Statins and Blood Pressure Regulation

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Hypertension and high serum cholesterol levels are two of the most relevant risk factors for cardiovascular diseases. A combined increase in both risk factors has been reported in a significant proportion of patients with coronary artery disease. Statins are the most widely used drugs to treat hypercholesterolemia, and they interact with blood pressure control in different populations of hypertensive patients. A significant reduction in blood pressure associated with the use of statins has been described in patients with untreated hypertension and in patients treated with antihypertensive drugs, particularly angiotensin converting enzyme inhibitors and calcium channel blockers. The effect of statins on blood pressure control has also been reported in diabetic patients. The mechanisms responsible for the hypotensive effect seem to be largely independent of the effect of statins on lipid profile, and are probably related to their interaction with endothelial function or angiotensin II receptors. The capacity of statins to improve blood pressure control could be a useful consideration for an integrated approach to better prevention of cardiovascular diseases.

Introduction

Coronary heart disease and cerebrovascular disease continue to be among the leading causes of illness and death among adults in Europe and North America [1]. Their prevalence is strongly related to the effects of many different risk factors, including high blood pressure, cigarette smoking, total plasma cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and diabetes [2–4]. Factors such as obesity, left ventricular hypertrophy, family history of premature coronary heart disease, and menopause have also been considered in defining the risk for coronary heart disease [5•]. Risk factor modification is an integral part of the optimal care of patients with and without cardiovascular disease, and its role is supported by basic science, clinical evidence, epidemiologic surveys, randomized trials, and cost-effective analyses.

Management of risk factors should be viewed as an integrated strategy of intervention aimed at correcting as many of the underlying causes of cardiovascular disease as possible. A combined approach to cardiovascular risk has been adopted as part of the framework of blood pressure (Joint National Committee, World Health Organization–International Society of Hypertension) and cholesterol (National Cholesterol Education Program) programs in the United States and Europe [6–8]. In addition, data from population studies have enabled long-term prediction of cardiovascular diseases based on algorithms that consider the combined influence of several risk factors, such as blood pressure, smoking habits, total cholesterol and HDL cholesterol levels, presence of diabetes, and left ventricular hypertrophy. These algorithms have been translated into easy-to-calculate scores that allow physicians to estimate multivariate cardiovascular risk in middle-aged men [5•]. The extent of risk of cardiovascular disease predicted by calculation of such scores, which are based on logistic functions, largely corresponds to that estimated through several observational studies that considered the combined influence of the different risk factors. This correspondence between calculated and actual findings strongly support the idea that the overall risk of cardiovascular disease in humans is better explained by the combined influence of many different risk factors.

Interactions Between Hypercholesterolemia and High Blood Pressure

Among the possible combinations of different risk factors, any approach that simply integrates blood pressure and cholesterol information can help explain a large proportion of the cumulative risk of cardiovascular disease [3], probably because of the primary role that the interaction between such risk factors can play in the development of cardiovascular events (Fig 1).

From an epidemiologic point of view, many observational surveys have observed that plasma cholesterol levels are significantly increased in hypertensive patients. An association between elevated plasma cholesterol levels and high blood pressure has been also noted in patients with mildly elevated blood pressure, as well as in patients with borderline hypertension [9,10]. In the latter group, an increase in serum cholesterol levels above the cutoff value of 200 mg/dL has been associated with a significant increase in 15-year risk of stable hypertension. This increased risk persists after adjust-

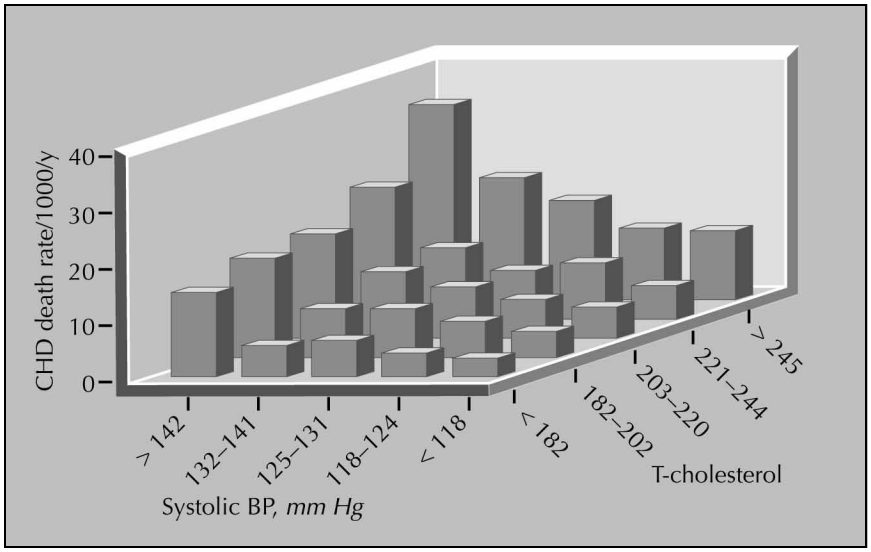

Figure 1. Relationship between systolic blood pressure (BP) and plasma cholesterol levels in the Multiple Risk Factor Intervention study sample. CHD—coronary heart disease; T-cholesterol—total cholesterol. (*Adapted from* Neaton *et al.* [3].)

ment for the main confounding risk factors: age, sex, body weight, family history of hypertension, and urinary sodium excretion [10]. These data suggest that elevated plasma cholesterol levels can be directly or indirectly implicated in some of the mechanisms responsible for the increase in blood pressure that characterizes patients with hypertension. Accordingly, any measure that decreases plasma cholesterol levels might interfere with the onset and progression of hypertensive disease and improve blood pressure control.

