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Managing Patients With Hypertension and Additional Risk Factors: Identifying and Treating Hypertensive Patients With Confounding Dyslipidemia

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MANAGING PATIENTS WITH HYPERTENSION AND ADDITIONAL RISK FACTORS: IDENTIFYING AND TREATING HYPERTENSIVE PATIENTS WITH CONFOUNDING DYSLIPIDEMIA

This special edition of the *Journal of Managed Care Medicine* is based on presentations and discussions at a clinical consensus meeting held Dec. 3, 2005, in Phoenix, Ariz., and sponsored by the National Association of Managed Care Physicians Inc. and Hospicom Inc.

Target Audience

This activity is intended to help managed care medical directors and formulary committee members develop guidelines for the optimal management of hypertensive patients with additional cardiovascular risk factors.

Needs Assessment

The appropriate utilization of cardiovascular interventions specific to the management of patients with multiple CV risk factors, including hypertension and hypercholesterolemia is a growing critical concern. Through a series of presentations and discussions, panel members reviewed evidence-based selection criteria for the management of CV disease, recent national guidelines including reports released by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) and the National Cholesterol Education Program (NCEP), the inadequate treatment of patients with multiple CV risk factors, medication adherence, and the role of healthcare providers as change managers to improve patient outcomes.

Learning Objectives

Upon completing this activity, the reader will be able to:

- Review the evidence-based literature on the diagnosis, management, and treatment of patients with hypertension and multiple cardiovascular risk factors.
- Identify strategies to ensure patient compliance with cardiovascular interventions
- Discuss recommendations for managing hypertension patient populations with multiple cardiovascular risk factors.

Accreditation and Designation

This activity has been planned and implemented in accordance to the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the National Association of Managed Care Physicians (NAMCP) and Hospicom. NAMCP is accredited by the ACCME to provide continuing medical education to physicians.

NAMCP designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Managing Patients With Hypertension and Additional Risk Factors: Identifying and Treating Hypertensive Patients With Confounding Dyslipidemia

Cardiovascular (CV) disease remains the leading cause of death in the United States, affecting about one in three American adults.¹ The costs associated with CV disease are considerable. In addition to the direct costs of healthcare, CV disease results in substantial indirect costs due to lost time from work and lost productivity in the workplace. The American Heart Association (AHA) estimates the direct and indirect costs of CV disease for 2006 at

\$403.1 billion.¹ As the U.S. population ages, the incidence of CV disease and related costs are expected to continue rising.

In 2002, the World Health Organization (WHO) released the first-ever global analysis of disease burden¹ due to major CV risks.² This analysis showed that in North America, about 44 percent of CV disease burden was attributed to high blood pressure, and 39 percent of CV disease burden was due to high cholesterol.² About 58 percent of the burden was due to higher than optimal levels of both blood pressure and cholesterol (see Exhibit 1). These two risk factors are not only important to the development of CV disease, but also are controllable through medical intervention—unlike other risk factors, such as age or gender.

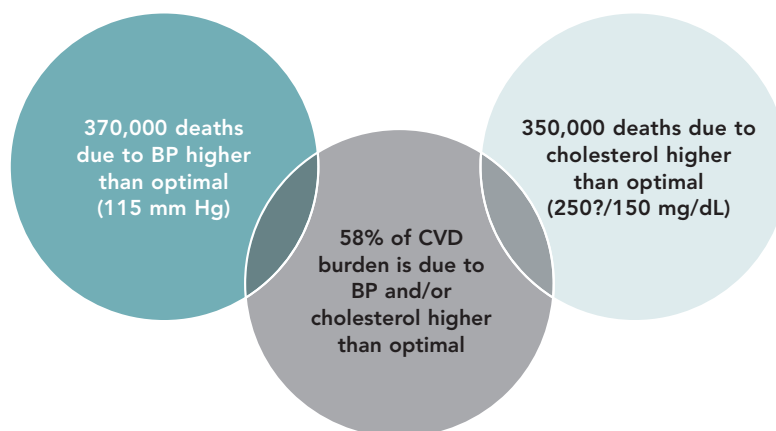
Prevalence, Co-Existence and Undertreatment of CV Risk Factors

Hypertension, high cholesterol, smoking, and obesity are well-known individual risk factors for developing CV disease. The risk becomes even greater when these risk factors occur concomitantly—even if the individual factors are

relatively mild. The total severity of multiple low-level risk factors often exceeds that of a single, severely elevated, risk factor³ (see Exhibit 2). Indeed, most CV events occur in patients with modest elevations of each risk factor and the presence of more than one risk factor.

Hypertension is the major risk factor for premature cardiovascular disease. The most recent classification of blood pressure offered by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) specifies normal blood pressure as systolic <120 mmHg and diastolic <80 mmHg. A new category called “pre-hypertension” was created for those with systolic pressures of 120 to 139 mmHg and diastolic pressures of 80 to 89 mmHg. Exhibit 3 applies the JNC 7 definitions of the stages of hypertension (normal, pre-hypertension, stage 1 and stage 2) against increases in CV disease risk. Essentially, the risk doubles as blood pressure increases from 115/75 mmHg to 135/85 mmHg. The risk at levels of 139/89 mmHg—which is the level traditionally considered as the

Exhibit 1: Hypertension and Dyslipidemia Impart a Substantial Disease Burden* in North America²



*Burden is defined as the total significance of disease for society beyond the immediate cost of treatment. It is measured in years of life lost to ill health as the difference between total life expectancy and disability-adjusted life expectancy.

Exhibit 2: Multiple Risk Factors Lead to Increased Risk for CHD³

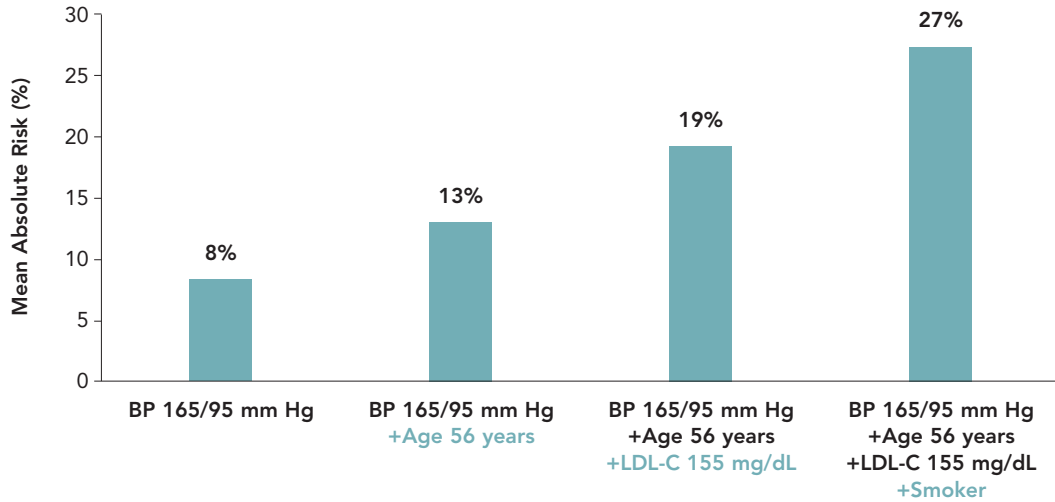


Exhibit 3: Hypertension and Pre-Hypertension Significantly Increase CVD Risk¹⁴

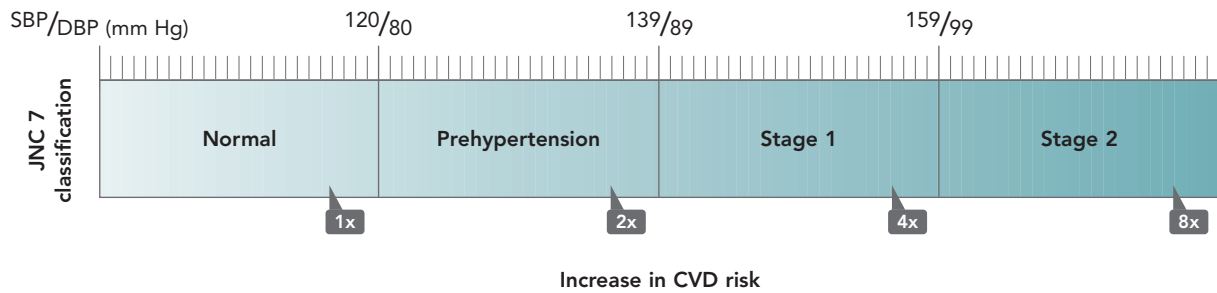
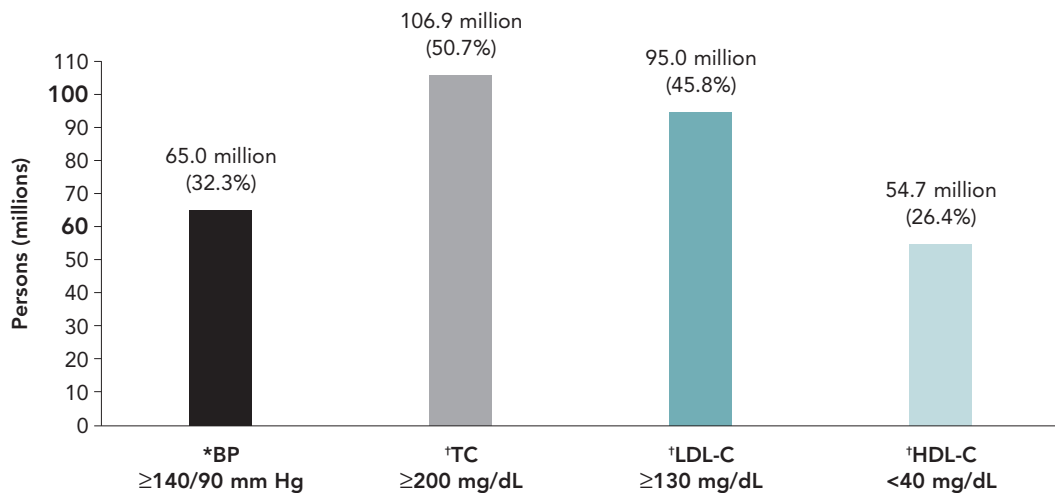


Exhibit 4: Prevalence of Hypertension and Suboptimal Cholesterol Values in the United States—Total Population, 2001 NHANES IV Data¹



BP = blood pressure; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.
 *BP and †lipid goals based on JNC VI and NCEP ATP III, respectively.

threshold for hypertension—is about two and a half times that of the lower blood pressure levels. At even higher levels, the risk increases proportionally.

