New Frontiers in CVD Risk Management: Optimizing Outcomes in Patients with Multiple Cardiovascular Risks
**US population at high risk**

Hypercholesterolemia*
- 106.9 million
- 94 million not treated

Hypertension†
- 65 million
- 27 million not treated

Diabetes‡
- 14.6 million diagnosed
- 6.2 million undiagnosed

**Patients with CHD/stroke:**
- 18.4 million/y

**Direct:** $105.7 billion/y
**Indirect:** $93.2 billion/y
**Total cost:** $198.9 billion/y

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*A: Total-C ≥200 mg/dL
†: BP ≥140/90 mm Hg
‡: FBG ≥126 mg/dL

AHA. Heart Disease and Stroke Statistics--2005 Update
Hagai I and Kotchen TA. JAMA. 2003;289:199-206

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**Heart disease in the US is a national epidemic resulting in staggering costs**

- According to national statistics, heart disease is the primary cause of morbidity and mortality across all ethnicities and genders.
- Hypertension, hypercholesterolemia, and diabetes are increasing at alarming rates and many individuals remain undiagnosed and untreated.
Development and progression of CVD

Pathophysiology of vascular disease

- Atherosclerosis is a lifelong disease in which the process of development of an initial lesion to an advanced raised lesion can take decades.
- Risk factors lead to an environment in which the three principal oxidative systems in the vascular wall are activated: xanthine oxidase, NADH/NAD(P)H, and uncoupled eNOS.
- Excessive production of reactive oxygen species overwhelms endogenous antioxidant mechanisms, leading to oxidation of lipoproteins, nucleic acids, carbohydrates, and proteins. The principal target of this oxidative stress is the vascular endothelium, although there may be other targets.
- Among the functional alterations induced by reactive oxygen species are impairment of endothelium-dependent vasorelaxation (following a reduction in nitric oxide bioavailability), increase in inflammatory mediators, and development of a procoagulant vascular surface.
- Ultimately structural alterations occur, including plaque growth, vascular wall remodeling, decreased fibrinolysis, vascular smooth muscle cell proliferation and migration, and other structural alterations. They can lead to the clinical sequelae of death, MI, stroke, ischemia, and congestive heart failure (CHF).
Genetic polymorphisms have broad CV implications

- Genetic predisposition for obesity, diabetes, and hypertension exacerbate the effects of these risk factors on clinical events (e.g., stroke and MI).
Multiple CV risk factors for middle-aged men and women continue to increase

- Percentages of men and women with hypertension and those with obesity have increased since the 1994 CDC survey.
- Significant decreases in total-C and LDL-C levels of men 60 years or older and women 50 years or older have been observed since the 1994 CDC survey, likely due to the increase in the use of lipid-lowering agents.¹
- The percentage of men and women with ≥ 1 CV risk factor has increased since 1994.

Synergistic interaction of traditional multiple risk factors on CVD risk

Interaction of CVD risk factors implies need for multiple interventions

- Modest reductions in several risk factors simultaneously may be more effective than a larger reduction in a single risk factor.
Obesity decreases life expectancy regardless of smoking

Framingham Heart Study

Years lost due to obesity were similar for smokers and nonsmokers

- In an analysis of the 1948 through 1990 follow-up of the Framingham Heart Study, the relationship between obesity and/or smoking to lifespan was assessed. Participants were 3457 people 30 to 49 years old at baseline.
- Women (mean age 40 years) lost on average the same number of years due to obesity regardless of smoking status:
  - 7.1 years lost due to obesity only in nonsmoking women.
  - 7.2 years lost due to obesity only in smoking women.
  - 13.3 years lost due to obesity and smoking (relative to normal-weight nonsmokers).
- Trends for men were similar.
Decline in smoking vs rise in obesity: A trade-off?

Decline in smoking may be offset by rising obesity rates nationwide

- This data is from the Behavioral Risk Factor Surveillance Survey (BRFSS), an annual, CDC-sponsored, state-wide telephone survey of randomly selected households that monitors a variety of risk behaviors linked to chronic disease and death.

- Although a strong inverse correlation exists between smoking and obesity rates, causative relationships cannot be ascertained.
Emerging biomarkers and their implications for vascular disease

- A subset of new biomarkers is considered to be particularly significant.
- Advancements in our understanding of CVD have led to the identification of a number of mediators and markers of the processes involved.
Traditional CVD risk factors

- Family history
- Older age
- Male gender
- Smoking
- Physical inactivity
- Overweight/obesity
- Total-C/LDL-C/HDL-C/TG
- BP
- Glucose


Traditional risk factors indicate probability of CVD development

- Some risk factors (eg, age) are useful even though their causal relationship to CVD is unknown.
- Body mass index (BMI) is used as a risk factor due to the ease of measurement, although other values such as abdominal fat deposition may be more significant.
- Risk factors have a correlative – not causative – association with CVD. Therefore, assessment of medication to reduce risk factors should include risk factor measurement as a clinical outcome.
Biomarkers help predict future disease onset

- As our understanding of the vascular biology of atherosclerosis grows, the list of potential mediators and markers of the disease process increases.
- Useful biomarkers are sensitive, specific, reliable, and account for a high proportion of the at-risk population.
- Biomarkers should be independent predictors of risk, thereby improving the predictive value of other markers and risk factors.
- The utility of genetic polymorphisms in a clinical setting is dependent on their prevalence in the population and the magnitude of the risk conferred.

<table>
<thead>
<tr>
<th><strong>Selected emerging biomarkers</strong></th>
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<tbody>
<tr>
<td><strong>Lipids</strong></td>
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<tr>
<td>Lp(a) apoA/apoB</td>
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<tr>
<td>Particle size/density</td>
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<tr>
<td><strong>Oxidation</strong></td>
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<tr>
<td>Ox-LDL</td>
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<tr>
<td>MPO</td>
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<tr>
<td><strong>Genetic</strong></td>
</tr>
<tr>
<td>Asp299Gly polymorphism</td>
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<tr>
<td>in TLR4 gene</td>
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<tr>
<td>MCP-1 2578G allele</td>
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<tr>
<td>CX3CR1 chemokine receptor</td>
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<tr>
<td>polymorphism V249I</td>
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<tr>
<td>16Gly variant of ( \beta_2 )-adrenergic receptor</td>
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<tr>
<td>260T/T CD14 allele</td>
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<tr>
<td>117 Thr/Thr variant of CSF</td>
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<tr>
<td>LIGHT</td>
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<tr>
<td><strong>Inflammation</strong></td>
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<tr>
<td>CRP</td>
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<tr>
<td>SAA</td>
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<td>IL-6</td>
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<td>IL-18</td>
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<tr>
<td>TNF</td>
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<tr>
<td>Adhesion mols</td>
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<tr>
<td>Lp-PLA_2</td>
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<tr>
<td>CD40L</td>
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<tr>
<td>CSF</td>
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<tr>
<td><strong>Hemostasis/Thrombosis</strong></td>
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<tr>
<td>Homocysteine</td>
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<tr>
<td>tPA/PAI-1</td>
</tr>
<tr>
<td>TAFI</td>
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<tr>
<td>Fibrinogen</td>
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<td>D-dimer</td>
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</table>

CSF = colony-stimulating factor
MPO = myeloperoxidase
TAFI = thrombin activatable fibrinolysis inhibitor

**LDL infiltration triggers inflammatory response**

**LDL particles activate vascular inflammation**

- Oxidation of LDL particles in the intima leads to release of phospholipids that trigger endothelial release of adhesion molecules and other inflammatory mediators.
Ox-LDL initiates cascade of monocyte binding, differentiation, and ultimate transformation into atherosclerotic foam cells

- Activated endothelial cells express leukocyte adhesion molecules that bind monocytes.
- Chemokines induce migration of the bound monocytes into the intima.
- Macrophage colony-stimulating factor (M-CSF) stimulates monocytes to differentiate into macrophages.
- Macrophage activation leads to secretion of cytokines, chemokines, proteases, and radicals that cause inflammation and tissue damage.
**Mechanisms linking hypertension and hypercholesterolemia**

- Data from animal studies suggest that elevated blood pressure facilitates lipoprotein entry into the vascular wall via pressure-induced convection of atherogenic lipoproteins and distension of the arterial wall.
**AT₁ and LOX-1 receptor cross-talk promotes adhesion molecule expression**

Interaction between RAAS and dyslipidemia

- Ang II, via the AT₁ receptor, increases LOX-1 expression. Conversely, ox-LDL, via LOX-1, upregulates the AT₁ receptor.

