Editorial Commentary

Do Optimal Antihypertensive Drug Regimens Allow Blood Pressure Normalization in All Patients With Resistant Hypertension?

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In the last decades, considerable efforts have been devoted to the diagnosis and treatment of arterial hypertension. The lowering blood pressure, obtained through lifestyle changes and drug treatment, has benefits in terms of cardiovascular morbidity and mortality which have now been extensively documented.\(^1,2\) In most adult hypertensive patients, it is presently recommended to decrease blood pressure \(<140/90\) mm Hg. However, this target is not easy to reach, despite the availability of drugs acting through different mechanisms and the possibility of combining them to increase antihypertensive efficacy. Many factors may contribute to insufficient control of blood pressure, ranging from limited access to medical care to nonoptimal therapeutic observance by patients and inertia of physicians in charge. Further complicating this state of affairs, the blood pressure of many patients is high in the medical office only, but not in the course of daily life activities.

It is important here to recall the definition of resistant hypertension as stated in the most recent recommendations. According to experts of the American Heart Association, hypertension is resistant if blood pressure remains \(\geq 140/90\) mm Hg, despite the simultaneous intake of \(\geq 3\) drugs acting through different mechanisms, all taken at optimal dosage, one of which ideally being a diuretic.\(^1\) As a corollary, hypertension is also considered resistant if 4 drugs are required to normalize blood pressure. Also pointed out in these guidelines, the possibility of pseudo-resistance (termed apparent treatment-resistant hypertension), which may arise, in particular, with technically suboptimal measurement of blood pressure, with poor therapeutic observance, or with white-coat hypertension. The NICE (National Institute for Health and Clinical Excellence) recommendations, elaborated in the United Kingdom, offer a slightly different definition of resistant hypertension, that is, a blood pressure \(\geq 140/90\) mm Hg, despite the combined intake a diuretic, an inhibitor of the renin–angiotensin system (whether targeting the angiotensin-converting enzyme or the angiotensin receptor), at doses that are either optimal or the highest one tolerated.\(^4\) Finally, in the joint recommendations by the European Society of Hypertension and the European Society of Cardiology that came out very recently, hypertension is deemed resistant if lifestyle changes and the intake of a diuretic plus 2 other drugs belonging to different antihypertensive classes fail to bring blood pressure \(<140/90\) mm Hg.\(^2\)

The aforementioned distinction between real and apparent or spurious resistance is also to be found in this last document.

The American Heart Association definition of resistant hypertension has recently been put to use by Egan et al\(^5\) who performed a study on the trends in blood pressure control from 1988 to 2008 in the United States. During this period, the prevalence of apparent treatment-resistant hypertension among drug-treated hypertensive patients increased from 15.9% (years 1998–2004) to 28.0% (2005–2008), a change that was highly significant statistically (\(P<0.001\)). Obviously, it was crucial to understand the possible reasons to this unfavorable evolution. In that respect, the present article by the same group provides some new and clinically relevant information.\(^6\) These authors exploited a very large and well-documented electronic patient database. The main originality of their work consists in the analysis of antihypertensive drug prescription in addition to quality of blood pressure control. Unfortunately, neither treatment adherence nor the technical quality of blood pressure measurements could be assessed.

Egans et al must be commended for proposing a definition of the ideal antihypertensive treatment in patients presenting with apparent treatment-resistant hypertension, the definition of which may be met in 2 sets of circumstances: (1) blood pressure \(\geq 140/90\) mm Hg, in spite of treatment with a diuretic plus \(\geq 2\) other drugs, prescribed at \(\geq 50\)% the recommended or approved dose, and (2) blood pressure \(<140/90\) mm Hg under a treatment comprising a diuretic and 3 other agents, prescribed at \(\geq 50\)% the recommended or approved dose.

This work included a total of 468,877 hypertensive patients, of whom 147,635 (31.5%) had uncontrolled blood pressure, whereas control was satisfactory in 321,242 patients (68.5%). This finding is encouraging, showing that, in a primary care setting, blood pressure can be normalized in almost 7 of 10 patients. By far the most interesting observation in patients with apparent treatment-resistant hypertension relates to the link established between antihypertensive drug prescription and control of blood pressure. Treatment was optimal in only half (49.6%) of patients with uncontrolled hypertension, which leaves substantial leeway for improving blood pressure control in treatment-resistant hypertension. Also of note, physicians’ therapeutic inertia was more marked in patients with

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apparent treatment-resistant hypertension, still pointing to the possibility for the improvement of blood pressure control.

The study by Egan et al would have been even more interesting, had data on therapeutic observance been available. Unfortunately, there is no easy and reliable way for assessing this parameter. Ideally, ambulatory or home blood pressure monitoring should have been used to exclude pseudo-resistant hypertension. Many patients with apparent treatment-resistant hypertension might not really need intensification of their antihypertensive drug regimen even with persistently elevated values of office blood pressure.

What course of action should be adopted by the physician, when challenged with apparent treatment-resistant hypertension? The Figure proposes a strategy which takes the present study into account. First and foremost, a secondary cause for hypertension should be excluded with as much certainty as possible. Then, pseudo-resistance must be distinguished from true resistance by means of ambulatory or home blood pressure monitoring. It is also necessary to discuss therapeutic adherence with the patient. The next step will be to prescribe an optimal regimen combining a diuretic, a blocker of the renin–angiotensin system and a calcium antagonist, with particular care taken to ensure adequate dosage. Other antihypertensive agents may occasionally be required, notably aldosterone antagonists, or even α- or β-blockers. With this approach, blood pressure can be normalized in the vast majority of cases, provided that the physician spends sufficient energy in having the regimen implemented and in convincing the patient to regularly take his/her medication(s). There are multiple methods to improve therapeutic observance, including high-quality patient information, self-monitoring of blood pressure at home, and simplification of drug regimen by the use of fixed dose combinations. These last 2 measures are particularly important: self-monitoring of blood pressure allows to detect white-coat hypertension so as to intensify treatment only when this is actually needed, and fixed-dose combinations most of the time make it possible to take daily no more than 3 medications.

In daily practice, the pragmatic definition of optimal antihypertensive treatment, in terms of drug number, type, and dosage, is very useful but not sufficient. In any particular case, the optimal treatment should not only normalize blood pressure but also achieve it without negative impact on quality of life. Such a regimen could be termed ideal. Interventional strategies, in particular renal denervation, might finally be considered if blood pressure control cannot be achieved using optimal pharmacotherapy in patients with true resistant hypertension.

Disclosures
None.

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