Moreover, aggressive treatment of plasma lipid abnormalities in hypertensive patients could also reduce the risk of coronary heart disease and enhance the effect of antihypertensive treatment on clinical outcome. The results of a primary prevention study that was done in Göteborg, Sweden [11], and involved patients with multiple risk factors, clearly showed that the risk of an acute coronary event can be greatly reduced in patients in whom both blood pressure and total cholesterol levels are reduced by antihypertensive and lipid-lowering treatment. Of interest, in the same study, analysis of cardiovascular morbidity as a function of the changes in blood pressure and serum cholesterol showed that the benefit of blood pressure reduction associated with antihypertensive treatment is significantly blunted in patients whose plasma cholesterol levels do not change or even increase. This finding confirms that in patients with hypertension and plasma lipid abnormalities, a combined reduction of both risk factors is mandatory to substantially reduce cardiovascular morbidity. Among the possible strategies of intervention, such goals can be achieved by activation of a "therapeutic crossover" between different drugs designed to treat a single risk factor in hypertension or lipid abnormalities.

Role of Statins in the Integrated Management of Cardiovascular Risk

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the most powerful agents for treating plasma lipid abnormalities, and landmark clinical trials have shown that these drugs (lovastatin, simvastatin, and pravastatin) reduce morbidity and mortality in patients at risk for cardiovascular disease [12••,13–15]. In particular, the benefit of statins has been demonstrated in a large group of patients (> 30,000) with and without coronary artery disease and across a wide range of plasma cholesterol levels (210 to 310 mg/dL). This finding suggests that statins could result in modulation of cardiovascular risk that extends beyond the anatomic regression of the atherosclerotic lesions. In addition, both simvastatin and pravastatin have significantly reduced the risk of acute cerebrovascular complications (stroke and transient ischemic attacks) in patients with coronary artery disease [13–15]. A recent report [16] has suggested that, according to the results a retrospective analysis of a large database, the risk of dementing illnesses can be significantly reduced in patients receiving statins.

During the past 2 to 3 years, researchers have reported intriguing data [17] on the possibility that a significant proportion of the beneficial effects of statins on preventing cardiovascular events may result from therapeutic crossover in patients with multiple risk factors [12••,17]. In particular, since the presence of plasma lipid abnormalities is common in patients with high blood pressure, the therapeutic effect of statins might be enhanced in patients in whom high cholesterol levels are combined with hypertension. Unfortunately, none of the large trials that assessed the clinical relevance of statins in patients with and without cardiovascular diseases have reported information on the extent of blood pressure control. In addition, the samples from these same studies were often poorly representative of the average hypertensive population because the prevalence of the disease was lower than that expected according to age and sex.

Experimental Evidence on the Role of Statins in Blood Pressure Control

The first study to show the capacity of statins to interfere with blood pressure control used Dahl salt-sensitive rats

Table 1. Summary of the results of clinical studies investigating the effects of statins on blood pressure control in different populations of normotensive and hypertensive patients

Study	Patients	Variable	Effects of statins
Sung *et al.* [23]	Normotensive	SBP response to stress	Significantly reduced
		Resting SBP	Not significantly reduced
Kool *et al.* [30]	Normotensive	Resting SBP	Unchanged
Sartor *et al.* [44]	Normotensive	Resting SBP and DBP	Unchanged
Antonicelli *et al.* [29]	Normotensive	Resting SBP and DBP	Unchanged
D'Agostino *et al.* [27]	Treated hypertensive*	Resting SBP and DBP	Unchanged
Straznicky *et al.* [25]	Untreated hypertensive	DBP response to A-II, NE	Significantly reduced
		SBP response to A-II, NE	Unchanged
Jarai *et al.* [24]	Untreated hypertensive	Resting SBP and DBP	Significantly reduced
Abetel *et al.* [26]	Untreated hypertensive	Resting SBP and DBP	Significantly reduced
Glorioso *et al.* [32••]	Untreated hypertensive	Resting SBP, DBP, and PP	Significantly reduced
		MBP response to cold pressure test	Significantly reduced
Nazzaro *et al.* [45]	Untreated hypertensive	Resting SBP and DBP	Significantly reduced
Velussi *et al.* [34•]	Treated hypertensive and type 2 diabetic	Resting SBP and DBP	Significantly reduced SBP
Borghi *et al.* [36•]	Treated hypertensive†	Resting SBP, DBP, MBP, and PP	Significantly reduced
Tonolo *et al.* [33•]	Treated hypertensive and type 2 diabetic	Resting SBP and DBP	Significantly reduced

*Well-controlled hypertension.
†Uncontrolled hypertension.
A-II—angiotensin II; DBP—diastolic blood pressure; MBP—mean blood pressure; NE—norepinephrine; PP—pulse pressure; SBP—systolic blood pressure.

