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Management of essential hypertension

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Introduction: Epidemiological studies have unequivocally shown that hypertension (HT)is a major cardiovascular (CV) risk factor and that a direct linear relationship exists between the severity of the blood pressure (BP) elevation and the occurrence of CV events.

Areas of agreement and controversy: The beneficial effects of the BP-lowering interventions have been recognized since a number of years. These include not only the reduction in CV morbidity and mortality but also the regression (or the delay of progression) of HT-related end-organ damage, such as left ventricular hypertrophy, vascular remodelling, endothelial dysfunction and renal damage. Along with these well-established features, antihypertensive drug treatment still faces a number of unmet goals and unanswered questions, such as the target BP values to achieve in high-risk patients, the threshold of treatment in low-risk patients as well as the choice of the therapeutic approach more likely to offer greater CV protection.

Conclusion: Despite unmet goals, antihypertensive treatment has provided throughout the years successful results. Future efforts will be need to achieve a better BP control in the population and thus to obtain a greater CV protection.

Keywords: hypertension/antihypertensive treatment/blood pressure control/cardioprotection/compliance to treatment

Introduction

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Hypertension (HT) represents a major health problem for the world population and is universally regarded as among the strongest prognostic markers of cardiovascular (CV) disease. A large amount of data support this statement.[1] First, no single factor is more important for increasing CV morbidity, CV mortality and overall mortality than a high blood pressure (BP) state. Secondly, HT is common throughout the world, with a prevalence of 15–20% in adults and 30–40% in elderly age strata. Thirdly, diseases associated with HT are mostly of a chronic disabling nature. Furthermore, in most instances, they require frequent hospitalizations, with expensive drug treatment and

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management procedures. This is exemplified by stroke, for which HT represents the most important risk factor (followed by cigarette smoking), together with coronary heart disease, congestive heat failure and chronic renal insufficiency.[1–4] Coronary heart disease is three times more frequent in hypertensive than in normotensive individuals, and the clinical manifestations of this condition (angina, myocardial infarction and sudden death) are no less dependent upon elevated BP than upon elevated serum cholesterol.[1–4] Finally, an elevated BP is, with diabetes, the major contributing factor for end-stage renal failure.[1–4]

This paper will first review the benefits of antihypertensive treatment. This will be followed by an overview of the therapeutic strategies employed to reduce elevated BP. It will finally examine the unmet goals of antihypertensive treatment and the unanswered questions related to the antihypertensive therapeutic intervention.

Benefits of antihypertensive treatment

Antihypertensive treatment is accompanied by a reduction in HT-related CV risk.[5–7] Originally demonstrated for malignant HT, this has been shown for virtually all types of HT, ranging across most spectra of severity and age. The risk is also reduced when treatment is implemented in isolated systolic HT, whose prevalence shows a marked progressive increase above 70 years of age. It has also been demonstrated that nearly all single complications of HT are reduced by treatment. Thus, in patients with mild-to-severe HT, a 5–6 mmHg reduction in diastolic BP is accompanied over a period of 5 years by a 40% reduction in the incidence of stroke. Similarly, clinical manifestations of coronary heart disease are reduced by about 15%, whereas in both middle-aged and elderly hypertensive individuals a marked reduction in heart failure is achieved by such a reduction in BP.[5,6]

There is also evidence that both in severe and in mild HT antihypertensive treatment favourably affects renal function and structure, preventing the development and/or delaying the progression of renal failure.[6,7] Finally, evidence is available that a BP reduction in hypertensive patients with diabetic nephropathy reduces microalbuminuria, albuminuria and the rate of renal deterioration. Although some antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists, seem to be more effective than others,[8,9] the associated nephroprotection is at least in part the result of the reduction in BP. Indeed, even in normotensive subjects with diabetic nephropathy, a BP reduction has been recently shown to be nephroprotective.[1] The concept that the favourable effects of

antihypertensive treatment depend on the BP-lowering effects *per se* also apply to the impact of treatment on other organ damage such as left ventricular hypertrophy, vascular remodelling, endothelial dysfunction and on global CV risk as well.[6,7] It may therefore be concluded that antihypertensive treatment is associated with a clear-cut benefit and that the incidence of all major CV complications of HT is substantially reduced by the BP-lowering effects of the therapeutic intervention.

