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Fixed combination therapies based on direct renin inhibition: a commentary to the ACCELERATE trial

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Despite the well-established concept that the treatment of high blood pressure (BP) represents a key strategy in reducing the burden of cardiovascular (CV) and renal diseases, arterial hypertension remains poorly controlled worldwide. To improve BP control in the hypertensive population, a more extensive use of combination therapies rather than monotherapies should be adopted, even as a first-line approach, in patients with grade 2–3 hypertension, in high-risk individuals or in those who need more ambitious BP goals (e.g., diabetics). Today, this represents an emerging clinical strategy for the daily clinical practice of hypertension, since recent randomized clinical trials have demonstrated the efficacy, safety and tolerability of such therapeutic approach.

Among the potentially effective antihypertensive-combination strategies currently available for the clinical management of hypertension, those based on the combination of drugs inhibiting the renin–angiotensin system (RAS) and calcium-channel blockers (CCBs) appear to ensure effective and extended control of BP levels, as well as CV and renal protection. The recent availability of a novel class of antihypertensive drugs, the direct renin inhibitors (DRI), has prompted studies to further investigate the use of combination strategies to achieve a rapid, persistent and effective BP control.

In the present article, we discuss the interesting findings of a recent randomized clinical trial, the Aliskiren and the Calcium Channel Blocker Amlodipine Combination as an Initial Treatment Strategy for Hypertension (ACCELERATE) trial, which investigated the BP lowering effect and the tolerability of the combination of two long-acting compounds, the calcium-channel blocker amlodipine besylate and the DRI aliskiren.

Fixed combination therapy for the clinical management of hypertension

Blood pressure elevation is paralleled by a progressive increase in the risk of developing major CV events, including myocardial infarction and stroke, independently of age and gender [1]. The reduction and, most importantly, normalization of BP levels in hypertensive patients is, in turn, associated with significant CV benefits [2]. Achievement of recommended BP targets, however, remains poorly accomplished in both western and developing countries, and recent international surveys demonstrated that almost three quarters of treated hypertensive patients are not normalized under pharmacological treatment [3–5].

Among the potential factors that may contribute to this disappointing observation, frequent presence of comorbidities, doctors' clinical inertia and the widespread use of monotherapy rather than combination therapy, may all play an important

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role for explaining uncontrolled BP levels in the clinical practice of hypertension [6]. In particular, since monotherapy allows an effective control of BP in no more than 35–40% of treated hypertensive patients [7], over the last few years, the use of therapeutic regimens based on combination therapies with different antihypertensive drug classes has been progressively encouraged, thus aiming for an improved BP control in the general population of hypertensive patients. Fixed combination strategies, in fact, fulfill key requirements for a modern and effective treatment of hypertension, since they provide:

- Reduction in the number of tablets and better compliance of patients to prescribed antihypertensive therapy;
- Synergistic mechanism of action of the components to optimize the BP lowering efficacy;
- Reciprocal reduction of the side effects by each component through the contra-regulatory mechanisms.

In this view, combination strategies based on the use of drugs blocking the RAS, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) and dihydropyridinic CCBs, have been repeatedly tested in randomized clinical trials [8–10], and today they are widely used in the daily clinical practice of the hypertensive population. Thus, based on the currently available clinical evidence [8–10], international guidelines for the treatment of hypertension recommend the use of antihypertensive therapy with these combinations at fixed dosages [11–13], even as initial therapies, when appropriate. This has also been reaffirmed in the recent 'reappraisal' of both US [14] and European [15] guideline recommendations for the clinical management of hypertension.

While it can be argued that a more extensive use of combination therapy may effectively improve BP control, conversely, several important answers remain unresolved. First of all, although different fixed combination therapies of antihypertensive drugs belonging to different classes are now available, it is difficult to support the fact that all of them can be considered equivalent or interchangeable, both in terms of antihypertensive efficacy and safety or tolerability. In addition, it is not quite clear whether starting treatment with these combination therapies prompts better results in terms of long-term BP control and CV outcomes. Finally, evidence on organ protection and CV disease prevention seem to recommend the use of specific compounds, which have gained sufficient evidence of CV and renal protection, rather than other antihypertensive drugs.

