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Tailoring treatment to comorbidities

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Abstract: Cardiovascular disease is the leading cause of death in many countries across the world, and is the final step in the interaction among several risk factors, including hypertension. The presence of additional cardiovascular risk factors is a common feature in more than 80% of hypertensive patients, and must be considered in the choice of blood pressure-lowering treatment. According to ESC-ESH guidelines, the combination of a renin-angiotensin system (RAS) inhibitor and a calcium-channel blocker and/or a diuretic can cover the large majority of therapeutic needs in patients with hypertension complicated by additional metabolic risk factors and target-organ damage. In particular, the results of the ASCOT and ADVANCE trials and their long-term follow-up have demonstrated the supremacy of angiotensin-converting enzyme ACE inhibitors (perindopril) combined with amlodipine and/or indapamide in high-risk and diabetic patients in comparison with other classes of first-line treatments. Furthermore, the results of the ASCOT-LLA study have demonstrated a favorable synergistic interaction between statins (atorvastatin) and blood pressure-lowering treatment with a larger benefit in terms of major cardiovascular events in patients treated with the combination of an ACE inhibitor and a calcium channel blocker. The differences in the individual response to separate treatment strategies are reasonably supported by distinct pathophysiological profiles, with a different level of involvement of the renin-angiotensin and calcium transport systems in patients with a higher probability of cardiovascular complications. The available evidence clearly supports the importance of an individualized choice of antihypertensive drugs in the treatment of patients with hypertension complicated by comorbidities contributing to the overall cardiovascular risk profile. ■ *Heart Metab*. 2019;79:21-24

Keywords: ACE inhibitor; hypertension; lipid; risk factor

Introduction

Cardiovascular disease (CVD) is the leading cause of death across the most developed countries and its prevalence is rapidly increasing in the developing countries as well.[1] The pathogenesis of CVD involves the interaction of several risk factors that contribute to the development and progression of cardiovascular disease. Among them, a primary role is played by hypertension, diabetes, obesity and being overweight, abnormalities of lipid control, and poor lifestyle.[2-4] High blood pressure is certainly the most important risk factor, affecting over 30% of the overall population, and is responsible for a significant increase in the risk of major cardiovascular complications including myocardial infarction, stroke, renal disease, and peripheral artery disease.[3] Hypertension is frequently associated with one or more additional risk factors for cardiovascular disease, as clearly evident from the hypertensive population of the Framingham Study and the Brisighella Heart Study,[5] where about 80% of subjects were affected by at least one additional risk factor with a large prevalence of lipid disorders (high total cholesterol and/or tryglicerides). An additional portion of cardiovascular risk in hypertension is the result of the presence of target-organ damage that primarily involves the heart (left ventricular hypertrophy—LVH), the kidney (various

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degrees of renal impairment and proteinuria) and the arterial vessels (reduced distensibility and increased vascular stiffness) and is responsible for an excess in the risk of cardiovascular complications beyond blood pressure control alone.[6,7] Finally, many recent studies have clearly demonstrated that the prevalence of hypertension is increased in several patient groups with non-cardiovascular diseases including chronic inflammatory diseases (eg, rheumatoid arthritis, psoriasic arthritis), psychiatric illness, headache, and hyperuricemia/gout.[8,9] In particular, elevated levels of serum uric acid have been demonstrated to increase the relative risk of new-onset hypertension as well as the rate of major cardiovascular complications (myocardial infarction, stroke, and heart failure) in patients with hypertensive disease, regardless of the presence of additional CV risk factors. Most of these additional risk factors coexist in the same hypertensive patients[5] and are responsible for a significant increase in the residual risk of major CV events[10] in patients with a satisfactory blood pressure control in response to treatment.[10]

All this evidence clearly suggests the importance of an integrated treatment of hypertension in patients with multiple risk factors and/or target-organ damage and/or additional non-cardiovascular disease. The choice of the antihypertensive strategy should be adapted to the characteristics of the patient and the concomitant disease according to the results of randomized clinical trials and additional evidence from observational studies and daily practice.

