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New Frontiers in CVD Risk Management Supporting Early Aggressive Therapy

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- Recent clinical evidence providing treatment strategies for patients at high risk of developing cardiovascular disease, including hypertension, dyslipidemia, and type 2 diabetes

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New Frontiers in CVD Risk

Introduction

Great advances have been made in the identification and validation of risk factors for cardiovascular disease (CVD) since the term was first used in the early 1960s to describe findings from the Framingham Study.[1] The list of traditional risk factors (eg, blood pressure [BP] smoking, hypertension, hyperlipidemia) and physical signs (eg, obesity, body mass index, ankle-branchial index) of disease have been augmented by an assortment of novel plasma-based and imaging-based biomarkers (Table 1).[1] Pulse pressure,[2] arterial compliance,[3] and genes linked to coronary heart disease[4] may be added to this armamentarium.

Further elucidation of novel biological mechanisms is required, and their application into clinical practice needs to be validated in large-cohort studies. Early findings suggest that, independently or in combination, many of these biomarkers may impact the etiology and course of CVD (Figure 1).[5]

Assessment of cardiovascular (CV) risk is still primarily based on traditional risk factors; further work is needed to determine whether biomarkers such as C-reactive protein (CRP) and interleukin-6 add significant prognostic information to risk scores based on the Framingham Heart Study and other research findings. However, recent data are increasing our understanding of biological pathways that link the newer biomarkers to these traditional factors. For example, adaptations to the shear stress on the surface of the endothelium stimulate a myriad of anti-inflammatory and anti-atherosclerotic effects, the molecular details of which are still being elucidated.[6] The ultimate goal of CVD risk factor and biomarker studies is to clarify the connection between the measurable marker and its part in the biological cascade of events that leads to CVD so that a therapy to treat it or an intervention to prevent its initial trigger can be developed.

Emerging concepts in the etiology of CVD and their relevance to clinical practice provide important information on new combination regimens that target multiple pathways of risk. This monograph discusses recently published results from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and related trials in the context of hypertension and dyslipidemia. These trials test the utility of treating patients with defined risk factors for CVD with agents that treat multiple mechanisms involved in this disease.

Mechanisms of Action: Emerging Concepts

Evidence suggests that dyslipidemia contributes to hypertension via mechanisms such as decreased nitric oxide (NO) bioavailability and activation of the renin-angiotensin-aldosterone system (RAAS).[7] Conversely, pressure-induced distension of arterial vessel walls may increase accumulation of lipoproteins in the vascular wall.

Given the interaction of these high-prevalence risk factors in the etiology and course of CVD, agents that act on dual mechanisms of action may provide both independent and synergistic effects.

Pleiotropic effects: In addition to their ability to inhibit cholesterol biosynthesis, statins have cholesterol-independent or pleiotropic effects (Figure 2).[8] Similarly, ACE inhibitors, angiotensin II type-1 (AT_1) receptor blockers (ARBs), and L-type calcium channel blockers (CCBs) have multiple effects that may result in vascular protection beyond direct BP lowering (Figure 3).[9-11] Thus, statins and antihypertensive agents appear to have a variety of effects that suggest potential advantages with their early combined use in patients with CV risk factors.

Additive effects of agents used in combination: Besides having single-agent pleiotropic effects on CVD, statins and CCBs appear to also act synergistically in some of these alternate pathways. A study of hypertensive, hypercholesterolemic patients (low-density lipoprotein cholesterol [LDL-C] levels >150 mg/dL) showed that atorvastatin had an additive effect to amlodipine in improving small arterial compliance.[12]

Results of a study in hypercholesterolemic, hypertensive patients with impaired fibrinolysis (due to insulin resistance) demonstrated additive effects of atorvastatin plus amlodipine on fibrinolytic balance. Compared with either agent alone, the combination had a greater effect on decreasing plasminogen activator inhibitor type 1 (PAI-1) activity as well as systolic and diastolic BP levels.[13] In dyslipidemic patients (mean LDL-C, 164 mg/dL) addition of an ACE inhibitor (ramipril) to statin therapy (simvastatin) resulted in additional improvement in endothelial function.[14]

