# Chapter 3

# Medical Need for Combination Treatment in Hypertension

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**Blood pressure (BP) is not optimally controlled in half or more patients with hypertension in most countries. Current guidelines call for more intensive management of hypertension, including use of combination treatment from diagnosis for most patients. These guidelines strongly support the use of single-tablet combinations from diagnosis for most patients, as this approach is more effective and better tolerated than titration of monotherapies, helps to avoid clinical inertia, and supports good adherence to the treatment regimen.**

## Sub-optimal control of hypertension is common

### *Prevalence of sub-optimal BP control in hypertension*

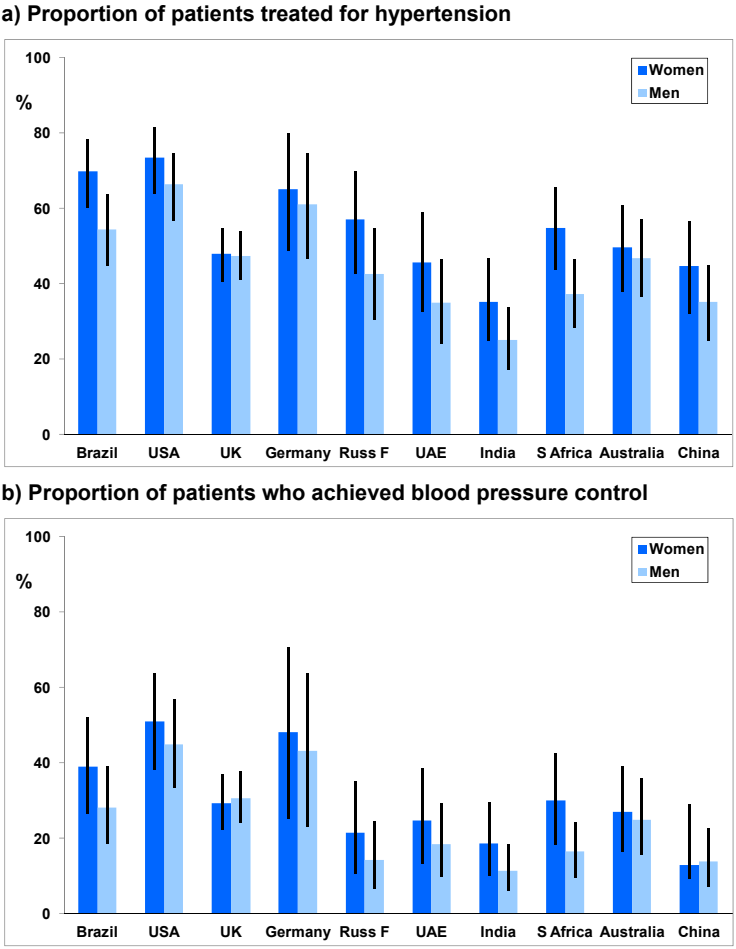
We have seen in the preceding chapters of this book that hypertension is prevalent world-wide, and that uncontrolled hypertension is associated with a major burden of premature cardiovascular morbidity and

mortality. We have also seen that major international guidelines provide targets for BP control in people with hypertension that, if achieved, will help to preserve cardiovascular health and reduce the risk of major adverse cardiovascular events.

So, how well are we doing? The Non-Communicable Disease Risk Factor Collaboration undertook a global survey of hypertension that included data from a total of 104 million individuals, with BP data from 1,204 individual studies [1]. The survey reported that, overall, 47% (95% confidence interval [CI], 43 to 51%) of women and 38% (95% CI, 35 to 41%) of men received treatment for hypertension, and hypertension was controlled in 23% (95% CI, 20 to 27%) of women and 18% (95% CI, 16 to 21%) of men in 2019. Figure 1 summarises some of these data from selected countries from different regions of the world. The proportions treated and controlled were highly variable between countries. Also, the rates of treatment and control were higher for women than for men in most of the countries, consistent with the results of the overall analysis.