**RAAS activation has implications for ox-LDL and BP**

- Formation of oxidized LDL (ox-LDL) is a key step in the pathogenesis of atherosclerosis. The ox-LDL receptor (LOX-1) is present mostly on the surface of endothelial cells, vascular smooth muscle cells, macrophages, and platelets. LOX-1–mediated ingestion of ox-LDL activates mitogen-activated protein kinases (MAPKs) in the cell, which in turn activate nuclear factor-κB (NF-κB), a transcriptional factor involved in expression of monocyte chemoattractant protein-1 (MCP-1). In turn, MCP-1 leads to adhesion molecule expression.
Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$)

- Produced by inflammatory cells
- Hydrolyzes oxidized phospholipids to generate proinflammatory molecules
  - Lysophosphatidylcholine
  - Oxidized fatty acids
- Upregulated in atherosclerotic lesions where it co-localizes with macrophages

*Lp-PLA$_2$ is linked to advanced atherosclerotic plaques*

- The enzyme platelet-activating factor acetylhydrolase (Lp-PLA$_2$) is associated with LDL particles.
- Lp-PLA$_2$ is upregulated in the atheroma, where it generates proinflammatory molecules.
Studies demonstrating association of Lp-PLA₂ with incident CHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Findings*</th>
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<tbody>
<tr>
<td>Packard et al</td>
<td>WOSCOPS subgroup LDL-C 174–232 mg/dL 580 cases, 1160 controls</td>
<td>RR 1.18 (1.05-1.33) per 1 SD ↑</td>
</tr>
<tr>
<td>Ballantyne et al</td>
<td>General population 608 cases, 740 controls</td>
<td>HR 1.78 (1.33-2.38) tertile 3 vs tertile 1</td>
</tr>
<tr>
<td>Koenig et al</td>
<td>General population 97 cases, 837 controls</td>
<td>HR 1.23 (1.02-1.47) per 1 SD ↑</td>
</tr>
<tr>
<td>Oei et al</td>
<td>General population 418 cases, 1820 controls</td>
<td>HR 1.97 (1.28-3.02) 4th vs 1st quartile</td>
</tr>
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</table>

*Adjusted relative risk (RR) or hazard ratio (HR)


Elevated Lp-PLA₂ level is an independent predictor of CHD

- The elevated Lp-PLA₂ risk factor is independent of traditional risk factors and inflammatory markers and is also a predictor of ischemic stroke.
- It is unknown if lipid-lowering drugs can affect Lp-PLA₂ levels within plaques.
Flow-mediated dilation is directly proportional to EPC number

- EPCs are bone marrow-derived cells capable of differentiating into endothelial cells.
- A correlative, but not causative, relationship between EPC number and endothelial function has been established in a small study of healthy men.
- Endothelial repair by EPCs may curtail CVD progression.
- The investigators speculate that age or other risk factor-induced depletion of EPCs exacerbate CVD progression.
**Number of endothelial progenitor cells (EPCs) is inversely related to CVD risk**

- New data show that a low number of circulating EPCs is associated with an increased risk of CV events.
- This finding supports the hypothesis that EPCs repair the endothelial damage caused by risk factors.
- Measurement of EPC number may help identify people at elevated risk of CVD.
Positive feedback loop between arterial stiffness and atherosclerosis

- Isolated systolic hypertension and high pulse pressure, consequences of stiff large arteries, are associated with high risk of stroke and coronary events.
- Hemodynamic stress promotes vascular endothelial damage, leading to coronary atherosclerosis.
Arterial stiffness occurs in young adults with multiple CV risk prior to CVD onset

- In the Bogalusa Heart Study, the relationship between number of CV risk factors and brachial artery distensibility (BrachD) was studied in young adults. Risk factors considered were age, BMI, systolic BP, DBP, total cholesterol, triglycerides, LDL-C, HDL-C, insulin, and glucose.
- BrachD measurements were used as a marker for subclinical vascular endothelial changes. Results indicated BrachD was lower in African American than in white participants (6.33% vs 6.76% Δ/mm Hg, P < 0.005).
Peripheral arterial stiffness is associated with subclinical atherosclerosis

N = 256

Arterial compliance can identify persons with subclinical atherosclerosis

- Herrington et al measured peripheral arterial compliance in 256 subjects. Abdominal aortic wall thickness was also assessed using magnetic resonance imaging.
- Peripheral arterial compliance was strongly and independently associated with degree of abdominal aortic thickening.
### Pleiotropic effects of statins on the vessel wall

- The mevalonate pathway is involved in activation of a number of enzyme systems; thus inhibition of HMG-CoA reductase has implications beyond reduction in cholesterol synthesis.

- A number of cholesterol-independent (pleiotropic) effects have been demonstrated in clinical and experimental studies.

- Accumulating evidence suggests that some of the pleiotropic effects may be contributing to the mechanism of benefit in clinical outcome trials of statins.
High-dose statin treatment reduces Ox-LDL markers

MIRACL study subgroup analysis, N = 2341 with ACS, atorvastatin 80 mg for 16 weeks

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoB-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>–33.0</td>
<td>–34.2, –31.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.8</td>
<td>4.6, 7.0</td>
</tr>
<tr>
<td>Total apoB-OxPL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>–29.7</td>
<td>–31.5, –28.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>–3.2</td>
<td>–2.4, 1.9</td>
</tr>
<tr>
<td>Total apoB-IC IgG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>–29.5</td>
<td>–31.9, –27.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.1</td>
<td>–1.1, 5.4</td>
</tr>
<tr>
<td>Total apoB-IC IgM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>–25.7</td>
<td>–28.1, –23.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>13.2</td>
<td>9.3, 17.3</td>
</tr>
</tbody>
</table>

MIRACL substudy suggests statin antioxidant effort

- The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study demonstrated that in-hospital initiation of atorvastatin 80 mg reduced CV events in patients with acute coronary syndromes (ACS).
- In a subgroup analysis, high-dose statin treatment was associated with reduction in the oxidized phospholipid (OxPL) content of circulating apolipoprotein B-100 (apoB-100) particles.
- Reduction in proinflammatory OxPLs may have contributed to the benefit observed.
Reduction in Lp-PLA\(_2\) activity with statin

- The effect of atorvastatin treatment on plasma Lp-PLA\(_2\) activity was assessed in 76 patients with dyslipidemia type IIA (LDL-C >160 mg/dL) or type IIB (LDL-C >160 mg/dL and triglycerides >200 mg/dL).

- The observed decrease in plasma Lp-PLA\(_2\) activity was due to a reduction in LDL-C levels, as well as a specific decrease in Lp-PLA\(_2\) activity on dense LDL-C subfractions.

- Although Lp-PLA\(_2\) is an independent CHD risk factor, its mechanistic role has not been established.
Potential new statin mechanism of benefit

- Vasa et al reported that short-term statin treatment of patients with CAD led to an increased number of circulating EPCs.

- Given the accumulating evidence that EPCs play an important role in endothelial repair, Vasa’s study suggests a new mechanism by which satins lower CVD risk both in the short and long term.
Intensive lipid lowering improves arterial compliance
N = 22 with ISH treated with atorvastatin 80 mg for 3 months


Statins reduce large artery stiffness

- In a study by Ferrier et al, patients with isolated systolic hypertension but with cholesterol levels not deemed high by current guidelines (LDL-C of approximately 132 mg/dL) were given placebo or high-dose statin in a crossover design (n=22).

- Statin treatment reduced LDL-C by 48% and significantly improved aortic compliance.

- This finding supports lower target levels of LDL-C in patients with isolated systolic hypertension.
Further evidence for pleiotropic effects of statins

• Landmesser et al randomized 20 patients with chronic heart failure to simvastatin 10 mg or ezetimibe 10 mg for 4 weeks.

• Simvastatin and ezetimibe reduced LDL-C similarly, by 15.6% and 15.4%, respectively.

• However, statin treatment, but not treatment with the cholesterol absorption inhibitor (ezetimibe), increased the number of circulating EPCs and activity of the vascular antioxidant enzyme system superoxide dismutase.
**Statins limit brain infarct size in stroke model**

- Brain infarct size was observed in live rats at 2, 24, and 48 hours subsequent to the permanent occlusion of the middle cerebral artery.
- Rats were either pre- or post-occlusion treated with either simvastatin or vehicle.
- Simvastatin, administered after the occlusion, reduced the brain infarct volume by 46.6% at 48 hours relative to the 2-hour time point, whereas vehicle treatment yielded an 89% increase at 48 hours.
- Pre-treatment with simvastatin yielded similar results to post-treatment (−30% statin-treated vs +21% vehicle-treated).
Pleiotropic effects of BP-lowering agents

- ACE inhibitors (ACEIs) and, more recently, AT1 receptor blockers (ARBs) have shown many vasculoprotective effects.
- Evidence is also emerging that calcium channel blockers have effects on vascular biology that are independent of their interaction with L-type calcium channels.
**Statin metabolite and CCB show additive antioxidant effect**

Human LDL incubated with O-hydroxy metabolite of atorvastatin (100 nmol/L), lovastatin (100 nmol/L), and amlodipine (2.5 μmol/L)

Inhibition of TBARS formation (%)

- Atorvastatin metabolite
- Amlodipine + Lovastatin
- Amlodipine + Atorvastatin metabolite

TBARS = thiobarbituric acid-reactive substances
*P < 0.0001 vs vehicle treatment

Mason RP et al. *Am J Cardiol.* 2005;96(suppl):11F-23F.

**Shared pleiotropic effects of statins and CCBs**

- The O-hydroxy metabolite of atorvastatin increases the resistance of LDL to oxidation via a mechanism proposed to involve quenching of free radicals.
- Amlodipine also has an antioxidant effect that is mediated by free-radical quenching.
- These effects are observed in vitro at physiologically relevant concentrations.
Synergistic benefits of statins and CCBs at the vascular wall

• Fogari et al treated 45 hypertensive, hypercholesterolemic patients with amlodipine, atorvastatin, or their combination in three crossover periods, each separated by a 4-week washout.