Table 1. Emerging Biomarkers for CVD

Source	Characteristic	Examples
Plasma	Lipids	Lipoprotein(a), ApoA, ApoB, particle size/density
	Inflammation	High-sensitivity CRP, serum amyloid A, IL-6, IL-18, tumor necrosis factor, cell adhesion molecules, CD40 ligand, myeloperoxidase, colony stimulating factor
	Hemostasis/ Thrombosis	Homocysteine, tPA/PAI-1 thrombin activatable fibrinolysis inhibitor, fibrinogen, D-dimer
	Oxidation	Oxidized LDL, glutathione
Genome	All of the above	Multiple polymorphisims currently identified
Imaging	Noninvasive	Carotid IMT, coronary calcification, magnetic resonance imaging angiography
	Invasive	Coronary angiography, intravascular ultrasound

Apo = apolipoprotein; CRP = C-reactive protein; IL = interleukin; IMT = intimal-medial thickening; tPA = tissue plasminogen activator

Adapted[1]

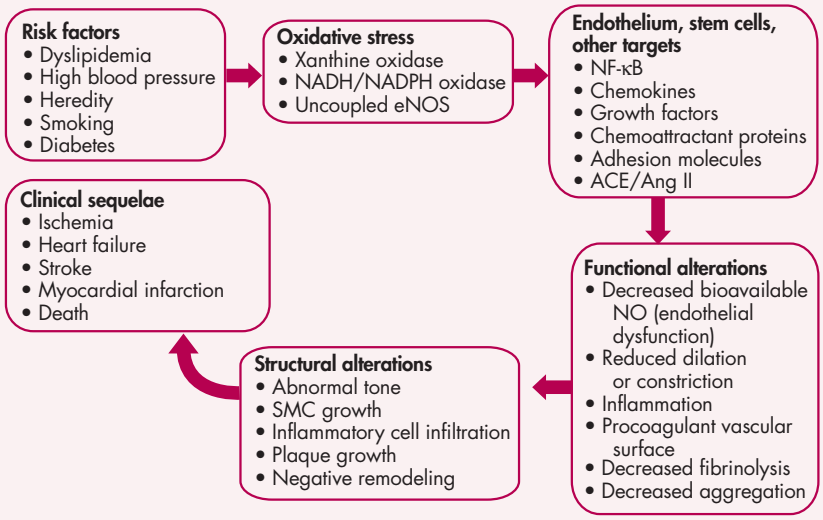

Figure 1. A model of vascular disease pathophysiology. Adapted.[5]

