Επίκαιρο Άρθρο

Which Drugs for Hypertension in 2017?

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ABSTRACT

There are a number of different classes of blood pressure lowering drugs that have been widely used in treating arterial hypertension. Overview and meta-analyses of a multitude of comparative randomized controlled trials support the recommendation that all major classes (diuretics, beta-blockers, calcium antagonists, angiotensin converting enzyme inhibitors and angiotensin receptor blockers) can be used for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in combinations with each other. However, some agents should be considered as the preferential choice in specific conditions. Furthermore, lengthy discussions on possible advantages of one or another type of monotherapy appears outdated and sterile, nowadays, that overwhelming evidence has accumulated that in the large majority of hypertensive patients blood pressure goals can only be achieved by combination therapy. Because the major limitation to the success of antihypertensive treatment is scarce adherence of patients to life long therapy, attention to adverse effects of drugs, either in monotherapy and in combination, is an important task of practicing physicians, together with an increasing use of two or three drugs combinations in single pills. Reducing the number of pills to be taken daily has been shown to improve adherence and to increase the rate of blood pressure control.

Are there clinically relevant differences between different classes on antihypertensive drugs?

There are a number of pharmacologically different classes of blood pressure (BP) lowering drugs that, because of these property, have been widely used in treating arterial hypertension. The existence of multiple classes and their discovery and introduction into therapeutic usage at different times have often stimulated experts at developing and discussing ranks or orders of choice or step-care systems, based sometimes on drug costs (older drugs are commonly cheaper than newer ones) or on the assumption of specific protective properties of some agents independent of the BP-lowering action or on the frequency of adverse effects[1], and different recommendations have been given in different guidelines.

However, there has been a very large number of randomized controlled trails (RCTs) comparing the effects on fatal and nonfatal cardiovascular events of different classes of antihypertensive agents between themselves or with placebo, and we have recently completed and published three different sets of meta-analyses that help doctors taking informed decisions. The body of evidence available consists in 1) 55 RCTs comparing in 195267 individuals the effects on cardiovascular events of each of the five major classes of antihypertensive drugs (diuretics, beta-blockers, calcium antagonists, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers) versus placebo[2]; 2) 50 RCTs directly (head-to-head) comparing the cardiovascular disease risk of at least two different classes of drugs[3]; and 3) 38 of the placebo-controlled RCTs

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and 37 of the head-to-head comparative RCTs providing data on treatment-induced adverse events leading to permanent treatment discontinuation[4].

The results of these large meta-analyses are summarized in a qualitative, but easy to understand way in Figure 1. Each major class of BP-lowering drugs when compared to placebo, is able to significantly reduce the risk of stroke and major cardiovascular events[5] and when compared head-to-head to other drug classes have comparable effects on major cardiovascular events considered together and on cardiovascular and all-cause death, but some differences are found in the prevention of cause-specific effects: in particular, diuretics appear to prevent the risk of heart failure better than the other classes, beta-blockers to reduce less effectively the risk of stroke, calcium antagonists to prevent the risk of stroke better and the risk of heart failure less than other classes, the ACE inhibitors to prevent stroke risk less and coronary heart disease risk better than other drugs, and angiotensin receptor blockers are slightly lesseffective than other classes in coronary risk prevention[3]. On the whole, Figure 1 clearly shows that similarities between the effects of the various classes on antihypertensive agents are largely preponderant over small differences.

Figure 1 also shows that, when compared to placebo, the reduction in cardiovascular risk obtained by each class of antihypertensive agents is accompanied by an increase in adverse events leading to treatment discontinuation, with the only exception of angiotensin receptor blockers (discontinuation non-significantly different from placebo) and, when directly compared between themselves, all classes have similar effects on major cardiovascular events, but angiotensin receptor blockers are accompanied by significantly fewer discontinuations due to adverse events[4].

Are there clinically relevant differences between different compounds within a given class of antihypertensive drugs?