• The combination improved fibrinolytic balance more than either monotherapy alone.
Interaction of RAAS inhibition and statins

- Ramipril and simvastatin therapy improves endothelial function in dyslipidemic patients (mean LDL-C 164 mg/dL).
- This finding supports the existence of beneficial interactions of statins and ACEIs at the vascular wall.
**Approaches to CVD prevention**

- **Lipid modification**
- **Lifestyle intervention**
- **Glucose lowering**
- **BP lowering**

**Optimal CV risk reduction**

*Existing risk assessment tools pose multiple challenges to the primary care physician*

- Newer risk factor measures, particularly those relevant to the clotting and fibrolytic systems, can provide additional useful information for clinicians wishing to further assess an individual’s level of risk.
Lifestyle changes reduce need for drug therapy

N = 3234 with IGT randomized to intensive lifestyle change, metformin 850 mg 2x/d, or placebo

• Lifestyle change goals
  – Weight reduction of ≥ 7% initial body weight via low-fat, low-calorie diet
  – Moderate-intensity physical activity ≥ 150 min/week

<table>
<thead>
<tr>
<th>At 3 years</th>
<th>Lifestyle</th>
<th>Metformin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP-lowering agents required</td>
<td>23%*</td>
<td>32%</td>
<td>31%</td>
</tr>
<tr>
<td>Lipid-lowering agents required</td>
<td>12%*</td>
<td>16%</td>
<td>16%</td>
</tr>
</tbody>
</table>

*P < 0.001 vs other groups

Participants with impaired glucose tolerance (IGT) lowered CVD risk factor status by intensive lifestyle changes

• After 3 years, CVD risk factor status was improved by intensive lifestyle changes.
• There was insufficient statistical power to test the effect of these changes on CVD event incidence, but there will be 5 more years of follow-up.
New lifestyle guidelines: More exercise, fruits and vegetables

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<tbody>
<tr>
<td><em>Exercise</em></td>
<td>≥ 30 minutes of moderate physical activity</td>
<td>≥ 30 minutes of moderately intense exercise every day</td>
</tr>
<tr>
<td><em>Duration</em></td>
<td>5-7 days/week</td>
<td>60 min to prevent weight gain</td>
</tr>
<tr>
<td><em>Fruits and vegetables</em></td>
<td>5 servings/day</td>
<td>≥ 9 servings/day</td>
</tr>
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HHS/USDA. www.healthierus.gov/dietaryguidelines.

*Reducing calories and increasing physical activity promotes a healthy lifestyle, regardless of CV risk*

- New dietary guidelines issued by the US government provide science-based advice to promote health and reduce the risk for major chronic diseases through diet and physical activity.
- The 2005 report places great emphasis on exercise. In addition to watching calories and food intake, Americans are urged to exercise 30 to 60 minutes (or more) daily to prevent chronic illness and stave off weight gain associated with aging.
Exercise reduces CV and all-cause mortality

N = 9791, moderate exercise vs little or no exercise
NHANES I Epidemiological Follow-up Survey (1971-1992)

Favors exercise Favors no exercise

<table>
<thead>
<tr>
<th>BP Status</th>
<th>HR</th>
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<tbody>
<tr>
<td>Normal BP</td>
<td>0.75</td>
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<tr>
<td>All-cause death</td>
<td>0.79</td>
</tr>
<tr>
<td>CV death</td>
<td>0.76</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>0.79</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.79</td>
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<tr>
<td>CV death</td>
<td>0.84</td>
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<tr>
<td>Hypertension</td>
<td>0.88</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.84</td>
</tr>
<tr>
<td>CV death</td>
<td>0.84</td>
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</table>

Benefit of exercise regardless of BP status

- NHANES I was conducted from 1971 to 1975. The NHANES I Epidemiological Follow-up Survey consisted of four additional surveys, the most recent of which was conducted in 1992.
- These data show that even moderate exercise is associated with reduction in all-cause and cardiovascular mortality.
- The association was most robust in hypertensive subjects, although a trend to benefit was also seen at lower BP levels.
Diet reduces mortality in primary prevention trials

2002 Physician’s Health Study (N = 20,551)*
2002 Nurses’ Health Study (N = 84,688)
2003 Cardiovascular Health Study (N = 5,201)*
2003 European Prospective Investigation into Cancer and Nutrition–Greek cohort (N = 22,043)†
2004 The Healthy Aging: A Longitudinal Study in Europe (N = 2339)

*Blood levels of n-3 fatty acids inversely related to death
†Greater adherence associated with lower mortality

Prospective cohort studies show significant improvements in CV mortality with Mediterranean-style diets

• The Cardiovascular Health Study followed 5201 subjects ≥65 years of age for 7 years. The Physician’s Health Study followed 20,551 men for 17 years. Both studies found an inverse association between blood levels of n-3 fatty acids and risk of death.

• The Nurses’ Health Study followed 84,688 women for 16 years. High consumption of fish (5/wk) was associated with 45% risk reduction in CHD death (RR 0.55, 95% CI 0.33–0.90).

• The Healthy Aging: A Longitudinal Study in Europe followed 2339 men and women, 70 years to 90 years of age, from 11 European countries. Adherence to a Mediterranean-style diet was associated with a 23% risk reduction in 10-year all-cause mortality (HR 0.77, 95% CI 0.68–0.88).

• Two reports from the European Prospective Investigation into Cancer and Nutrition quantified adherence to a Mediterranean-style diet on a scale of 0 to 9, with a higher number indicating greater adherence. Both demonstrated that greater adherence was associated with lower mortality.
# Potential cardioprotective mechanisms of dietary components

<table>
<thead>
<tr>
<th>Omega-3 fatty acids</th>
<th>Folic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antiarrhythmic</td>
<td>• Antioxidant</td>
</tr>
<tr>
<td>• Antithrombogenic</td>
<td>• ↑NO bioavailability</td>
</tr>
<tr>
<td>• Antiinflammatory</td>
<td>• Improved endothelial function</td>
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<tr>
<td>• Antihypertensive</td>
<td></td>
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<tr>
<td>• Improved endothelial function</td>
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**Folic acid and omega-3 fatty acids may improve cardiovascular health**

- Dietary or supplemental folic acid may have a cardioprotective role independent from its homocysteine-lowering effects, although more data is needed.
- Omega-3 fatty acids have a significant but mild hypotensive effect.
- Large-scale epidemiological studies on the effects of omega-3 fatty acid consumption on cardiovascular health support the AHA guidelines for fish consumption.
Non-pharmacologic interventions and BP reduction

Meta-analyses of lifestyle changes indicate BP reductions

- Meta-analysis of data from 54 randomized, controlled trials (N = 2419) indicate aerobic exercise significantly decreases systolic and diastolic blood pressure in overweight, normal-weight, hypertensive, and nonhypertensive people.

- Comparing exercise results to 3 other meta-analyses, Messerli et al found that the decrease in blood pressure due to exercise exceeded the magnitude of the reduction due to low-salt diet (32 trials, N = 2635), alcohol reduction (15 trials, N = 2234), and potassium supplements (33 trials, N = 2609).
Benefit of multifactorial interventions

Lipid modification

Lifestyle intervention

Glucose lowering

BP lowering

Optimal CV risk reduction
**Recent lipid-lowering trials indicate CV benefits**
PROVE IT-TIMI 22 assessed whether a more intensive LDL-C–lowering regimen would reduce major CV events in recently hospitalized ACS patients

- The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial was conducted in 4162 patients hospitalized for acute coronary syndromes (ACS) within the preceding 10 days.

- Subjects were randomized to pravastatin 40 mg or atorvastatin 80 mg. Mean follow-up was 24 months.

- The primary outcome was a composite of all-cause death, MI, hospitalization for unstable angina, coronary revascularization, and stroke.
PROVE IT-TIMI 22: Early benefit with intensive lipid lowering

PRavastatin Or AtorVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22
N = 4162 with ACS

Early, high-dose statin therapy is associated with early benefit

- Baseline LDL-C was 106 mg/dL in each group, and was reduced to 95 mg/dL and 62 mg/dL in the pravastatin and atorvastatin groups, respectively (P < 0.001).

- The primary outcome occurred in 26.3% and 22.4% of the pravastatin and atorvastatin groups, respectively (16% RRR in favor of atorvastatin, P = 0.005).

- Separation of the curves occurred as early as 30 days. Statistically significant benefit was evident at 4 months.
**Benefit of high-dose statin therapy evident at 30 days**

- The high-dose statin group had a 17% nonsignificant reduction in risk of death or major cardiovascular event (MCE) at 30 days. This rapid clinical effect confirms observations from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial.

- By the end of the follow-up, the primary outcome (death or MCE) occurred in 26.3% and 22.4% of the standard-dose pravastatin and high-dose atorvastatin groups, respectively (16% RRR in favor of atorvastatin, P = 0.005).

- Significant benefits were observed for the high-dose atorvastatin group relative to the standard-dose pravastatin in some primary endpoint components:
  - 14% reduction in need for revascularization (P = 0.04)
  - 29% reduction in risk of unstable angina (P = 0.02)

- There was no evidence of increased toxicity for the high-dose statin group. At 2 years, the discontinuation rates due to either adverse events or other reasons were similar (P = 0.11):
  - 33.0% for the high-dose group
  - 30.4% for the low-dose group
Lower CRP levels correspond with improved outcomes regardless of LDL-C levels

- Patients with posttreatment C-reactive protein (CRP) levels of 2 mg/L had lower event rates (2.8 vs 3.9 events/100 person-years, P = 0.006) vs patients with higher CRP levels regardless of LDL-C level.
- Although the atorvastatin group achieved lower mean LDL-C and CRP levels, individuals who achieved lower levels of LDL-C and CRP had better outcomes, regardless of the particular statin treatment used to achieve these goals.
PROVE IT-TIMI 22: Clinical implications

• In patients with recent ACS, aggressive lipid lowering was associated with greater clinical benefit vs less aggressive lipid lowering:
  — 16% RRR in all-cause death, MI, UA, revascularization, stroke

• Benefit evident at 30 days and may be mediated in part by anti-inflammatory effect

• No relationship between achieved LDL-C level and risk of adverse events
  — No excess risk even at levels ≤ 40 mg/dL

Results show favorable benefit/risk for lower LDL-C goals

• No cases of rhabdomyolysis occurred in either group. Muscle-related study drug discontinuation occurred in 2.7% and 3.3% of pravastatin and atorvastatin groups, respectively (P = 0.23).