Other published data support these findings. Data from the nationally representative National Health and Nutrition Survey (NHANES) 2015–2018 cohort in the United States of America (USA) reported that only 22.3% of women and 18.2% of men with hypertension had their BP controlled [2]. This was even lower than the global survey, although it should be noted that these data were generated using the US BP target of <130/80 mmHg (see Chapter 2 of this book), rather than the <140/90 mmHg cut-off used in the global survey. A 2017 survey using data from 6,546 individuals across ten countries and three continents found that treatment and BP control rates (<140/90 mmHg) were 48.0% (range, 33.5 to 74.1%) and 38.6% (range, 10.1 to 55.3%), respectively [3]. The World Health Organization has reported that 42.0% of adults with hypertension are diagnosed and treated, and only 21.0% achieve BP control [4]. Elsewhere, control of hypertension was achieved in 38.1% (95% CI, 37.8 to 38.4%) of 100,000 treated hypertensive patients in the United Kingdom (UK) (<140/90 mmHg, 2021) [5]; in 47.3% (standard deviation, 1.17) of 3,969 hypertensive patients in Korea (<140/90 mmHg, 2016–2017) [6]; in 51.6% of treated patients with hypertension in Ireland (<140/90 mmHg, 2009–2011) [7]; in 64.6%

**Figure 1 Proportion of patients with hypertension who (a) received treatment and (b) achieved adequate blood pressure control (<140/90 mmHg) from a global survey on hypertension [1].**




Russ F: Russian Federation; S Africa: South Africa; UAE: United Arab Emirates; UK: United Kingdom; USA: United States of America.

of hypertensive patients in Canada (<140/90 mmHg, 2009) [8]; and in 49.9% of treated hypertensive patients in Guinea-Bissau, West Africa (<140/90 mmHg, 2021) [9].

## Need for combination therapy in hypertension

### *Superior clinical efficacy of antihypertensive combinations versus monotherapy*

The clinical evidence summarised above confirms that a substantial proportion of people with hypertension are under treated. Three strategies are available for increasing the effectiveness of antihypertensive therapy: (1) switching to another drug (i.e. sequential antihypertensive monotherapy); (2) titrating the dose of another drug; or (3) adding one or more new drugs to the regimen.

A randomised trial compared all three strategies during 9 months of treatment. More patients with hypertension achieved BP <140/90 mmHg following initial treatment with a single-tablet, low-dose combination of perindopril (an angiotensin-converting enzyme inhibitor), a thiazide, and indapamide, compared with sequential monotherapy with atenolol (a β-blocker), losartan, and amlodipine (a calcium channel blocker), or 'stepped care' where monotherapy with valsartan (an angiotensin II receptor blocker [ARB]) was titrated and a thiazide added if required (Table 1) [10]. A second randomised trial in 605 patients with previously untreated hypertension compared strategies (1) and (3) directly [11]. Patients in two study arms received the ARB losartan or the thiazide diuretic hydrochlorothiazide for 8 weeks, followed by crossing over to the other monotherapy for a further 8 weeks. Patients in a third study arm received both drugs together for the 16-week treatment period. The mean change in clinic BP was –23.8/–13.4 mmHg for combination therapy versus –13.7/–7.1 mmHg for sequential monotherapy (mean treatment difference –10.1/–6.31 mmHg, $p<0.001$). Thus, initial combination therapy is more effective than sequential monotherapy for controlling high BP. A third randomised trial, where perindopril plus indapamide were given as initial antihypertensive therapy to drug-naïve

**Table 1 Greater antihypertensive efficacy with a single-tablet combination of two antihypertensive agents compared with sequential monotherapies or a stepped care approach during 9 months of treatment in patients with hypertension [10].**

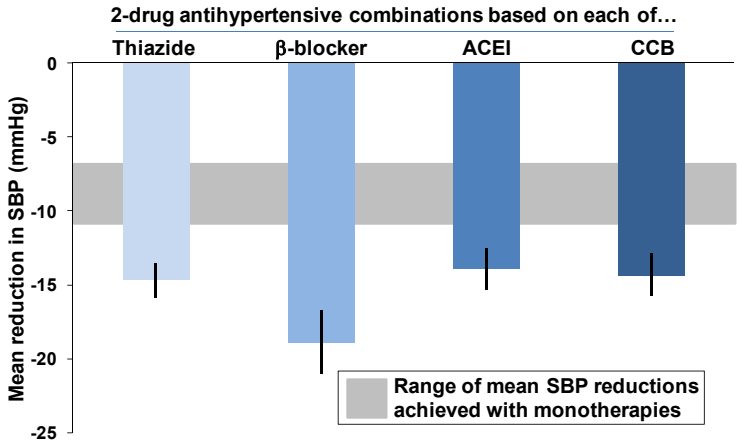
| | Mean change in systolic/diastolic blood pressure (mmHg) | Percent of patients with blood pressure <140/90 mmHg |
|---|---|---|
| **Initial single-tablet combination approach** (indapamide + perindopril[a]) | –26.6*/–13.6 | 62* |
| **Sequential monotherapy approach** (atenolol → losartan → amlodipine[b]) | –22.6/–12.5 | 49 |
| **Stepped care approach** (valsartan 40–80 mg + additional hydrochlorothiazide if needed[c]) | –21.5/–12.1 | 47 |

