CONTROVERSY

Treatment of Hypertension: Monotherapy or Combination Therapy

Monotherapy In Hypertension

ALFONSO BRYCE [1]

Is there a place for monotherapy?

Yes, there is a place for monotherapy.

According to the Seventh report of the Joint National Committee in 2003 (1) and the European guidelines from 2007 (2) and 2009 (3), the first step in hypertension control is changing lifestyle before initiating medical treatment.

According to the baseline blood pressure and the presence or absence of target organ damage and risk factors, it appears reasonable to initiate therapy either with a low dose of a single agent or with a low-dose combination of two agents. If low-dose monotherapy is chosen and blood pressure control is not achieved, the next step is to switch to a low dose of a different agent, or to increase the previous agent to full dose. Combination therapy may be used according to the circumstances (Figure 1) if target blood pressure values are not achieved: systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg in adults and <130/80 in special populations (patients with diabetes, equivalent diseases or chronic renal diseases).

Non-pharmacological measures may suffice to normalize blood pressure in patients with grade 1 (mild) hypertension. Grade 2 hypertension may be treated with monotherapy, with two drugs or with fixed-dose combinations (Figure 2). The 2003 American guidelines recommend the use of diuretics as initial therapy for most patients; however, this indication is currently controversial.

Before initiating any antihypertensive treatment, patient's risk should be stratified following the Latin American guidelines, according to the II Latin American Consensus Statement on Hypertension from 2008 and published in 2009, (4) which were based on the European guidelines. Patients with prehypertension or high-normal blood pressure have greater risk depending on the presence of risk factors, especially those with three risk factors, subclinical target organ damage or metabolic syndrome and, undoubtedly, diabetics. In this group of patients who have certain degree of cardiovascular impairment, pharmacological treatment should be considered with monotherapy associated with lifestyle modifications. The Latin American guidelines have incorporated an interesting concept: "societal risk conditions" which implies that patient's risk might vary according to the environment, cultural conditions and availability to access to medical care. For this reason, these guidelines mention to pay special attention to the economic and

