

Combined Therapy with Angiotensin-Converting Enzyme Inhibitors and Calcium Channel Blockers is the Treatment of Choice to Reduce Cardiovascular Risk in Patients with Hypertension

Agonist

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HYPERTENSION: THE MAIN CAUSE OF DEATH AROUND THE WORLD IS NO NEWS

On May 5, 2008, newspapers front pages all around the world reported 10,000 people dead in Myanmar as a consequence of a cyclone.

Two days before, *The Lancet* (1) had published a report of the WHO stating that hypertension and its complications are the leading cause of death in the world, causing 20,281 victims each day. Surprisingly, this news was no news.

A PREMALIGNANT DISEASE

Hypertension is a continuum that starts with a rise in blood pressure, evolves to target organ damage (left ventricular hypertrophy, proteinuria or endothelial dysfunction), and, **insofar as it is not adequately treated or controlled**, finally leads to the development of complications, the most relevant of which are stroke (S) and heart failure (HF).

Stroke is the main complication of hypertension and the second cause of death, but most important, it is the leading cause of disability.

Samsa et al (2) reported a 24-month survival of 66% after a first stroke from a Medicare sample in USA. However, in patients with recurrent stroke this number decreased to only 51%.

Dementia is the most dreadful complication after a stroke, and the Framingham study demonstrated that stroke **doubled the risk of dementia**. (3)

Regarding **heart failure**, the other complication of hypertension, Karl Swedberg stated: "In 1987 the CONSENSUS trial documented the importance of enalapril in severe heart failure. However, after 10 years all the patients in the CONSENSUS trial had died".

An editorial by Mc Murray et al. (4) posed the following question: **Is heart failure more 'malignant' than cancer?** After a first admission for heart failure, 5-year survival rate was worse in both sexes

compared to breast cancer, bowel cancer, ovarian cancer and prostate cancer, with the notable exception of lung cancer.

In summary, considering that the two main adverse outcomes of hypertension are stroke and heart failure, two conditions as "malignant" as many common types of cancer, my personal point of view is that **uncontrolled hypertension** is a **pre-malignant disease** and the presence of **target organ damage** is a **"tumor marker"**. **As it happens with cancer**, early detection of these markers is mandatory for a proper therapy to achieve regression or normalization so as to prevent the progression of hypertension towards stroke and heart failure.

Target Organ Damage or "Tumor Markers"

Next, I shall mention some of the most important markers.

Microalbuminuria - proteinuria

Klausen et al. (5) demonstrated that microalbuminuria *per se* doubled the risk of coronary heart disease and death.

The CARE trial showed that proteinuria by itself duplicated the risk of total mortality in patients with coronary artery disease.

We may conclude that the presence of microalbuminuria or proteinuria is an important marker not only of renal disease but also of cardiovascular risk.

Left ventricular hypertrophy

Left ventricular hypertrophy has been associated with a marked increased risk of cardiovascular disease.

Verdecchia et al. (6) demonstrated that the risk of stroke was lower in patients who never developed left ventricular hypertrophy or with regression of left ventricular hypertrophy after adequate therapy. Conversely, the risk of stroke was greater in cases of lack of regression or new development of left ventricular hypertrophy.

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Atrial fibrillation and left atrium size

During the last years, the presence and prognostic significance of left atrial enlargement in the development of atrial fibrillation has drawn our attention.

Atrial fibrillation is more likely to occur in hypertensive patients with left ventricular hypertrophy and left atrial enlargement.

I would like to mention just one study from the Mayo Clinic, (7) that reported high morbidity and mortality rates in atrial fibrillation. The study included 4618 patients with atrial fibrillation; after 5 years of follow-up 67% were dead.

Hypertension and risk of new-onset diabetes mellitus

The risk of new-onset diabetes mellitus is high in hypertensive patients.

Antihypertensive therapy might have some influence on this risk. The **ARIC** study demonstrated that traditional beta blockers increased the risk of new-onset diabetes in 28% of hypertensive patients. (8)

Prognosis of patients who develop new-onset diabetes mellitus is similar to those already diabetic. Thus, antihypertensive therapy should not only prevent the risk of new-onset diabetes but also reduce it.