Some of the available classes of antihypertensive agents include compounds with different pharmacokinetic and pharmacodynamic properties and mechanisms of action, but unfortunately no RCT head-to head comparing different compounds within a given class has been performed yet, and, therefore, definitive evidence to answer this question is not available. However, indirect evidence based on placebo-controlled trials suggests no substantial difference exists.

Among diuretics, pharmacological differences exist between chlorthalidone, indapamide and hydrochlorothiazide, with chlorthalidone being, milligram by milligram, a more potent diuretic than hydrochlorothiazide, but when each of these compounds was compared with placebo in RCTs all three compounds were found capable of significantly reducing cardiovascular event risk[2]. The diuretic action of spironolactone has a different mechanism, namely,

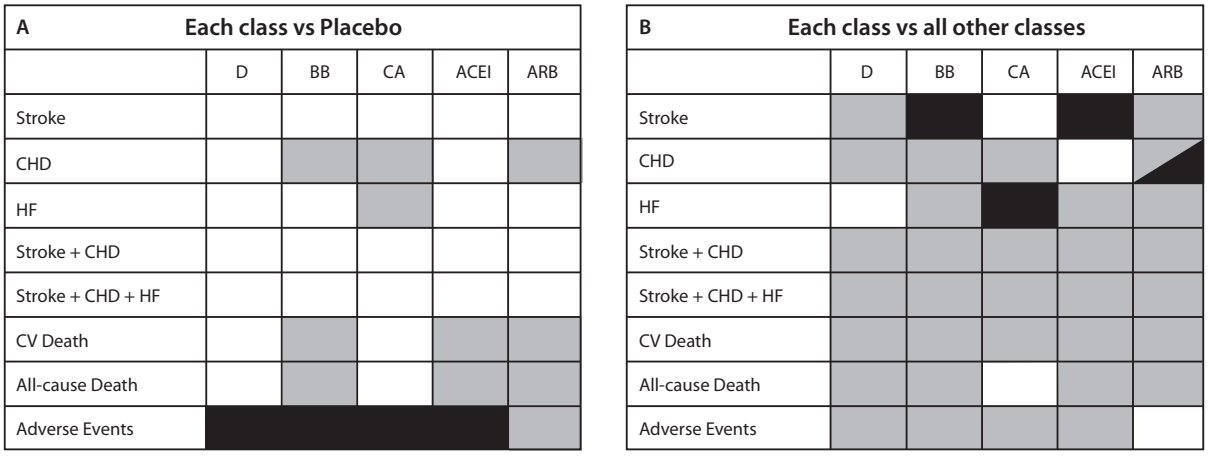

Figure 1. *Comparisons of each of five major classes of antihypertensive agents versus placebo and comparisons of each class versus all other classes on seven major outcomes and treatment discontinuations because of adverse events. The effect of each drug class indicated on the top of the columns versus the comparator (A. placebo, B. all other drugs) are indicated as follows: White, better effect; Grey, non-significant difference in effect; Black, worse effect. D, diuretics; BB, beta-blockers; CA, calcium antagonists, ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers. CHD, coronary heart disease events; CV, cardiovascular; HF, Heart failure (from data in Thomopoulos, Parati, Zanchetti, references 2-4).*

antagonism of mineralcorticoid receptors, and has been found to be particularly effective in lowering BP in so-called treatment resistant hypertension[5].

As far as beta-blockers are concerned, most of available RCTs have used atenolol, whose limited effectiveness in stroke prevention has been attributed to a limited capacity of lowering central blood pressure[6], a limitation that is not shared by the subclass of vasodilating beta-blockers, such as nebivolol[7]. Calcium antagonists are also a heterogeneous class of agents. Most of the RCTs comparing calcium antagonists with other classes have used dihydropyridines, but a number of RCTs have also used non-dihydropyridines: meta-analyses separately considering the two subclasses have not shown substantial differences in effectiveness[3]. In summary, when choosing a compound within a given class of antihypertensive agents, the recommendation has been given to select a compound that (i) has a sufficiently long duration of action to allow once-daily administration, (ii) has been used in an event-based RCT, and (iii) has a lower cost for the patients or for the national health system[8].

