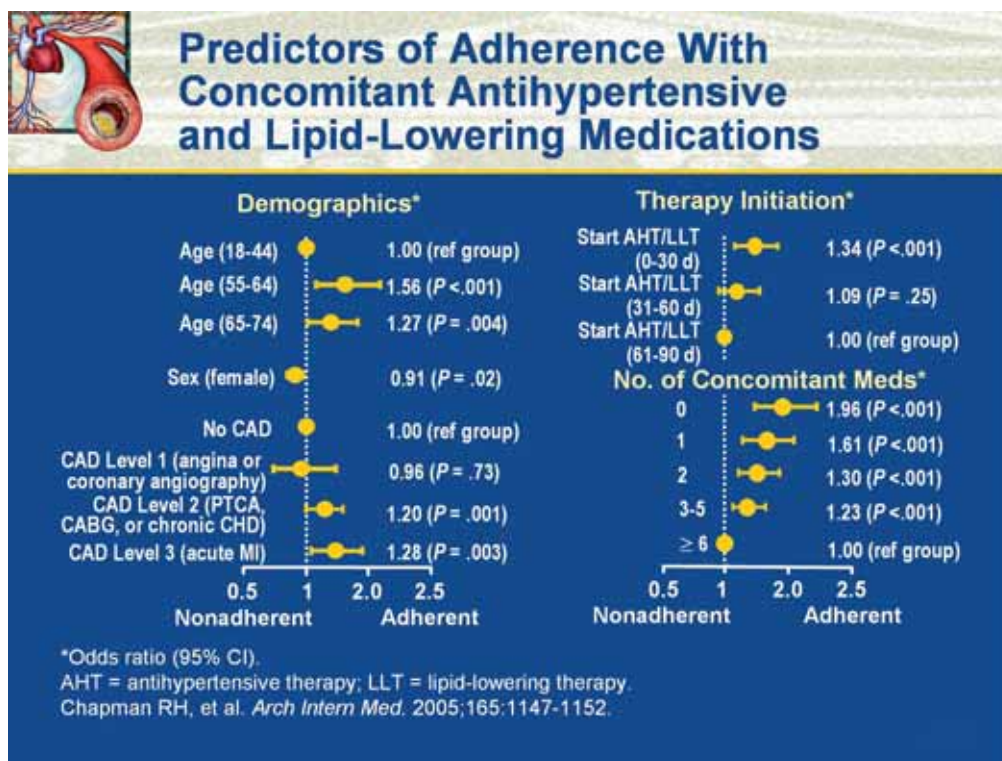


Combination Therapy in CV Risk Management

- ▶ Frequently necessary, especially with more aggressive 2004 NCEP Update goals
- ▶ Need to answer 3 specific questions when making decisions for combination treatment
 - ▶ Safety
 - ▶ Efficacy
 - ▶ Cost
- ▶ Limitations of fixed-dose combination therapy include potential difficulty in titration and determining the cause of adverse effects

Slide 31

- ▶ Together, the data covered in this slide presentation suggest that many patients at risk for CV events will require intensive lifestyle management and a number of pharmacologic agents. Those who require a number of pharmacologic agents might benefit from fixed-dose combination therapy to simplify their CV risk management regimen.
- ▶ Three questions must be addressed when assessing the value of such therapy:
 - ▶ First, is the combination therapy safe?
 - ▶ Second, is it effective?
 - ▶ Third, is it cost-effective?
- ▶ While fixed-dose combination therapy may increase adherence to therapy, limitations can include the potential for difficulties with titration to the appropriate dose of each agent in the fixed-dose combination and determining the cause of adverse effects, if such effects occur.



Slide 32

- ▶ Across disease states and regardless of severity of disease, adherence to therapy is an important issue. Hypertension and dyslipidemia, in the absence of overt CV events, are “silent” diseases, increasing the risk for nonadherence.
- ▶ In a retrospective cohort study, Chapman and colleagues evaluated predictors of adherence with concomitant antihypertensive and lipid-lowering medications.
- ▶ Patients were considered adherent if they had filled prescriptions sufficient to cover at least 80% of the days with both classes of medications.
- ▶ The percentage of patients who were adherent to therapy declined rapidly following treatment initiation. After 3 months, 44.7% of patients remained adherent to therapy. After 12 months, only 35.8% of patients were adherent.
- ▶ This slide shows predictors of adherence with concomitant antihypertensive and lipid-lowering medications. Significant predictors of adherence included severe CAD, simultaneous initiation of antihypertensive and lipid-lowering treatment, and the number of concomitant medications.

Reference

Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med.* 2005;165:1147-1152.