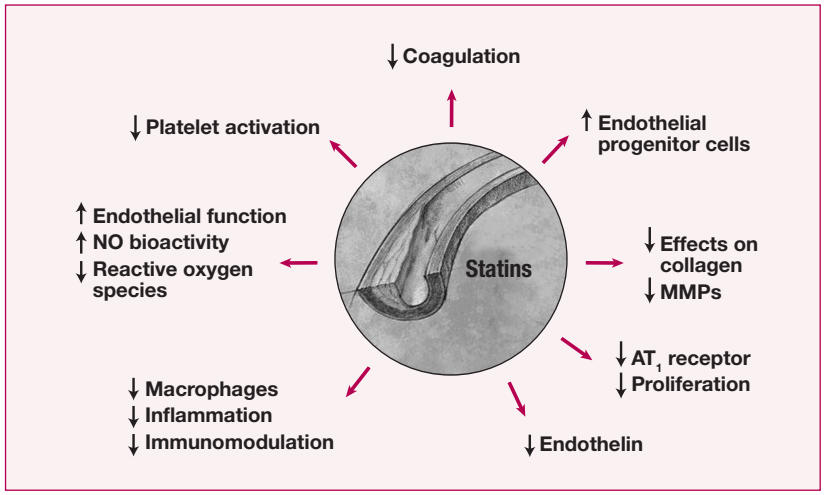

Figure 2. Some pleiotropic effects of statins. The mevalonate pathway is involved in activation of a number of enzyme systems, thus inhibition of HMG-CoA reductase has implications beyond reduction in cholesterol synthesis. A number of cholesterol-independent, pleiotropic effects have been demonstrated in clinical and experimental studies. Accumulating evidence suggests that some of the pleiotropic effects may contribute to the mechanism of benefit in clinical outcome trials of statins. MMP = matrix metalloproteinase.[8]

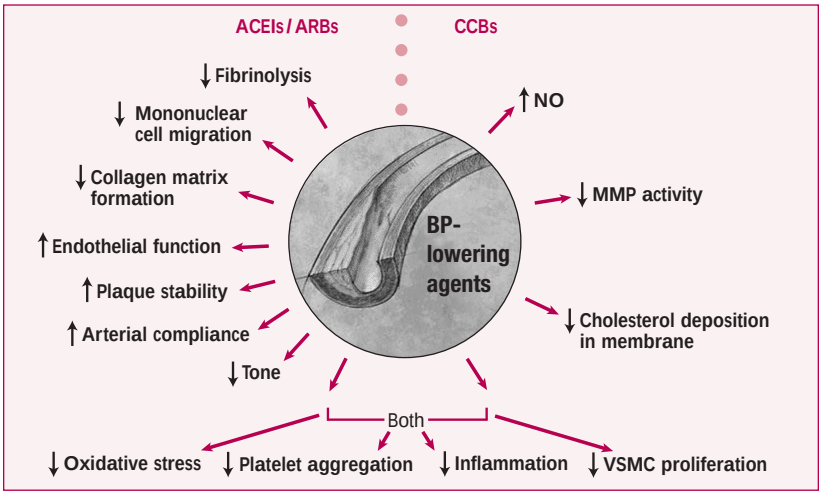

Figure 3. Some pleiotropic effects of ACEIs/ARBs and CCBs. ACE inhibitors (ACEIs) and more recently angiotensin receptor blockers (ARBs) have shown many vasculoprotective effects. Evidence is also emerging that CCBs have effects on vascular biology independent of their interaction with L-type calcium channels. Thus, new data indicate that these antihypertensive agents have effects on renin-angiotensin-aldosterone system (RAAS) modulation and calcium channel blockade that extend beyond BP reduction. VSMC = vascular smooth muscle cell. Adapted.[9-11]

Increased understanding of the pleiotropic mechanisms of action of BP-lowering agents and statins suggests that these agents might have multiple beneficial effects on CVD. Results of recent trials provide evidence of clinical benefit to patients derived from emerging concepts in the etiology of this complex disease and the mechanisms of action of lipid- and BP-lowering agents.

Statins and antihypertensive agents appear to have a variety of effects that suggest potential advantages with their early combined use in patients with certain risk factors.

ASCOT: Lipid and BP Lowering Confers Early Protection from Heart Disease

ASCOT-LLA: Results from the ASCOT–Lipid Lowering Arm (ASCOT-LLA) trial demonstrated the early beneficial effects of lipid lowering in hypertensive patients with only moderately elevated LDL-C (mean, 133 mg/dL).[15] Compared with placebo, cholesterol lowering with atorvastatin 10 mg led to a 36% reduction in fatal coronary heart disease (CHD) and nonfatal myocardial infarction (MI) in 10,305 hypertensive patients (Figure 4). The beneficial treatment effects were already evident at 1 year when total cholesterol and calculated LDL-C were 24% and 35% lower in the atorvastatin group vs placebo, while BP levels were similar in both groups. The trial was stopped at 3.3 years' follow-up instead of the planned 5 years due to the early emergence of significant benefits on the