Life-style changes

Life-style changes should be instituted, whenever appropriate, in all hypertensive patients as well as in individuals with a BP $<140/90$ mmHg, in whom there is a high- or very high-risk condition, because, under these circumstances, drug-induced BP reductions have been shown to be beneficial.[1] This is because their implementation may lower BP, reduce the number and doses of the drugs that may have to be subsequently employed and favourably affect total CV risk. The life-style measures that should be considered are: (i) smoking cessation, (ii) weight reduction in overweight patients, (iii) moderation of alcohol consumption, (iv) physical activity, (v) reduction of salt intake and (vi) increase in fruit and vegetable dietary intake together with a reduction in saturated and total fat intake.[1] It should, however, not be forgotten that life-style measures have never been tested for their ability to prevent CV complications. Furthermore, their BP-lowering effect is generally modest and for some measures absent on the long term, with a high between-patients variability in the response. Restriction of sodium intake, for example, lowers BP in a fraction of hypertensive patients, has no effect in an additional fraction and in rare cases actually triggers a BP increase due to stimulation of the sympathetic and the renin–angiotensin systems.[10]

Finally, long-term compliance with life-style changes is extremely low.[1] Thus, there should be a skeptical attitude to this strategy. When life-style changes represent the main therapeutic option, patients follow-up should be intensified to avoid their living without an adequate BP reduction, and physicians should be prepared to institute timely drug treatment when lack of BP control is detected.

Single-drug treatment

Monotherapy with progressive dose increase

Decades ago, a widespread opinion was to initiate drug treatment with one compound and to progressively increase its dose until BP control

was achieved. This strategy is now regarded as obsolete for several reasons. First, the BP-lowering effect of some drug classes (e.g. diuretics) does not show a substantial increase above a given dose range.

Secondly, unfortunately side effects have a close relation to the dose employed for several drug classes, e.g. diuretics, beta-blockers and calcium antagonists.[11] Even when the side effect–dose relationship is less clear or absent, e.g. for angiotensin receptor antagonists and ACE inhibitors,[11] 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 BP does not exceed 50% of the hypertensive population, of which no more than 20–25% may attain control.[12]

Sequential monotherapy

A popular strategy in clinical practice is to switch from one monotherapy to another in the hope to find the monotherapy which controls BP and thus avoid the 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, suggesting that the ineffectiveness of one monotherapy does not preclude an adequate response to another. However, as mentioned above, the ability of any monotherapy to control BP is limited, presumably because a single mechanism of action is frequently ineffective against a multiregulated variable such as BP. 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 BP reduction or the appearance of serious side effects, substitution of one monotherapy with another cannot be regarded as the best strategy to use to control BP in the general hypertensive population.[1]

Drug combination treatment

The stepped-care strategy

The stepped-care strategy consists of an 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 BP control is achieved. This is recommended by international guidelines because, compared with monotherapy, progression to combination treatment guarantees a much greater BP-lowering effect[1] and rate of BP control with favourable consequences also on the incidence of side effects and acceptance of the prescribed treatment by the patient.[13] Recommendations on the initial drugs to be used, as well as on the subsequent combinations between two and three drugs, have considerably changed in the last three decades. The already mentioned guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC)[1] recommend to initiate treatment with a thiazide diuretic, an ACE-inhibitor, a calcium antagonist, an angiotensin receptor antagonist or a beta-blocker because for each of these classes, there is evidence of CV protection from large-scale randomized trials (Fig. 1).[1–5,7–9] They also recommend to combine drugs (after a full dose of the initial monotherapy has been shown to be ineffective) according to few well-defined criteria. First, the drugs to be combined should have different and complementary mechanisms of action. Secondly, the BP-lowering effect of the combination should be greater than that of the combination components, possibly also with a reduction of their side effects. Thirdly, compared with its components, the combination should also have a greater protective effect on HT-related organ damage and, at least potentially, on the incidence of CV morbid and fatal events. With the exception of the last requirement (which is difficult to be investigated and on which evidence is limited), several two-drug combinations meet the above criteria and their use can thus be recommended. As shown by the thick lines in Figure 1, they are the combination of