• In a separate analysis, Wiviott et al classified the incidence of muscle-related or liver-related side effects according to on-treatment LDL-C. No increased risk was noted even at LDL-C below 40 mg/dL.
A to Z assessed two different lipid-lowering strategies

• The Aggrastat to Zocor (A to Z) trial randomized 4497 patients with ACS to one of two lipid-management strategies:
  – Intensive: Simvastatin 40 mg for 1 month, followed by 80 mg thereafter.
  – Less intensive: Placebo for 4 months, followed by simvastatin 20 mg thereafter.
**Rapid effect of simvastatin 40 mg vs placebo**

- During the placebo-controlled phase, there was a large LDL-C differential between the two arms.
- This differential diminished when simvastatin 20 mg was initiated in the placebo arm after 4 months.
**Delayed anti-inflammatory effect**

- C-reactive protein (CRP) levels were not significantly different between the two arms at 1 month, despite the large lipid differential.
- A significant effect on CRP levels was noted at 4 and 8 months.
**Delayed benefit with higher-dose simvastatin strategy**

- The primary outcome occurred in 14.4% and 16.7% of the intensive therapy and less-intensive therapy groups, respectively (11% relative risk reduction, \( P = 0.14 \)).

- Post hoc analysis revealed benefits after 4 months. There was no difference between groups during the first 4 months of the study; but a 25% relative risk reduction in favor of the intensive-therapy group occurred between 4 months and study end (\( P = 0.02 \)).

- The lack of early benefit in A to Z was unexpected, given that the LDL-C differential achieved at 4 months was 62 mg/dL. The lack of an early anti-inflammatory effect may have contributed to the delay in benefit.\(^1\)

---


**Delayed treatment effect on clinical outcomes**

- Post hoc analysis showed that no difference in the primary outcome occurred between the two arms over the first 4 months (placebo period) of the trial.

- From 4 months through study end, a treatment effect in favor of the more aggressive lipid-lowering therapy occurred (HR 0.75, 95% CI 0.66–0.95, \( P = 0.002 \)).
A to Z: Clinical implications
Aggrastat to Zocor

• In patients with recent ACS, early initiation of a moderate/high-dose simvastatin regimen vs delayed initiation of a low-dose regimen resulted in nonsignificant trend toward reduction in major CV events
  – 11% RRR in CV death, nonfatal MI, ACS readmission, stroke
• No difference between the treatment groups was observed within the first 4 months

Findings are consistent with MIRAACL and PROVE IT-TIMI 22
  • Early benefits may be due to anti-inflammatory effects
  • Late benefits may be due to lipid lowering

Ray KK et al. Am J Cardiol. 2005;96(suppl):54F-60F.

A to Z results add to evidence from other trials of aggressive lipid lowering

• The direction of the results in A to Z are consistent with those of MICRAACL and PROVE IT-TIMI 22.
• A to Z and other investigators have and hypothesized that the failure to reach clinical significance may have been due, in part, to the lack of an early anti-inflammatory effect.
• Late benefits of statin therapy may be due to removal of lipids from plaque and subsequent remodeling.
TNT: A comparison of two different intensities of lipid lowering

- TNT tested the hypothesis that intensive lipid lowering would be associated with better clinical outcomes than less intensive treatment in patients with stable CHD.
- TNT extends the results of PROVE IT-TIMI 22, which evaluated intensive lipid lowering in patients with ACS.
Treatment strategies resulted in marked differences in lipid lowering

- Study subjects received open-label atorvastatin 10 mg for 8 weeks, then were randomized to continue on that dose or to receive an 80-mg dose.
- Mean LDL-C levels during the study were 77 mg/dL and 101 mg/dL in the intensive and less-intensive groups, respectively.
TNT demonstrates benefit of intensive lipid lowering in stable CHD

- The higher dose showed significantly greater efficacy.
### TNT: Incidence of elevated liver or muscle enzymes

Treating to New Targets  
N = 10,001

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin 10 mg (%) (n = 5006)</th>
<th>Atorvastatin 80 mg (%) (n = 4995)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT and/or AST &gt;3xULN</td>
<td>0.2</td>
<td>1.2*</td>
</tr>
<tr>
<td>CK &gt;10xULN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0.06</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*P < 0.001 vs atorvastatin 10 mg  
ALT = alanine aminotransferase  
AST = aspartate aminotransferase  
ULN = upper limit of normal


---

**Intensive treatment strategy was well tolerated**

- Discontinuation because of adverse events occurred in 7.2% and 5.3% of the intensive and less-intensive groups, respectively.
In patients with stable CHD, aggressive lipid lowering was associated with greater clinical benefit vs less intensive lipid lowering:

- 22% RRR in CHD death, MI, resuscitation after cardiac arrest, and fatal/nonfatal stroke

*TNT supports lower LDL-C goal in patients with stable CHD*

_**TNT confirms clinical benefit of aggressively lowering LDL-C levels well below current recommendations**_
Potential factors contributing to early statin benefit

• High baseline risk
• Intensive LDL-C lowering
• Rapid anti-inflammatory effect

Potential modulators of early benefit

• As discussed by Carl J. Pepine, MD, and Andrew P. Selwyn, MD, in a recent VBWG publication, there are several potential factors contributing to early benefit with aggressive statin therapy.
**Compelling evidence for the importance of LDL-C lowering in diabetes**

- **HPS:** The Heart Protection Study included 5963 persons with diabetes (33% prior CHD) randomized to simvastatin 40 mg daily or placebo regardless of baseline lipid levels. Primary outcome: MI or coronary death; mean follow-up, 4.8 years.

  **Results:**
  - LDL-C: Statin treatment reduced LDL-C from 124 mg/dL to 85 mg/dL.
  - Primary outcome: 27% relative risk reduction in MI or coronary death and 24% relative risk reduction in stroke (P < 0.0001, both comparisons).

- **CARDS:** The Collaborative Atorvastatin Diabetes Study was the first prospective evaluation of a statin in a population comprised solely of persons with type 2 diabetes. CARDS randomized 2838 patients with type 2 diabetes plus ≥1 other CV risk factors (but no history of CHD, MI, or stroke) to atorvastatin 10 mg or placebo. Primary outcome: composite of major coronary events, revascularization, unstable angina, resuscitated cardiac arrest, and stroke. Study was terminated 2 years early, after median follow-up of 3.9 years.

  **Results:**
  - LDL-C: Statin treatment reduced LDL-C from 118 mg/dL to 82 mg/dL.
  - Primary outcome: 37% relative risk reduction (HR 0.63, 95% CI 0.48–0.83, P = 0.001); 48% relative risk reduction in stroke (HR 0.52, 95% CI 0.31–0.89, P value not reported).
### CARDS: Adverse events

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Placebo (n=1410)</th>
<th>Placebo (% of patients with event)</th>
<th>Placebo (%)</th>
<th>Atorvastatin 10 mg (n=1426)</th>
<th>Atorvastatin 10 mg (% of patients with event)</th>
<th>Atorvastatin 10 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse event (AE)*</td>
<td>20 (1.1)</td>
<td>19 (1.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued for AE</td>
<td>145 (10)</td>
<td>122 (9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myopathy</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT ≥3 ULN</td>
<td>14 (1)</td>
<td>17 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST ≥3 ULN</td>
<td>4 (0.3)</td>
<td>6 (0.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Judged by attending clinician to be possibly associated with study drug
ALT = alanine transaminase
AST = aspartate transaminase
ULN = upper limit of normal


**Statin treatment was well tolerated**

- Discontinuation because of an adverse event occurred in 10% and 9% of the placebo and statin groups, respectively.
**4D Trial: Neutral effect of statin in hemodialysis patients with diabetes**

N = 1255 randomized to atorvastatin 20 mg or placebo for 4 years

![Graph](image)


*Relative risk reduction

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**4D showed neutral effect of statin in patients at very high risk of CVD**

- Die Deutsche Diabetes Dialysis (4D) randomized 1255 patients with type 2 diabetes receiving maintenance hemodialysis to placebo or atorvastatin 20 mg. The primary outcome was a composite of cardiac death, nonfatal MI, and stroke.

- Despite a median 42% reduction in LDL-C to 72 mg/dL, statin treatment had a neutral effect on the primary outcome and its components (with the exception of coronary events).
Statins reduce all-cause death: Meta-analysis of 14 trials

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Events (%)</th>
<th>Treatment (n = 45,054)</th>
<th>Control (n = 45,002)</th>
<th>Treatment better</th>
<th>Control better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular causes:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>3.4</td>
<td>4.4</td>
<td></td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.6</td>
<td>0.6</td>
<td></td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Other vascular</td>
<td>0.6</td>
<td>0.7</td>
<td></td>
<td>0.95</td>
<td>0.93</td>
</tr>
<tr>
<td>Any non-CHD vascular</td>
<td>1.2</td>
<td>1.3</td>
<td></td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Any vascular</td>
<td>4.7</td>
<td>5.7</td>
<td></td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Nonvascular causes:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>2.4</td>
<td>2.4</td>
<td></td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>0.2</td>
<td>0.3</td>
<td></td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>1.1</td>
<td>1.2</td>
<td></td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Any nonvascular</td>
<td>3.8</td>
<td>4.0</td>
<td></td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Any death</td>
<td>8.5</td>
<td>9.7</td>
<td></td>
<td>0.88</td>
<td></td>
</tr>
</tbody>
</table>


**Meta-analysis confirms statin benefits**

- The Cholesterol Treatment Trialists’ (CTT) meta-analysis of 14 major statin trials confirms that statins reduce major vascular events without increasing risk of cancer or other nonvascular outcomes.