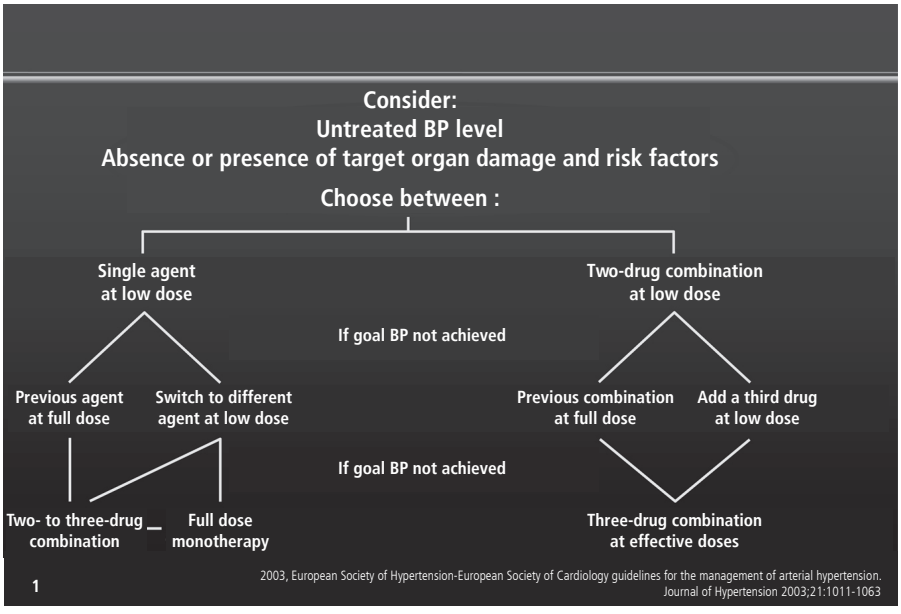

Fig. 1. Choosing between monotherapy and combined therapy

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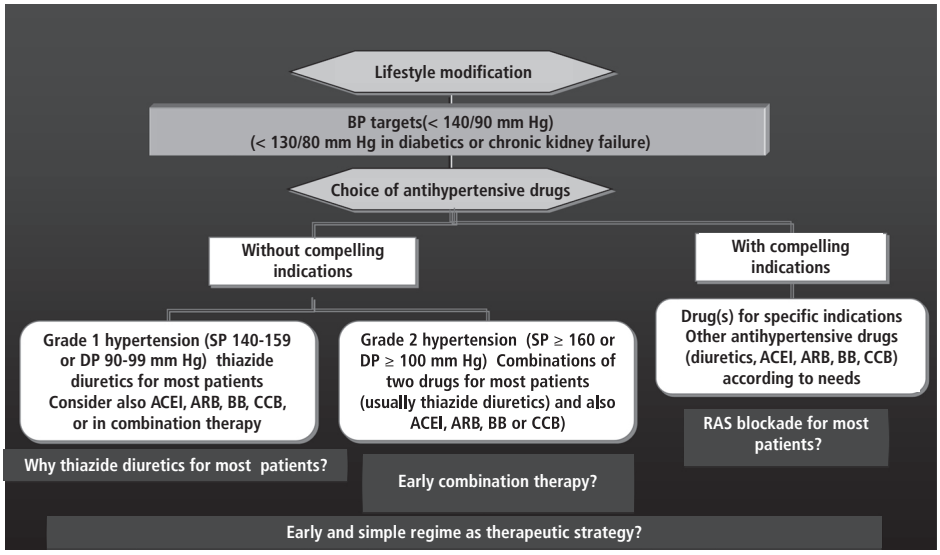

Fig. 2. Algorithm for treatment of hypertension (JNC 8; Williams B; 2009).

social conditions in Latin America which should be considered another risk factor.

Prehypertension, a concept developed by the American guidelines, might be currently questioned and should be better defined. For this reason, some experts met (5) and informed to be worried and concerned about how:

1. To analyze the impact of delayed and inappropriate diagnosis.
2. To recognize the importance of early diagnosis and aggressive treatment.
3. To recommend individual treatment options.
4. To discuss the impact of effectively controlling hypertension on the development of co-morbidities and diabetes mellitus.
5. To evaluate the benefit of well-managed hypertension (quality of life and productivity).

We might ask ourselves: is prehypertension relevant?

Let's consider some concepts:

– Prehypertension progresses to clinical hyperten sion at a rate of 19% over 4 years. The risk of car diovascular events increases progressively throughout the range of blood pressure.
– High normal blood pressure increases cardiovascu lar risk in both men and women.
– As compared with optimal blood pressure, high-normal blood pressure is associated with higher relative risk if cardiovascular events. (6)

Then, the new question would be: should we treat all patients with prehypertension? (7) It is currently accepted that pharmacological treatment associated with lifestyle modifications should be initiated in patients with high-normal blood pressure (prehypertensive subjects) with multiple risk factors, subclinical target organ damage or metabolic syndrome, and undoubtedly, in diabetics.

The preventive effect of lowering blood pressure levels and the additional effects of antihypertensive agents for risk factors control are important for the cardiovascular continuum of hypertension. Subclinical target organ damage should also be evaluated before the development of the established disease. Early markers of the disease are omnipresent before blood pressure elevation is sustained; therefore, hypertension cannot be classified solely by blood pressure thresholds. (8)

Management and treatment of prehypertension is controversial. Patients with prehypertension have greater risk than patients with normal blood pressure but lower compared to hypertensive patients. For this reason, Law et al. (9) stated in 2009 that "the use of blood pressure lowering drugs should not be limited to people with high blood pressure."

On the contrary, Arguedas et al. (10) demonstrated that lowering blood pressure levels is not associated with a significant reduction in the most relevant outcomes, including total mortality, myocardial infarction, stroke and congestive heart failure, among others. The authors concluded that there is no evidence of success in achieving blood pressure targets below 140 mm Hg and 90 mm Hg for systolic and diastolic blood pressure, repectively.