PHARMACOLOGIC TREATMENT OF HYPERTENSION

As patients usually need two or more drugs to achieve blood pressure control we must think of the best **treatment schedule for management of hypertension and regression of target organ damage; in addition drug therapy should not produce metabolic disorders which might decrease the benefit obtained with the therapy, or even neutralize it.**

The reasons why renin-angiotensin system blockers (ACEI o angiotensin-receptor blocking agents) and calcium channel blockers are currently the best option to treat hypertension instead of diuretics and beta blockers are detailed below.

I shall start the discussion with the last two types of drugs.

Diuretics: similar, but not identical

Some experts have speculated about the differences between hydrochlorothiazide (HCTZ) and chlorthalidone. The MRFIT trial gave a possible answer. (9)

Patients were assigned to treatment with HCTZ or with chlorthalidone. In the group of patients treated with HCTZ mortality was 44% higher than therapy with chlorthalidone. The Committee on Ethics changed the protocol near the end of the trial to exclusively use chlorthalidone; the trend was reversed after the protocol was changed to chlorthalidone, and they then had a 28% lower risk.

Afterwards, the **SHEP and ALLHAT trials**, two megatrials conducted in USA, **used chlorthalidone.**

Patients who developed hypokalemia in the **SHEP** study presented more events than those who received placebo. For this reason when these drugs which are effective in preventing events are used, it is necessary to perform a close surveillance of metabolic parameters, specially potassium, glucose and uric acid blood levels.

Beta blockers in hypertension: should they still be considered drugs of first choice in hypertensive patients?

Traditional beta blockers, especially atenolol, have little impact on target organ damage. Even more, they increase the risk of new-onset diabetes mellitus and, therefore, its adverse outcomes.

In addition, beta blockers may yield erectile dysfunction, which is closely related to treatment discontinuation and with reduction in quality of life.

Furthermore, the **ASCOT** trial demonstrated that these drugs worsened metabolic syndrome parameters. (10)

For these reasons, although **ESH-ESC Practice Guidelines** (11) agree to prescribe beta blockers to treat hypertension, they suggest not to use them in particular associated with diuretics in patients with metabolic disorders. It should be noted that 50% of hypertensive patients have overweight or metabolic disorders.

During the last 4 years, several meta-analyses (12) have demonstrated that beta blockers reduce the risk of stroke in about 15% compared with a reduction of almost 30-40% achieved with calcium channel blockers or angiotensin-receptor blocking agents.

It stands to reason that beta blockers are effective for the treatment of coronary artery disease as they were developed as anti-ischemic drugs rather than antihypertensive drugs.

In contrast, third-generation beta blockers such as carvedilol and nebivolol produce vasodilatation and are beneficial for metabolic parameters, endothelial dysfunction, microalbuminuria and left ventricular hypertrophy.

Renin-angiotensin system blockers

A meta-analysis published this year comparing the effects of angiotensin-converting enzyme inhibitors with angiotensin-receptor blocking agents demonstrated that both types of drugs were similar to prevent cardiovascular events. (13)

Apart from the antihypertensive effect both drugs are effective in **preventing target organ damage** as described below, as they produce:

- **Regression of left ventricular hypertrophy and reduction in left atrial size and myocardial fibrosis**, demonstrated by the LIFE study. (14)
- **Improvement in arterial remodeling, arterial dysfunction, and anti-atherosclerotic effect** as indicated by Shiffirin and Ferrario.

- **Reduction in proteinuria**, shown in LIFE and IRMA 2 trials (15) with irbesartan and MARVAL study (16) with valsartan.
- **Risk reduction of 22% in new-onset diabetes** demonstrated by evidence from megatrials and meta-analysis. (17)
On the contrary, traditional beta blockers and diuretics increase the risk of developing diabetes probably as a consequence of hypokalemia.
- **Prevention of atrial fibrillation.** The role of the angiotensin-receptor blocking agents losartan, candesartan and valsartan in reducing the risk of developing atrial fibrillation was demonstrated in the LIFE, (18) CHARM (19) and VALUE, (20) trials.