Combination Drugs for Treatment of Diabetes, Dyslipidemia, and Hypertension

Condition	Combination Product
Hypertension	<ul style="list-style-type: none">▶ Antihypertensive/diuretic*▶ Benazepril/amlodipine▶ Trandolapril/verapamil
Dyslipidemia	<ul style="list-style-type: none">▶ Ezetimibe/simvastatin▶ Lovastatin/niacin
Diabetes	<ul style="list-style-type: none">▶ Metformin/glipizide▶ Metformin/glyburide▶ Pioglitazone/metformin▶ Rosiglitazone/metformin
Hypertension/Dyslipidemia	<ul style="list-style-type: none">▶ Amlodipine/atorvastatin

*Established combinations of diuretics and antihypertensive agents too numerous to list.
Adapted from Leichter SB, Thomas S. *Clin Diab.* 2003;21:175-178.

Slide 33

▶ As shown in this slide, a number of combination therapies are available for the management of hypertension, dyslipidemia, diabetes, and combined hypertension and dyslipidemia.

Reference

Leichter SB, Thomas S. Combination medications in diabetes care: an opportunity that merits more attention. *Clin Diab.* 2003;21:175-178.



Total CV Risk Management: State of the Art in 2006

- ▶ CV risk factors tend to cluster
- ▶ Influence of risk factors on risk of CVD may be linked through endothelial dysfunction
- ▶ Risk of CHD and stroke increases with number of risk factors
- ▶ Intensive intervention for multiple risk factors may improve outcomes
- ▶ Combination therapies may improve adherence

Slide 34

- ▶ In summary, CV risk factors tend to cluster. In part, this clustering may be caused by underlying endothelial dysfunction.
- ▶ Cardiovascular risk factors additively, or even synergistically, increase the risk for CV events.
- ▶ As shown in a variety of clinical trials, including ASCOT and Steno-2, multifactorial intervention for multiple risk factors improves CV outcomes.
- ▶ Multifactorial intervention may be achieved through prescribing intensive lifestyle modification, as well as a number of pharmacologic agents, as indicated. Fixed-dose combination therapies may increase adherence with treatment.



Case Study: How Would You Manage This Patient's CV Risk?

- ▶ 71-year-old man, 6'1", 179 lbs, waist 32"
- ▶ BP 133/82 mm Hg on benazepril 40 mg/d and HCTZ 50 mg/d
- ▶ T2DM well controlled on metformin 850 mg bid and rosiglitazone 4 mg bid
- ▶ Fastidious about diet and exercise; quit smoking in 1974
- ▶ Has complained of excessive fatigue while walking, but thallium stress test in 2004 was negative
- ▶ Father died of stroke at age 55
- ▶ Other data
 - ▶ TC: 241 mg/dL
 - ▶ TG: 170 mg/dL
 - ▶ LDL-C: 145 mg/dL
 - ▶ HDL-C: 38 mg/dL
 - ▶ Fasting glucose: 92 mg/dL
 - ▶ A1C: 6.2%
 - ▶ Creatinine 1.2 mg/dL
 - ▶ Microalbuminuria (46 µg/mg creatinine)
 - ▶ Hepatic function WNL
 - ▶ ECG: normal

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- ▶ The patient is a 71-year-old white man who is 6'1" in height, weighs 179 lbs, and has a waist circumference of 32".
- ▶ His BP is 133/82 mm Hg on a regimen of benazepril and hydrochlorothiazide. He has type 2 diabetes, which is well controlled on a regimen of metformin and rosiglitazone.
- ▶ The patient has been very adherent to recommendations for lifestyle management. He has complained of excessive fatigue while walking, but a thallium stress test in 2004 was negative.
- ▶ Family history is notable for a fatal stroke in his father at age 55.
- ▶ Laboratory values are as shown above.



Clinical Pearls and Pitfalls

- ▶ Is comprehensive CV risk assessment needed in this patient? If so, what would you do?
- ▶ Would you adjust this patient's BP regimen? If so, how?
- ▶ Should this patient receive a statin?
- ▶ Would you adjust this patient's glucose management regimen? If so, how?
- ▶ Other questions for the faculty?

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- ▶ In the question-and-answer period with the faculty, you might consider how the clinical guidelines and clinical trial results presented earlier would affect your management of the case just presented. What would be the clinical pearls and pitfalls?
- ▶ Possible questions for discussion with the faculty are listed above. Of course, feel free to ask the faculty member about other clinical pearls and pitfalls relevant to the management of CV risk.



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- ▶ As a reminder, be sure to visit the official Web site of the PCE, www.practicingclinicians.com, for information on the CV risk symposium series, the CV risk home study workbook, and other programs offered by the PCE.

