

## Initial combination treatment in the 2018 ESC/ESH hypertension guidelines

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The most important novelty of the 2018 Hypertension Guidelines of the European Society of Cardiology and the European Society of Hypertension (ESC/ESH) (1) is the decision to abandon the step-care treatment approach, i.e., initial monotherapy followed by the sequential addition of one, two, or more antihypertensive agents, as the most important treatment strategy to lower elevated blood pressure (BP) and achieve BP control. The guidelines now recommend two antihypertensive drugs as the most important initial treatment strategy, moving to a three-drug combination and then to the addition of more drugs if BP reduction is still insufficient and BP target is not achieved. The reason for abandoning monotherapy as the most common first-step treatment is that evidence indicates that initial monotherapy maximizes two major barriers to BP control, i.e., low adherence to the prescribed treatment regimen (1) and the so-called therapeutic inertia (1). Low adherence to treatment prevents persistent BP control and markedly increases the risk of death and hospitalization due to cardiovascular events (2). Therapeutic inertia maintains patients in monotherapy even when BP is not controlled and addition of other drugs is necessary (3), which substantially contributes to the low number of hypertensive patients in whom treatment achieves the recommended BP target (4). This goal that requires concomitant administration of two or more antihypertensive drugs (5) with different (and complementary) mechanisms of action in most patients (> 80%) because BP is a multiregulated variable, whereas hypertension depends on several causative factors and mechanisms.

In the previous ESH/ESC guidelines (6), initial dual combination treatment was recommended only in patients with a more marked BP elevation or a high or very high cardiovascular risk (e.g., history of a cardiovascular event) because it was thought that the prompt BP reduction, which is associated with the initial administration of two drugs, provides a more timely protection against the elevated cardiovascular risk. However, evidence has

since become available that the advantages of initial combination treatment extend to the more general hypertensive population, particularly that initial dual drug combinations favor adherence to treatment and bypass therapeutic inertia (3). Compared with initial monotherapy, the initial administration of two antihypertensive drugs has been found to be associated with a marked reduction in the risk of treatment discontinuation during chronic antihypertensive treatment (7). The initial administration of two antihypertensive agents obviously overcomes the problem concerning a large number of patients who remain in initial monotherapy due to therapeutic inertia (8). Finally and most importantly, evidence is available that initial combination therapy is associated with better long-term (1 year) BP control than initial administration of only one drug (9) and that this results in a reduced number of cardiovascular events in real-life medical settings (8, 10).

The above evidence and considerations provide a basis for the ESC/ESH hypertension guidelines to consider initial dual combination therapy as the treatment strategy to be adopted in most hypertensive patients. This is complemented by the recommendation of using single pill combinations whenever possible because treatment simplification (i.e., reduction in the number of pills to be taken every day) is accompanied by an increased adherence to treatment (11). At variance from the general hypertensive population (12), initial monotherapy remains confined to some subgroups of patients such as the extremely elderly or frail hypertensives in whom two initial BP-lowering drugs may result in an excessive BP reduction and favor injurious falls, which may be accompanied by dramatic consequences (13). It may also continue to be an appropriate treatment strategy in patients with a high BP (130–139/85–89 mm Hg) who need reduction in BP because of a history of cardiovascular disease (1). In these patients, only a modest BP-lowering effect is required to achieve the recommended BP target, which is set at <130/80 mm Hg, a goal that can be easily achieved with the administration of one drug only.

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**Accepted Date:** 30.07.2019

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DOI:10.14744/AnatolJCardiol.2019.03292



Despite the availability of several effective antihypertensive drugs and drug combinations, BP control in the hypertensive population remains poor, with high BP as the major cause of death and disease burden worldwide (10). The new treatment recommendations by the ESC/ESH guidelines represent an attempt to substantially modify this situation and make therapeutic BP control common in individuals who have a high BP. Although, this goal is challenging given that initial monotherapy is still the most common first-step treatment of hypertension to date (3), the potential advantages make the attempt worthwhile.

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