First-line management of hypertension

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EDITION

Recent evidence indicates that initiation of antihypertensive treatment with a combination may also be useful in patients with mild hypertension. First-step combination therapy offers several advantages compared with monotherapy. In addition to better adherence, it may provide faster blood pressure control, thus avoiding the frustration of a long-lasting search for effective monotherapy. Combination therapy with lower doses of each component drug often leads to a greater antihypertensive effect and fewer side effects.

by E. Agabiti-Rosei, Italy

Experimental and clinical research in hypertension has produced extraordinary results, which represent one of the major successes of modern medicine. However, despite the availability of effective and well-tolerated antihypertensive drugs, blood pressure (BP) control in the hypertensive population remains far from optimal. In fact, only approximately half of those who take antihypertensive treatment have BP <140/90 mm Hg. Although several factors may be responsible, poor adherence to antihypertensive treatment and therapeutic inertia by doctors represent main causes of poor BP control.

It has been widely recognized that the majority of hypertensive patients require two or more drugs in combination in order to reach BP target. However, current guidelines for the management of hypertension, particularly European guidelines, recommend initiation of treatment with combination therapy only for patients with moderate-to-severe hypertension or for those at high/very high cardiovascular risk. They nevertheless suggest that a single-pill combination may simplify treatment and hence favor adherence to the prescribed therapeutic regimen. Better adherence to treatment may translate into better cardioprotection and reduced morbidity and mortality.

Recent evidence indicates that initiation of antihypertensive treatment with a combination may also be useful in patients with mild hypertension. First-step combination therapy offers several advantages compared with monotherapy. In addition to better adherence, it may provide faster BP control, thus avoiding the frustration of a long-lasting search for effective monotherapy. Combination therapy with lower doses of each component drug often leads to a greater antihypertensive effect and fewer side effects.

BP is, in fact, regulated by multiple mechanisms, and the effect of a given drug may be modified by activation of compensatory pathways. A meta-analysis by Wald et al. indicated that combining two drugs of different classes with different mechanisms of action produces a BP reduction approximately five times greater than doubling the dose of one drug. Information from randomized trials on drug combinations that may effectively reduce cardiovascular outcomes is only indirect. A two-drug combination has been used systematically in only three trials: the Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE), which compared the angiotensin-converting enzyme (ACE) inhibitor perindopril plus the diuretic indapamide versus placebo; FEVER (Felodipine EVEnt Reduction), which compared the calcium antagonist felodipine plus the diuretic hydrochloro-
In all other trials treatment was initiated with monotherapy and another drug was added if needed. In summary, the combinations that were associated with significant benefit in randomized clinical trials and hence those that should be considered preferred combinations include: ACE inhibitor + calcium antagonist or diuretic; angiotensin receptor blocker + diuretic; and calcium antagonist + diuretic. Although the combination of angiotensin receptor blocker + calcium antagonist seems rational, effective, and well tolerated, it has never been systematically used in an outcome trial. A -blocker + diuretic combination was as effective as other combinations in several trials, but it appears to induce more cases of new-onset diabetes in some predisposed patients, compared with other combinations. The only combination that cannot be indicated, on the basis of the results of ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial)11 and ALTITUDE (Aliskiren Trial In Type 2 diabetes Using carDio-renal Endpoints),12 is two blockers of the renin-angiotensin system (RAS). In about 15% to 20% of patients, BP cannot be adequately controlled by a two-drug combination. In these cases a three drug combination is required and the most rational choice here seems to be a blocker of the RAS, a calcium antagonist, and a diuretic.2 This was the most commonly used combination in the intensive treatment arm of SPRINT (Systolic blood Pressure Intervention Trial),13 a recent trial that suggested that lower systolic BP targets may be of benefit in at least some subgroups of patients.

Thus, earlier treatment with combination therapy may help to reach lower BP targets in a more effective way. Indeed, it has been proposed that a simplified antihypertensive algorithm using initial low-dose combination therapy may be useful for the treatment of patients with hypertension, including mild hypertension.5,7 Recently, two large studies assessed the efficacy and tolerability of a single-pill first-line strategy combination of perindopril + amlodipine, starting with a low dose of each component.

In the first study,14 a perindopril/amlodipine combination initiated at a low dose and then uptitrated to higher doses was compared with a stepped-care strategy, initiated with monotherapy of an ARB and then uptitrated in combination with amlodipine. The conclusion of this three-month study was that the three-step strategy of initiation with single-pill perindopril/amlodipine produced greater lowering of BP and a more rapid rate of control of hypertension. In the second study,15 a low- and fixed-dose combination of perindopril/amlodipine was more effective than either component given singly and was noninferior to both component drugs given at their initial clinically approved doses. Adverse events with the low-dose combination were also less frequent.

In conclusion, first-line combination treatment given at adapted dosages even to patients with mild hypertension enables treatment via a dual mode of action, which is more effective than monotherapy and may possibly have fewer side effects. It is reasonable to expect that this will provide benefits beyond better BP control, such as improved compliance and more effective cardioprotection.

References
First-line antihypertensive treatment: should we move on from monotherapy? – Agabiti-Rosei

Keywords: arterial hypertension; antihypertensive treatment; combination treatment; fixed-dose combination; treatment adherence; adapted-dose combination
The impact of first-line treatment on the global burden of hypertension

by R. E. Schmieder and A. Jumar, Germany

Recent data from Europe indicate that only 40% of patients manage to achieve an adequate level of blood pressure (BP) control. The 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines discussed the question of whether combination therapy should always be preceded by an attempt to use monotherapy or not. This article will review the impact of first-line treatment on the global burden of hypertension in the light of current treatment guidelines. Poor BP control in Europe has led to an urgent call to action and the proposal of measures to improve BP control. In patients with mild BP elevation and low/moderate cardiovascular risk, the 2013 ESH/ESC guidelines recommend treatment initiation with a single antihypertensive agent. However, recent data indicate that initiating therapy with a single-pill combination may have some major advantages compared to monotherapy. Patients receiving initial combination therapy have a lower drop-out rate than patients given any monotherapy. Target BP has been shown to be reached faster when using initial combination therapy compared to add-on therapy. Adapted-dose combinations have been introduced, and these achieve effective BP control with fewer side effects than monotherapy, thereby improving adherence. Fast BP reduction after treatment initiation increases adherence further and improves cardiovascular outcomes. There is still an unmet need to improve BP control in treated and untreated patients with hypertension, and the evaluation of adapted-dose combinations will be a key issue in the future.

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High blood pressure (BP) was identified as the number one, dominant risk factor for global disease burden in 2010. The increase in annual mortality between 1990 and 2010 accounted for more than 2 million deaths. Despite the availability of treatment guidelines and a wide range of therapies, BP control is still suboptimal in many countries. Recent data for Europe indicate that only 40% of patients manage to achieve an adequate level of BP control. In 2008, there was an urgent call to action from international experts, who identified six key issues that were preventing better BP control: inadequate primary prevention, faulty awareness of risk, lack of treatment simplicity, therapeutic inertia, insufficient patient empowerment, and unsupportive health-care systems. Nevertheless, in 2016, BP control is still suboptimal, with only 39% of hypertensive patients achieving a BP target of less than 140/90 mm Hg. This article will review the impact of first-line treatment on the global burden of hypertension in the light of current treatment guidelines.
**Current guidelines on first-line treatment in hypertension**

European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines currently recommend targeting BP <140/90 mm Hg with drugs, in addition to lifestyle changes, in patients with grade 1 and 2 hypertension with no or 1 to 2 risk factors. To be more precise, antihypertensive medication should be started in patients with grade 1 hypertension when elevated BP has been confirmed by several BP measurements or when ambulatory BP is elevated despite the implementation of lifestyle changes for an appropriate length of time. The current guidelines from 2013 reconfirmed that diuretics, -blockers, calcium antagonists, angiotensin-convert- ing enzyme inhibitors, and angiotensin receptor blockers are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or combination therapy. The guidelines emphasized that the major mechanism for the benefits of antihypertensive therapy is the lowering of BP per se, the effects on cause-specific outcomes of the various agents are similar or differ by only a minor degree, and the type of outcome in a given patient is unpredictable. Nevertheless, all classes of antihypertensive agents have their advantages and contraindications.

The 2007 ESH/ESC guidelines mentioned that, no matter which drug is used, monotherapy can effectively reduce BP in only a limited number of hypertensive patients and that most patients require the combination of at least two drugs to achieve BP control. The next set of ESH/ESC guidelines in 2013 discussed the question of whether combination therapy should always be preceded by an attempt to use monotherapy or whether it was preferable to use combination therapy as an initial approach. The guidelines emphasized that treatment initiation with monotherapy allows effectiveness and adverse effects to be ascribed to that agent. Disadvantages of this approach were also discussed: finding an alternative, more effective monotherapy when the previous monotherapy is insufficiently effective or ineffective may be a painstaking process and discourage adherence, the pivotal prerequisite to achieving long-lasting BP control. The current guidelines mention that patients receiving combination therapy have a lower dropout rate than patients given any monotherapy and that a meta-analysis of more than 40 studies has revealed that combining two agents from any two classes of antihypertensive drugs reduces BP much more than increasing the dose of one agent. Other advantages of initial combination therapy are: a prompter response in a large number of patients; and a greater probability of achieving target BP in patients with higher BP values. Even though the advantages stated above were discussed in the 2013 ESH/ESC guidelines, the guideline experts ultimately reconfirmed the suggestion given in the 2007 ESH/ESC guidelines, in other words initiating treatment with a drug combination only in patients at high risk or with markedly high baseline BP.

**Adherence and physician inertia**

Global epidemiological studies show that poor BP control rates are linked to several factors, including poor adherence to treatment and physician inertia. This in turn has a negative impact on BP control and the global burden of hypertension.

**Adherence – a key factor in poor blood pressure control**

Low adherence concerns a large number of patients. After six months of treatment, at least one-third of patients will have stopped their initial treatment. On a daily basis, around 10% of patients forget to take their medication. Therefore, adherence is a key factor in the 2013 ESH/ESC guidelines advice on how to improve BP control. It has been shown in 4783 patients in 21 phase 4 trials evaluated by a medication-event monitoring system that compliance and persistence with antihypertensive therapy typically falls to less than 50% in one year. The fall in persistence is attributed to discontinuation of treatment and fall in adherence to poor execution of the dosing regimen. It is known that patients with high persistence show a significantly greater time-to-first-hypertension-related-event compared to patients with low persistence. More precisely, better adherence to antihypertensive agents significantly reduces cardiovascular risk, risk for chronic heart failure, and risk for coronary artery disease. A reduced risk of cardiovascular events due to good adherence has also been demonstrated in a large patient sample in Europe. A large systematic review and meta-analysis of

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CHEP</td>
<td>Canadian Hypertension Education Program</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>ESH</td>
<td>European Society of Hypertension</td>
</tr>
<tr>
<td>INVEST</td>
<td>International VEnapamil-SR/trandolapril STudy</td>
</tr>
<tr>
<td>LIFE</td>
<td>Losartan Intervention For Endpoint reduction in hypertension</td>
</tr>
<tr>
<td>SHARE</td>
<td>Supporting Hypertension Awareness and Research Europe-wide</td>
</tr>
<tr>
<td>VALUE</td>
<td>Valsartan Antihypertensive Long-term Use Evaluation</td>
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44 prospective studies showed that 9% of cardiovascular disease events in Europe could be attributed to poor adherence to vascular medications.13

It has been demonstrated for the major drug classes that the incremental effect on systolic BP lowering of doubling the dose of monotherapy is around 20% of that achieved by adding a drug from another class.16 Data from an analysis of 653 patients from three clinical trials revealed that single-pill combination therapy improves BP normalization ratios.17 Daily intake of more than two pills may lead to adherence below 50%.18 There is evidence that the improvement of adherence with single-pill combinations takes place regardless of concomitant medications.19 2013 ESH/ESC guidelines also favor the use of a combination of two antihypertensive drugs at fixed doses in a single tablet to improve daily adherence. A single-pill combination makes use of two pharmacological mechanisms,20 thereby increasing efficacy and sometimes reducing side effects, eg, the combination of perindopril with amiodipine substantially reduces the occurrence of edema.21,22

Active participation of the patient in the prevention and treatment of hypertension is key to increasing adherence, as emphasized by hypertension experts.1 Empowerment requires the patient to accept responsibility for their own health, commit to making lifestyle changes, and adhere to treatment.1 There is a wide range of tools and solutions available to empower patients, such as for example home BP monitoring, easy-to-use decision tools, hypertensive patient associations, and educational programs.7

**Physician inertia – the doctor as a risk factor for uncontrolled BP**

In a large sample of hypertensive patients (2014 individuals) treated by cardiologists and general practitioners it was demonstrated that more motivated physicians had higher rates of patients with controlled BP.23 This has been attributed to the more confident and optimistic approach to hypertension of these physicians and their more empathetic and supportive patient treatment. Even after adjustment for sociodemographic, clinical, and psychological patient-related variables, separate analyses for the patient groups included in the survey found that the gradient of systolic BP reduction decreased significantly according to physicians’ level of motivation.23 These results underline the importance of physicians’ perception of hypertension, aside from their compliance with international guidelines, for the successful management of hypertensive patients.23

Physician inertia was found to be a major reason for lack of up titration of treatment and BP control in large randomized controlled trials in hypertension.24 Major examples of these include LIFE (Losartan Intervention For Endpoint reduction in hypertension), VALUE (Valsartan Antihypertensive Long-term Use Evaluation), ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), and ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension).1 In a large retrospective cohort study including 62 US practices and conducted in 7252 hypertensive individuals, antihypertensive therapy was increased in only 13.1% of visits with uncontrolled BP.25 It was estimated that if we could eliminate inertia, systolic BP would be 13.8 mm Hg and diastolic BP 4.5 mm Hg lower.

Possible reasons for physicians’ inertia in hypertension are overestimation of the care provided, the use of “soft” reasons to avoid intensification of therapy, and a lack of education, training, or practice organization aimed at achieving treatment goals. It has been proposed by a European survey of physicians’ attitudes, SHARE (Supporting Hypertension Awareness and Research Europe-wide), that physicians may lack confidence in BP measurements and be hesitant to reduce BP further.26 The SHARE trial revealed that on average physicians were satisfied with a mean systolic BP of 131.6 mm Hg, were concerned by a mean systolic BP of 148.8 mm Hg, and took immediate action when mean systolic BP was 168.2 mm Hg.27 The question remains to what degree do these findings from SHARE accurately reflect the perceptions of physicians in the real world.

The 2013 ESH/ESC guidelines stress the role of team-based strategies in disease management, such as for example the involvement of nurses in implementing lifestyle changes. Team-based care has been shown to reduce systolic BP by around 10 mm Hg and increase BP control by 22%.28,29 One example of the success of team-based care in BP control is a North American professional education program called CHEP (Canadian Hypertension Education Program). CHEP provides annually updated simple recommendations and clinical practice guidelines for the detection, treatment, and control of hypertension. In the first four years after initiation of CHEP, dramatic increases have been observed in the diagnosis and treatment of hypertension.1,22,27 These improvements in hypertension management have been associated with major benefits in terms of reduction in cardiovascular deaths and hospitalization rates.26

**Are we going wrong from the very beginning? Our intention to catch up**

Could therapy initiation with adapted-dose combinations help to improve BP control and therefore reduce the global burden of hypertension?

Interestingly, in contrast to the epidemiologic data on worldwide BP control presented above, several clinical trials show that it is possible to achieve BP control in the majority of patients.29 This has been, for example, demonstrated in VALUE, a study including 15 314 patients that took place in a regular clinical setting, in which patients received either valsartan or amiodipine-based treatment. Systolic BP control (<140 mm Hg)
at 3 months increased from 21.9% at baseline to 62.2%, diastolic BP control (<90 mm Hg) from 54.2% to 90.2%, and combined control from 18.9% to 60.5%. Similarly, the majority of patients in ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), INVEST (International Vascular Arterioply-sarmin-SR/Endoplasmol Piril Study), ASCOT, and ACCOMPLISH—patients who received combination therapy with two or more drugs—also had BP that was controlled.20,21

There is mounting evidence that initial treatment with adapted-dose combinations can help to improve BP control. Target BP has been shown to be reached faster when using initial combination therapy compared to add-on therapy.22 Faster BP control in VALUE resulted in better BP control in the first 6 months of therapy and also fewer stroke events.33 It has been shown that fast BP reduction after the start of pill intake increases adherence. There is evidence that achievement of target BP is associated with a significantly smaller risk of cardiovascular events and total mortality.23 It will be very interesting to evaluate the direct comparison of adapted-dose combinations versus monotherapy in future clinical trials, not only with respect to BP control but also to hard end points. Indeed, preliminary data point to a lower incidence of events with adapted-dose-combinations (personal communication).

Conclusion

The continuing need to improve the control of high BP has recently been highlighted in a report from the World Health Organization24 and a fact sheet issued by the World Hypertension League and the International Society of Hypertension.25 In 2015, a working group of European investigators summarized the main challenges affecting the improvement of BP control today and suggested six key measures: (i) identify a BP treatment target of less than 140/90 mm Hg for the majority of patients; (ii) simplify treatment strategies and encourage pill reduction; (iii) decrease therapeutic inertia; (iv) improve patient empowerment; (v) involve health-care systems; and (vi) reduce the prevailing focus on drug costs.1 In this context, the evaluation of adapted-dose combinations is urgently needed. The improvement of BP control rates in untreated and treated populations will be a key issue in the future.

References

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pressure control goals. Hypertension. 2006;47:345-351.


Keywords: adapted-dose combination; hypertension; first-line treatment; global burden; adherence

The impact of first-line treatment on the global burden of hypertension – Schmieder and Jumar
Untreated hypertensive patients are usually stratified in hypertension grades (stages) according to systolic and diastolic blood pressure (BP) to guide therapeutic decisions. Old placebo-controlled randomized trials focused on so-called “mild hypertension,” but its definition nowadays is problematic and different to that of grade (stage) 1 hypertension, endorsed by hypertension societies worldwide. There has been much scientific debate on whether or not it is beneficial to treat grade 1 hypertensive patients. However, recent meta-analyses using different designs (individual versus tabular data) and approaches (selection of trials with untreated patients; restricting analyses in low/moderate risk; stratifying hypertension grade by using both systolic and diastolic BP) have provided evidence that grade 1 hypertension should be treated, except in special cases. Early treatment of hypertension is further supported by the notion that any delay, whether due to clinical inertia or not, significantly increases cardiovascular events. Indeed, aging and ongoing adverse cardiovascular adaptations in untreated hypertension heighten both the individual cardiovascular risk and the residual risk of treated patients, years after the initial diagnosis. The clinical approach to office grade 1 hypertension in untreated patients should be directed toward the confirmation of BP levels with out-of-clinic measurements and also toward taking into account the age and overall health of patients. On top of lifestyle changes, single-drug antihypertensive treatment to reach and remain within BP target can initially be implemented. In cases of failure to achieve the desirable BP level, fixed-dose combinations containing low doses of each component agent might be an option to pursue. However, special attention should be paid to the tolerability of each selected drug, especially in the elderly.

Grade 1 hypertension versus “mild hypertension”

According to the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines on the management of arterial hypertension, grade 1 hypertension defines the category of hypertension with systolic blood pressure (SBP) levels between 140 mm Hg and 159 mm Hg and/or diastolic blood pressure (DBP) levels between 90 and 99 mm Hg. The same thresholds have been endorsed in the seventh report of the Joint National Committee to define stage 1 hypertension. Grade or stage 1 hypertension is not synonymous with “mild hypertension” because the latter term was used some decades before to define different “mild” increases in DBP without paying attention to baseline SBP levels.
Mild hypertension trials were performed before 1993 and examined the effect of blood pressure lowering on various outcomes in patients at low cardiovascular risk, judged by DBP levels only. However, patients enrolled in “mild hypertension” trials were not always at low risk and, in addition, their SBP and DBP were in most cases well above current thresholds that define grade 1 hypertension. Due to the misleading clinical qualification of “mild” alongside “hypertension,” the principal clinical question is whether or not we should pharmacologically treat patients with grade 1 hypertension, especially those at low/moderate total cardiovascular risk.

The evidence so far...

It should be acknowledged that the evidence so far in the treatment of grade 1 hypertension is weak because the majority of blood pressure-lowering trials were performed in patients with baseline SBP ≥160 mm Hg and because the majority of blood pressure-lowering trials were performed in patients at low cardiovascular risk, judged by DBP levels only. However, patients enrolled in “mild hypertension” trials were not always at low risk and, in addition, their SBP and DBP were in most cases well above current thresholds that define grade 1 hypertension. Due to the misleading clinical qualification of “mild” alongside “hypertension,” the principal clinical question is whether or not we should pharmacologically treat patients with grade 1 hypertension, especially those at low/moderate total cardiovascular risk.

The analysis by Czernichow et al.4 which included a large number of trials in patients at different baseline SBP and DBP levels, indicated significant cardiovascular outcome reductions at all baseline blood pressure grades, including grade 1. However, this analysis considered patients who were already treated at baseline and thus the results cannot be extended to untreated grade 1 hypertension. The large meta-analysis by Law et al.5 was also conducted in patients on treatment at the time of randomization, and risk reductions were calculated separately for SBP and DBP, whereas hypertension grade definition requires simultaneous consideration of both SBP and DBP to include trials that comply with the definition of grade 1 hypertension. Law et al.5 included heart failure and postmyocardial infarction trials, which makes the applicability of the results in grade 1 hypertension at least disputable. The latter shortcomings were also detected in the meta-analysis by Thompson et al.6 who studied the effect of blood pressure lowering in patients with apparent (because of background treatment) normotension.

### Table I. Evidence on risk reduction from meta-analyses in grade 1 hypertension.

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Number of trials</th>
<th>Baseline treatment</th>
<th>Inclusion of trials in HF or post-MI?</th>
<th>Hypertension grade 1 definition*</th>
<th>Outcome risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czernichow et al.4</td>
<td>13</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>↓ major CV events</td>
</tr>
<tr>
<td>Law et al.5</td>
<td>19</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>↓ stroke</td>
</tr>
<tr>
<td>Thompson et al.6</td>
<td>8</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>↓ stroke</td>
</tr>
<tr>
<td>Cochrane Collaboration7</td>
<td>4</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>– No risk reduction</td>
</tr>
<tr>
<td>BPLTTC8</td>
<td>13</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>↓ stroke</td>
</tr>
<tr>
<td>Thomopoulos et al.9</td>
<td>6 (or minor)</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>↓ stroke</td>
</tr>
</tbody>
</table>

* Systolic and diastolic blood pressures were considered together.

“Mild hypertension” trials were performed before 1993 and examined the effect of blood pressure lowering on various outcomes in patients at low cardiovascular risk, judged by DBP levels only. However, patients enrolled in “mild hypertension” trials were not always at low risk and, in addition, their SBP and DBP were in most cases well above current thresholds that define grade 1 hypertension. Due to the misleading clinical qualification of “mild” alongside “hypertension,” the principal clinical question is whether or not we should pharmacologically treat patients with grade 1 hypertension, especially those at low/moderate total cardiovascular risk.
Grade 1 hypertension: to treat or not to treat? – Thomopoulos

The Cochrane Collaboration meta-analysis by Diao et al. considered old “mild hypertension” trials. Individualized data from correctly defined grade 1 hypertensive patients were used. Although the analysis was largely underpowered (30 strokes; 122 coronary events; and 165 major cardiovascular events), they concluded that pharmacotherapy of grade 1 hypertension was unable to reduce outcomes, with stroke marginally lacking statistical significance (relative risk, 0.51; 95% confidence interval, 0.24 to 1.08).

The Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) enriched the previously reported Cochrane Collaboration by also using available individualized data from nine more trials after post hoc selection of patients with grade 1 hypertension. The BPLTTC meta-analysis, which included 15,266 patients with grade 1 hypertension, reported risk reductions in stroke, cardiovascular death, and all-cause death following blood pressure-lowering treatment. However, even here, background antihypertensive treatment at baseline was substantial, suggesting that some patients only had apparent grade 1 hypertension. Finally, this pool of patients had a significant level of overall cardiovascular risk (6.2% risk of cardiovascular death over ten years), and this result can hardly be applicable to patients with true grade 1 hypertension and low/moderate total cardiovascular risk.

The benefit on various cardiovascular outcomes after treatment initiation in patients with grade 1 hypertension has been demonstrated by Thomopoulos et al. in a recent meta-analysis of 32 trials that included 104,359 patients categorized by average baseline blood pressure values into the three grades of hypertension. Grade 1 hypertension was represented by six trials and 16,036 participants. It was shown that blood pressure lowering reduced major cardiovascular events (fatal and nonfatal coronary heart disease and stroke), cardiovascular death, and all-cause death by 20%, 22%, and 18%, respectively. The benefit was not different to that observed following blood pressure lowering in untreated grade 2 and grade 3 hypertension (Figure 1A). The authors then restricted their analysis to patients with mild/moderate overall cardiovascular risk and reproduced the same results, except for the reduction in cardiovascular death (Figure 1B). In this latter analysis, which included 8,975 patients with grade 1 hypertension and an overall cardiovascular risk <5%, the reduction in absolute risk was also noteworthy: blood pressure lowering prevented 21 strokes, 34 major cardiovascular events, and 19 deaths for every 1000 patients treated for five years (Figure 1B). These effects remained almost unchanged when the HOPE-3 (Heart Outcomes Prevention and Evaluation 3) trial, with its predefined upper blood pressure subgroup, was added in the analysis (unpublished data).

The evidence from grade 1 hypertension trials considered in all the meta-analyses was derived from office blood pressure measurements. Although ambulatory blood pressure monitoring may offer more precise measurements and exclude white-coat hypertension, its value has never been tested in large hypertension trials.

What do the current guidelines say?

The 2013 ESH/ESC guidelines on the management of arterial hypertension as well as the American and International...
Societies of Hypertension recommend drug treatment in low/moderate risk grade 1 hypertension on top of previously prescribed lifestyle changes, when these latter measures alone fail to control blood pressure below 140/90 mm Hg for several weeks. The United Kingdom’s National Institute for Health and Care Excellence 2011 hypertension guidelines recommend restricting drug treatment only to those grade 1 hypertensive patients with high total cardiovascular risk or with evidence of target organ damage. These guidelines also recommend confirming grade 1 hypertension by ambulatory blood pressure monitoring. Members of the Eighth Joint National Committee report (JNC 8) suggest initiation of drug treatment in stage (grade) 1 hypertension based on “mild hypertension” trials and expert opinion for diastolic and systolic blood pressure components, respectively.

A clinical approach

**Apparent (on treatment) grade 1 hypertension**

Figure 2 shows what might be a clinical approach to treatment of grade 1 hypertension. First, it has to be established whether or not the patient who presents to the clinician with blood pressure values in the range of grade 1 hypertension is already being treated. With patients on antihypertensive treatment, apparent grade 1 hypertension indicates that a higher grade of hypertension has remained uncontrolled. Lowering blood pressure below 140/90 mm Hg is beneficial, as demonstrated in large meta-analyses of trials including both primary and secondary prevention patients on antihypertensive treatment at the time of randomization. In previously treated elderly patients in overall good health presenting with apparent grade 1 hypertension, pursuing blood pressure lowering below 140/90 mm Hg might be desirable, and careful drug titration should be used to reach this target while avoiding drug-related side effects. However, clinical decisions should be individualized, and special attention should be paid to establishing whether blood pressure lowering is well tolerated. In the very elderly (octogenarians), there is no evidence available for treatment initiation in grade 1 hypertension because the only available trial in this population, HYVET (Hypertension in the Very Elderly Trial), recruited fit patients with SBP ≥160 mm Hg. In this trial, SBP in the active group (on indapamide, alone or in combination with perindopril) reached 144.7 mm Hg, suggesting that octogenarians should not discontinue well-tolerated treatment.

**True (untreated) grade 1 hypertension**

Untreated patients with grade 1 hypertension are younger (below 65 years of age) and have not had previous cardiovascular events (primary prevention). The prescription of lifestyle changes is mandatory, and drug treatment should be immediately initiated in those with target organ damage, chronic kidney disease with reduced glomerular filtration rate, or diabetes mellitus because these conditions suggest high total cardiovascular risk. In patients with low/moderate total cardiovascular risk, after the prescription of lifestyle changes the potential benefit of drug treatment has to be balanced against potential harm, according to the following considerations:

1. Reduction in the relative and absolute risks of major cardiovascular events, all-cause death, and cardiovascular death with blood pressure lowering in grade 1 hypertension has recently been shown in a meta-analysis by Thomopoulos et al., strengthening previous evidence from a meta-analysis by the BPLTTC. In the former meta-analysis, it was also shown...
that all grades of untreated hypertension (or hypertension for which minor treatment has been prescribed) benefit from blood pressure lowering, and that treatment initiation in low/moderate grade 1 hypertension is favorable. Finally, the predefined grade 1 hypertension subgroup (baseline SBP 154 mm Hg) of the recently published HOPE-3 showed a 27% reduction in the risk of major cardiovascular events among patients at moderate cardiovascular risk, which translates into the prevention of one event for every 63 patients treated for five years.

2. The greatest benefit of blood pressure lowering is achieved in low/moderate risk patients because the higher the total cardiovascular risk, the higher the residual risk. Thus, treatment initiation at a lower hypertension grade in patients at low/moderate risk not only prevents cardiovascular events, but it is also accompanied by a reduction in treatment failure. Waiting for total cardiovascular risk to increase before treatment initiation might expose individuals to increased risk of cardiovascular events, development of target organ damage, and most importantly unmodifiable risk, because high risk once present is not always reversible.

3. Patients with grade 1 hypertension at low/moderate risk should be treated with one drug initially and possibly at a follow-up visits. A fixed-dose combination containing low doses of each active agent may provide an alternative to monotherapy if hypertension remains uncontrolled. In the elderly, cardiovascular risk is usually high, and initiation of treatment is indicated with grade 1 hypertension. However, particular attention should be paid to drug-related adverse events, since the presentation of drug-related adverse events increases with the extent of blood pressure lowering, targeting to 130 to 140 mm Hg might minimize drug tolerance issues.

4. Elderly patients (at least those younger than 80 years) with untreated grade 1 hypertension without a history of cardiovascular events should not be considered at low/moderate risk because older individuals are usually at high risk. In this particular case, blood pressure might be lowered below 140/90 mm Hg provided that treatment is well tolerated, but this decision is not evidence-based because trials in this population recruited patients with at least grade 2 hypertension.

5. Young individuals at low risk of isolated grade 1 systolic hypertension should not be treated by drug treatment and only lifestyle measures should be prescribed. Because of scanty data in this particular group, close follow-up is desirable.

◆ Practical issues

In previously untreated patients with grade 1 hypertension, the decision about whether or not to initiate treatment depends on the overall clinical evaluation. First, blood pressure should be adequately measured at the office. It is also reasonable to assume that ambulatory blood pressure monitoring or home blood pressure measurements can help confirm the diagnosis. Evaluation of 10-year cardiovascular death risk is based on SCORE (Systematic Coronary Risk Evaluation) criteria and rates ≥5% indicate high risk. The presence of diabetes, chronic kidney disease of stage 3 or more, or signs of target organ damage directly classify patients at high or very high risk. In some cases, patients at low/moderate risk may be prescribed lifestyle changes for several weeks before pharmacological treatment is initiated. When pharmacological treatment is finally prescribed, efforts to change lifestyle should not discontinue. Single-drug therapy at a standard dose should be introduced, and blood pressure control and tolerance evaluated at follow-up visits. A fixed-dose combination containing low doses of each active agent may provide an alternative to monotherapy if hypertension remains uncontrolled. In the elderly, cardiovascular risk is usually high, and initiation of treatment is indicated with grade 1 hypertension. However, particular attention should be paid to drug-related adverse events, and treatment escalation should be done carefully.

Conclusion

Grade 1 hypertension, with only some exceptions, should be treated pharmacologically on top of lifestyle changes even in those at low/moderate risk. Of late, the synthesis of evidence through meta-analysis has shown clear benefits in starting drug treatment early. This evidence is further supported by the notion that delaying the treatment of hypertension significantly increases cardiovascular events. Indeed, aging and ongoing adverse cardiovascular adaptations in untreated hypertension increase both the individual cardiovascular risk and the residual risk of patients treated, years after the initial diagnosis.

References


Keywords: grade 1 hypertension; total cardiovascular risk; mild hypertension; cardiovascular outcomes; guidelines
It is apparent that that time-to-goal matters and should be reduced to the shortest time compatible with optimal safety and tolerability. It is clear that long-term BP control is necessary to provide continuing cardiovascular protection, and that the simplicity and tolerability of the treatment regimen are critical considerations in achieving these goals. Using appropriate agents and dosing regimens, the default use of initial combination therapy advances these objectives...“

The association between blood pressure (BP) elevation and cardiovascular risk is robust and consistent across disparate populations.1,2 In clinical trials evaluating antihypertensive agents, cardiovascular protection occurs primarily in response to BP reduction, and less in response to the specific pharmacologic properties of individual drugs or drug classes.3 Although the effectiveness of antihypertensive therapy is well-established, prophylactic treatment, as currently practiced, prevents only about a third of clinical events, including stroke and myocardial infarction, which are statistically related to BP elevation.4 This modest and incomplete degree of cardiovascular protection highlights the enormous potential offered by more effective methods of BP management and control. Combination therapy has been used since the early days of antihypertensive drug treatment,5 and ≈75% of hypertensive patients require more than one drug to achieve target BP.6

Faster blood pressure control for earlier cardiovascular protection

by A. H. Gradman, USA

Initial combination therapy facilitates the achievement and maintenance of target blood pressure (BP). It accelerates the time-to-goal, increases mean BP reduction, and improves responder rates even in patients with stage 1 hypertension. It does so by blocking multiple pressor pathways, interfering with counterregulatory responses, and influencing the behavior of patients and physicians in ways which improve BP management. By reducing pill burden, patient adherence is improved when single-pill combinations are used. Three community-based studies involving ethnically diverse populations have evaluated end point reduction with initial combination versus initial monotherapy in patients with hypertension; all have reported better outcomes. In the one study that evaluated the interrelationship between BP reduction, goal attainment, and cardiovascular events, cardiovascular risk was reduced by 34%. Most of the risk reduction was attributable to earlier achievement of goal BP. It is noteworthy that 54% of patients in this study had stage 1 hypertension and would not generally be considered candidates for initial combination treatment according to current treatment guidelines. Selection of drugs for initial combination therapy is focused preferentially on agents with evidence of cardiovascular protection in long-term clinical trials. Development of simplified dosing regimens adapted for use in a general population of patients promotes the other primary goal of antihypertensive therapy today: the practical application of proven treatment strategies to the broad worldwide population of patients placed at elevated cardiovascular risk by treatable BP elevation.

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In general, combining drugs from pharmacologically complimentary classes is approximately five times more effective in lowering BP than increasing the dose of one drug. Although the need to use multiple drugs in many patients has always been recognized, “stepped-care” therapy became and remains the recommended paradigm for initiating treatment in Europe and the United States. Using this approach, treatment of patients is begun with a single drug and its dosage titrated upward in an attempt to achieve target BP. Only if goal BP cannot be achieved with monotherapy is a second drug added. In 2003, the seventh Joint National Committee (JNC 7) recommended the use of initial combination therapy in patients with baseline BP ≥20/10 mm Hg above goal. The current European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines suggest that initial combination therapy be considered “in patients at high risk or with markedly high baseline BP.” At present, however, ≈75% of stage 1 and 2 patients in the US begin treatment with monotherapy. 

There is accumulating evidence that routine initiation of a drug combination rather than a single agent may prove to be a surprisingly effective strategy for improving the long-term results of antihypertensive therapy. In this paper, the rationale and evidence supporting this evolution in the treatment of hypertension will be discussed.

The importance of early blood pressure control

The stepped-care paradigm is predicated on a measured approach to the management of hypertension. The underlying assumption is that hypertension is a chronic condition which develops over many years, poses little immediate risk to health, and can be treated by the gradual reduction of BP into the normal range. Depending upon baseline cardiovascular risk, the 2013 ESC/ESH guidelines recommend variably effective programs of “lifestyle modification”—weight loss, salt restriction, and increased exercise—which are continued for up to “several months” in patients with stage 1 hypertension and up to “several weeks” in those with stage 2 hypertension. This strategy usually delays the initiation of more effective drug treatment. Once drug therapy is begun, the time frame for achievement of BP control is not clearly specified, and it was not thought, until recently, to exert a major influence on the long-term results of therapy.

Recent studies call these assumptions into question. While the optimal time frame for achieving target BP has not been defined, there is evidence that prompt BP control confers advantages in terms of end point reduction. In the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial, which compared initial treatment with valsartan versus amiodipine, amiodipine-treated patients demonstrated 3-4 mm Hg greater BP reduction during the first 6 months of treatment and suffered fewer cardiovascular end points concurrently. BP response after only 1 month of treatment predicted events and survival, and achievement of BP ≤140/90 mm Hg during the first 6 months of treatment predicted fewer cardiovascular events over the 5-year duration of the study, regardless of treatment assignment. No difference was seen in end point occurrence after the first 6 months when BP differences between treatment groups narrowed, indicating it was the BP—not the drugs—which determined the early study results. These results suggest both short- and long-term benefits of early BP control.

Initial combination therapy

Effects on early BP reduction

An example of the effects of initial combination therapy on early BP control was shown in the ACCELERATE (Aliskiren and the Calcium Channel BlockER amlodipine combination as an initial treatment strATEgy for hypertension control) study. Patients, the majority of whom were stage 2 (mean baseline BP =161/92 mm Hg), were randomized to begin treatment with amiodipine 5 mg, aliskiren 150 mg, or the combination of amiodipine 5 mg/aliskiren 150 mg. These doses were doubled after 8 weeks. At 16 weeks, the group assigned to the initial combination showed a clear advantage in terms of BP reduction (Figure 1, page 98). At this juncture, all patients were placed on the high-dose combination of amiodipine 10 mg/aliskiren 300 mg. Within 8 weeks, BP differences between treatment groups were reduced to 2/1 mm Hg. However, integrated over the first 6 months of therapy (by visual inspection), average BPs were considerably higher in the monotherapy groups. There was no significant difference in treatment-related adverse events.

More rapid BP control has also been observed in patients with stage 1 hypertension. Weir et al compared the time-to-goal in 4278 patients treated initially with several doses of valsar-
First-line management of hypertension

Faster blood pressure control for earlier cardiovascular protection – Gradman

**Figure 1. ACCELERATE: blood pressure reduction in randomized treatment groups.**
Patients had a doubling of their doses at 8 weeks. At 16 weeks, patients on monotherapy advanced to combination treatment.

*At 24 weeks, HCTZ was added if systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg. Abbreviations: ACCELERATE, Aliskiren and the Calcium Channel blocker amlodipine combination as an initial treatment strategy for hypertension control; HCTZ, hydrochlorothiazide.

**Figure 2. Time-to-goal blood pressure (<140/90 mm Hg) in patients with stage 1 hypertension.**
Abbreviations: BP, blood pressure; HCTZ, hydrochlorothiazide; Val, valsartan.


In a community practice setting, the STITCH (Simplified Treatment Intervention To Control Hypertension) study compared the effectiveness of a simple treatment algorithm using an initial fixed-dose combination (either angiotensin-converting enzyme [ACE] inhibitor/HCTZ or angiotensin receptor blocker [ARB]/HCTZ) to direct application of the Canadian Hypertension Education Program guidelines by practicing physicians. The proportion of patients who achieved BP target within 6 months was 65% in those initiated on the combination and 53% in patients who received guideline-based therapy.

**Effects on long-term BP control**
Egan et al examined the effects of initial combination therapy on BP control after ≈1 year in a cohort of >100,000 subjects participating in the US National Health and Nutrition Examination Survey. Patients receiving initial combinations were divided into those receiving single-pill combinations and “free” combinations, ie, two pills from different pharmacologic class-
es. During follow-up, 32% of patients started on monotherapy had additional agents added. Among all patients, 59% initiated on free combinations and monotherapy, and 68% begun on single-pill combinations were controlled after 396 days of treatment. The median time to 50% BP control for the single-pill combination was 195 days, compared to 269 days for the free-dose combinations and 280 days for monotherapy. Among the factors independently associated with worse BP control were the number of BP pills prescribed and evidence of therapeutic inertia (ie, failure to intensify treatment when indicated) on the part of the treating practicing physician.

The results of this large study illustrate the importance of examining real-world practice data in addition to the results of clinical trials. “Free” drug combinations are no less effective than fixed-dose combinations, provided the drugs and doses selected are those which produce additive BP reduction. In patients initiated on monotherapy, treating physicians had the option of adding additional drugs as needed and did so in 32% of patients. As illustrated in ACCELERATE, where all patients begun on monotherapy were uptitrated to combination treatment, little long-term difference in achieved BP would be expected if the principles of stepped-care treatment were followed consistently. What then accounts for the superior long-term BP control in patients initiated on single-pill combinations?

Although pharmacologic factors may be important, the causes of superior BP control relate to the human aspects of medical care. BP reduction requires patient adherence, which is inversely related to the number of pills prescribed.15-17 In this study, the use of “free” combinations, with a higher pill burden, predicted worse BP control. Therapeutic decisions, in the community practice setting, represent the judgment of individual physicians, who differ in their knowledge base and time available to follow optimal treatment patterns. Single-pill combinations simplify treatment for patients. Their use also takes much of the uncertainty out of decision-making for practitioners by providing marketed combinations that have undergone rigorous testing and have been found to be safe and effective.

The BP data are consistent that initial combination therapy facilitates both the achievement and maintenance of BP control. Since BP reduction is the primary determinant of end point reduction, it would be predicted on the basis of these data that initial combination therapy would improve long-term outcomes.

**Effects on cardiovascular end points**

Three community-based studies involving ethnically diverse populations have evaluated initial combination versus initial monotherapy on cardiovascular events; all have reported improved outcomes. Corrao et al conducted a population-based case-control study involving >40 000 patients comparing newly treated Italian patients who did and did not experience a subsequent cardiovascular event.18 Patients initiated on a combination had an 11% risk reduction, including both cardiac and cerebrovascular events, compared to those initiated on monotherapy. When patients maintained on either monotherapy or combination treatment for the entire treatment period were compared, initial combination therapy was associated with a 26% risk reduction. Patients begun on monotherapy and later switched to a combination had outcomes indistinguishable from the monotherapy cohort. The authors reasoned that the protective effects associated with initial combination treatment might reflect better BP reduction and/or direct pharmacologic effects resulting from the simultaneous use of agents that block multiple pharmacologic pathways.

Gradman et al assessed the impact of initial versus delayed combination therapy on the risk of cardiovascular events, and evaluated the interrelationship between BP reduction, goal attainment, and cardiovascular risk.19 Using electronic medical records from a large integrated health-care delivery network in the United States, 1762 adult patients initiating combination therapy (either single-pill or “free” combinations) were identified and compared to a similar population matched 1:1 according to baseline clinical characteristics. Mean baseline BP was 150/84 mm Hg and 54% had stage 1 hypertension. Initial treatment with a drug combination was associated with a 34% risk reduction for cardiovascular events (myocardial infarction, stroke/transient ischemic attack, hospitalization for heart failure) or death, relative to patients initiated on monotherapy and subsequently switched to a combination by their physician ($P$=0.0008) (Figure 3, page 100).

The cumulative effect of initial versus delayed combination therapy on target BP achievement is shown in Figure 4 (page 100).19 There was early separation of the Kaplan-Meier curves and, after 6 months, 40.9% and 32.6% of patients with initial versus delayed combination treatment reached target BP. During follow-up, the overall proportion of patients achieving target BP was consistently higher in the combination therapy cohort, resulting in a shorter median time-to-goal BP achievement (9.7 versus 11.9 months; log-rank $P$=0.004). After ~30 months, control rates in the two treatment groups converged, reaching ~80%. These findings are consistent with ACCELERATE and other studies, which document a lag time in BP goal attainment when patients initiated on monotherapy and later uptitrated to combination treatment are compared to those begun on a combination. The length of this lag time is variable and highly dependent upon the time course of drug titration. In this study, uptitration at the discretion of the individual practicing physicians occurred an average of 13.5 months after treatment initiation.

Achieving target BP at any time was associated with a significant risk reduction of 23% in cardiovascular events or death. Using a second statistical model in which each BP assessment was used to update the systolic BP stage, the results showed that systolic BP >160 mm Hg at the last reading was
associated with a 2.2-fold increased risk of developing a cardiovascular event or death compared to a systolic BP reading of 120-139 mm Hg ($P<0.0001$). In this study, which documented improved BP control for >2 years in the initial combination therapy cohort, most of the end point reduction was attributable to BP reduction. The residual risk reduction of 16% associated with initial combination therapy approached, but did not reach, statistical significance ($P=0.09$). It is unclear whether this effect is due to the pharmacologic effects of drug combinations or to unmeasured effects on BP, which would be clarified through the use of more sophisticated methods of BP measurement, such as 24-hour ambulatory BP monitoring.

This study directly compared patients who received initial combination therapy to those receiving delayed combination therapy, not permanent monotherapy. It therefore mimics a comparison of initial combination therapy to stepped-care treatment in individuals who will require >1 drug to control BP. It documents an advantage of initial usage of combination therapy as opposed to its eventual usage in a population the majority of whom had stage 1 hypertension. It also documents the value of reaching BP targets earlier rather than later, although it does not clarify the optimal time frame for achieving BP control. The results are consistent with Corrao’s study, in that outcomes were superior in patients initiating combination therapy compared to those begun on monotherapy and switched to combination treatment. The study also documented a 9% reduction in the use of health-care resources, including urgent care and outpatient services, associated with initial combination treatment.

In a community-based Chinese study, Yu reported reduction in short-term stroke incidence when 4926 hypertensive patients initiating treatment with a drug combination were compared to 32 682 patients initiating treatment with monotherapy.$^{20}$ Mean baseline BP was 148/90 mm Hg in the initial combination therapy cohort and statistically greater than the 146/89 mm Hg seen in those who received initial monotherapy. Although there were no differences in BP control rates at 6 months or at subsequent time intervals reported in the manuscript, the authors state that “the target BP control rate was significantly higher in the combination group than in the monotherapy group before the 6th follow-up month” (data not included). Additionally, the mean reduction in systolic BP at 6 months was greater in the combination

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**Figure 3.** Initial combination versus add-on therapy: incidence of cardiovascular end points.

*Number of patients with an event per 100-person years.

Abbreviations: CV, cardiovascular; HF, heart failure; MI, myocardial infarction; TIA, transient ischemic attack.


**Figure 4.** Estimates of patients achieving target BP: initial combination versus add-on treatment.

Abbreviation: BP, blood pressure.

therapy group (13.8 mm Hg versus 12.5 mm Hg; *P* = 0.0003). The 6-month incidence of stroke in the combination therapy cohort was 36% lower than in patients who received monotherapy. No significant group differences were observed at 12, 24, or 42 months. The authors interpreted the results of the study as unrelated to BP control. A more likely explanation is that, as in the VALUE trial, a transient early advantage in BP reduction translated into an early reduction in stroke incidence.

