Hypertension and dyslipidemia are the most prevalent cardiovascular risk factors in adults. They often coexist in the same patient, resulting in a high or very high risk of developing cardiac, cerebral, or vascular events due to accelerated atherosclerosis. Despite the availability of very effective therapies to control either hypertension or dyslipidemia, and thus reduce the global cardiovascular morbidity and mortality, neither hypertension nor dyslipidemia are adequately controlled in populations. Today, still too many individuals are not aware of being hypertensive or dyslipidemic, and among those who are aware and treated, less than 50% attain the blood pressure (BP) or the low-density lipoprotein (LDL) levels recommended by international guidelines. Among the many causes of insufficient BP and LDL control is a low adherence and persistence, often attributed to the complexity of prescribed regimens. To avoid these problems, the use of single-pill combinations is strongly recommended for the treatment of hypertension and, to a certain degree, for the management of dyslipidemia. This approach makes possible the simplification of therapy, the reduction in pill burden, and thus improvement in adherence and persistence. So far, most single-pill combinations address only one risk factor. There are, however, good arguments to encourage the development of new single pills acting across diseases, such as the association of antihypertensive drugs and lipid-lowering agents in a single tablet. The first combination of this kind associated amlodipine and atorvastatin. Today, several pills combining one or two antihypertensive drugs and a statin have become available. These combinations should make possible the adequate control of more patients with hypertension and dyslipidemia. Simultaneously treating hypertension and dyslipidemia in patients at risk of cardiovascular events might help support the observed decline in cardiovascular mortality.

**Why do we need a combined approach for the treatment of hypertension and dyslipidemia?**

**by M. Burnier, Switzerland**

_Hypertension and dyslipidemia belong to the most prevalent risk factors for the occurrence of cardiovascular diseases (CVD) in adults. Multiple epidemiological studies have demonstrated that elevated blood pressure (BP) and high cholesterol levels are the two major contributing risk factors for the development of myocardial infarction, heart failure, stroke, and vascular and renal complications. Hypertension and dyslipidemia frequently coexist in the same patient, and the risk of cardiovascular_
Complications associated with comorbid hypertension and dyslipidemia are more multifaceted than just the addition of the risk of the individual factors.\(^1\)\(^3\) Today, the prevalence of the coexistence of hypertension and dyslipidemia ranges between 15% and 50% depending on the studied populations and the presence of comorbidities.\(^1\)\(^3\) It is particularly high in the elderly.\(^1\) In this latter population, dyslipidemia increases the CVD risk mainly in those patients with a normal BP, whereas it has less impact on the incidence of new cardiovascular events in those who are already hypertensive.\(^2\)

**Evidence for a combined management of hypertension and dyslipidemia**

Lowering BP and cholesterol levels to recommended targets, as shown in Table I, can reduce cardiovascular events by almost 50%.\(^4\) Therefore, most recent guidelines for the management of hypertension in adults recommend not only to control BP but also to lower serum cholesterol with diet and/or statins in line with the specific recommendations of the European Society of Cardiology.\(^1\) The benefits of simultaneously controlling BP and cholesterol levels have been clearly demonstrated in the original publication of ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial).\(^6\)\(^7\) a randomized controlled trial performed in 19,342 men and women with hypertension, which included a blood-pressure–lowering arm (BPLA) and a lipid-lowering arm (LLA). Enrolled patients were aged 40 to 79 years and had at least three other cardiovascular risk factors than hypertension. In a subanalysis of this trial, atorvastatin reduced the relative risk of coronary heart disease events by 53% (P < 0.0001) among those allocated the amlodipine-perindopril regimen, and by 16% (P, not significant) among those allocated the atenolol-thiazide regimen (P = 0.025 for heterogeneity).\(^8\) Of note, the rate of fatal myocardial infarction and nonfatal coronary heart disease and the rate of fatal and nonfatal stroke were reduced by 48% and 44% respectively in the amlodipine + perindopril + statin group as compared with the atenolol + thiazide + placebo group. Recently, the authors of the trial reported the mortality of the patients in the United Kingdom (UK) after 16 years of follow-up.\(^6\) Interestingly, the benefits of simultaneous treatment of hypertension and dyslipidemia were still present even though the difference between the two treatment strategies was not significantly different for total death and cardiovascular deaths. However, there was a significant difference in stroke death in favor of the amlodipine group. In patients randomized to the LLA, significantly fewer cardiovascular deaths (hazard ratio [HR], 0.85 [0.72-0.99]; P = 0.0395) occurred among patients assigned to statin (865 deaths) than among those assigned placebo (903 deaths). In patients not participating in the LLA, there were fewer cardiovascular deaths (adjusted HR, 0.79 [0.67-0.93]; P = 0.0046) among those assigned to amiodipine-based treatment (745 deaths) than atenolol-based treatment (769 deaths). Thus, the follow-up of this trial tends to confirm the earlier observations that both BP-lowering and lipid-lowering treatments confer long-term cardiovascular benefits. Hence, these data provide good rationale for combining antihypertensive and lipid-lowering drugs, possibly in a single pill.

