The correct use of combination therapy is crucial both to improve blood pressure control and to reduce cardiovascular events. Antihypertensive drugs can be effectively combined if they have different and complementary mechanisms of action. Thus, a typical combination contains drugs blocking (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker) and stimulating (calcium antagonist or diuretic) the renin angiotensin system. An effective combination therapy is a combination with additive or synergistic effects. The effect of a combination is additive when the blood pressure reduction it induces is the sum of the single effects of each of its components, while it is synergistic when its clinical efficacy is greater than the sum of the effects of the single components. A synergistic effect is clearly demonstrated when, despite similar blood pressure control, one drug combination leads to a better outcome than another drug combination. This was the case in ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) and ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension), two trials that demonstrated that ACE inhibitor/calcium antagonist combination results in significant better protection than β-blocker/diuretic or ACE inhibitor/diuretic combination, respectively. It is worth noting that there is currently no evidence showing that angiotensin receptor blocker/calcium antagonist combination is as effective as ACE inhibitor/calcium antagonist combination. In conclusion, in hypertensive patients, optimal treatment should be based on combination therapy, and the combination of an ACE inhibitor with a calcium antagonist should be the first choice. This strategy should lead to improved blood pressure control and better protection from cardiovascular events.

What are the advantages of combining multiple-action drugs from the pharmacological and clinical perspectives?

Usually, in the treatment of essential hypertension, a great emphasis is placed on choosing the right drug for treatment initiation, despite the demonstration that monotherapy can normalize blood pressure values in no more than 30% to 40% of patients with grade 1 and 2 hypertension, and that it is absolutely not effective in patients with grade 3 hypertension. Thus, for the majority of patients, combination therapy should not be an option, but the cornerstone of antihypertensive treatment.
However, merely combining antihypertensive drugs together is not enough to obtain an effective combination treatment, and expert selection of specific compounds with definite characteristics leading to a positive interaction is required. This is a crucial issue since the combination of antihypertensive drugs can lead to different results. In terms of blood pressure reduction, combining antihypertensive drugs can theoretically produce the following effects. (i) A combination that is not rational may have negative effects, which means that it produces the same (or lower!) blood pressure reduction as each of its single components. Combinations with a positive interaction can either have (ii) additive or (iii) synergistic effects. The effect of a combination is additive when its blood pressure-lowering effect is the sum of the effects of each single component. In contrast, a combination has a synergistic effect when it produces an effect that is greater than the sum of the effects of its single components. However, while negative or additive effects are defined according to the extent of blood pressure reduction, synergistic effects are related to blood pressure–independent cardiovascular protection.

Basically, when used rationally, combination therapy should overcome the several limitations of antihypertensive drugs used as monotherapy. The mechanisms determining the superiority of combination therapy over single-drug administration involve the pharmacological and clinical characteristics of drug classes. Concerning antihypertensive efficacy, one major problem of monotherapy is the activation of reflex mechanisms that counterbalance, and therefore limit, the degree of blood pressure reduction. For example, diuretics and calcium antagonists may cause reflex activation of the renin angiotensin system (RAS), while angiotensin receptor blockers (ARBs) increase plasma concentrations of angiotensin II (whose beneficial effect on AT$_2$ receptors has never been demonstrated in clinical conditions), and reductions in angiotensin II and aldosterone plasma concentrations with ACE inhibitors can be counterbalanced by angiotensin escape. This explains why the antihypertensive potency of drugs used as monotherapy is relatively modest: a single drug can easily lower blood pressure values, but only in rare cases will it be able to normalize this clinical parameter.

In contrast, combination therapy can overcome these limitations, but only if the drugs to be combined are selected on account of their different and complementary mechanisms of action. Thus, it is wise to combine a drug blocking the RAS (ACE inhibitors, ARBs, β-blockers) with drugs that stimulate this system (calcium antagonists, diuretics, vasodilators). In the same way, drugs activating the sympathetic nervous system should be combined with drugs blocking sympathetic activity. This is a fundamental aspect, which should be considered when choosing combinations of antihypertensive drugs. Unfortunately, this is not always the case in clinical practice. A typical example is the combination of an ACE inhibitor with a β-blocker. This combination is used in the treatment of hypertensive patients because of its effective cardiovascular protection in specific clinical conditions such as post–myocardial infarction or heart failure. However, it has no additive effect on blood pressure reduction since both drugs block the RAS, as clearly demonstrated in the ALLHAT study (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), where the blood pressure reduction obtained with the combination of lisinopril and atenolol was significantly inferior to that obtained with the combination of chlorthalidone or amlodipine with atenolol.

