Chapter 2

Historical review of combination therapy

Multifactorial approach to the treatment of hypertension

Hypertension is a multi-etiological disease for which a multifactorial treatment approach has been advocated [1]. The multifactorial approach comprises lifestyle modification and/or administration of antihypertensive medications (Figure 2.1).

The main modifiable causes of hypertension are shown in Figure 2.2. Lifestyle modification to address some, or all, of these factors will definitely reduce blood pressure in hypertensive patients; however, it is possible to rely on this type of treatment too long. Non-pharmacological treatment is the first step in the management of all hypertensive patients, but it may be applied for anything from a few weeks to several years. During this time, cardiovascular damage may occur, leading to an increased risk of cardiovascular disease. Such

Multifactorial approach to the treatment of hypertension

- Lifestyle modification is recommended for all hypertensive individuals [2]
  - for individuals with pre-hypertension it may prevent progression to hypertension
  - changes to as many main modifiable causes (see Figure 2.2) as possible advocated for all individuals with hypertension, whether or not taking antihypertensive medication
- Antihypertensive medication(s)
  - blood pressure control rates are poor in hypertensive patients who have been prescribed antihypertensive medication
  - achieving target blood pressure depends on both efficacy of antihypertensive treatment and patient compliance [3]
  - many patients who have been prescribed antihypertensive drug therapy do not adhere to their treatment regimen, or discontinue use within 1 year
  - there are several potential causes of non-adherence to antihypertensive therapy (see Figure 3.11)

Figure 2.1 Multifactorial approach to the treatment of hypertension.

J. M. Neutel, *Combination Therapy in Hypertension*,
DOI: 10.1007/978-1-908517-28-9_2, © Springer Healthcare 2011

The main modifiable causes of hypertension
• Diet
– ideally, should be low in saturated fat, cholesterol, and total fat
– should be rich in potassium, magnesium, calcium, protein, and fiber
– increased consumption of fruit, vegetables, low-fat dairy products, whole grains, fish, poultry, and nuts is advocated
• High salt intake
– sodium reduction recommended for patients with high salt content in their diet
• Lack of exercise
– increasing aerobic exercise to 30–45 minutes per day is recommended
• Overweight/obesity
– assessing overall target weight and setting incremental weight loss targets may help patient focus on steady weight loss
• Excessive alcohol intake
– limitation of alcohol intake recommended; patients may require continuous support to ensure success
• Smoking
– smoking cessation advised; continuous monitoring and support may be required to ensure long-term success

Figure 2.2 The main modifiable causes of hypertension.

damage might have been prevented with earlier administration of pharmacological therapy.

Non-pharmacological treatment is considered by physicians to fail in the majority of patients because they are not compliant. Therefore, a better approach for the physician could be to prescribe antihypertensive medication from the time of initial diagnosis while also actively advocating a range of lifestyle modifications. Pharmacological treatment of hypertension represents a cost-effective way for preventing cardiovascular and renal complications [4].

Popularization of the stepped-care approach

The stepped-care approach to the management of hypertension comprises titration of initial monotherapy with antihypertensive drug, followed by addition of other antihypertensive medications with complementary modes of action, as necessary, to achieve blood pressure control (Figure 2.3). The concept of stepped care in the treatment of hypertension was devised in the 1960s when it became apparent that many hypertensive patients were not treated systematically to normotensive blood pressure levels [5]. The first Joint National Committee Report on Detection, Evaluation and Treatment of High

Stepped-care approach to the management of hypertension

1. Monotherapy is initiated with a low dose of antihypertensive drug
2. Dose of antihypertensive drug is increased in an attempt to achieve blood pressure control
3. Antihypertensive drug is substituted or new antihypertensive(s) added until blood pressure control is achieved

Figure 2.3 Stepped-care approach to the management of hypertension.

Blood Pressure published the stepped-care approach in 1977 [6], and this committee has advocated it for the management of hypertension ever since. The principle of the stepped-care approach is to treat people with a chronic illness with as few drugs as possible at the lowest doses possible. It has been described as a simple approach that enables individualization [5], and has been the preferred strategy for managing hypertension [7–9]. An algorithm for stepped-care treatment of hypertension is shown in Figure 2.4 [10].