More recently, the results of the HOPE-3 trial (Heart Outcomes Prevention Evaluation 3), conducted in persons at intermediate cardiovascular risk who did not have CVD and who had

<table>
<thead>
<tr>
<th>Blood-pressure target</th>
<th>Lipid target</th>
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<tr>
<td>The first objective of treatment should be to lower BP to &lt;140/90 mm Hg.</td>
<td>For patients at low-moderate cardiovascular risk, statins should be considered to achieve an LDL-C value of &lt;3.0 mmol/L.</td>
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<tr>
<td>Provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mm Hg or lower in most patients.</td>
<td>For patients at high cardiovascular risk, statins are recommended to achieve an LDL-C goal of &lt;2.6 mmol/L, or a reduction of &gt;50% if the baseline LDL-C is 2.6-5.2 mmol/L.</td>
</tr>
<tr>
<td>In patients &lt;65 years, it is recommended that systolic BP should be lowered to a BP range of 120 to &lt;130 mm Hg in most patients.</td>
<td>For patients at very high cardiovascular risk, statins are recommended to achieve LDL-C levels of &lt;1.8 mmol/L, or a reduction of &gt;50% if the baseline LDL-C is 1.8-3.5 mmol/L.</td>
</tr>
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**Table I. Target values for blood pressure and lipid control according to the 2018 ESC/ESH guidelines on hypertension management in adults.**

**Abbreviations:** BP, blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; LDL-C, low-density-lipoprotein cholesterol.

**After reference 4:** Williams et al. J Hypertens. 2018;36(10):1953-2041. © 2018, Wolters Kluwer Health, Inc. All rights reserved.

**Selected Abbreviations and Acronyms**

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACCOMPLISH</td>
<td>Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension</td>
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<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lip-Lowering treatment to prevent Heart Attack Trial</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>EURIKA</td>
<td>European Study on Cardiovascular Risk</td>
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<tr>
<td>EUROASPHERE III</td>
<td>European Action on Secondary and Primary Prevention by Intervention to Reduce Events III</td>
</tr>
<tr>
<td>HOPE-3</td>
<td>Heart Outcomes Prevention Evaluation 3 (trial)</td>
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<tr>
<td>LDL-C</td>
<td>low-density-lipoprotein cholesterol</td>
</tr>
<tr>
<td>PAPA-CAD</td>
<td>Perindopril plus Amlodipine in PAtients with Coronary Artery Disease</td>
</tr>
<tr>
<td>PURE</td>
<td>Prospective Urban Rural Epidemiology (study)</td>
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Combining hypertension and dyslipidemia treatments – Burnier
a systolic BP of less than 160 mm Hg, further confirmed the benefits of a combined management of hypertension and dyslipidemia as reported in ASCOT. HOPE-3 was a trial with a 2-by-2 factorial design, in which 12,705 individuals with no CVD were randomized to rosvastatin (10 mg per day) or placebo and to candesartan (16 mg per day) plus hydrochlorothiazide (12.5 mg per day) or placebo. The primary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. For the secondary outcome, heart failure, cardiac arrest, or revascularization were added. The study showed that rosvastatin reduced CVD by 26.5%, but that BP lowering (BP reduction of 6/13 mm Hg) was only associated with a modest 7% relative risk reduction (RRR) in CVD. However, in a prespecified subgroup analysis of those with SBP in the highest tertile (>143 mm Hg), there was a 27% RRR in CVD with BP lowering.