In patients with prehypertension and in "high-risk" hypertensive patients, reducing blood pressure below 120/70 mm Hg may magnify the "J-curve", particularly in the group of patients with diabetes and coronary artery disease. (11) The J-curve refers to impaired coronary perfusion during diastole which is more evident when pulse pressure is higher, increasing the risk of coronary events. This evidence was demonstrated in the INVEST study (12) which reported that lowering systolic blood pressure < 130 mm Hg in patients with diabetes and coronary artery disease was associated with adverse outcomes. In addition, as the ACCORD study showed that reducing systolic blood pressure < 115 mm Hg was associated

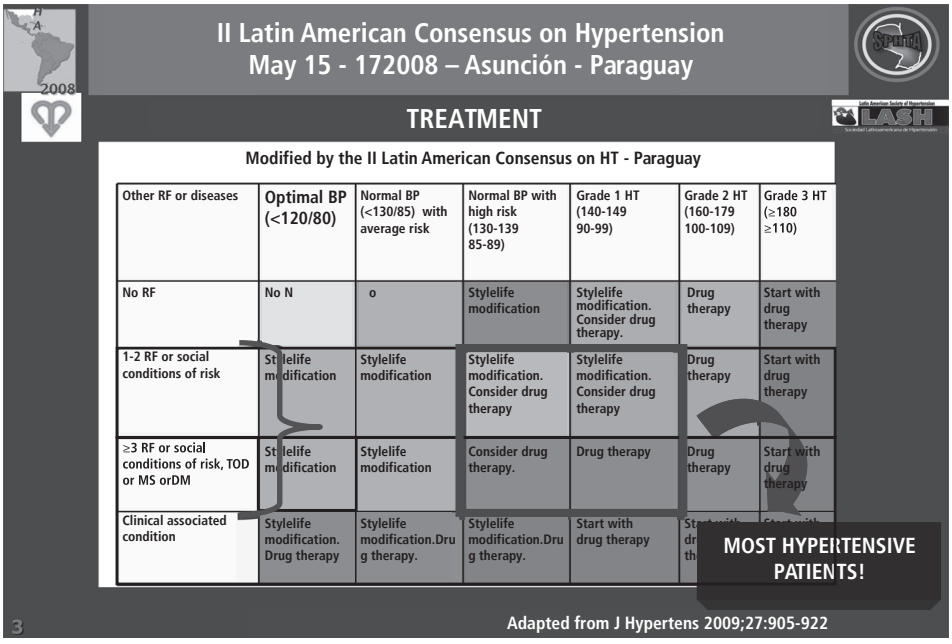

Fig. 3. Treatment of hypertension according to the Latin American Guidelines (II Latin American Consensus Statement on Hypertension).

with greater mortality, (13) shouldn't we reconsider blood pressure targets in high-risk patients, as those with diabetes and coronary artery disease?

The concept of lowering only blood pressure levels to reduce cardiovascular risk should be revisited, as controlling other risk factors and inflammation is also important; thus "management of hypertension should be related to quantification of total cardiovascular risk". (14)

Blood pressure reduction is the main goal. Targets should be based on the recommendations of evidence-based medicine. It is more important to identify the "fragile patient" than to discuss if the J-curve exists or not. Fragile patients include those with nonrevascularized coronary artery disease, severe isolated systolic hypertension, orthostatic hypotension, severe left ventricular dysfunction, and long-standing coronary artery disease or diabetes.

It is extremely useful to treat target organ damage in the initial evaluation and during follow-up; other aspects, as prediabetes or insulin resistance should also be considered important predictors of cardiovascular events.