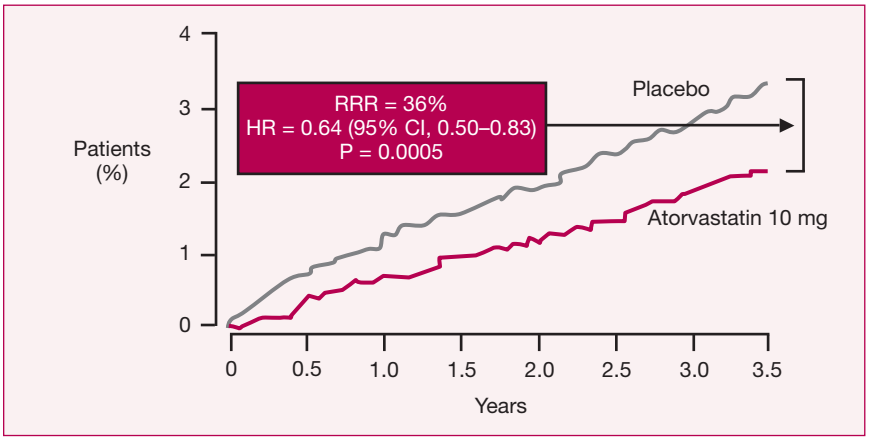

Figure 4. ASCOT-LLA: Reduction in CV events with lipid lowering in hypertensive patients. Note the early separation of the survival curves.[15]

primary and many secondary outcomes. Patients with and without renal dysfunction benefited from atorvastatin treatment.[15]

A later analysis of these data indicate that relative risk reductions in coronary artery disease (CAD) events for atorvastatin compared with placebo became apparent at 30 days and significantly different at 3 months.[16] Risk reduction in stroke also became apparent at 30 days. These data suggest different mechanisms for CAD and stroke prevention for statins with, perhaps, a contribution of pleiotropic non–lipid-lowering pathways.

ASCOT-BPLA: The ASCOT–Blood Pressure Lowering Arm (ASCOT-BPLA) trial showed that hypertensive patients at moderate risk of CV events benefit more from a CCB-based regimen (amlodipine) than from a β-blocker–based regimen (atenolol).[17] This study enrolled 19,257 patients with untreated or not-well-controlled hypertension plus at least three other risk factors for CVD (male gender, age >55 years, smoking, electrocardiogram (ECG) abnormalities, left ventricular hypertrophy (LVH), microalbuminuria, peripheral artery disease, history of stroke, family history of CHD, total-C/HDL-C ratio ≥6.0). Patients were randomized to receive either atenolol 50–100 mg ± bendroflumethiazide 1.25–2.5 mg prn or amlodipine 5–10 mg ± perindopril 4–8 mg prn. The trial stopped prematurely after a 5.5-year median follow-up because of a higher death rate with the atenolol-based regimen.

BP values were mildly but consistently lower in the amlodipine-treated group for the duration of the trial compared with the atenolol-treated group. The largest difference occurred early in the trial, at 3 months. By the end of the trial 78% of patients were taking at least two antihypertensive agents. There was no significant difference in the number of patients who stopped therapy, but more patients stopped therapy because of serious adverse events in the atenolol-treated group (3%) compared with the amlodipine group (2%; P < 0.0001). By the end of the trial the average mean reduction in BP for all patients was 26.6±21.7/16.6±11.5 mm Hg.

The amlodipine-based treatment group experienced a 10% reduction in the primary outcome (nonfatal MI plus fatal CHD). According to the statistical plan, by the early termination of this trial not enough individuals experienced the primary outcome to detect a statistically significant difference between the two treatment groups. However, significant reductions in relative risk (RRR) were noted in nonfatal MI (excluding silent MI) plus fatal CHD, total coronary events, total CV events and procedures, all-cause mortality, CV mortality, fatal and nonfatal stroke, and new-onset diabetes. (Table 2).