Prevalence of Dyslipidemia in Hypertensive Patients

The most recent National Health and Nutrition Examination Survey (NHANES) IV data indicates that about 65 million Americans, or 32 percent of the population, have hypertension¹ (see Exhibit 4). This percentage is based on an estimated blood pressure >140/90 mmHg—a target level that is currently being redefined. Because JNC 7 guidelines are recommending even lower blood pressure target levels of 130/80 mmHg for those at high risk, the actual impact of blood pressure on CV disease in the U.S. may be even greater than that reported in NHANES IV.

The same data also indicate that about 50 percent of Americans have an elevated total cholesterol (TC), defined as >200 mg/dL. However, it's now known that the actual risk of death from heart attacks among U.S. males begins at a TC level of 180 mg/dL. So, again, the actual number of Americans at risk is likely to be greater.

Likewise, about 46 percent of the American population has an LDL-C value above 130 mg/dL, a target level

that is also higher than that recommended by newer guidelines. The current recommendation in the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP ATP III) calls for a low-density lipoprotein cholesterol (LDL-C) level of <100 mg/dL for patients at high risk, and <70 mg/dL for very high-risk patients.⁴ In NHANES III, more than 85 percent of hypertensive patients had LDL-C levels \geq 100 mg/dL.⁵

The prevalence of hypertension increases with age, regardless of gender or race. More than 50 percent of the population over 60 years of age is hypertensive, and the prevalence continues to rise with increasing age. Notably, after the age of 50 or 60 years, the increases in blood pressure occur primarily in systolic blood pressure, reflecting the increases in arterial stiffness.

A meta-analysis of 61 prospective studies assessed the age-specific relationship of blood pressure to cause-specific mortality.⁶ The findings showed that throughout middle and old age blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold, down to at least 115/75 mm Hg. At the relative young age of 50 to 59

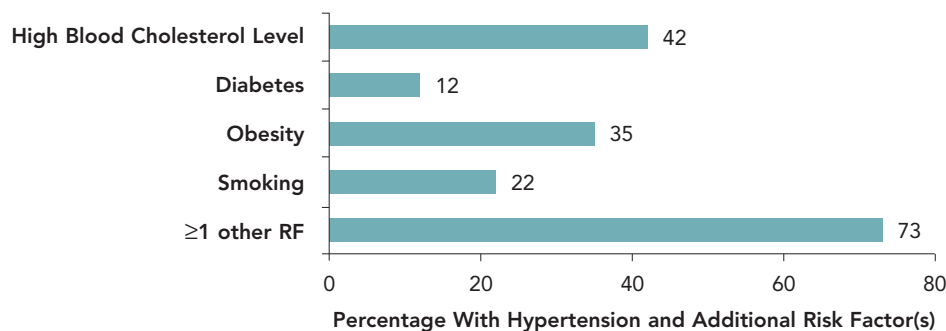
years, the risk of a stroke with a systolic pressure of 140 mmHg is three times greater than it is with a systolic pressure of 115 mmHg. Similarly, in the same age group, the risk of dying of a heart attack with a systolic blood pressure of 140 mmHg is twice that than at a systolic blood pressure of 115 mmHg. At ages 40 to 69 years, an increase of 20 mmHg in systolic blood pressure is associated with more than a twofold increase in the stroke death rate and in the death rates from ischemic heart disease and other vascular causes.

Co-existence of Hypertension With Other Risk Factors

The prevalence of co-existing risk factors in persons with hypertension is increasing.⁷ In 1999, 73 percent of persons who reported hypertension had at least one additional self-reported risk factor—an increase from 66 percent in 1991 (see Exhibit 5). About 42 percent of these patients reported high cholesterol levels, up from 36 percent in 1991. Another 12 percent reported having diabetes, while 35 percent had concurrent obesity, and 22 percent were current smokers.

Hypertension with confounding dyslipidemia is a serious and significant problem in the U.S., as shown by data from the NHANES III, phase 2 (1991–1994).⁵ Hypertension and hyperlipidemia occurred

Exhibit 5: U.S. Adults With Self-Reported Hypertension Who Report Having Other Risk Factors—1999 Behavioral Risk Factor Surveillance System* (N=109,754)⁷



*Percentages are weighted to state population estimates and age adjusted to the 2000 U.S. standard population using four age groups.

together in 30 million adults, or 15 percent of the population. Almost two out of three hypertensive patients have concurrent dyslipidemia, and almost one out of two patients with dyslipidemia also have hypertension (see Exhibit 6). The majority of hypertensive patients had LDL-C levels above 130 mg/dL, a level for which treatment is unequivocally mandated (see Exhibit 7).

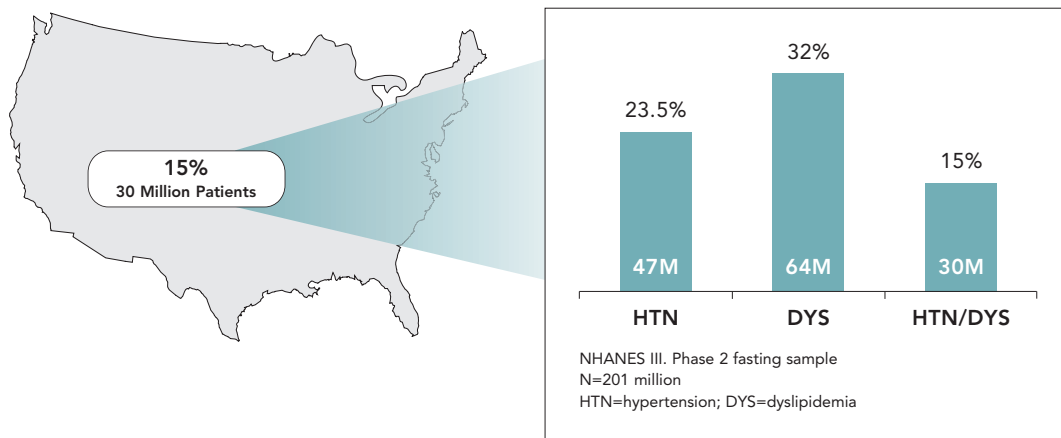
The prevalence of hypertension and dyslipidemia was also examined

in a managed care database of 2.1 million U.S. adults. The prevalence of hypertension was 23.8 percent, while the prevalence of dyslipidemia was 17.6 percent. More than half of the individuals with one condition had the other condition as well.⁸ Typically, increases in both hypertension and dyslipidemia were age-related for both men and women. The data showed a jump of 9 percent in the prevalence of concomitant hypertension and dyslipidemia in women aged 55 to

64 years, compared to women aged 45 to 54 years. The prevalence increased another 9 percent in women aged 65 years and older.⁸ Similarly, in men the prevalence of concomitant hypertension and dyslipidemia increased eight percent from the 45-to-54 year age group to the 55-to-64 year age group—with another nine percent increase after age 65 years.⁸

Racial background also had an impact on prevalence of hypertension and dyslipidemia (see

Exhibit 6: In the United States, Concurrent Hypertension and Dyslipidemia Is Highly Prevalent⁸



- 64% of patients with hypertension (almost 2 out of 3) also have dyslipidemia
- 47% of patients with dyslipidemia (almost 1 out of 2) also have hypertension

Exhibit 7: Majority of Hypertensive Patients Have LDL-C ≥ 100 mg/dL

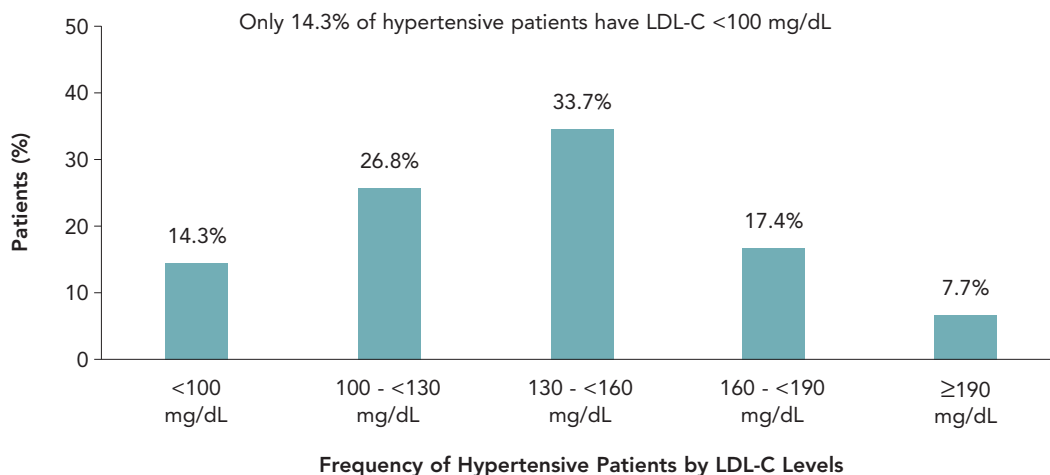


Exhibit 8). An analysis of data from NHANES III showed that the prevalence of hypertension was greater in blacks at every age category than in whites. The greatest disparity in prevalence was in the 40- to 59-year age group⁵, where 50 percent of middle-aged blacks had hypertension, compared with 30 percent of middle-aged whites. The prevalence of dyslipidemia increased with increasing age in both groups,