[18], where lovastatin therapy attenuated the onset and progression of hypertension and prevented renal injury. These findings were confirmed in the same rat model with the use of a different HMG-CoA reductase inhibitor, pravastatin [19•], whose pharmacologic profile differs substantially from that of lovastatin. The administration of pravastatin in Dahl salt-sensitive rats prevented hypertension and reduced the degree of proteinuria and renal glomerular injury associated with hypertension, acting through a mechanism that did not depend on the direct inhibition of renal sodium reabsorption [19•].

Jiang and Roman [20] investigated the effects of statins in spontaneously hypertensive rats (SHRs). They reported that long-term lovastatin treatment (20 mg/kg of body weight per day) in this non–salt-sensitive model of hypertension shifts the relation between renal perfusion pressure and sodium excretion toward lower blood pressure and attenuates the development of hypertension and renal vascular damage. The mechanism by which statins attenuate the development of hypertension is still poorly understood. In Jiang and Roman's study, the treated SHRs showed a 33% reduction in plasma cholesterol levels, but it remains unclear whether the effects of lovastatin on preventing the blood pressure increase are directly or indirectly related to its hypolipidemic effects.

The plasma lipid levels in SHRs are not elevated, and it is not known whether a reduction in plasma cholesterol levels from normal baseline levels affects the mechanisms involved in blood pressure control. The most intriguing hypothesis suggests that the antihypertensive effect of statins in rat experimental models is related to the drugs' ability to prevent renal vascular hypertrophy, thus improving the pressure-natriuresis relationship [20]. The effect of statins would be largely independent of their lipid-lowering activity and more directly related to their ability to inhibit the synthesis of mevalonate, which is the precursor of the synthesis of isoprenoids; the latter are deeply involved in the post-translational isoprenylation of many proteins that help control structure and function of vascular smooth muscle cells [21]. These data suggest a role for statins per se in the modulation of the some of the mechanisms responsible for the progressive increase and maintenance of elevated blood pressure, and they clearly support the possibility that statins may be involved in blood pressure control regardless of their capacity to modulate plasma lipid profile.

Statins and Blood Pressure Control in Humans

In addition to what was described in the different experimental models of arterial hypertension, the possibility that statins can favorably affect blood pressure control has been extended to humans (Table 1). In 1995, a retrospective review of many different studies conducted with a variety of lipid-lowering strategies [22] suggested that the reduction of plasma cholesterol in patients with hyperlipemia is associated with a reduction in blood pressure that was clinically significant (from 3 to 5 mm Hg in diastolic blood pressure), directly related to the decrease in serum choles-