Multivariate analysis of ASCOT-BPLA indicate that BP reduction was an important factor but did not account for all of the benefit; this suggests that other mechanisms may be involved in providing the beneficial effects of CCB-based therapy.[18]

Table 2. ASCOT–BPLA: Significant Relative Risk Reductions With Amlodipine-Based Regimen[17]

	RRR	P
Nonfatal MI (excluding silent MI)	13%	0.0458
Total coronary events	13%	0.007
Total CV events/procedures	16%	<0.0001
All-cause mortality	11%	0.0247
CV mortality	24%	0.001
Fatal and nonfatal stroke	23%	0.0003
New-onset diabetes	30%	<0.0001

ASCOT: Combined results. In an early analysis of combined results from the ASCOT-BPLA and ASCOT-LLA trials, differences were noted in statin therapy versus placebo when added to each of the two antihypertensive regimens. Relative to placebo, atorvastatin added to amlodipine ± perindopril was associated with a 53% (P < 0.0001) reduction in the primary endpoint, nonfatal MI (including silent) and fatal CHD. Atorvastatin also resulted in significant risk reductions in total CV events and procedures (27%), total coronary events (42%), and non-significant risk reductions in fatal and nonfatal strokes (31%) (Figure 5).[19]

In a corresponding RRR, relative to placebo, atorvastatin added to atenolol ± bendroflumethiazide was 16% (P = 0.295) for nonfatal MI and fatal CHD; nonsignificant reductions in other endpoints were also observed (Figure 5).[19] A complete analysis of these combined results should provide interesting insights into this promising combination-therapy approach.

Additional Lipid-Lowering Clinical Trials

PROVE IT–TIMI 22: Analysis of data from the 4162 patients enrolled in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial suggest that, compared with standard-dose pravastatin (40 mg), high-dose atorvastatin (80 mg) may provide early (4-month) CV risk reduction in patients with acute coronary syndromes (ACS).[20] Patients with low levels of both LDL-C and CRP achieved the lowest risk of cardiac death or MI. Predictably, these patients were also more likely to be in the high-dose treatment group.

There are important differences between PROVE IT–TIMI 22 and ASCOT-LLA in addition to the more aggressive atorvastatin dosage (80 mg vs 10 mg) used in PROVE IT–TIMI 22. Patients in the PROVE IT–TIMI 22 trial had a higher level of morbidity than those enrolled in ASCOT-LLA. PROVE IT–TIMI 22 patients had to have been hospitalized for ACS within the previous 10 days and meet criteria that were exclusion criteria in ASCOT (eg, previous MI, high-risk or treated angina). However, requirements for total cholesterol levels

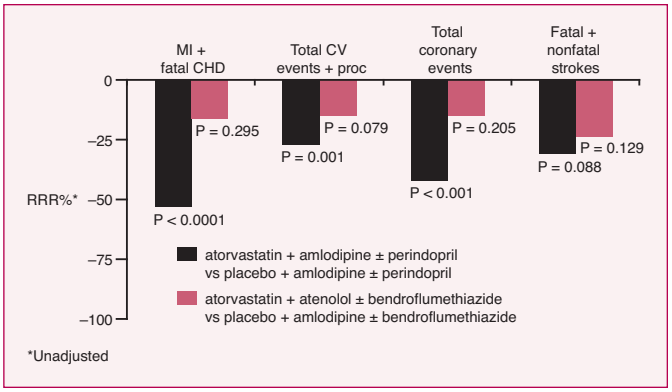

Figure 5. ASCOT combined results. Benefit of combined lipid and BP lowering vs BP lowering alone. RRR = relative risk reduction.[19]

were similar in the two studies (240 mg/dL for PROVE IT–TIMI 22 vs 251 mg/dL for ASCOT).