The impact of low adherence and persistence
The poor results measured today in population surveys cannot be attributed to a lack of drug efficacy. It is well recognized that there is a huge gap between what is observed in clinical trials, in which BP can be controlled in up to 70% to 80% of patients, and what is observed in real life. Indeed, in the ACCOMPLISH trial (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension), 74.5% of the patients reached a target BP of less than 140/90 mm Hg, and in the ALLHAT study (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), the BP target of less than 140/90 mm Hg was obtained in more than 60% of patients in all treatment groups. However, in the multinational PURE study (Prospective Urban Rural Epidemiology), only a third of participants achieved BP control. The same is true with lipid-lowering drugs and the control of dyslipidemia. It is not drug efficacy that poses the main problem but rather the noninitiation of drug therapy, the high discontinuation rate, and the low adherence rate (Figure 1).

The failure of controlling hypertension and dyslipidemia in real life
In real life, however, the management of hypertension and dyslipidemia suffers from similar problems. Many individuals are not aware that they have either an elevated BP or a high cholesterol level or both, and among those who know their BP or cholesterol levels, many are not treated. Furthermore, when treated, most of them are not well controlled. In the EUROASPIRE III survey (European Action on Secondary and Primary Prevention by Intervention to Reduce Events III) performed in 2006 and 2007 in 76 centers from 22 European countries, patients with a clinical diagnosis of coronary heart disease were identified retrospectively and then followed-up, interviewed, and examined at least 6 months after their event. In this high cardiovascular risk population, 56% had a BP of 140/90 mm Hg or higher, and 51% had a serum total cholesterol level of 4.5 mmol/L or higher. However, only 26.3% of patients using antihypertensive medication had achieved the BP goal, and 30.6% of patients on lipid-lowering medication had reached the total cholesterol goal. These figures improved in recent surveys but the rate of control of both hypertension and dyslipidemia remains globally unsatisfactory. Other data come from the EURIKKA survey (European Study on Cardiovascular Risk), a study conducted with 7641 outpatients aged at least 50 years, free of clinical CVD and with at least one major CVD risk factor, selected from 12 European countries in 2009. In this study, among treated hypertensives (94.2%), only 38.8% achieved a BP of less than 140/90 mm Hg, and among treated dyslipidemic patients (74.4%), 41.2% attained both the total- and LDL-cholesterol (LDL-C) targets of less than 5 mmol/L and less than 3 mmol/L, respectively. In EUROASPIRE V, conducted in 27 European countries, the most recent data show that 42% of patients had a BP at or above 140/90 mm Hg (≥ 140/85 mm Hg if diabetic), 71% had LDL-C at or above 1.8 mmol/L (≥70 mg/dL), and 29% reported having diabetes.

The index date was defined as the date concomitant therapy (ie, second drug) was initiated. The impact of low adherence and persistence

Figure 1. Patterns of patient adherence to concomitant hypertension and lipid-lowering therapy over 3 years.

The index date was defined as the date concomitant therapy (ie, second drug) was initiated.

Acknowledgments: AH, antihypertensive; LL, lipid-lowering.