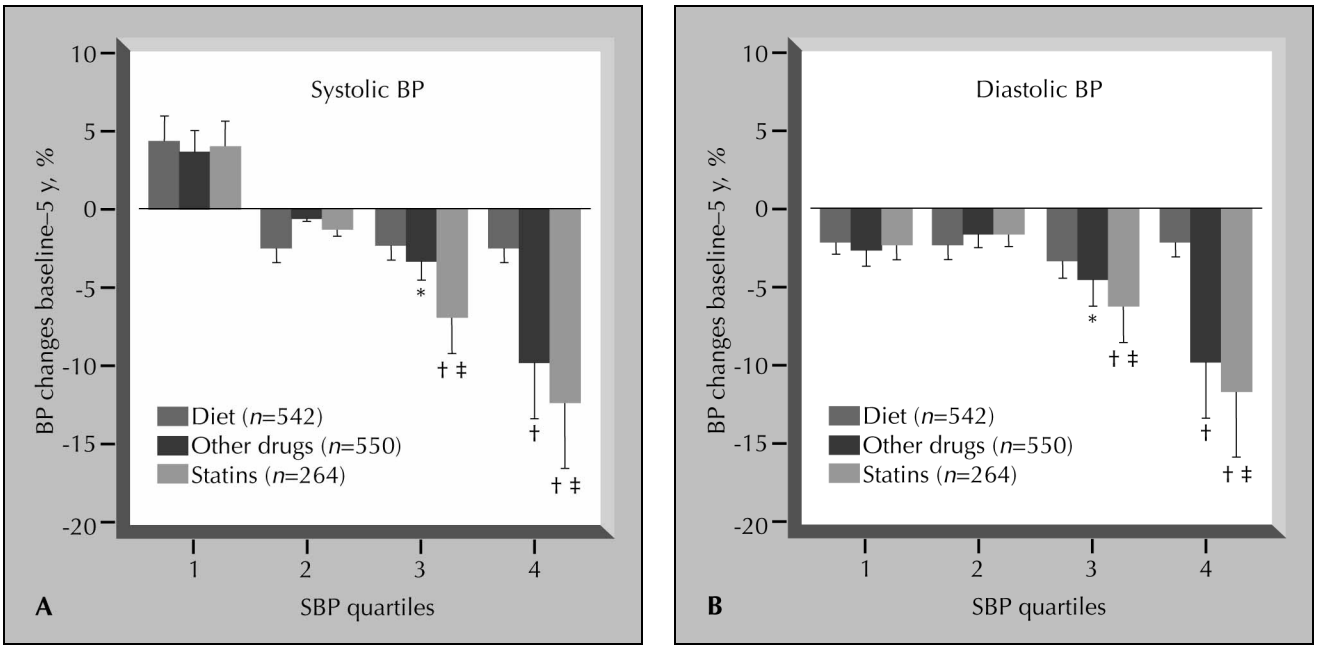

Figure 2. Five-year changes in systolic blood pressure (SBP) (**A**) and diastolic blood pressure (**B**) in patients treated with low-cholesterol diet, statins, and other lipid-lowering drugs (fibrates or cholestyramine) in the Brisighella Heart Study. $^{*}P < 0.05$. $^{\dagger}P < 0.05$ versus diet. $^{\ddagger}P < 0.05$ versus other drugs.

terol levels, and larger in patients treated with statins. The stronger evidence supporting the idea that long-term statin treatment can reduce systemic blood pressure comes from epidemiologic and clinical studies done mainly in high-risk patients with hypertension and hypercholesterolemia [23–26], although another study conducted in a comparable group of patients did not confirm this finding [27]. In normotensive subjects with high cholesterol levels, the available clinical data do not support a significant effect of statins on blood pressure [28–30], despite some significant changes in the systemic hemodynamic profile [28]. As expected, no clinical trials have studied patients with hypertension and normal plasma cholesterol levels, primarily because the approved use of statins is restricted to patients with lipid abnormalities.

From the epidemiologic point of view, some intriguing observations on statins and blood pressure control come from the retrospective analysis of a subgroup of more than 1500 patients included in a larger database of the Brisighella Heart Study [31]; this subgroup had high plasma cholesterol levels (total cholesterol level > 239 mg/dL) and at least one additional cardiovascular risk factor. These patients were initially subdivided into four quartiles of systolic blood pressure and were treated with a low-cholesterol diet for 6 months. After this period, patients who were considered nonresponders to dietary treatment (total cholesterol levels > 239 mg/dL) were prospectively allocated to receive statin therapy (mainly simvastatin, 20 to 40 mg/d) or to receive other lipid-lowering drugs (fibrates or cholestyramine) in a proportion of 1:2. All the patients have been reevaluated every 6 months for a cumulative period of 5 years to assess changes in lipid profile and blood pressure control. After 5 years of treatment, the patients taking lipid-lowering drugs showed a greater decrease in systolic and diastolic blood pressure than patients who continued to be treated with a low-cholesterol diet (Fig. 2).

The blood pressure reduction, which was already significant after 6 months of treatment, was restricted to hypertensive patients whose systolic blood pressure was in the higher two quartiles (>150 mm Hg). Among the subgroup treated with lipid-lowering drugs, the blood pressure decrease was significantly greater in patients receiving statins; this decrease accounted for a larger proportion of the cumulative hypotensive response in the patients receiving lipid-lowering drugs (Fig. 2). The effects of statins on blood pressure were largely independent of the reduction in plasma cholesterol levels. In addition, in the subgroup treated with statins, only a weak and marginally significant correlation ($r = 0.16$; $P < 0.044$) has been found between the reduction in total plasma cholesterol level and the decrease in systolic blood pressure.

Despite obvious limitations attributable to the observational nature of the Brisighella Heart Study, the data strongly suggest that long-term treatment with lipid-lowering drugs can improve blood pressure control in patients at high risk for cardiovascular disease. Of interest, the effect of statins on blood pressure seems to be limited to patients with hypertension. This finding suggests that, as is seen with most antihypertensive agents, statins may decrease elevated but not normal blood pressure. These data agree with those reported in normotensive persons [28–30] and

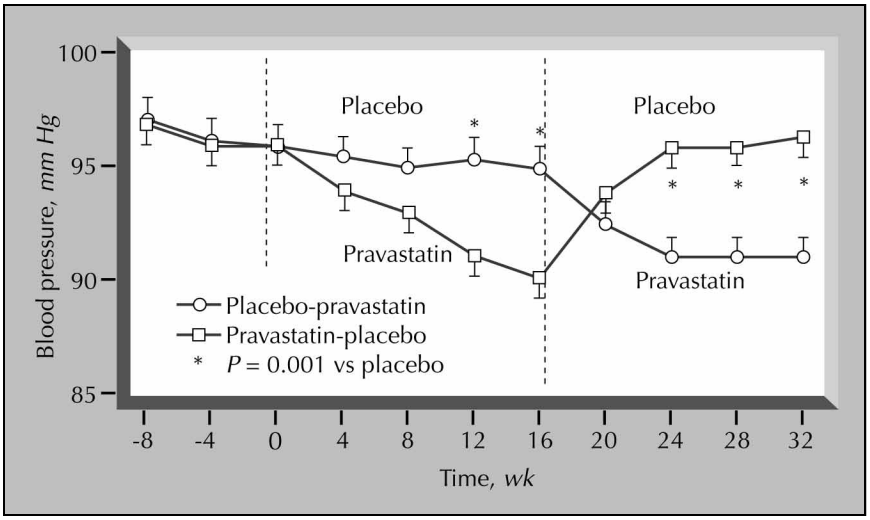

Figure 3. Diastolic blood pressure modifications in response to pravastatin treatment in patients with untreated arterial hypertension and hypercholesterolemia. (*Adapted from* Glorioso *et al.* [32••].)

further support the possibility that statins might exert their favorable effects by counteracting some of the mechanisms responsible for the development and maintenance of hypertension.