The recent availability of another pharmacologic approach to antagonize RAS, which is the DRI by aliskiren (Figure 1), has prompted studies to characterize the effectiveness and tolerability of the combination of this component in patients with hypertension at various stages [16].

Impact of DRIs on blood pressure control

Antihypertensive therapy based on aliskiren has been tested in several randomized clinical trials, which demonstrated a BP lowering efficacy that was comparable to other classes of antihypertensive agents, in the presence of a good tolerability profile [16]. As an example, in an 8-week, multicenter, randomized, double-blind, placebo-controlled, multifactorial, parallel-group, performed in 2776 patients with grade 2 hypertension, combination therapy based on aliskiren 300 mg plus hydrochlorothiazide 25 mg was superior to each monotherapy in reducing systolic and diastolic BP levels [17]. In another 6-week, multicenter, randomized, double-blind, multifactorial, parallel-group, clinical trial, performed in 545 patients with grade 2 hypertension who were inadequately controlled with amlodipine monotherapy, combination therapy based on aliskiren 300 mg plus amlodipine 5 mg was superior to amlodipine monotherapy in reducing systolic and diastolic BP levels. In both studies, antihypertensive strategy based on aliskiren resulted into a significantly improved responder rate than that obtained with monotherapy [17,18].

Aliskiren therapy was also effectively combined with other RAS blocking agents, including both ACE inhibitors and ARBs. In a 8-week, multicenter, randomized, double-blind, multifactorial, parallel-group, clinical trial, performed in 837 patients with diabetes mellitus and grade 2 hypertension, the combination therapy based on aliskiren 300 mg plus ramipril 10 mg significantly reduced both systolic and diastolic BP reductions as compared with that obtained with ramipril or aliskiren monotherapy [19]. Responder rates were significantly higher with combination therapy based on aliskiren plus ramipril and aliskiren monotherapy, than that observed with ramipril monotherapy [19]. Finally, in an 8-week, multicenter, double-blind, randomized, placebo and active-controlled, clinical trial, performed in 1797 patients with grade 2 hypertension, combination therapy with aliskiren 300 mg and valsartan 320 mg reduced mean systolic BP levels by 17.2 mmHg and mean diastolic BP levels by 12.2 mmHg, a significantly greater BP reduction than either monotherapy [20]. BP control rate in the combination therapy with aliskiren 300 mg and valsartan 320 mg group was significantly higher than that observed in the valsartan 320 mg monotherapy group or the aliskiren 300 mg monotherapy group [20].

Overall, the main findings of these trials demonstrated the BP lowering efficacy and safety of combination strategies based on the DRI aliskiren with all currently available antihypertensive drug classes [16]. More recently, the