Hypercholesterolemia

In practical terms the most common comorbidity in the hypertensive population is a lipid disorder, in particular an increase in the plasma LDL-cholesterol.[3] The treatment of these patients is based on the concomitant use of antihypertensive drugs and statins with or without additional lipid-lowering drugs. The 2018 ESC-ESH Guidelines for hypertension[7] clearly support the use of drug combinations since most of these patients have a medium-to-high risk profile that can be managed by the use of RAS blockers, diuretics, and calcium channel blockers. On the other hand, the results of the Cholesterol Collaborative Trialist Group have reported the efficacy of statin treatment in hypertensive patients with a relative risk reduction of major CV events comparable to those observed in the normotensive population.[11] The results of the CCT meta-analysis have been confirmed by the results of the ASCOT-LLA study, where treatment with 20 mg of atorvastatin in patients with hypertension has reduced the rate of major cardiovascular events.[12] Recently, the benefit of statin treatment was confirmed over 15 years of follow-up, despite a massive uptake of statin therapy in the group of patients originally allocated to placebo control.[13] Regarding the best antihypertensive treatment in patients with hypercholesterolemia, the results of the ASCOT-LLA[14] *(Figure 1)* clearly suggest the supremacy of concomitant administration of an ACE inhibitor (perindopril) with a dihydropyridine calcium channel blocker (CC—amlodipine) over the treatment with a β-blocker (atenolol) and a diuretic (hydrochlorothiazide). The combination of ACEI and CCB was responsible for a great proportion of the benefit observed in the study in terms of prevention of coronary artery disease and stroke as a probable consequence of some favorable interaction between the drugs and the mechanisms responsible for the progression of atherosclerosis. According to the results of the ASCOT BPLA study,[12] the same combination of ACE inhibitor and CCB should be recommended in patients with metabolic syndrome that affects a high proportion of the hypertensive population and is associated with an increase in serum TG in over 30% of the patients.[3] In particular, the condition of insulin resistance, which is usually observed in these patients, can promote an overactivation of the tissue renin-angiotensin system that can contribute to explaining both the higher rate of cardiovascular events and the favorable response to renin-angiotensin and calcium channel blockade. The same mechanism is prob-

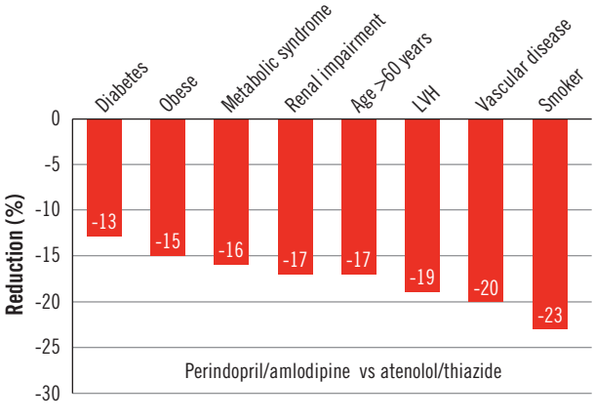

Figure 1 *Effects of treatment with perindopril/amlodipine vs atenolol/thiazide in different subgroups of comorbid hypertensive patients in the ASCOT BPLA study.*

ably involved in the favorable effect of perindopril and amlodipine in patients with elevated LDL-cholesterol with a large involvement of a common pathophysiological pathway in the excess of cardiovascular risk observed in patients where hypertension is complicated by lipid disorders.

Diabetes

Among the different conditions complicating hypertensive disease, the presence of diabetes, and in particular type 2 diabetes, is very common. Glucose abnormalities significantly increase the risk of major cardiovascular complications associated with hypertension with a probability of coronary artery disease that is as much as twice that in patients with normoglycemia and the same level of blood pressure control.[15] In patients with hypertension and diabetes, the guidelines emphasize the importance of blood pressure control and the achievement of appropriate targets of treatment with the extensive use of drug combinations as first-line strategy. Renin-angiotensin inhibitors are certainly the drugs of choice according to their cardiovascular and renal protective effect and should be combined with diuretics and/or calcium channel blockers. The effectiveness of the double combination of ACE inhibitors and CCBs in diabetic patients has been demonstrated by the prespecified subgroup analysis of the ASCOT-BPLA study, where the administration of perindopril and amlodipine resulted in a significant decrease in the rate of the primary end point (-13%, *P*=0.02). Similar results have not been obtained with the use of angiotensin receptor blockers (ARBs) despite a comparable reduction in blood pressure, and the outcome results of clinical trials involving angiotensin II receptor blockers and CCBs are still awaited. As far as the clinical efficacy of the combination of an RAS blocker with a diuretic in the diabetic population is concerned, the results of the ADVANCE trial[16] have clearly demonstrated that perindopril with indapamide favorably affects the primary end point (Hazard Ratio=0.91; 095% CI: 0.83-1.00 *P*=0.041) when compared with placebo despite the inclusion of an open-label ACE inhibitor in the control group. Similar results have been obtained with the use of ARBs (Losartan, Valsartan)[17,18] in combination with hydrocholorothiazide despite very different study designs that involved nondiabetic patients and were actually based on a comparison between single drugs instead of combinations. The clinical benefit observed in the ADVANCE trial with the combination of perindopril and indapamide was increased in patients adding calcium channel blockers,[19] thus confirming the importance of combination treatment and the reliability of the guideline assumptions in terms of recommended drugs. The results of the ADVANCE study have been extended by the long-term observation of the population in the ADVANCE-ON study[20] where the benefit of randomized treatment was maintained after the withdrawal of double-blind therapy. Reasonably, the further step of personalized treatment in patients with diabetes at risk of cardiovascular disease will be the extensive use of the most recent antidiabetic drugs (GLP-1 agonists, DPP-4 inhibitors) and in particular SGLT-2 inhibitors, that have been shown to improve blood pressure control and cardiovascular outcome.[21] Among the first-line glucose-lowering drugs only metformin and gliclazide have been proven to exert some degree of cardiovascular protection in patients with diabetes and impaired metabolic control. In particular the factorial analysis of the ADVANCE study[22] has confirmed some favorable interaction in patients treated with the combination of ACE inhibitor, diuretic, and gliclazide suggesting the importance of an integrated control of concomitant risk factors in patients with hypertension and metabolic diseases.