Other limitations of monotherapy are related to adverse metabolic effects or the incidence of side effects. It is well established that diuretics can significantly alter carbohydrate and lipid profiles, and that patients very often have to stop treatment with calcium antagonists, despite effective blood pressure reduction, because of ankle edema. Most of these limitations can be significantly reduced by combination therapy and it has been demonstrated that RAS blockers can limit both metabolic alterations induced by diuretics and ankle edema caused by calcium antagonists.

Finally, combination therapy can also offer adjunctive advantages from a clinical point of view. Rapid normalization of blood pressure is an important target of antihypertensive treatment, especially in patients at high or very high risk. In line with this recommendation, recent evidence, although obtained by retrospective analysis, indicates that antihypertensive treatment initiated with combination therapy can induce a more rapid blood pressure reduction and/or normalization than monotherapy, and that this more rapid blood pressure control is associated with a better outcome. In addition, combination therapy results in a significantly greater reduction in global cardiovascular, coronary, and cerebrovascular events than monotherapy, independent of drug classes or blood pressure control.

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</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>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular Disease</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>ASCOT-BPLA</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm</td>
</tr>
<tr>
<td>EUROPA</td>
<td>EUropean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease</td>
</tr>
<tr>
<td>HYVET</td>
<td>Hypertension in the Very Elderly Trial</td>
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<tr>
<td>RAS</td>
<td>renin angiotensin system</td>
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Thus, there is solid evidence that combination therapy offers great advantages over monotherapy, not only in terms of blood pressure reduction, but also because it provides specific cardiovascular protection. However, there are differences in efficacy among the different possible combinations of antihypertensive drugs, and, therefore, it is crucial to choose certain combinations over others.

**Which properties/effects of combination therapy are considered to be additive?**

As previously mentioned, the effects of combination therapy that are considered to be additive are related to blood pressure reduction. Usually, the combination of drugs with complementary mechanisms of action makes it possible to obtain a reduction in blood pressure that is the sum of the effects of its single components. Thus, from a clinical point of view, it is important to avoid those combinations that do not produce an additive effect or those that have been clearly demonstrated to be inferior to other options.

In addition to the already mentioned ACE inhibitor (or ARB)/β-blocker combination, other drug classes that should never be combined are ACE inhibitors and ARBs, since both block the RAS. Finally, another combination that should be absolutely avoided because of its negative effect is that of doxazosin—an α₁-blocker—with clonidine—an α₂-agonist. In this case, considering that the specificity for a receptor subtype is always relative, especially in clinical conditions, one drug reduces the blood pressure–lowering effect of the other, and the outcome is, therefore, negative.

Apart from these specific examples, all other combinations of antihypertensive drugs have additive effects and are, therefore, useful to obtain better blood pressure control. This is highlighted by the availability of fixed combinations that increase the compliance of hypertensive patients considerably.

In addition to classical fixed combinations of RAS blockers or β-blockers with diuretics, new fixed combinations of RAS blockers with calcium antagonists are now available and increase the chance of choosing the best therapeutic strategy for hypertensive patients.

Is there any clinical difference between the use of a RAS blocker/diuretic combination and a RAS blocker/calcium antagonist combination? Concerning blood pressure lowering, both regimens seem to be similarly effective. Their tolerability is also similar, especially considering that RAS blockers reduce the metabolic alterations induced by diuretics and ankle edema induced by calcium antagonists.

However, blood pressure reduction is not the only mechanism for cardiovascular protection and since scientific evidence clearly indicates that some drug classes are better than others, as a consequence, some drug combinations are also better than others.

In line with this are the results of ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) and ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension), which demonstrated that the combination of an ACE inhibitor with a calcium antagonist results in significantly greater cardiovascular protection than β-blocker/diuretic or ACE inhibitor/diuretic combinations, respectively.