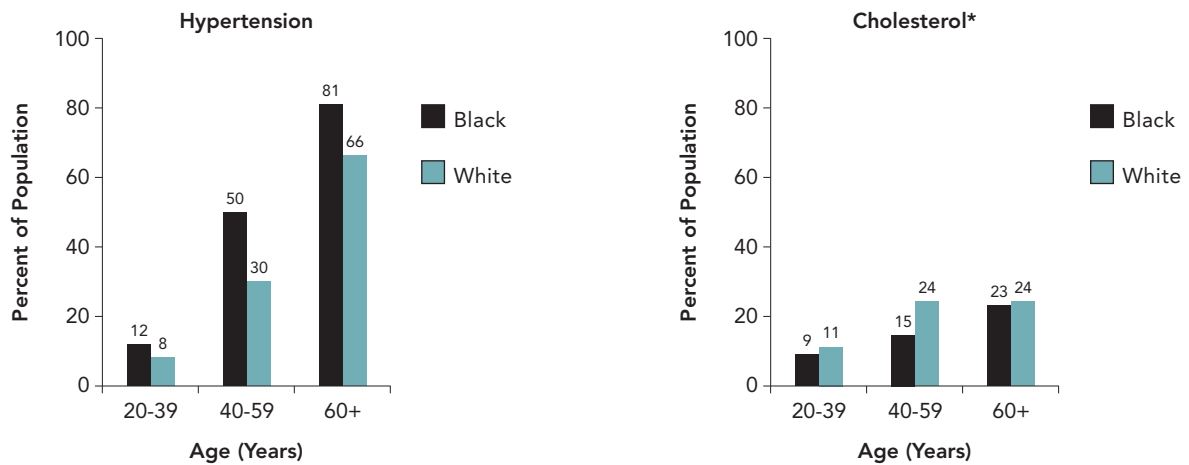
although the differences between the races was not striking.

The Framingham Heart Study data also revealed a continuous relationship between levels of cholesterol and risk of developing CV disease over eight years. This relationship was graded and continuous, and not just confined to the upper centiles.⁹

When multiple risk factors are present, even mildly or moderately

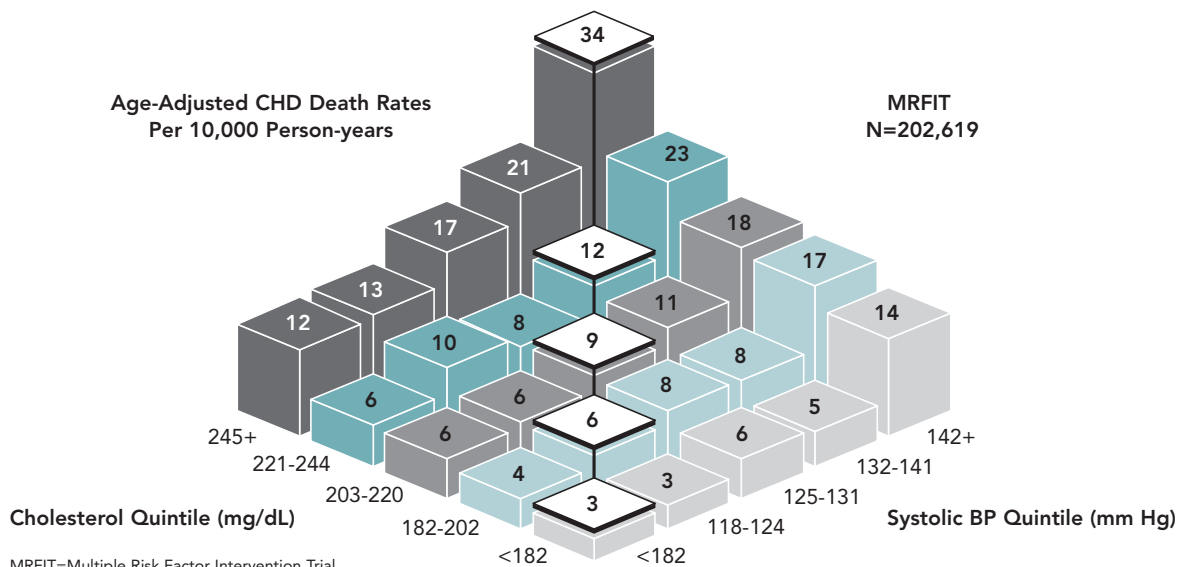
elevated risk factors substantially increase overall risk of CV disease. The Multiple Risk Factor Intervention Trial (MRFIT) showed that moderately elevated blood pressure and lipids impart a risk level similar to that of a severe elevation of either condition alone¹⁰ (see Exhibit 9). For example, an individual with a systolic blood pressure of 135 mmHg and a TC of 230 mg/dL—values that traditionally

Exhibit 8: Prevalence of Hypertension and Dyslipidemia by Race and Age



*Total cholesterol ≥ 240 mg/dL
Pfizer Facts. Racial differences in cardiovascular health findings from the National Health and Nutrition Examination Surveys (NHANES) III and 1999-2000.

Exhibit 9: Impact of Elevated Systolic BP and Total Cholesterol on CHD Mortality—MRFIT¹⁰



haven't been considered for anti-hyper-tensive therapy and lipid-lowering—has a four times greater risk of dying of heart disease than an individual with systolic blood pressure <118 mmHg and a TC <182 mg/dL. By the same token, once the patient is hypertensive, any increase in cholesterol imparts a significant increase in CV risk.

Undertreatment of Blood Pressure and Lipids in Patients With Hypertension

Analyses of NHANES III data on the awareness, treatment, and control of hypertension and hyper-

cholesterolemia showed that neither condition is well controlled in the United States.^{11,12} Although 69 percent of documented hypertensive patients in the U.S. were aware of their hypertension, only 58 percent were treated for hypertension, and only 31 percent had their hypertension controlled as defined by blood pressure <140/90 mm Hg¹¹ (see Exhibit 10).

The evidence also shows that most hypertensive patients with confounding dyslipidemia do not attain both goals.¹³ In fact, as the number of CV risk factors increase, the rate of goal attainment

decreases. Pettitt et al. studied the rate of attainment of systolic blood pressure and lipid goals in a large managed care population of 2.1 million members, aged ≥20 years.¹³ The results showed that <10 percent of hypertensive patients with concomitant dyslipidemia (N=154,235) were at goals for both conditions according to JNC 6 and NCEP ATP III (see Exhibit 11). The rate of goal attainment declined as the number of risk factors increased. Only 2.5 percent of patients who had diabetes mellitus in addition to hypertension and dyslipidemia were at goal for all three conditions.

Exhibit 10: Awareness, Treatment, and Control of Hypertension and Hypercholesterolemia—NHANES 1999-2000^{11,12}

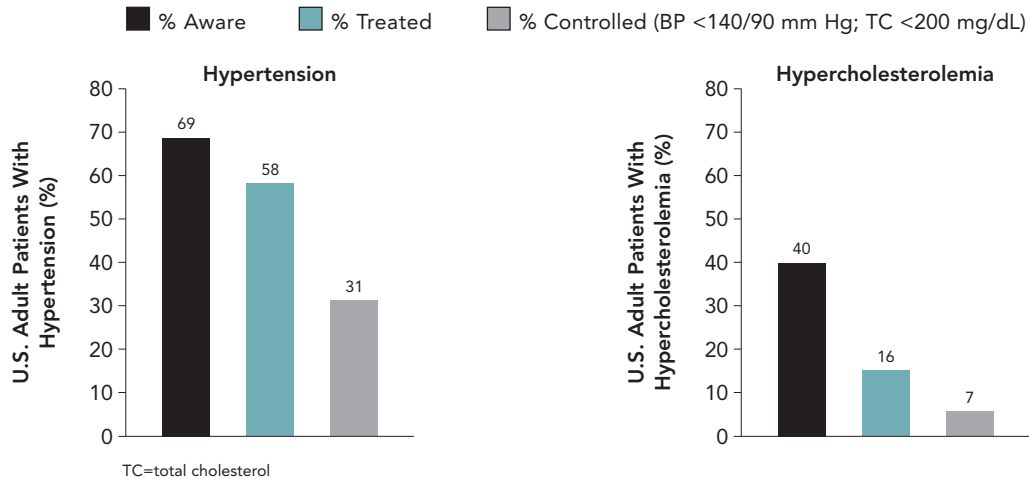
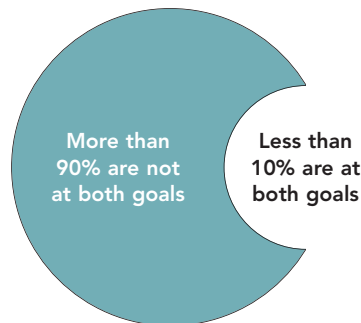


Exhibit 11: Most Patients Diagnosed With Hypertension and Dyslipidemia Are Not at Both Goals¹³

In a managed care population, the vast majority of patients diagnosed with hypertension and dyslipidemia (N=154,235) were not at both goals



As the number of cardiovascular risk factors increased, the rate of goal attainment decreased.

National guidelines now recognize the relationship between hypertension and dyslipidemia. Both JNC 7 and NCEP ATP III have set treatment goals based on overall risk. The JNC 7 recommends assessing a patient's lipid profile when setting appropriate blood pressure treatment goals.¹⁴ The NCEP ATP III recognizes hypertension as a major risk factor that modifies lipid goals.⁴

Evidence of Clinical Benefit by Treating Hypertension

Clinical trials in hypertensive patients have shown that differences in systolic blood pressure account for most of the differences in outcomes. In 2003, Staessen et al. performed a complex meta-analysis of recent evidence, which supported the concept that lower systolic blood pressure is better.¹⁵ The investigators looked at differences in achieved systolic blood pressure and the incidence of total and CV mortality, CV events, stroke, myocardial infarction (MI), and heart failure. The results showed that the degree

of systolic blood pressure reduction largely accounted for differences in CV outcomes, rather than the type of drug used to treat hypertension.