A review of 11 clinical trials, which included 56,308 patients with diverse cardiovascular disorders, showed that ACEI or angiotensin-receptor blocking agents exerted a beneficial effect in reducing recurrences of atrial fibrillation. (21)

In summary, **it is undoubtedly that blocking the renin-angiotensin system involves in protection and regression of target organ damage.**

Calcium channel blockers

These drugs have demonstrated to have a strong antihypertensive effect and antiatherogenic action which are related with the correction of endothelial dysfunction and to their antioxidant effects.

Different dihydropyridines have demonstrated to be effective in slowing the atherogenic process in trials that compared the progression of carotid intima-media thickness with the use of nifedipine GITS (**INSIGHT** study [22]) or lacidipine (**ELSA** study [23]) versus diuretics and atenolol, respectively.

It should be highlighted that the reduction of blood pressure achieved was similar with dihydropyridines and comparative drugs. This is another piece of evidence of the vascular protection associated with calcium channel blockers.

Above all, these drugs have demonstrated to be efficient in reducing the risk of stroke, which is the main complication of hypertension. A meta-analysis conducted by Jan A. Staessen, (24) compared calcium channel blockers with other antihypertensive drugs and demonstrated that, at the same blood pressure level, calcium channel blockers conferred protection towards stroke beyond its blood pressure-lowering properties.

The **CAMELOT** and **ASCOT** trials have proved that these agents are effective to prevent clinical events in patients with **coronary artery disease**.

In contrast, calcium channel blockers seem not to be effective in preventing the development of heart failure.

CLINICAL TRIALS: TRUTH OR CONSEQUENCE

All blood pressure-lowering drugs have similar anti-hypertensive actions; however, they have different mechanisms of action for protection and regression of target organ damage.

These intermediate endpoints might need to be tested in randomized clinical studies with “**hard**” endpoints such as global and cardiovascular mortality, stroke, myocardial infarction or heart failure.

The **LIFE** study included 9,194 patients with hypertension and left ventricular hypertrophy. For the same level of blood pressure control, patients with isolated systolic hypertension treated with an angiotensin-receptor blocking agent presented a risk reduction of 40% in stroke compared to patients who received atenolol. The results were similar in patients with a history of atrial fibrillation.

The **ASCOT** trial, which included 19,257 high-risk patients, compared treatment with atenolol and thiazide diuretics with amlodipine and perindopril. The trial was stopped early by the steering committee because analysis showed a significant improvement in cardiovascular outcomes in the amlodipine-perindopril group, with a risk reduction of 24% in cardiovascular mortality, 23% in fatal and non fatal stroke, 30% in new-onset diabetes mellitus, 32% in fatal and non fatal myocardial infarction and unstable angina, 35% in peripheral vascular disease and development of new cases of renal failure.

As a consequence of these findings, the **British NICE clinical guidelines** (25) relegated antihypertensive therapy with beta blockers to fourth place.

The ACCOMPLISH study, the end of the story

The results of the **ACCOMPLISH** study were presented during the Annual Scientific Session of the American College of Cardiology. The **ACCOMPLISH** trial was the first major hypertension outcomes trial that randomized subjects to a specific fixed-dose combination drug as initial therapy: benazepril plus hydrochlorothiazide or benazepril plus amlodipine.

The study included 11,344 who were at high risk for cardiovascular events; the reduction in blood pressure from baseline was similar between the two groups.

The data and safety monitoring committee recommended early termination of this study due to a reduction of 20% in the primary endpoint (cardiovascular mortality, stroke and myocardial infarction) in the arm treated with benazepril plus amlodipine.

The results of this study are essential to end with the controversy of which is the best treatment schedule for hypertensive patients; however, it should be noted that both **ACCOMPLISH** and **ASCOT** trials included high-risk patients.

LOW-RISK PATIENTS

Fix-dose combinations of a calcium channel blocker plus an angiotensin-converting enzyme inhibitor are most effective for low-risk hypertensive patients or for patients who need a slight reduction in blood pressure levels due to their potent blood pressure lowering action.

Renin-angiotensin system blockers are useful as initial therapy for young patients and calcium channel blockers for elderly patients.