The pivotal paper by Glorioso *et al.* [32••] has better defined the effects of statins on blood pressure. This double-blind crossover study was specifically designed to investigate the effects of pravastatin on resting and stimulated (cold pressure test) systolic and diastolic blood pressure of patients with untreated hypertension and high cholesterol levels. After 8 weeks of a run-in period during which patients received placebo and a low-cholesterol diet, the hypertensive patients were randomly allocated to placebo or pravastatin (20 to 40 mg/d). After completion of the double-blind phase of treatment, pravastatin decreased systolic (Fig. 3), diastolic, and pulse pressure and blunted the pressor response to the cold pressure test. The effects of pravastatin on blood pressure control were independent of adjustment for sex and age and were not related to baseline plasma levels of LDL and HDL cholesterol. This study has also excluded any possible interactions between statins and another vasoconstrictive pathway—the endothelin system; thus, it confirms the possibility that statins can significantly interfere with some of the basic mechanisms responsible for blood pressure control.

In agreement with the previous finding of the Brisighella Heart Study, the effects of statins on blood pressure seem to be largely independent of the effect of the drugs over the reduction in LDL or total cholesterol levels. In particular, the results of a recent study that compared simvastatin and cholestyramine in patients with type 2 diabetes [33•] showed that although the two drugs were equally effective in reducing total and LDL cholesterol levels, only statins significantly decreased diastolic blood pressure and 24-hour urinary albumin excretion. The relative independence of blood pressure reduction from the lipid-lowering activity of statins can play a prominent role in terms of cardiovascular protection: The therapeutic impact of such compounds could be increased because they can separately interact with two different targets of cardiovascular prevention.

The favorable effects of statins on blood pressure have also been confirmed in the high-risk population of patients with type 2 diabetes and hypertension. Among these patients, the combination of high blood pressure and lipid abnormalities is responsible for a large increase in the risk of cardiovascular complications. Atorvastatin at an average dosage of 10 mg/d has been reported to improve diastolic blood pressure control in these patients without necessitating a change in the current antihypertensive treatment [34•]. According to that study, blood pressure reduction was associated with an obvious improvement in lipid profile (reduction in LDL cholesterol and an increase in HDL cholesterol levels), and with a significant reduction in microalbuminuria and plasma fibrinogen levels. These changes largely contribute to the wide benefit reported in large-scale trials of statins in patients with diabetes [13,14].

In addition to their ability to primarily modulate the blood pressure in untreated hypertensive patients compared with placebo or other lipid-lowering strategies (cholestyramine or fibrates), statins have been reported to improve blood pressure control in patients currently treated with antihypertensive drugs. Sposito *et al.* [35•] first showed a positive interaction between simvastatin and antihypertensive agents. These authors reported that the concomitant administration of pravastatin or lovastatin can significantly enhance the antihypertensive effect of enalapril or lisinopril in a small group of patients with hypertension and high serum total cholesterol levels. These findings have been confirmed and extended by a study conducted in our institution in a larger sample of patients (n = 127) with poorly controlled hypertension and hypercholesterolemia who received different antihypertensive drugs [36••]. In particular, our experience confirmed that the extent of systolic and diastolic blood pressure response to antihypertensive treatment can be significantly enhanced by concomitant pravastatin or simvastatin therapy (Fig. 4).

In a separate stratifying analysis, we investigated the extent of interaction between the changes in blood pressure and the use of different classes of antihypertensive drugs in the subgroup of patients treated with statins. This retrospective analysis of data showed that the effects on blood pressure control were enhanced in patients treated with statins in combination with angiotensin converting enzyme inhibitors and calcium channel blockers (Fig. 4), whereas no significant interactions have been observed with other widely prescribed antihypertensive drugs (*eg*, β-blockers and diuretics). In patients treated with statins, a slight but marginally significant correlation has been observed between the decrease in diastolic blood pressure and the decrease in both serum total cholesterol and LDL cholesterol levels ($r = 0.37$, $P = 0.043$; $r = 0.39$, $P = 0.041$); in contrast, no relationship has been found with changes in systolic blood pressure.

These findings largely confirm those reported by most of the clinical studies conducted in this field, and again suggest that statins can specifically interact with some of the mechanisms responsible for the blood pressure increase. Because the extent of drug interaction seems to be enhanced for drugs acting mainly at the level of the vascular wall (angiotensin converting enzyme inhibitors, calcium channel blockers), we also suggest that statins may significantly improve the capacity of some classes of drugs to reduce the peripheral vascular tone and improve peripheral vasodilator capacity. This mechanism could be responsible for a kind of "synergism" between different drugs addressing the same target, with a great enhancement of the therapeutic impact of each drug.

