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Hypertension and dyslipidemia: where are we?

Part I: Latest developments in diagnosis and treatment according to recent hypertension guidelines

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Recent updates in hypertension guidelines in the United States, Europe, and other areas throughout the world are remarkably consistent on almost all major aspects of diagnosis and treatment of the disease. The main disagreement is found within the redefinition of hypertension in US guidance to a lower seated office blood pressure (BP) than that used in the rest of the world, a move made to encourage consideration of lifestyle interventions in patients at a low level of hypertension, with drug treatment reserved for those at higher cardiovascular (CV) risk. Both US and European guidance emphasize the importance of CV risk assessment for CV prevention. Evidence indicates that although with existing medications BP control rates of 80% or higher in routine clinical practice should be possible, fewer than one in seven patients are detected, treated, and controlled. Thus, the treatment strategy must change; simplification of the drug treatment strategy (such as with single-pill drug combinations) was a major theme in European guidance. Across the world, recommended BP targets were reduced. Although all guidelines advise to improve lifestyle factors to reduce CV risk, additional strategies to reduce CV risk factors beyond BP lowering are needed, especially for those with high or very high risk and in those for whom achieving BP targets is difficult. To this effect, European guidance recommends additional use of statins, as well as antiplatelet therapy in secondary prevention. This review looks briefly at these latest developments.

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Introduction

Guidelines development involves the evaluation and grading of the evidence from clinical studies to create recommendations for the screening, diagnosis, and treatment of hypertension. New guidelines are often eagerly anticipated, and there have been major recent updates in hypertension guidelines in the United States (2017) and in Europe (2018).[1,2] These have been followed by updated guidelines in many other parts of the world. Unlike previous iterations of global guidelines, a major feature of these new guideline developments is the level of consistency rather than disagreement on almost all major aspects of diagnosis and treatment of hypertension.[3]

BP treatment thresholds and the classification of hypertension

The main disagreement between guidelines was the decision of the US guideline developers to reclassify the definition of hypertension as a seated office blood pressure (BP) of ≥130/80 mm Hg, whereas in the rest of the world, the classification of

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hypertension has remained unchanged at ≥140/90 mm Hg. The latter based the definition of hypertension as the level of BP at which drug treatment should be considered. The US guidance based their new definition of hypertension largely on epidemiological evidence of increased cardiovascular (CV) risk at BP levels above 130/80 mm Hg and suggested that patients with this level of BP have stage 1 hypertension and should be considered for lifestyle interventions, with drug treatment reserved for those at higher levels of CV risk (ie, 10% risk over 10 years). Whereas this has attracted a lot of discussion and debate, the debate has overshadowed the remarkable consistency of the guidelines with regard to diagnosis of hypertension (advocating wider use of out-of-office BP) and the treatment strategy (advocating use of similar combinations of drugs and wider and earlier use of single-pill combination therapy to improve adherence to treatment and speed and effectiveness of BP control).[3]

US guidance and European Society of Cardiology (ESC)–European Society of Hypertension (ESH) guidelines both emphasized the importance of CV risk assessment for CV disease prevention, but the ESC-ESH guideline went further in recommending the concomitant use of statin therapy for all high- and very-high-risk patients and the consideration of the wider use of statin therapy in patients at low-to-moderate CV disease risk to further reduce their risk beyond the impact of improved BP control, see below.[2]

Poor detection, treatment, and control of BP–the impetus for change

Despite numerous iterations of guidelines over decades, high BP remains the leading preventable cause of death globally and is projected to retain this standing by 2040.[4] Moreover, on average, less than half of patients with hypertension are detected by existing screening programs (47%), less than half are treated (41%), and of those treated, only about one-third (35%) are controlled to a BP <140/90 mm Hg.[5] This means that of all people with hypertension globally, less than one in seven patients is detected, treated, and controlled. By any standards, this is unacceptable. It is also a tragedy because existing evidence suggests that it would not be difficult with existing medications to easily achieve BP control rates of 80% or more in routine clinical practice. So, how can this be fixed? As trials have shown much better control rates than routine practice, it is clear that there is nothing wrong with the drugs used to treat hypertension; it was the treatment strategy that needed to change.