Beta blockers and diuretics may control blood pressure; however it should always be taken into account that most hypertensive patients require lifelong treatment and both drugs produce metabolic disorders, especially new-onset diabetes which leads to unfavorable outcomes in hypertensive patients.

Therefore, ACEI, angiotensin-receptor blocking agents or calcium channel blockers are first-choice drugs in patients with metabolic disorders. In case additional reduction in blood pressure levels is needed, the combination of two of these drugs may be an excellent option.

When appearances are deceptive

The **APROS** study (26) included 1,074 untreated individuals who were identified on the basis of diagnostic routine procedures. According to routine classification, 18.7% were considered at low risk and 81.3% at medium risk. Patients were submitted to ultrasound examinations of heart and carotid arteries. After this second assessment, 50% of the patients previously classified at low-medium risk were found to be at high absolute risk. The authors concluded that a proper assessment of hypertensive patients is necessary as after a second evaluation more than 50% of those patients previously considered at low risk and with no need of treatment were found to gain benefit from blood pressure lowering therapy.

It is currently necessary to perform an adequate assessment of hypertensive patients, especially of those at low risk, as a high percentage of cases will be reclassified and may gain benefit from adequate pharmacological therapy.

CONCLUSIONS, THOUGHT AND FINAL MESSAGE

Hypertension is much more than a number controlled by one or two pills; it is the main cause of death world wide and, even worst, its incidence is increasing.

We should emphasize the importance of preventing hypertension through educational and community-based programs in healthy people, especially in young subjects, with particular reference to healthy diet, daily physical activity and absence of smoking habits.

However, once we are facing a hypertensive patient, our responsibility is to control blood pressure

levels and to prevent, detect and produce regression of target organ disease in case it is present.

Undoubtedly there is current evidence demonstrating that the best drugs that achieve these goals are renin-angiotensin system blockers (ACEI or angiotensin-receptor blocking agents) and calcium channel blockers, as evidenced by three large trials, **LIFE**, **ASCOT AND ACCOMPLISH**, with more than 40,000 patients. The latter two studies were stopped early by a steering committee.

BIBLIOGRAPHY

1. Lawes CM, Vander Hoorn S, Rodgers A; International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008;371:1513-8.
2. Samsa GP, Bian J, Lipscomb J, Matchar DB. Epidemiology of recurrent cerebral infarction: a medicare claims-based comparison of first and recurrent strokes on 2-year survival and cost. *Stroke* 1999;30:338-49.
3. Ivan CS, Seshadri S, Beiser A, Au R, Kase CS, Kelly-Hayes M, et al. Dementia after stroke: the Framingham Study. *Stroke* 2004; 35:1264-8.
4. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. *Eur J Heart Fail* 2001;3:315-22.
5. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, Jensen G, Clausen P, Scharling H, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 2004;110:32-5.
6. Verdecchia P, Angeli F, Gattobigio R, Sardone M, Pede S, Reboldi GP. Regression of left ventricular hypertrophy and prevention of stroke in hypertensive subjects. *Am J Hypertens* 2006;19:493-9.
7. Miyasaka Y, Barnes ME, Bailey KR, Cha SS, Gersh BJ, Seward JB, et al. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. *J Am Coll Cardiol* 2007; 49:986-92.
8. Bell DS. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med* 2000;343:580.
9. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. *Hypertension* 2004;43:4-9.
10. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366:895-906.
11. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, ESH-ESC Task Force on the Management of Arterial Hypertension. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens* 2007;25:1751-62.
12. Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular protection using beta-blockers: a critical review of the evidence. *J Am Coll Cardiol* 2007;50:563-72.
13. Reboldi G, Angeli F, Cavallini C, Gentile G, Mancia G, Verdecchia P. Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis. *J Hypertens* 2008;26:1282-9.

14. Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al; LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:995-1003.
15. Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P; Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870-8.
16. Viberti G, Wheeldon NM; MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation* 2002;106:672-8.
17. Mancia G, Grassi G, Zanchetti A. New-onset diabetes and anti-hypertensive drugs. *J Hypertens* 2006;24:3-10.
18. Wachtell K, Horneštam B, Lehto M, Slotwiner DJ, Gerds E, Olsen MH, et al. Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: The Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol* 2005;45:705-11.
19. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, et al; CHARM Investigators. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;47:1997-2004.
20. Schmieder R, Kjeldsen SE, Julius S, McInnes GT, Zanchetti A. Reduced incidence of new onset atrial fibrillation with angiotensin II receptor blockade: the VALUE-trial. *J Hypertens* 2006;24:S3.
21. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005;45:1832-9.
22. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000; 356:366-72.
23. Zanchetti A, Bond MG, Hennig M, Neiss A, Mancia G, Dal Palù C, et al; European Lacidipine Study on Atherosclerosis investigators. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation* 2002;106:2422-7.
24. Angeli F, Verdecchia P, Reboldi GP, Gattobigio R, Bentivoglio M, Staessen JA, et al. Calcium channel blockade to prevent stroke in hypertension: a meta-analysis of 13 studies with 103,793 subjects. *Am J Hypertens* 2004;17:817-22.
25. Hypertension: management of hypertension in adults in primary care. NICE www.nice.org.uk June 2006.
26. Cuspidi C, Ambrosioni E, Mancia G, Pessina AC, Trimarco B, Zanchetti A; APROS Investigators. Role of echocardiography and carotid ultrasonography in stratifying risk in patients with essential hypertension: the Assessment of Prognostic Risk Observational Survey. *J Hypertens* 2002;20:1307-14.

Antagonist

MÓNICA DÍAZ

Hypertension (HT) is the most common risk factor for cardiovascular disease (CVD) and its treatment reduces cardiovascular morbidity and mortality; however, a large proportion of hypertensive patients (HPs) have inadequate blood pressure control. The aim of HP treatment is to achieve the maximum cardiovascular risk (CVR) reduction and this goal may be attained with blood pressure (BP) control and adequate management of other risk factors. Current guidelines recommend a reduction in BP levels to < 140/90 mm Hg in the general hypertensive population and < 130/80 mm Hg in high-risk populations – HPs with diabetes mellitus or renal involvement. The decision to start drug therapy is based on BP level as well as on patient's CVR. (1-4)

DOES THE BENEFIT OF ANTIHYPERTENSIVE TREATMENT DEPEND ON BLOOD PRESSURE REDUCTION *PER SE* OR ON THE TYPE OF DRUG PRESCRIBED THAT PRODUCED BLOOD PRESSURE LOWERING?

Although the first studies in HT have demonstrated that blood pressure reduction decreases CVR, the development of new antihypertensive drugs has posed

another question: *Can diverse types of antihypertensive drugs with similar blood pressure lowering effect offer different degrees of cardiovascular protection?* Few studies comparing different drugs show that for a similar reduction in BP levels, the difference achieved in cardiovascular morbidity and mortality is small; this conclusion reinforces the concept that the benefits attained with antihypertensive therapy depend mostly on blood pressure reduction *per se*. The small number of studies comparing different drugs leads to conclusions based on few data; even more, current studies in hypertension are designed to achieve a strict blood pressure control, which requires the addition of a second, a third and even a fourth drug to each study group; thus it is more difficult to draw conclusions from these data. The BPLTTC study (Blood Pressure Lowering Treatment Trialists' Collaboration) gives an excellent description of the importance of blood pressure reduction regardless of the drug used. The authors concluded that antihypertensive therapy with any commonly used regimes reduced the risk of total major cardiovascular events, demonstrating that blood pressure reduction is beneficial by itself and a reduction of 10 mm Hg in systolic blood

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pressure (SBP) considerably decreases the likelihood of stroke or myocardial infarction. (5)

WHICH IS THE BEST ANTIHYPERTENSIVE COMBINATION THERAPY?

Nowadays it is frequent to prescribe two or more antihypertensive drugs in order to achieve blood pressure therapeutic goals, especially in high-risk patients; therefore, discussion should focus on the ideal antihypertensive combination therapy. Most combined treatments include a thiazide diuretic: ACEI/thiazide, AIIIRA/thiazide, BB/thiazide, CCB/thiazide, thiazide/potassium-sparing diuretic and CCB/ACEI. Firstly, we must be aware of the pros and cons of a CCB/ACEI combination therapy before evaluating if this combination should be the treatment of choice for HPs.