Monotherapy is inadequate for blood pressure control in the majority of hypertensive patients [2,7]. Hypertension is a complex, multifactorial disease (see Chapter 1); therefore, the interruption of a single physiological pathway is often insufficient to normalize blood pressure in hypertensive patients. The percentage of hypertensive patients who achieve meaningful blood pressure control (responders) ranges from 30% to 60% with any class of drug given as monotherapy (Figure 2.5). The remaining patients will require a combination of at least two (and perhaps as many as four) antihypertensive drugs to achieve blood pressure control.

One of the factors that contribute to poor blood pressure control is the reluctance of physicians to titrate antihypertensive medication (see Figure 2.5). Physicians may accept slightly elevated blood pressures (i.e. inadequate blood pressure control) in treated hypertensive patients rather than titrating medication, changing drugs or adding another drug. This reluctance by physicians to change the treatment regimens may be explained by concerns about increased incidence of adverse events and adverse metabolic consequences with increased dose, higher cost, and patient resistance to polypharmacy and/or higher doses of medication. Also, physicians may be reluctant to add a second antihypertensive drug to the treatment regimen because there are few data available on the efficacy of the second drug in terms of blood pressure lowering, the prevention of hard outcomes, and the incidence of cardiovascular disease [11]. Choosing which second drug to add to initial therapy is, therefore, largely empirical and is not based on the best standards of evidence-based medicine [11]. As blood pressure control with monotherapy

Algorithm for stepped-care treatment of hypertension

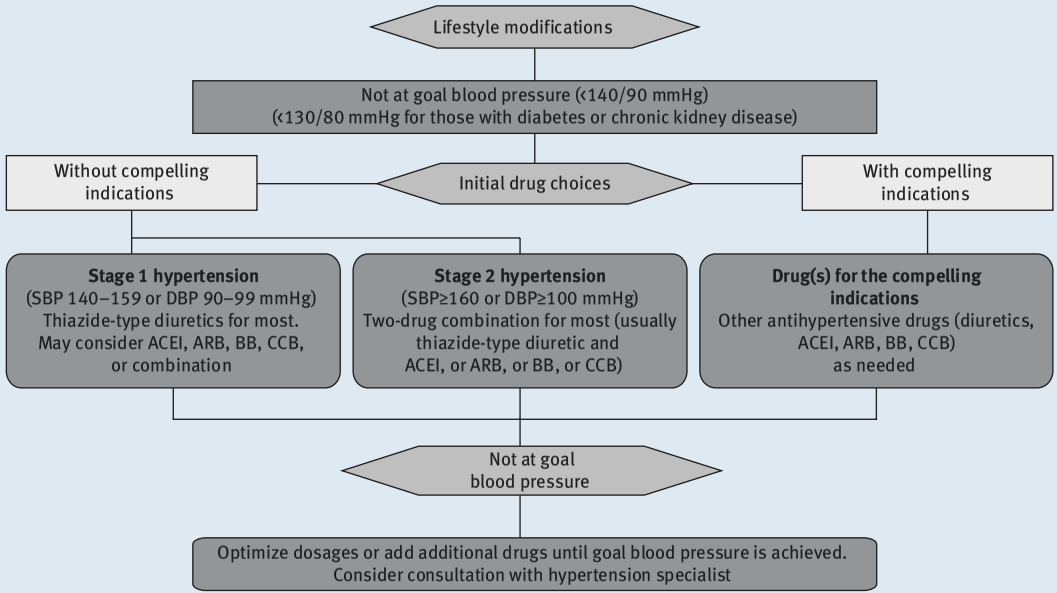


Figure 2.4 Algorithm for stepped-care treatment of hypertension. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, β blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure. Reproduced with permission from Chobanian AV, Bakris GL, Black HR et al, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289(19):2560–72.