- A significant 12% reduction in risk of all-cause mortality is seen.
Proportional reduction in risk is independent of baseline lipid levels

- The CTT analysis indicates that a reduction in LDL-C of 39 mg/dL sustained for 5 years would result in a reduction in risk of major vascular events of approximately 20%, regardless of the baseline LDL-C.
### HPS: Assessing relation of statin benefit to baseline LDL-C

**Heart Protection Study**

| **Population:** | 20,536 patients with total-C ≥135 mg/dL and history of diabetes, treated hypertension, CAD, stroke, or PAD |
| **Treatment:** | Randomized to simvastatin 40 mg or placebo |
| **Primary outcome:** | Mortality (for overall analysis) and fatal or non-fatal vascular events (for subcategory analyses) |
| **Follow-up:** | 5 years |


**HPS aimed to assess morbidity and mortality of LDL reduction in patients with diabetes**

- The Heart Protection Study (HPS) included 5963 adults with known diabetes and 14,573 adults with occlusive arterial disease. Patients were randomized to receive 40 mg simvastatin daily or placebo.
- Outcomes included first major coronary or vascular event.
**Reduction in coronary and cerebrovascular events with statin**

- In the Heart Protection Study (HPS), simvastatin 40 mg reduced the risk of coronary events, stroke, and revascularizations compared with placebo.

---

**HPS: Effects on specific major vascular events**

<table>
<thead>
<tr>
<th>Vascular event</th>
<th>Statin (10,269)</th>
<th>Placebo (10,267)</th>
<th>Event rate ratio</th>
<th>Statin better</th>
<th>Placebo better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>898</td>
<td>1,212</td>
<td>0.76 (95% CI, 0.72–0.81)</td>
<td>P &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Any stroke</td>
<td>444</td>
<td>585</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any revascularization</td>
<td>939</td>
<td>1,205</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>2,033 (19.8%)</td>
<td>2,585 (25.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In HPS, benefit was independent of baseline cholesterol

- Similar reductions in major vascular events with statin treatment occurred in patients with baseline LDL-C above and below 100 mg/dL.
**Heart Protection Study**

<table>
<thead>
<tr>
<th>Event rate (%)</th>
<th>Simvastatin n = 10,269</th>
<th>Placebo n = 10,267</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C &lt;116 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With diabetes</td>
<td>15.7</td>
<td>20.9</td>
</tr>
<tr>
<td>No diabetes</td>
<td>18.8</td>
<td>22.9</td>
</tr>
<tr>
<td>LDL-C ≥116 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With diabetes</td>
<td>23.3</td>
<td>27.9</td>
</tr>
<tr>
<td>No diabetes</td>
<td>20.0</td>
<td>26.2</td>
</tr>
<tr>
<td>All patients</td>
<td>19.8</td>
<td>25.2</td>
</tr>
</tbody>
</table>

Statin better Placebo better

*24% reduction*  
P < 0.0001

**Cholesterol-lowering therapy is beneficial for people with diabetes, independent of manifest coronary disease**

- The proportional reduction in risk did not appear to be influenced by pretreatment lipid values.
- Risk reduction appeared to be independent of the interval since diabetes diagnosis, type of diabetes, degree of glycemic control upon initiation of statin therapy, or reduction in A1C.
### HPS: Incidence of elevated liver or muscle enzymes

**Heart Protection Study**

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin (%) (n = 10,269)</th>
<th>Placebo (%) (n = 10,267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated ALT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4xULN</td>
<td>1.35</td>
<td>1.28</td>
</tr>
<tr>
<td>&gt;4xULN</td>
<td>0.42</td>
<td>0.31</td>
</tr>
<tr>
<td>Elevated CK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–10xULN</td>
<td>0.19</td>
<td>0.13</td>
</tr>
<tr>
<td>&gt;10xULN</td>
<td>0.11</td>
<td>0.06</td>
</tr>
<tr>
<td>Myopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No rhabdomyolysis</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0.05</td>
<td>0.03</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase  
ULN = upper limit of normal  

**Statin comparable to placebo in tolerability**

- Treatment discontinuation because of adverse events occurred in 4.8% and 5.1% of statin and placebo patients, respectively.
Behavioral and pharmacologic interventions can help reduce CV disease
BP-lowering trials indicate benefits in hypertension and CVD
**Increased stroke risk for β-blockers shown in meta-analysis**

N = 105,951

<table>
<thead>
<tr>
<th>Stroke</th>
<th>Favors β-blocker</th>
<th>Favors other drug</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-BPLA</td>
<td>1.29 (1.12–1.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONVINCE</td>
<td>0.87 (0.68–1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELSA</td>
<td>1.58 (0.69–3.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAPPY</td>
<td>0.77 (0.49–1.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INVEST</td>
<td>1.14 (0.93–1.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIFE</td>
<td>1.34 (1.13–1.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC Old</td>
<td>1.22 (0.83–1.79)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NORDIL</td>
<td>1.22 (0.99–1.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STOP-2</td>
<td>1.12 (0.96–1.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UKPDS</td>
<td>0.90 (0.48–1.69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yurenev</td>
<td>0.56 (0.21–1.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC</td>
<td>2.28 (1.31–3.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>1.16 (1.04–1.30)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 22.39$ (P = 0.02)

---

**β-blockers in stroke risk**

- Meta-analysis of 12 randomized, controlled trials indicated a 16% (95% CI 4%–30%) greater risk of stroke for β-blockers relative to other hypertensive treatment.
- Relative to placebo or no treatment, there was a 19% reduction (95% CI 7%–29%) for β-blockers in 7 studies.
- Risk of MI or death was similar for β-blockers relative to other hypertensives.
BPLTTC meta-analysis suggests particular benefit with CCBs in stroke prevention

- 27 randomized trials were analyzed (33,395 subjects with diabetes; 125,314 subjects without diabetes).
- Analysis compared the effects of BP-lowering treatments on CV events and death.
- Benefit appeared to be independent of diabetes.
BPLTTC meta-analysis suggests benefit with ACEIs in CHD

- Benefit was most evident in diabetes.
VALUE: Assessing different antihypertensive classes in high-risk hypertensives

- The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was conducted in 15,245 hypertensive patients at high risk of CV events. Subjects were randomized to amlodipine 10 mg or valsartan 160 mg. Hydrochlorothiazide was added to each treatment arm as needed.

- Study subjects were designated high risk due to the presence of CVD risk factors; either atherosclerotic disease of the coronary, cerebral, or peripheral arteries; or left ventricular hypertrophy.

- The primary hypothesis dictated that for the same level of BP control, the valsartan-based regimen would be better than the amlodipine-based regimen in reducing the primary outcome.
**Nonsuperiority of valsartan**

- Results showed no difference between valsartan and amlodipine treatment in CVD outcome.
**Faster BP control associated with clinical benefit**

- At study end, BP levels were similar in both groups. However, BP reduction was faster with amlodipine vs valsartan, with the greatest difference (of almost 4 mm Hg systolic) evident at 3 months.
- Event rates followed a similar pattern: At study end, there was no difference between the groups. However, at 3 months, the odds ratios tended to favor amlodipine.
VALUE: Clinical implications

- No difference in primary outcome between treatment groups
- Unequal reductions in BP might account for differences between groups in cause-specific outcomes

Rapid BP control in hypertensive patients at high CVD risk is essential


VALUE supports importance of rapid BP control

- VALUE results did not support the trial hypothesis. At study end, both treatments reduced the primary outcome by comparable amounts.
- Results, however, do support the need for rapid BP reduction.
CAMELOT: Trial of BP reduction with ACEI or CCB in CAD patients without HF

**Comparison of AMLodipine vs Enalapril to Limit Occurrences of Thrombosis**

**Study design:** Randomized, double-blind, multicenter, 24-month trial in patients with angiographically documented CAD, LVEF ≥40%, and no HF (N = 1991)

**Treatment:** Amlodipine (10 mg), enalapril (20 mg), or placebo added to background therapy with β-blockers and/or diuretics

**Primary outcome:** Incidence of CV events for amlodipine vs placebo

**IVUS substudy:** Measurement of atherosclerosis progression using IVUS (n = 274)

**Outcome:** Change in percentage of atheroma volume


**Assessment of 2 BP reduction strategies**

- 1991 participants had normal diastolic BP (<100 mm Hg) and CAD (>20% stenosis by angiography).

- After 2 weeks on a placebo, patients demonstrating at least 80% compliance were assigned to a daily dose of 5 mg amlodipine, 10 mg enalapril, or placebo (added to any background therapy). After 2 weeks of treatment, patients doubled the dose, and maintained this dose if tolerated for the remainder of the study.

- Mean final dosages were 8.6 mg amlodipine or 17.4 mg enalapril; 86.7% of the amlodipine, 84.3% of the enalapril, and 89.8% of the placebo groups received the full target dosage.
Amlodipine reduced incidence of CV events

- The primary outcome occurred in 23.1% of placebo-treated patients, 16.6% of amlodipine-treated patients (HR 0.69, 95% CI 0.54–0.88, \( P = 0.003 \) vs placebo), and 20.2% of enalapril-treated patients (HR 0.85, 95% CI 0.67–1.07, \( P = 0.16 \) vs placebo).