The only two studies that used ACEI/CCB combination therapy in one of their treatment arms were the ACCOMPLISH trial (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension) (6) and the ASCOT-BPLA trial (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm). (7) Although both studies used the same combination therapy in one of their arms (ACEI/CCB) drugs were administered in a completely different fashion. The former used a fixed combination of ACEI/CCB, benazepril-amlodipine; doses were force-titrated to maximal benazepril dose levels of 40 mg, and the latter started with monotherapy with a CCB (amlodipine); amlodipine dose could be doubled and then an ACEI could be added: perindopril 2 and 4 mg (the traditional stepwise treatment). The ASCOT-BPLA study is a randomized clinical trial performed in HPs with three or more cardiovascular risk factors. The study evaluated if therapy with amlodipine alone or combined with perindopril was superior to treatment with atenolol alone or combined with bendroflumethiazide in terms of incidence of non fatal AMI and cardiovascular death. The amlodipine-based regime had a non-significant 10% risk reduction in the primary outcome, and a lower incidence of stroke and new-onset diabetes. It should be noted that BP in patients allocated to the amlodipine arm was 5.9/2.4 mm Hg lower than in patients in the atenolol-based regime after 3 months of treatment, and amlodipine produced a 2.7mm Hg systolic blood-pressure difference throughout the study. After analyzing this study we may conclude that it was designed to assess the efficacy and safety between "old drugs" and "new drugs"; if so, one may ask why diuretics were not used as first option therapy considering that thiazide diuretics are the oldest drugs currently used in HT and have demonstrated to be more efficient than atenolol. Furthermore, as we shall see later, chlorthalidone would have been a better comparator drug taking into account the experience of the ALHATT (Antihypertensive and Lipid-Lowering

to Prevent Heart Attack Trial) study, (8) among many others. In addition, as 63% of patients were older than 60 years, atenolol was not the best option due not only to the presence of adverse events in elderly patients but mainly to the wide experience and favorable outcomes with CCBs in this population. Probably this combination might have "tipped the scales" towards the amlodipine-based regime. Another piece of information that should be taken into account is the possibility that the benefit obtained with amlodipine was a consequence of the reduction in BP seen through the whole study (2.7 mm Hg). As a conclusion, this study is indicating that amlodipine (alone or combined with perindopril) is better than atenolol (alone or combined with bendroflumethiazide) to prevent stroke and new-onset diabetes mellitus in high-risk hypertensive patients. In addition, amlodipine alone or combined with perindopril is an efficient blood pressure lowering drug that achieved and maintained low blood pressure levels through the whole study, which might explain the benefits obtained.

The ACCOMPLISH study is a multicenter, randomized trial designed to assess the effect of two different **fixed-dose combination** drugs (ACEI/CCB versus ACEI/HCTZ) on CVR in high-risk HPs. The study included 11,400 high-risk patients (diabetics, elderly patients and patients with renal failure). High-risk HPs were allocated to one of the two combination therapies; doses were force-titrated during the first two months to achieve 40 mg of benazepril plus 5 mg of amlodipine or 12,5 mg of HCTZ. During the first three months, doses could be increased to 10/40 mg of amlodipine/benazepril or 25/40 mg of HCTZ/benazepril. After 30 months, around 80% of patients in both treatment groups achieved target blood pressure, compared with 37% at entry to the study. And perhaps even more surprisingly, 50% of patients achieved BP control with only one pill of any of both combinations. Systolic blood pressure decreased from 145 to 132 mm Hg in the general population and in special populations as diabetic HPs (from 145 to 131 mm Hg) and HPs with renal failure (from 149 to 136 mm Hg). After 40 months of follow-up, the trial was terminated early due to a relative risk reduction of 20% in morbidity and mortality in the ACEI/CCB group compared to ACEI/HCTZ group (unpublished data).