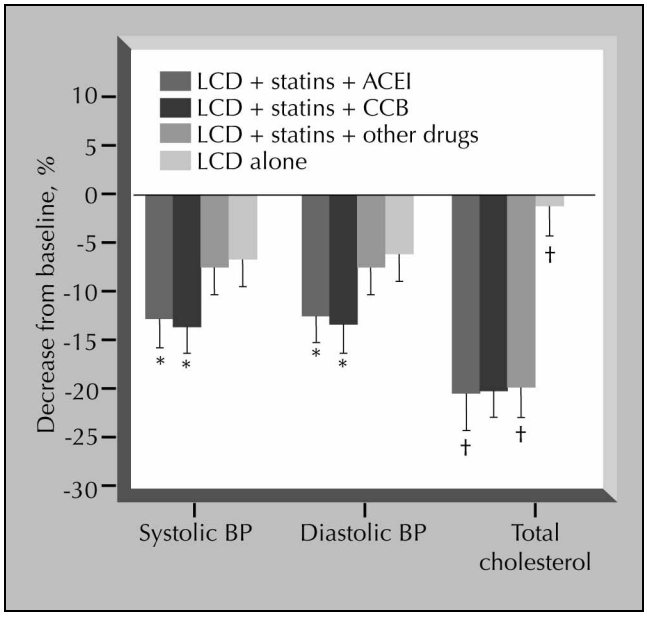

Figure 4. Changes in systolic and diastolic blood pressure (BP) and total cholesterol in patients with hypertension who were treated with low-cholesterol diet (LCD) and different classes of antihypertensive drugs. Effects of the combination with statins. *$P < 0.05$. †$P < 0.005$ versus LCD. ACEI—angiotensin converting enzyme inhibitor; CCB—calcium channel blocker. (*Adapted from* Borghi *et al.* [36••].)

Statins and Blood Pressure Control: Proposed Mechanisms of Interaction

Among the possible explanations for the effect of statins on blood pressure control, the easier to invoke is the vasodilatory effect that could follow these drugs' capacity to improve endothelium-dependent vasorelaxation [37,38]. Impaired peripheral arterial compliance has been described in patients with high serum cholesterol levels [39] and could contribute to increased blood pressure. By reducing serum cholesterol levels, statin treatment can increase arterial compliance and thereby improve the vasodilator capacity of the large arteries. This could contribute to the overall blood pressure–lowering effect observed in many studies and, in particular, could explain the reduction of pulse pressure values in patients receiving antihypertensive drugs plus statins. In addition, statin treatment could promote upregulation of vascular nitric oxide synthase [40••,41]. This upregulation has been described in experimental conditions, particularly with pravastatin and simvastatin, and could help modulate the peripheral vascular tone regardless of the reduction in plasma cholesterol levels [41].

An additional mechanism could reside in the capacity of statins to blunt the vasoconstrictive and pressor response to vascular agonists, such as angiotensin II and norepinephrine [25,42••]; this might further help reduce peripheral vascular tone. Of interest, all these conditions could significantly increase the sensitivity of the vessel wall to the vasodilating effect of drugs such as angiotensin converting enzyme inhibitors, calcium channel blockers, and angiotensin II receptor inhibitors. This would thereby provide a suitable explanation for the previously reported pharmacodynamic interaction between statins and some classes of antihypertensive drugs.

However, the most intriguing possible mechanism for the effects of statins on blood pressure regulation is their interaction with the activity of the renin-angiotensin-aldosterone system. In a seminal paper, Nickenig *et al.* [42••] clearly showed that hypercholesterolemia is associated with upregulation of vascular AT_1 receptors, which could explain the increased pressor reactivity to angiotensin II infusion observed in this condition [41,42••]. Statin can also decrease the density of AT_1 receptors, thus explaining the reduction in vascular sensitivity to angiotensin II and the decrease in plasma levels of aldosterone [43] that has been described in experimental conditions and that could help reduce blood pressure. The downregulation of the number and density of AT_1 receptors might have some important pathophysiologic and clinical implications because it could rapidly improve vascular relaxation, reduce blood pressure, and prevent the progression of vascular hypertrophy and atherosclerotic disease; as a result, the therapeutic impact of any strategy designed to control blood pressure and plasma lipids would be significantly increased.

Taken together, these highly promising findings could open a new scenario for cardiovascular prevention that is based on the multiple interaction between drugs that focus on the same target but act through different pathways.

Conclusions

In conclusion, the available information strongly supports a role for statins in the regulation of arterial blood pressure in patients with hypertension. The effects of statins on blood pressure control seem to be partially independent of their lipid-lowering activity and more strictly related to their capacity to directly interact with some mechanisms responsible for blood pressure regulation. If confirmed by large-scale trials, these effects could significantly strengthen the clinical impact of cardiovascular prevention. Further data on this issue are warranted.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. American Heart Association: *Heart and Stroke Statistical Update.* Dallas: American Heart Association; 2000.
2. Kannel WB: **Blood pressure as a cardiovascular risk factor: prevention and treatment.** *JAMA* 1996, **275:**1571–1576.
3. Neaton JD, Blackburn H, Jacobs D, *et al.*: **Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group.** *Arch Intern Med* 1992, **152:**1490–1500.
4. Alderman MH, Cohen H, Madhavan S: **Diabetes and cardiovascular events in hypertensive patients.** *Hypertension* 1999, **33:**1130–1134.
5. • Wilson PWF, D'Agostino RB, Levy D, *et al.*: **Prediction of coronary heart disease using risk factor categories.** *Circulation* 1998, **97:**1837–1847.