Progression from prehypertension to hypertension can be delayed or reverted with adequate medication and lifestyle modifications; these measures, aimed at reducing blood pressure levels and cardiovascular risk, are mentioned in all the guidelines: smoking cessation, aerobic physical exercise on a regular basis, weight reduction and stabilization, decrease in saturated and total fat intake, reduction of salt intake, moderation of alcohol consumption and increase in fruit and vegetable intake. Several efforts have been made to demonstrate the importance of diet in the management of hypertension; as an example, we can mention the well-known DASH diet. (15)

Cardiovascular risk is also influenced by genetic (hereditary) and environmental factors. Thus, the development of hypertension may occur earlier or later depending on patient's genetics and social, cultural, environmental and economic risk factors, which may also modify cardiovascular morbidity and mortality. (16)

Therefore, modern life and culture have their benefits, costs and consequences.

In the United States, one out of every six adolescents is overweight; in Perú, 35% is overweight according to the Centro Nacional de Alimentación y Nutrición (CENAN 2009). In Lima, 66% eats fast food and 87% of the population nationwide eats fried food at least once a week. Which is the solution to this problem? Ignoring lifestyle modifications? Using a statin to neutralize the cardiovascular risk of unhealthy dietary choices, as Ferenczi (17) has recently proposed with the use of a "McStatin"? Does this mean that man is again deteriorating the metabolic status? The current profile in Latin America shows increase in obesity, smoking habits, sedentary life, diabetes and bad eating habits, especially in children. This demonstrates that the problem begins very early. Hippocrates recognized that obesity was not only a disease but led to other diseases. Sir Thomas Pickering stated that it is easier to convince patients with hypertension to take medication than to convince patients with prehypertension to change their lifestyle.

Lifestyle modifications have demonstrated to reduce blood pressure levels; (18) most high-risk patients with hypertension are subjects with high-normal blood pressure with multiple risk factors, subclinical target organ damage or metabolic syndrome and subjects with grade 1 or mild hypertension (Figure 3).

These subjects constitute the group of hypertensive patients in whom the indication of MONOTHERAPY is determinant and categorical.

This strategy has not been invalidated by the ACCOMPLISH (19) and the recent ACCELERATE (20) (aliskiren/amlodipine) studies, which showed that blood pressure targets were achieved earlier with combined therapy compared to initial monotherapy.

Prevention is the most important strategy. Does the world really need the polypill? What is wrong with a healthy lifestyle? Which would be the extent of the problem if we avoided smoking, ate healthy food, lost weight and reduced waist circumference, increased daily physical activity, detected and treated hypertension and learnt how to recognize our risk (glycemia, lipid profile, among others)?

Egan et al. (21) demonstrated that blood pressure control improved in an estimated 50 % of all patients with hypertension in NHANES 2007-2008. Hypertension control was significantly lower among younger than middle-aged individuals and older adults, and Hispanic vs. white individuals.

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Fixed-Dose Combinations

ANTONIO COCA

Hypertension is still one of the main causes of cardiovascular death worldwide (1) and plays a major role in the development of ischemic heart disease, cerebrovascular disease and renal failure. (2) The relationship between blood pressure (BP) levels and cardiovascular morbidity and mortality is linear; (3) therefore, lowering BP levels is essential to improve the outcomes of hypertensive patients. In this way, a greater reduction in BP levels may reduce the cardiovascular risk. (4)

However, despite the benefit demonstrated by antihypertensive treatment and the availability of