**Choice of drugs**

Although a thorough discussion of this complex topic is beyond the scope of this paper, several points can be made regarding agents to be included in combinations targeted for first-line use. It is important to choose drugs which: (i) produce additive BP reduction; (ii) improve outcomes in long-term clinical trials; and (iii) possess a favorable safety and tolerability profile when combined. After consideration of these factors, combinations of ACE inhibitors and ARBs with diuretics or calcium channel blockers (CCBs) were designated as preferred combinations in the 2010 American Society of Hypertension position paper on combination therapy. Some authorities recommend ACE inhibitors in preference to ARBs, particularly in patients at high risk for coronary events, because of evidence of non-BP–related cardioprotection with these agents. Single-pill combinations are preferred as they reduce pill burden and improve adherence.

The ACCOMPLISH (Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension) study was the only major hypertension trial to utilize first-line combination therapy. The study tested whether initial therapy with a fixed-dose combination of an ACE inhibitor and a CCB differs from that with a fixed-dose combination of an ACE inhibitor and a diuretic with regard to clinical outcomes in high-risk hypertensive patients. Despite comparable BP reduction, the ACE inhibitor/CCB (benazepril/amlodipine) combination reduced the combined end point of cardiovascular death, myocardial infarction, and stroke by 20% compared to the ACE inhibitor/diuretic combination. Of note, 60% of patients were diabetic, and a large percentage had evidence of ischemic heart disease. There are few data from other sources to distinguish between preferred combinations. In the community-based end point studies discussed above, the long-term effects of the various combinations used as initial treatment were not compared.

**Dosage**

Selection of doses for first-line administration in individual patients involves a careful evaluation of efficacy, safety, and tolerability. Baseline BP is of particular importance. In stage 2 patients, for whom initial combination therapy is most often recommended, higher initial doses are well-tolerated and appropriate as the primary goal is earlier BP control. In the ACCELERATE study, patients in the initial combination therapy arm received both of the component drugs at the same dose given to patients in the monotherapy arms. After 8 weeks of treatment, BP reduction was a robust 21.5/10 mm Hg. This dosing strategy and a similar magnitude of BP reduction has been observed in other studies with combinations of renin–angiotensin–aldosterone system blockers and CCBs. This dosing strategy is not optimal for all patients. Some stage 2 patients are frail, elderly, or suffer from other conditions that predispose to complications associated with marked short-term BP reduction. In these patients and in those with stage 1 hypertension in whom baseline BP is not markedly elevated, there is a need for less potent initial treatment. Up titration of low initial combination doses of perindopril (2 mg) and indapamide (0.625 mg) was used in the STRATHE (STRAtegies of Treatment in Hypertension: Evaluation) study. This treatment strategy resulted in higher rates of goal BP attainment compared to patients treated with the stepped-care approach or “sequential monotherapy,” in which up to three drugs were administered sequentially in an attempt to achieve BP control.

The need to develop simple, effective strategies for rapidly achieving target BP has led to new formulations of perindopril and amlodipine, two drugs that have reported excellent cardiovascular end point reduction in previous studies. Three perindopril/amlodipine formulations will be available: 3.5/2.5 mg, 7.0/5.0 mg, and 14/10 mg. The starting dose has been shown to be more potent than monotherapy with valsartan (80 mg), irbesartan (150 mg), or perindopril (5 mg), with a comparable safety profile. Dosing involves doubling the previous dose of both agents with each titration. Use of this strategy with the addition of indapamide 1.5 mg SR if needed as an additional step resulted in goal BP (<140/90 mm Hg) achievement in 86% of 881 patients, 80% of whom had stage 2 and 20% stage 1 hypertension. This was higher than goal BP attainment using valsartan and amlodipine administered via a stepped-care approach.

**Perspective**

The challenge in antihypertensive therapy today is to realize its potential, to apply proven therapeutic approaches to a much greater fraction of the worldwide hypertensive population. This requires the prompt achievement and maintenance of target BP in individual patients. It is apparent that that time-to-goal matters and should be reduced to the shortest time compatible with optimal safety and tolerability. It is clear that long-term BP control is necessary to provide continuing cardiovascular protection, and that the simplicity and tolerability of the treatment regimen are critical considerations in achieving these goals. Using appropriate agents and dosing regimens, the default use of initial combination therapy advances these objectives and represents an important evolutionary development in the treatment of hypertension.
References


Keywords: hypertension; drug treatment; combination therapy; cardiovascular protection; time to goal

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**First-line management of hypertension**

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**Keywords:** hypertension; drug treatment; combination therapy; cardiovascular protection; time to goal
The use of low-dose single-pill combinations presents theoretical advantages in regards to superior effectiveness and safety as compared to conventional monotherapy-based regimens. Further, single-pill combination therapy leads to improved adherence and overall higher rates of blood pressure control in hypertensive patient populations. Additionally, those patients initiated on combination antihypertensive therapy demonstrate lower rates of cardiovascular events.”

“Nothing is more powerful than an idea whose time has come.”
Victor Hugo—French novelist and poet (1802-1885)

In the context of the broader pharmacopeia used across medicine, the resistance to the use of low-dose single-pill combinations early in the management of hypertension can only be viewed as anomalous. For a range of disorders, initial combination therapy is the standard, including for the treatment of infections (trimethoprim/sulfamethoxazole for urinary tract infections), for pain relief (nonsteroidal anti-inflammatory drugs/codeine), and for the management of asthma (β-adrenergic agonists/steroids). However, despite the continuing challenges that we have in achieving better blood pressure control on a global basis and the generalized appreciation that we need multidrug therapy for blood pressure control in the vast majority of patients with hypertension, health-care providers are reluctant to use single-pill combinations as their first-line choice. In this review I will summarize what I see as some of the key factors responsible for suboptimal blood pressure control and how the greater use of single-pill combination therapy as initial treatment may improve this situation.
Key determinants of suboptimal blood pressure control: patient and health-care provider factors

The major factors leading to suboptimal blood pressure control can probably be grouped into issues related to: (i) health-care delivery barriers; (ii) financial barriers (both individual and societal); (iii) health-care professional–related factors; and (iv) patient-related factors. In most developed countries, the main factors remain patient-related and health-care professional-related. In regards to these latter two factors, the greater use of single-pill combination therapy in hypertension management would be an important advance.

Patient-related factors: nonadherence and therapeutic turbulence

The major patient-related factor impeding blood pressure control is nonadherence (also known as noncompliance, nonconvergence, or nonconcordance). Nonadherence leading to suboptimal disease management is common to a range of diseases, but especially notable for those diseases that are asymptomatic until complications supervene (like dyslipidemia, diabetes, and atrial fibrillation). In hypertension, nonadherence rates—reflecting both a failure to implement a dosing regimen and failure to continue therapy—have been reported at rates as high as 50% at one year.1 However, in the setting of patients with apparently resistant hypertension, the rate is probably closer to 10% to 20%.3 A number of factors have been implicated in predisposing to nonadherence with anti-hypertensive drug regimens. They include: (i) mistaken patient beliefs/attitudes, including the belief that long-term medication use is harmful or that hypertension is “cured” if blood pressure readings are normal; and (ii) treatment-ascribed symptoms (whether drug-related or not).

Beyond patients’ beliefs and attitudes, the complexity of antihypertensive medication regimens has also been an important determinant of poor adherence. Specifically, the risk of nonadherence increases both with increasing number of daily doses and increasing number of tablets.3 4 Further, our traditional approach of sequential replacement of monotherapies as the initial prescribing strategy for blood pressure control has been shown to reduce adherence. This approach of increasing the dose of monotherapy and, in the setting of a lack of or partial response, replacing one drug with a drug from another class, leads to reduced adherence and hence reduced blood pressure control. This phenomenon, termed “therapeutic turbulence,” has been shown to lead to an ≈25% increase in nonadherence consequent to two or more cycles of dose escalation and substitution.5

Health-care provider-related factors: therapeutic inertia and the prescription of suboptimal medication regimens

Of perhaps the greatest importance as a health provider–centered determinant of suboptimal blood pressure control is the phenomenon of clinical inertia, ie, the failure of a health-care provider to initiate or intensify therapy when therapeutic goals are not reached. Clinical inertia is a major factor leading to delayed treatment initiation, follow-up, and ultimately blood pressure control and to increased risk of an acute cardiovascular event or death.6 7 It has been estimated to occur in as many as two thirds of clinic visits of patients with hypertension.1 3 4

Multiple factors have been suggested to contribute to clinical inertia, including overestimation of the impact of provided care, assuming elevated clinic blood pressures represent white-coat effects, overreliance on health behavior change strategies, and knowledge gaps.1 7 The complexity of antihypertensive regimens required to achieve blood pressure control would also be expected to be a significant contributing effect to the development of clinical inertia. This complexity primarily relates to: (i) the number of medications required to achieve blood pressure control, eg, three to four drugs required to reach the lower blood pressure targets recommended for higher risk (SPRINT [Systolic blood Pressure Intervention Trial]-type) patients;8 and (ii) the number of medications currently available for blood pressure treatment and the thousands of combinations and permutations of drugs to choose among, compounded by the competing voices of guidelines organizations and pharmaceutical companies on how best to manage patients with hypertension. However, regardless of the determinants of clinical inertia, its impact on blood pressure control rates on a practicewide basis is enormous. As illustrated by Okonofua and colleagues,9 the difference between blood pressure control rates in practices with the highest extent of clinical inertia versus those practices with the lowest was greater than 70%, ie, control rates of less than 10% in the practices demonstrating the greatest extent of clinical inertia versus more than 70% in those practices exhibiting the least. The prescription of suboptimal therapeutic regimens by health-care providers is probably the most underappreciated contributor to suboptimal blood pressure control. The impact of suboptimal therapeutic regimens on blood pressure control was perhaps best illustrated by the study of Garg and colleagues.2 In their survey of patients with apparently “resistant hypertension” they found that for almost 60% of them the primary determinant of poor blood pressure control could be ascribed to “drug-related causes”—predominantly the prescription of a suboptimal medical regimen.

Selected Abbreviations and Acronyms

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<th>Abbreviation</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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<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<td>ARB</td>
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<td>HOPE</td>
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<td>RAS</td>
<td>renin-angiotensin system</td>
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<td>SPRINT</td>
<td>Systolic blood Pressure Intervention Trial</td>
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<td>STITCH</td>
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The rest of this review will focus on how the early use of low-dose single-pill combinations in the management of hypertension can ameliorate both patient-centered and health-care professional–centered determinants of suboptimal blood pressure control. This will include consideration of their: (i) greater efficacy (versus monotherapy); (ii) more favorable safety profile, greater global effectiveness (ie, in the context of racial differences in antihypertensive drug responses); (iii) greater effectiveness in achieving blood pressure control from a practicewide perspective; and (iv) greater effectiveness in reducing hypertension-related cardiovascular complications.

Combining antihypertensive drugs is always more effective than doubling the dose of monotherapy

It is a pharmacological truism that at maximal doses of a monotherapy, adding a second antihypertensive drug leads to greater blood pressure lowering. But even down to subtherapeutic doses, combining agents is three to five times more effective than dose-doubling. Further, whereas there are racial differences in the antihypertensive effectiveness of specific classes of antihypertensive drugs (eg, reduced effectiveness of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in black patients with hypertension), no such racial differences are evident when those agents are combined with an antihypertensive agent from a different class (eg, as with the use of an ACE inhibitor/diuretic combination).1

Lower incidence of adverse effects with combinations, especially at low doses, than with doubling the dose of monotherapy

For most antihypertensive drugs the dose relationship for their most common adverse effects (eg, peripheral edema with calcium channel blockers) occurs over the same range as their antihypertensive effects. However, at half standard doses (typically approximating the starting dose) the aggregate adverse effects of most antihypertensive drugs approximates zero (versus placebo) and increases to ~10% above placebo as dosage is increased to a standard dose level. Thus when a monotherapy dose is doubled it is expected that the probability of an adverse effect will increase by 10%. However, if instead, that drug (used at a starting or, even better, at a subtherapeutic dose) is combined with a low dose of another antihypertensive drug it would be expected that the aggregate probability of an adverse effect would still approximate that of placebo, ie, the probability of an adverse effect would be far lower than if a monotherapy dose were doubled. Further, when combined, there may be a lower incidence of some of the side effects of those specific drugs had they been used as monotherapies. For example, the incidence of disorders in serum potassium concentrations of both diuretics and renin-angiotensin system (RAS) inhibitors are reduced when they are combined. Likewise, the incidence of peripheral edema with calcium channel blockers is significantly reduced when combined with a RAS inhibitor.13

In summary, from the perspectives of effectiveness and safety, greater use of single-pill combinations would seem to be warranted.

Single-pill combinations outperform “free combinations” in respect to adherence

Two recent systematic reviews have both concluded that there is superior patient adherence with the use of single-pill combinations versus the use of “free” equivalents. Further, as illustrated by the study of Taylor and colleagues, greater use of single-pill combinations would be expected to translate into both improved adherence and decreased medical resource utilization.16

Initial low-dose single-pill combination strategies outperform initial monotherapy-based strategies for blood pressure control

Initiating antihypertensive therapy with a single-pill combination has been previously shown in more rigorous clinical trial settings.17,18 These studies utilized strict protocol-driven dosage adjustments when single-pill combinations were prescribed and at closely monitored fixed intervals. Thus, it might be argued that the greater blood pressure–lowering effectiveness seen in patients randomized to the single-pill combination treatment arms was due to intrinsic differences in antihypertensive effectiveness between treatment arms (ie, the more rapid introduction of a more efficacious two-drug-therapy regimen in the combination group, with more rapid titration) rather than superiority of the single-pill combination formulation versus the free combination alternative. In that context the STITCH (Simplified Treatment Intervention To Control Hypertension) study was a more naturalistic comparison of the effectiveness of a single-pill combination strategy versus a traditional sequential monotherapy strategy.19,20

The STITCH study used a more pragmatic design than the preceding single-pill combination effectiveness studies. In it, practices were randomized to either being instructed to manage patients using a more traditional approach as outlined by the Canadian Hypertension Education Program recommendations—focusing on initial monotherapy (in most cases) versus managing patients utilizing the STITCH algorithm that featured the initial use of low-dose single-pill combinations, started at a dose simulating the antihypertensive effect of initial monotherapy. The effectiveness of the competing strategies could be examined in the absence of the requirement of a rigid clinical trial dosing protocol as used in conventional clinical trials. In the STITCH study the primary outcome was the practice-based 6-month blood pressure control rates in the subset of practice patients with uncontrolled hypertension at study entry in the STITCH-care versus guidelines-care group. In the STITCH study, in those practices randomized to instruction on the utility of the initial use of low-dose single-pill combinations, practice-wide blood pressure control was significantly greater than in those practices instructed on a more
traditional guidelines-based strategy, with a 23% greater relative improvement. Further, on average, blood pressure reduction in patients in practices randomized to the STITCH-care arm was 6/3 mm Hg greater.

**Does initial therapy with single-pill combinations “work” outside of clinical trial settings?**

The real-life utility of the early use of single-pill combinations, regardless of the stage of hypertension, is most evident from the experience of the Kaiser Permanente health system. In their guidelines for hypertension management, a single-pill combination is the preferred form of treatment in both stage 1 and stage 2 hypertension—analogous to the STITCH care management pathway. Utilizing this strategy, the Kaiser Permanente hypertension program reports blood pressure control rates in excess of 80%—the highest reported health-care system hypertension control rates globally.

**Initiation of combination therapy versus monotherapy in reducing hypertension-related cardiovascular complications**

The relative utility of initiating therapy with drug combinations versus monotherapy in regards to hypertension-related cardiovascular risk reduction has been examined in two cohort studies. In the first, Corrao and colleagues performed a population-based case-control study from a cohort of 209,650 patients from Lombardy, Italy, studying the 10,668 patients hospitalized for cardiovascular disease.\(^22\) Patients starting on combination therapy had an 11% reduction in cardiovascular risk compared to those initiated with monotherapy. In the second study, Gradman and colleagues examined the record of 1762 patients with hypertension who were initiated on combination therapy matched 1:1 with similar patients initiated on monotherapy and then subsequently transitioned to combination therapy. They reported that those patients on initial combination therapy had a 34% lower cardiovascular event rate (fatal and nonfatal) compared to those initiated on monotherapy.\(^23\) These studies, although both observational in design, support on aggregate the benefit of initial combination therapy on harder cardiovascular disease outcomes.

**Barriers to wider acceptance of single-pill combinations as initial therapy for the management of hypertension**

From a hypertension guidelines perspective, internationally there has only been limited acceptance of the role of single-pill combinations as initial therapy in the management of hypertension and then only under specific conditions. Several national guidelines do recommend the initial use of single-pill combinations when blood pressures are more than 20 mm Hg above target for systolic blood pressure or 10 mm Hg above target for diastolic.\(^24\) However, there is little appreciation of the utility of low-dose combinations as initial therapy for stage 1 hypertension based on their superior performance in terms of adherence, effectiveness, or safety. In some guidelines systems, the road block to greater adoption of single-pill combinations earlier in the management of hypertension has been the lack of adequate clinical trials evidence demonstrating the effectiveness of combination therapy as the “lead treatment” (ie, either in initiating therapy or as an add-on) in large cardiovascular event-driven (hard outcome) randomized clinical trials. This barrier has been viewed by many to have been surmounted with the publication of the HOPE-3 (Heart Outcomes Prevention Evaluation–3) study.\(^25\)

The overall results of this study on the effectiveness of achieving lower target blood pressures in this intermediate-risk patient population were admittedly neutral. However, in the subgroup of patients with the highest tertile of blood pressures on entry (ie, greater than 143 mm Hg systolic, a prespecified subgroup), those randomized to the active treatment arm, who received the single-pill combination of candesartan/hydrochlorothiazide, demonstrated an approximately 25% reduction in cardiovascular events. These findings support the case for initial therapy with a single-pill combination as an effective way to reduce both blood pressure and cardiovascular event rates—in other words, the findings meet the minimum requirements of guidelines writers for the evidence needed to recommend a single-pill combination as a first-line choice.

**Initial treatment with single-pill antihypertensive combinations could lead to:**

- Reduced incidence and severity of adverse effects\(^12,13\)
- Improved adherence (and decreased medical resource utilization)\(^14,15\)
- Better blood pressure control rates\(^16\)
- Reduced rates of hypertension-related cardiovascular complications\(^20,22\)

**Box 1. Potential advantages of initial single-pill combination-based antihypertensive treatment.**

*Preferred choices include angiotensin receptor blocker/diuretic and angiotensin-converting enzyme inhibitor/calcium channel blocker.*

**Is there a preferred single-pill combination?**

Using the Canadian guidelines standard that a first-line hypertension treatment must be shown both to reduce blood pressure and cardiovascular risk, the HOPE-3 study would support the recommendation of a diuretic/ARB combination as the preferred first-line single-pill combination choice. However, findings from the ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension) study would support the designation of an ACE inhibitor/calcium channel blocker single-pill combination as a preferred choice as well.\(^25\) In the ACCOMPLISH study, patients randomized to the benazepril/amlodipine single-pill combination had a 20% lower cardiovascular event rate versus those randomized to therapy with the benazepril/hydrochlorothiazide single-pill combination.\(^25\) Based on the ACCOMPLISH study, both the Canadian Hyperten-
sion Education Program guidelines27 and the UK National Institute for Health and Care Excellence guidelines28 have recommended a RAS inhibitor/calcium channel blocker combination as the preferred single-pill combination choice. Notably, the development of these recommendations preceded the publication of HOPE-3. Thus, in the absence of direct head-to-head studies, the evidence to date supports the recommendation of both ARB/diuretic and ACE inhibitor/calcium channel blocker as the preferred single-pill combinations for initiating antihypertensive therapy (Box 1).

Summary

Despite the significant advances we have made in hypertension control and the wide availability of a range of effective antihypertensive drugs, we are still far short of the levels of blood pressure control achievable under the most optimal conditions (i.e., in the setting of rigorous clinical trials protocols). Key factors contributing to this treatment gap include patient-centered factors, such as nonadherence; as well as health-care provider–centered factors, which include clinical inertia and the prescription of suboptimal treatment regimens. The use of low-dose single-pill combinations presents theoretical advantages in regards to superior effectiveness and safety as compared to conventional monotherapy-based regimens. Further, single-pill combination therapy leads to improved adherence and overall higher rates of blood pressure control in hypertensive patient populations. Additionally, those patients initiated on combination antihypertensive therapy demonstrate lower rates of cardiovascular events.

With greater appreciation of the effectiveness of treatment regimens featuring the use of single-pill combinations, there is a reasonable expectation that the early use of single-pill combinations will increasingly be incorporated into national and international hypertension guidelines and consequently implemented more broadly into clinical practice.

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Keywords: hypertension; initial therapy; nonadherence; therapeutic turbulence; therapeutic inertia; suboptimal medication regimen; blood pressure control; single-pill combination; cardiovascular complication

Building the case for drug combinations as initial therapy of hypertension - Feldman
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What is the place of lifestyle changes in the treatment of hypertension?

Hypertension guidelines, for example the 2013 European Society of Hypertension/European Society of Cardiology guidelines in hypertension, recommend a trial period of lifestyle changes prior to the start of antihypertensive therapy. However, recent evidence suggests that the benefits of lifestyle changes are limited, only allowing for a small reduction in blood pressure. In light of this, do lifestyle changes still have a place in the everyday management of hypertension and, if so, in which clinical circumstances are they most applicable?

1. J. Börgel, Germany
2. D. A. Castán Flores, Mexico
3. J. R. Guillén Moreno, Guatemala
4. P. C. B. Veiga Jardim, Brazil
5. K. Kostka-Jeziorny, Poland
6. S. Kumar, India
7. N. Kupstytė, Lithuania
8. L. Mishchenko, Ukraine
9. A. Vachulova, Slovak Republic
1. J. Börgel, Germany

Jan BÖRGEL, MD
Head of the Department of Internal Medicine Cardiology, Pneumology, Intensive Care Medicine and Hypertension-Unit Hochdruckklinik St. Barbara-Clinic, Teaching Hospital, University of Münster, Hameln, GERMANY
(email: jboergel@barbaraklinik.de)

The relationship between arterial hypertension and cardiovascular morbidity and mortality represents a major challenge for clinicians and health-care systems. Elevated blood pressure is a risk factor for coronary artery disease, heart failure, cerebrovascular disease, peripheral artery disease, chronic kidney disease, and atrial fibrillation. Many patients with arterial hypertension are asymptomatic, and too often high blood pressure values are recognized by chance. Based on the current European Society of Cardiology (ESC) hypertension guidelines,1 the initial step in the management of hypertension comprises lifestyle changes. Lately attention has shifted towards these measures of prevention, with the publication of the ESC guidelines on cardiovascular disease prevention in clinical practice.2 Lifestyle changes may delay or prevent hypertension in nonhypertensive subjects, delay or prevent medical therapy in grade 1 hypertensive patients, and contribute to blood pressure reduction in hypertensive individuals already on medical therapy. Nevertheless, lifestyle changes should not delay the initiation of drug therapy in individuals at a high total cardiovascular risk. Recommendations for lifestyle changes include:

- Weight reduction – reduction to 25 kg/m² is recommended, and an average weight loss of 5.1 kg was associated with a decrease in blood pressure of 4.4/3.6 mm Hg.
- Salt restriction – reducing intake to 5-6 g/day lowers systolic blood pressure by 4-5 mm Hg in hypertensive individuals.
- Moderation of alcohol consumption – there is a linear relationship between alcohol consumption and hypertension.
- Regular physical activity – aerobic endurance training reduces resting systolic and diastolic blood pressure by 4.9/4.9 mm Hg in hypertensive subjects.
- Smoking cessation – smoking one cigarette increases blood pressure for over 15 minutes, and
- Dietary changes – increased consumption of vegetables, fruit, and low-fat products is recommended.