The drug-treatment strategy for hypertension

Simplifying the drug-treatment strategy was a major theme of the ESC-ESH guideline.[2] The guideline noted the following: (i) combinations of at least two drugs would be required to control BP to the new BP targets; (ii) treatment should usually begin with a two-drug combination, the only exceptions being people with mild grade 1 hypertension in whom BP might be controlled with one drug (usually younger patients) or in frail older patients in whom more gentle lowering of BP may be needed for safety reasons; (iii) because combinations of drugs will now be used for the majority of patients, these should ideally be prescribed as single-pill combinations to reduce the pill burden and tackle the problem of poor adherence to treatment, which appears to be strongly influenced by the number of pills[6]; (iv) the treatment strategy for most patients should be based on a triad of treatments, ie, renin-angiotensin-system (RAS) blockade (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]) in combination with calcium channel blockade (CCB) and/or thiazide-like diuretics[7]; and finally, (v) the β-blockers should still be used, at any stage of the treatment pathway, when there is a specific indication for their use, eg, in patients with angina or heart failure or who require heart rate control.[1,2] These simple principles allowed the creation of a simple treatment algorithm that is applicable for almost all patient groups *(Figure 1),* with modified algorithms provided for those patients with specific comorbidities requiring adjustments to the treatment algorithm, eg, heart failure, atrial fibril-

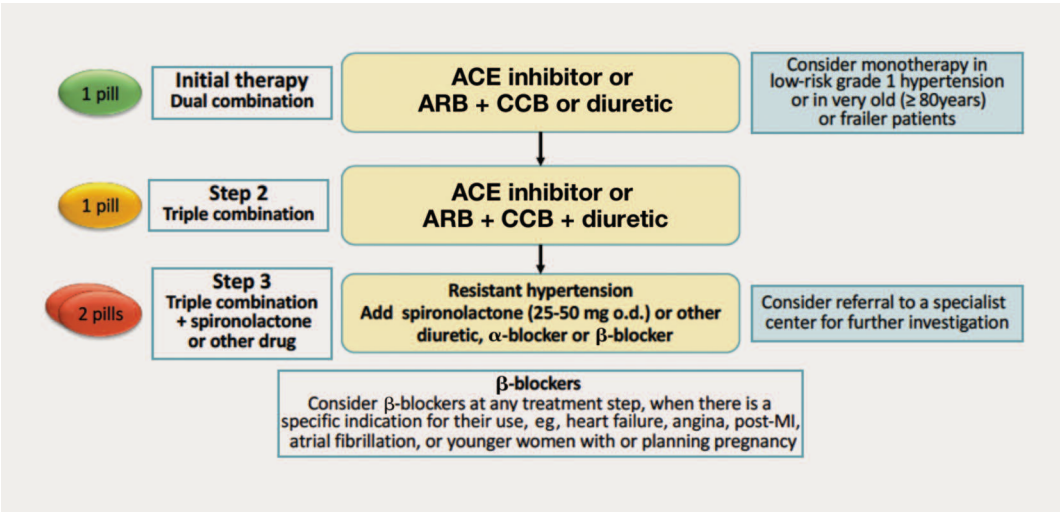

Figure 1. *2018 ESC-ESH Hypertension treatment algorithm.*

Core drug-treatment strategy for uncomplicated hypertension and most patients with hypertension-mediated organ damage, cerebrovascular disease, diabetes, or peripheral vascular disease.
Abbreviations: *ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB calcium channel blocker; MI myocardial infarction; O.D., once daily.*
After reference 2: *Williams et al.* Eur Heart J. *2018;39(33): 3021-3104.*

lation, and chronic kidney disease.[2] The expectation is that the application of this treatment algorithm and wider use of single-pill combinations will simplify and transform the treatment of hypertension and double BP control rates.

In the US guideline[1] and others around the world, a similar treatment strategy using similar drug combinations has been advocated. These guidelines also advocate consideration of initial therapy with a two-drug combination and the wide use of single-pill combination therapies to reduce pill burden. This is reassuring as it suggests widespread similarities in interpretation of the evidence and for the optimal drug treatment of hypertension.

Finally, with respect to drug treatment, all guidelines recommend that when BP is not controlled by best-tolerated doses of the recommended three BP-lowering drugs, this is termed resistant hypertension and the best treatment option is the addition of low-dose spironolactone (25-50 mg daily) provided that the renal function is not substantially impaired (ie, estimated glomerular filtration rate [eGFR] ≥45 mL/min/1.72m^2) with β-blockers, α-blockers, other mineralocorticoid receptor antagonists, amiloride or additional diuretics as an alternative when spironolactone is not tolerated.[1,2,8,9]