REVERSAL: The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial showed that aggressive lipid-lowering treatment with atorvastatin 80 mg reduced progression of coronary artery atheroma compared with standard-dose (40 mg) pravastatin. These investigators examined changes in atherosclerotic disease burden as assessed by intravascular ultrasound in 654 patients randomized to the same regimens as PROVE IT–TIMI 22.[21] Inclusion criteria included coronary angiography for a clinical indication and at least one obstruction with minimum angiographic luminal diameter narrowing of 20%.

Compared with baseline values, 18 months of high-dose atorvastatin halted progression of atherosclerosis (measured as percentage change in atheroma volume), whereas significant disease progression occurred with standard-dose pravastatin. These outcomes might be explained by the significantly greater reduction in CRP, triglycerides, and apolipoprotein B associated with the high-dose treatment. Larger-scale clinical trials are needed to determine whether these parameters impact risk of death and MI.

Data from PROVE IT–TIMI 22 and REVERSAL on the benefit of high-dose atorvastatin raise the issue of potential incremental benefit for the 80-mg dose compared with the 10-mg dose used in ASCOT-LLA.

A to Z: The Aggrastat to Zocor (A to Z) trial randomized 4497 patients with ACS to one of two lipid-management strategies[22]:

- *Intensive:* simvastatin 40 mg for 1 month, followed by 80 mg thereafter.
- *Less intensive:* placebo for 4 months, followed by simvastatin 20 mg thereafter.

The primary outcome was CV death, nonfatal MI, readmission for ACS, and stroke. This outcome occurred in 14.4% and 16.7% of the intensive-therapy and less-intensive-therapy groups, respectively (11% RRR, P = 0.14). In posthoc analysis, benefit appeared to emerge only after 4 months. There was no difference between the groups during the first 4 months of the study, but there was a 25% RRR in favor of the intensive-therapy group from 4 months through the end of the study (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 A to Z investigators suggested that the lack of an early anti-inflammatory effect may have contributed to the delay in benefit.

The TNT data suggest the potential incremental benefit of lowering LDL-C to levels below those currently recommended by national guidelines.

TNT: Results from the Treating to New Targets (TNT) study of 10,001 patients with clinically evident CHD and LDL-C <130 mg/dL showed that high-dose atorvastatin (80 mg) provided a significant clinical benefit compared with moderate-dose atorvastatin (10 mg) by reducing LDL-C to levels well below 100 mg/dL.[23] After a median follow-up of 4.9 years, the high-dose group had a significantly lower overall risk for major CV events (hazard ratio [HR] 0.78, 95% CI 0.69–0.89; P < 0.001), nonfatal and non–procedure-related MI (HR 0.78, 95% CI 0.66–0.93; P = 0.004), and fatal or nonfatal stroke (HR 0.75, 95% CI 0.59–0.96; P = 0.02). Differences in other primary outcome measures (death from CHD, resuscitation after cardiac arrest) were not statistically significant.

The TNT data suggest the potential incremental benefit of lowering LDL-C to levels below those currently recommended by national guidelines. Before extrapolating from these results to other patient populations, it is important to remember that patients in TNT had more advanced disease (ie, previous MI, previous or current angina with objective evidence of atherosclerotic CHD, and/or a history of coronary revascularization) than those enrolled in ASCOT (who had untreated hypertension and three other risk factors for CVD, but no previous MI or currently treated angina).

CTT: Results from the Cholesterol Treatment Trialists (CTT) meta-analysis support the primary and secondary outcomes from the ASCOT-LLA trial. The CTT's analyses of data from 90,056 patients (47% with preexisting CHD) in 14 randomized statin trials demonstrated a 12% (event rate ratio 0.88, 95% CI 0.84–0.91; P < 0.001) proportional reduction in all-cause mortality per 1 mmol/L* absolute reduction in LDL-C, primarily due to a 19% (event rate ratio 0.81, 95% CI 0.76–0.85; P < 0.0001) reduction in coronary mortality per 1 mmol/L reduction in LDL-C.[24] This benefit reflected reductions in MI or CHD death, need for coronary revascularization, and fatal or nonfatal stroke (combined major vascular event rate ratio 0.79, 95% CI 0.77–0.81; P < 0.0001) without any evidence of increased cancer incidence. Risk reductions appeared to be independent of baseline lipid levels or other characteristics noted at presentation.