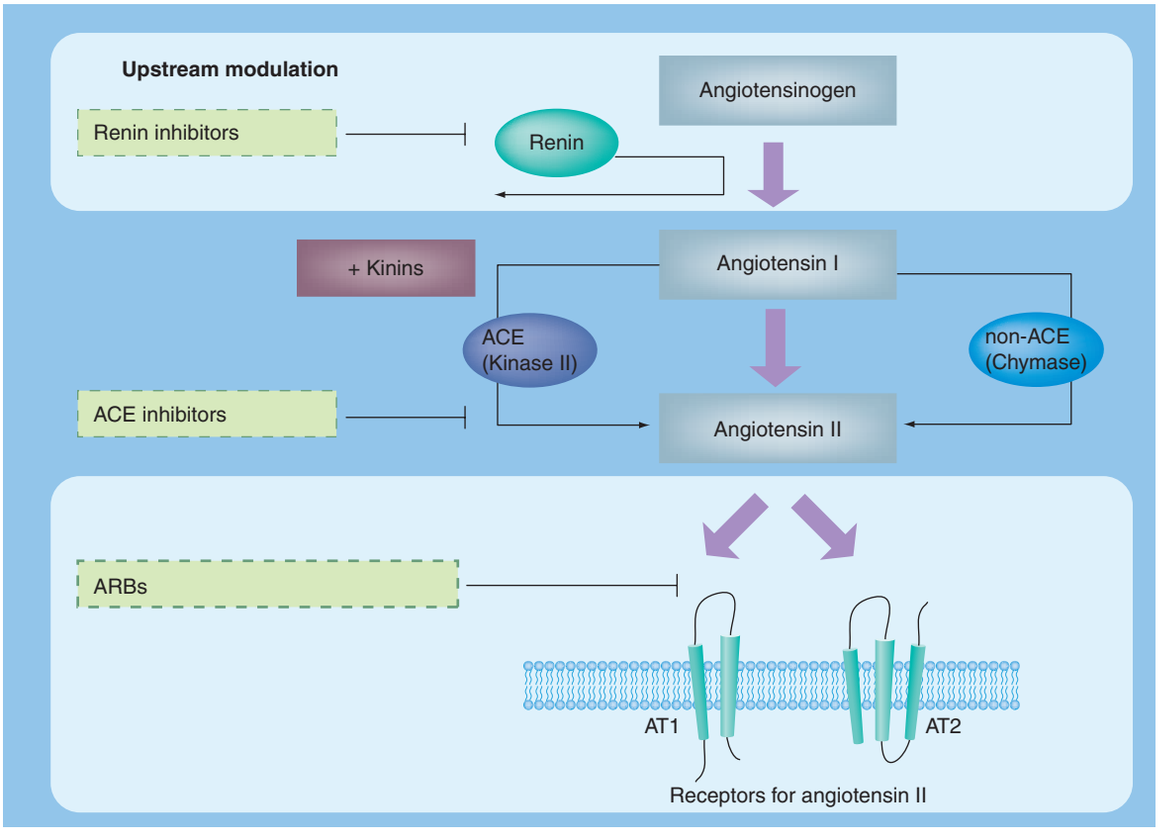

Figure 1. The hypothesis of 'dual blockade' of the renin–angiotensin system, based on both 'upstream' modulation generated by direct renin inhibitors and 'downstream' modulation. Renin–angiotensin system activity is normally regulated by compensatory feedback inhibition by the angiotensin AT1 receptor on the release of renin, the rate-limiting step of the system. ACE inhibitors and ARBs disrupt this feedback loop, stimulating increased renin activity, and thus increase angiotensin I generation. Only direct renin inhibitors can effectively block this cycle.
ACE: Angiotensin-converting enzyme; ARB: Angiotensin II receptor blocker.
Modified from [16].

combination of aliskiren and amlodipine has been evaluated in the Aliskiren and the Calcium Channel Blocker Amlodipine Combination as an Initial Treatment Strategy for Hypertension (ACCELERATE) trial [21], to test the hypothesis that a combination therapy based on the association between aliskiren and amlodipine would provide better and earlier BP control as compared with either monotherapies in hypertensive patients.

Main findings of the ACCELERATE trial

The ACCELERATE study was a double-blind, randomised, parallel-group, superiority trial, performed in grade 2 hypertensive patients, who had systolic BP between 150 and 180 mmHg at baseline (wash-out period) [21]. In the first phase of the trial (0–16 weeks), patients were randomly assigned to antihypertensive treatment with aliskiren 150 mg (n = 312), amlodipine 5 mg (n = 313), or aliskiren 150 mg plus amlodipine 5 mg (n = 604). At week 8, the initial dose was doubled. Then, in the second phase (16–24 weeks), all patients received combination therapy with aliskiren 300 mg plus amlodipine 10 mg. Thus, according to the study protocol, in the first phase, half the patients started monotherapy with either aliskiren or amlodipine, and half started a combination of aliskiren plus amlodipine, while in the second phase, all patients received the same combination of aliskiren plus amlodipine. In the third phase (24–32 weeks), patients can be titrated to an add-on therapy with hydrochlorothiazide 12.5–25 mg or placebo, if needed (BP levels above the recommended targets of ≤140/90 mmHg). The primary end points were the adjusted mean reduction in systolic BP from baseline to 24 weeks, and then the final reduction at 24 weeks [21].