Although the positive effects of adherence to lifestyle changes have been well documented, earlier pharmacological intervention may be useful because lifestyle benefits may be overvalued. To put the controversy into context, UK hypertension guidelines show that the average blood pressure decrease over 6 months in hypertensive patients who undergo a combined lifestyle intervention is limited (5.5/4.5 mm Hg).3 Furthermore, patient adherence to lifestyle changes is suboptimal; most patients do not adhere to healthy lifestyle recommendations.4 Thus, in the majority of patients with newly diagnosed hypertension, lack of adherence to lifestyle changes leads to delayed hypertension control. Delayed control of high systolic blood pressure >150 mm Hg is associated with increased cardiovascular risk.5 Although lifestyle changes remain an important adjunct in the treatment of hypertension, earlier pharmacological intervention may be a therapeutically rational choice, even in patients with mild hypertension.6 Patients with additional cardiovascular risk factors, in particular, benefit from rigorous pharmacological blood pressure control, and thus therapy initiation in these individuals should not be delayed.7 Despite this evidence, international guidelines for hypertension8 continue to promote a period of lifestyle changes before treatment initiation. The newer cardiovascular prevention guidelines state that lifestyle changes with close blood pressure monitoring should be recommended in young individuals with isolated moderate elevation of brachial systolic blood pressure as well as in individuals with high-normal blood pressure who are at low or moderate risk.

Clearly, the initiation, maintenance, and regular checking of lifestyle changes is mandatory for every hypertensive patient, but one has to recognize the logistic challenges as well. The decision to initiate antihypertensive treatment depends on blood pressure level and total cardiovascular risk, but lifestyle changes remain the cornerstone of prevention in the downstream management of every hypertensive patient.

References
Hypertension is one of the most important chronic conditions related to increased risk of cardiovascular morbidity and mortality. According to the World Health Organization, each year around the world the number of deaths associated with hypertension is almost 8 million. Evidence has demonstrated the existence of a relationship between lifestyle patterns, excess weight, and outcomes in hypertension. Therefore, reaching pharmacological and nonpharmacological goals is the cornerstone of treatment to reduce cardiovascular morbidity and mortality.

Lifestyle interventions in hypertension involve weight loss in patients who are overweight or obese, although the long-term effects of weight reduction remain unclear. A reduction in dietary sodium to less than 2300 mg/day (about one teaspoonful of salt) is recommended. A recent meta-analysis concluded that a modest reduction in salt intake over a period of four or more weeks produces a significant fall in blood pressure in a hypertensive population (and even normotensive people), with no gender or ethnic differences. Furthermore, increasing aerobic exercise—such as walking or jogging, cycling, and swimming, reaching 40%-60% of maximal age-based heart rate for up to 180 minutes weekly—and smoking cessation can also reduce blood pressure.

The role of early pharmacological treatment relies on cardiovascular outcomes avoidance by preventing endothelial remodelling and myocardial concentric hypertrophy, therefore reducing the possibility of stroke or coronary artery disease. In relation to this, fixed-dose combinations of antihypertensive drugs have been shown to have more benefits than monotherapy, such as well-defined tolerability, enhanced treatment adherence, and better effectiveness. As such, they represent a useful tool in treatment for hypertension.

Once antihypertensive treatment has been initiated, it is unlikely that patients can revert to blood pressure control by lifestyle change alone. Withdrawal of antihypertensive drugs would probably only be safe in a small proportion of young male patients on a monotherapy regimen who were following an effective behavioral change program. For the heterogeneous group of moderate-to-high high cardiovascular risk older male patients this would not be the case. For these patients, a fixed-dose combination (perindopril/amlodipine, for example) would be needed to control blood pressure, helping most of these patients reach blood pressure goals in three months on average. In short, once started it is strongly suggested that antihypertensive medical treatment should continue, regardless of the implementation or not of lifestyle changes, unless there is proven evidence of serious side effects or lack of efficacy.

Based on this evidence, we would be able to strongly recommend lifestyle interventions “the earlier, the better” to improve outcomes in hypertensive patients. Nevertheless, most of the time, patients come to us with high or very high cardiovascular risk already and so, according to current guidelines, lifestyle modifications would not be enough to reach goals and thus reduce cardiovascular risk.
Hypertension is the most common chronic condition dealt with by primary care physicians and other health practitioners. It is a major contributor to the onset and progression of chronic heart and kidney failure and, importantly, a major risk factor for stroke and coronary heart disease. Understanding its incidence, prevalence, and role in cardiovascular disease is crucial, as is an in-depth knowledge of risk factors, pathophysiology, and levels of hypertension. Knowledge of the epidemiology of the disease is the first step towards appropriate treatment.

Although the pharmacological management of hypertension has been studied since the 1950s and has been refined over the years, it is only in the last decade or so that the importance of lifestyle has been established in the treatment of hypertension. In the 1980s, the association between hypertension, diabetes, dyslipidemia, smoking, and cardiovascular risk was defined, so a lot of effort since then has been directed at drug treatment, smoking reduction, and specific control of these diseases. Ongoing research over the years has shown that the goal of treatment should not only be to decrease the value of blood pressure and maintain lipid and glucose levels within normal ranges. Above and beyond these objectives, management of risk should also include changes in lifestyle. These kinds of changes reflect a comprehensive approach towards risk that is multicausal in origin.

Currently, management of hypertensive patients begins with the categorization of risk by assessment of blood pressure level and risk factors. Once the category of risk has been determined, recommendations focus on the use of antihypertensive drugs and changes in lifestyle. Lifestyle modifications are indicated for all patients, regardless of whether or not they are on drug therapy. In addition to lowering blood pressure, recommended lifestyle changes confer health benefits and improve outcomes in several common, chronic diseases, not only those that are cardiovascular-related.

Lifestyle recommendations in hypertensive patients are based on: 1. Smoking cessation – smoking causes an immediate increase in blood pressure and in heart rate that persists for over 15 minutes for one cigarette. It is a strong independent risk factor. The recommendation is simple: stop immediately! 2. Nutrition and salt intake – a healthy diet (containing fruit, vegetables, wholegrain foods, unprocessed meats, poultry, fish, and moderate amounts of polyunsaturated and monounsaturated fats) is important, but so too is controlling salt intake. Added salt (at the table) should be avoided. 3. Water consumption – the recommendation is 1.5 liters/day to be drunk slowly throughout the day between meals. 4. Alcohol – limit intake to a maximum of one or two standard drinks per day (for women and men, respectively) as well as planning at least two alcohol-free days per week. 5. Physical activity – moderate intensity cardiovascular exercise (walking, cycling, swimming, etc) 20-50 minutes a day, 150-180 minutes a week, 5 to 7 days per week. 6. Body weight – body mass index should be less than 25 kg/m². Weight reduction confers other benefits, reducing insulin resistance, hyperlipidemia, risk of left ventricular hypertrophy, and obstructive sleep apnea. 7. Obstructive sleep apnea – an independent risk factor that is also associated with sudden cardiac death.

Several studies have shown that to reduce morbidity/mortality and improve quality of blood pressure control in hypertension, all risk factors must be considered. Lifestyle encompasses a number of these and is one of the most important modifiable elements in hypertension and cardiovascular disease. The health community has understood that hypertension is really multicausal in nature, which is why the current recommendation worldwide in the treatment of this pathology is no longer just pharmacological, but also now includes lifestyle changes.

References
The beneficial effects of nonpharmacological treatment (i.e., healthy lifestyle) on blood pressure are well established.1,2 Studies of up to 24 months’ duration that combined moderate-to-intense physical activity with dietary interventions reduced mean systolic blood pressure by 4.5 mm Hg and mean diastolic blood pressure by 1.1 mm Hg after 12 months. Other shorter-term studies, ranging from 12 to 24 months, showed a reduction of 2.3 mm Hg and 1.0 mm Hg in systolic and diastolic blood pressure, respectively.1 Nevertheless, no scientific evidence shows that blood pressure treatment using only nonpharmacological strategies changes the natural history of the disease. In contrast, clear evidence is available showing that pharmacological treatment combined with nonpharmacological treatment decreases cardiovascular morbidity and mortality in hypertensive patients.2-5

This information shows us clearly the importance of adopting a healthy lifestyle as an adjuvant in the care of hypertensive patients, since it decreases the number of drugs needed and avoids or at least delays the onset of other cardiovascular risk factors (dyslipidemia, diabetes, obesity, etc). From this point on, the question is related to two other aspects of hypertension treatment.

The first regards how long one should wait before starting pharmacological treatment. In this matter, there is a consensus that patients with stages 2 and 3 hypertension and those with high cardiovascular risk or with established cardiovascular disease, even in stage 1 hypertension and low cardiovascular risk remains as yet unanswered. For this scenario, there are no studies showing the right time, only expert opinions recommending several weeks to months of lifestyle changes (normally 3 to 6 months) before starting pharmacological treatment.2,3

The second aspect is related to the choice of antihypertensive monotherapy or drug combinations at the beginning of treatment. As before, there are no clinical studies that have been designed to specifically answer this question, and the answer will probably not be based on strong scientific evidence. However, it is well known that 70% of patients will need drug combinations to achieve blood pressure goals established by international guidelines. It is also clear that by getting blood pressure under control as early as possible, benefits are better for high-risk subjects, with marked changes in disease evolution.2-4

For patients with low or moderate cardiovascular risk, there are limited data available showing the advantages of starting combination therapy early, even though antihypertensive drug combinations are used to achieve blood pressure control in the majority of studies in hypertension. It is well known that achieving blood pressure goals is important, achieving these goals fast is beneficial, and, furthermore, difficulties in achieving these goals lead to lower treatment adherence rates.2-6

An interesting real-world study published in 2013 showed that patients who started treatment on drug combinations had a 34% reduction in the risk of cardiovascular events or death compared with those who started treatment on monotherapy. In addition to this, there was a 9% decrease in the use of health services in the group that started treatment on a combination.6

From the set of available information, two important points should be kept in mind: (i) there will always be a place for healthy lifestyle as an adjuvant in the care of hypertensive patients; and (ii) pharmacological treatment must be initiated early, with drug combinations being considered a first-line approach for most patients since they promote better and faster blood pressure control, improve adherence, and decrease the risk of cardiovascular events.

References

What is the place of lifestyle changes in the treatment of hypertension?
What is the place of lifestyle changes in the treatment of hypertension?

The 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) hypertension guidelines clearly and strongly underline the importance of appropriate lifestyle changes in hypertensive treatment (Class I, level A/B). This said, lifestyle changes should never delay the initiation of antihypertensive drug treatment in patients with a high level of risk.

Measures that help control blood pressure include: salt restriction, regular physical exercise, weight reduction, smoking cessation, moderation of alcohol consumption, high consumption of vegetables and fruits, and low-fat and other types of diet. A single change in one of the lifestyle measures listed above can help prevent or control high blood pressure, while changes to several measures result in even better prevention or blood pressure reduction.

Beside their blood pressure–lowering effect, lifestyle changes contribute to the control of other cardiovascular risk factors and clinical conditions. For example, combined dietary and physical activity interventions in prediabetic patients have a protective effect against the incidence of diabetes. Sodium restriction may reduce the number of doses and dosage of antihypertensive drugs, although effective salt reduction is by no means easy to achieve. Epidemiological papers suggest that regular, aerobic physical activity may be beneficial for the prevention of hypertension and as antihypertensive treatment. Physical activity might also lower cardiovascular risk and mortality. It should be noted that, for the moment, isometric exercises are not recommended. Everybody knows that smoking is major risk factor for atherosclerotic cardiovascular diseases, so we should recommend that our patients quit smoking and offer them assistance, including treatment with nicotine replacement therapy, bupropion, or varenicline.

Every hypertensive patient should be advised to eat vegetables, low-fat dairy products, dietary and soluble fiber, whole grain cereals, protein from plant sources (reduced in saturated fat and cholesterol), and fish (at least twice a week). Fresh foods are also recommended for patients with normal weight, because carbohydrates may promote weight gain.

I want to mention one more important risk factor of arterial hypertension that is often omitted from guidelines: hyperuricemia. Even though the latest European hypertension guidelines recommend the routine measurement of serum uric acid levels, the algorithm for evaluating total cardiovascular risk does not include this parameter. Observational studies have shown that the relative risk of hypertension increases with increasing serum uric acid, independently of regular risk factors. This finding was confirmed by a meta-analysis of 18 prospective cohort studies in patients who were not hypertensive at baseline. The pooled adjusted relative risk for incident hypertension was greater in patients with hyperuricemia than in those without. It was later found that hyperuricemia is an independent predictor of new-onset hypertension. So, in my opinion, we should recommend a low-purine diet in hypertensive patients with hyperuricemia. According to the American College of Rheumatology, a diet that has an excessive amount of the following foods can lead to hyperuricemia: seafood, red meat, sugary beverages, and alcohol.

The implementation of lifestyles that most favorably reduce blood pressure has implications for the prevention and treatment of hypertension and for population-based strategies to shift the overall distribution of risk downwards. Even if lifestyle modifications do not produce a sufficient reduction in blood pressure to avoid drug therapy, fewer medications and lower dosages of these may be needed for blood pressure control.
Hypertension is a key risk factor for stroke and coronary heart disease and is also a major contributor to the initiation and progression of chronic heart failure and chronic renal failure. Effective, specific lifestyle modifications should be the first step in the management of hypertension because these can delay initiation of drug treatment and may help reduce the number and dose of drugs when they are required to control blood pressure. In addition to achieving the immediate goal of blood pressure lowering, lifestyle changes also serve to reduce total cardiovascular risk. Current international guidelines recommend that in patients with hypertension no more severe than stage 1 (systolic blood pressure 140 to 159 mm Hg and/or diastolic blood pressure 90-99 mm Hg) without evidence of target organ damage or other cardiovascular risk factors, 6 to 12 months of lifestyle changes can be attempted. However, it is considered prudent to start treatment sooner if blood pressure does not respond to lifestyle methods or if other risk factors appear. For more severe hypertension, lifestyle changes should be regarded as complementary to drug therapy.

The following lifestyle changes are recommended:

- **Weight reduction.** Blood pressure reduction is proportional to weight loss, and every 10 kg of weight lost can result in a reduction of systolic blood pressure of 5-20 mm Hg. The aim of weight loss should be to achieve normal body weight (body mass index, 18.5-24.9 kg/m²).
- **Healthy eating.** A healthy way of eating based on the DASH (Dietary Approach to Stop Hypertension) diet can lower systolic blood pressure by 8-15 mm Hg. The DASH diet contains fruit, vegetables, whole grain cereals, low-fat dairy products, and dietary fiber, and low levels of dietary sodium, cholesterol, and saturated fat. High-dose (at least 3 g/day) omega-3-polyunsaturated fatty acid supplement (fish oil) may lower blood pressure in hypertension. Potassium-rich whole foods—such as bananas, kiwi fruit, avocado, potatoes, nuts, etc—are more effective in reducing systolic blood pressure in hypertensive individuals (4-8 mm Hg) than in normotensive individuals (2 mm Hg).
- **Salt restriction.** An average reduction of systolic blood pressure of 2 to 8 mm Hg occurs following a reduction in salt intake. The recommendation is to restrict dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride). Practical steps towards this end are to choose fresh, rather than processed, food and to reduce salt added to food for cooking and seasoning.
- **Physical activity.** Engaging in regular, aerobic physical activity, such as brisk walking, for at least 30 minutes per day on most days of the week can reduce systolic blood pressure by 4-9 mm Hg.
- **Smoking.** People who smoke have higher ambulatory blood pressure levels than nonsmokers. Since smoking is a major independent cardiovascular risk factor, hypertensive patients must be strongly urged to discontinue this habit.
- **Alcohol consumption.** More than 2 drinks (ie, 30 mL ethanol, 672 mL of beer, 280 mL of wine, or 84 mL of 80% proof whiskey) per day in most men, and more than one drink per day in women and lighter men, can raise blood pressure and should thus be discouraged.

The lifestyle changes mentioned above not only lower blood pressure significantly, but also confer other important cardiovascular health benefits. All hypertensive patients should be advised to adopt and maintain healthy lifestyle behaviors.

**References**

The importance of lifestyle modification cannot be denied. Nevertheless, a short conversation about physical activity, diet, and weight is often not enough to motivate patients to change lifestyle. The time required, from initial idea to implementation of change, may actually be months or even years.4 Nevertheless, a short conversation about physical activity, the time required, from initial idea to implementation of change, may actually be months or even years.4 Maintenance of motivation is necessary. Regular counseling on dietary change and physical activity would be ideal, but time required, from initial idea to implementation of change, may actually be months or even years.4 Even specialized hypertension treatment centers have difficulty helping patients achieve target blood pressure, with patients’ failure to follow medication regimens more important than the inability to modify lifestyle.5,6 The flexibility of modern pharmaceutical treatments of hypertension, such as the combining drugs or prescribing one tablet per day, assist good medication compliance. Other cardiovascular risk factors, like dyslipidemia, should be simultaneously corrected for high-risk patients. Combining drugs and simplifying medication regimens have positive effects in hypertension treatment. Compliance with drug treatment is better when fewer tablets are prescribed.7 At a national level in Lithuania, there is a demand for the development of programs for the primary and secondary prevention of cardiovascular diseases. At a personal level, every cardiologist and family doctor should focus on individualized treatment (assessment of motivation) and consider patients’ perceived problems with hypertension and attitudes towards its medical treatment. Factors to consider include patient education on the use of medicines, a good doctor-patient relationship, continuous monitoring and assessment of treatment, a nonjudgmental attitude, and a willingness to assist. Patient education programs and the development of tools to measure patients’ adherence to healthy lifestyle recommendations would help. Ultimately, both lifestyle modification and early, effective pharmaceutical treatment are needed to promptly reach target blood pressure.

Lifestyle modifications are an important factor, but in the treatment of arterial hypertension optimal pharmaceutical treatment is often crucial even in mild hypertension. Since long-term lifestyle modification strategies, special programs, and the ability to monitor clinical results are unavailable, I do not support the promotion of a period of lifestyle changes before treatment initiation in hypertension.

References
Lifestyle modification is a cornerstone of the management of arterial hypertension. All hypertensive patients, regardless of blood pressure level, should be recommended to restrict salt consumption, moderate alcohol intake, stick to a diet rich in vegetables and fruit, reduce consumption of saturated fats and cholesterol, lose weight, and do regular physical exercise. These recommendations are based on the results of large clinical trials that demonstrate significant blood pressure reduction, from 3 to 8 mm Hg, for each type of lifestyle changes measure. Lifestyle modification—smoking cessation, first, and healthy diet and physical exercise—reduces the risk of cardiovascular disease as well as improving blood pressure control.

The data from the randomized clinical trial of Pimenta et al are relevant in this context. On the one hand, the results confirm the causal relationship between high sodium intake and blood pressure elevation and, on the other hand, they show the significant antihypertensive effect of a low-sodium diet in patients with resistant hypertension. Office blood pressure was decreased by 22.7/9.1 mm Hg in this group of patients in comparison to patients on a high-sodium diet. The substantial antihypertensive impact of a low-sodium diet has been confirmed with ambulatory blood pressure measurement: daytime and nighttime blood pressures were correspondingly lowered by 20.7/9.6 mm Hg and 20.3/9.1 mm Hg. Such a meaningful blood pressure reduction with a low-sodium diet indicates that resistant hypertension is characterized by high salt sensitivity.

The main challenge of antihypertensive therapy, both pharmacological and nondrug (lifestyle changes), is still adherence to treatment, which is determined by individual factors of the patient and the doctor as well as social conditions. Getting patients to commit to a healthy lifestyle and tackling the issue of cardiovascular risk factors are critical medical and social problems, whose solutions could improve blood pressure control in the hypertensive population and significantly reduce the risk of cardiovascular disease.

References
A nihypertensive treatment is of paramount importance for protecting patients from the consequences of untreated hypertension: stroke, heart failure, coronary artery disease, and kidney failure. There is strong evidence from randomized clinical trials that the administration of blood pressure-lowering drugs reduces the risk of major clinical cardiovascular outcomes. The question is when should drug therapy be initiated. On the one hand, appropriate lifestyle changes are the cornerstone for the prevention and treatment of hypertension. However, lifestyle changes should never delay the initiation of drug therapy. Many important concerns remain about the best way in which to combine pharmacological treatment with lifestyle interventions.

Do patients adhere to recommendations of lifestyle changes? In my daily practice, I recommend lifestyle changes to all hypertensive patients both initially, at the time of diagnosis of arterial hypertension, and then regularly thereafter. However, adherence to these recommendations among hypertensive patients from my practice is poor, not only in older patients, but especially in younger ones. The reasons might be that, first, arterial hypertension is a painless disease at the beginning and, second, not all patients wish to know the consequences of their disease. Data from literature also show that only a small proportion of patients adhere to healthy lifestyle recommendations. In Slovakia, there are very few strong health-care teams or patient organizations that provide support for patients wanting to adhere to these recommendations. One of the few existing initiatives is a campaign, which has taken place every year from 2006 to 2016 in September, as part of “Cardiac Topics Month”. This campaign informs the general public about blood pressure management and lifestyle changes.

Blood pressure decrease and lifestyle changes

Lifestyle changes do have a real place in hypertension management in daily practice, but by themselves they may not be enough to protect our hypertensive patients. There are very good data on how lifestyle changes contribute to reducing blood pressure. In my daily practice, only a small number of patients adhere to nonpharmacological intervention, both in the short and long term. Also, evidence shows that the average blood pressure decrease over 6 months in hypertensive patients who undergo lifestyle intervention is only 5.5/4.5 mm Hg. The impact of this decrease in blood pressure is not sufficient to protect hypertensive patients for a long time. To obtain adequate blood pressure control, it is better to combine lifestyle changes with pharmacological treatment, even in patients with mild hypertension.

Time to achievement of target blood pressure

The most advantageous time frame for achieving target blood pressure has never been defined in the literature nor in clinical practice. We know, notwithstanding, that an earlier decrease of blood pressure is better. Evidence also shows that delayed control of systolic blood pressure >150 mm Hg leads to increased cardiovascular risk. These findings should prevent clinical inertia when treatment goals are not reached by lifestyle changes. Because of advantages of rapid control of blood pressure, earlier pharmacological intervention is important. Hypertension is a complex disease that impacts the cardiovascular system, and earlier blood pressure control is associated with early cardiovascular protection.

In conclusion, now is the time to reconsider the management strategy of hypertensive patients. For reducing their blood pressure, we recommend that both interventions—lifestyle changes and pharmacological treatment—start simultaneously.

Reference

Hypertension remains undertreated and poorly controlled worldwide. An unmet need in the management of hypertension is for simpler treatment regimens that effectively control blood pressure (BP) and that are used by patients in the long term because of good tolerability. Rapid and effective BP lowering with first-line combination therapy remains underutilized. Perindopril and amlodipine have an established history of clinical use, are well tolerated, have complementary mechanisms of action (and thus reduce BP in an additive fashion), and have reduced end points in long-term clinical trials. Adapted-dose perindopril/amlodipine 3.5/2.5 mg has been developed for first-line use to provide hypertensive patients with a combination option that possesses optimal efficacy with the best tolerability. The efficacy of first-line treatment with this adapted-dose strategy versus a monotherapy stepped-care strategy has been compared in three large randomized controlled trials. Perindopril/amlodipine 3.5/2.5 mg was shown to provide superior or noninferior BP reduction, with benefits observed from the first month of treatment. A combined analysis in patients with mild-to-moderate hypertension confirmed the superior efficacy of perindopril/amlodipine 3.5/2.5 mg versus monotherapy. The tolerability of perindopril/amlodipine 3.5/2.5 mg was better than that of the lowest approved doses of its components. Trial results with perindopril/amlodipine 3.5/2.5 mg provide support for broadening the recommendation for this adapted-dose strategy in future hypertension guidelines to include newly diagnosed patients.