[a]For the initial combination tablet approach, the dose of the combination could be titrated if required.
[b]In the sequential monotherapy approach, monotherapies were replaced if blood pressure remained uncontrolled.
[c]For the stepped care approach, valsartan monotherapy could be titrated followed by addition of hydrochlorothiazide if needed.
*p<0.05 or better vs. both other treatment groups.
Data are from the end of the study (9 months of treatment).
Compiled from data presented in Mourad et al. [10]

patients, or to uncontrolled hypertensive patients as replacement for a monotherapy or in addition to an existing monotherapy, reported control rates for hypertension of 67–70% across the three groups, which is higher than expected in usual routine care, as described above [12].

A meta-analysis of 42 clinical trials (including 10,968 participants), which compared two-drug combinations with one or more of their components as monotherapy, showed that addition of a second antihypertensive drug to a thiazide diuretic produced reductions in BP that were clearly larger than those obtained with monotherapies (Figure 2) [13]. This study also showed that adding an additional antihypertensive agent delivered BP reduction that was five-fold higher than titrating an existing monotherapy. Another meta-analysis showed that patients with hypertension taking combination antihypertensive therapy were more likely to achieve their BP goal compared with monotherapy [14]. Finally, a real-world evidence study compared strategies of single-tablet combination therapy, a free combination of antihypertensive agents, and monotherapy during the first treatment year [15]. The likelihood of achieving BP control was higher for the single-tablet or free combination versus monotherapy

**Figure 2 Mean reduction in systolic blood pressure in patients receiving two-drug combination therapy compared with monotherapy [13].**




Bars represent 95% confidence intervals.
ACEI: angiotensin converting enzyme inhibitor; CCB: calcium channel blocker; SBP: systolic blood pressure.

(hazard ratio, 1.53 [95% CI, 1.47 to 1.58] and 1.34 [95% CI, 1.31 to 1.37]), respectively.

A number of other randomised trials have confirmed the superior efficacy of initial combination therapy for increasing BP control rates in populations with hypertension [16]. These data further confirm the superior efficacy of the combination therapy approach for increasing the effectiveness of antihypertensive treatment, compared with monotherapy.

## *Experience from clinical trials of intensive BP control*

Several clinical trials have evaluated the effects on outcomes of intensive BP control in various populations, in order to explore the clinical validity of guideline BP targets. These trials have required the use of multiple antihypertensive agents to achieve their intensive BP control targets. For example, patients in the intensive control arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial (in people with type 2 diabetes and hypertension) received an average of 3.4 antihypertensive

agents (compared with an average of 2.1 agents for the standard control group) [17]. Similar findings came from the intensive and standard control groups in the Systolic Blood Pressure Intervention Trial (SPRINT) in hypertensive patients at elevated cardiovascular risk (2.8 versus 1.8 agents, respectively) [18], and the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial in older patients with hypertension (1.9 versus 1.5 agents, respectively) [19].

## Advantages of single-tablet combinations

### *Overcoming clinical inertia in hypertension*

The definition of therapeutic inertia is a "*failure of healthcare providers to initiate or intensify therapy according to current guidelines*" [20, 21]. In the setting of hypertension management this means a failure to initiate or to intensify antihypertensive therapy despite a patient's BP being above the current guideline goal.

Therapeutic inertia is common in the management of hypertension, for reasons related to the healthcare provider, the patients themselves, and the healthcare system [22]. A recent (2021) cohort study in the Netherlands found that this applied to 87% of a population of hypertensive patients above their guideline BP goal while receiving one or two antihypertensive drugs [23]. Older age, having BP close to the goal, and comorbid diabetes were associated with therapeutic inertia in this study. Physicians cited a preference for optimising lifestyle intervention and waiting for the next set of results among the reasons for not intensifying therapy. The prevalence of therapeutic inertia in the standard and intensive BP management arms of the randomised SPRINT trial varied between 56–60%, with some evidence of differences according to ethnicity [24]. Almost half of the patients with Stage 1 or 2 hypertension remained on monotherapy over 8 years in Belgium and Luxembourg, despite uncontrolled BP [25]. A systematic review suggested that a range of interventions designed to reduce therapeutic inertia increased the likelihood of achieving BP control by 19% [20].

