Invited review

Therapeutic strategies to lower and control high blood pressure

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Abstract

Epidemiological studies have documented that a close linear relationship exists between blood pressure reduction and cardiovascular disease. Evidence has also been provided that blood pressure reduction by antihypertensive drugs confers cardiovascular protection and that a more aggressive blood pressure target may provide greater cardiovascular benefits. This paper will review the main non-pharmacological as well as pharmacological approaches used to lower elevated blood pressure and thus reduce cardiovascular risk. The main advantages and limitations of each approach will be discussed in the light of the recent recommendations issued by the European Society of Hypertension/European Society of Cardiology.

Key words: antihypertensive treatment, lifestyle changes, drug treatment, guidelines.

Introduction

Hypertension is universally accepted as among the strongest prognostic markers of cerebrovascular disease, coronary heart disease and premature death [1], with blood pressure values bearing a continuous linear relationship with the incidence of cardiac and cerebrovascular events. It is also universally accepted that the hypertension-related risk is not irreversible and that antihypertensive treatment is effective in reducing the elevated incidence of cardiovascular morbid and fatal events associated with hypertension [2]. Evidence is also available that the degree of benefit largely depends on blood pressure lowering, "per se" (i.e., independently of how it is obtained) [3-5], and that treatment optimization requires blood pressure to be lowered to <140/90 mm Hg [6-8] in all hypertensive patients and to <130/80 mm Hg in patients at high or very high cardiovascular risk because of the coexistence of diabetes, a history of coronary or cerebrovascular disease, and possibly multiple risk factors [9]. The above means that a great deal of attention must be devoted to strategies that can effectively achieve target blood pressure values in the majority of hypertensive individuals. This paper reviews these strategies and addresses their main advantages and disadvantages.

Lifestyle changes

Lifestyle changes should be instituted, whenever appropriate, in all hypertensive patients, as well as in individuals with a blood pressure

<140/90 mm Hg in whom there is a high or very high risk condition, because, under these circumstances, drug-induced blood pressure reductions have been shown to be beneficial [10-13]. This is because their implementation may lower blood pressure, reduce the number and doses of the drugs that may have to be subsequently employed, and favourably affect total cardiovascular risk. The lifestyle measures that should be considered are: a) smoking cessation, b) weight reduction in overweight or obese patients, c) moderation of alcohol consumption, d) physical activity, e) reduction of salt intake, and f) increase in fruit and vegetable intake together with a reduction in saturated and total fat intake [9]. It should, however, be mentioned that lifestyle measures have never been tested for their effectiveness in preventing cardiovascular complications. Furthermore, their blood pressure lowering effect is small and, for some measures, absent in the long-term, with a high between-patient variability in the response. Salt restriction, for example, lowers blood pressure in a fraction of hypertensive patients, has no effect in an additional fraction, and occasionally causes a blood pressure increase due to stimulation of the sympathetic and the renin-angiotensin systems [14]. Finally, long-term compliance with lifestyle changes is extremely low [15]. Thus, there should be no fideist approach to this strategy. On the contrary, when lifestyle changes represent the main therapeutic option, patient follow-up should be intensified to avoid their living without an adequate blood pressure reduction, and to be prepared to timely institute drug treatment when lack of blood pressure control is detected.

Monotherapy with progressive increase in drug doses

Decades ago, a widespread opinion was to initiate drug treatment with one compound and to progressively increase its dose in case of an insufficient blood pressure lowering effect until blood pressure control was achieved. This strategy is now regarded as obsolete for several reasons. First, the blood pressure lowering effect of some drug classes (e.g., diuretics) does not show a substantial increase above a given dose range. Second, unfortunately this is not the case for side effects, which have a close relation with the dose employed for several drug classes, e.g., diuretics, β-blockers, and calcium antagonists [16]. Even when the side effect to dose relationship is less clear or absent, e.g., for angiotensin receptor antagonists and angiotensin-converting enzyme (ACE) inhibitors [16], a treatment strategy based on a progressive increase in the dose of the initial drug should not be encouraged because, in several instances, this means a substantial increase in cost. Furthermore, even when high doses are used, the ability of monotherapy to effectively reduce blood pressure does not exceed 50% of the hypertensive population, of which no more than 20-25% may attain control [17, 18].