Hypertension remains the single largest contributor to the global burden of disease and to global mortality, with an estimated 1.13 billion hypertensive people worldwide in 2015. Its prevalence is increasing with an estimated 23.5 million newly diagnosed patients per year. With recent evidence showing that delays in controlling blood pressure (BP) significantly increase cardiovascular morbidity and mortality, the identification, treatment, and control of hypertension should be a top public health priority. However, despite its importance, BP control remains poor worldwide, with only one-third of treated patients reaching BP targets of <140/90 mm Hg.

A number of factors are implicated in poor BP control, including poor adherence to treatment, therapeutic inertia, and inequalities in health-care services. Mancia et al recently proposed a fourth important factor: the reluctance to adopt drug treat-
ment strategies that reduce elevated BP more effectively. A stepped-care approach—in which a single agent is initiated and titrated to its maximum tolerated dose before the addition of a second therapy is considered—has long been the preferred strategy for the management of hypertension. The rationale for this approach is based on the often unfounded assumptions that monotherapy is more convenient than combination therapy, is associated with fewer side effects, allows easier identification of which drug is causing an adverse event if it occurs, and is less expensive. In reality, the vast majority of patients with hypertension require at least two agents to reach target BP, with a large international study demonstrating that only 30% of hypertensive patients were treated satisfactorily with a single antihypertensive drug. A stepped-care approach is also more likely to increase the risk of side effects due to higher drug doses and lead to problems with medication adherence. Furthermore, delays in drug titration can lead to patients’ BP remaining uncontrolled for long periods of time. Recent evidence shows that inaction—waiting until SBP is >150 mm Hg before initiation or uptitration of antihypertensive treatment, delays >1.4 months in the initiation or uptitration of treatment after SBP elevation, or delays >2.7 months before follow-up of BP following medication intensification—significantly increased the risk of an acute cardiovascular event or death. A separate study reported that BP control was nearly a fifth (18.5%) faster with combination therapy versus monotherapy, which led to a 34% reduction in risk of cardiovascular events and death.

Despite substantial evidence that the use of single-pill, optimized-dose combination therapy as first-line treatment represents a more effective alternative to add-on therapy or sequential monotherapies, current guidelines only recommend first-line combination therapy in high-risk patients who require rapid BP control. As things stand, the majority of untreated hypertensive patients have grade 1 hypertension (62%), defined as a systolic blood pressure (SBP)/diastolic blood pressure (DBP) of 140-159/90-99 mm Hg, and therefore by following guideline recommendations would be treated with monotherapy. With data showing that at least 75% of patients require combination therapy to achieve BP targets, these patients may endure months of suboptimal treatment before their BP is controlled, exposing them to unnecessarily increased cardiovascular risk.

Whether treating patients with grade 1 hypertension is beneficial in terms of cardiovascular outcomes has been debated. Due to a lack of specific trials, meta-analyses have been used to examine this issue. When limited to trials of individuals with mild hypertension, some have suggested limited benefits and others more substantial effects. Another, different meta-analytical approach—one that allowed a large number of trials to be analyzed, avoided selection bias, and increased statistical power—has also been tried. This type of meta-analysis allowed the inclusion of all BP-lowering trials, provided that no antihypertensive treatment was present at randomization, which allowed average baseline SBP/DBP values to be used for classifying each trial in a given hypertension grade. With this approach, BP lowering in low-to-moderate risk patients with grade 1 hypertension was associated with significant relative risk reductions for stroke, coronary heart disease, the composite of stroke and coronary heart disease, cardiovascular mortality, and all-cause mortality. Only a marked reduction in the risk of heart failure did not reach statistical significance.

With evidence in favor of more rapid achievement of BP control and treating newly diagnosed patients with mild hypertension to reduce cardiovascular outcomes, it is perhaps time to challenge our current way of management and begin using treatment strategies that guarantee the highest rate of success from the start. With this in mind, a new first-line treatment in hypertension containing adapted doses of perindopril (3.5 mg) and amlodipine (2.5 mg), Viacoram®, has been developed. The aim of this review is to summarize the evidence in support of single-pill perindopril/amlodipine 3.5/2.5 mg as a new first-line treatment in hypertension.

Benefits of first-line combination antihypertensive treatment

More rapid control, fewer side effects, and earlier cardioprotection

It is common clinical practice to reserve combination therapy as a second-line treatment in the management of hypertension, after first-line monotherapy. However, there are a number of potential benefits of first-line combination antihypertensive therapy versus high-dose monotherapy, which result from the activation of multiple BP-regulating mechanisms and the avoidance of effect blunting by compensatory mechanisms. Wald et al have shown that combining two drugs from different classes is five times more effective at reducing BP than doubling the dose of a monotherapy. A number of other studies have shown that combination therapy achieves more rapid and greater reductions in BP. The use of antihypertensive combinations containing adapted doses—de-
developed to provide optimal efficacy with the best tolerability for first-line use—provides greater BP reductions than full doses of the monotherapy components. Thus, in the STITCH (Simplified Treatment Intervention To Control Hypertension) trial, superior BP-lowering efficacy was demonstrated in practices assigned to use an algorithm in which initial combination therapy with half-standard doses of each therapeutic class was the first step compared with guideline-based recommendations for the management of hypertension, ie, monotherapy. In addition, a meta-analysis of BP cohort studies and of trials determining the BP-lowering effects of drugs according to dose showed that in 60- to 69-year-old patients with mild hypertension (DBP before treatment of 90 mm Hg), three drugs at half-standard dose in combination reduced the risk of coronary heart disease and stroke by an estimated 46% and 62%, whereas the risk reductions for one drug at standard dose were 24% and 35%, respectively, and for two drugs at standard dose, 40% and 56%. The use of lower doses of individual components in a combination treatment is also associated with fewer side effects.

A case control study published by Corrao et al in 2011 analyzed data from 10 688 patients who were newly treated with antihypertensive drugs and who were hospitalized for cardiovascular disease in the 7 years following their initial prescription. They found that patients initiated on combination therapy had 11% less risk compared with those initiated on monotherapy. A comparison of patients who persisted with either monotherapy or combination therapy for the full follow-up period showed that combination therapy was associated with a 26% reduction in cardiovascular risk. Interestingly, patients who were switched from monotherapy to combination therapy did not show a significant difference in cardiovascular event rates compared to patients who received long-term monotherapy.

The findings of Corrao et al are supported by a more recent matched cohort analysis of 1762 adult patients with hypertension, who were either prescribed initial combination therapy or initial monotherapy and later switched to combination therapy. Initiation with combination therapy versus monotherapy not only led to faster achievement of BP target (9.7 versus 11.9 months) and more effective BP control (40.3% versus 32.6%), but it was also linked to a 34% reduction in cardiovascular events or death. The authors noted that the lag time to uptitration in the monotherapy arm (13.5 months after treatment initiation) may have reflected therapeutic inertia, a factor that is known to contribute to poor BP control.

Improved adherence and reduced therapeutic inertia

The use of single-pill combinations in the treatment of cardiovascular disease has been shown to markedly improve patient adherence, and improved adherence is associated with greater BP control and reduced cardiovascular events. Patients’ perceptions of adverse effects contribute significantly to decisions regarding medication adherence and are frequently listed as the most common concern among patients who are nonadherent to their antihypertensive medication. The potential to use lower doses in combination therapy than in monotherapy may help to reduce adverse events and increase adherence to medication regimens.

Physicians, like patients, may also adopt the standpoint that it is better to avoid the risk of developing side effects and leave things as they are than to intensify antihypertensive treatment. Such therapeutic inertia, or failure to initiate or intensify therapy despite an inadequate treatment response, has multiple causes (relating to physicians, patients, and health-care systems). Inertia can, however, be dispelled by improving efficacy and tolerability at the same time as reducing dosing complexity, which can be done with single-pill combination regimens.

Viacoram®, a new first-line treatment in hypertension

What is Viacoram®?

Viacoram® is a new first-line antihypertensive treatment containing perindopril and amlodipine in a single pill at dosages adapted for initiation of antihypertensive treatment (3.5/2.5 mg). It is currently marketed in approximately 10 countries worldwide, and it is available in doses of 3.5/2.5 mg and 7.5 mg (plus 14/10 mg in certain countries).

Why perindopril and why amlodipine?

An angiotensin-converting enzyme (ACE) inhibitor plus calcium channel blocker (CCB) is one of the preferred combinations of antihypertensive drugs recommended by medical practice guidelines as being safe and effective for the management of hypertension. The two classes of agent also have a number of complementary effects. CCBs stimulate the sympathetic nervous system and, indirectly, the renin-angiotensin system (RAS), whereas ACE inhibitors have the opposite effects. These complementary effects also have a positive impact on adverse events. For example, combining an ACE inhibitor with a dihydropyridine CCB reduces the adverse dose-dependent vasodilatory effects of the CCB, with an estimated 54% decrease in the occurrence of leg edema. CCBs reduce ACE inhibitor–related cough by decreasing prostaglandin synthesis induced by Bradykinin.

The rationale for the treatment of hypertension with a combination of perindopril and amlodipine is multifaceted. Both perindopril and amlodipine have individually demonstrated efficacy and safety in the management of essential hypertension in a wide range of patients, and are registered in all European countries. The two drugs have been frequently prescribed in free combination since the publication of the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure–Lowering Arm) trial, which demonstrated highly significant benefits of an amlodipine + perindopril regimen in reducing major cardiovascular
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**Therapeutic Outlook**

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**Efficacy versus monotherapy**

Four trials have compared the efficacy of Viacoram® vs. a range of monotherapy strategies: three evaluated strategies based on perindopril/amlodipine 3.5 mg/2.5 mg⁵²-⁵⁴ and one evaluated the dose of perindopril/amlodipine 14/10 mg.⁵⁵

In the first study in 1581 patients with mild-to-moderate hypertension, combination therapy with perindopril/amlodipine 3.5/2.5 mg was compared with perindopril or amlodipine monotherapy at the same dose, the lowest approved doses of the two agents (5 mg), and placebo. The primary efficacy end point was the change from baseline in mean supine DBP at the end of the 8-week study period. Secondary end points included change from baseline in mean supine SBP and the proportion of patients with normalization of BP at the end of the treatment period.

Perindopril/amlodipine 3.5/2.5 mg produced significant and clinically relevant decreases in BP compared with placebo (between-group differences: SBP, −7.22 mm Hg; DBP, −4.12 mm Hg; \( P < 0.001 \) for both). The efficacy of the combination was better than either monotherapy at the same dose, and it was also superior to perindopril and noninferior to amlodipine at their lowest approved doses of 5 mg in terms of BP-lowering efficacy (Figure 1). There were significantly more patients with normalized BP at the end of treatment in the combination group than the placebo group (43.5% vs. 26.6%; intergroup difference, 16.9% [\( P = 0.001 \)]): A numerical difference quickly became apparent (30.6% vs. 16.2% after 2 weeks), and this difference was confirmed by a subanalysis showing that efficacy was significantly better with perindopril/amlodipine 3.5/2.5 mg after 1 month.⁵⁶

**Figure 1.** Blood-pressure lowering efficacy of perindopril/amlodipine 3.5/2.5 mg compared with the lowest approved doses of its monotherapy components. Based on data from reference 52.

events and all-cause mortality compared with an atenolol ± bendroflumethiazide regimen.⁵⁶ Evidence for synergy between perindopril and a CCB was suggested by a subanalysis of the EUROPA (European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) trial in patients with stable coronary artery disease, which demonstrated a significantly greater reduction in the primary end point of cardiovascular death, myocardial infarction, or cardiac arrest in patients receiving perindopril and a CCB compared with those receiving perindopril alone or CCB alone. The difference in outcomes was greater than would have been predicted by the simple addition of their individual effects.⁵⁷

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**Figure 2.** A. Proportion of patients with controlled blood pressure (<140/90 mm Hg) with the adapted-dose first-line strategy (initiation with perindopril/amlodipine 3.5/2.5 mg) compared with the initial monotherapy (valsartan 80 mg) followed by stepped-care strategy. **B.** Time required to achieve blood pressure control with the adapted-dose first-line strategy compared with the initial monotherapy stepped-care strategy.

Abbreviations: amlo, amlodipine; BP, blood pressure; per, perindopril; RCT, randomized controlled trial; val, valsartan.

In a separate trial with a stepped-care design, Mancia and colleagues randomized 1774 patients to perindopril/amlodipine 3.5/2.5 mg or valsartan 80 mg. Patients could be up-titrated at 1, 2, and 3 months if their BP remained uncontrolled (≥140/90 mm Hg). This involved two dose-doubling phases for perindopril plus amlodipine, with the later addition of indapamide slow release 1.5 mg. Similarly, for the valsartan arm, treatment was initially doubled and then included amlodipine 5 mg and then 10 mg. Treatment with perindopril/amlodipine initiated at a dose of 3.5/2.5 mg was associated with significantly better rates of BP control than the valsartan stepped-care strategy, with a 23% greater number of patients controlled at 1 month, and 27% greater number of patients controlled at 2 months compared with the valsartan monotherapies at different doses. Importantly, the initiation of first-line therapy with adapted-dose perindopril/amlodipine (3.5/2.5 mg) reduced the time required to achieve BP control by 20% compared with the valsartan stepped-care strategy (74 versus 93 days) (Figure 2). Although cardiovascular outcomes were not assessed in this study, a similar improvement in the time to BP control was demonstrated in a large retrospective cohort study by Gradman et al, which assessed the impact of initial versus delayed combination therapy on the risk of developing a cardiovascular event. In the Gradman et al analysis, initial treatment with a drug combination was associated with a 34% reduction in the risk of cardiovascular events or death. Faster achievement of target BP was found to be the main contributor to the estimated risk reduction.

In a similarly designed stepped-care trial, Poulter et al randomized 3270 patients, 37.5% of whom had grade 1 hypertension, to initial therapy with perindopril/amlodipine 3.5/2.5 mg or irbesartan 150 mg. Perindopril/amlodipine was up-titrated from 3.5/2.5 mg to 7/5 mg, 14/5 mg, and then 14/10 mg. In the other arm, patients went from irbesartan 150 mg to irbesartan±hydrochlorothiazide 150/12.5 mg, 300/12.5 mg, and finally 300/25 mg. BP control increased at each evaluation with the first-line combination strategy up to 6 months (primary end point): 21%, 30% (P<0.001), 37% (P<0.001), and 42% (P=0.003) at 1, 2, 3, and 6 months, respectively. Over the next 3 months, up until 9 months, the percentage of patients with BP control remained largely unchanged.

In the fourth trial, 837 subjects with mild-to-moderate hypertension were enrolled and randomized to perindopril arginine/amlodipine (14/10 mg/day), perindopril erbumine (16 mg/day), or amlodipine (10 mg/day). Change in seated BP was largest in seated BP at day 42 of treatment, nearly all the BP response (both systolic and diastolic) was observed after only half that time (21 days of therapy).

A combined-analysis of data from the Laurent et al, Mancia et al, and Poulter et al trials compared the BP-lowering efficacy of 1-month treatment with perindopril/amlodipine 3.5/2.5 mg versus monotherapy with a RAS inhibitor. The analysis included 5507 patients with mild-to-moderate hypertension and similar baseline BP levels. The decrease in SBP/DBP achieved with perindopril/amlodipine 3.5/2.5 mg was superior to the decrease achieved with each RAS blocker monotherapy after only 1 month of treatment, with an overall significant difference in SBP and DBP reduction of 2.4 mm Hg (P<0.002) and 1.3 mm Hg (P=0.005) in favor of perindopril/amlodipine 3.5/2.5 mg (Figure 3).

◆ Tolerability versus monotherapy

European hypertension guidelines stress that efforts should be made to limit drug-related side effects, in part, because adverse events are the most important causes of treatment nonadherence. Perindopril/amlodipine 3.5/2.5 mg has been demonstrated to have better tolerability than the lowest ap-
proved doses of its components as monotherapy. The single-pill combination and its components had similar incidences of all emergent adverse events: 18.9% for perindopril/amlodipine 3.5/2.5 mg versus 18.7% for perindopril 3.5 mg and 18.6% for amlodipine 2.5 mg. For comparison, the incidence with placebo was 15.9%, while the highest rate of emergent adverse events was observed in another comparator group, the amlodipine 5 mg group (21.6%). The number of patients reporting lower limb edema was greater in the amlodipine 5 mg group than the combination group (14 [5.3%] versus 4 [1.6%]; intergroup difference, –3.7 [95% confidence interval, –6.8 to –0.6]). With perindopril/amlodipine 3.5/2.5 mg, the incidences of headache (1.2%) and cough (0.8%) were low and no different to those observed in the perindopril 5 mg and amlodipine 5 mg groups.

In the Mancia et al study and Poulter et al studies, the pattern of specific emergent adverse events was consistent with the known safety profile of the individual components, and no safety concerns were raised. Perindopril/amlodipine 14/10 mg was associated with a 42% reduction in the incidence of peripheral edema versus amlodipine (7.2% [20/279] versus 12.5% [35/280]) in the three-arm trial, in which it was compared with perindopril erbumine and amlodipine. Finally, a meta-analysis of the perindopril/amlodipine 3.5/2.5 mg trials showed that tolerability was similar in all groups with an incidence of emergent adverse events of 28.4% for perindopril/amlodipine 3.5/2.5 mg versus 28.2% for monotherapy comparators (P=0.929).

Cough was more frequent in the perindopril/amlodipine 3.5/2.5 mg group (4.5%), while headache (3%) and diarrhea (0.8%) were more frequent in the RAS blocker group. None of the trials reported any serious treatment-related adverse events or detected any clinically relevant changes or differences between treatment groups in blood biochemistry or hematology in laboratory analyses.

Discussion
There is unequivocal evidence that hypertension is a major cardiovascular risk factor and that BP-lowering strategies substantially reduce this risk. It is also clear that target BP levels are not achieved in a high proportion of patients. There is therefore a strong need to detect and treat more hypertensive patients as well as to improve the efficacy of ongoing treatment.

Three main causes of the low rate of BP control in real life have been described: (i) physicians’ therapeutic inertia; (ii) low adherence to a prescribed treatment regimen by patients; and (iii) deficiencies of health-care systems in their approach to chronic diseases. A fourth factor has also recently been put forward as important: the reluctance to adopt drug treatment strategies that reduce elevated BP more effectively.

According to the latest European hypertension management guidelines, the first-line use of antihypertensive drug combinations should be reserved for high-risk patients or patients with particularly elevated baseline BP. By implication, treatment with monotherapy should be initiated in patients with less risk and less elevated baseline BP. The problem with the monotherapeutic approach to the control of BP is that it works in so few hypertensive patients; most will need more than one antihypertensive agent to control BP. Given this undisputed fact, one could legitimately argue that we are approaching this treatment dilemma from the wrong direction. Perhaps we ought to be asking whether the initiation of antihypertensive treatment with combination therapy should be preceded by monotherapy.

In the treatment of patients with mild-to-moderate (grade 1) hypertension, there is increasing evidence that combinations containing adapted doses (developed to provide optimal efficacy with the best tolerability for first-line use) are particularly beneficial. BP has multiple regulatory pathways, and combining agents from different antihypertensive drug classes has positive effects on BP control—allowing earlier, larger, and more sustained reductions in BP than uptitration of monotherapy and a sequential add-on regimen—leading to earlier cardioprotection. By simplifying the dosing regimen and improving tolerability, combination therapy can also improve medication adherence and reduce therapeutic inertia.

Conclusion
Initial combination therapy could lessen the long-term impact of hypertension on cardiovascular disease and mortality, and the findings outlined in this paper support the case for the first-line use of adapted-dose antihypertensive combinations in future hypertension guidelines. A large-scale dossier of development studies shows clinically significant reductions in BP with adapted-dose perindopril/amlodipine 3.5/2.5 mg that were superior or noninferior to perindopril and amlodipine monotherapies at their lowest approved doses, with BP-lowering efficacy seen as early as 4 weeks after the start of treatment. Adapted-dose perindopril/amlodipine 3.5/2.5 mg was well tolerated and reduced the time required to achieve BP control compared with stepped-care strategies. In short, the data presented in this review strongly support the use of adapted-dose perindopril/amlodipine 3.5/2.5 mg as a first-line treatment of hypertension in a wide range of patients, including those with mild-to-moderate hypertension.

**Keywords:** adapted-dose strategy; hypertension; antihypertensive treatment; Viacoram; first-line; newly diagnosed; perindopril/amlodipine
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A new first-line treatment in hypertension – Lhoste


Several factors are known to present a barrier in the hypertensive population to blood pressure control, which is notoriously low worldwide. They can be grouped into four major categories: (i) deficiencies of health-care systems, which are especially prominent in the area of cardiovascular prevention; (ii) physician inertia, ie, the fact that many physicians fail to modify treatment when, at a given visit, they see the blood pressure of the patient to be above control values; (iii) physicians’ unawareness or unwillingness to give preference to antihypertensive treatment strategies that have been shown to effectively control blood pressure, such as the combination of two or more drugs rather than monotherapy; and (iv) poor adherence to the prescribed treatment, a devastating phenomenon that is probably the number one reason for the poor blood pressure control in hypertensive individuals.

Poor adherence to treatment is an important factor leading to low rates of blood pressure control identified by the most recent 2013 European hypertension guidelines. What measures can be taken to improve patients’ confidence in their treatment and thus improve adherence?

The 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) hypertension guidelines emphasize the importance of poor adherence to antihypertensive treatment as perhaps the main cause of poor blood pressure control in the hypertensive population. Since their publication, the perception has grown that this is perhaps the main barrier to overcome in order to improve the number of patients with blood pressure control. The number of studies devoted to how to measure adherence, determine which factors favor or oppose it, and examine the relationship adherence has with the risk of cardiovascular events and mortality has grown alongside. Thanks to these studies, we know that adherence is an extremely complicated phenomenon because: (i) there are many different nonadherence patterns; and (ii) no patient can be defined “tout court” as adherent or nonadherent.

Patients can be fully adherent to a prescribed treatment regimen over a given fraction of their life and not adherent at all at other times. Factors involved in adherence to treatment are multiple and interactive. In our analysis of the Lombardy database (10 million residents in the region), we saw that adherence to antihypertensive treat-
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How can adherence be improved?

Many steps are potentially useful, and some have been tested with reasonably good results. It is well known that adherence can be improved by: (i) using drugs with a good tolerability profile because side effects are a major cause of treatment discontinuation; (ii) privileging the use of combination treatment because of its association with better blood pressure control, which reassures patients and encourages them to continue treatment; and (iii) using simple treatment strategies. Single-tablet combinations, for example, have been repeatedly shown to improve adherence to treatment with respect to free combinations and, as a consequence, single-tablet combinations favor blood pressure control.

It is also well known that other measures can have favorable effects: better awareness of the protective effect of treatment by the patient, involvement of close relatives in the treatment schedule, and self-measurement of blood pressure at home. There are also hopes for the future that electronic devices and interventions, such as telemetry (which improves physicians’ feedback on patients’ needs and queries) and sound alerts on mobile phones, etc, may have a real impact on adherence, although studies on their usefulness are still at an initial phase. It should, in this context, be emphasized that studying the effects of a given measure of adherence to treatment is by no means easy. Most current measures of adherence are indirect and inaccurate. The few direct measures available are difficult to apply in a continuous fashion (multiple assessments over time), which is needed to cope with the dynamic nature of adherence. In addition, studies must be done under conditions that are pertinent to real life. Studying adherence in clinical trials has limited value because recruitment alters patients’ behavior (the so-called Hawthorne effect).

Physician inertia has also been identified by the most recent 2013 European hypertension guidelines as a key factor impacting blood pressure control. How can the use of combination treatment from diagnosis reduce this inertia?