VALUE: Achieving Rapid Blood Pressure Lowering in High-Risk Hypertensive Patients

The importance of achieving rapid blood pressure reduction in hypertensive patients at high CV risk was emphasized in the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial.¹⁶ VALUE was designed primarily to establish the CV benefit of an angiotensin receptor blocker (ARB), valsartan, by comparing it to the calcium channel blocker (CCB), amlodipine, as initial therapy. The VALUE study involved more than 15,000 patients, aged 50 years or older with treated or untreated hypertension and a high risk of cardiac events.

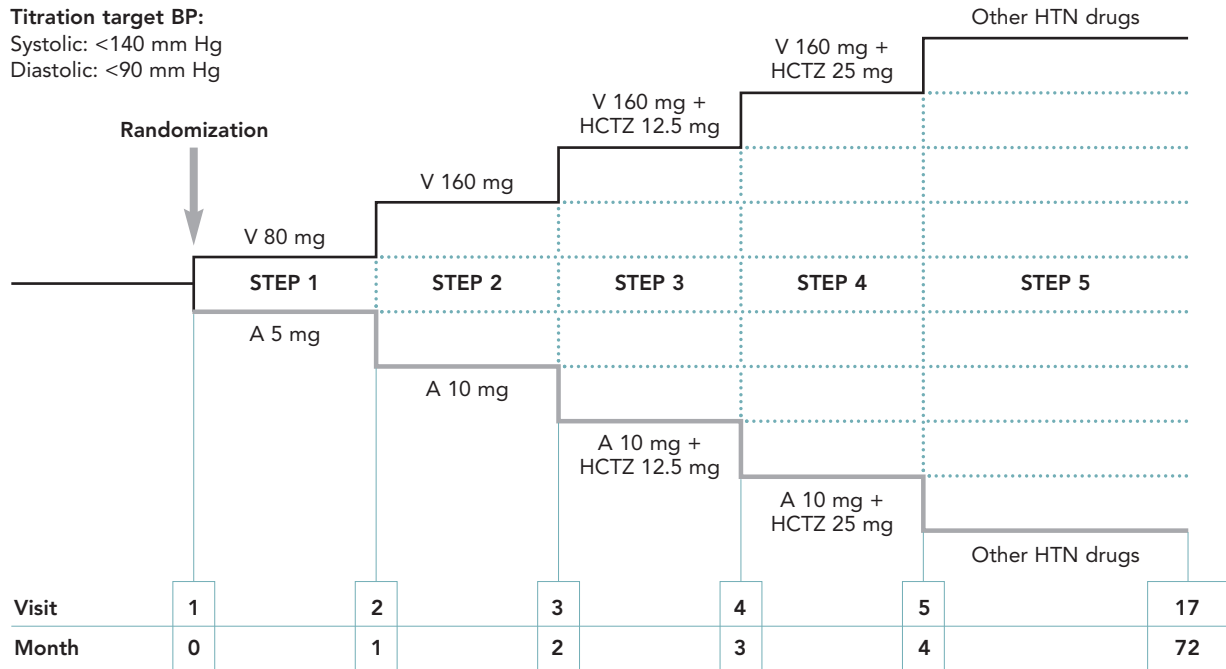
Patients were randomly assigned to amlodipine (5 mg), or valsartan (80 mg), and dose increases were made at monthly intervals for the first four months (see Exhibit 12).

Hydrochlorothiazide (12.5 mg and 25 mg) could be added until the goal blood pressure was reached. If necessary, other drugs (except an ARB or CCB) could be added. The target for blood pressure reduction in the VALUE study was <140/90 mmHg. The primary endpoint was a composite of cardiac mortality and morbidity. Patients were followed up for a mean of 4.2 years.

The results showed no difference in the primary end point between the two therapies. However, when the components of the composite endpoint were examined, the risk of MI was significantly lower among those receiving the amlodipine-based regimen, compared to those in whom valsartan was the initial therapy. This difference in MI was apparent early in the trial. There was also a nonsignificant lower rate of stroke in the amlodipine-assigned group, compared with the valsartan group. The risk for CHF (higher in the amlodipine group) was not significantly different between the two treatment regimens.

Exhibit 12: VALUE–Study Design¹⁶

Titration target BP:
Systolic: <140 mm Hg
Diastolic: <90 mm Hg



V = valsartan; A = amlodipine; HCTZ = hydrochlorothiazide.

For both regimens, there was a significant lowering of blood pressure, both systolic and diastolic, compared to baseline, throughout the trial; however, the effects of the amlodipine-based regimen were more pronounced, especially in the early period. The difference in blood pressure was most striking during the first three months of the study when the drugs were being titrated (see Exhibit 13). This is the time period when the differences in MI between the two groups were also the greatest.

A similar analysis of stroke events showed fewer strokes with amlodipine than with valsartan. Although the difference did not reach statistical significance, the greatest difference was seen in the first three months of therapy, when monotherapy and titration occurred, and when the amlodipine treatment was associated with an earlier and

greater reduction in blood pressure than that observed with valsartan.

In summary, the results of the VALUE trial showed that an amlodipine-based treatment regimen reduced blood pressure, and hence CV events, more rapidly than a valsartan-based treatment regimen. There were fewer CV events when blood pressure was reduced more rapidly.

ASCOT: Role of statins in Reducing Major Cardiovascular Events

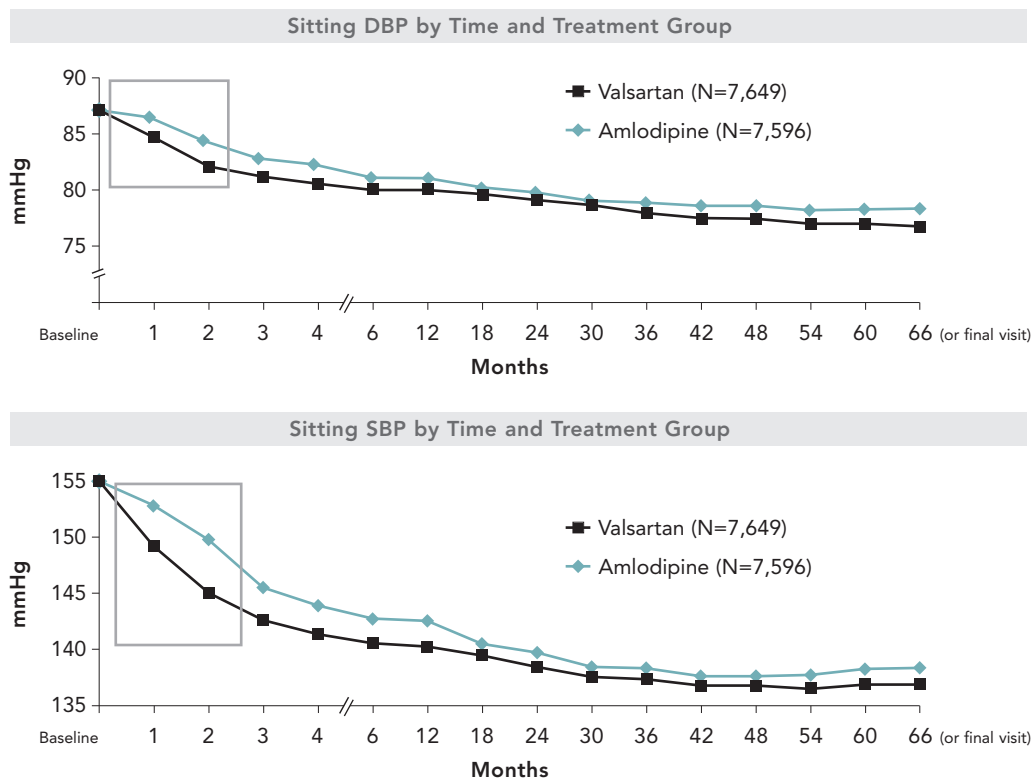
The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was a randomized, multicenter study that evaluated the effects of antihypertensive therapy on cardiac outcomes in 19,342 hypertensive patients with at least three additional risk factors and no history of coronary heart disease (CHD).¹⁷

The trial involved two treatment comparisons in a factorial design. In

the ASCOT-Blood Pressure Lowering Arm (ASCOT-BPLA), all patients were randomized to receive either amlodipine (5 to 10 mg/day ± perindopril, 4 to 8 mg/day) or atenolol (50 to 100 mg/day ± bendroflumethiazide-K+, 1.25 to 2.5 mg/day) in a PROBE fashion. Antihypertensive drug therapy was titrated and add-on therapy with doxazosin gastrointestinal transport system (GITS), 4 to 8 mg/day, was allowed at the third step to achieve blood pressure goals of <140/90 mmHg for nondiabetic patients and <130/80 mmHg for patients with diabetes.

The second treatment comparison, the ASCOT-Lipid Lowering Arm (ASCOT-LLA), included a sub-sample of the hypertensive patients studied in ASCOT-BPLA.¹⁷ Patients (N=10,305) with TC levels 250 mg/dL were randomized to receive atorvastatin calcium 10 mg/day

Exhibit 13: VALUE: More Rapid BP Reduction With Amlodipine¹⁶



"The most consistent and statistically significant difference between the groups was in BP control: amlodipine-based therapy was significantly more efficacious in reducing BP, especially in the early phases of treatment."

(N=5,168) or placebo (N=5,137) in a double-blind fashion. No dosage titration occurred in the lipid-lowering arm of the study. Patients with TC levels >250 mg/dL were not eligible for the lipid-lowering arm of the study and had their lipids managed according to routine practice. The primary end point was a composite of two important and clinically relevant events: fatal CHD and nonfatal MI. For both arms, a five-year planned follow-up was intended.