Sequential monotherapy

A popular strategy in clinical practice is to switch from one monotherapy to another in the hope of finding the monotherapy which controls blood pressure and thus avoid use of multiple drugs. This has a scientific basis because, in a given individual, the antihypertensive response to one class of drugs does not invariably reflect that to a different class of drugs [19], suggesting that the ineffectiveness of one monotherapy does not preclude an adequate response to another. However, as I have mentioned above, the ability of any monotherapy to control blood pressure is limited, presumably because a single mechanism of action is frequently ineffective against a multiregulated variable such as blood pressure. In addition, it is obvious that, because the full effect of several antihypertensive drugs may become evident only after several weeks, sequential monotherapy is a time-consuming strategy that may prevent identification of successful treatment for months, leading to physician's frustration and loss of patients' confidence, motivation, and compliance. Thus, unless required from the absence of any blood pressure reduction or the appearance of serious side effects, substitution of one monotherapy with another cannot be regarded as the best strategy to control blood pressure in the general hypertensive population.

Stepped-care strategy

The stepped-care strategy consists of initial monotherapy followed, once the proper dose of the first drug is employed, by the addition of a second, a third, and even a fourth drug, until blood pressure control is achieved (Figure 1). This is recommended by international guidelines because, compared to monotherapy, progression to combination treatment guarantees a much greater blood pressure lowering effect [16] and rate of blood pressure control, with favourable consequences also for the incidence of side effects and the acceptance of prescribed treatment by the patient [20]. Recommendations on the initial drugs to be used, as well as on the subsequent combinations between two and three drugs, have changed considerably in the last three decades [21-24]. The latest guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) [9] recommend initiating treatment with a thiazide diuretic, an ACE inhibitor, a calcium antagonist, an angiotensin

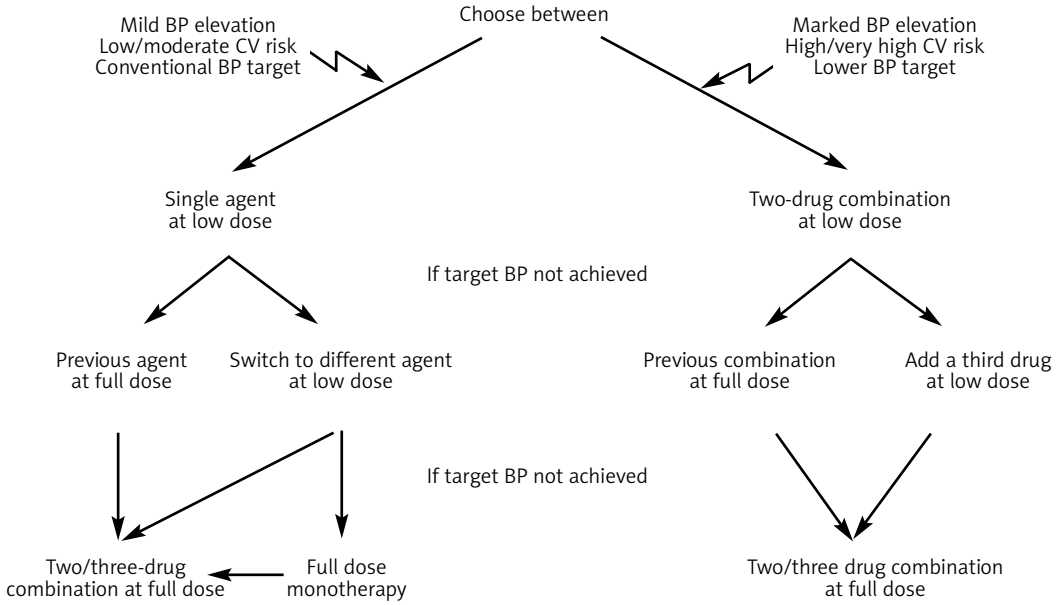

Figure 1. Criteria to be adopted for choosing between monotherapy and combination treatment, according to the European Society of Hypertension /European Society of Cardiology 2007 Guidelines. Figure taken from ref. [9]
BP – blood pressure, CV – cardiovascular