Do patients' characteristics or accompanying conditions make a class of antihypertensive agents preferable in some group of patients?

There is no evidence from RCTs that the various classes of antihypertensive drugs differ in their capacity of reducing cardiovascular risk according to age[9] or sex[10] (except for caution in using renin-angiotensin system blockers in women with childbearing potential because of possible teratogenic effects in case of pregnancy) or level of cardiovascular risk[3]. Recent evidence from a meta-analysis shows that, in hypertensive patients with type-2 diabetes, blockers of the renin-angiotensin system have some greater effectiveness in preventing cardiovascular and renal events than other drug classes[11]. Furthermore, it is known that blockers of the renin-angiotensin system appear to be less protective from cardiovascular events in blacks than in whites[12]. Finally, the European guidelines indicate other conditions in which some antihypertensive drug classes appear to be preferable (Tables) as well as a limited

Table 1. Drugs to be preferred in specific conditions

Condition	Drug
Asymptomatic organ damage	
LVH	ACE inhibitor, Calcium antagonist, ARB
Asymptomatic atherosclerosis htraatherosclerosisatherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB
Clinical event	
Previous stroke	Any agent effectively lowering BP
Previous myocardial infarction	BB, ACE inhibitor, ARB
Angina pectoris	Beta-blocker, Calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, Mineralocorticoid receptor antagonist
Aortic aneurysm	Beta-blocker
Atrial fibrillation, prevention	Consider ARB, ACE inhibitor and Beta-blocker or Mineralocorticoid receptor antagonist
Atrial fibrillation, ventricular rate control	BB, Non-dihydropyridine calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, Calcium antagonist
Other	
ISH (elderly)	Diuretic, Calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, Beta-blocker, Calcium antagonist
Blacks	Diuretic, Calcium antagonist

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BB, beta blocker; BP, blood pressure; ESRD, end stage renal disease; ISH, isolated systolic hypertension; LVH, left ventricular hypertrophy.

number of conditions to be considered as contraindications or limited indications for any specific class of drugs.

How to initiate antihypertensive treatment: monotherapy or combination therapy?

There is no doubt that monotherapy can seldom achieve goal BP values, that is systolic BP of about 130 mmHg and diastolic BP of about 80 mmHg, except in individuals with very mild BP elevations, and therefore there is general agreement that in most hypertensive patients recourse should be made to combination therapy, that is using two or more drugs in association. The point is whether initiation of treatment should always, or at least in most cases, be done by using a single drug with subsequent change to drug combination when BP goal is not attained, or whether treatment should always, or in most cases, initiate by administering a two-drug combination. In principle, there are advantages and limitations inherent to both approaches[13]. Initiating by a single agent has the advantage that the effectiveness or lack of effectiveness of that agent can be determined, and eventual adverse events can be safely ascribed to a given agent. Furthermore, the administration of an ineffective drug can be avoided. The limitation is that the sequential search of the most effective agent may take time, delay the achievement of the BP goal, and the laborious changes of monotherapies may discourage patients and lead some of them to discontinue treatment.

Initiating by a combination of two drugs has the obvious advantage that BP goal can be more easily and promptly obtained, a significant advantage in hypertensive patients at high or very high cardiovascular risk and also a psychological incentive for patients to continue with BP lowering treatment. The major limitations is that patients may receive long term not tern treatment with an ineffective or scarcely effective drug, and the frequent habit to add other drugs or other drug combinations on top of an initial combination when BP goal is not obtained may lead to the simultaneous use of four or more different agents without knowing how many of these drugs are really effective in lowering BP in a specific patient. Likewise, initiation with combination therapy makes it more difficult to identify the drug responsible of eventual adverse events.