Combining hypertension and dyslipidemia treatments – Burnier
remains particularly low (around 36% in 2014) in patients with dyslipidemia who have not yet experienced a cardiac event, whereas in patients initiating treatment after a myocardial infarction, high adherence was observed in 63.8% of patients.27 Data suggest that discontinuing lipid-lowering treatments may have a major negative impact on the development of carotid plaques.28 Data from a meta-analysis on 376,162 patients from 20 studies assessing adherence using prescription-refill frequency for aspirin, statins, and antihypertensive drug classes in primary and secondary prevention have shown that adherence is below 60% for all drugs in primary prevention and between 60% and 75% in secondary prevention.29 In a recent survey among Swiss patients with type 2 diabetes and chronic kidney disease managed by primary care physicians, only 2.2% of the 1359 patients reached simultaneously the therapeutic objectives for BP, blood glucose, and lipids, indicating that much work is still needed (Figure 2).30

How to improve the control of hypertension and dyslipidemia

In order to improve the management of cardiovascular risk factors such as hypertension, dyslipidemia, or diabetes, reduction in the clinical impact of low adherence and persistence has become an important topic of recently published guidelines.43 Thus, European hypertension guidelines recommend using single-pill combinations as first-line therapy in order to reduce the pill burden and to facilitate the patients’ daily drug intake.4 In the last guidelines from the US, the recommendation is to dose antihypertensive medications once daily rather than multiple times daily to improve adherence, and to use combination pills rather than free individual components to improve adherence to antihypertensive therapy.31 This therapeutic strategy, which had been proposed in 2013 guidelines already, is now well established. Today, its implementation is favored by the development of many single-pill combinations containing either two or three drugs belonging to the antihypertensive classes recommended as first-line therapy, ie, blockers of the renin-angiotensin system, diuretics, and calcium channel blockers. In the field of dyslipidemia, the most popular single-pill combination associates a statin and ezetimibe.

Considering the fact that CVDs are multifactorial with various risk factors existing simultaneously and the observation that hypertension and dyslipidemia frequently coexist, combining antihypertensive and lipid-lowering drugs in a single tablet appears to be a reasonable therapeutic approach for the primary or secondary prevention of CVD. This is the case, for example, in hypertensive patients with a mild elevation of serum cholesterol and hence a moderate-to-high CV risk. In-
deed, as a principle, it appears more reasonable to reduce the absolute risk of a future cardiovascular event than to target an individual risk factor. Based on the results of ASCOT, the first drug combining an antihypertensive drug and a lipid-lowering agent was a single pill associating amlodipine and atorvastatin. In clinical studies, this single-pill combination effectively reduced systolic BP and LDL-C levels, and enabled more patients to achieve BP and LDL-C goals than single-agent or placebo therapy. In addition, the combination of amlodipine with atorvastatin resulted in pharmacodynamic effects that were not observed with the individual components or were at least less intensive. This includes improvements in endothelium-dependent vasodilation, decreased levels of the inflammatory marker serum C-reactive protein, improved insulin sensitivity, and beneficial effects on atherosclerotic plaque size and composition.

Drug adherence to the amlodipine/atorvastatin single pill improved significantly compared with free drugs, but the amelioration in statin adherence appeared to be significant, mainly in those patients who were already adherent to atorvastatin before starting the combination. In many countries, the success of the single pill of amlodipine and atorvastatin was mitigated. Among reasons evoked by physicians for not prescribing this association, one can cite an unclear definition of the target population, a lack of flexibility, and the cost. Moreover, a monotherapy based on a calcium channel blocker does not control BP in more than 40% of hypertensive patients. Yet, this does not mean that the concept of combining antihypertensive and lipid-lowering drugs should be abandoned. It should rather be reconsidered in light of new hypertension recommendations, avoiding, if possible, the usual criticisms addressed to single-pill combinations.