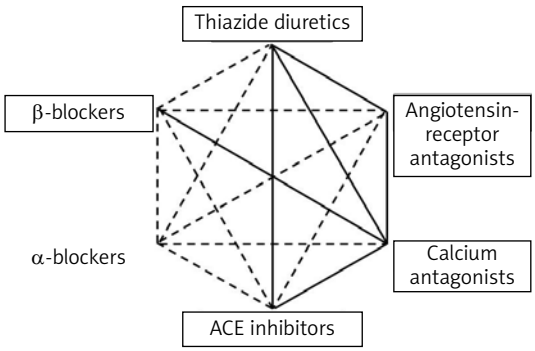

Figure 2. Possible combinations between different classes of antihypertensive drug treatments, according to the European Society of Hypertension/ European Society of Cardiology 2007 Guidelines. Figure taken from ref. [9]
The preferred combinations in the general hypertensive population are represented as thick lines. The frames indicate classes of agents proven to be beneficial in controlled intervention trials

receptor antagonist, or a β-blocker because, for each of these classes, there is evidence of cardiovascular protection from large-scale randomized trials [1, 2, 5, 25]. In the above-mentioned Guidelines when dealing with the choice of antihypertensive drugs it is explicitly mentioned that "each of the recommended classes may have specific properties, advantages and limitations which are discussed thereafter so that doctors may make the most appropriate choice in the individual patient" [9]. Guidelines also recommend combining drugs (after a full dose of the initial monotherapy has been shown to be ineffective) according to a few well defined criteria. First, the drugs to be combined should have different and complementary mechanisms of action. Second, the blood pressure lowering effect of the combination should be greater than that of the combination components, possibly also with a reduction of their side effects. Third, compared to its components, the combination should also have a greater protective effect on hypertension-related organ damage and, at least potentially, on the incidence of cardiovascular morbid and fatal events. With the exception of the last requirement (which is difficult to investigate and for which evidence is limited), several two-drug combinations meet the above criteria, and their use can thus be recommended. As shown by the tick lines of Figure 2 [9] they are the combination of a thiazide diuretic with an ACE-inhibitor or an angiotensin receptor antagonist, a calcium antagonist with an ACE-inhibitor and an angiotensin receptor antagonist, a calcium antagonist with a thiazide diuretic, and a β-blocker with a calcium antagonist of the dihydropyridine type. However, other combinations (those indicated in Figure 2 by the dashed lines) can also be used and may indeed offer advantages or even be electively required in some clinical circumstances, though less advantageous in others. The time-honoured combination of a β-blocker with a thiazide diuretic, for example, is not recommended in patients with a metabolic syndrome because it may further increase the already high risk of incident diabetes associated with this condition [2, 6, 26]. It can, on the other hand, be profitably employed in hypertensive patients with congestive heart failure, angina pectoris, or a recent history of myocardial infarction [9], i.e., conditions

in which β-blockers have been shown to be protective and the addition of diuretics to the treatment regimen may be important to improve the symptomatic picture or to achieve blood pressure control. The combination of an ACE inhibitor and an angiotensin receptor antagonist, although probably not particularly effective for achieving blood pressure control in the general hypertensive population, may enhance the ability of antihypertensive treatment to reduce proteinuria [27] in patients with renal damage, with favourable consequences for renal survival, and cardiovascular risk [28]. Although in clinical practice α-blockers are now rarely used as first-choice drugs, they can be usefully combined with several other drugs in the attempt to bring blood pressure values under control, and this has indeed been successfully done in important trials [29]. This is the case also for central agents, as well as for drugs such as those opposing the effect of aldosterone, which can exert an independent protective effect in heart failure [30] and help achieve blood pressure control when part of the multidrug treatment regimen in resistant hypertension [31].