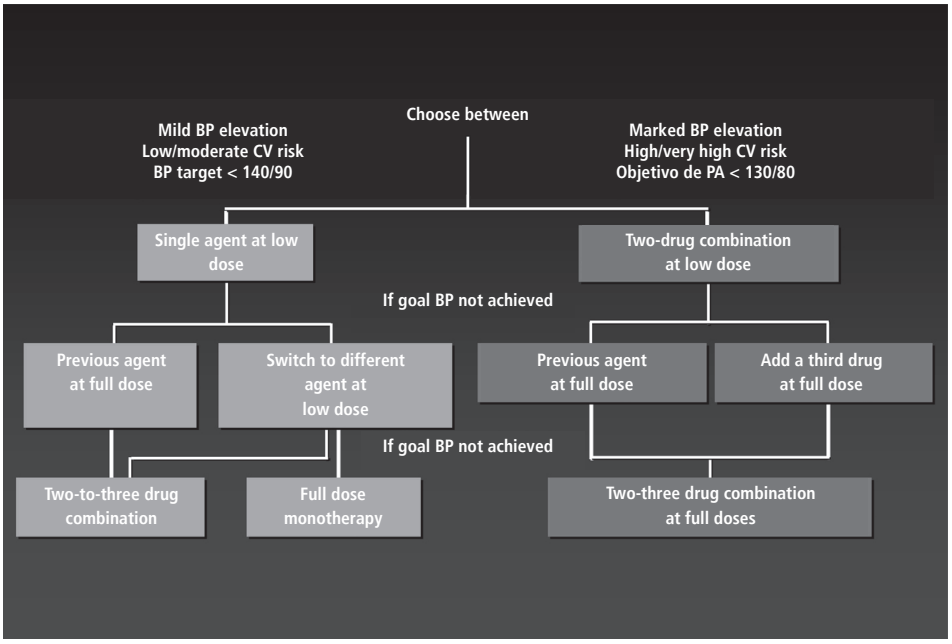

Fig. 1. Algorithm for the management of the hypertensive patient.

multiple drugs, adequate BP control is still insufficient. (5, 6) Inadequate BP control is due to multiple causes, starting from patients' lack of awareness about the high cardiovascular risk associated with poor BP control to physicians' suboptimal therapeutic management. Many physicians start pharmacological treatment with monotherapy, then titrate the dose upwards or switch to other agents in most hypertensive patients, regardless of patient's global risk and BP targets. This behavior leads to more medical visits and to a greater probability of "therapeutic inertia". (7)

A review by Backris et. al (8) demonstrated several years ago that most high-risk patients, particularly those with type 2 diabetes mellitus, need a mean of three antihypertensive agents to achieve blood pressure targets.

For this reason, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) (9), the guidelines of the European Society of Hypertension-European Society of Cardiology (ESH-ESC) (10) of 2007 and the critical reappraisal published in 2009 (11) recommend that the combination of different classes of drugs is the most effective strategy to achieve BP control in most hypertensive patients. Addition of a drug from another class to the initially prescribed one should thus be regarded as a recommendable treatment strategy, unless the initial drug needs to be withdrawn because of the appearance of side-effects or the absence of any BP-lowering effect.

The ESH/ESC guidelines recommend a combination of two drugs as first step treatment when: 1) initial BP levels are very high (≥ 160 and/or 100 mm Hg), 2) BP is markedly above the hypertension threshold (e.g. more than 20mm Hg systolic or 10mm Hg diastolic), and, 3) goal BP should be achieved more promptly due to high or very high total cardiovascular risk. (10)

Figure 1 shows the algorithm developed by the ESH/ESC for the management of hypertension. (10) Unlike other guidelines, as the JNC VII or the NICE, the European guidelines do not recommend any antihypertensive agent to initiate treatment and suggest that physicians should choose the agents according to the patients' needs.

The benefit of combination therapy to achieve BP targets was demonstrated in the meta-analysis by Wald et al., (12) which included 10,968 participants from 42 trials. The study concluded that the extra blood pressure reduction of combining drugs from two different classes is approximately five times greater than doubling the dose of one drug. In 2009 the Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document was published, (11) confirming that any agent used in monotherapy is ineffective or scarcely effective in a number of patients and emphasizing the use of combination therapy to attain the goal of substantially improving BP control worldwide. The European Society of Hypertension recommends the combination of an ACE inhibitor or an angiotensin receptor antagonist with a calcium antagonist or diuretic for priority use due to their strong antihypertensive effect, tolerability and efficacy in reducing morbidity and mortality in hypertensive patients. (11) When three drugs are required, the most rational combination appears to be an ACEI or an angiotensin receptor antagonist, a calcium antagonist, and a diuretic. (11)

Recent studies as the VALUE trial (13) have demonstrated that reaching blood pressure control within the first 3 months of treatment is associated