Estimated efficacy of monotherapy in the treatment of hypertension

Drug	Responders (%)
Thiazides	50–55
β Blockers	45–50
Angiotension-converting enzyme inhibitors	50–60
Calcium channel blockers	40–60
α Blockers (prazosin)	35–40
Central agonists	30–35

Figure 2.5 Estimated efficacy of monotherapy in the treatment of hypertension. Reproduced with permission from Neutel JM. The use of combination drug therapy in the treatment of hypertension. Prog Cardiovasc Nurs 2002; 17(2):81–8. Data derived from Chobanian AV. Effects of beta blockers and other antihypertensive drugs on cardiovascular risk. Am J Cardiol 1987; 59(13):48–52F.

is very difficult or impossible to achieve in the majority of patients, and as physicians often will not titrate for inadequately controlled blood pressure, the stepped-care approach may result in a significant number of hypertensive patients being inadequately controlled. Indeed, current control rates for hypertension indicate that this approach is insufficiently effective in the management of hypertension [12].

The rationale for the stepped-care approach in the treatment of hypertension has been based mainly on the assumptions that monotherapy is more convenient than combination therapy, is associated with fewer side effects, enables easier identification of the drug causing an adverse event if one occurs, and is less expensive. These assumptions are incorrect [7] (see Chapter 3).

Fixed-dose combination therapy

Although monotherapy is often the preferred choice for initiating treatment of hypertension, this approach is only modestly effective in many patients and target blood pressure goals are often not reached [13]. There is increasing awareness that the elusive goal of a 'normal' blood pressure is achieved only if multiple drug therapy is used [14]. Most hypertensive patients require the co-administration of two or more drugs from different therapeutic classes to achieve a blood pressure of less than 140/90 mmHg [15].

There are two options for multiple drug therapy in the treatment of hypertension: one option, the stepped-care approach, is to add drugs sequentially until an effective multiple drug regimen is achieved (see above); the other option is fixed-dose combination therapy. Fixed-dose combination drugs combine two agents at each of the highest recommended doses into one tablet for convenience.

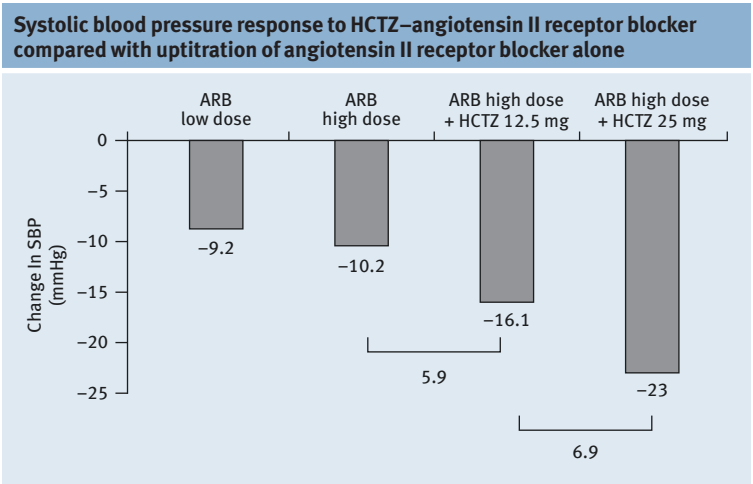


Figure 2.6 Systolic blood pressure response to HCTZ–angiotensin II receptor blocker compared with uptitration of angiotensin II receptor blocker alone. ARB, angiotensin II receptor blocker; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure. Reproduced with permission from Neutel JM. The role of combination therapy in the management of hypertension. Nephrol Dial Transplant 2006; 21(6):1469–74.

These are clearly distinguishable from low-dose combination drugs, which use low doses of each component drug to provide additive hypotensive effects with relatively few side effects. High-dose fixed combinations have become more popular with the introduction of well-tolerated drugs that have complimentary side effect profiles such as high dose angiotensin II receptor blocker (ARB) with hydrochlorothiazide (HCTZ) – HCTZ is potassium losing, ARBs are potassium sparing, and the net result is no change in potassium.

The concept of fixed-dose combination therapy was developed in the 1950s [14] and this treatment approach has been used since the 1960s [16]. The rationale behind fixed-dose combination therapy has remained constant since this approach was developed [14,17–21]:

- Two drugs, each typically working at a separate site, block different effector pathways; therefore, blood pressure-lowering effect may be enhanced when two drug classes are co-administered.
- One of the drugs may counteract counter-regulatory mechanisms that are triggered by the other drug, thereby potentially improving efficacy.
- Combination therapy is often associated with fewer adverse effects than high-dose monotherapy, which may lead to improved patient compliance.

