



## Review

## A guide for easy- and difficult-to-treat hypertension

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## ABSTRACT

Although the blood pressure (BP) of many patients can be controlled using standard combinations, treatment of hypertension frequently represents a clinical challenge to the primary care physician. This article will review best practices for managing patients with easy- and difficult-to-treat hypertension, including preferred antihypertensive combinations, optimizing adherence and persistence, recognizing white-coat hypertension, and intensifying therapy for treatment-resistant patients. Each physician must decide based on his or her own level of experience at what point a patient becomes too challenging and would benefit from referral to a hypertension specialist for more intensive management and to complete the exclusion of secondary forms of arterial hypertension. With intensive pharmacotherapy, many patients with difficult-to-treat hypertension can achieve BP control. If it fails, interventional strategies (e.g., renal denervation) are a valid option to get BP controlled.

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## 1. Introduction

Treating hypertension is a common challenge faced by primary care physicians (PCPs). Elevated blood pressure (BP) is an extremely common health problem and is associated with increased risk of cardiovascular disease. Worldwide, 62% of cerebrovascular disease, 49% of ischemic heart disease, and 13% of all deaths are attributable to elevated BP [1]; therefore, controlling hypertension is a fundamental task of primary care. As many PCPs have experienced, some patients with hypertension respond well to pharmacotherapy, while others are more difficult to treat. Different treatment strategies may be appropriate for patients starting antihypertensive therapy, but the real challenge is represented by those patients who have cycled through several treatment regimens without achieving BP control.

## 2. Identifying “easy-” and “difficult-to-treat” patients

According to the 2009 reappraisal of the European guidelines on hypertension management [2] (and reconfirmed by updated guidelines published in June 2013), an office BP of <140/90 mm Hg is an appropriate target for all patients with hypertension. Although a lower target has sometimes been recommended for patients with comorbidities such as

diabetes, this recommendation is not strongly supported by prospective trials with hard endpoints [3,4].

We suggest using the following 2 terms that may guide the therapeutic management of hypertensive patients in primary care [3,4]. “Easy-to-treat” hypertension is defined as BP that is controlled on  $\leq 3$  antihypertensive medications. Some patients, however, require more extensive pharmacotherapy. “Difficult-to-treat” hypertension is defined as BP that remains uncontrolled on  $> 3$  antihypertensive drugs.

Developing an effective regimen for a patient with difficult-to-treat hypertension can be a real challenge. Every physician must decide based on his or her own level of experience at what point a patient becomes too difficult to treat. Challenging patients should be referred to a hypertension specialist for more intensive management. With intensive pharmacotherapy, many patients with difficult-to-treat hypertension can achieve BP control [5], but side effects must be monitored closely.

## 3. Important issues in the management of the patient with easy-to-treat hypertension

## 3.1. Adherence to the treatment regimen

Adherence and persistence are common management challenges with any type of long-term therapy. Patients benefit from antihypertensive therapy only if they follow their treatment regimens; yet they rarely follow the regimen as prescribed, and the rate of long-term continuation on therapy is generally low [6–9]. In a retrospective study of patients starting treatment with a single antihypertensive

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agent [6], high adherence was associated with a reduced risk of the first hypertension-associated event, such as stroke or myocardial infarction.

In a retrospective study [7], the percentage of patients staying on their initial antihypertensive therapy at 12 months was determined. Persistence ranged from 38% to 64%, depending on the antihypertensive regimen prescribed. An additional 6% to 9% of patients switched to another drug class, and 29% to 56% of patients, depending on the initial drug class prescribed, discontinued treatment completely by 12 months. Although the causes of discontinuation were not available for this study population, persistence correlated with the tolerability profile of each drug. More patients were persistent in the groups that received drugs with fewer side effects. Age was also a factor. Patients of older age were more likely to continue therapy than younger patients.

Persistence with antihypertensive therapy lowers the risk of heart attack and stroke. In a retrospective study of more than 77,000 patients in the Netherlands [9], discontinuation of antihypertensive therapy within 2 years of initiation was associated with a 15% increased risk of acute myocardial infarction, as well as a 28% increased risk of stroke. Risk was adjusted for gender, age, and other relevant covariates.

Because achieving consistent adherence to antihypertensive therapy is such an important management issue, many strategies to encourage it have been studied. A systematic review of interventions to improve adherence in patients with hypertension [10] found that although no single strategy consistently promoted a high level of adherence to therapy, some strategies were more effective than others. The review found that simple patient educational interventions caused no increase in adherence. Motivational strategies had varying results, from minimal improvement up to a 23% increase in adherence. Complex interventions involving >1 technique achieved variable results, with improvements ranging from a 5% to a 41% increase in adherence. Simplifying the dosing regimen by reducing the number of daily doses of medication was the most consistently successful strategy, resulting in an 8% to 19% increase in adherence, and was therefore recommended as a first-line strategy for increasing adherence.