*1 mmol/L = 39 mg/dL of LDL-C

Additional BP-Lowering Clinical Trials

INVEST: Regardless of differences in the regimens studied, conclusions from the International Verapamil-Trandolapril Study (INVEST) mirror those of ASCOT-BPLA in emphasizing the clinical benefits of aggressive BP control using a multidrug strategy.

INVEST compared all-cause death, nonfatal MI, and nonfatal stroke in 22,576 clinically stable CAD patients with hypertension randomized to treatment with calcium-antagonist–based therapy (verapamil) or β-blocker–based therapy (atenolol).[25] By study end most patients were taking either the combination of verapamil plus trandolapril (CCB/ACEI) or atenolol plus hydrochlorothiazide (β-blocker/diuretic). The CCB/ACEI and β-blocker/diuretic treatment strategies produced equivalent outcomes in prevention of the primary outcomes. New-onset diabetes was less frequent

in the CCB/ACEI treatment group (15% RRR). Futhermore, the results document that >70% of patients can reach the <140/90 mm Hg BP target with a multidrug strategy.

VALUE: The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial supports the importance of early BP control in hypertensive patients at high risk for CVD. VALUE randomized 15,245 hypertensive patients with high CV risk to treatment with an ARB (valsartan) or a CCB (amlodipine).[26]

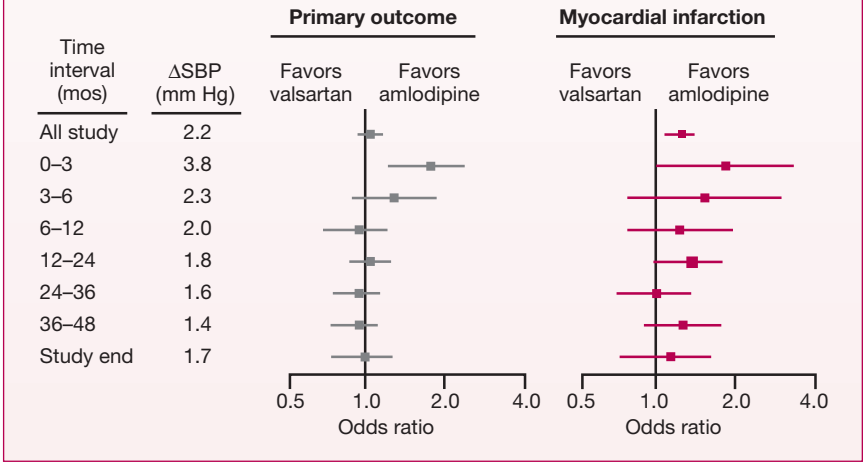

Figure 6. VALUE: Rapid reduction in BP associated with early benefit.
SBP = systolic blood pressure.[26]

After a mean follow-up of 4.2 years, the between-group primary outcome measure (composite of cardiac morbidity and mortality and all-cause mortality) did not differ. Consistent with the ASCOT-BPLA study, CCB-based therapy provided more rapid BP control than ARB-based therapy in the first year of treatment. The faster BP reduction associated with the CCB-based regimen in VALUE appeared to be associated with early clinical benefit, with the difference between the treatment groups diminishing as the study progressed and the BP differential grew smaller (Figure 6).

Conclusions from the International Verapamil-Trandolapril Study (INVEST) mirror those of ASCOT-BPLA in emphasizing the clinical benefits of aggressive blood pressure control using a multidrug strategy.