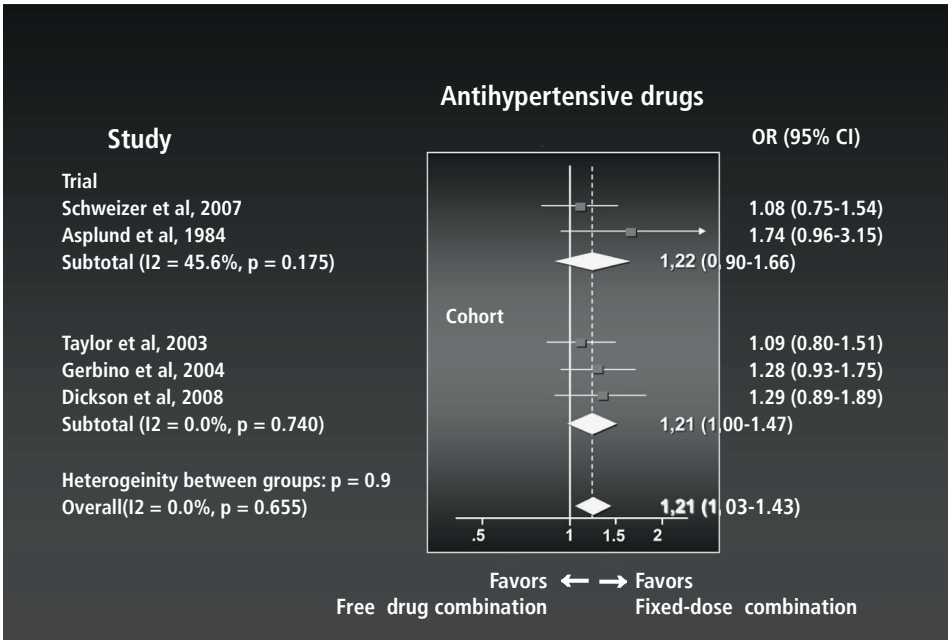

Fig. 2. Results of combination therapy.

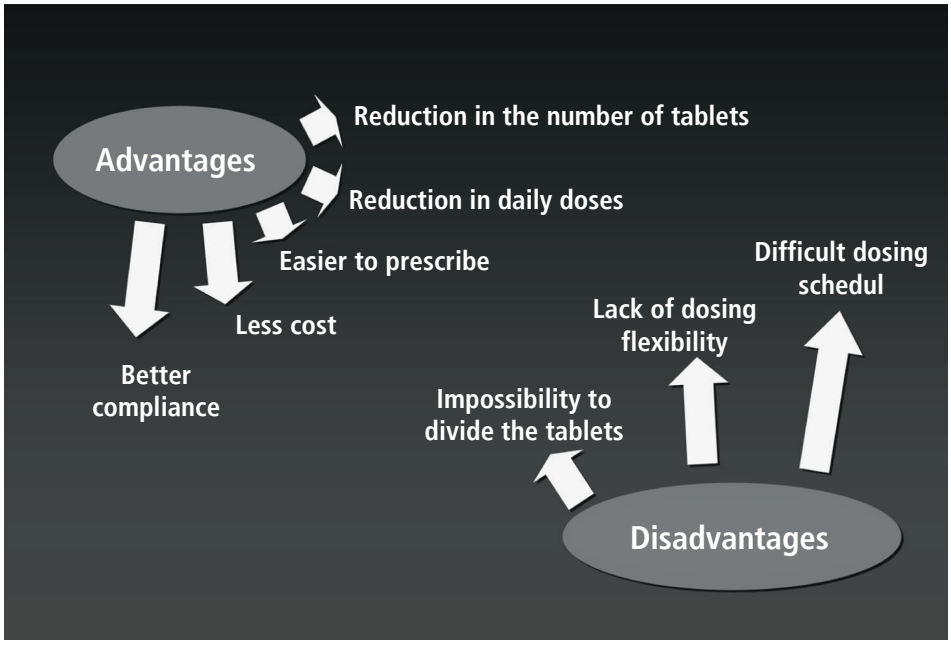

Fig. 3. Advantages and disadvantages of fixed-dose combinations.