As I mentioned before, this is another important barrier to blood pressure control. Several studies have shown that in real-life medicine, a large number of physicians fail to take action when they see that a patient has blood pressure values above the recommended target. Interestingly, adoption of a wait-and-see attitude rather than one of upgrading treatment when blood pressure is still high has also been shown in trials, ie, where physicians are required to control blood pressure by upgrading treatment according to a predetermined algorithm. The result can be highly damaging because blood pressure values measured at any given visit have an independent predictive value for outcome.

By analyzing data from INVEST (International VErapamil-SR/tandolapril Study), which included about 23 000 hypertensive patients with coronary disease, we found that for any given on-treatment average blood pressure, cardiovascular risk was progressively lower as the number of visits with blood pressure control increased. Improvement may have come from a better awareness by the doctor of the benefits of blood pres-
sure control. It may also have come from making patients more demanding via self-measurement of blood pressure. It may finally have come from greater use of initial combination treatment, which bypasses physicians’ reluctance to add further drugs to initial monotherapy.

In practice, what are the benefits of initiating combination treatment in patients as soon as hypertension is diagnosed?

No randomized trial has looked at whether starting treatment with two drugs reduces cardiovascular events more than starting treatment with one drug and moving to combination treatment (whenever needed) later. Support comes, however, from many observational studies that suggest that the prompter blood pressure control that can be obtained by the initial use of two antihypertensive drugs may have several advantages over the delayed control that often accompanies initial monotherapy and combination treatment at a later time only.

First, in a post hoc analysis of the hypertensive patients with high cardiovascular risk of VALUE (Valsartan Antihypertensive Long-term Use Evaluation), prompt blood pressure control (ie, control within one month) was associated with a lower risk of outcomes compared to later control. Second, prompt blood pressure control shortens the titration phase, reduces the number of visits (and thus initial treatment costs), and attenuates the therapeutic inertia phenomenon. Third, recent large scale studies have shown that starting treatment with drug combinations is accompanied by less treatment discontinuation; this being the case both when combinations including a diuretic are compared with diuretic monotherapy, and when combinations without a diuretic are compared with monotherapies other than a diuretic. This is probably the factor predominantly responsible for the fact that patients on initial combination treatment have a much greater chance of having their blood pressure controlled in the long term, ie, after one or two years.

Fourth, better long-term adherence to treatment and blood pressure control are probably also responsible for the evidence from two observational studies that initial combination treatment is associated with greater cardiovascular protection. One of these studies was based on the large number of patients in the Lombardy database. There was 26% less hospitalization for coronary and cerebrovascular events in patients in whom treatment was started and continued with a drug combination than in those who started treatment with a single drug and moved to a combination later.

What are the potential problems, in practice, of initiating a combination treatment in patients from the diagnosis of hypertension, and how can these be overcome?

The 2013 ESH/ESC hypertension guidelines mention problems related to initial combination treatment, namely: (i) in patients in whom blood pressure could be controlled by monotherapy one unnecessary drug is prescribed; (ii) two drugs prescribed together make attribution of drug-dependent side effects more difficult; and (iii) if single tablet combinations are used, titration to blood pressure control may be less flexible, ie, increasing dose involves two drugs simultaneously, rather than one drug at a time.

However, these problems are more theoretical than real because the number of patients in whom blood pressure can be controlled by one drug only is small, particularly if elevated blood pressure is in the moderate or severe range. The tolerability profile of most combinations is by no means worse (indeed, it can be better) than that of single drugs. Furthermore, many single-tablet combinations are now available in a variety of different dosages of the combination components, which makes up- or downtitration of treatment almost as flexible as if drugs were used in free combination form.

What are the ideal antihypertensive drug classes to combine when initiating combination treatment?

According to the 2013 ESH/ESC guidelines, many combinations can be used and certain ones may be preferred in special clinical circumstances. In fact, the only combination that is not recommended is that of an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor antagonist (or a renin inhibitor with one or the other drug class) because of serious shortcomings observed in clinical trials. At the other end of the spectrum, some priority-use combinations have also been identified, ie, a RAS blocker with a calcium channel blocker, a RAS blocker with a diuretic (hydrochlorothiazide, indapamide, or chlorthalidone), and a diuretic with a calcium channel blocker. Both ACE inhibitors and angiotensin receptor antagonists are considered suitable RAS blockers, ACE inhibitors having the advantage of more widespread use in outcome trials, including the best trial so far performed for combination treatment comparisons, ACCOMPLISH (Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension).

Interestingly, although ACCOMPLISH found the ACE inhibitor/calcium channel blocker combination to be more protective than the ACE inhibitor/hydrochlorothiazide combination, the European guidelines consider both combinations of equal worth because in trials comparing initially administered calcium channel blockers and diuretics, no superiority of one drug versus the other has usually been found. Choice may be guided by the clinical characteristics of the patient. For example, a diuretic-based combination may be more appropriate in patients with hypervolemia whereas a calcium antagonist-based combination may be more appropriate in patients with metabolic abnormalities, which may be worsened by diuretics.
Is there evidence to support the use of combination therapy as initial treatment, from diagnosis, in grade 1 hypertension?

Doctors should consider initial combination treatment in patients at high cardiovascular risk, which means patients with blood pressures clearly above 140/90 mm Hg (grade 2 or 3 hypertension), according to the 2013 European hypertension guidelines. This should also, however, include patients with more modest blood pressure elevation (grade 1 hypertension), provided their cardiovascular risk is high because of diabetes, cardiovascular disease, renal disease, or advanced organ damage. This is largely based on “common sense” considerations, namely the fact that in high cardiovascular risk individuals an event can occur within a short time, so achieving prompt blood pressure control is a highly desirable goal.

Based on recent evidence, however, prompter blood pressure control associated with the use of initial combination treatment may also offer advantages in patients with grade 1 hypertension and low-to-moderate cardiovascular risk. Long-term advantages of initial combination treatment (improved adherence, reduced therapeutic inertia, and reduced cardiovascular events) have been reported for general hypertensive populations, ie, populations largely including grade 1 hypertension. At variance with previous reports, recent meta-analyses show that in these patients antihypertensive treatment is accompanied by clear-cut cardiovascular protection. Finally, in the recently published HOPE-3 (Heart Outcomes Prevention Evaluation 3) trial, initial combination treatment (a RAS blocker and a diuretic) was found to significantly reduce outcomes (-23%) in patients with grade 1 hypertension (systolic blood pressure >143 mm Hg, mean 154 mm Hg) and moderate cardiovascular risk.

Keywords: blood pressure control; hypertension guidelines; adherence; physician inertia; initial treatment; combination therapy; preferred combination

References

Keywords: blood pressure control; hypertension guidelines; adherence; physician inertia; initial treatment; combination therapy; preferred combination
Over 50 years of investigation have not defined the molecular mechanisms that underlie arterial hypertension; more than 90% of cases are still called “essential hypertension,” ie, hypertension without an identified cause. Factors that increase cardiac output and/or total peripheral resistance, eg, vasoconstriction of the arterioles or reduced diuresis, will raise blood pressure, as blood pressure is directly related to these parameters. Many different pharmacological options are available to lower elevated blood pressure, and the main classes of antihypertensive drugs have been widely investigated and are well known: diuretics (thiazide-type and thiazide-like), renin-angiotensin system inhibitors (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers, and direct renin inhibitors), calcium channel blockers (CCBs), and β-blockers. The variety of different pharmacological effects of these main classes reflects the diversity of mechanisms implicated in hypertension. From a pharmacological perspective, there may be good reasons for preferring antihypertensive combination therapy to monotherapy: components that act on different hypertensive mechanisms can reduce counterregulatory responses; and side effects can be attenuated via dose reduction and/or complementary pleiotropic effects of one or both components. Additional benefits of antihypertensive combinations include faster blood pressure control and greater end point reduction, and three in four hypertensive patients will ultimately require combination therapy for blood pressure control. Not all combinations are equal, and the choice of a “preferred” combination, such as ACE inhibitor/CCB, confers additional treatment benefits.

Regulation of blood pressure

Guyton’s view

Blood pressure (BP) is related to cardiac output (CO) and total peripheral resistance (TPR) by the equation BP = CO × TPR. Increases in either cardiac output or total peripheral vascular resistance produce hypertension. The control of BP by the body is an integrated response that includes regulation by neural receptors, hormones, and renal fluid balance. The handling of sodium within the kidney is one of the major factors that regulates BP (Figure 1, page 132). Hence, in the pathogenesis of hypertension, abnormal renal Na+ excretion increases intravascular volume, which is the primary determinant of increased cardiac output and therefore elevated BP. The importance of renal fluid balance in the control of BP is a widely accepted concept that has been extensively reviewed.
Vascular smooth muscle contraction and hypertension

A number of classes of antihypertensive agent effectively lower BP. Changes in vascular tone result in changes in total peripheral resistance and in either hyper- or hypotension, for example, vasopressor agents increase BP, whereas vasodilating drugs induce hypotension. Experimental models allow us to identify the effects of the different pathways regulating vasomotor tone. Investigators have genetically modified mice to produce abnormalities in vasomotor tone. Knock-out mice were produced and BP measured: in the β1 receptor subunit knock-out, estrogen receptor β knock-out, vascular smooth muscle cell ATP channel knock-out, and endothelial nitric oxide synthase knock-out. All of these mice had both vascular dysfunction and hypertension, but data from these experiments confirm that vascular dysfunction, specifically vasoconstriction, produces hypertension.

Classes of antihypertensive drugs

Diuretics

Treatment of hypertension using a diuretic-based strategy was effective in preventing stroke and cardiovascular disease in the earliest randomized clinical trials in the 1960s. Elevated BP in a large proportion of hypertensive patients, especially those of African origin, can be well controlled on simple two-drug regimens combining a diuretic with either a β-blocker or an angiotensin-converting enzyme (ACE) inhibitor. Three major diuretic classes are used to treat hypertension: (i) thiazides; (ii) loop-active agents; and (iii) potassium-sparing agents, which act as either mineralocorticoid antagonists or inhibitors of the epithelial sodium channel of the late distal renal tubule or collecting duct. Thiazide diuretics can be subdivided into thiazide-like (eg, indapamide and chlorthalidone) and thiazide-type (eg, hydrochlorothiazide) diuretics. Thiazide-like diuretics have a longer elimination half-life compared with thiazide-type diuretics and have been shown to exert additional pharmacological effects, which may be responsible for the greater reductions in cardiovascular events demonstrated by thiazide-like versus thiazide-type diuretics. Figure 2 displays the sites at which the different diuretic subclasses have their greatest effects on electrolyte and water reabsorption in the nephron after glomerular filtration has occurred.

β-Blockers

-Blockers are competitive antagonists for endogenous catecholamines, epinephrine and norepinephrine, on adrenergic receptors. Some β-blockers bind to all types of adrenergic receptors, while others are more selective for β1 (in the heart and kidneys), β2 (in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle), or β3 receptors (in fat cells). -Blockers interfere with the binding to the receptors of epinephrine and weaken its effects on the cardiovascular system. Although they are no longer the first choice for initial treatment in most patients, -blockers are still widely used, particularly in hypertensive patients with concomitant coronary artery disease. However, there are several reasons why -blockers are relatively ineffective in the prevention of cardiovascular events in hypertensive patients. -Blockers have certain disadvantages compared with other antihypertensive agents:

Figure 1. Control of arterial blood pressure by dilation of arterioles and diuresis in the kidney.

Arterial blood pressure is the product of total peripheral resistance and cardiac output (TPR × CO). Changes in Na+ reabsorption will modify the intravascular volume and result in an increase or decrease cardiac output and, in turn, arterial blood pressure. Similarly, alterations in vascular tone affect the TPR, which leads to an increase (vasoconstriction) or decrease (vasodilation) in blood pressure.

Abbreviations: Na, sodium; TPR, total peripheral resistance.

Figure 2. Sites and mechanisms of action for thiazide-related and potassium-sparing diuretics. All effects on electrolytes take place on the luminal side of the epithelial cell.

Abbreviation: HCTZ, hydrochlorothiazide.
The renin-angiotensin system (RAS) is involved in the regulation of plasma sodium concentration and arterial BP. When plasma sodium concentration, and/or renal blood flow, and/or arterial pressure in the proximal glomerular artery are too low, the juxtaglomerular cells in the kidneys convert prorenin into renin, which is then secreted directly into the circulation. Plasma renin cleaves angiotensin I off the plasma protein angiotensinogen. Angiotensin I is then converted by ACE into angiotensin II, a potent vasoactive peptide that causes arterioles to constrict, resulting in increased arterial BP. Secretion of aldosterone from the adrenal cortex is regulated by angiotensin II. Aldosterone enhances ion transport in renal tubular epithelial cells in two ways: sodium ion reabsorption (from the tubular fluid back into the blood) and potassium ion excretion (into the tubular fluid) are increased (Figure 2). Increase in the concentration of sodium in blood results in an increase in intravascular volume and plays a role in increasing BP.

Three families of drugs can block the effects of the RAS: direct renin inhibitors, ACE inhibitors, and angiotensin receptor blockers (ARBs). Despite exciting promise and potential, clinical trials of direct renin inhibition have not been convincing. We will thus focus on ACE inhibitors and ARBs.

**Calcium channels blockers**
The extracellular concentration of calcium (Ca²⁺) is normally about 10 000-fold higher than the concentration inside cells. In vascular smooth muscle cells, an increase in intracellular calcium through membrane-embedded calcium channels induces vasoconstriction. Calcium channel blockers (CCBs) prevent or reduce the opening of these channels thereby reducing these vasomotor effects and BP elevation.

Several subclasses of CCB exist; however, almost all CCBs preferentially block the L-type voltage-gated calcium channel. These channels are responsible for excitation-contraction coupling of smooth and cardiac muscle. In the heart, they are also involved in the conduction of pacemaker signals. CCBs have three main effects:

- Reduction of vascular smooth muscle tone, vasodilation, and lowering of arterial BP
- Negative inotropic and chronotropic effects
- Reduction of aldosterone production, leading to BP lowering

Cardiac oxygen demand is reduced with the use of dihydropyridines because they lower arterial BP and afterload; at therapeutic doses, dihydropyridines do not weaken cardiac contraction nor do they modulate cardiac rhythm. The vasodilatory properties of CCBs explain common side effects, such as flushing, headache, dizziness, and hypotension. These side effects, though unwelcome, are possibly of less importance than others, like peripheral edema and ankle swelling, which often curtail the use of dihydropyridines.¹¹

**Blockers of the renin-angiotensin system**
The renin-angiotensin system (RAS) is involved in the regulation of plasma sodium concentration and arterial BP. When plasma sodium concentration, and/or renal blood flow, and/or arterial pressure in the proximal glomerular artery are too low, the juxtaglomerular cells in the kidneys convert prorenin into renin, which is then secreted directly into the circulation. Plasma renin cleaves angiotensin I off the plasma protein angiotensinogen. Angiotensin I is then converted by ACE into angiotensin II, a potent vasoactive peptide that causes arterioles to constrict, resulting in increased arterial BP. Secretion of aldosterone from the adrenal cortex is regulated by angiotensin II. Aldosterone enhances ion transport in renal tubular epithelial cells in two ways: sodium ion reabsorption (from the tubular fluid back into the blood) and potassium ion excretion (into the tubular fluid) are increased (Figure 2). Increase in the concentration of sodium in blood results in an increase in intravascular volume and plays a role in increasing BP.

Three families of drugs can block the effects of the RAS: direct renin inhibitors, ACE inhibitors, and angiotensin receptor blockers (ARBs). Despite exciting promise and potential, clinical trials of direct renin inhibition have not been convincing. We will thus focus on ACE inhibitors and ARBs.

**ACE inhibitors**
Angiotensinogen and bradykinin are important substrates of the peptidase ACE. These substrates have a role in BP control, hematopoiesis, renal function, and immune response. Two experimental approaches have been used to discriminate between the physiological effects of angiotensin II and other ACE substrates. Firstly, mice with null mutations in ACE have been compared with mice lacking other components of the RAS, such as angiotensinogen or the angiotensin 1 (AT₁) receptor. Secondly, the effects of ACE inhibitors have been compared to those of ARBs in animals and humans. Both approaches have shown that for the physiological regulation of BP, the ACE-mediated production of angiotensin II is essential.¹² Both ACE inhibitors and ARBs have similar long-term effects on elevated BP in hypertension. However, because ARBs do not affect the kinin-bradykinin system, the clinical effect of ACE inhibitors and ARBs may differ substantially. Tissue and plasma bradykinin levels are elevated during the blockade of ACE.¹³ Bradykinin binds to the bradykinin receptors B₁ and B₂. Expression of the B₁ receptor is induced by tissue injury, such as ischemia and inflammation, in contrast to B₂ receptor expression, which occurs under normal conditions.¹⁴

When bradykinin binds to the B₂ receptor, nitric oxide is produced and prostacyclin released, which lead to vasodilation and increased vascular permeability. At the renal level, bradykinin promotes natriuresis. Inducing bradykinin formation in experimental models of hypertension reduces BP; thus, besides reducing angiotensin II production, ACE inhibitors contribute to the control of BP by increasing the concentration of bradykinin. The effect of ACE inhibitors on bradykinin is

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Acronym</th>
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<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>AT</td>
<td>angiotensin [receptor]</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
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<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
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<tr>
<td>RAS</td>
<td>renin-angiotensin system</td>
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linked to certain side effects (eg, cough), but notwithstanding this it is also linked to several beneficial effects, especially the reversal of low-grade inflammation and cardiac and vascular remodeling.

**Angiotensin receptor blockers**
The direct molecular targets for angiotensin II are the AT₁ and AT₂ receptors. The angiotensin receptor family also includes an AT₂ receptor, whose ligand is not the same but rather the breakdown product of angiotensin II, angiotensin IV.  

Although ARBs and ACE inhibitors are used for the same indications (hypertension, heart failure, post-myocardial infarction), their mechanisms of action are very different. ARBs are receptor antagonists that block AT₁ receptors on blood vessels and other tissues, such as the heart. AT₁ receptor blockade inhibits cellular actions of angiotensin II mediated by the AT₁ receptor, including mitogenic activity, cytokine production, reactive oxygen species formation, and aldosterone production. ARBs and ACE inhibitors have the following effects in common; they both:

- Diminish arterial pressure and cardiac preload and afterload by dilating arteries and veins
- Negatively modulate the sympathetic adrenergic activity by disrupting the action of angiotensin II on sympathetic nerve release and norepinephrine reuptake
- Enhance excretion of sodium and water by the kidneys by disrupting the renal action of angiotensin II and secretion of aldosterone

Several pharmacologic effects of ARBs may be attributable to actions independent of their inhibition of AT₁ receptor activation with its consequent BP-lowering effect. AT₂ receptor blockade by ARBs also allows angiotensin II to bind to AT₂ receptors, which mediates several actions. Despite the impossibility of designing a clinical trial that could unequivocally identify an AT₂ receptor–independent pharmacologic effect of ARBs in patients, it has been shown that activation of the AT₂ receptor in normotensive young rats results in vasodilation. Having said this, the vascular AT₂ receptor phenotype switches from relaxation to contraction in spontaneously hypertensive rats and in ageing normotensive animals. The cardiovascular trophic effect of AT₂ stimulation is still controversial; whereas the majority of authors have reported an antifibrotic effect with AT₂ receptor stimulation, in experimental models the AT₂ receptor has also been documented to exert a stimulatory effect in arterial and ventricular hypertrophy, cardiac fibrosis, and heart failure. Mice with AT₂ receptor overexpression were found to develop severe cardiac fibrosis, heart failure, and intrinsic myocyte contractile dysfunction.

**Combinations of antihypertensive drugs**
Despite the usual recommendation of initial monotherapy, the use of initial combination therapy in a broad population of hypertensive patients may facilitate key objectives of treatment, like rapid control of BP and reduction in long-term end points. In fact, several large clinical trials have shown that in patients with hypertension and one or more other cardiovascular risk factors, treatment with multiple antihypertensive medications is generally necessary to attain BP goals recommended by guidelines. Combination therapy is necessary in approximately 75% of patients with hypertension.

**Rationale for bitherapy**

- **Acting on different mechanisms of hypertension**
Drug selection in hypertension should be based both on efficacy in lowering BP and in reducing stroke, myocardial infarction, and heart failure. Although the choice of initial drug therapy may modify long-term outcomes, BP reduction per se remains the primary determinant of cardiovascular risk reduction. Elevated BP is multifactorial in nature; thus, acting on multiple hypertensive mechanisms leads to greater BP reduction and higher responder rates. Furthermore, halving the dose of most antihypertensive drugs has been demonstrated to substantially reduce the prevalence of adverse effects while only reducing the BP-lowering effect by approximately 20%, which supports proposals for the use of combinations in the first-line treatment of hypertension. Combinations containing lower doses of each antihypertensive component should, in theory, lower BP as much as or more than monotherapy because of the association of two or more agents that target different hypertensive mechanisms thus preventing counterregulatory responses. Counterregulatory responses are a deleterious mechanism that can negate the efficacy of antihypertensive treatment. For example, the antihypertensive effect of a dihydropyridine would be weakened by compensatory activation of the RAS. Concurrent RAS blockade would thus enhance the effect of CCB.

Supplemental BP lowering may also be possible with antihypertensive combinations. Although BP reduction varies little between antihypertensive classes (by just a few millimeters of mercury), when agents from different classes are combined the resultant antihypertensive effect can vary greatly. Supplemental BP lowering may also be possible with antihypertensive combinations. Although BP reduction varies little between antihypertensive classes (by just a few millimeters of mercury), when agents from different classes are combined the resultant antihypertensive effect can vary greatly. Associating drugs from complementary classes is about five times more effective in reducing BP than giving twice the dose of one drug.

**Pharmacokinetic compatibility**
Another important requirement of a combination is smooth and continuous BP reduction over 24 hours, ie, between two doses. For this to be possible, there needs to be pharmacokinetic compatibility between the two drugs to be combined.

**Minimizing side effects**
Because antihypertensive drugs are prescribed long-term for an asymptomatic condition, good tolerability is of fundamental importance. Adherence to antihypertensive treatment could be problematic, especially in patients receiving multiple medications for other indications.
Pharmacological considerations in choosing antihypertensive therapy – Lévy

**Figure 3.** Dose response curves for the expected (therapeutic) effects and side effects of pharmacotherapy.

Figure 3 shows a schematic view of the dose-effect relationships of a given drug for both the expected (therapeutic) effects and side effects. The latter curve is shifted right; so side effects are absent or minimal in the lower dose range. A perfect drug would have no side effects at higher therapeutic doses. In fact, side effects occur in most cases at usual therapeutic doses. Because all antihypertensive agents produce dose-dependent side effects, high-dose monotherapy inevitably leads to adverse events. When a more effective antihypertensive treatment is needed, increasing the dose of monotherapy may induce significant side effects. Combining another class of antihypertensive drug in a single pill while minimizing the doses of both components would attenuate the impact of side effects for each component, which could improve long-term compliance to treatment, especially if additional BP reduction is achieved.