- One component of a fixed-dose combination therapy may effectively neutralize some of the adverse effects of the other component.
- Simplicity of administration of fixed-dose combination therapy may improve compliance; thereby, preventing treatment failures that might result from missed doses.

Fixed-dose combination antihypertensive therapy has been available for almost a half-century. During that time, considerable progress has been made in the development of physiologically appropriate combinations [22]. Fixed-dose combination therapy has a proven record of reducing blood pressure. Many physicians have used fixed-dose combination therapy even when academic approval and enthusiasm for this therapeutic approach were lacking [14]. Fixed-dose combinations are becoming increasingly popular as physicians realize that bringing patients to blood pressure goal quickly is likely to improve clinical outcomes.

The inadequate control of systolic blood pressure is well known to be the major factor contributing to poor rates of blood pressure control. Systolic hypertension is volume dependent and, therefore, very responsive to diuretics. However, high doses of diuretics are associated with adverse events and metabolic adverse effects; therefore, the maximal dose of the diuretic, HCTZ, that should be administered to a hypertensive patient is generally agreed to be 12.5 mg. Nevertheless, many new combination drugs contain HCTZ at a 25 mg dose. The reasons for this are exemplified in Figure 2.6. This shows that uptitration of an ARB from a low dose to a high dose causes only a slight further reduction in systolic blood pressure, i.e. this drug has a flat dose–response curve. In contrast, the addition of HCTZ 12.5 mg to the high-dose ARB causes a very impressive further reduction in systolic blood pressure [23]. The addition of a further 12.5 mg HCTZ (total 25 mg HCTZ) may be expected to result in a flat dose–response curve; however, the additional 12.5 mg HCTZ causes a further decrease that is similar to that with the initial 12.5 mg [24]. This further decrease in systolic blood pressure is not unexpected, given that systolic hypertension is volume dependent and, therefore, very responsive to diuretics. The adverse event profile with high-dose fixed ARB and HCTZ combination therapy is similar to that with high-dose HCTZ monotherapy [25]. The complementary nature of these agents enables greater reductions in systolic blood pressure without substantially impacting the adverse event profile.

Simplification of the antihypertensive drug regimen is critical for the effective management of hypertension. Addition of antihypertensive drugs to a treatment regimen has been shown to significantly decrease compliance with treatment, even if the drugs are given once daily [25]. However, use of a fixed-dose combination therapy simplifies the dosing regimen and is associated

with improved compliance rates compared with monotherapy. Blood pressure control is achieved more rapidly with combination therapy compared with monotherapy (even at high doses), and this improves patient compliance and decreases the incidence of cardiovascular disease.

Low-dose combination therapy

The aim of low-dose combination therapy is to achieve blood pressure control with small doses of each agent, thereby eliciting fewer dose-dependent adverse effects than would be seen with higher doses of either agent as monotherapy. The concept of low-dose combination therapy arose mainly from experience with diuretics, which are useful in combination with other classes of antihypertensive drugs because they reduce the fluid retention often associated with vasodilators. Thiazide diuretics were initially prescribed, and were very effective, in high doses (at least 100 mg), but they were associated with many metabolic side effects and other adverse events. Lower doses of diuretics were shown still to provide blood pressure control, but with an improved adverse metabolic effect profile and adverse event profile. Most adverse effects with diuretics were, therefore, shown to be dose dependent. Diuretics are increasingly being prescribed in low-dose combination therapies to provide blood pressure control with minimal side effects.

As physicians recognize that most patients with hypertension require combination therapy to achieve blood pressure goals, fixed-dose preparations are becoming increasingly popular in clinical practice [26,27]. The inclusion of fixed-dose preparations, preferably fixed low-dose combinations, as a first-line option for the treatment of hypertension in hypertension guidelines in the USA and Europe has also widened their acceptance and increased their popularity [20]. Greater use of combination therapy has been associated with an increase in control rates.

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http://www.springer.com/978-1-908517-25-8

Combination Therapy in Hypertension
Neutel, J.M.
2011, VII, 84 p. 43 illus., 3 illus. in color., Softcover
ISBN: 978-1-908517-25-8