- The difference in primary outcome for amlodipine vs enalapril was not significant (HR 0.81, 95% CI 0.63–1.04, \( P = 0.10 \)).
**CAMELOT: Clinical implications**

- Optimal SBP levels in CAD patients ~120 mm Hg
- Regression of CAD suggested with SBP reduction >10 mm Hg
- Hemodynamic effects may also modulate clinical outcome
- Increasing evidence to support the following strategies:
  - Combinations of drugs with differing modes of action
  - Lower BP targets in special populations


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**Optimal systolic BP may be lower than commonly believed**

- The CAMELOT results suggest that the optimal systolic BP level in CAD patients without HF may be <140 mm Hg and perhaps in the 120 mm Hg range.
- Atherosclerosis progression appeared to be related to the degree of BP reduction, with no observed progression with a systolic BP reduction of ~10 mm Hg. Regression of atherosclerosis was suggested with a systolic BP reduction >10 mm Hg.
- The relation of BP reduction to clinical outcome in CAD patients is complex. Hemodynamic effects may also modulate clinical outcome.
- Further studies are needed to evaluate different BP levels and BP-lowering strategies in this patient population.
Pharmacotherapy in new-onset diabetes

- A number of trials in addition to HOPE have demonstrated reduction in new-onset diabetes with newer therapies based on RAAS modulation or calcium channel blockade compared with placebo or therapies with diuretics or β-blockers.
Improving time to benefit in clinical outcomes studies

Lipid modification

Lifestyle intervention

Optimal CV risk reduction

Glucose lowering

BP lowering
**PROactive: Study design**

**Objective:** Assess the effects of pioglitazone on reducing macrovascular events in type 2 diabetes

**Design:** Randomized, double-blind, placebo-controlled

**Population:** N = 5238 with type 2 diabetes and history of macrovascular disease

**Treatment:** Pioglitazone (up to 45 mg) or placebo

**Primary outcome:** Composite of all-cause mortality, MI, ACS, coronary or peripheral revascularization, amputation, stroke

**Secondary outcomes:** Individual components of primary outcome, CV mortality

**Follow-up:** 4 years

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**Large-scale trial conducted in patients with high-risk type 2 diabetes**

- PROactive was conducted in 5238 patients with type 2 diabetes and at high risk of CV events due to atherosclerotic disease of the coronary, cerebral, or peripheral arteries.
- Subjects were randomized to pioglitazone (initial dose 15 mg, with forced titration to 30 mg or 45 mg, depending on tolerability) or placebo.
**PROactive: Reduction in primary outcome**

**Pioglitazone treatment led to a nonsignificant 10% reduction in primary outcome compared with placebo**

- The primary outcome (all-cause mortality, nonfatal MI, stroke, ACS, leg amputation, coronary or leg revascularization) was not significantly reduced in pioglitazone patients.

- Confirmed divergence in the survival curves suggests that significant risk reduction might have been achieved with longer treatment duration.
Pioglitazone treatment led to a significant 16% risk reduction in secondary outcome compared with placebo

- The main secondary outcome of all-cause mortality, MI, or stroke was significantly reduced in pioglitazone patients.
**PROactive: Clinical implications**

Pioglitazone added to standard antidiabetic and CV therapies showed:

- 10% RRR in primary outcome
  - Composite all-cause mortality, nonfatal MI (including silent MI), stroke, ACS, leg amputation, coronary or leg revascularization
- 16% RRR in secondary outcome
  - All-cause mortality, nonfatal MI (excluding silent MI) or stroke
- No difference between groups in HF mortality
- Continued divergence in survival curves
  - Greater benefit with longer treatment duration hypothesized

**PROactive results support use of PPARγ modulator in patients with diabetes at high CVD risk**

– May improve CVD outcomes and decrease need to start insulin


**Overall positive findings… but more studies needed**

- In an accompanying editorial, Yki-Järvinen concluded, “[PROactive] showed that pioglitazone is beneficial in patients with type 2 diabetes and pre-existing macrovascular disease who do not develop heart failure.”

- Studies are needed to:
  - Confirm the benefit of thiazolidinediones in patients with type 2 diabetes
  - More fully characterize the mechanism of benefit
  - More fully characterize the mechanism and prognosis of treatment-related heart failure

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Multifactorial approaches in CVD prevention

Lipid modification

Lifestyle intervention

Glucose lowering

Optimal CV risk reduction

BP lowering
Potential benefits of multifactorial therapies are limited by low patient adherence

- Improved adherence is achieved if multiple therapies are initiated concomitantly.
Suggested mnemonic for CV prevention

- Adherence to both lifestyle and pharmaceutical interventions yield cardioprotective benefits
Steno-2 supports aggressive multifactorial intervention in type 2 diabetes

Objective: Target-driven, long-term, intensified intervention aimed at multiple risk factors compared with conventional therapy

N = 160 patients with type 2 diabetes and microalbuminuria

Intensive treatment targets
- BP <130/80 mm Hg
- A1C <6.5%
- Total-C <175 mg/dL
- Triglycerides <150 mg/dL

Risk of CV events reduced in diabetic patients undergoing multifactorial intervention

- Steno-2 compared the effects of an intensive, multifactorial intervention to usual care in patients with type 2 diabetes and microalbuminuria.

- 80 patients each received either:
  - Conventional treatment in accordance with national guidelines, or
  - Lifestyle and multifactorial pharmacologic therapy with specific target goals.

- The primary outcome was a composite of CV death, nonfatal MI or stroke, revascularization, and amputation.
**Steno-2: Effects of multifactorial intervention on macrovascular outcomes**

*Greater overall impact on risk factors with multifactorial vs usual care*

- Compared with usual care, more patients in the intensive therapy group reached goals for glucose, cholesterol, and BP.

- The intensive therapy group had a significantly lower relative risk of CVD (53%, 95% CI 0.24–0.73). These differences were maintained throughout the study.
Most Americans fail to follow healthy lifestyles

- Reeves et al used BRFSS data from 153,805 respondents, ages 18 to 74 years, surveyed in 2000.
- In all, 24% to 78% of respondents smoked, had a body mass index (BMI) $\geq 25$ kg/m$^2$, did not consume fruits and vegetables regularly, or did not engage in physical activity of moderate intensity on a regular basis.
- The data illustrate that the majority of Americans do not follow a healthy lifestyle. In contrast, only 16.8% of respondents (data not shown) included all four healthy lifestyle characteristics in their lifestyles:
  - Nonsmoking
  - Healthy weight (BMI $\leq 25$ kg/m$^2$)
  - Regular consumption of fruits and vegetables ($\geq 5$ times daily)
  - Regular exercise ($\geq 5$ times weekly)
Adherence with concomitant antihypertension and lipid-lowering agents is poor when multiple pills are used and treatment is delayed

- In a retrospective cohort study, Chapman et al examined 8406 enrollees of US managed care plans with antihypertensive and statin therapies within a 90-day period. Adherence was measured as the proportion of days covered in each 3-month interval following initiation of concomitant therapy (mean follow-up, 12.9 months).
- Results showed that both treatments declined sharply, with 44.7% and 35.9% of patients adherent at 3 and 6 months, respectively.
- Patients were more likely to be adherent if they initiated both antihypertensive and lipid-lowering agents simultaneously, had a history of CHD or congestive heart failure, or took fewer other medications.
### Combination drugs for treatment of hypertension, dyslipidemia, and diabetes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Combination product</th>
</tr>
</thead>
</table>
| Hypertension       | • Antihypertensive/diuretic*  
                     |   • Benazepril/amlodipine  
                     |   • Trandolapril/verapamil |
| Dyslipidemia       | • Ezetimibe/simvastatin  
                     |   • Lovastatin/niacin      |
| Diabetes           | • Metformin/glipizide  
                     |   • Metformin/glyburide    
                     |   • Pioglitazone/metformin |
                     |   • Rosiglitazone/metformin     |
| Hypertension/dyslipidemia | • Amlodipine/atorvastatin |

*Numerous combinations

**Multiple options available for treatment of BP, lipids, and glucose**

- The range of options available affords clinicians flexibility in the combinations of drug classes used.
Gemini: More than 55% of patients achieved both BP and LDL-C goals

Amlodipine/Atorvastatin Gemini Study
N = 1220, 14 weeks with amlodipine/atorvastatin single-pill therapy

Single-pill combination therapy showed efficacy in reducing both BP and lipid levels and in helping patients achieve goals for both hypertension and dyslipidemia

- At study end, 57.7% of patients had achieved both their BP and LDL-C goals.
- The mean dose of study medication at end point was amlodipine component 7.1 mg and atorvastatin component 26.2 mg.
More patients at BP goal with fixed-dose combination vs conventional strategy

N = 214 with type 2 diabetes and hypertension, BP <130/85 mm Hg

Data support fixed-dose combination therapy in high-risk patients

Adjunctive HCTZ required in 44% of fixed-dose combination and 61% of conventional strategy

**Fixed-dose combination strategy more effective than stepwise therapy at accomplishing BP goals in diabetic patients**

- Bakris et al randomized 214 patients with hypertension and type 2 diabetes to a fixed-dose regimen (amlodipine/benazepril 5/10 mg) or to enalapril 10 mg. At 4 weeks, subjects not at goal (<130/85 mm Hg) were titrated up to 5/20 mg or 20 mg, respectively. At 8 weeks, hydrochlorothiazide 12.5 mg was added for subjects in each treatment arm not at goal.
- At 3 months, 63% of patients on fixed-dose combination therapy had reached BP goals vs 37% of patients on conventional monotherapy.
New paradigm of multiple risk factor management

The future of drug therapy belongs to prevention, which is just now being addressed, and to intensive management of all cardiovascular risk factors, in particular, dyslipidemia

