How to Intensify Treatment in Older Patients With Hypertension: Is There a Single Answer?

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Randomized trials show that half-dose antihypertensive bitherapies reduce blood pressure (BP) more than full-dose monotherapies, with no more adverse effects (1). Indeed, combining two drugs has an additive effect on BP reduction whereas increasing the dose of a drug is less than additive (2): a half dose is only 25% less potent than a full dose. Under these assumptions, the expected potency of antihypertensive drug combinations can be approximated (Table 1). For example, the combination of two drugs at half dose is expected to be 50% more potent than a single drug at full dose. Using half doses also reduces the adverse effects of thiazide diuretics and calcium-channel blockers (2); and combination with a renin-angiotensin system blocker further reduces some of them, such as thiazide induced hypokalemia and calcium channel blockers induced peripheral edema.

The main drawback of bitherapies is the number of pills needed. However, many can be prescribed as single-pill combinations (SPC), with improved adherence and persistence compared to free-equivalent combinations (3). Large cohorts of real-life patients have shown that initiating hypertension treatment with a drug combination (usually as SPC), rather than a single drug, is associated with fewer treatment discontinuation (4), better BP control (5), and ultimately a lower risk of cardiovascular events (6,7).

The evidence available to guide intensification when treated patients do not reach their BP goal is more limited. When all existing drugs are already at full dose, we add a new drug. But when at least one drug is not at full dose, should we add a new drug or first maximize existing drugs? The pharmacological rationale suggests that adding a half-dose new drug is more potent with fewer adverse effects but the use of SPC is not always possible in this case, and more pills can lead to poorer adherence and treatment discontinuation.

A study published in this issue addresses the question of treatment intensification in hypertensive patients (8). No less than 178,562 veterans with systolic BP > 130 mmHg and at least one antihypertensive drug not at full dose had their antihypertensive regimen intensified: 45,575 (26%) by drug addition and 132,987 (74%) by dose maximization. Outcomes were then compared after adjustment for baseline characteristics. Drug addition was less frequently sustained at three months than dose maximization (49.8% versus 65.0%) but the 12-month mean systolic BP decrease was nonetheless 1.1 mmHg larger (5.6 versus 4.5 mmHg).

This study includes a vast number of elderly patients, who are underrepresented in clinical trials. Sophisticated statistical methods intend to emulate a clinical trial from this observational cohort but the results remain vulnerable to bias and confounding. For example, the assessment of BP relied on unstandardized office measurements. This adds noise to the outcome data and might bias the results in unpredictable ways, especially since white-coat hypertension is common in this age group (9).

However, the main shortcoming of the study lies in the broad spectrum of baseline situations. The logic of treatment intensification differs with the baseline number and doses of antihypertensive drugs, number of pills per day, BP level, and clinical condition including comorbidities and fitness (especially in older patients). Encompassing such a heterogeneous case-mix prevents definitive conclusions on how best to intensify treatment in uncontrolled hypertensive patients, in general or in any given situation.

Consider a patient not at his BP goal while on a SPC with two half-dose drugs (combination potency 150 in one pill, see Table 1). We could favor maximizing the dose of the two drugs of the SPC (potency 200 in one pill) rather than adding a third drug at half dose (potency 225 but two pills). Staying with a single pill offsets the more limited potency increase (+50 instead of +75) and warrants an attempt. Now consider the same patient not at his goal while on a SPC with one full-dose and one half-dose drug (potency 175 in one pill). Here we could first favor adding a third drug at half dose (two pills but potency 250) rather than maximizing the second drug of the existing SPC (one pill but

potency 200). The larger potency increase (+75 instead of +25) is worth the burden of adding one pill, provided the patient agrees with this strategy. These two oversimplified examples only scratch the surface of diverse situations requiring individualized and shared decision-making.

Nonetheless, two results must be stressed. First, whatever the chosen strategy, treatment intensification leads to large BP decreases in patients who need it the most. Figure 2 of the paper shows that the mean 12-month systolic BP decrease is about 8 mmHg in patients with baseline systolic BP between 140 and 160 mmHg and about 20 mmHg in those with baseline systolic BP over 160 mmHg.

Second, both intensification strategies are associated with roughly similar 12-month BP decreases in the emulated intention-to-treat analysis. In this analysis, mean BP decrease is the compound result of persistence and BP-lowering potency. Similar mean BP decrease despite lower persistence is, therefore, confirmatory evidence that drug addition is more potent than dose maximization in those who persist. When a large BP decrease is needed, drug addition should be preferred together with promoting persistence, for example with SPC and patient education (3,10).

In practice, this study provides support to several general principles of antihypertensive drug prescription. When intensification is indicated, we should not waste time with elaborate reasoning, either add a drug or maximize the dose of existing drugs, whichever seems to fit best with the patient current treatment, clinical state, and preferences. We must try to keep the treatment as simple as possible but remember that increasing the dose of a single drug has a limited effect on the overall potency of a combination. We should use SPC whenever it simplifies the treatment and explain any unavoidable complexification with the patient. A follow-up visit must be planned about one month later to assess adherence, tolerance and effectiveness, and perform further adjustments if needed.

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Table 1. Expected approximate potency of antihypertensive combinations according to the number of drugs (from different classes) and their doses.

	Monotherapy	Bitherapy	Tritherapy
Half-dose	75	150	225
Full-dose	100	200	300

Potencies are expressed as a percentage of the BP decrease expected from a single full-dose drug. The potency of any combination can be approximated by adding the potency of all its component drugs. For example, a bitherapy with one full-dose drug and one half-dose drug will have a 100 + 75 = 175 potency.