**Toward new single-pill combinations**

As mentioned previously, new European guidelines for the treatment of hypertension in adults recommend starting all new treatments with a dual therapy in a single pill, except in low-risk grade 1 hypertension (SBP<150 mm Hg) or in very old (>80 years) or frail patients, where monotherapy may still be used. Therefore, new single-pill combinations of antihypertensive and lipid-lowering drugs should now associate at least two first-line antihypertensive drug classes and onestatin in order to be able to control BP and lipid levels in about 60% of patients. The target population should be primarily hypertensive patients in primary prevention with a mild to moderate dyslipidemia that does not need high doses of statin but whose BP can be lowered to target with a dual antihypertensive therapy. Patients with hypertension and stable coronary heart disease may be another target population. In this perspective, a triple combination associating perindopril, amlodipine, and atorvastatin has been launched. This triple combination may have clear advantages in terms of treatment efficacy but also adherence and reduction in global cardiovascular risk. In a post hoc analysis of the PAPA-CAD non-interventional trial (Hungarian Perindopril plus Amlodipine in PA tients with Coronary Artery Disease), in which patients received the fixed-dose combination of perindopril/a mloidipine and atorvastatin as a second drug, more patients achieved BP targets, and metabolic parameters were improved.

**Benefits and risks of triple combinations**

Actually, besides the ability to improve drug adherence and persistence, adding a statin to a dual antihypertensive therapy might have additional benefits as discussed above. Thus, studies have suggested that BP control is improved with these associations, as observed in the Hungarian study. Indeed, although the issue remains controversial, there is increasing evidence of a positive interaction between statins and antihypertensive drugs leading to a slightly greater decrease in BP when the two therapeutic approaches are combined.

A priori, through their positive impact on adherence and persistence, single pills associating antihypertensive and lipid-lowering drugs should have a major impact on the incidence of cardiovascular events and on the cost-effectiveness of treatments. Today, this has not been formally demonstrated in prospective randomized trials, but post hoc analyses of published studies suggest that this approach may indeed be cost effective. A post hoc analysis of the ASCOT trial has evaluated the cost effectiveness of the different strategies applied in the trial.

Using a Markov model, it appeared that the combination of amlodipine-based therapy and atorvastatin is cost effective in patients with hypertension and three or more additional risk factors according to the UK or Swedish societal perspective. Moreover, in patients who occasionally miss doses of antihypertensives, modest differences in the rate of loss of antihypertensive effect after treatment interruption may have a clinically relevant impact on BP reduction and CVD risk.

Are there any risks associated with the use of triple combinations including antihypertensive and lipid-lowering drugs? In theory, there should not be more side effects with a triple combination than with three free drugs of the same compounds, provided drugs are taken regularly as prescribed. A frequent argument against single-pill combinations is that it might be more difficult to attribute new side effects to the right component of the combination. In fact, this is rarely the case because the side effects of statins, amlodipine, and blockers of the renin-angiotensin system are well-known after more than 20 years of use. Therefore, side effects are easily recognized. The flexibility of the treatment, another potential concern, can be improved with an adequate choice of dosing possibilities and defining a precise stepped-care approach, which takes into account the need to control hypertension, as well as dyslipidemia. One of the issues is probably linked to eventual discontinuations for any reasons. In that case, the pa-
tient will interrupt the therapy of two risk factors at once, which may lead to a rebound effect and the occurrence of a cardio-
vacular event.

**Conclusion**

The majority of cardiovascular events occur in patients with moderate increases in BP and/or serum cholesterol in combin-
ation with other risk factors, such as smoking, diabetes, and obesity. In the last 10 years, cardiovascular mortality has
decreased continuously in developed countries. The most effective means of reducing CV risk and cardiovascular mor-
tality further is to manage simultaneously all risk factors. The development of new, effective, and well-tolerated single pills
combining two antihypertensive classes and one lipid-lowing
der drug will provide additional opportunities to increase the
percentage of patients achieving their BP and LDL-C treat-
ment targets and thereby helps support the observed decline
in cardiovascular mortality.

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Keywords: adherence; blood pressure; interaction; lipid; persistence; single-pill combination; target