The prevalent opinion now is that the pros of initiating with combination therapy outnumbers the cons, and in most cases antihypertensive treatment can be started with a two drug combination, whereas monotherapy should be reserved to hypertensive individuals with mild BP elevation (grade 1: SBP 140-159 vs. DBP 90-99 mmHg) and low to moderate level of cardiovascular risk[13]. However, combination therapy remains an alternative initial approach even in these patients, and is supported by recent data from the HOPE-3 trial[14], in which patients with grade 1 hypertension (but not those with high normal BP) and moderate cardiovascular risk showed a reduction of cardiovascular events by a fixed combination treatment when compared to placebo treatment.

Which drug combinations should be preferably used?

There is strong trial evidence against the use of full doses of two renin-angiotensin system blockers together. Dual combination of an ACE inhibitor and an angiotensin receptor blocker showed no further reduction of cardiovascular events accompanied by an excess of renal adverse events as compared to monotherapy in the ONTARGET[15] and VA-NEPHRON-D[16] trials. Likewise, combination of the renin inhibitor, aliskiren, with either an ACE inhibitor or an angiotensin receptor blocker was also shown to produce an excess of renal adverse events in the patients with diabetes of the ALTITUDE trial[17].

All other different drug classes can be combined together with at least an increased BP lowering effect as compared with monotherapy. Direct evidence of a greater reduction in cardiovascular events is scanty, however, as RCTs confirming different dual combinations are few and, sometimes, contradictory. Anyway, a large number of RCTs initiated with a single drug have subsequently added other drugs whenever BP goal was not obtained, and therefore provide evidence on the suitability, if not on the benefits, of combination therapy. The well-known hexagone suggested by European guidelines[13] (Figure 2) indicates that useful experience is available with combinations of either an ACE-inhibitor or an angiotensin receptor blocker with either a calcium antagonist or a thiazide diuretic, and of a calcium antagonist with a thiazide diuretic. Favourable experience is also available with the combination of a beta-blocker and a thiazide diuretic, with the warning that, at least in individuals with the metabolic syndrome, this combination may facilitate the onset of diabetes mellitus.

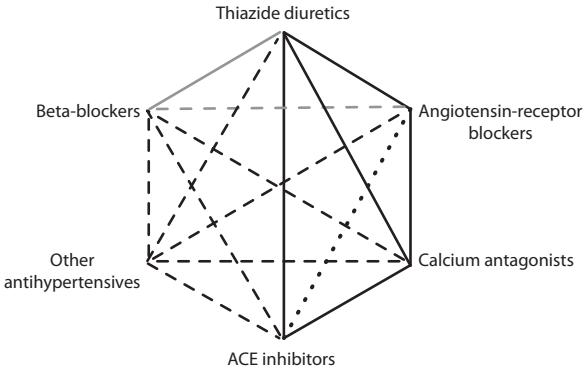

Figure 2. *Possible combinations of classes of antihypertensive drugs. Black continuous lines: preferred combinations; Gray continuous lines: useful combination (with some limitations); Dashed lines: possible but less well-tested combinations: Dotted line: not recommended combination. Only dihydropyridine calcium antagonists should normally be combined with beta-blockers (from reference 13).*

Recommendations of guidelines

On the basis of this body of evidence, the recommendations on choice of antihypertensive drugs provided by the 2013 European Society of Hypertension and European Society of Cardiology hypertension guidelines[13] appear to be well founded. Diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers are all suitable and recommended for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in combinations with each other. However, some agents should be considered as the preferential choice in specific conditions or because of greater effectiveness in specific types of organ damage. The recommendation to leave the choice of the drug (or the drug combination) to be used in an individual hypertensive to the practicing physician is also based on the awareness that, while the benefits of BP-lowering by any antihypertensive agent (i.e., prevention of cardiovascular events) cannot be measured in the individual patients (they can only be measured epidemiologically), individual decisions on the drugs to be used will be taken fundamentally on the base of the achievement of BP goals and the eventual occurrence of adverse effects, which can and should all be carefully measured in the follow-up of individual patients[18].