with greater cardiovascular protection and reduction of cardiovascular and cerebrovascular events. (14) In consequence, the old paradigm "The lower the better…" has been replaced by "The earlier the better…" (11)

The efficacy, tolerability and effectiveness to achieve BP targets with low-dose combination therapy has proved to be greater than monotherapy at full dose, not only in the magnitude of the effect but also in the time taken to control BP levels. (12) Combination therapy may be given as two tablets or as fixed-dose combinations (two drugs in a single tablet). The 2007 ESH/ESC recommend using fixed combinations of two drugs as they can simplify treatment schedule and favor compliance. (10) Similarly, the World Health Organization (WHO) - International Society of Hypertension (ISH) guidelines suggested more than ten years ago that "it is often preferable to add a small dose of a second drug rather than increasing the dose of the original drug. This allows both the first and second drugs to be used in a low dose range that is more likely to be free of side effects. In this context, the use of the fixed-low dose combination as that are increasingly available in the United States and Europe may be advantageous." (15)

When we analyze the causes that currently

contribute to the lack of achieving BP targets, we should not forget tolerance to antihypertensive agents, compliance to therapy and costs. (16) The results of surveys reported that compliance to treatment in chronic diseases is about 30%, with important implications in terms of cardiovascular morbidity and mortality. (17) In this sense, to goal of fixed-dose combinations is to make BP control more cost-effective, minimizing the development of adverse effects and, thus, improving tolerance and compliance.

Fixed-dose combinations are gaining position as the treatment of choice for the management of hypertensive patients due to several advantages. Firstly, the physiopathological mechanisms involved in the development of HT are different and particular in each patient, and difficult to detect. The response to combination therapy working at different sites has a priori more probability of achieving BP targets compared to a single drug blocking only one mechanism. (16) Secondly, fixed-low dose combinations are designed to simplify the medication regimen and potentially improve compliance. (17, 18) The meta analysis by Gupta et al. (19) demonstrated that combination therapy associated with a 21% ($p < 0.0001$) increase in compliance with medications (Figure 2) suggesting a better control of BP levels and a significant reduction in hospitalization rate, mortality and heath care costs. Finally, dose-related adverse effects tend to minimize with fixed-dose combinations. The simultaneous use of two antihypertensive drugs produces an additive synergy of the antihypertensive effects of the two components. Thus, low doses of each agent are enough to achieve significant reductions in BP levels. (16)

Although the advantages of fixed-dose combinations overcome the disadvantages, some limitations should be mentioned (Figure 3). The need of using different doses of each of the components of the combination or of associating a higher dose of one of the drugs in a different tablet to achieve BP targets is one of the limitations, as the medication regime becomes more complex and compliance decreases. However, this is a minor problem as there are different combinations available in the market for the different dosage regimes of most of the medications. Most antihypertensive fixed-dose combinations do not provide the necessary doses to treat patients with angina or heart failure, two co-morbidities that are frequent in hypertensive patients. (16) In many occasions, the use of a single tablet does not allow individual adjustments for the circadian profile of each patient.

Yet, low-dose fixed combinations are prescribed to most hypertensive patients due to proven efficacy, tolerability, compliance, and persistence of the therapeutic effect.

In short, reducing BP levels in a rapid and efficient fashion decreases vascular risk and improves the outcomes of hypertensive patients. The use of combination therapy, specially using fixed-low doses has proved to be particularly effective to reduce BP levels rapidly, safely and in a well-tolerated fashion, particularly focused on patients with high or very high cardiovascular risk. This approach has been associated with better compliance and adherence to treatment, clearly contributing to achieve BP targets and reduce morbidity and mortality.

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REPLY IN FAVOUR OF MONOTHERAPY

Lifestyle modification is essential for the treatment of hypertension.

