Editorial

Effect of initial antihypertensive combination therapy on primary stroke prevention

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Cardiovascular disease is the leading cause of morbidity and mortality globally, as the result of a high prevalence of cardiovascular risk factors and a failure to control them (1-4). Hypertension is considered the most important cardiovascular risk factor because of its very high prevalence, with at least 1 billion adults affected worldwide (2), and the direct and linear relationship between blood pressure and cardiovascular events (5). Hypertension is associated with an estimated 9.4 million deaths every year; it is responsible for at least 45% of deaths due to heart disease, and 51% of deaths due to stroke worldwide (1,2).

Despite the availability of effective antihypertensive agents, hypertension remains poorly controlled in the majority of patients (3). Most current clinical hypertension guidelines—for instance those from the European Society of Hypertension (ESH)/European Society of Cardiology (ESC), the Joint National Committee 8—recommend the initiation of antihypertensive treatment with a monotherapy or a combination therapy, depending on the grade of hypertension and the cardiovascular risk profile of the patient (6,7). However, only a third or less of patients will have their blood pressure controlled with a single drug, even those with grade 1 or 2 hypertension (according to the 2013 ESH/ESC classification), while two third need at least two drugs (7,8).

Basically, the pharmacological rationale of combination therapy is to combine drugs acting on different physiological systems involved in blood pressure regulation in a situation where the hypertensive phenotype—which determines individual responsiveness to antihypertensive drugs—is not known and where a pharmacological "attack" on two (or more) systems will have a greater impact on blood pressure reduction than blind monotherapy (9). Furthermore, combination therapy is an attempt to block counter-regulatory responses that are activated by the perturbation of the blood pressure regulatory mechanisms when a physiological system is blocked with single-drug therapy (9). Clinically, besides an increased rate of blood pressure control during the initial phase of hypertension treatment, combination therapy as compared to monotherapy has been shown to induce a more rapid blood pressure reduction and/or normalization (10). This is particularly crucial for patients with severe hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg) and those with high/very high cardiovascular risk profile (7). Indeed, for every 20 mmHg increase in systolic blood pressure, there is an approximate doubling of the risk of a future cardiovascular event. Hence, the aim of antihypertensive therapy should always be to both improve blood pressure control and to reduce cardiovascular events (5). In this regard, combination therapy produces a significantly greater reduction in global cardiovascular, coronary, and cerebrovascular events versus monotherapy, independent of blood pressure control (10,11). Therefore, there is convincing evidence that combination therapy offers important advantages over monotherapy.

Although randomized controlled trials provide the best quality of evidence on efficacy of any treatment, they do present some shortcomings. One of these is the problem of patient selection in a clinical trial which may not resemble patient characteristics in routine clinical practice. Additionally, populations from some ethnic and geographic background are often not represented.

Therefore, after efficacy of antihypertensive treatments has been demonstrated under controlled trial conditions, there is a need to collect data from larger heterogeneous patient populations in order to gain a better understanding of the effectiveness and tolerability of these treatments when used in routine clinical practice.

In the context of underrepresentation of Asian populations in controlled trials on the benefit of initial combination therapy on primary cardiovascular prevention, the study by Yu *et al.* published in the current issue explored the preventive effect of combination antihypertensive therapy on stroke based on a very large sample of Chinese hypertensive patients in real-world practice (12). The study analyzed the data of 37,608 Chinese subjects with uncontrolled blood pressure and without a history of stroke from the "Shanghai Electronic Health Record Management System of Community Residents (SEHRMSCR)". Based on the initial treatment, subjects were divided into an initial monotherapy group (32,682 patients) and initial dual combination therapy group (4,926 patients) and followed for 42 months.

The authors found a significantly greater reduction of systolic blood pressure in the initial combination group than in the initial monotherapy group during all the 42 months of follow-up, while the reduction of diastolic blood pressure was higher in the combination group only in the 42th follow-up month. Furthermore, although the target blood pressure control rate was achieved slowly in both groups, it was significantly higher in the combination group before the 6th follow-up month; it was reversely higher in the monotherapy group after the 13th follow-up month. The incidence of stroke in the combination therapy group was significantly lower than in the monotherapy group (adjusted hazard ration 0.64; 95% CI: 0.30-0.93) at 6 months, but no significant difference was observed at 12, 24, and 42 months (12).

Several issues influence the interpretation of the results. As for many retrospective observational studies, the primary limitations of this study included confounding factors that might not be equally distributed across the population. Indeed, there were significant differences pertaining to several cardiovascular risk factors between the two groups. Furthermore, several factors that are known to influence the efficacy of antihypertensive treatment such as medication adherence, concomitant lifestyle modification and individual physicians' practice were not investigated as potential confounders. There was also a lack of standardization of the diagnostic criteria of stroke, as well as of blood pressure measurement and treatment. Actually, it is not known whether patients were prescribed the appropriate therapeutic regimen in accordance with relevant hypertension guidelines. Finally, the authors did not stratify outcome analyses based on the grade of hypertension. Such approach might have provided information on potential difference in the efficacy of dual therapy versus monotherapy in patients with grade 1 versus grade 2 hypertension.

What are we to conclude from this study? Clearly, initial dual antihypertensive therapy is more effective than monotherapy in the prevention of a first stroke during the first 6 months of treatment in Chinese patients. This finding is consistent with evidence from some previous observational studies that demonstrated a significantly higher reduction of the occurrence of cardiovascular events including stroke with initial combination antihypertensive therapy as compared to monotherapy (10,11). However, Yu *et al.* did not found a significant difference between groups in the reduction of stroke occurrence after 6 months. This might be due to the loss of protective effect of dual therapy in the significant number of patients initially on dual therapy who switched to monotherapy or traditional Chinese drugs after 6 months of treatment once blood pressure target was reached.

While this study reinforces the potential benefit of dual antihypertensive therapy as an initial strategy for early stroke prevention, it stresses the need of further prospective observational studies to compare the effectiveness and tolerability of different antihypertensive combinations on the prevention of stroke and other cardiovascular diseases in real-world clinical practice, especially in understudied populations.

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