ASCOT-LLA. In the lipid-lowering arm of ASCOT, 100 percent of patients were hypertensive, as was required for inclusion in ASCOT. Participants were primarily male, older than 55 years of age, and being treated for hypertension. Approximately 33 percent were smokers, 24 percent had type 2 diabetes, and 62 percent had proteinuria as a risk factor. Participants were mainly white (95 percent) and male (81 percent), with a mean age of 63 years. The average number of additional CV risk factors required for inclusion in the trial was 3.7. Baseline blood pressure in both groups was 164/95 mmHg; LDL-C was 133 mg/dL. (Note: The ASCOT-LLA patients had no

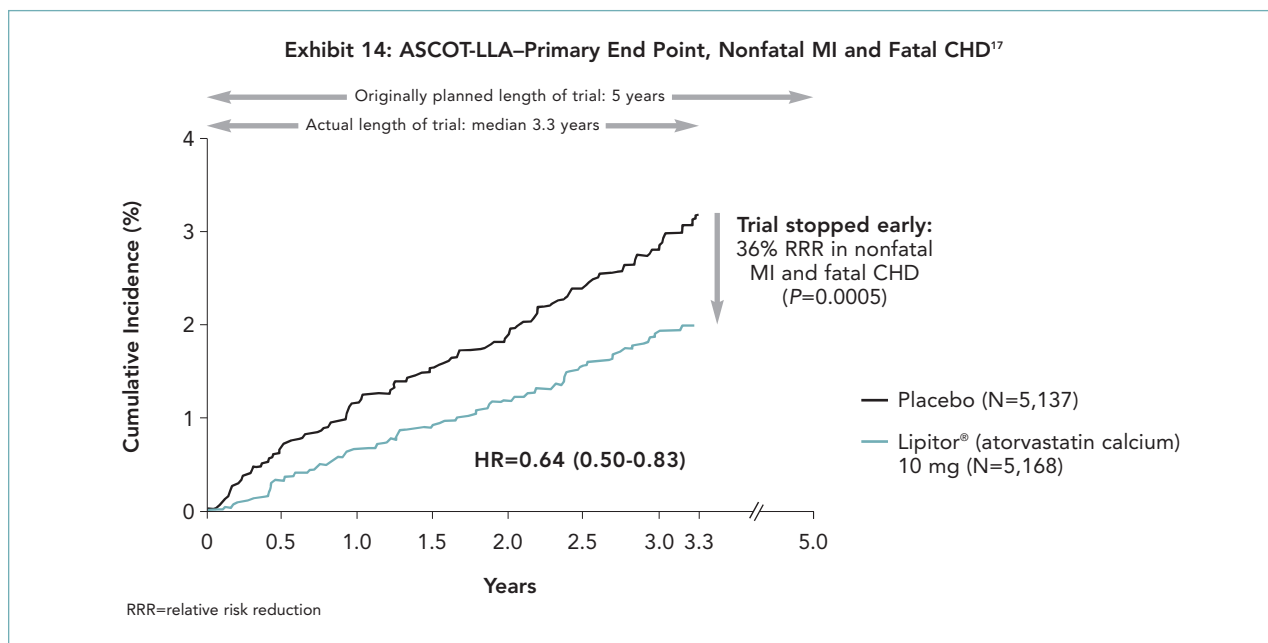
clinically evident CHD and would not traditionally be treated with a lipid-lowering agent. At the time of the study, the mean baseline LDL-C value of 133 mg/dL was not considered dyslipidemic.)

Blood pressure lowering in the two randomized arms (atorvastatin or placebo) was identical. Blood pressure control throughout the trial was similar in the patients assigned to atorvastatin treatment or placebo, with a final mean value of 138/80 mmHg. However, the LDL-C levels were predictably lower in those receiving atorvastatin—a significant 46 mg/dL lower than in the placebo arm at one year, and 38.7 mg/dL lower at three years. The mean LDL-C in the atorvastatin calcium arm was maintained at lower than 100 mg/dL.

Although a five-year follow-up was planned, ASCOT-LLA was stopped at 3.3 years because of the significant reduction in nonfatal MI and fatal CHD in the patients receiving blood pressure treatment and lipid treatment, compared to those who only received blood pressure treatment. The composite primary endpoint was significantly lower by 36 percent ($P=0.0005$) in the atorvastatin group compared

with the placebo group (see Exhibit 14); 100 primary events had occurred in the atorvastatin group compared with 154 events in the placebo group ($P=0.0005$). When comparing the two components of this composite endpoint, atorvastatin reduced the relative risk of nonfatal MI by 45 percent ($P=0.0002$), and the relative risk of fatal CHD by 11 percent (NS). Also, a 27 percent reduction in fatal and nonfatal stroke (89 atorvastatin versus 121 placebo, $P=0.024$) was associated with atorvastatin, making ASCOT-LLA one of the first studies to show that statins can reduce stroke as well.

ASCOT-BPLA. This component of ASCOT was stopped before the planned end of the study because of a significant difference in total mortality in favor of the amlodipine-based regimen. Compared with atenolol/thiazide, amlodipine/perindopril resulted in a reduction of about 15 percent in all-cause mortality ($P\leq 0.005$). For the primary endpoint of nonfatal MI and fatal CHD, there was a nonsignificant reduction of about 10 percent. There were highly significant reductions of about 15 percent for all coronary events ($P\leq 0.005$), 25 percent in fatal and nonfatal stroke



($P \leq 0.001$), 15 percent for all CV events and procedures ($P \leq 0.001$), 25 percent for CV mortality ($P \leq 0.005$), and 30 percent ($P \leq 0.001$) for new-onset diabetes.

Baseline characteristics were not significantly different than those in the lipid-lowering arm; the average blood pressure was 164/95 mmHg, and the average individual had 3.7 risk factors. Overall, blood pressure was lowered by 28/16 mmHg. Early differences in blood pressure were observed between treatment groups, with lower levels in the amlodipine group compared to the atenolol group. Blood pressure differences decreased over time and mean trial differences were 2.9 mmHg systolic and 1.8 mmHg diastolic.

CAMELOT: Amlodipine Reduces CV Events in Patients With CAD

Administration of amlodipine to patients with coronary artery disease (CAD) resulted in reduced adverse CV events, and a slowing of atherosclerosis progression.¹⁸ The CAMELOT (Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis)

trial was a double-blind, randomized, multicenter, 24-month trial that enrolled 1,991 patients with angiographically documented CAD and diastolic blood pressure <100 mmHg. (Not all of the patients in this study were hypertensive.) CAMELOT compared the effects of amlodipine (10 mg) or enalapril (20 mg) versus placebo on CV events in CAD patients to determine whether an ACE inhibitor was more cardioprotective than treatment with the CCB amlodipine. A sub-study of 274 patients measured atherosclerosis progression by intravascular ultrasound (IVUS). The primary endpoint was a composite of CV death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, and new diagnosis of peripheral vascular disease.

Although there were no differences in blood pressure lowering between the two drug treatments, the event rate was lower in the amlodipine group than in

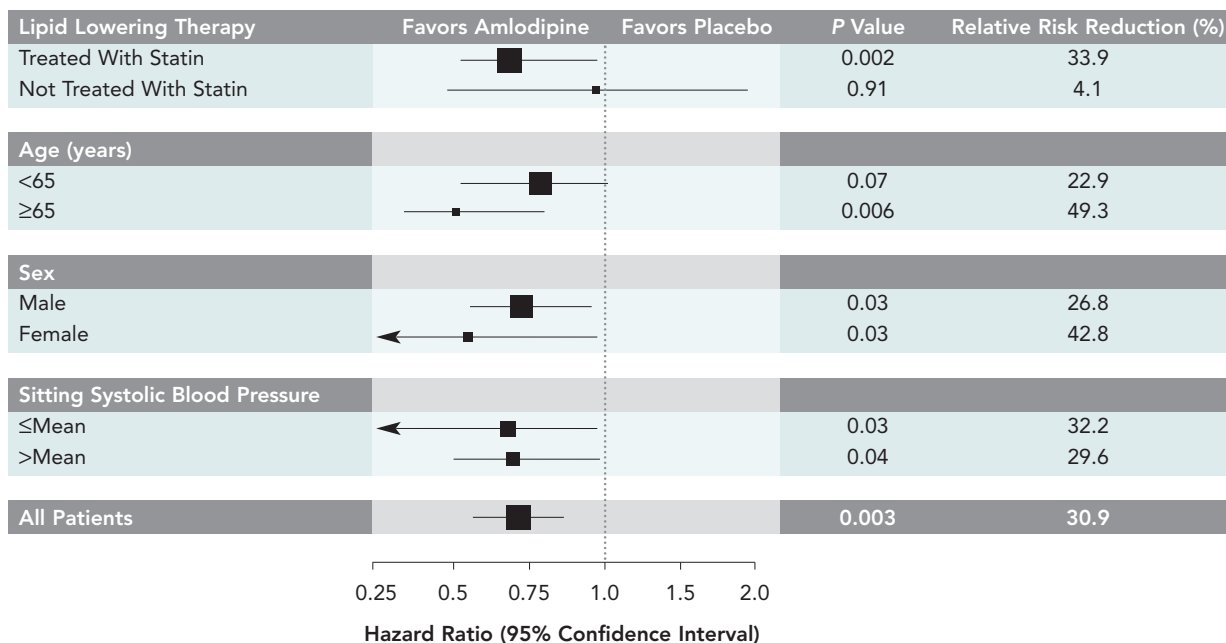
the enalapril group. In subgroup analyses, patients treated with statins improved more if they were receiving amlodipine rather than placebo (see Exhibit 15). Endpoint reduction was independent of age, gender, or sitting blood pressure. The intravascular ultrasound sub-study showed a trend toward regression of atheroma volume as a function of systolic blood pressure reduction (see Exhibit 16). Again, this suggests that amlodipine may slow plaque progression in the coronary arteries of certain patients, which may further contribute to improved outcomes.