Modelling studies have also addressed this issue. A therapeutic inertia score, based on disparities between expected and actual changes in medication, predicted a reduction in BP (patients in the lowest quartile of the score) or an increase in BP (patients in the highest quartile) [26]. Reproducing routine clinical practice in a Monte Carlo simulation suggested that therapeutic inertia may be responsible for as many as half of all hypertensive patients failing to meet their BP target during 10 years of follow-up [27].

The American Medical Association recommends four strategies for reducing therapeutic inertia in the management of hypertension [28]:

- Using single-tablet combinations (to simplify the regimen).
- Paying careful attention to dosages prescribed (so that a second agent can be prescribed before titrating a monotherapy to its maximum dosage thereby reducing the potential for side effects).
- Identifying barriers to adherence (e.g. side effects, forgetting to take medication).
- Encouraging patients to self-monitor their BP (to ensure adequate BP readings are available to support good prescribing decisions).

## *Supporting good adherence to the therapeutic regimen*

People with hypertension, especially older patients, often have additional comorbidities leading to a need for polypharmacy, which is a risk factor for sub-optimal adherence to the therapeutic regimen [29–31]. Simplifying the regimen improves adherence; clinical studies have reported better adherence to once-daily, single-tablet combinations, compared with free combinations of two or more agents [32–35], twice-daily treatment [36], or antihypertensive monotherapy [37, 38].

A systematic review reported improved adherence to a single-tablet combination compared with a free, co-administered combination, and that this was associated with a larger decrease in BP (treatment difference –4.0/1.5 mmHg) [39]. Another systematic review not only reported better antihypertensive goal achievement with single-tablet versus free combinations, but also reported a significantly reduced need for outpatient visits, emergency room visits and hospitalisations for patients with

hypertension and/or dyslipidaemia [40]. Better adherence to antihypertensive therapy has also been significantly associated with a lower risk of adverse cardiovascular outcomes in a large database study from the USA [41]. The improved adherence associated with single-tablet combinations therefore has functional significance for patients.

### *Maximising efficacy while minimising side-effects*

Titrating an antihypertensive therapy beyond half of its maximum indicated dose is unlikely to produce marked additional BP lowering efficacy, instead increasing the potential for side effects [42]. Combination tablets are more effective for BP control than monotherapy from therapy initiation, as described above, while the low dose of each individual component of the combination tablet supports good tolerability. For example, single-tablet antihypertensive combination therapy was better tolerated than either sequential monotherapy or stepped care in one of the randomised trials reviewed above. The number of patients achieving BP <140/90 mmHg without side effects was 66% for the single-tablet combination, compared with 42% for sequential monotherapy or stepped care ($p=0.001$ and $p=0.004$, respectively) [10].

## What the guidelines say

The current European guideline for the management of hypertension provides strong support for the prescription of combination antihypertensive therapy [43], especially using a combination of agents within a single tablet, for the majority of patients at the time of diagnosis of hypertension. This is to "*improve the speed, efficiency, and predictability of BP control*". Antihypertensive monotherapy is reserved in this guideline for patients with systolic BP <150 mmHg, patients with high-normal BP who are at very high cardiovascular risk, or frail or very elderly patients. US guidelines recommend consideration of antihypertensive combination therapy for patients with BP ≥140/90 mmHg (Stage 2 hypertension) [44].

The use of additional antihypertensive drugs beyond a two-drug combination is also supported strongly in this guideline, with recommendations on the appropriate use of a third or fourth agent, if needed. These recommendations are consistent with the observation that multi-drug combinations were needed to control BP in the intensive control arms of large outcomes trials, as described above.

The European guideline for the management of hypertension considers that insufficient use of combination therapy is likely a contributing factor to the low rates of hypertension control described above. The guideline writers did not provide evidence for this, but several recent studies suggest that a majority of patients across various countries with newly diagnosed hypertension have been prescribed antihypertensive monotherapy, rather than combination therapy [45–48].

## Conclusions

BP is controlled to guideline targets in less than half of the people treated for hypertension in most countries, leaving millions of people with hypertension at an unnecessarily increased risk of adverse cardiovascular outcomes. Under-treatment of hypertension, associated with clinical inertia, contributes to low rates of treatment and control of high BP. Current guidelines for the management of hypertension recommend that most patients should receive combination antihypertensive therapies, usually from the time of diagnosis of hypertension. Antihypertensive combinations, delivered by single tablets, are an effective approach to the delivery of combination antihypertensive therapy in a way that is convenient for patients, better tolerated than high doses of monotherapy, and supports good adherence to the antihypertensive regimen.

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