Conclusion

Hypertension is typically accompanied by comorbidities that act as additional risk factors in over 80% of patients. The treatment of arterial hypertension is largely based on blood pressure control but the choice of the antihypertensive strategy should be individualized according to patient characteristics, available evidence from randomized clinical trials, hypertension guidelines, and pathophysiological background, with an almost universal support for first-line combinations of drugs inhibiting the renin-angiotensin system, vascular calcium handling, and the salt and water axis. ■

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REFERENCES

1. Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*. 2006;367(9524):1747e57.
2. Tunstall-Pedoe H, Chen R, Kramarz P. Prevalence of individuals with both raised blood pressure and raised cholesterol in WHO MONICA Project population surveys 1989-97. *Pharmacoepidemiol Drug Saf.* 2004;13(suppl 1):S307-S308.
3. Mancia G, Parati G, Borghi C, et al, for SMOOTH investigators. Hypertension prevalence, awareness, control and association with metabolic abnormalities in the San Marino population: the SMOOTH study. *J Hypertens.* 2006;24(5):837-843.
4. Egan BM, Li J, Qanungo S, Wolfman TE. Blood pressure and cholesterol control in hypertensive hypercholesterolemic patients: national health and nutrition examination surveys 1988-2010. *Circulation*. 2013;128(1):29-41.
5. Borghi C, Dormi A, Ambrosioni E, et al, On behalf of the Brisighella Heart Study working party. Relative role of systolic, diastolic and pulse pressure as risk factors for cardiovascular events in the Brisighella Heart Study. *J Hypertens*. 2002;20(9):1737-1742.
6. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of BloodCholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;139(25):e1082-e1143.
7. Williams B, Mancia G, Spiering W, et al; Authors/Task Force Members. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens*. 2018;36(10):1953-2041.
8. van Breukelen-van der Stoep DF, van Zeben D, Klop B, et al. Marked underdiagnosis and undertreatment of hypertension and hypercholesterolaemia in rheumatoid arthritis. *Rheumatology (Oxford).* 2016 ;55(7):1210-1216.
9. Borghi C, Rosei EA, Bardin T, et al., Serum uric acid and the risk of cardiovascular and renal disease, *J Hypertens.* 2015;33:1729-1741.
10. Neaton, JD, Wentworth D, & The Multiple Risk Factor Intervention Trial Research Group. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: Overall findings and differences by age for 316,099 white men. *Arch Intern Med*. 1992;152:56-64.
11. Cholesterol Treatment Trialists (CTT) Collaboration. Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174000 participants in 27 randomised trials. *Lancet*. 2015; 385(9976):1397-1405.
12. Dahlöf B, Sever PS, Poulter NR, 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(9489):895-906.
13. Gupta A, Mackay J, Whitehouse A, et al. Long-term mortality after blood pressure-lowering and lipid-lowering treatment in patients with hypertension in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy study: 16-year follow-up results of a randomised factorial trial. *Lancet.* 2018;392(10153):1127-1137.
14. Sever PS, Dahlof B, Poulter NR, et al, ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361(9364):1149-1158.
15. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention. *Trial Diabetes Care*. 1993;16(2):434-444.
16. Patel A et al, ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet.* 2007;370(9590):829-840.
17. Dahlöf B, Devereux RB, Kjeldsen SE, 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(9311):995-1003.
18. Julius S, Kjeldsen SE, Weber M, et al; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet.* 2004;363(9426):2022-2031.
19. Chalmers J, Arima H, Woodward M, et al. Effects of combination of perindopril, indapamide, and calcium channel blockers in patients with type 2 diabetes mellitus: results from the Action In Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) trial. *Hypertension.* 2014;63(2):259-264.
20. Zoungas S, Chalmers J, Neal B, et al; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med.* 2014;371(15):1392-1406.
21. Baker WL, Buckley LF, Kelly MS, et al. Effects of sodium-glucose cotransporter 2 inhibitors on 24-hour ambulatory blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc.* 2017;6(5).
22. Zoungas S, Arima H, Gerstein HC, Holman RR, et al; Collaborators on Trials of Lowering Glucose (CONTROL) group. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. *Lancet Diabetes Endocrinol.* 2017;5(6):431-437.