An antihypertensive strategy based on combination therapy as first-line approach induced earlier and greater systolic BP reductions as compared with both monotherapies in the first phase (Figure 2) [21]. Further BP reductions were observed in hypertensive patients

initially treated with monotherapy, when they were shifted to double- or triple-combination therapy in the second and third phases, respectively [21]. At 24 weeks, the reduction in systolic BP was -27 ± 4 mmHg in the initial combination group and -25 ± 9 mmHg across the monotherapy groups, with a between groups difference of -1.4 mmHg (p = 0.059) [21]. The same efficacy provided by the combination therapy was observed with regard to diastolic BP levels.

Of note, the efficacy of the initial combination therapy was paralleled by a very high proportion of patients who achieved BP control in the early phase of the study (Figure 3) [21]. This rapid BP control was maintained over time in the group of patients randomized to receive initial combination therapy as compared with those who were treated with monotherapies. These latter groups showed a significant improvement in BP control rate when they were shifted to combination as a second stage approach [21]. In addition, although the addition of hydrochlorothiazide was similar in each group of patients (164 [27%] on initial combination therapy vs 162 [26%] on initial monotherapy), a persistent difference in BP control rates in favor of initial combination treatment as compared with monotherapies was recorded at the end of the study period [21].

As expected, analyses of plasma renin activity and plasma renin concentration demonstrated that the combination therapy and aliskiren reduced initial plasma renin activity, but increased plasma renin concentration [21]. Finally, all tested antihypertensive strategies were generally well tolerated, and only a few serious events were reported [21].

Future perspective

The control of BP remains a key target in CV prevention. To overcome the poor achievement of BP control, the use of effective fixed-combination therapies should be promoted in the clinical management of arterial hypertension.

In the ACCELERATE trial, performed in grade 2 hypertensive patients, the use of combination therapy based on the DRI aliskiren plus the CCB amlodipine as a first-line approach has been demonstrated to effectively, safely and rapidly reduce systolic BP levels better than the comparators (either aliskiren or amlodipine) used in monotherapy at the dosages currently applied for the daily clinical practice of hypertension [21]. In addition, uptitration to such combination therapy in those patients initially treated with monotherapy induced further marked reductions of systolic BP levels in patients initially not controlled on either monotherapies. The results of this trial confirm previous studies, such as the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [9] and in the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trials, which demonstrated that the initial use of combination therapy based on RAS blocking agents and dihydropyridinic CCBs led