The paper suggests a simple way to calculate and understand the importance of cumulative cardiovascular risk factors.

6. The JNC-VI Sub-Committee: **The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure.** *Arch Intern Med* 1997, **157:**2413–2446.
7. Chalmers J, MacMahon S, Mancia G, *et al.*: **1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. Guidelines sub-committee of the World Health Organization.** *Clin Exp Hypertens* 1999, **21:**1009–1060.
8. **Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel in Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II).** *JAMA* 1993, **269:**3015–3033.
9. Julius S, Jamerson K, Mejia A, *et al.*: **The association of borderline hypertension with target organ changes and higher coronary risk. Tecumseh Blood Pressure study.** *JAMA* 1990, **264:**354–358.
10. Borghi C, Bacchelli S, Degli Esposti D, *et al.*: **Pressor and metabolic correlates to long-term development of stable hypertension in borderline hypertensive patients [abstract].** *J Hypertens* 1997, **15:**S111.
11. Samuelsson O, Wilhelmsen L, Andersson OK, *et al.*: **Cardiovascular morbidity in relation to change in blood pressure and serum cholesterol levels in treated hypertension. Results from the primary prevention trial in Göteborg, Sweden.** *JAMA* 1987, **258:**1768–1776.
12. •• Maron DJ, Fazio S, Linton, Mac Rae F: **Current perspectives on statin.** *Circulation* 2000, **101:**207–213.

This paper clearly summarizes the potential preventive and therapeutic role of statins in patients at risk for cardiovascular disease. It describes the importance of the effects of statins not directly related to lipid management.

13. Simvastatin Simvastatin Survival Study Group: **Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S).** *Lancet* 1994, **344:**1383–1389.
14. Sacks FM, Pfeffer MA, Moye LA, *et al.*: **The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators.** *N Engl J Med* 1996, **335(14):**1001–1009.
15. Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group: **Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group.** *N Engl J Med* 1998, **339:**1349–1357.
16. Wolozin B, Kelleman W, Rousseau P, *et al.*: **Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-metylglutaryl coenzyme A reductase inhibitors.** *Arch Neurol* 2000, **57:**1439–1443.
17. Vaughan CJ, Gotto AM, Basson CT: **The evolving role of statins in the management of atherosclerosis.** *J Am Coll Cardiol* 1999, **35:**1–10.
18. O'Donnell MP, Kasiske BL, Katz SA, *et al.*: **Lovastatin but not enalapril reduces glomerular injury in Dahl salt-sensitive rats.** *Hypertension* 1992, **20:**651–658.
19. • Wilson TW, Alonso-Galicia M, Roman RJ: **Effects of lipid-lowering agents in the Dahl salt-sensitive rat.** *Hypertension* 1998, **31(1 Pt 2):**225–231.

The paper describes an interesting interaction between the use of statins and changes in renal function. This mechanism could provide a strong rationale for the preventive effect of statins on the development of experimental hypertension.

20. Jiang J, Roman RJ: **Lovastatin prevents development of hypertension in spontaneously hypertensive rats.** *Hypertension* 1997, **30:**968–974.
21. Clarke SL: **Protein isoprenylation and methylation at carboxyl-terminal cysteine residues.** *Ann Rev Biochem* 1992, **61:**355–386.
22. Goode GK, Miller JP, Heagerty AM: **Hyperlipidaemia, hypertension, and coronary heart disease.** *Lancet* 1995, **345:**362–364.
23. Sung BH, Izzo JL, Wilson MF: **Effects of cholesterol reduction on BP response to mental stress in patients with high cholesterol.** *Am J Hypertens* 1997, **10:**592–599.
24. Jarai Z, Kapocsi J, Farsang C, *et al.*: **Effect of fluvastatin on serum lipid levels in essential hypertension.** *Orv Hetil* 1996, **137:**1857–1859.
25. Straznicky NE, Howes LG, Lam W, *et al.*: **Effects of pravastatin on cardiovascular reactivity to norepinephrine and angiotensin II in patients with hypercholesterolemia and systemic hypertension.** *Am J Cardiol* 1995, **75:**582–586.
26. Abetel G, Poget PN, Bonnabry JP: **Hypotensive effect of an inhibitor of cholesterol synthesis (fluvastatin). A pilot study.** *Schweiz Med Wochenschr* 1998, **128:**272–277.
27. D'Agostino RB, Kannel WB, Stepanians MN, *et al.*: **Efficacy and tolerability of lovastatin in hypercholesterolemia in patients with systemic hypertension.** *Am J Cardiol* 1993, **71:**82–87.
28. Muramatsu J, Kobayashi A, Hasegawa N, *et al.*: **Hemodynamic changes associated with reduction in total cholesterol by treatment with the HMG-CoA reductase inhibitor pravastatin.** *Atherosclerosis* 1997, **130:**179–182.