Fixed-dose combination pills offer an attractive option for simplifying treatment. Both adherence [11] and persistence [12] are better with fixed-dose combinations than with individual pills. Therefore, simplifying treatment by prescribing combination pills is recommended to help patients follow the treatment regimen successfully. Methods for evaluating adherence include the assessment of prescription follow-up, pill counting, assays for drugs or chemical markers, and the use of electronic pill dispensers. Unfortunately, there is no ideal method for assessing how regularly patients take their prescribed medication [13]. Some hints are depicted in Table 1.

### 3.2. Substances that interfere with antihypertensive therapy

The efficacy of antihypertensive agents may be reduced if the patient consumes substances that interfere with their action. Common substances that interfere with antihypertensives include high-dose aspirin and other nonsteroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors, sympathomimetic agents, amphetamines, cocaine, caffeine, alcohol, oral contraceptives, glucocorticoids, cyclosporine, erythropoietin, vascular endothelial growth factor inhibitors,

natural licorice, anorectics, and some herbal compounds [5,14]. Patients should be questioned specifically about use or abuse of interfering substances, e.g. pain-relieving substances because they may neglect to mention them in the course of a general health history.

### 3.3. Options when low-dose monotherapy fails

Although it may be appropriate to introduce antihypertensive therapy with a single agent, many patients do not achieve BP control on monotherapy. It may seem intuitive to increase the dose (e.g., doubling the dose) of a single agent before moving to combination therapy in order to keep the regimen simple; however, if the treatment regimen must be intensified, the introduction of combination therapy is preferred. A meta-analysis of 354 randomized, double-blind placebo-controlled trials of antihypertensive agents showed that doubling the dosage of an antihypertensive agent resulted in a further decrease in BP by approximately 2/1 mm Hg, whereas combination therapy resulted in a further reduction in BP by 6–7/3–4 mm Hg [15]. In another subsequent meta-analysis of 11,000 participants from 42 trials, a similar result was found: doubling the dose of 1 drug had approximately one-fifth of the equivalent incremental effect of combination therapy [16]. Thus, combination therapy has a clear advantage in terms of BP reduction over intensified monotherapy.

In the OSCAR trial, after a short run-in phase with monotherapy, combination therapy was compared to intensified monotherapy with respect to cardiovascular outcome [17]. Monotherapy with a high-dose angiotensin receptor blocker (ARB) (40-mg olmesartan) was compared with combination therapy of a low-dose ARB (20-mg olmesartan) plus calcium channel blocker (CCB) (amlodipine or azelnidipine). In order to achieve effective BP control, additional drugs could be applied in both treatment arms when needed. The average BP between the 2 treatment arms was similar. Most striking, combination therapy reduced the incidence of cardiovascular events and death in high-risk patients with a history of cardiovascular morbidity at baseline [17].

In the ASCOT trial, different combinations were compared: angiotensin-converting enzyme (ACE) inhibitor plus CCB vs beta blocker plus diuretic. At similar office BP reductions, the combination of the ACE inhibitor with CCB had a significantly lower incidence of cardiovascular endpoints [18]. In the ACCOMPLISH study [19], the combination partner of a renin-angiotensin system (RAS) blocker was analyzed. An ACE inhibitor and CCB combination (benazepril and amlodipine) was superior to an ACE inhibitor and diuretic combination (benazepril and hydrochlorothiazide) in reducing cardiovascular endpoints in high-risk patients. These studies support the concept that blocking the RAS in combination with amlodipine is a cornerstone in antihypertensive therapy to prevent cardiovascular morbidities. Please note that in ACCOMPLISH patients with heart failure or chronic kidney disease have been excluded in whom a diuretic is the preferred combination partner.

Combination therapy can have the added advantage of mitigating side effects of a single antihypertensive agent. For example, a CCB and ACE inhibitor combination or CCB and ARB combination mitigates CCB-associated edema [20–23], while ARBs and ACE inhibitor reduce hydrochlorothiazide-induced hypokalemia [24].

Combination therapy also offers improved adherence, if given as a single-pill combination [11]. Moreover, in a population-based case-control study with 209,650 patients, it was found that combination therapy initiated as the first step of an antihypertensive therapy was associated with better cardiovascular, coronary, and cerebrovascular outcomes in comparison to monotherapy [25].

For patients not controlled with a 2-drug combination, triple-combination therapy provides further BP reduction. In the BP-CRUSH trial [26], a treatment algorithm in which patients were titrated to triple therapy with amlodipine, olmesartan, and hydrochlorothiazide, 90% of patients achieved BP control. In another trial [27], a 3-drug combination of valsartan, hydrochlorothiazide, and amlodipine resulted in

**Table 1**  
Hints of nonadherence to pharmacologic therapy.

|                                                                        |
|------------------------------------------------------------------------|
| Prescription refill intervals longer than expected                     |
| Analytic measurements, e.g., with the use of HCTZ                      |
| Indirect indicators, e.g., low renin despite RAS                       |
| Questioning spouse or partner about adherence                          |
| Memory deficiency of patients                                          |
| Complicated treatment regimen/high number of tablets to be taken daily |

HCTZ, hydrochlorothiazide; RAS, renin-angiotensin system.

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