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**Aggressive risk factor management reduces CVD**

- Clinical practice is moving from a goal of treating CV events to preventing them.
- Such a strategy requires early and aggressive management of all modifiable risk factors.
ALLHAT: Design

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial and ALLHAT–Lipid-Lowering Trial

ALLHAT: N = 42,418: stage 1/2 hypertension + ≥1 CV risk factor

- Chlorthalidone 12.5–25 mg/d
  n = 15,255
- Amlodipine 2.5–10 mg/d
  n = 9,048
- Losartan 10–40 mg/d
  n = 9,054
- Doxazosin 2–8 mg/d
  n = 9,061

**Step 1: titration**

- Step 2: open-label atenolol 25–100 mg/d, clonidine 0.1–0.3 mg bid, reserpine 0.05–0.2 mg/d

**Step 2: open-label hydralazine 25–100 mg bid**

- Pravastatin 40 mg/d (n = 5,170)
- Usual care (n = 5,185)

**ALLHAT-LLT:**

N = 10,355; CHD, LDL-C 100 to 129 mg/dL or no CHD, LDL-C 120 to 189 mg/dL

- Pravastatin 40 mg/d (n = 5,170)
- Usual care (n = 5,185)

*Arm discontinued


**ALLHAT-LLT: Assessing multifactorial therapy**

- The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) evaluated the long-term effects of three blood pressure (BP)–lowering regimens: a thiazide diuretic (chlorthalidone), the calcium channel blocker (CCB) amlodipine, and an ACE inhibitor (lisinopril). (A fourth arm, a doxazosin-based regimen, was terminated early).

- In the Lipid-Lowering Trial (LLT) component of ALLHAT, 10,355 hypertensive patients were randomized to pravastatin 40 mg/d or usual care, which could include drug treatments for LDL-C lowering at their physician’s discretion.

- These patients had baseline LDL-C 120–189 mg/dL with no CHD or 100–129 mg/dL and known CHD.

- ALLHAT participants originally assigned to doxazosin continued in the LLT and were offered open-label chlorthalidone for antihypertensive treatment.
**ALLHAT: Neutral effect on primary outcome**

- No differences occurred in the primary outcome of fatal CHD and nonfatal MI among the three treatment groups. The comparative 6-year risk rates for the treatments were chlorthalidone 11.5%, lisinopril 11.4%, and amlodipine 11.3%.
ALLHAT-LLT: Neutral effects of statin or usual care on outcomes

- The primary outcome of ALLHAT-LLT, all-cause mortality, was similar for pravastatin vs usual care (relative risk 0.99; 95% CI, 0.89 to 1.11).
- The secondary outcome, CHD death plus nonfatal MI, was slightly lower with pravastatin, but not significantly (relative risk 0.91; 95% CI, 0.79 to 1.04).
- LDL-C levels at year 4 were reduced by 28% in the pravastatin group vs 11% with usual care (not shown).
**ALLHAT: Clinical implications**

**Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial**

- BP-lowering trial
  - Diuretic, ACEI, CCB equivalent in ↓ CHD death and MI
- Lipid-lowering trial (ALLHAT-LLT)
  - Statin, usual care equivalent in ↓ all-cause mortality
  - Modest differential in on-treatment cholesterol levels may have contributed to result

**ALLHAT BP** results support importance of BP lowering, regardless of drug class used
**ALLHAT-LLT** results are consistent with other statin trials

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**Statin treatment similar to usual care in treatment of older patients**

- Pravastatin was similar to usual care in mortality and CHD.
- The safety and efficacy findings of this study were similar to other large, long-term statin trials.
Comparisons of newer vs older combination regimens

- The International Verapamil SR/Trandolapril (INVEST) Study was conducted in 22,576 patients with hypertension and CAD. Investigators hypothesized that CCB-based strategy would be equivalent in reduction of clinical events to non-CCB–based strategy.

- The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) was conducted in 19,257 patients with hypertension and ≥3 other CV risk factors. Investigators hypothesized that the newer regimen would be more effective in reducing CV outcomes compared with the older strategy.
### INVEST: Assessment of combination regimens in hypertension + CAD

#### INternational VErapamil SR/Trandolapril

<table>
<thead>
<tr>
<th>Population:</th>
<th>22,576 patients ≥50 years of age with hypertension and CAD</th>
</tr>
</thead>
</table>
| Treatment:                            | Verapamil SR 120–480 mg ± trandolapril  
                                          0.5-8 mg ± HCTZ 12.5–100 mg  
                                          Atenolol 25–200 mg ± trandolapril 0.5–8 mg  
                                          ± HCTZ 12.5–100 mg |
| Primary outcome:                      | All-cause death, stroke, MI |
| Secondary outcomes:                   | Individual components of primary outcome |
| Follow-up:                            | 2.7 years |


**INVEST compared two different multidrug strategies**

- The study hypothesis dictated that the CCB-based strategy would be equivalent in reduction of clinical events to the non-CCB–based strategy.
Both treatment strategies reduced BP by comparable amounts

- At 24 months, mean reductions of 18.7/10.0 mm Hg and 19.0/10.2 mm Hg were observed in the CCB and non-CCB strategy groups, respectively.
INVEST: Comparable effects of treatments on primary outcome

INternational VErapamil SR/Trandolapril
N = 22,576 with hypertension and CAD

Treatment strategies were equivalent, continuing the study hypothesis

- The hazard ratio was 0.98 (95% CI, 0.91 to 1.07, P = 0.69) for the CCB-based vs non-CCB–based strategy.
- Similar results were observed for all-cause mortality, CV death, CV hospitalization, and BP control.
**INVEST: Clinical implications**

_INternational VErapamil SR/Tlandopril_  

- In patients with hypertension and clinically stable CAD:
  - 70% of both treatment groups achieved BP <140/90 mm Hg
  - CCB + ACEI was equivalent to β-blocker + diuretic in preventing death, MI, or stroke
  - Relative risk reduction of 15% for newly diagnosed diabetes in the CCB + ACEI treatment group

**INVEST demonstrates that BP targets can be achieved in the majority of hypertensive patients with CAD using a multidrug strategy**


**INVEST demonstrated BP goals through aggressive combination therapy**

- Benefits of lipid lowering were additional to those of good BP control and were at least as large as those previously demonstrated in patients with dyslipidemia but without hypertension.
ASCOT: Rationale

• High prevalence of dyslipidemia in hypertensive patients
• No trial specifically addressing benefits of lipid lowering in primary prevention of CHD in hypertensive patients not conventionally deemed dyslipidemic
• Less-than-expected CHD prevention using standard BP-lowering therapy
• Insufficient outcome data on newer types of BP-lowering agents, especially in specific combination treatment regimens
• Combination risk factors synergistically cause CHD

ASCOT has helped change the way we look at treating multiple risk factors for CVD

• ASCOT findings provide support for utilizing a global risk assessment in guiding treatment strategies, aggressively treating patients at multiple risk for CVD, and using newer treatment regimens.
ASCOT: Design

Anglo-Scandinavian Cardiac Outcomes Trial

BP ≥160/100 mm Hg (untreated); BP ≥140/90 mm Hg (treated)

Randomized, open-label, blinded outcome

Amlodipine 5–10 mg ± perindopril 4–8 mg

Atenolol 50–100 mg ± bendroflumethiazide 1.25–2.5 mg*

Total-C ≤250 mg/dL

Atorvastatin 10 mg

Placebo

Randomized, double blind

*Plus K supplement if needed


ASCOT study assessed two antihypertensive strategies

- Participants ranged from 40–79 years, with untreated systolic BP (SBP) ≥ 160 mm Hg and untreated diastolic BP (DBP) ≥ 100 mm Hg, or treated SBP ≥ 140 mm Hg and treated DBP ≥ 90 mm Hg.
ASCOT-LLA patients had hypertension plus ≥3 risk factors

- In addition to hypertension, the most common modifiable risk factors were proteinuria, smoking, dyslipidemia, and atherosclerotic vascular disease.
**ASCOT-BPLA: Study design**

**Design:** Double-blind, placebo controlled, randomized

**Population:** N = 19,257 with hypertension and ≥3 other CV risk factors

**Treatment:**
- Amlodipine 5–10 mg ± perindopril 4–8 mg prn (n = 9639)
- Atenolol 50–100 mg ± bendroflumethiazide 1.25–2.5 mg/potassium prn (n = 9618)

**Primary outcome:** Nonfatal MI (including silent MI) and fatal CHD

**Secondary outcome:** All-cause mortality, stroke, nonfatal MI (excluding silent MI), all coronary events, CV events/procedures, CV mortality, fatal/nonfatal HF


**BP-lowering arm of ASCOT**

- CCB with or without ACEI therapy was compared with β-blocker with or without diuretic therapy in a large (N = 19,257), placebo-controlled study.
The amlodipine-based regimen showed rapid and sustained benefits in BP reduction

- On average, both treatment groups showed a combined average BP reduction of 26.6/16.6 over time.
- The group receiving the amlodipine-based regimen showed lower BP values throughout the trial compared with those in the atenolol-based regimen.
- Differences were largest at 3 months.
**ASCOT-BPLA: Reduction in primary outcome (nonfatal MI and fatal CHD)**

*Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm*

*N = 19,257*

- Proportion of events (%)
- Time since randomization (years)
- RRR = 10%
- HR = 0.90 (95% CI, 0.79–1.02)
- *P* = 0.1052

- Atenolol-based regimen
- Amlodipine-based regimen

\[\text{RRR} = 10\%\]
\[\text{HR} = 0.90 \text{ (95\% CI, 0.79–1.02)}\]
\[\text{*P*} = 0.1052\]