29. Antonicelli R, Onorato G, Pagelli P, *et al.*: **Simvastatin in the treatment of hypercholesterolemia in elderly patients.** *Clin Ther* 1990, **12:**165–171.
30. Kool M, Lustermans F, Kragten H, *et al.*: **Does lowering of cholesterol levels influence functional properties of large arteries?** *Eur J Clin Pharmacol* 1995, **48:**217–223.
31. Borghi C, Gaddi A, Ambrosioni E, *et al.*: **Improved blood pressure control in hypertensive patients treated with statins.** *J Am Coll Cardiol* 2001, **37(suppl A):**233A–234A.
32.•• Glorioso N, Troffa C, Filigheddu F, *et al.*: **Effect of the HMG-CoA reductase inhibitors on blood pressure in patients with essential hypertension and primary hypercholesterolemia.** *Hypertension* 1999, **34:**1281–1286.
This is the only published paper reporting the results of a double-blind, crossover, randomized study done to establish the capacity of statins to reduce blood pressure in hypertensive men. It demonstrates the blood pressure–lowering efficacy of statins as well as their capacity to reduce pressor response to stress.
33.• Tonolo G, Melis MG, Formato M, *et al.*: **Additive effects of simvastatin beyond its effects on LDL cholesterol in hypertensive type 2 diabetic patients.** *Eur J Clin Invest* 2000, **11:**980–987.
The authors report that the effects of statins on blood pressure control cannot be achieved with the use of cholestyramine.
34.• Velussi M, Cernigoi AM, Tortul C, *et al.*: **Atrovastatin for the management of type-2 diabetic patients with dyslipidemia. A mid-term (9-month) treatment experience.** *Diabetes Nutr Metab* 1999, **12:**407–412.
This paper confirms that statins can reduce blood pressure in diabetic patients.
35.• Sposito AC, Mansur AP, Coelho OR, *et al.*: **Additional reduction in blood pressure after cholesterol-lowering treatment by statins (lovastatin or pravastatin) in hypercholesterolemic patients using angiotensin-converting enzyme inhibitors (enalapril or lisinopril).** *Am J Cardiol* 1999, **83:**1497–1499.
This is the first published paper reporting a possible pharmacodynamic interaction between statins and antihypertensive drugs. The data reported in the study are limited to ACE inhibitors that could be considered a good solution for combining with statins.
36.•• Borghi C, Prandin MG, Costa FV, *et al.*: **Use of statins and blood pressure control in hypertensive patients with hypercholesterolemia.** *J Cardiovasc Pharmacol* 2000, **35:**549–555.
This paper demonstrates the importance of statin treatment for improving blood pressure control in treated hypertensive patients. The effect of statins is enhanced in patients treated with ACE inhibitors and calcium channel blockers, and is largely independent of the lipid-lowering activity.
37. Egashira K, Hirooka Y, Kai H, *et al.*: **Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia.** *Circulation* 1994, **89:**2519–2524.
38. O'Driscoll G, Green D, Taylor RR: **Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month.** *Circulation* 1997, **95:**1126–1131.
39. Lewis TV, Cooper BA, Dart AM, *et al.*: **Responses to endothelium-dependent agonists in subcutaneous arteries excised from hypercholesterolaemic men.** *Br J Pharmacol* 1998, **124:**222–228.
40.•• Laufs U, La Fata V, Plutzky J, *et al.*: **Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors.** *Circulation* 1998, **97:**1129–1135.
This report shows the capacity of statins to regulate the endothelial function acting through the activity of NO synthase. This mechanism might be involved in the blood pressure–lowering effect of statins.
41. Kaesemeyer WH, Caldwell RB, Huang J, Caldwell RW: **Pravastatin sodium activates endothelial nitric oxide synthase independent of its cholesterol-lowering actions.** *J Am Coll Cardiol* 1999, **33:**234–241.
42.•• Nickenig G, Baumer AT, Temur Y, *et al.*: **Statin-sensitive dysregulated AT1 receptor function and density in hypercholesterolemic men.** *Circulation* 1999, **100:**2131–2134.
The paper describes the capacity of high cholesterol levels and statins to modulate the expression of AT_1 receptors in men. This effect of statins could be responsible for the changes in pressor reactivity to angiotensin II observed in patients with hypercholestrolemia before and after the treatment with statins. An active modulation of AT_1 receptors may help to explain the blood pressure–lowering effect of statins.
43. Ide H, Fujiya S, Aanuma Y, *et al.*: **Effects of simvastatin, an HMG-CoA reductase inhibitor, on plasma lipids and steroid hormones.** *Clin Ther* 1990, **12(5):**410–420.
44. Sartor G, Katzman P, Eizyk E, *et al.*: **Simvastatin treatment of hypercholesterolemia in patients with insulin dependent diabetes mellitus.** *Int J Clin Pharmacol Ther* 1995, **33:**3–6.
45. Nazzaro P, Manzari M, Merlo M, *et al.*: **Distinct and combined vascular effects of ACE blockade and HMG-CoA reductase inhibition in hypertensive subjects.** *Hypertension* 1999, **33:**719–725.