BPLTTC: The importance of BP reduction and, possibly, of lower BP goals is further supported by results from the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) meta-analysis of 27 randomized trials. This meta-analysis compared the effects of different BP-lowering regimens on CV events and death in 33,395 patients with diabetes and 125,314 without diabetes.[27]

This analysis supports the importance of BP reduction with most major classes of antihypertensive agents to reduce risk of morbidity and mortality in patients with diabetes. Furthermore, results from this analysis suggest that, particularly in diabetic patients, more intensive BP-lowering regimens provide better protection from major CV events, CV mortality, and total mortality than less intensive regimens.

Combined Lipid and BP Lowering in Clinical Practice

Current guidelines support intensive combination therapy in the clinical management of CVD. According to the National Cholesterol Education Program (NCEP) updated clinical guidelines for cholesterol testing and management, the goal for patients with CHD and CHD-risk equivalents is to attain LDL-C levels <70 mg/dL; most patients with CHD will require lipid-lowering therapy to help them achieve these goals.[28] The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure indicates that many classes of drugs (including thiazide diuretics, ACE inhibitors, ARBs, β-blockers, and CCBs) will reduce the complications of hypertension and that most patients will require two or more antihypertensive medications.[29]

One key to the effectiveness of any therapy is patient adherence, which remains a problem. A recent retrospective prescription-filling study of adherence to concomitant antihypertension and lipid-lowering therapy showed that 3 months after initiation of therapy 45% of patients were adherent to both therapies and 36% remained adherent after 12 months.[30] Simplifying medication regimens is presumed to improve patient adherence to therapy.

A move in the direction of simplifying medication regimens was evaluated in the Amlodipine/Atorvastatin Gemini study. This trial enrolled 1220 patients with uncontrolled hypertension and dyslipidemia in a 14-week, open-label, noncomparative, office-based, multicenter trial. A single-pill combination of amlodipine/atorvastatin was administered at electively titrated eight-step escalating doses to achieve BP and LDL-C goals.[31] By the study's end, 57.7% of all patients, 51.9% of patients with uncontrolled LDL-C, and >75% of patients without CHD or CHD-risk equivalents had achieved both goals. This study suggests that single-pill combination agents might be of value in the management of high-risk patients who need aggressive hypertensive and lipid-lowering therapy.

Clinical Implications

Accumulated clinical trial data lend support to the effectiveness and safety of CCBs in CV risk reduction used alone to control hypertension (especially when concerned about stroke reduction) or as add-on treatment to achieve desired BP control (except for heart failure associated with systolic dysfunction). These data also suggest that early and effective BP reduction reduces the incidence of poor outcomes in patients with elevated BP.

Accumulated data also suggest that many hypertensive patients with only modestly elevated lipid levels according to current guidelines may benefit from statin therapy. These findings provide further support for the important role of global risk assessment in guiding treatment strategies.

Self-Assessment Questions

Please mark your answers on the Answer Sheet and return with Instruction Sheet.

1. Statins, ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers all reduce oxidative stress.
   a. True
   b. False

2. In the ASCOT-LLA trial, addition of a statin to baseline antihypertensive therapy in patients with hypertension and only modestly elevated cholesterol resulted in additional clinical benefit.
   a. True
   b. False

3. In the TNT study, atorvastatin 80 mg vs 10 mg was associated with a relative risk reduction in major CV events of approximately how much?
   a. 5%–9%
   b. 10%–14%
   c. 15%–19%
   d. 20%–25%

4. The Cholesterol Treatment Trialists' meta-analysis reported a reduction in all-cause mortality with statins of approximately how much?
   a. 5%–9%
   b. 10%–14%
   c. 15%–19%

5. In the VALUE trial, a CCB ± diuretic antihypertensive regimen was equivalent to an ARB ± diuretic antihypertensive regimen in long-term reduction of CV events.
   a. True
   b. False

6. In the INVEST study, the CCB/ACE inhibitor regimen reduced the risk of new-onset diabetes vs the β-blocker/diuretic regimen by approximately how much?
   a. 5%–9%
   b. 10%–14%
   c. 15%–19%

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2. [A] [B]
3. [A] [B] [C] [D]
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