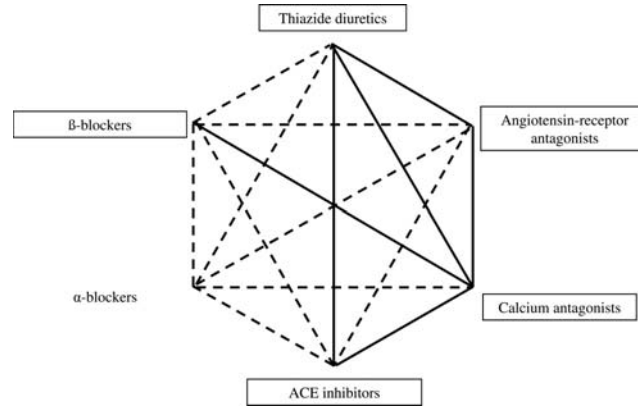

Fig. 1 Possible combinations between different classes of antihypertensive drugs. The preferred combinations are shown as thick lines. The frames indicate classes of agents proven to be beneficial in controlled intervention trials. Modified from Guidelines Committee,[1] by permission.

a thiazide diuretic with an ACE-inhibitor or an angiotensin receptor antagonist, a calcium antagonist with a thiazide diuretic and a beta-blocker with calcium antagonist of the dihydropiridine type. However, other combinations (those indicated in Fig. 1 by the dashed lines) can also be used and may indeed offer advantages or even be electively required in some clinical circumstances, although being less advantageous in others. The time-honoured combination of a beta-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.[1]

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,[1] i.e. conditions in which beta-blockers have been shown to be protective and addition of diuretics to the treatment regimen may be important to improve the symptomatic picture or to achieve BP control. The combination of an ACE-inhibitor and an angiotensin receptor antagonist, although promising, in theory, was not confirmed by the recent Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and thus, at least at high dosage and in older high-risk subjects, should not be recommended in clinical practice.[14]

Two further aspects of the stepped-care treatment strategies need to be briefly mentioned. First, the importance of combination treatment for achieving BP control cannot be overemphasized because it is also indisputably documented by its exceedingly common use in most recent trials aimed at achieving BP control.[12] Secondly, in the stepped-care treatment strategy, the role of combinations of more than two drugs is by no means marginal. This is supported by the evidence that in several trials, an average of more than two or even three drugs was used. In the three (or more than three) drug combinations, inclusion of a diuretic agent is often important.

Combination drug treatment as first treatment choice

The 2007 ESH/ESC guidelines[1] and the recently published update guidelines document[15] recommended to consider combination 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. Although initiating treatment with two drugs may potentially expose the patient to an unnecessary agent, this approach may 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

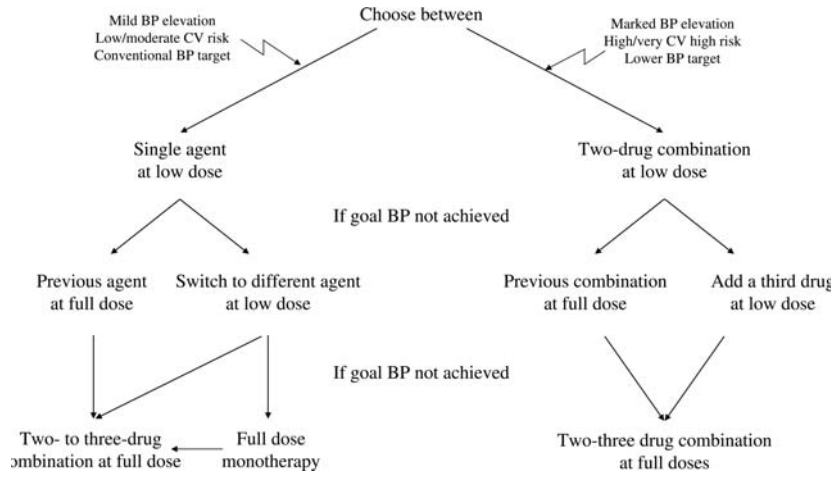

Fig. 2 Criteria to be adopted for choosing between monotherapy and combination treatment. Modified from Guidelines Committee,[1] by permission.

effects compared with full-dose monotherapy, keeping in mind that side effects are the major cause of low compliance and withdrawal from treatment.[16]