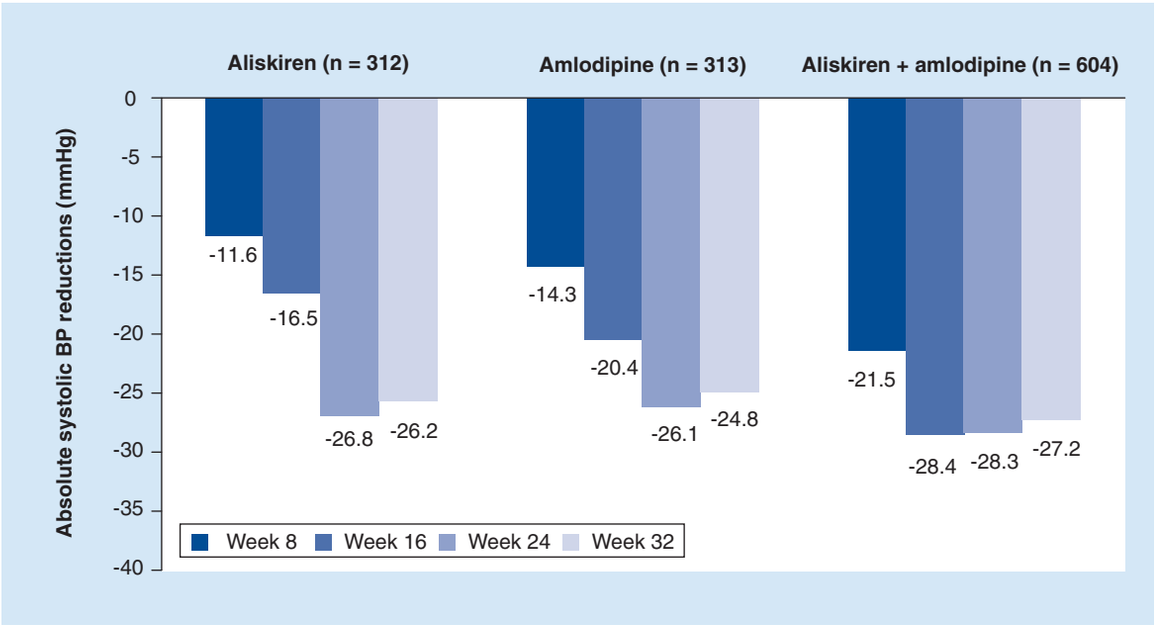

Figure 2. Effect of study-treatment strategies on mean sitting systolic blood pressure levels in patients with grade 2 hypertension.
Data taken from [21].

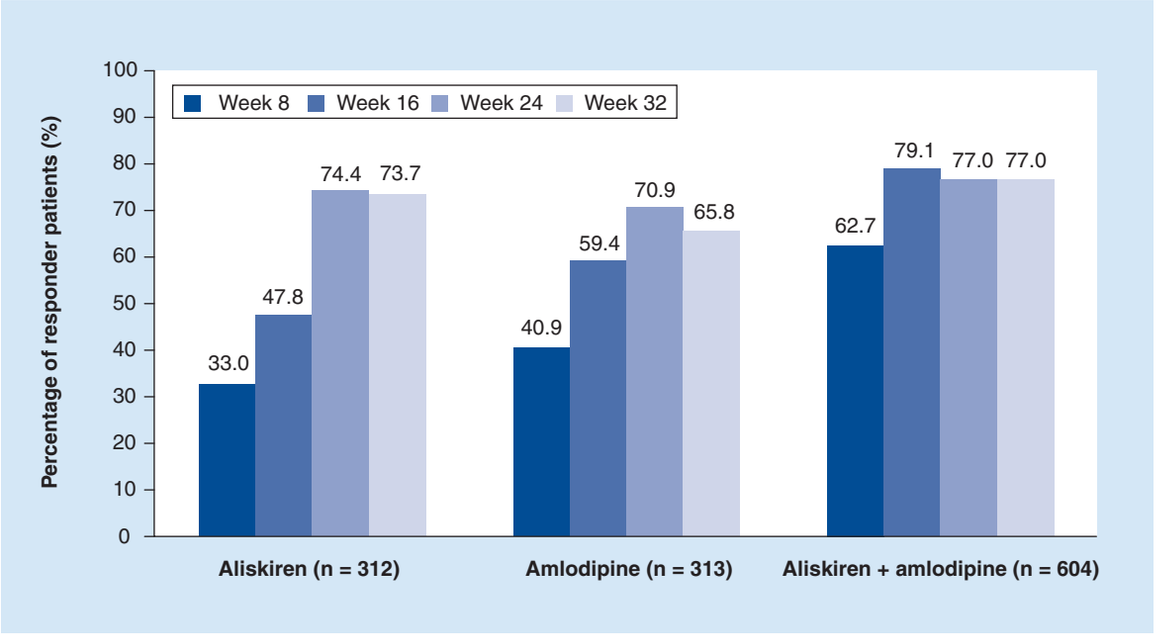

Figure 3. Effect of study treatment strategies on blood pressure responder rates (blood pressure levels ≤140/90 mmHg) in patients with grade 2 hypertension.
Data taken from [21].

to early adequate and sustained BP control [10]. However, this trial provides evidence in favor of the use of fixed combination therapy as a first-line approach to high risk, grade 2 hypertensive patients, in order to achieve rapid and effective BP control and high responder rate even in the early phases of study treatment [21].

Such an approach may be viewed as a modern and effective strategy to treat hypertension, since the reduced number of tablets, the better compliance of patients to prescribed antihypertensive therapy, the synergistic mechanism of action and the reciprocal reduction of the side effects, may all substantially contribute to improve BP control and reduce the burden of CV disease in hypertension. The possibility of adding thiazide diuretics to the aliskiren/amlodipine fixed-dose combination therapy may provide further efficacy in patients with more severe, uncontrolled hypertension and the clinical development of this triple combination therapy is currently being actively pursued.

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