During the ESH/ISH Hypertension 2008 in Berlin the following conclusions were reported regarding the ACCOMPLISH study:

- Starting hypertension treatment with fixed dose combinations produced "remarkable" blood pressure control rates:

Currently, millions of HPs are taking blood pressure lowering drugs; yet their blood pressure levels are not under control and they are still at risk of cardiovascular events; therefore the degree of blood pressure control achieved by these studies is

highly beneficial and surprising. Nevertheless, it should be remembered that each treatment group was force-titrated over the first two months independently of patient's BP values. Particularly in this study this meant that two months after enrolment, patients should be receiving 40 mg of benazepril plus 5 mg of amlodipine or 1.5 mg of HCTZ regardless of their BP levels. Therefore, the following statement should be added to the authors' conclusions: "...from a fixed combination with maximal doses of one of its components", far different from the fixed low-dose combination suggested in the guidelines.

Most elderly patients are considered to be at high-risk and we are aware of the benefits derived from blood pressure lowering therapies in these patients; however, we also know that the great difference between these patients and the rest of the hypertensive population is that the reduction in blood pressure levels should be achieved gradually to avoid hypotension and its deleterious effects. Sudden hypotension in an elder patient can produce substantial changes in his/her quality of life and in costs in health. Indeed, blood pressure control should be achieved in these patients with evidence that favors a step-by-step approach in antihypertensive treatment; however, benefit from fixed high-dose combination therapy is limited only to the results of this study. There is not enough support to recommend this type of aggressive therapy in elderly patients or in subjects with clinical evidence of cardiovascular disease. Recently, the HYVET trial (HYpertension in the Very Elderly Trial) (9) demonstrated the benefit of combination therapy with perindopril/indapamide in very elderly HPs. However, doses were increased in two steps. The initial therapy with this fixed high-dose combination of ACEI/CCB still needs to demonstrate similar results to those of the aforementioned study and to the findings of the studies published during the nineties. Meanwhile, the best option for elderly HPs is gradual BP control.

High-risk HPs are not all the same: For example, a 65 year-old man with a stroke and SBP value of 133 mm Hg is considered a high-risk patient, and according to the European guidelines and to the Argentine Consensus of HT recommendations, he should start with drug therapy and lifestyle changes. According to the results of the present study, the initial therapy for this high-risk patient should be a fixed combination of 40 mg of benazepril and 5 mg of amlodipine. Cardiovascular risk increases progressively from BP values of 115 mm Hg; nevertheless, there is no strong evidence to support BP reduction below 130 mm Hg in these patients. Furthermore, there is few data available only in diabetic patients; therefore there is not enough evidence to support an aggressive initial

therapy with a fixed-dose combination of 40 mg of benazepril and 5 mg of amlodipine in these patients.

The only two studies that have assessed a combination therapy with ACEI/CCB are the ASCOT trial, which did not show any benefit in the primary endpoint, and the ACCOMPLISH trial, that reported favorable outcomes with a fixed-dose combination with maximal doses of benazepril. Therefore, we may conclude that:

- Both studies were performed predominantly on high-risk patients; therefore their conclusions should not be extrapolated to the all hypertensive population.
- There is lack of evidence of the superiority of the combination ACEI/CCB above other combination therapies for low-risk hypertensive patients.
- The combination CCB/ACEI used in the ASCOT-BPLA study did not show any significant benefit in the primary endpoint and, even more, the benefit obtained in the secondary endpoints might be attributed to lower BP values achieved in the amlodipine-based regime and not to the effect related to the drug or to drug combination.
- This combination proved to be effective in the ACCOMPLISH study; however it should be considered that this benefit might be related to the way these drugs were administered, with fixed -high doses as initial treatment rather than to the combination therapy.
- The treatment schedule of the ACCOMPLISH trial should not be used in very elderly HPs or in patients with prehypertension with clinical evidence of cardiovascular disease. Although both groups of patients are at high risk, there is not enough evidence yet to recommend this treatment.

Finally, we must take into account that most hypertensive patients need more than one drug to achieve BP control, and more than two drugs are required in patients with diabetes or renal failure. The experience shows that a HP without coronary artery disease who needs three drugs for BP control is receiving a triple combination of ACEI/AIIRA-diuretic-CCB. In light of these results, it does not matter in which order these drugs are prescribed in so far as the great benefit is achieved by the blood pressure lowering effect.

