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COMMENTARY

Use of Fixed Combination Therapies to Improve Blood Pressure Control in the Clinical Management of Hypertension: A Key Opportunity

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Hypertension is a major modifiable risk factor, which significantly and independently increases the risk of developing cardiovascular and renal complications [1]. Pharmacological treatment of hypertension aimed at achieving the recommended therapeutic targets [i.e. blood pressure (BP) levels below 140/90 mmHg] substantially reduces the risk of complications in different clinical settings [2]. Despite these benefits, worldwide rates of BP control are still reported to be largely unsatisfactory, thus contributing to a persistently high burden of hypertension-related diseases [3, 4].

Over the last decades, several interventions have been proposed at both national and local levels in order to improve hypertension management and control, although with various outcomes. Among these interventions, a larger use of combination therapies, mostly in fixed formulations, has been promoted by international guidelines in the recent years. In fact, the use of combination therapies of different drug classes, particularly when included in a single pill, has demonstrated to improve patients' adherence and compliance to prescribed medications [5] and reduce incidence of drug-related side effects in various clinical studies [6, 7]. In addition, several randomized clinical trials have convincingly and independently demonstrated the clinical benefits derived from such an approach in terms of reduced incidence of major cardiovascular and renal complications, beyond the BP lowering efficacy, with a good tolerability profile [8–13]. Although there is currently only one randomized clinical trial performed with a fixed dose combination therapy based on Angiotensin-Converting Enzyme (ACE) inhibitor and either thiazide diuretic or calcium-channel blocker in hypertensive patients with high cardiovascular risk profile [14], it has been widely recognized that antihypertensive strategies based on the use of these drug classes can promote the achievement of better BP control rates and reduce the hypertension-related burden of cardiovascular diseases in several clinical settings.

On the basis of the currently available evidence, both European [15] and Italian [16] guidelines promote the use of combination therapies for the clinical management of hypertension, suggesting the use of drugs inhibiting the renin–angiotensin system (either ACE inhibitor or angiotensin receptor blockers) combined with either diuretic or calcium-channel blocker or both in dual or triple formulations, to achieve the recommended therapeutic targets.

Although the same guidelines do not provide clear indications for choosing among different components within the same drug class of antihypertensive agents [15, 16], some practical considerations for helping physicians on the most appropriate therapeutic choice can be made on the basis of the currently available evidence. First of all, it would be useful to adopt antihypertensive strategies based on single molecules that can be used both as monotherapy and in fixed combination therapies, in order to limit the "pill burden" and ensure high level of adherence to prescribed medications. Secondly, it should be limited the use of molecules with proven evidence of cardiovascular protection, both in terms of regression of organ damage (e.g. left ventricular hypertrophy, vascular alterations, renal impairment) and of reduction of major cardiovascular

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events (e.g. myocardial infarction, stroke, heart failure, and cardiovascular death). Thirdly, it should be preferred the use of molecules which have demonstrated both in monotherapy and in combination therapy to provide a sustained antihypertensive efficacy and a favourable metabolic profile. Finally, it should be favoured the use of combination therapies with lower incidence of drug-related side effects or adverse reaction compared to either components or placebo.

In this volume of *High Blood Pressure & Cardiovascular Prevention*, Karpov YA and colleagues reported the main findings of the PRORYV-2 study [17]. This was an open-label study which examined the effect of substituting ineffective antihypertensive treatment with the fixed combination therapy based on perindopril/amlodipine on clinic, home and ambulatory blood pressure in a large group of patients with uncontrolled hypertension at high/very high cardiovascular risk. The authors used different dosage of the two component (perindopril/amlodipine: 5/5, 10/5 or 10/10 mg) in a relatively large sample of adult hypertensive patients in Russia. This led to a rapid (2 weeks) and significant ($p < 0.001$) reduction of clinic BP levels, which was maintained after 3 months (−33.7/17.1 mmHg from baseline). Of note, both 24-h ambulatory BP monitoring and home BP monitoring confirmed the BP decrease. Thus, the authors concluded that substituting ineffective antihypertensive therapy with FDC perindopril/amlodipine resulted in a rapid, pronounced and sustained antihypertensive effectiveness.

With the well known limitations of the open-label design, the study was able to demonstrate that a more extended use of rational, effective and well tolerated combination therapies (mostly in fixed formulation) can rapidly and markedly improve BP control rates and reduce BP variability in treated uncontrolled hypertensive patients. Such an approach should be encouraged and adopted in the clinical practice, to improve the clinical management of hypertension and achieve the recommended therapeutic targets.

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