Furthermore, the tolerability profile of one antihypertensive agent can be improved by the addition of another, when the adverse effects of one component are counteracted by properties of the other. For example, the incidence and magnitude of hypokalemia with diuretics is reduced by adding an ACE inhibitor to therapy because of the aldosterone-inhibiting effect of ACE inhibitor. Another example involving ACE inhibitor drug class is the addition of this drug class to therapy in a patient who develops edema with dihydropyridine CCB at high doses. This not only allows the dose of CCB to be reduced without impacting BP control, but also for edema to be controlled,\(^7\) ostensibly via pleiotropic ACE inhibitor-induced veno-dilation.\(^31\)

**Choice of classes for a combination**

Two-drug combinations can be divided into three categories: “preferred,” “acceptable,” and “less effective.”\(^37\) Categorization is based, in part, on BP-reducing efficacy and tolerability. In monotherapy, ARBs and ACE inhibitors are the best tolerated agents and diuretics the least well tolerated. Preferred combinations contain drugs from classes that have performed consistently well in long-term trials: ACE inhibitors and ARBs, long-acting CCBs, and diuretics. \(^-\)Blocker combinations are less valuable and have been excluded from the “preferred” category because they reduce end points, particularly stroke, less well than active comparators.\(^29\) Other combinations, such as ACE inhibitor and CCB, may be more valuable because of BP lowering-independent effects. ACE inhibitors appear to be the best antihypertensive agent at reducing LVH, followed by CCBs.\(^36\) The ability of ACE inhibitors to regress LVH at doses that do not affect BP shows that the cardiac RAS plays a role in heart structure and function.\(^26\) One could thus argue that an ACE inhibitor/CCB combination is potentially better at preventing cardiac hypertrophy and myocardial remodeling than other combinations. Table I summarizes the effects of both ACE inhibitors and CCBs on several target organs: kidney, arterial wall, and heart.\(^25\)

From basic and clinical research, long-acting CCBs, especially dihydropyridines such as amlodipine, appear to be an evident choice as part of an antihypertensive combination. A preferred combination is that of a CCB plus a blocker of the RAS, either an ACE inhibitor or ARB. Evidence from basic research allows us to demonstrate that ACE inhibitors and ARBs affect the cardiovascular system in different ways: basically, ACE inhibitors increase the tissue bradykinin concentration and activate the nitric oxide pathway, whereas ARBs have no effect on these mechanisms, but activate the angiotensin II receptor subtype AT\(_2\), resulting not only in vasodilation, but also decreased angiogenesis and possible cardiovascular trophic effects.

<table>
<thead>
<tr>
<th>Pharmacological target</th>
<th>Dihydropyridine CCB</th>
<th>ACE inhibitor</th>
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<tbody>
<tr>
<td><strong>Kidney</strong></td>
<td></td>
<td></td>
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<tr>
<td>Renal blood flow</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Efferent glomerular artery</td>
<td>Vasodilation</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Afferent glomerular artery</td>
<td>Vasodilation</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Microproteinuria</td>
<td>Slight decrease</td>
<td>Decreased</td>
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<tr>
<td><strong>Arterial wall</strong></td>
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<td></td>
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<tr>
<td>Nitric oxide release</td>
<td>Unchanged</td>
<td>Increased</td>
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<tr>
<td>Arterial compliance</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Vascular hypertrophy</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Atherogenesis</td>
<td>Delayed</td>
<td>Delayed</td>
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<tr>
<td><strong>Heart</strong></td>
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<tr>
<td>Left ventricular hypertrophy</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Coronary flow</td>
<td>Increased</td>
<td>Increased</td>
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**Table I.** Possible synergy resulting from a combination of a dihydropyridine calcium channel blocker (CCB) and an angiotensin-converting enzyme (ACE) inhibitor.

Based on data from reference 34.
Two recent meta-analyses compared the effect of both RAS blockers. Yang and colleagues compared the effects of ACE inhibitors and ARBs on insulin sensitivity in hypertensive patients without diabetes. Compared to ARBs, treatment with ACE inhibitors resulted in a more effective improvement of insulin sensitivity in hypertensive patients without diabetes, although these two drugs did not show significant differences with regards to fasting plasma glucose, insulin plasma concentration, or BP. Thus, in hypertensive patients without diabetes and no significant difference in BP control, ACE inhibitors were more effective at improving insulin sensitivity than ARBs. Brugts and coworkers analyzed prospective, randomized, controlled morbidity-mortality trials (68 343 RAS inhibitor and 84 543 control subjects [on placebo or non-RAS regimen] with a mean follow-up of 4.3 years) to assess the effectiveness of RAS inhibitors in preventing all-cause death, cardiovascular death, myocardial infarction, and stroke in hypertensive patients by considering the number needed to treat. ACE inhibitors were used in 7 trials and ARBs in 11 trials. The median number of patients that needed to be treated to prevent one death was 113 in favor of RAS inhibitors, which was driven by ACE inhibitors rather than ARBs. Results for cardiovascular mortality and myocardial infarction also appeared to be driven by ACE inhibitors. There was no significant difference between ARBs and ACE inhibitors for stroke incidence. The authors concluded that in hypertensive patients, ACE inhibitors—but not ARBs—substantially reduce all-cause mortality, cardiovascular mortality, and myocardial infarction.

Conclusion

Most hypertensive patients need two or more antihypertensive drugs to reach target BP. European guidelines recommend combining drugs from different antihypertensive classes, preferably in a single pill, as simple therapy encourages good adherence. Improved adherence to antihypertensive therapy is a worthwhile goal because it leads to enhanced cardioprotection and attenuated morbidity and mortality. Dual-agent combinations as an initial treatment strategy are mentioned in the guidelines, one of the best being ACE inhibitor/CCB. In patients with hypertension, major cardiovascular events and mortality are better prevented by ACE inhibitor/CCB than other combinations, such as -blocker/diuretic or ACE inhibitor/thiazide diuretic. Combining ACE inhibitor and CCB may also reduce the frequency and severity of dose-dependent adverse effects related to vasodilation induced by CCB, notably leg edema.

References


Keywords: blood pressure regulation; vascular smooth muscle; antihypertensive drug class; hypertensive mechanism; compatibility; side effect reduction

Pharmacological considerations in choosing antihypertensive therapy – Levy
The recent findings of SPRINT (Systolic blood Pressure Intervention Trial), a landmark trial in hypertension, suggest that there are significant benefits in targeting a systolic blood pressure lower than 120 mm Hg in patients at high cardiovascular risk, rather than the classic target of lower than 140 mm Hg. Following this trial, the medical world continues to debate these benefits. This article reviews current evidence for and against lower blood pressure targets, the potential impact of this evidence on lowering blood pressure targets in future guidelines, the importance of the method of measuring blood pressure if one is to intensify antihypertensive treatment to achieve these new lower blood pressure goals for treatment, and the role that initiation with combination therapy may have in reaching these lower targets.

SPRINT (Systolic blood Pressure Intervention Trial) was developed to investigate whether hypertensive patients at high cardiovascular risk benefited from being treated to a systolic blood pressure (BP) lower than 120 mm Hg, in contrast to the usual target systolic BP of 140 mm Hg. Previous trials in this population (SHEP [Systolic Hypertension in the Elderly Programme], Syst-Eur [Systolic Hypertension in Europe], and HYVET [Hypertension in the Very Elderly Trial], the latter only in subjects aged more than 80 years old) had demonstrated efficacy in prevention of cardiovascular events when systolic BP was lowered to below 150 mm Hg (HYVET) or close to or below 140 mm Hg (in the other trials). There was no evidence on whether lowering systolic BP much below 140 mm Hg would produce additional benefits. Accordingly, there was equipoise between a standard therapy group treated to below 140 mm Hg, and an intensive therapy group treated to a systolic BP of less than 120 mm Hg.

The trial recruited individuals aged more than 50 years old, already treated or not with antihypertensive agents. Subjects were required to have systolic BP between 130 and 180 mm Hg, and another risk factor for cardiovascular events. This risk factor could be age above 75 years (28% of subjects), chronic kidney disease (CKD) patients with estimated glomerular filtration rate (eGFR) 20-59 mL/min/1.73 m² (28%), clinical or asymptomatic cardiovascular disease, or a Framingham Risk Score for 10-year cardiovascular disease risk >15%. Because diabetic patients were part of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, which was taking place when the SPRINT trial was being designed, and the same applied to patients with prior stroke in the SPS3 (Secondary Prevention of Small Subcor-
tlogical Stroke) trial, these patients were excluded. Also excluded were CKD patients with eGFR <20 mL/min/1.73 m² and patients with congestive heart failure, polycystic kidney disease, proteinuria >1 g/day, orthostatic hypotension with systolic BP <110 mm Hg, or adherence concerns. Excluded as well were individuals residing in nursing homes or those with a diagnosis of dementia. The study was funded by the US National Institutes of Health through the National Heart, Lung and Blood Institute.

For SPRINT, 14 692 subjects were screened, and 9361 were randomized into an intensive therapy group with a target systolic BP of less than 120 mm Hg (4678 subjects) or a standard therapy group with a target systolic BP of less than 140 mm Hg (4683 subjects). On August 20, 2015, the National Heart, Lung and Blood Institute ordered the study stopped after a mean duration of 3.26 years because of dramatic benefit in the intensified therapy group. The results were presented on November 8, 2015, at the scientific sessions of the American Heart Association and published that day online in the New England Journal of Medicine and in print the following December. The systolic BP of 121.5 mm Hg in the intensive therapy group versus 134.6 mm Hg in the standard therapy group in SPRINT was associated with a 25% relative risk reduction of the primary end point (all myocardial infarction, non-myocardial infarction acute coronary syndrome, all stroke, all heart failure, and cardiovascular death).

Of interest, among the components of the primary outcome, heart failure experienced a significant relative risk reduction of 38% and cardiovascular death of 43%, whereas myocardial infarction, acute coronary syndrome, and stroke were not significantly reduced. There was a significant relative risk reduction of all-cause mortality of 27%. Benefits occurred consistently across all prespecified groups, including those with or without prior CKD, age older or younger than 75 years, female or male, African-American or not, prior cardiovascular disease or not, and systolic BP at entry <132, >132 to <145 mm Hg, or ≥145 mm Hg. There was a trend toward greater benefit with lower systolic BP at entry, although this was not statistically significant. Whether this may have resulted from allowing BP to drift upward in those patients entering the study with lower baseline systolic BPs who were randomized to standard therapy and who accordingly had to be downtitrated, which might have harmed high cardiovascular risk patients whose BP had previously been intensively controlled, will need to be clarified. Patients with CKD and those without CKD did not differ with respect to renal outcomes on either treatment, although among those without CKD at baseline, significantly more subjects under intensified therapy than in the standard group exhibited a more than 30% reduction in eGFR to a value of less than 60 mL/min/1.73 m², a change whose significance remains unclear.

In a more recent publication, it was shown that the subjects older than 75 years of age benefited as much as the total group if they were in the intensive therapy group, whether or not they were fit or less fit. This result is particularly important considering that some guidelines have allowed target systolic BP for elderly subjects over 60 years of age to drift upward to less than 150 mm Hg, and most others have recommended a goal systolic BP of less than 150 mm Hg for the very elderly above 80 years old, based on HYVET.

Serious adverse effects occurred with relatively low frequency in both the intensified and the standard therapy group. Hypotension, syncope, electrolyte abnormalities (such as hyponatremia and hypokalemia), acute kidney injury, and acute renal failure occurred with low frequency, but to a greater extent in the intensified therapy group. Interestingly, orthostatic hypotension was more frequent, but rare, in the standard therapy group. There was no difference in injurious falls between the groups.

The conclusions to be drawn from SPRINT are that more intensive treatment of BP leads to a reduction in cardiovascular events and all-cause mortality, with no difference in serious adverse events, and that treatment benefit is consistent across prespecified subgroups. The SPRINT findings are consistent with meta-analyses that suggest the benefits of more intensive treatment. In a meta-analysis of 123 studies including 623 815 subjects, Ettehad et al showed that BP lowering significantly reduces vascular risk across various baseline BP levels and comorbidities, providing support for lowering systolic BP to less than 130 mm Hg. These results suggest that BP-lowering treatment should be provided to individuals with a history of cardiovascular disease, coronary heart disease, stroke, diabetes, heart failure, and/or CKD. Further supportive data for this position come from a meta-analysis of 14 studies by Xie et al, comprising 43 483 subjects, a follow-up of 3.8 years, and a mean BP reduction of 7 mm Hg. These authors showed that intensive BP lowering provided greater vascular protection than standard regimens. In high-risk patients, there were additional benefits from more intensive BP

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACCORD</td>
<td>Action to Control CardioVascular Risk in Diabetes</td>
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<tr>
<td>ABBP</td>
<td>Automated office blood pressure</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
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<tr>
<td>HYVET</td>
<td>Hypertension in the Very Elderly Trial</td>
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<td>SHEP</td>
<td>Systolic Hypertension in the Elderly Programme</td>
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<tr>
<td>SPRINT</td>
<td>Systolic blood pressure Intervention Trial</td>
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<tr>
<td>SP3S</td>
<td>Secondary Prevention of Small Subcortical Strokes</td>
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<tr>
<td>STITCH</td>
<td>Simplified Treatment Intervention To Control Hypertension</td>
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<tr>
<td>Syst-Eur</td>
<td>Systolic Hypertension in Europe</td>
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lowering, including for those with systolic BP below 140 mm Hg. The number-needed-to-treat in the high-risk population trials was 94 and in lower risk trials, 186.14

In contrast to SPRINT,5 ACCORD6 failed to prove that intensive BP lowering was superior to standard BP lowering for diabetic subjects. Since diabetic persons are at high risk of cardiovascular events—in many ways similar to SPRINT patients—why did the two studies produce differing results? For one, the results actually went in the same direction, but ACCORD was probably underpowered. Secondly, it could be that the factorial design, with a hypoglycemic and a lipid-lowering arm, could have contributed to the absence of a positive outcome. So perhaps a new, adequately powered study in diabetic patients will now be needed to know how low to go with BP in diabetes.

Based on the quite dramatic results of SPRINT, Hypertension Canada has already introduced a SPRINT-based recommendation for new goals and intensified treatment of hypertensive patients with high cardiovascular risk.12 We recently published our arguments for this recommendation that essentially replicates the inclusion and exclusion criteria of SPRINT and recommends a systolic BP goal of 120 mm Hg or less for SPRINT-like patients.16 However, it should be noted that Hypertension Canada guidelines recommend automated office blood pressure (AOBP) measurement as the preferred method for measuring BP.15 Several studies have shown that when measuring BP with a manual technique, BP values are 10-15 mm Hg higher than those obtained using AOBP measurement.17

In fact, simply having the health-care professional leave the side of the patient while BP is being measured with AOBP (unattended or unobserved AOBP) will result in lower BP values.18 Since unattended AOBP measurement was part of the protocol in SPRINT, and generally seems to have been carried out during the study, Hypertension Canada’s recommendation for intensified treatment goals (systolic BP ≤120 mm Hg) requires the use of unattended AOBP measurement.19 For this reason, the International Society of Hypertension has issued the following recommendation: “The practical message from the International Society of Hypertension is to strive for a systolic BP target of 130 mm Hg in most patients with hypertension.” This is especially important considering that BP measurements in the community worldwide are not likely to be performed using the SPRINT protocol. Advocating a target of ≤120 mm Hg is not justified in clinical practice, and in any case would incur the costs of increased clinic visits, more intensive health care, and more medications. This applies particularly to low- and middle-income countries with resource-poor health-care systems.12

Do we need a new definition of hypertension after SPRINT? We have made some recommendations in this regard.19 Since AOBP measurement is not yet 100% available, when BP is measured with manual BP instruments, the definition of hypertension should remain BP ≥140/90 mm Hg, with a target for treatment in general <140/90 mm Hg, although the goal in most patients should be close to 130/80 mm Hg. The target BP in high cardiovascular risk, including CKD, elderly, patients with a Framingham Risk Score of ≥15%, and probably diabetic subjects,11,15 should be <130/80 mm Hg. However, if BP is measured with guideline-directed unattended AOBP following a 5-minute rest period, as in SPRINT, the definition of hypertension should be BP ≥130/80 mm Hg. In high cardiovascular risk subjects the threshold for treatment should be BP ≥130/80 mm Hg, with a target systolic BP of ≤120 mm Hg.15,16 For those subjects that do not fit the SPRINT criteria, including uncomplicated hypertension without target organ damage (although without any evidence and as an extrapolation from SPRINT), target BP should be <130/80 mm Hg when measuring BP with unattended AOBP.

I believe that the major conclusions to be derived from SPRINT for management of hypertension are that with the increase in research and popularity as well as use of AOBP measurement, after more than 100 years we finally have an approach to reliably and accurately measure BP in the office. Beyond the SPRINT target BP, one of the more important conclusions to draw from this trial is the idea that intensifying treatment will improve outcomes, including in the elderly.

The question now remains, how do we intensify treatment and overcome the hurdle that multiple pills represent for adherence to treatment?20 This is particularly so for high cardiovascular risk patients who need, in addition to BP medications, lipid-lowering agents and other additional drugs, for example antidiabetic agents. Diabetic subjects often require several hypoglycemic medications, which adds up to many medications (and sometimes more pills) to be taken daily. We know that in SPRINT the group receiving intensified therapy took an average of 2.8 antihypertensive agents compared to the standard therapy group that only took an average of 1.8 medications.5 This is similar to other trials where in order to achieve greater control of BP, it has been necessary to give two to four agents. However, it has been shown that combining two drugs at half the standard dose of each is superior to monotherapy, and that additive BP-lowering effects of two drugs are not associated with additive adverse effects.21,22

We also know that the more medications there are, the lower the adherence to treatment.20 The answer to this is single-pill combinations for the treatment of hypertension, including in some cases drugs for the treatment of dyslipidemia as well. The most frequent reason for resistance to treatment relates to medication-related causes, including a suboptimal regimen of drugs leading to nonadherence.23 Frequent changes in drugs, so called therapeutic turbulence,23 and therapeutic inertia24 both lead to poor BP control. As a consequence, this has led to studies that showed that combining antihypertensive drugs may result in greater antihypertensive benefits than...
intensifying monotherapy, with a lower incidence of adverse events.\textsuperscript{12,13} Following these studies it was demonstrated that initiating treatment with hypertension with combination therapy resulted in fewer BP-related complications, including cardiovascular, coronary, and cerebrovascular outcomes.\textsuperscript{2,26} Use of low-dose combinations was effective in rapidly controlling BP in the STITCH (Simplified Treatment Intervention To Control Hypertension) trial.\textsuperscript{27} In fact, the STITCH trial was able to demonstrate more rapid BP control using half doses of antihypertensive agents in combination than using a guide-line-directed protocol,\textsuperscript{27} which could result in a reduction of cardiovascular events. Combination therapy has indeed been shown to have a better tolerability profile than individual antihypertensive agents.\textsuperscript{28}

In conclusion, measuring BP accurately (preferably with ABP), intensifying treatment, and using single-pill combinations to address both adherence and tolerability concerns will go a long way to improving outcomes and preventing cardiovascular events in patients with hypertension.
In 1739, Buffon was appointed Superintendent of the King’s Garden. Buffon was a shrewd entrepreneur and a true man of business. Maurepas knew well what he was doing when he entrusted a still politically unstable institution to the hands of a capable and amiable courtier. Buffon’s headship lasted for more than fifty years. In the process, he accumulated wealth and won honors and became one of the most published naturalists of all time. The Garden grew with him.”

Established in 1626, the King’s Garden aroused suspicions and the fierce opposition of the Paris Medical Faculty. Its founder, Guy de La Brosse, achieved much before dying in 1641. Activities continued with difficulty, hampered by strong opposition. Yet, by the beginning of the eighteenth century, the central state authorities became convinced that the Garden could do much to help French agriculture, medicine, and pharmacy, and the supply of raw materials from all over the world. The pursuit of natural knowledge was deemed essential to social peace, dynastic ambitions, military needs, and colonial expansion. The decision in 1739 to appoint the Count of Buffon as the head of the institution proved an institutional and public opinion success. Buffon expanded the Garden, attracted top naturalists, and made the natural sciences fashionable. His Histoire naturelle, published between 1749 and 1788, became a world best seller, issued (and pirated) in thousands of copies, translated in all major languages. Buffon was a very independent thinker and a very able courtier. He was a darling of fashionable salons, a master of the French language, and kept at a safe distance from radical philosophers, who on the whole disliked him. At the Revolution, when the King’s Garden risked being abolished as a monarchic institution, officers (all appointed by Buffon, who had died in 1787) denounced him as an aristocratic centralizer, a master of style rather than of knowledge, and made vociferous protestations of Republican patriotism. They succeeded. On June 11, 1793, the King’s Garden became the National Museum of Natural History, one of the most prestigious research institutions in the world.
When the Jardin du Roi, the King’s Garden, opened in Paris in 1640, few contemporaries would have believed it was destined to become a major landmark of the French capital, loved by tourists and Parisians alike. Louis XIII established the King’s Garden on July 6, 1626, to circumvent the University’s reluctance to embark upon new subjects and new ways of learning about nature and the health of people. Yet, real work started only in 1635, under the direction of Guy de La Brosse (1586-1641), the true mastermind of the project. He had been pleading for a deep reform of teaching and research within the medical establishment and spared no effort—financial, scientific, or political—to reach his goal. The establishment of the Garden was a victory, but one that did not last long. The Faculty of Medicine silently and openly opposed all its undertakings, and professors and leading practitioners were not unhappy when de La Brosse, a believer in the possibilities offered by botanical and chemical research to improve medical knowledge and practice, died a few years later in 1641. His worst sin—in the eyes of academic doctors—was that he was a follower of Paracelsus and chemical medicine, and showed no sympathy for Galen, who was still considered at that time the most authoritative medical thinker.

For the next half a century the Garden barely survived, though it would be unfair to say that its presence was not felt on the medical scene of the capital. Firstly, de La Brosse had managed to start the cultivation of more than two thousands plants and to initiate the collection known as “The King’s Cabinet,” designed to gather natural riches and curiosities. Secondly, chemical and medical teaching continued; its relative success finds a paradoxical testimony in the repeated attempts by the Faculty to stop it altogether through acts of parliament and public denunciations. In 1673, the Faculty of Medicine even tried to put a stop to the demonstration of the circulation of blood that William Harvey had announced in 1628, a “novelty” that High Medicine throughout Europe spared no energy to silence. Royal protection, though, effectively sheltered the innovative and controversial institution, which clearly served an important function in training chemists, pharmacists, and botanists.

The appointment in 1693 of Guy-Crescent Fagon (1638-1718) to the post of superintendent marked a shift in the fortunes of the Garden. In spite of his questionable practice of bleeding patients to death, Fagon was a respected practitioner, the private physician to Louis XIV and the Royal Family. He had literally been born in the Garden, since his mother was a
niece of Guy de La Brosse who enjoyed her uncle’s hospitality. Fagon had taught chemistry and medicinal botany at the Garden since 1665, and had a keen eye for talent. He strongly supported the work of his two demonstrators for botany, Joseph Pitton de Tournefort (1656-1708, appointed in 1683) and Antoine de Jussieu (1686-1758), who took over from Tournefort and continued his work. Antoine de Jussieu, and especially his brother Bernard (1699-1777), started the tradition of excellence in botanical research for which the King’s Garden became famous. Fagon also built a lecture hall with six hundred seats and improved the cultivation beds and the infrastructure of the institution.

Individual dedication and good science, however, would not have been sufficient to make the Garden the model to be followed throughout Europe, and the Natural History Museum (which followed the Garden in 1793) the center of world natural sciences for most of the nineteenth century. Wider social and cultural phenomena made this growth possible and fuelled the boundless ambition of the chief protagonist of the spatial and intellectual expansion of the Garden during the XVIII century: Georges-Louis Leclerc, Count of Buffon (1707-1788).

The century of nature
During the eighteenth century, France was the most populous kingdom of the Western world. Its political centralism was a choice inevitable in a country marred by fierce traditions of regional independence from Paris. A strong state required sophisticated administration and imposed on the body politic new tasks, especially as far as defense, public order, and territorial expansion were concerned. France was constantly in a state of war against its neighbors. This entailed growing demands for provisions, armaments, and fiscal support. At the same time, famine recurrently struck towns and villages, fuelling revolt and attack against the aristocratic landowners and state officials. Concurrently, colonial ambitions and the fear of being encircled and outmaneuvered by maritime states such as Spain, England, and Holland imposed new demands on technology and forced broadly scientific concerns to the attention of politicians and the ruling aristocracy.