In summary, amlodipine provided CV benefits to patients with CAD in addition to effectively and safely reducing blood pressure. The anti-anginal and anti-hypertensive effects of amlodipine may contribute to the reduction in CV events in CAD patients.

The Case for Aggressive LDL-C Lowering in High-Risk Patients

A number of recent studies, outlined below, have shown that

Exhibit 15: CAMELOT—Primary Endpoint in Patient Subgroups¹⁸



statin therapy is of benefit to high-risk patients.

HPS. The Heart Protection Study included more than 20,000 individuals at high risk of CV events due to diabetes, coronary disease, peripheral arterial disease, or other occlusive disease.¹⁹ The addition of simvastatin, 40 mg daily, to existing treatments resulted in an 18 percent reduction in coronary death rate when compared with patients receiving placebo. These benefits were observed regardless of initial LDL-C concentration. The HPS also demonstrated that statin therapy reduced the incidence of ischemic strokes as well as coronary events, even among individuals who did not have high baseline LDL-C levels.²⁰ Therapy with simvastatin resulted in reductions of 24 percent in first stroke, 20 percent in any major vascular event, 23 percent in first coronary event, and 32 percent in first revascularization.

CARDS. The Collaborative Atorvastatin Diabetes Study (CARDS) was the first prospective evaluation

of a statin in a population consisting solely of persons with type 2 diabetes.²¹ In this trial, 2,838 patients with no previous history of CV disease were randomized to placebo or atorvastatin, 10 mg daily. Patients on statin therapy had reductions of 37 percent in major CV events ($P=0.001$), including a 36 percent reduction in acute CHD, a 31 percent reduction in coronary revascularization, a 48 percent reduction in stroke, and a 27 percent reduction in deaths. The trial was terminated two years earlier than expected because the pre-specified early stopping rule for efficacy had been met.

NCEP ATP III. The latest update to the NCEP ATP III guidelines now call for more aggressive approaches in treating dyslipidemia, based on the findings of major clinical trials of statin therapy.²² These guidelines recommend that the LDL-C treatment goal remain at <100 mg/dL for high-risk patients. However, a target of <70 mg/dL is considered a reasonable clinical strategy for patients at very high risk.

The argument for aggressive

statin therapy is strengthened further by the findings of beneficial statin effects beyond lowering LDL-C levels. Some of the reported cholesterol-independent or “pleiotropic” effects of statins include improved endothelial function, enhanced stability of atherosclerotic plaques, decreased oxidative stress and inflammation, and inhibition of the thrombogenic response²³ (see Exhibit 17). Data on the anti-inflammatory effects of statins demonstrate that higher doses of statins lower high-sensitivity C-reactive protein (hs-CRP), an anti-inflammatory marker that correlates with risk reduction of CV disease and with lower levels of LDL-C. Although an LDL-C goal of 130 mg/dL can be reached with less aggressive statin doses, these lower doses have little effect on hs-CRP, thus leaving some vascular risk potentially untreated.

Several recent studies have evaluated a regimen of aggressive statin therapy compared with a lower-dose statin regimen:

REVERSAL. The Reversal of

Exhibit 16: CAMELOT-IVUS Results, Reduction in SBP and Atheroma Volume¹⁸

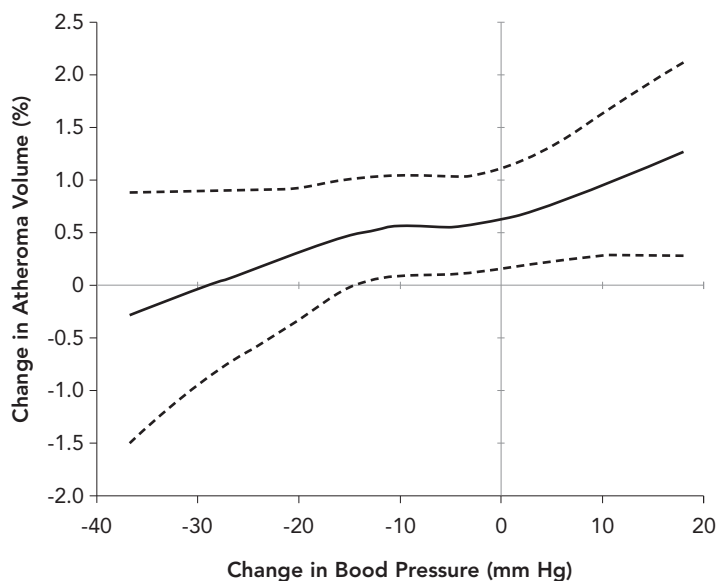
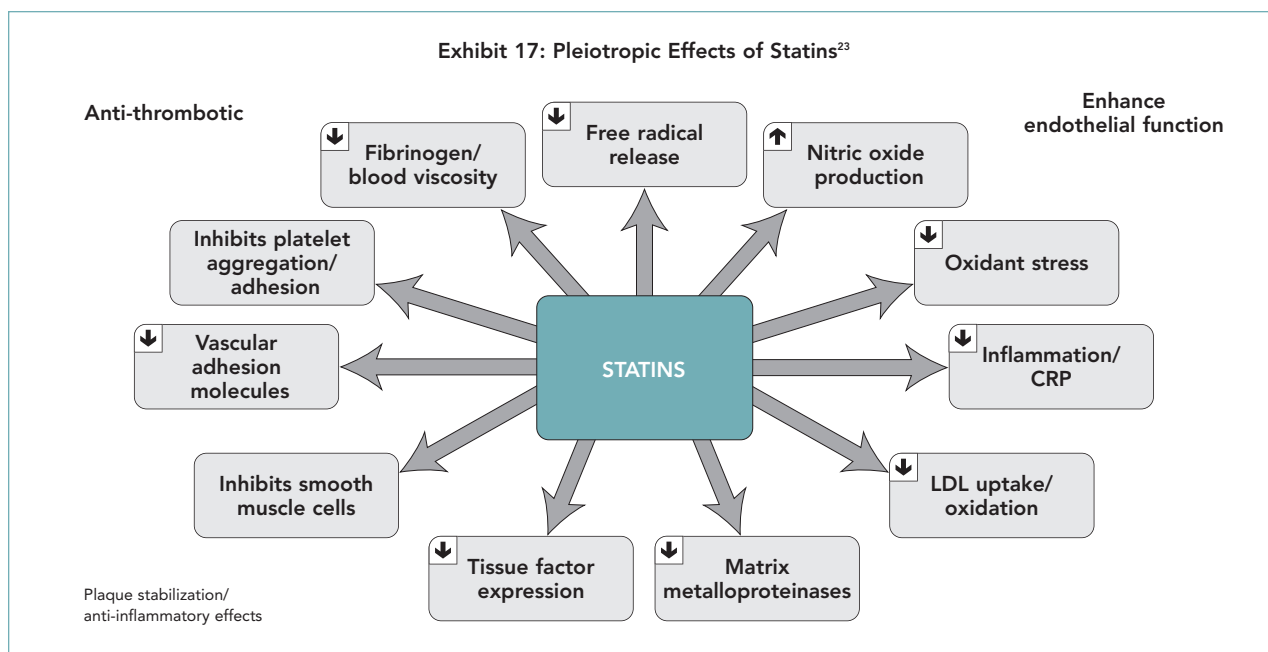


Exhibit 17: Pleiotropic Effects of Statins²³



Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial examined the effects of moderate versus intensive lipid lowering on coronary artery atheroma burden and progression, as measured by intravascular ultrasound.²⁴ In this study, 654 patients with coronary heart disease were randomized to intensive lipid lowering with atorvastatin (80 mg daily) versus a moderate lipid-lowering regimen with pravastatin (40 mg daily) administered for 18 months. Compared with baseline values, patients treated with atorvastatin had no change in atheroma burden; those treated with the less intensive pravastatin therapy showed progression of coronary atherosclerosis (2.7 percent; $P=0.001$). Both the change in LDL-C and the change in hs-CRP were significantly correlated with the change in atheroma volume. Thus, it appears that optimal anti-atherosclerotic effects result not just from reduction of LDL-C but also from the reduction of LDL-C and inflammation.

PROVE IT-TIMI 22. Aggressive lipid lowering with 80 mg per day of atorvastatin provided more protection from death and CV events

than less aggressive statin therapy with 40 mg per day of pravastatin, as shown by the results of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 trial. This study included 4,000 patients recently hospitalized with acute coronary syndromes.²⁵ The results demonstrated a statistically significant benefit of the more intensive statin treatment, with a 16 percent reduction in the risk of death and major CV events. This benefit emerged as early as 30 days and was consistent over the subsequent two years following an acute coronary syndrome. The median LDL-C level achieved during treatment was 95 mg/dL in the standard-dose pravastatin group and 62 mg/dL in the high-dose atorvastatin group ($P<0.001$).

In a recent analysis of the PROVE-IT TIMI 22 data, Ridker et al. demonstrated that patients who had low hs-CRP levels after statin therapy had better clinical outcomes than those with higher hs-CRP levels, regardless of their LDL-C levels. Exhibit 18 shows combined data of the cumulative incidence of recurrent MI or death from coronary causes, according to

the achieved levels of both LDL-C and hs-CRP. This suggests that strategies to lower CV risk with statins should include monitoring of hs-CRP as well as cholesterol.

TNT. The Treating to New Targets (TNT) study assessed the efficacy and safety of lowering LDL-C levels below 100 mg/dL in patients with stable CHD.²⁶ In this trial, aggressive lipid lowering with 80 mg per day of atorvastatin provided greater protection from major CV events than treatment with 10 mg of atorvastatin per day in stable CHD patients. A primary event occurred in 8.7 percent of patients receiving 80 mg of atorvastatin, as compared with 10.9 percent receiving 10 mg of atorvastatin. This represented an absolute reduction in the rate of major CV events of 2.2 percent, and a 22 percent relative reduction in risk ($P<0.001$). A consistent and significant benefit of intensive therapy was observed on most measures of CHD-related morbidity and mortality and cerebrovascular events (see Exhibit 19).