*Atenolol 50–100 mg ± bendroflumethiazide

1.25–2.5 mg/potassium

†Amlodipine 5–10 mg ± perindopril 4–8 mg


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**The amlodipine-based regimen prevented more major CV events**

- The study was stopped prematurely after 5.5 years’ median follow-up and accumulated in total 106,153 patient-years of observation.
- Study was powered for 1150 patients; only 903 patients were studied because of early termination.
- Antihypertensive drug regimen starting with amlodipine adding perindopril as required is better than one starting with atenolol adding thiazide.
Fewer fatal and nonfatal strokes were observed in the amlodipine group

- The amlodipine group had a 23% reduction in risk of stroke relative to the atenolol group (95% CI, 0.66–0.89, P = 0.0003).
ASCOT-BPLA: Additional reductions with amlodipine-based regimen

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Amlodipine-based* (n = 9639)</th>
<th>Atenolol-based † (n = 9618)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI (excluding silent) + fatal CHD</td>
<td>7.4</td>
<td>8.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total coronary endpoint</td>
<td>14.6</td>
<td>16.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total CV events and procedures</td>
<td>27.4</td>
<td>32.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>13.9</td>
<td>15.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CV mortality</td>
<td>4.9</td>
<td>6.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatal/nonfatal stroke</td>
<td>6.2</td>
<td>8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal/nonfatal HF</td>
<td>2.5</td>
<td>3.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Tertiary endpoints**

| Development of diabetes                                  | 11.0                         | 15.9                         | <0.0001|
| Development of renal impairment                          | 7.7                          | 9.1                          | <0.05 |

* Amlodipine 5–10 mg ± perindopril 4–8 mg
† Atenolol 50–100 mg ± bendroflumethiazide 1.25–2.5 mg/potassium

Unadjusted hazard ratio

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**Consistent evidence of benefit**

- By trial end, most patients (78%; 14,974 of 19,242) were taking at least 2 antihypertensive agents.
- The benefits of the amlodipine-based regimen in lowering BP and preventing CV events were greater than those of the β-blocker ± diuretic combination.
- Major CV events were reduced by 16%; new-onset diabetes by 30%; stroke by 23%; and mortality by 11% in the amlodipine ± perindopril group.
- Better BP control with amlodipine ± perindopril (mean in-trial systolic BP difference 2.7 mm Hg vs atenolol regimen) may explain some, but not all, of the benefits.

**Metabolic benefit of newer regimens**

- Consistent with other studies, the β-blocker–based regimen was associated with a higher risk for new-onset diabetes than the CCB-based regimen.

- The accumulated data suggest that CCBs are metabolically neutral, while ACEIs may be protective.
### ASCOT-LLA: Assessing lipid lowering in hypertensive patients

**Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm**

| **Design:** | 10,305 ASCOT patients with mean baseline LDL-C 133 mg/dL and ≥3 other risk factors |
| **Treatment:** | Randomized to atorvastatin 10 mg or placebo |
| **Primary outcome:** | Nonfatal MI and fatal CHD |
| **Secondary outcomes:** | Total CV events/procedures, total coronary events, all-cause mortality, CV mortality, stroke, HF |
| **Follow-up:** | 5 years |


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**ASCOT-LLA: Assessing statin treatment in patients with hypertension**

- The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) included 10,305 patients with total cholesterol ≤250 mg/dL plus ≥3 other cardiovascular risk factors.
- At baseline, mean LDL-C was 133 mg/dL. These patients would not be conventionally deemed dyslipidemic.
- Planned follow-up was 5 years, but the trial was stopped after 3 years due to the clear benefit of statin treatment.
**ASCOT-LLA: Atorvastatin reduces primary outcome in hypertensive patients**

**Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm**  
N = 10,305, baseline LDL-C 133 mg/dL

**Significant benefits observed within 1 year of treatment**

- After 3 years, atorvastatin 10 mg reduced LDL-C by 32% from baseline (from 133 mg/dL to 90 mg/dL).

- Nonfatal MI and fatal CHD occurred in 1.9% of the atorvastatin group vs 3.0% of the placebo group, a relative risk reduction of 36%.

- The benefit of treatment emerged in the first year of follow-up.
Relative risk reductions for coronary artery disease were greatest during the first few months of treatment with atorvastatin and stabilized thereafter

- A trend for benefit with atorvastatin occurred as early as 1 month after randomization.
- Significant benefit occurred at 3 months (7 vs 21 events); 6 months (19 vs 36 events), and 2 years (60 vs 96 events).
ASCOT-LLA subanalysis: Atorvastatin reduces CV events in patients with diabetes and hypertension

Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm
N = 2532, baseline LDL-C 128 mg/dL

CV events/ procedures, cumulative events* (%)

Follow-up (years)

RRR = 23%
HR = 0.77 (95% CI, 0.61–0.98)
P = 0.036

Statin benefit in coexisting diabetes and hypertension

- The relative reduction among the ASCOT-LLA subgroup with diabetes was less than among those without diabetes.
- However, there were only 84 events among patients with diabetes, which suggests that this finding may reflect inadequate power of the study, particularly in view of the shortened follow-up period.
ASCOT: Differing effect of statin added to β-blocker–based or CCB-based therapy

Statin added to CCB-based therapy reduced CV events and procedures

- Statin added to CCB-based therapy reduced CV events and procedures relative to statin plus β-blocker–based therapy (21.3 vs 27.0 events/1000 patient-years, respectively; P = 0.021).
- Statin added to CCB-based therapy also reduced CV events and procedures 27% (CI 0.60–0.88; P = 0.001) relative to CCB therapy alone.
**Statin added to CCB-based therapy reduced stroke**

- Statin added to CCB-based therapy reduced stroke relative to statin plus β-blocker–based therapy (4.2 vs 6.5 events/1000 patient-years, respectively; P = 0.04).
- Statin added to CCB-based therapy also reduced stroke 31% (CI 0.45–1.06; P = 0.09) relative to CCB therapy alone.
ASCOT: Differing effect of statin added to β-blocker–based or CCB-based therapy

Statin added to CCB-based therapy reduces fatal CHD and nonfatal MI

- Statin added to CCB-based therapy reduced fatal CHD and nonfatal MI relative to statin plus β-blocker–based therapy (4.6 vs 7.5 events/1000 patient-years, respectively; P = 0.015).

- Statin added to CCB-based therapy also reduced fatal CHD and nonfatal MI 53% (CI 0.32–0.69; P < 0.0001) relative to CCB therapy alone.
ASCOT: Clinical implications

- ASCOT-BPLA demonstrated greater benefits of CCB ± ACEI vs β-blocker ± diuretic in lowering BP and preventing CVD
  - Improved BP control with amlodipine ± perindopril may explain some, but not all, of the benefit
- ASCOT-LLA extended benefit of lipid lowering to hypertensive patients
  - Survival curves separated almost immediately, with significant difference at 90 days

ASCOT supports use of newer BP drugs and statins, especially in patients with complicated hypertension
Treatment should depend on global assessment of risk, not on individual risk factors

ASCOT provides strong support for combination therapy targeting multiple risk factors

- ASCOT demonstrated advantages of newer antihypertensive combination regimens over older regimens.
- ASCOT also extended the benefits of lipid lowering to patients with high-risk hypertension.
- Taken in aggregate, these data support multiple risk factor reduction in high-risk hypertension.

Summary: Optimizing outcomes in patients with multiple CVD risks

**Strategy for recognizing, treating, and managing patients at high risk for CVD**

- Combination, fixed-dose agents that target multiple mechanisms involved in hypertension and dyslipidemia contribute to better adherence.
- Therapy with combination agents target multiple mechanisms better than independent therapy alone.
Physician tools
3-minute lifestyle interview: Nutrition

- How many servings do you eat per day:
  - Fruits and vegetables?
  - Whole grains?
- How many servings of fish do you eat per week?
- How often do you eat desserts?
- What are your favorite snack foods?
- Do you eat because you are hungry or because there is food around?
- Do you weigh the most now that you’ve ever weighed?
- Are you interested in losing weight?

Adapted from Eckel RH, AHA. http://scientificsessions.americanheart.org.

The American Heart Association (AHA) recently provided a quick questionnaire for healthcare professionals to determine the nutritional quality of their patients’ diets
3-Minute lifestyle interview:
Physical activity

• How many steps do you take each day?
• Do you have a regular exercise program?
• Do you typically take elevators or escalators or climb the stairs?
• Do you park as close as you can to your destination?
• What limits your level of physical activity?
• Have you been evaluated for this?
• Would you like to become more active?

Adapted from Eckel RH. AHA. http://scientificsessions.americanheart.org.

The AHA provided a quick questionnaire to assess patients’ physical fitness
### Effective smoking cessation strategies

#### Counseling/Behavioral
- Practical counseling
  - Problem solving
  - Skills training
- Social support
  - Intra- and extra-treatment

#### Pharmacotherapies
- **First line**
  - Bupropion SR
  - Nicotine gum, inhaler, nasal spray, patch
- **Second line**
  - Clonidine
  - Nortriptyline

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#### Behavioral and pharmacotherapies in smoking cessation

- The 2000 US Department of Health and Human Services clinical practice guideline for treating tobacco use indicate practical counseling and behavioral therapies should be used with all patients attempting smoking cessation. More intensive counseling and behavioral therapies correlate with efficacy.

- The first-line pharmacotherapies that reliably increase long-term smoking abstinence are indicated, and should be used with all patients attempting to stop smoking when not contraindicated.

- Second-line pharmacotherapies may be considered if the first-line therapies are ineffective.