Pharmacological treatment associated with lifestyle modifications should be initiated in patients with high-normal blood pressure with three risk factors or greater, subclinical target organ damage or metabolic syndrome, and undoubtedly, in diabetics

Most hypertensive patients worldwide are those high-risk prehypertensive subjects and subjects with grade 1 or mild hypertension. In all these patients monotherapy is recommended as the initial treatment.

Comparing monotherapy with combination therapy (Table 1), we should consider the following:

– Lifestyle modification is essential.
– Monotherapy may be indicated as initial treatment in the presence of metabolic syndrome or subclinical target organ damage, yet...
– Combined therapy should be preferred in patients with diabetes.

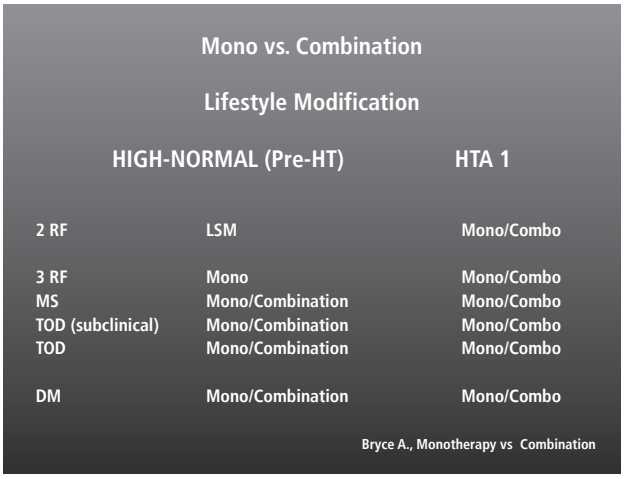
Recently, Dr. Alberto Zanchetti (J Hypertens 2011;29:1-3) expressed his opinion and made some questions about the future management of hypertension:

– Whom should we treat?
– Should we also treat uncomplicated hypertensive patients and individuals with high normal blood pressure if complicated by metabolic disturbances, diabetes or concurrent cardiovascular disease?
– How far should blood pressure be reduced?
– Is goal blood pressure different in complicated or uncomplicated hypertension, in the elderly and in the young hypertensive patients?

Among these complex questions, probably the optimal blood pressure level is the most important aspect to consider for the treatment of hypertension, particularly in "high risk" patients in whom a slight reduction in blood pressure level may significantly increase the benefit or the risk.

Dr. Alfonso Bryce

Table 1. Monotherapy versus combination therapy.



REPLY IN FAVOUR OF FIXED-DOSE THERAPY

When I spoke about the benefits of combination therapy, I also recognized that monotherapy is effective in lowering BP levels in about 30% of hypertensive patients: those with grade 1 hypertension (<160/100) without subclinical target organ damage and fewer than 3 cardiovascular risk factors (CRFs). This group represents less than 30% of patients attending the primary health care level in Spain, compared to 70% of patients who might benefit from combination therapy according to the European guidelines. Low-dose combination therapy is also effective in low risk grade 1 hypertension to reach BP targets earlier and improves compliance.

Dr. Bryce is in favor of monotherapy in prehypertension. As he perfectly describes, this term fails to define the clinical situation. A subject with "high-normal" BP defined by the European guidelines may have a different CVR depending on the presence of co-morbidities and associated CRFs, which will determine whether antihypertensive drugs are indicated or not and which approach will be followed: monotherapy or combination therapy. Patients with "high-normal" BP and high risk may even receive combination therapy to achieve BP control earlier. We should not forget that the current scientific evidence has replaced the paradigm "The lower the better…" by "The earlier the better…" in the critical reappraisal of the European guidelines in 2009. Patients with "high-normal" BP and low cardiovascular risk should be advised to modify lifestyle; antihypertensive drugs

are not indicated in these patients, not even in low doses as the only evidence available is that medication reduces the incidence of established hypertension in these patients but does not reduce morbidity or life expectancy.

Dr. Antonio Coca