This has important drawbacks, given the evidence that a high compliance to treatment and a better BP control are associated with less events and greater survival.[17] Secondly, as mentioned above, the frustration of repetitively and mainly searching for an effective monotherapy may be avoided. Thirdly, starting treatment with a two-drug combination may allow BP targets to be achieved earlier than with monotherapy, which may be of crucial importance in high-risk patients in whom even few months of ineffective BP control lead to an increased incidence of CV morbid and fatal events.[18] The approach proposed by the 2007 ESH/ESC Guidelines[1] is shown in Figure 2. Physicians may favour initial monotherapy when HT is mild and the total CV 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 BP elevation or a high or very high CV risk. This is justified by the need to obtain a pronounced BP reduction in a relatively short time as well as to hit a low BP target, which is very difficult to achieve with a single-drug treatment regimen.

Fixed drug 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 BP control and CV 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.[1] Their level of acceptance by the doctor is also high and this may substantially alleviate a major problem of HT treatment today, i.e. low rate of BP control. For some drugs, fixed combinations are now provided at different doses which can minimize the problem of the reduced flexibility.

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 over life time), it is of marginal relevance which drug is used as monotherapy during the first few weeks after treatment initiation. 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 for 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. Suffice here to mention that according to 2007 ESH/ESC guidelines[1] and the update document[15] the general criteria on which to base selection of a given drug or drug combination are the following. First, the previous favourable or unfavourable experience of the individual patient with a given drug class in terms of both BP effects and tolerability. Secondly, the effect of drugs on CV risk factors, in relation to the CV risk profile of the individual patient. Thirdly, the presence of subclinical organ damage, renal disease, cerebrovascular disease or diabetes, which may be more effectively treated by some drugs than by others. Fourthly, the presence of coexisting disorders also because their treatment may interfere with antihypertensive drugs both pharmacodynamically and pharmacokinetically. Fifthly, the cost of drugs either to the individual patient or to the health-care 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 BP throughout the 24 h, because 24 h BP values are prognostically important over and above office BP values.[19]

Unmet goals and open questions

Despite the enormous progress obtained in the past 20 years in the treatment of HT, several goals of antihypertensive treatment cannot be regarded as achieved. This refers in particular to the issue related to BP control, given the evidence, collected both in clinical trials and in current clinical practice,[20–25] that BP control is unsatisfactory and that this is particularly the case for systolic BP. A further at least partially unmet goal of antihypertensive treatment refers to the need that all the BPs available in current clinical practice (clinic, home and 24 h BP) should be controlled by antihypertensive treatment (Table 1).

This is because of the evidence, collected by our group in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) Study, that each of these pressures carries an independent risk and thus needs to be properly managed.[26]

Along with the above-mentioned unmet goals, modern antihypertensive drug treatment needs to face with a number of unanswered questions. These refer, for example, to the issue concerning the level of BP to which drug treatment should be initiated in specific groups of patients, such as those with BP values within the high-normal range but a low CV risk.[27] These also refer to the level of BP to be achieved in high-risk patients or in diabetic hypertensive patients.[27] The issue has also been discussed in the already mentioned recent update document of the ESH guidelines.[15]

Table 1 Therapeutic issues to be addressed by future investigations.

Unmet goals of antihypertensive drug treatment
Improved organ protection
Better systolic BP control
Control of clinic, home and 24 h BP
Better treatment of associated risk factors
Favourable impact of antihypertensive drug treatment on BP variability
Unanswered questions about antihypertensive drug treatment
To what levels systolic BP should be safely lowered?
Should subjects with normal BP, but elevated CV risk, be pharmacologically treated?
Should patients with a hypertensive grade 1 state, but low CV risk, be pharmacologically treated?
Should low-dose combination drug treatment become the initial antihypertensive therapeutic approach?
Which therapeutic indications, if existing, for specific drug combinations (e.g. ACE-inhibitors/angiotensin II receptor blockers)?

The suggested recommendation is that although no evidence is available from clinical trials, the target BP to be reached during treatment should be <140/90 mmHg and closed to 130/80 mmHg. Finally, guidelines and recommendations emphasize the importance of the combination drug treatment approach to lower BP values to target.[1,15] They also emphasize the need to improve patient's compliance as well as to obtain a better control of concomitant risk factors. This emphasizes the potentials of the polypill approach (which includes an antihypertensive drug, a statin and aspirin), with promising results for CV risk profile as the results of a recent clinical trial do suggest.[28]

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