Two further aspects of stepped-care treatment strategies need to be briefly mentioned. First, the importance of combination treatment for achieving blood pressure control cannot be overemphasized because it is also indisputably documented by its exceedingly extensive use in most recent trials aimed at achieving blood pressure control. Secondly, in the stepped-care treatment strategy, the role of combinations of more than two drugs is by no means marginal. This is shown in Figure 3, which illustrates that, in several trials, an average of more than two or even three drugs were used. In three or more than three drug combinations, inclusion of a diuretic is often important.

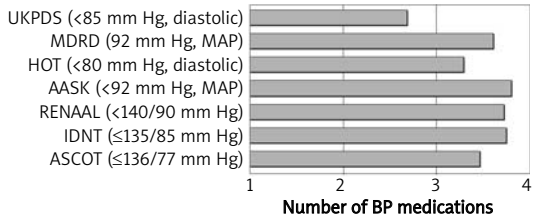

Figure 3. Number of medications required to achieve blood pressure (BP) target in different clinical trials

UKPDS – United Kingdom Prospective Diabetes Study, MDRD – Modification of Diet in Renal Disease, HOT – Hypertension Optimal Treatment, AASK – African American Study of Kidney Disease, RENAAL – Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan, IDNT – Irbesartan Diabetic Nephropathy Trial, ASCOT – Anglo-Scandinavian Cardiac Outcomes Trial, MAP – mean arterial pressure

Combination treatment as first choice

The 2007 ESH-ESC Guidelines [9] recommended considering combinations of two antihypertensive drugs, not only as a step frequently necessary after an unsuccessful monotherapy, but also as an alternative to monotherapy to start antihypertensive treatment. This approach may indeed have several advantages. First, by using a combination as first-step treatment, either combination component can be given in the low dose range, which is more likely to be free of side effects compared to full dose monotherapy, keeping in mind that side effects are the major cause of low compliance and withdrawal from treatment [20]. Second, as mentioned above, the frustration of repetitively and mainly searching for an effective monotherapy may be avoided. Third, starting treatment with a two-drug combination may allow blood pressure targets to be achieved earlier than with monotherapy, which may be of crucial importance in high-risk patients in whom even a few months of ineffective blood pressure control can lead to an increased incidence of cardiovascular morbid and fatal events [6]. The approach proposed by the 2007 ESH-ESC Guidelines [9] is shown in Figure 1. Physicians may favour initial monotherapy when hypertension is mild and the total cardiovascular risk not high or very high. They may on the other hand decide to use combination treatment as the first step in patients with a marked blood pressure elevation or a high or very high cardiovascular risk. This is justified by the need to obtain a pronounced blood pressure reduction in a relatively short time as well as to hit a low blood pressure target, which is very difficult to achieve with a single drug treatment regimen.

Fixed combinations

An issue which has long been debated is whether fixed combinations, i.e., predetermined doses of the combination components in the same tablet, should be preferred to extemporaneous combinations, i.e., separate administration of the combination components. The most obvious merit of extemporaneous combinations is flexibility, that is, the possibility of increasing the use of one drug when that of the other is kept unchanged in relation to the physician's perception of the chance of achieving blood pressure control and cardiovascular protection with no or limited side effects. Furthermore, when drugs are given separately, their role in the appearance of side effects can be more easily detected, and drug substitution more rationally effected. However, fixed-dose combinations reduce the number of tablets to be taken daily, which has a measurable effect on patients' compliance. Their level of acceptance by the doctor is also high, and this may substantially contribute to improving a major problem of hypertension treatment today, i.e., low rate of blood pressure control. For some drugs, fixed combinations are now provided at different doses, which can minimize the problem of reduced flexibility.