Attention to adverse effects of drugs is an important task of the practicing physician taking charge of hypertensive patients, because adverse effects of antihypertensive agents, though rarely relevant for health, are nonetheless one of the most frequent causes of low adherence of patients to antihypertensive treatment. Low treatment adherence remains the most frequent obstacle to taking advantage of all the well known benefits of BP lowering therapy, and probably represents the most important target to be aimed at by research in the next future.

An important step forward in this direction consists in using two or three combinations therapy in single pills at fixed combinations. Reducing the number of pills to be taken daily has been shown to improve adherence and to increase the rate of BP control[19]. This approach is now facilitated by the availability of several single-pill combinations of the same two or three drugs with different doses, thus allowing the possibility of modifying the dose of one drug independently of the other. It is an easy prediction that fixed-dose combinations of different drugs in a single pill will increasingly be the antihypertensive drugs of the near future.

REFERENCES

1. Mancia G, Zanchetti A. Choice of antihypertensive drugs in the European Society of Hypertension-European Society of Cardiology guidelines: specific indications rather than ranking for general usage. *J Hypertens.* 2008; 26: 164-168.
2. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs – overview and meta-analyses. *J Hypertens*. 2015; 33: 195-211.
3. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering on outcome incidence in hypertension: 5. Head-to-head comparisons of various classes of antihypertensive drugs – overview and meta-analyses. *J Hypertens*. 2015; 33: 1321-1341.
4. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: meta-analyses of randomized trials. *J Hypertens*. 2016; 34: 1921-1932.
5. Williams B, MacDonald TM, Morant S. et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015; 386: 2059-2068.
6. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006; 113: 1213-1225.
7. Dhakam Z, Yasmin, McEniery CM, Burton T, Brown MJ, Wilkinson IB. A comparison of atenolol and nebivolol in isolated systolic hypertension. *J Hypertens*. 2008; 26: 351-356.

8. Coca A, Lopez-Jaramillo P, Thomopoulos C, Zanchetti A. Best antihypertensive strategies to improve blood pressure control in Latin America: position of the Latin American Society of Hypertension. *J Hypertens*, in publication.

9. Turnbull F, Neal B, Ninomiya T, et al. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *Brit Med J*. 2008; 336: 1121-1123.

10. Turnbull F, Woodward M, Neal B, et al. Blood Pressure Lowering Treatment Trialists' Collaboration. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. *Eur Heart J*. 2008; 29: 2669-2680.

11. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 – Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. *J Hypertens*. 2017; 35: 922-944.

12. Ogedegbe G, Shah NR, Phillips C, et al. Comparative effectiveness of angiotensin-converting enzyme inhibitor-based treatment on cardiovascular outcomes in hypertensive blacks versus whites. *J Am Coll Cardiol*. 2015; 66: 1224-1233.

13. Mancia G, Fagard R, Narkiewicz K, et al. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2013 ESH/ESC Guidelines for the management of arterial hypertension. *J Hypertens*. 2013; 31: 1281-1357.

14. Lonn EM, Bosch J, López-Jaramillo P, et al. HOPE-3 Investigators. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016; 374: 2009-2020.

15. Yusuf S, Teo KK, Pogue J, et al. ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008; 358: 1547-1559.

16. Fried LF, Emanuele N, Zhang JH, et al. VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013; 369: 1892-1903.

17. Parving HH, Brenner BM, McMurray JJ, et al. ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012; 367: 2204-2213.

18. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering treatment in hypertension: 8. Outcome reductions vs. discontinuations because of adverse drug events – meta-analyses of randomized trials. *J Hypertens*. 2016; 34: 1451-1463.

19. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension*. 2010; 55: 399-407.