It is clear from this line of evidence that (i) different combinations of antihypertensive drugs, while producing a similar blood pressure reduction, have a different impact on clinical outcomes, and that (ii) the combination of an ACE inhibitor with a calcium antagonist offers the best cardiovascular protection in hypertensive patients. In addition to the previously mentioned ASCOT and ACCOMPLISH trials, an interesting analysis of the results of EUROPA (EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) demonstrated a significant synergy between perindopril and calcium antagonists, with a significant supplementary impact on cardiac outcomes and mortality.

Whether the beneficial effect of ACE inhibitor/calcium antagonist combination might be extrapolated to ARB/calcium antagonist combination is an interesting question. It should be stated that it is scientifically incorrect to credit ARBs with the same efficacy as ACE inhibitors. A meta-analysis evaluating studies performed in hypertensive patients has demonstrated that ACE inhibitors, but not ARBs, can significantly reduce total mortality further than comparators, the most important clinical end point. It is worth noting that this beneficial effect was essentially driven by the results of ASCOT, ADVANCE (Action in Diabetes and Vascular Disease), and HYVET (Hypertension in the Very Elderly Trial), which are all perindopril-based clinical trials. This evidence was further reinforced by another meta-analysis comparing the effect of ACE inhibitors or ARBs versus placebo in high-risk patients. The results of this study confirmed that ACE inhibitors, but not ARBs, can significantly reduce several hard end points such as myocardial infarction, heart failure, and total mortality, but that ARBs, as a class, do not.

Another fundamental argument against the equivalence of ARB/calcium antagonist combination and ACE inhibitor/calcium antagonist combination is the lack of specific trials, such as ASCOT-BPLA or ACCOMPLISH, evaluating the effective-

**What does pharmacological and/or clinical synergy mean?**

A combination has a clearly demonstrated synergistic effect when, despite similar blood pressure control, it leads to a better outcome than another drug combination. This kind of evidence indicates that the beneficial effect of treatment is determined by specific mechanisms that amplify the outcome related to blood pressure reduction.
ness of ARB/calcium antagonist combination versus any other combination of antihypertensive drugs, a lack of evidence which was clearly highlighted in the European Hypertension Guidelines.

In conclusion, combination therapy should be the first option for effective hypertension management. This therapeutic strategy can lead to a more rapid reduction, and possibly normalization, of blood pressure values and to a consequent decrease in cardiovascular risk. In addition, available scientific evidence clearly indicates that combining ACE inhibitors and calcium antagonists can specifically provide adjunctive protection from clinical events.

Although ACE inhibitors are considered to be first-choice drugs, especially on the basis of the results of recent meta-analyses, it may be time for us to change our attitude in clinical practice and start considering ACE inhibitor/calcium antagonist combination as the first-choice treatment for the best protection from cardiovascular events.

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Keywords: ACE inhibitors; angiotensin receptor blockers; calcium antagonists; essential hypertension; cardiovascular risk; perindopril

Les associations dans l’hypertension et la prévention cardiovasculaire : sont-elles synergiques ou additives ?

Bien utiliser les associations médicamenteuses est essentiel afin d’améliorer le contrôle de la pression artérielle et de diminuer le nombre d’événements cardiovasculaires. Des antihypertenseurs aux mécanismes d’action différents et complémentaires peuvent être associés efficacement. Une association classique contiendra donc des médicaments bloquant le système rénine angiotensine (inhibiteur de l’enzyme de conversion [IEC] ou antagoniste du récepteur de l’angiotensine [ARA]) et d’autres le stimulant (antagoniste calcique [AC] ou diurétique). Un traitement d’association efficace combine des effets additifs ou synergiques. L’effet est additif lorsque la diminution de pression artérielle induite représente la somme de chacun des effets de chaque composant. L’effet est synergique lorsque l’efficacité clinique est supérieure à la somme des effets des composants pris isolément. L’action synergique est evidente lorsque les résultats d’une association médicamenteuse sont meilleurs que ceux d’une autre, et ce, malgré un contrôle identique de la pression artérielle. C’était le cas des études ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) et ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) dans lesquelles, respectivement, la protection obtenue par l’association IEC/AC s’est montrée significativement meilleure que celle des associations bêtabloquantes/diurétiques ou IEC/diurétiques. Remarquons qu’il n’existe actuellement pas de preuves d’une équivalence d’efficacité entre l’association ARA/AC et l’association IEC/AC. Pour conclure, un traitement antihypertenseur optimal est une association qui comporte en première intention un IEO et un AC, ce qui devrait offrir un meilleur contrôle de la pression artérielle et une meilleure protection contre les événements cardiovasculaires.
In 2013, the paper entitled “Combinations in hypertension and cardiovascular prevention: are they additive or synergistic?” was pioneering in discussing combination therapy as a specific and effective treatment for hypertension. At that time, the effectiveness of therapy, especially concerning cardiovascular end points, was based on the results obtained with a single drug class, while the rationale behind combination treatment was limited to the need of increasing the blood pressure-lowering effect. A typical example was the association of a renin-angiotensin system blocker with a very low diuretic dose (ie, hydrochlorothiazide 12.5 mg daily). With this combination, organ protection was determined by the angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), while the diuretic was necessary to activate the renin-angiotensin system and, as a consequence, increase their blood pressure-reducing ability.