BIBLIOGRAPHY

1. Consenso de Hipertensión Arterial. Consejo Argentino de Hipertensión Arterial "Dr. Eduardo Braun Menéndez". Rev Argent Cardiol 2007;75(Supl 3).
2. Consenso Latinoamericano de Hipertensión Arterial. Consejo de Hipertensión Arterial "Dr. Eduardo Braun Menéndez" (SAC). J Hypertens (edición en español) 2001;6:83-110.

3. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al; Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007;25:1105-87.
4. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
5. Turnbull F; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003;362:1527-35.
6. Jamerson K, Bakris GL, Dahlöf B, Pitt B, Velazquez E, Gupta J, et al; ACCOMPLISH Investigators. Exceptional early blood pressure control rates: the ACCOMPLISH trial. *Blood Press* 2007;16:80-6.
7. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366:895-906.
8. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97.
9. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of Hypertension in Patients 80 Years of Age or Older. *N Engl J Med* 2008;358:1887-98.

A REPLY FROM THE AGONIST

I agree with Dr. Mónica Diaz when she states that the only two trials that used combination therapy with ACEI/CCB in one of their arms are the ACCOMPLISH trial and the ASCOT trial.

She emphasizes that although both studies used the same combination therapy in one of their drug regimes, they were administered in a completely different fashion.

In the ACCOMPLISH trial doses were forced-titrated to maximal levels and the ASCOT trial used a stepwise treatment to achieve the therapeutic goal.

I would like to point out that both studies presented similar results using different treatments and were stopped early by the steering committee due to the results obtained in the arm ACEI/CCB compared to other drugs.

I also agree when she emphasizes that in the ASCOT study the greatest reduction in blood pressure occurred in the amlodipine-perindopril arm.

Again, I want to point out that we all know that the most important effect in hypertensive patients is blood pressure reduction which was achieved with this treatment schedule.

Finally, Dr. Díaz mentions that the primary endpoint of the ASCOT study was not statistically significant, but this was related to the fact that the steering committee stopped the trial early in October 2004 due to a reduction in mortality and in other secondary outcomes as stroke.

ACEIs have demonstrated that beyond being excellent antihypertensive drugs, they may prevent coronary events and heart failure.

In addition, calcium channel blockers have demonstrated to be excellent blood pressure lowering drugs with antianginal properties and efficient in stroke prevention.

The combination of these drugs produces a significant reduction in blood pressure levels, prevents target organ damage and decreases the incidence of adverse events, such as edema related to amlodipine.

On the contrary, beta blockers and diuretics potentiate their adverse events, particularly new-onset diabetes and sexual dysfunction with a worse quality of life.

Finally, as we all know, the aim in hypertension treatment is blood pressure control; in most cases two or more drugs are needed to achieve this goal.

At present, two studies early interrupted by a steering committee have demonstrated that angiotensin-converting enzyme inhibitors and calcium channel blockers are the drugs of choice.

Dr. Guillermo Fábregues

A REPLY FROM THE ANTAGONIST

I agree with Dr. Fábregues' concepts on beta blockers; however, my opinion with diuretics is slightly different. Although they may produce metabolic disorders, several studies have demonstrated that these drugs reduce cardiovascular events, and this is the effect we are looking for when we treat a hypertensive patient: we are trying to avoid cardiovascular events. We all know that a considerable number of hypertensive patients need the addition of a third drug, and in these cases diuretics are clearly indicated. Diuretics have demonstrated to reduce blood pressure levels and CVE when added as a second or third option in large trials.

I agree with the opinion regarding renin-angiotensin-aldosterone system inhibitors and calcium channel blockers; however, there are few data to reply the question of the controversy: which is the "best combination"? The answer may not be so simple, as the studies designed to compare "head to head" iso-

lated or combined drugs are also designed to achieve strict blood pressure control. Therefore, a third or fourth drug is added to each treatment group, making the interpretation of the results even more difficult.

Both drugs are excellent and the ACCOMPLISH study has demonstrated the efficacy of combination

therapy with ACEI-CCB; nevertheless, we should not forget the wide experience we have with combined therapy with diuretics. Finally, I think that BP control offers a great benefit as reduced BP level is a protective factor by itself.

Dra. Mónica Díaz