During the second half of the seventeenth century, Jean-Baptiste Colbert (1619-1683), the powerful minister of finance for the last twenty years of his life, embodied and promoted a new view of the state as the main agent of reform, technological and administrative improvement, and scientific proficiency. Under his aegis, the Académie des sciences he had established in 1666 was increasingly asked to provide expert advice on matters concerning navigation, the application of chemistry to war (for instance, the tanning of leather on a large scale to guarantee a sufficient supply to the military), and the approval of new production technologies and the granting of patents. "Colbertism" became, and still is, a well-known term in economics, indicating state intervention and strong protectionist measures.
Throughout the eighteenth century, few believed that industry and technological innovation alone were going to increase the wealth of nations or, more importantly, to feed the masses: public order and the human demands of ever-expanding armies required reliable agriculture. Nature, it was repeated by philosophers and economists, was the sole producer of wealth. Industry only reworked nature’s products, and commerce distributed them. Modern agriculture guaranteed food supplies, population growth, and was the pre-condition for dynastic and colonial ambitions. Historians have argued that the “agricultural revolution” that occurred during the middle decades of the eighteenth century in several European countries, especially in France and the British Isles, constituted the pre-condition of the industrial revolution: it created wealth together with a large supply of cheap labor, as farmhands were laid off due to the rationalization of agricultural processes. Whatever the bigger picture, there is little doubt that the popularity of natural pursuits gained enormously from the aforementioned view of a bountiful nature.

Colonial expansion also added to the value of natural knowledge. There was a world of natural riches to be exploited for the benefit of the metropolis. Travel narratives and novels about travels fired the imagination with descriptions of happy islands where food grew on trees, and vegetables and animals provided for all needs. During the last quarter of the eighteenth century, great hope was placed on the possibility of acclimatizing the tree of bread in the metropolis; sophisticated greenhouses were built in the Garden to favor the introduction into France of several vegetable species that appeared to be capable of solving all subsistence problems.

The anecdote still told today of a famous dinner wholly based on potato dishes offered to the King, or the popular “pommes Parmentier,” keeps alive in popular culture the name of one of the chief protagonists of the systematic exploration of the nutritional potential of imported species, Antoine-Augustin Parmentier (1737-1813). Throughout the nineteenth century, potatoes nourished the masses throughout Europe, and research on the tubers was carried out in scientific institutions that later on paved the way for the development of modern genetics.

It was not just food agronomists and politicians who hoped to gain from the systematic exploitation of the natural world. Exotic plants, minerals, and animal products were seen as capable of providing new medicaments. Indigenous knowledge throughout the world had to be canvassed in order to learn more about the wonderful properties of barks, flowers and seeds, stones, and organic compounds. Quinine was a success, whereas other supposed medicaments proved ineffective, if not dangerous. At the same time, the acclimatization of animal species, the merino sheep from Spain, for instance, or of plants such as the sugar beet, contributed to the development of new industries.

It is in this context of needs and demands, of national and global policies directly or indirectly concerning knowledge of nature, that the career of Buffon, the greatest ever director of the Garden, flowered.

**The age of Buffon**

Early in his career, Buffon shared a contemporary passion for Newtonian physics and mathematics. He had moved to Paris in 1732, after spells in Dijon and Angers, to pursue his studies. Intelligent and well mannered, he soon acquired the social skills that ensured the patronage of Jean-Frédéric Phélypeaux, Count Maurepas (1701-1781). Buffon became known for articles he published on Newtonian calculus and on the
calculus of probability as applied to games, two fashionable
topics at court. Still, it was thanks to Maurepas that he was
elected to the Académie des sciences in 1734. After joining 
this learned company, Buffon undertook research at the re-
quest of his patron on the mechanical resistance of wood, 
a key issue for the improvement of the French navy that the 
powerful Maurepas was promoting. In 1739, Buffon was ap-
pointed Superintendent of the King's Garden. Maurepas knew 
well what he was doing when he entrusted a still politically 
unstable institution to the hands of a capable and amiable 
courtier. Buffon's headship lasted for more than fifty years. In 
the process, he accumulated wealth and won honors and be-
came one of the most published naturalists of all time. The 
Garden grew with him.

Buffon was a shrewd entrepreneur and a true man of busi-
ness. In his hometown of Montbard (Province of Burgundy), 
he established an iron-smelting factory that generated con-
siderable income. At the Garden, he undertook a vast pro-
gram of acquisitions and requisition of adjacent property and 
considerably extended buildings and facilities. Contempo-
raries commented, as have some historians, that it was dif-
ficult to separate Buffon's private interests from the institu-
tions. The allegation may have some truth in it, but one has 
to consider that this was the case for all public offices held 
under the Old Regime. Moreover, business, institutional re-
sponsibilities, and research were never kept in separate com-
partments. Thus, for instance, his iron-smelting factory was 
also the appropriate location for the experiments Buffon paid 
for out of his own pocket to study the cooling of balls of iron 
of various sizes. This was part of his research program on the 
history of the Earth.

Buffon believed that a collision between the sun and a comet 
had projected into space masses of melted minerals at a very 
high temperature. On cooling, these became planets, the Earth 
included. It was therefore important to know how long it took for 
the surface to become cool enough to support life. The growth 
of the Garden, especially of the King's Cabinet, that Buffon 
masterminded was essential for the composition of the Histoire 
naturelle, générale et particulière that he published in 36 
volumes, plus supplements and additions, from 1749 to 1788.

Buffon started his lifelong publishing venture with a first am-
bitious broadside of three volumes, discussing the founda-
tions of natural history, the history of the Earth and of life, and 
the history of man. Concerning the history of the Earth, we 
have already alluded to his cosmological convictions on the 
formation of the solar system. What apparently struck con-
temporaries was the timespan his theory required, though 
Buffon had kept his cards close to his chest and hinted that 
the Earth could be several tens of thousands of years old. 
In 1751 he was duly reprimanded by the Sorbonne, though 
all ended with his retraction and promise to stick to more 
orthodox views.

This story has been repeatedly told as an example of reli-
gious encroachment on science. Yet, personally, I am not con-
vinced. If it is true that “officially” the church authorities en-
dorsed the biblical chronology established by Bishop James 
Ussher (1581-1656)—the Earth had been created at 6 pm on 
October 23, 4004 BC—a plurality of opinions was still enter-
tained on the subject. After all, Saint Augustine of Hippo (354 
AD - 430 AD) had already argued that the days of creation prob-
ably referred to lengthy periods of time. The late Jacques 
Roger, the great historian of biology and the leading expert 
on Buffon, pointed out years ago that the entire procedure 
looks as if it had been arranged between the naturalist and 
the theological authorities. After all, Buffon was already a dar-
ing at court, and a famous author: it is difficult to believe he 
could be treated as a simple commoner.

I would like to suggest that what the Church and conserva-
tive thinkers feared most was not a debate on a few hundred 
centuries, but the inroads that eternalist atomism was mak-
ing in philosophical circles. The Latin work De rerum natura 
by the poet Lucretius (1st century bc), a favorite author with-
in erudite and freethinking circles, effectively promoted the view of the eternity of matter. This was a doctrine that no religion and no biblical exegesis could accommodate. The sacrifice asked of Buffon was purely nominal, an expression of compliance with the theological authorities. The naturalist continued to promote his expanded chronology up to the end of his life, though he always published figures less shocking to pious minds than the ones he had in fact come up with. A true courtier, he had no wish to appear subversive.

If his views on the age of the Earth did not please theologians, Buffon’s critique of classifications shocked naturalists even more. As a matter of fact, the great naturalist did not believe in classifications. He had abrasive words against the great Swedish botanist Carl Linnaeus (1707-1778), the father of the system of classification of living beings we basically still use today. Buffon believed that nature takes a step in every direction; species shade from one into another. The claim that it was possible to arrange organisms in a well-defined hierarchical structure (orders, classes, genera, and species) was grounded in the foolish belief that the human mind could impose its own logical rules on nature.

If taxonomy (a word introduced well after Buffon’s death) was epistemologically impracticable, then the description of living nature could only proceed according to man’s needs and interests. The knowledge of man as a natural being was, naturally and sensibly, our most important field of research. The study of man was followed by the natural history of the horse, man’s noblest conquest, as Buffon put it. Then came all the animals indispensable to our survival, as providers of food and clothing or employed in agricultural work, or even studied and collected for amusement and aesthetic reasons, such as birds. If Linnaeus decided to get rid of pages-long descriptions of species, and proposed to call man “homo sapiens,” subdivided into four different geographical subgroups (europaeus, afer, asiaticus, and americanus), Buffon theorized that style and eloquent prose were required to account for the richness of living nature.

As far as man was concerned, Buffon was a strong believer in the unity of the human species. He was convinced that the original man was white. Climatic conditions throughout the globe had produced different degrees of degeneration from the original perfect form. The unity of the species was confirmed by interfecundity: all individuals capable of producing a viable offspring belonged to the same species. Horses and donkeys were close enough to produce offspring, but mules were sterile. So, donkeys and horses were different species. There was a further criterion Buffon insisted upon: language, and therefore reason. In a page vividly describing the miserable life and demeanor of Hottentots, using a language we would today consider as intolerably racist, Buffon ended the portrait of the poor degraded beings with the affirmation: but they speak. Buffon had no doubt that even more degraded human beings (from his perspective) could improve if transplanted to more favorable climatic and living conditions. During the eighteenth century, the growth of colonialism was slowly and dramatically changing European perceptions of the inhabitants of the regions of the world invaded by white settlers. The good savage turned into the vicious being it was our duty to civilize or exterminate. By the end of his life, Buffon was one of the few naturalists to uphold the biological identity of all human beings.

In his last major work, Epochs of Nature (1778), Buffon joined the debate on the history of the Earth he had helped to launch thirty years earlier. He updated and modified his earlier views,
Colored engravings of a red curlew, turkey, cockarel, and parrot (from left to right and top to bottom) from *Histoire naturelle des oiseaux* by Georges de Buffon (1707-1788).
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Some of the 7000 specimens on display at the Grande Galerie de l’Évolution at the National Museum of Natural History in Paris.

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and added his reconstruction of the history of life on Earth. Buffon was not an evolutionist, as some commentators have assumed over the last two centuries. He came, however, to believe that certain species are so similar that they are probably the descendants of prototypes now lost. This assumption explained why several allied species did procreate offspring, albeit infertile. Communality of descent did not impinge upon the biological conviction that species did exist, and they remained stable in their main characteristics.

The popular success of his works did not mean that Buffon had many friends within the circles of the great protagonists of the Enlightenment. True, Denis Diderot admired his biological theories and adopted several of them. But Voltaire lost no opportunity to make fun of him in conversation, and the philosopher’s witticisms were reported with gusto, as gossip always is. Thus, Buffon’s definition of the horse, to which we have alluded, as man’s noblest conquest, was turned by Voltaire into tangible evidence that the naturalist was in fact an able writer who substituted flowery style for lack of knowledge.

Following Buffon’s death, the Marquis de Condorcet launched a stinging attack on his deceased colleague in a vitriolic funeral eulogy delivered to the Académie. Buffon did not understand, de Condorcet asserted, the difference between science and rhetoric; he had been a poet rather than a naturalist, though he indulged in too many fantasies to be good even at that; he had answered the objections of his peers by multiplying the number and daring of his hypotheses; he cared more for his success with the great dames at court than for the approval of his scientific colleagues.

There was some truth in these allegations. Buffon liked to read chapters of his works aloud to his powerful lady friends at court, and kept at a disdainful distance from philosophers: a point de Condorcet insisted upon when he claimed that in a century engaged in breaking the chains of superstition and tyranny, Buffon had been notable by his absence. Still, the personal and intellectual animosity from prominent philosophers cannot and should not hide the fact that tens of thousands of people throughout the Western world read and admired his books, and many authors imitated his style. Not to speak of Jean-Jacques Rousseau, who theatrically—as was his habit—kissed the step leading into the small garden house in the Montbard castle where Buffon composed all his works. More importantly, Buffon left a legacy that would outlive the naturalist, was in fact an able writer who substituted flowery style for lack of knowledge.

Science in revolution: from the King’s Garden to the Natural History Museum

Buffon died on April 16, 1788. He had been ill for a few years, besieged by painful kidney stones. He was, however, proud of his achievements. The King’s Garden enjoyed universal acclaim. He had been very shrewd in ensuring the cooperation of the best botanists, zoologists, mineralogists, and chemists available in the country. Many of them pursued a successful career after the death of their mentor, such as Jean-Baptiste Lamarck (1744-1829), André Thouin (1747-1824), Antoine-Laurent de Jussieu (1748-1836), Bernard-Germain-Étienne de La Ville-sur-Illon, Count Lacépède (1756-1825), and Antoine-François Fourcroy (1755-1809). Some were more than a good scientific choice, though Buffon could not have foreseen that Fourcroy and Lacépède were destined to occupy positions of considerable power during the Revolution and the Empire, thus assuring the continuation of state patronage for the institution he had done so much for.

Already at the time of Buffon’s death, the King’s Garden constituted the largest and most impressive scientific community of the Western world. A few score families involved in the cultivation of the beds, the classification of animals and plants, and the systematic pursuit of collections from all over the world lived inside the Garden, as did Buffon, during the few months he spent in Paris every year. Provided they did not iritate him by speaking of Linnaeus, the staff at the Garden enjoyed considerable freedom in their work. Distinguished visitors especially sought out botanists, since botanizing was a fashionable undertaking for members of the aristocracy throughout the 1770s and the 1780s. Merchants of naturalia and exotic, very much in demand by wealthy owners of private museums and collections, were also frequent visitors.

The Revolution came as a major threat, and a wonderful opportunity. During 1792 and the first half of 1793, there was much debate concerning the abolition of all institutions linked to the monarchy; the King’s Garden could not be more monarchical. Yet, officers there, and the politicians among them, played their cards very well indeed. Whereas the Académie des sciences, the universities, and other state agencies were closed down early in 1793, the officers of the Garden expressed their patriotic and revolutionary zeal in a series of petitions addressed to the National Assembly. The Garden, they argued, was a property of the Nation. It could do much more to educate the people and provide for their needs, if run on a democratic principle and in the name of the Revolution. The scientific personnel thus proposed a reform, following which all of them would become professors, on an equal basis; the position of superintendent was to be abolished; and a director would be appointed on a yearly basis. The riches of nature, properly investigated in the patriotic institution, were going to benefit the entire nation.

For the first time in Western history, a Museum of Natural History, endowed with twelve professorial, specialized chairs, was established on June 10, 1793. Posts of gardeners, demonstrators, and keepers of collections were filled; a librarian and a painter to illustrate the collections were also envisaged, continuing a long-standing tradition. As soon as the Revolution-
ary armies repelled attempted invasions and moved on to conquer neighboring countries, and even more so during the Napoleonic Empire, major natural history collections throughout Europe were requisitioned and brought to Paris. The Muséum became the largest repository of natural history collections of the Western world. Naturalists from all over Europe, and North and Latin America, had to spend time in its galleries and in the library, even if they wished to study the fauna and flora of their own countries. The Muséum hosted precious comparative material, indispensable for species determination and identification. At the same time, the Muséum favored natural history expeditions, drew up instructions for travelers, and taught them how and what to collect. As Georges Cuvier—who became a professor only in 1802—pointed out, the Muséum became the major hub for merchants of specimens, at a scale much larger than Buffon could ever have imagined.

Much was still to be achieved. A zoo opened in 1794 to study animal behavior; the amphitheater had been enlarged and could now seat two thousand people; new, magnificent galleries were built during the whole of the nineteenth century. The St Victor Quarter, where the Muséum was located, was not as elegant and posh as it is today. Visitors complained that to reach the Muséum one had to go through narrow and miserable streets, which were rather unpleasant at night. The urban developments that Paris underwent during the nineteenth century much benefited the Muséum: no late eighteenth or early nineteenth century visitor would today recognize the surrounding areas.

And where was Buffon in all this? Since the start, the professors of the Muséum kept fighting against amateurs and the practice of natural history as a literary exercise. They wanted to demarcate themselves as a professional body of experts, using a technical vocabulary hardly accessible to the ordinary cultivated reader. They were mostly writing for their peers, not necessarily for the general public. Many of them openly dissociated themselves from Buffon. During the Revolution, he was represented as a corrupt courtier, a lover of privilege and despotism. His son Georges Louis (1764-1794), nicknamed “Buffonet,” was executed a few days before the fall of Robespierre.

When the revolutionary decade was over, “official” science continued to disdain Buffon’s works, as too speculative and too literary. Yet, the presses of France and of Europe continued to print edition upon edition of Buffon’s works. Up to the Second World War, anthologized excerpts from his works were compulsory reading for French high school students, as among the best examples of French prose. Yet, ultimately, the Muséum national d’histoire naturelle undoubtedly remains the lasting monument to his work and his long career.
International Advisory Committee

Algeria
Mr. G. SELMI
GPS - Servier Algérie
Panorama Business Center
33 rue des pins, Hydra
Alger 16 000
Tel: +213 21 61 43 05

Argentina
Mr. G. RENCADO
Servier Argentina S.A.
Av. Libertador 5905, Piso 8
C1425ARP - Buenos Aires
Tel: +54 11 4706 5800/5801

Armenia
Mr. G. VELLUYAN
Les Laboratoires Servier
Representative Office
Hyusisain Ave.,
« NORD » - Business Centre
Building 1, 3rd floor
001 - Yerevan
Tel: +374 10 550574

Australia
Mr. F. BOGLOT
Servier Laboratories Pty Ltd
Servier House,
8 Cato Street
Servier House,
Servier Laboratories Pty Ltd
Mr. F. PARISOT
Australia
0001 - Yerevan
Building 1, 3rd floor
« Hyusisain Ave.
Representative Office
Mr. G. VELIJANYAN
Armenia

Canada
Mr. F. RASANO
Servier Canada Inc.
205, boulevard Armand Frappier
Laval, Québec H7V 4V7
Tel: +1 450 9799700

China (PRC)
Mr. S. MASCARAU
Servier (Français) Pharmaceuti-
cal Co., Beijing Office
5th Floor, West Building
World Financial Centre
No. 1 East 3rd Ring,
Midde Road
Changyang District
Beijing 100020 P.R.C.
Tel: +86 10 66610341

Colombia
Mr. F. LERMO
Les Laboratoires Servier de
Colombia SA
Edificio Centro Empresarial
98 x 28, Piso 4°
Transversal 19A - No 98-28
Bogota D.C.
Tel: +57 1 742 9369

Croatia
Mr. M. MIATIĆ
Servier Pharma d.o.o.
Trgkinova 37
10000 Zagreb
Tel: +385 1 3016 222

Czech Republic
Mr. F. BOYER
Servier SRO
Florentinium
Na Florenci 216/15
110 00 Praha 1
Tel: +420 2 22118602

Denmark
Mr. F. TEJEDOR
Servier Danmark A/S
Lyngbyvej 2
2100 Copenhagen
Servier Laboratories Ltd
Mr. F. DRUGUET
Ireland

Egypt
Mr. G. CHARLES
Servier Egypt
Scientific Office
67, El Horreya St., PO Box 123
Helipolis - Cairo
Tel: +20 22 90 60 77

Estonia
Mr. F. DEBAILLON-VESQUE
Servier Italia SpA
Via Luca Passi, 65
00166 Roma
Tel: +39 06 689 061

Finland
Mr. F. DEBAILLON-VESQUE
Servier Italia SpA
Via Luca Passi, 65
00166 Roma
Tel: +39 06 689 061

France
Mr. M. CHARTIER
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes Cedex
Tel: +33 1 55 72 60 00

Georgia
Dr. M. KETSURIANI
LRS Representative Office
44 Kote Aepshazi Street
0105 Tbilisi
Tel: +995 32 243 93 90

Germany
Mr. C. KIRSIT
Servier Deutschland GmbH
Ehrenhainerstr. 53
80687 München
Tel: +49 89 5709501

Gulf Countries
Mr. F. FOUILLOUX
Servier-office,
7, Fragolakias stras.
151 25 Maroussi
Tel: +302 10 9391000

Hong Kong
Mr. L. GARMER
Servier Hong Kong Ltd
Room 4021/03, 42/F
248 Queen’s Road East
Wanchai, Hong Kong
Tel: +852 2577 1922

Hungary
Mr. J. F. KESSELHUT
Servier Hungaria KFT
Westend Office
B tower, 3rd floor, Váci út 1-3
Budapest 1052
Tel: +36 1 238 7799

India
Mr. Y. GIRARD
Servier Laboratories Ltd
Mr. B. BOULLE
Servier Laboratories Ltd
Mr. F. DARCHEZ
Selangor Darul Ehsan.
47400 Petaling Jaya
Damansara Uptown
1301, Level 13, Uptown 2
Servier Malaysia SDN BHD
Dr. K. PANSE
India

Indonesia
Mr. A. NEROT
Servier Indonesia
Menara Kadin Indonesia
18th Floor
Jakarta 12950
Tel: +62 21 57003040

Ireland
Mr. F. DRUGUET
Servier Laboratories Ltd
Block 2
West Pier Business Campus
Old Dunleary Road
West Pier Business Campus
Block 2
Servier Laboratories Ltd
Mr. F. TEXIER
Ireland

Japan
Mr. E. DELANGE
Servier Company Ltd
1-28-04, Hongo,
Bunkyo-Ku,
113-0033 Tokyo
Tel: +81 3 5842 7111

Kazakhstan
Mr. G. RENACCO
Les Laboratoires Servier
Representative Office
310 G DOSYTV, av. 3rd Floor
050 000 Alma
Tel: +7 727 386 76 62

Korea
Mr. C. ROUCHES
Servier Korea Ltd,
5th Floor, 215, Seochjong-ang
Seocho-gu
Seoul 137-802
Tel: +82 212243863

Latvia
Mr. F. BRETHOUS
Servier Laboratories Ltd
Mr. A. BRETHOUS
Luxembourg

Luxembourg
Mr. A. BRETHOUS
Servier Luxembourg SA
17B, rue du Chemin de Fer
L-6013 Bertrange
Tel: +352 49 35 35

Malaysia
Mr. F. PANSE
Servier Laboratories Ltd
Mr. F. PARISOT
Australia

Mexico
Mr. F. PARISOT
Servier Laboratories Ltd
Mr. F. PARISOT
Australia

Morocco
Mr. J. L. LEUA
Servier Laboratories Ltd
Mr. A. BRETHOUS
Luxembourg

Myanmar
Mr. B. BOULLE
Servier Laboratories Ltd
Mr. F. PARISOT
Australia

Netherlands
Mr. P. ETORRE
Servier Laboratories Ltd
Mr. P. ETORRE
France

New Zealand
Mr. G. VELIJANYAN
Les Laboratoires Servier
Representative Office
Hyusisain Ave.,
« NORD » - Business Centre
Building 1, 3rd floor
001 - Yerevan
Tel: +374 10 550574

Norway
Mr. G. VELIJANYAN
Les Laboratoires Servier
Representative Office
Hyusisain Ave.,
« NORD » - Business Centre
Building 1, 3rd floor
001 - Yerevan
Tel: +374 10 550574

Poland
Mr. P. BOYER
Servier SRO
Mr. F. TEXIER
Finland

Portugal
Mr. J. F. KESSELHUT
Servier Hungaria KFT
Westend Office
B tower, 3rd floor, Váci út 1-3
Budapest 1052
Tel: +36 1 238 7799

Romania
Mr. F. TEXIER
Servier Laboratories Ltd
Mr. F. TEXIER
Finland

Russia
Mr. D. KETTENBERG
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

Singapore
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

South Africa
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

Spain
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

Sweden
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

Switzerland
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

Turkey
Mr. F. FOUILLOUX
Servier-office,
7, Fragolakias stras.
151 25 Maroussi
Tel: +302 10 9391000

Ukraine
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

United Kingdom
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

United States
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

Uruguay
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

Vietnam
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

Yemen
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

Zimbabwe
Mr. F. TEJEDOR
Servier Laboratories Ltd
Mr. F. TEJEDOR
Finland

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