The scenario changed with the results of studies, including ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure–Lowering Arm) and ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension), which demonstrated that some combinations were superior to other combinations in terms of cardiovascular protection, despite a similar blood pressure control.

The ACCOMPLISH study, which compared two single-pill combinations, including the same ACE inhibitor (benazepril) with a calcium antagonist (amlodipine) or a diuretic (hydrochlorothiazide), produced incontrovertible results. Despite the fact that there is no evidence in the scientific literature that calcium antagonists are superior to diuretics in the prevention of cardiovascular events, the combination of these two drug classes with an ACE inhibitor produced a different beneficial effect. The important message from this trial was that, while the blood pressure-lowering effect derives from an additive interaction, the beneficial effect on cardiovascular end points derives from the synergistic interaction between the components. Thus, not all combinations are equal and the different efficacy depends on the positive, synergistic interaction of the single component.

In line with this concept, the ASCOT-LLA trial (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm) demonstrated that the statin atorvastatin produced a greater reduction in cardiovascular events when associated with the combination of perindopril and amlodipine as compared with the association with the combination of atenolol and bendroflumethiazide, despite a similar reduction in low-density lipoprotein cholesterol.
Thus, the possibility of a synergistic interaction is not just confined to antihypertensive drugs, but it can be also applied to other aspects of cardiovascular protection.

The fundamental relevance of combination therapy was highlighted in the 2018 European Society of Cardiology/European Society of Hypertension (ESH/ESC) hypertension guidelines, which state that, in most hypertensive patients, pharmacological treatment should start with combination therapy, including the association of a renin-angiotensin system blocker with a calcium antagonist or a diuretic, possibly prescribed as a single-pill combination. If blood pressure is not controlled, the second step should be the administration of a three-drug combination, including a renin-angiotensin system blocker, a calcium antagonist, and a diuretic, again possibly prescribed as a single-pill combination.

This approach is absolutely correct, but, as expressed, the indication is generic and not all the aspects seem to be scientifically supported. First, the guidelines classify this indication as “grade 1; level A,” which means the higher level of scientific evidence since it is supported by results of controlled clinical trials and meta-analyses. However, concerning the combination of renin-angiotensin system blockers with calcium antagonists, while the strength of the indication is true for ACE inhibitors, such evidence is scanty for ARBs. Thus, it should be clear that the administration of the combination of an ARB with a calcium antagonist, albeit rational from the pharmacological point of view, has no evidence of being effective on hard end points in controlled clinical trials. Thus, by definition, such a combination can be defined as additive and not synergistic, and the eventual translation of ARBs/calcium antagonists to the positive evidence documented with ACE inhibitors/calcium antagonists is scientifically unfair.

On the other hand, ACE inhibitors and ARBs have deep differences in their mechanisms of action and their effectiveness, which, when considered as single drug classes, is not equivalent. While ACE inhibitors can significantly reduce the incidence of coronary artery disease and total mortality, ARBs have not documented a positive effect on such crucial hard end points. Concerning the combination treatment, it is conceivable that the ACE inhibitor-mediated increase in bradykinin tissue concentrations might interact with the antioxidant properties of calcium antagonists and produce a beneficial effect at the level of endothelial function and structural vascular alterations.

In conclusion, only therapeutic strategies whose effectiveness has been documented in controlled clinical trials can really have a significant impact on the cardiovascular prognosis of patients with essential hypertension, and, therefore, they should be considered as first-line treatment.

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