IDEAL. Intensive lipid-lowering therapy was studied further in another recently published trial, the Incremental Decrease in End

Exhibit 18: Effect of LDL Lowering and CRP Reduction on Outcomes After ACS

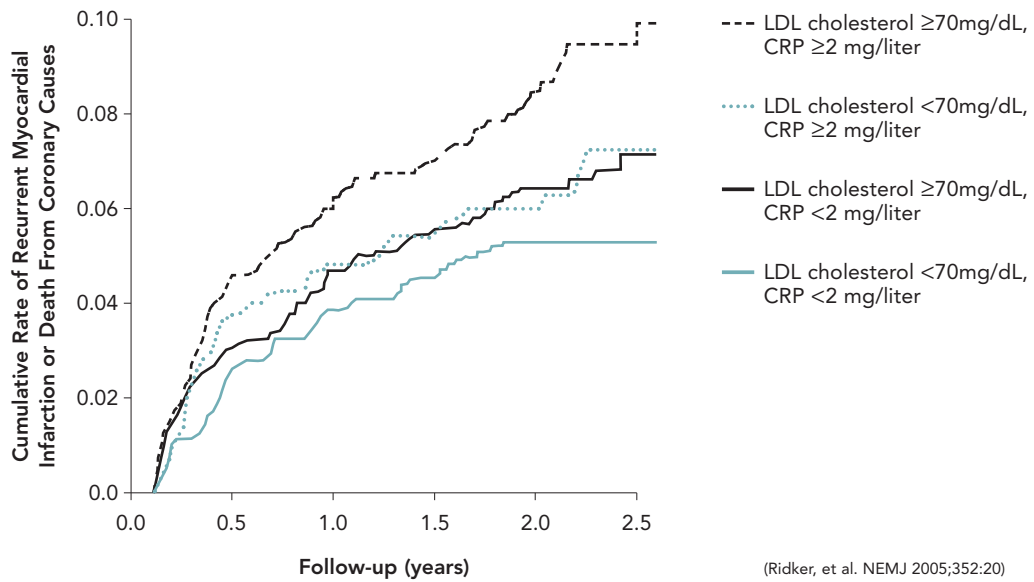
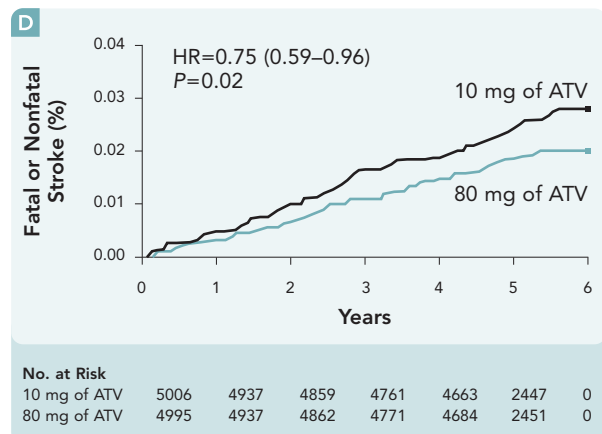
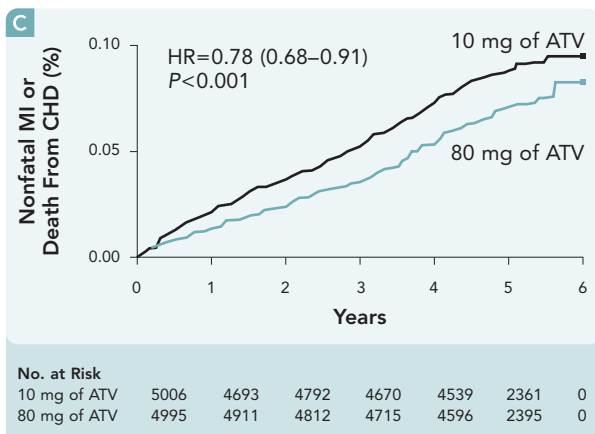
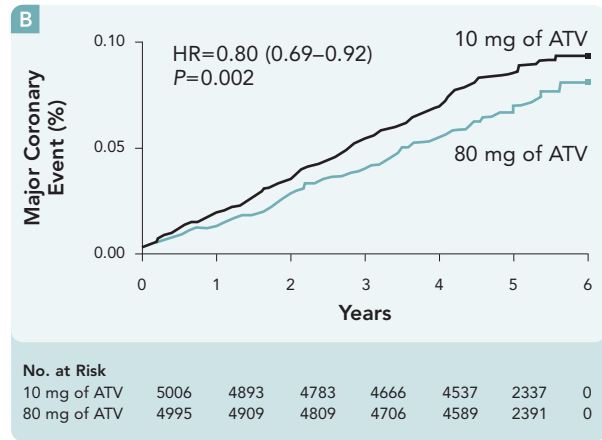
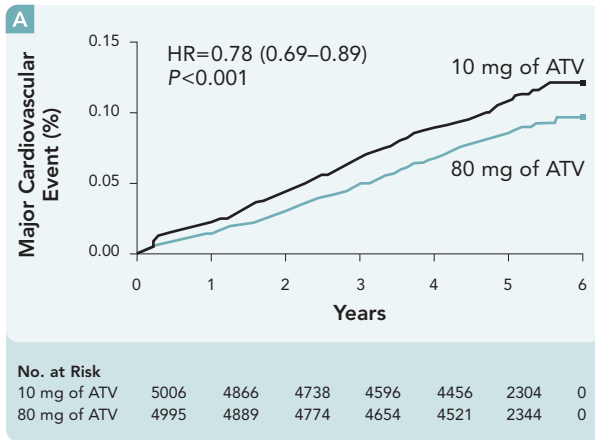


Exhibit 19: TNT Trial—Risk Reduction With Intensive Statin Therapy



Points Through Aggressive Lipid Lowering (IDEAL) trial.²⁷ IDEAL compared atorvastatin, 80 mg/d, with simvastatin 20 to 40 mg/d, in 888 patients ≤80 years with a history of MI. Intensive lowering of LDL-C did not result in a significant reduction in the primary outcome of major coronary events (9.3 percent in the atorvastatin group versus 10.4 percent in the simvastatin group). However, the more intensive therapy reduced the risk of other composite secondary endpoints and nonfatal acute MI. There were no differences in CV or all-cause mortality; the primary differences were in the nonfatal end points. The investigators concluded that patients with MI may benefit from intensive lowering of LDL-C without an increase in non-CV mortality or other serious adverse reactions.

In summary, clinical evidence supports the use of aggressive statin therapy rather than more cautious statin therapy.

Cardiovascular Drug Adherence

Numerous clinical trials have

concluded that antihypertensive and lipid-lowering therapy reduces the risk of CV disease of patients at risk. However, to achieve the greatest benefit, long-term adherence to prescribed drug therapy is essential. In hypertensive patients with concomitant dyslipidemia, adherence with concomitant therapy is especially critical.

To better understand the patterns and predictors of adherence, Claxton et al. reviewed 76 studies to examine associations between dose frequency and medication compliance (measured by electronic monitoring devices). For patients with hypertension, mean dose-taking compliance was about 73 percent and declined as the number of daily doses increased.²⁸

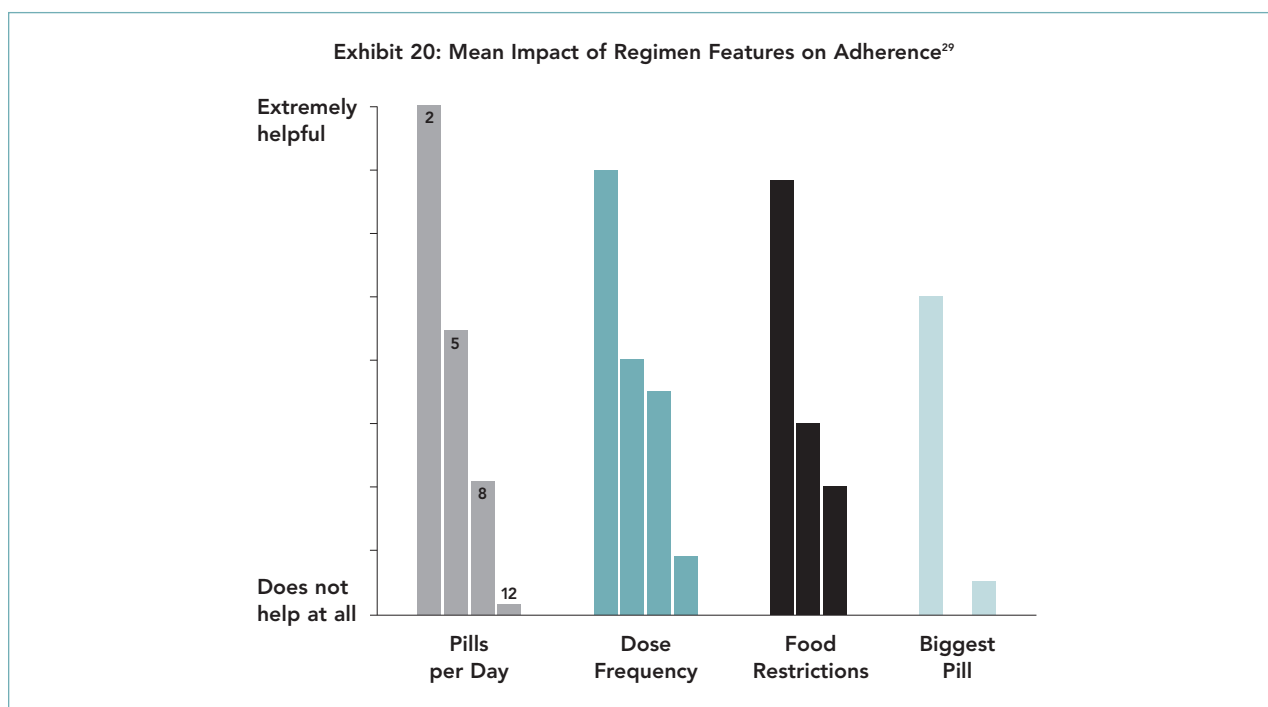
The number of pills taken per day has been found to strongly correlate with adherence (see Exhibit 20). Patients most often prefer a once-daily regimen that has no food restrictions and is reasonably easy to follow.²⁹ This finding is particularly true in patients with hypertension since these patients frequently require multiple drugs due to co-morbidities

or uncontrolled hypertension.