Table I. Conditions favouring use of some antihypertensive drugs versus others according to ESH/ESC guidelines

Thiazide diuretics	β-blockers	Calcium antagonists (dihydropyridines)	Calcium antagonists (verapamil/diltiazem)
• Isolated systolic hypertension (elderly) • Heart failure • Hypertension in blacks	• Angina pectoris • Post-myocardial infarction • Heart failure • Tachyarrhythmias • Glaucoma • Pregnancy	• Isolated systolic hypertension (elderly) • Angina pectoris • LV hypertrophy • Carotid/coronary atherosclerosis • Pregnancy • Hypertension in blacks	• Angina pectoris • Carotid atherosclerosis • Supraventricular tachycardia
ACE inhibitors	**Angiotensin receptor antagonists**	**Diuretics (antialdosterone)**	**Loop diuretics**
• Heart failure • LV dysfunction • Post-myocardial infarction • Diabetic nephropathy • Non-diabetic nephropathy • LV hypertrophy • Carotid atherosclerosis • Proteinuria/microalbuminuria • Atrial fibrillation • Metabolic syndrome	• Heart failure • Post-myocardial infarction • Diabetic nephropathy • Proteinuria/ microalbuminuria • LV hypertrophy • Atrial fibrillation • Metabolic syndrome • ACEI-induced cough	• Heart failure • Post-myocardial infarction	• End stage renal disease • Heart failure

ACEI – ACE inhibitors, LV – left ventricle

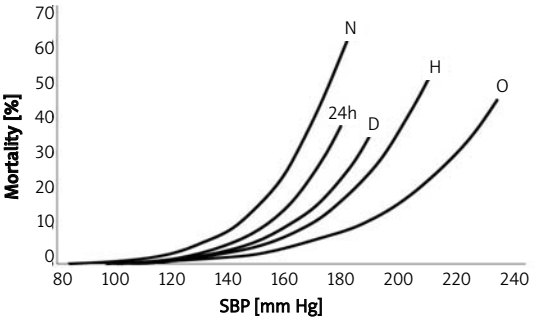

Figure 4. Office (O), Home (H) and 24-h mean (24 h) daytime (D) and nighttime (N) systolic blood pressure (SBP) at entry as predictors of 11-year risk of cardiovascular death in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study. Modified from ref. [32]

Selection of individual drugs or drug combinations

Identification of the drug to be used as first-step antihypertensive treatment has always been a debated issue. However, this can now be considered somewhat outdated because, if combination treatment is needed in most patients (and treatment must be continued for life), which drug is used alone in the first few weeks after treatment initiation is of marginal relevance. The important issue appears more to be which drug(s) should be included in a combination, given that drug classes (and sometimes even drugs within the same class) differ in the frequency of the side effects they may induce, as well as for their effects on risk factors, organ damage, cause-specific events, and protective properties in specific groups of patients (Table I). According to 2007 ESH-ESC guidelines [9], the general criteria on which to base selection of a given drug or drug combination are the following: 1) the previous favourable or unfavourable experience of the individual patient with a given drug class, both in terms of blood pressure effects and tolerability; 2) the effect of drugs on cardiovascular risk factors in relation to the cardiovascular risk profile of the individual patient; 3) the presence of subclinical organ damage, renal disease, cerebrovascular disease, or diabetes, which may be more effectively treated by some drugs than by others; 4) the presence of coexisting disorders, because their treatment may interfere with antihypertensive drugs, both pharmacodynamically and pharmacokinetically; 5) the cost of drugs, either to the individual patient or to the healthcare provider, although cost considerations should never predominate over the need to give patients the most protective and best tolerated treatment. Finally, physicians should give preference to drugs that effectively reduce blood pressure throughout each 24-hour period, because 24-hour blood pressure values are prognostically important over and above office blood pressure values (Figure 4) [32]. This will allow better blood pressure control to be achieved and thus greater cardiovascular protection.

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