A retrospective cohort study examined the patterns and predictors of adherence with concomitant antihypertensive and lipid-lowering therapy in a managed care population (N=8,406).³⁰ The results showed that when patients initiated antihypertensive and lipid-lowering therapy within 90 days of each other, they were less likely to refill their antihypertensive and lipid-lowering prescriptions as their total number of prescriptions increased.³⁰ Compared to patients with six or more prescription medications, those with three to five medications were 23 percent more likely to refill their antihypertensive and lipid-lowering therapies. Those with two additional medications were 30 percent more likely to refill their prescriptions, and those with one additional medication were 61 percent more likely to refill.

Metabolic Syndrome

Hypertensive patients with the metabolic syndrome, a clustering of metabolic disorders, have a marked increase in risk for CV disease. The metabolic syndrome, a



predisposing factor to the development of type 2 diabetes mellitus, is closely linked to insulin resistance, a disorder in which the normal actions of insulin are impaired. The other components of the metabolic syndrome include obesity (especially abdominal obesity), atherogenic dyslipidemia, elevated blood pressure, and a prethrombotic state. All of these factors impact the endothelium, now widely believed to play a crucial role in maintaining vascular function. Endothelial dysfunction results in a number of events that give rise to atherogenesis and increased CV risk.

The metabolic syndrome is present in about 23.7 percent of the U.S. adult population—an estimated 47.7 million adults.³¹ Hypertension and dyslipidemia are common in the majority of metabolic syndrome patients.

Increased awareness of the diagnosis of metabolic syndrome can lead to the identification of additional CV risk factors in high-risk patients. The NCEP ATP III has proposed a definition of the metabolic syndrome that only requires readily available clinical variables. The diagnosis of metabolic syndrome is made when three or more of the following risk determinants are present:

- Increased waist circumference (>40 in. for men; >35 in. for women)
- Elevated triglycerides (≥ 150 mg/dL)
- Low HDL-C (<40 mg/dL for men; <50 mg/dL for women)
- Elevated blood pressure ($\geq 130/85$ mmHg)
- Elevated fasting glucose (≥ 100 mg/dL)

These determinants are easily measured in clinical practice, and can readily identify patients at excess CV risk. Drug therapy may be necessary in many patients to achieve recommended goals in controlling lipids, blood pressure, and glucose, and to reduce the risk of thrombosis.

Consensus and Recommendations

Following the panel discussion, a number of consensus points emerged:

Multiple risk factors greatly increase risk of CV disease. When multiple risk factors coexist, even mildly or moderately elevated risk factors substantially increase the overall risk of CV disease. Most CV events occur in patients with modest abnormalities and more than one CV risk factor. The concurrence of hypertension and dyslipidemia increases the risk of CV disease more than the sum of the risks associated with each factor alone.³

Dyslipidemia is common in hypertensive patients. Almost two out of three hypertensive patients have concurrent dyslipidemia, and almost one out of two patients with dyslipidemia also have hypertension.⁵ These two CV risk factors co-exist in an estimated 15 percent of the U.S. population. The magnitude of the hypertension/dyslipidemia problem is significant, and contributes to a considerable CV disease burden.

Hypertension/dyslipidemia is severely undertreated. Although dyslipidemia is highly prevalent in hypertensive adults, fewer than one-third of hypertensive adults with dyslipidemia are receiving treatment with lipid-regulating drugs, and fewer than half of those treated achieve recommended goals.³² About nine of 10 dyslipidemic hypertensive adults have untreated or undertreated dyslipidemia.³² The rate of goal attainment declines as the number of risk factors increase.

Recommendations

1. Identify and treat multiple risk factors. Many CV risk factors remain undetected and untreated. Clearly, many cases of CV disease can be prevented by identifying modifiable risk factors and treating or controlling them. Even small reductions in blood

pressure and cholesterol levels could reduce the substantial CV disease burden. Risk should be viewed not as a particular “level” but as a continuous spectrum.

Multiple factors often cluster in individual patients, significantly increasing CV risk. As a general rule, when hypertension or dyslipidemia is diagnosed, test for the other condition—as well as for other CV risk factors using the simple criteria described for diagnosing the metabolic syndrome. Just the presence of hypertension can be considered an indicator of other possible risk factors, particularly dyslipidemia.

Managing *all risk factors* is critical for CV risk reduction. The national guidelines recommend drug treatment of hypertensive patients with concurrent dyslipidemia. Lowering both blood pressure and LDL-C result in the best outcomes. Even hypertensive patients with “normal” lipids will benefit from lowering lipid levels. Essentially, there should be a good reason not to prescribe a statin for hypertensive patients, completely independent of their blood lipid levels.

2. Treat aggressively. Hypertensive patients need aggressive treatment for both blood pressure and lipids to truly decrease CV risk. Aggressive blood pressure and cholesterol lowering is necessary for optimal risk reduction. Start intensive blood pressure lowering early to improve outcomes; most patients with hypertension require more than one antihypertensive medication to gain control. Clinical evidence has shown improved outcomes with the use of aggressive LDL-C lowering in high-risk patients. The argument for aggressive statin therapy is strengthened by the findings of beneficial statin effects beyond lowering LDL-C levels. Again, there should be a good reason not to start a statin in hypertensive patients.

3. Lower is better. In hypertensive patients, multiple medications are

needed for early and aggressive control of blood pressure and lipids. Many clinical trials indicate that lower target goals are better for both blood pressure and LDL-C. The newer trials have focused on shifting the goals downward, so an important point to note is that target levels for blood pressure cholesterol are different now than they were even 10 years ago.

4. Simplify therapy. Long-term adherence to prescribed drug therapy is essential for hypertensive patients with confounding dyslipidemia. Physicians may be able to significantly improve adherence by giving instructions as carefully and slowly as needed, and repeating them if necessary. Since adherence improves as the number of pills decrease, new therapies that lower blood pressure and LDL-C with a single pill are a reasonable option. Reducing pill burden is particularly helpful for patients with hypertension since these patients frequently require multiple drugs due to co-morbidities or uncontrolled hypertension. **JMCM**

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INSTRUCTIONS

1. Read the monograph.
2. Complete the post test and mark your answers on the provided answer sheet (or make a copy).
3. Send completed post test and evaluation to: CME Department, NAMCP, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060, or by fax to 804-747-5316.
4. You will receive your certificate within three weeks of receipt. Certificates will be sent via e-mail unless otherwise noted. Please contact Ann Patrick or Katie Eads at 804-527-1905 with any questions.

Note: There is only one correct answer for each question.

1. Unlike all risk factors of cardiovascular disease, hypertension and dyslipidemia are controllable through medical interventions.

- a. True
- b. False

2. Low blood pressure is the major risk factor for premature cardiovascular disease.

- a. True
- b. False

3. According to the National Health and Nutrition Examination Survey, 32 percent of the U.S. population has hypertension, and 50 percent has elevated total cholesterol.

- a. True
- b. False

4. The prevalence of hypertension decreases for white males as they age.

- a. True
- b. False

5. Typically, both men and women have age-related increases in hypertension and dyslipidemia.

- a. True
- b. False

6. Only 35 percent of treated hypertensive patients reach treatment goal of <140/90 mm Hg.

- a. True
- b. False

7. Clinical results have shown that the degree of systolic blood pressure reduction did not account for differences in cardiovascular outcomes.

- a. True
- b. False

8. The VALUE trial showed fewer cardiovascular events when blood pressure was reduced more rapidly.

- a. True
- b. False

9. ASCOT-LLA was stopped at 4.5 years due to the reduction in nonfatal MI and fatal CHD in those patients receiving blood pressure and lipid treatment.

- a. True
- b. False

10. Reported cholesterol-independent effects of statins include:

- a. Improved endothelial function
- b. Enhanced stability of atherosclerotic plaques
- c. Decreased oxidative stress and inflammation
- d. Inhibition of the thrombogenic response
- e. All of the above

11. Adherence of concomitant therapy for hypertension and dyslipidemia is especially critical.

- a. True
- b. False

12. Endothelial dysfunction plays no role in the rise of atherogenesis and increased cardiovascular risk.

- a. True
- b. False

13. Hypertension and dyslipidemia are common factors in metabolic syndrome patients.

- a. True
- b. False

14. Consensus recommendations include

- a. Identify and treat multiple risk factors
- b. Treatment does not need to be aggressive
- c. Lower blood pressure and LDL-C is better
- d. Simplify therapy to increase adherence
- e. A, C, D
- f. B, C, D
- g. A, B, C, D

ANSWER SHEET

There is only one correct answer per question.
Circle your answers clearly.

- | | |
|--------|-------------------|
| 1. a b | 8. a b |
| 2. a b | 9. a b |
| 3. a b | 10. a b c d e |
| 4. a b | 11. a b |
| 5. a b | 12. a b |
| 6. a b | 13. a b |
| 7. a b | 14. a b c d e f g |

ACTIVITY EVALUATION

1. Please evaluate this activity based on the following scale:

4 Excellent 3 Good 2 Fair 1 Poor

Conducive method of learning

4 3 2 1

Content was understandable

4 3 2 1

Content was without commercial bias

4 3 2 1

Activity met my expectations

4 3 2 1

Activity met the learning objectives

4 3 2 1

2. My practice patterns will change:

Yes No

3. What is one learned item from this activity?

4. What other topics interest you?

For accurate CME records, all contact information is required.

Name: _____

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