BP treatment targets

Recommended BP treatment targets have been reduced across the world. In the United States, a BP goal of <130/80 mm Hg is recommended for all.[1] In Europe, the target is more graded.[2] In Europe, the guideline states that the first objective is to get BP <140/90 mm Hg in all treated patients. The next objective is to aim for a BP of 130/80 mm Hg if possible and consider going lower—ie, <130/80 mm Hg—in younger patients (<65 years) but not older patients (≥65 years).[2] The European guideline also introduced a "target range" with a lower safety boundary, ie, in younger patients, aim for <130/80 mm Hg but not usually lower than 120/70 mm Hg, and in older patients, <140/90 mm Hg but not usually less than 130/80 mm Hg. All guidelines recognize that these targets may not be achievable in all, especially in older and frailer patients, who may be less tolerant of more aggressive BP lowering and in whom the monitoring for adverse effects and tolerability of BP lowering is important. In this regard, the European target range concept encourages a personalized approach to treatment, accepting the fact that not everybody will be able to reach the lower boundaries of the target. In reality, the approach to BP targets adopted in Europe (and most other parts of the world) is not radically different to that adopted in the United States, except for the target in elderly patients, which is more aggressive in the United States at <130/80 mm Hg for all.

Going beyond BP to reduce CV disease risk

There is no doubt that improving BP control in more patients with the new treatment strategy and the lower BP targets should substantially reduce morbidity and mortality from CV disease. However, this alone is not enough. It is well documented that many patients with hypertension have additional risk factors for CV disease, notably, dyslipidemia and glucose intolerance, as well as lifestyle risk factors such as obesity, unhealthy diet, sedentary lifestyle, and smoking.[10,11] Thus, BP lowering alone will not achieve all that could be achieved in terms of CV risk reduction.

Lifestyle interventions are important

All guidelines provide advice to improve lifestyle factors to reduce CV disease risk. Some of these interventions can also help prevent the development of hypertension, reduce the amount of medication needed to control BP, and help reduce BP further in treated patients. All guidelines recommend maintaining an ideal body weight, increased physical activity, moderation of salt and alcohol intake, and a healthy balanced diet.

Such lifestyle interventions have been advocated for years with variable success in implementation. As discussed above, a key motivation behind the reclassification of hypertension in the US guideline was to encourage earlier concerted use of lifestyle interventions in patients with a BP ≥130/80 mm Hg

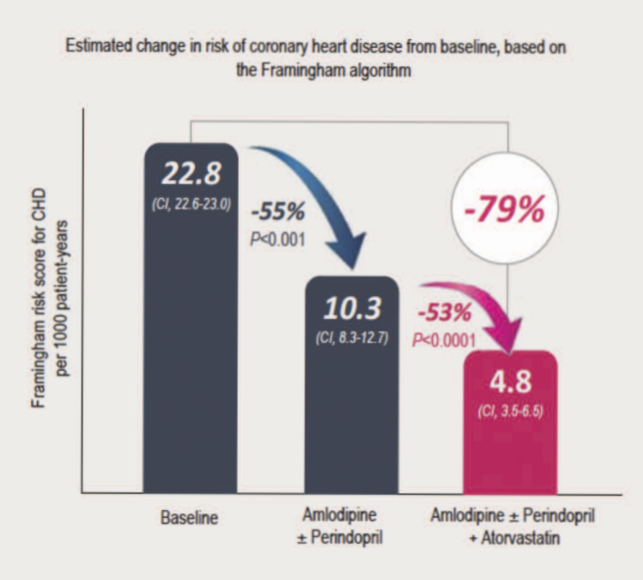

Figure 2. Predicted reduction in coronary heart disease risk with optimal treatment for hypertension and lipid lowering with a statin in the ASCOT trial.

Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CHD, coronary heart disease; CI, confidence interval.
After reference 14: Sever et al. Int J Cardiol. *2009;135(2):218-222.*

to try and prevent the development of more significant hypertension and reduce CV risk. However, it is an inescapable fact that lifestyle interventions are often poorly adhered to, especially over the longer term, and additional strategies to reduce CV risk beyond BP lowering are needed, especially for high- or very-high-risk patients and/or in those in whom achieving the recommended BP targets is difficult.

Concomitant drug therapy to reduce CV risk in hypertensive patients

Beyond and in addition to lifestyle interventions, there are two strategies advocated by the ESC-ESH guideline to further reduce CV risk in hypertensive patients: (i) the recommendation to use statins alongside BP-lowering treatment to reduce risk in high- and very-high-risk patients and to also consider the routine use of statins even in patients with treated hypertension at low-to-moderate risk; and (ii) to use antiplatelet therapy (usually low-dose aspirin) for secondary prevention but not for primary prevention.[2]

These are radical and important statements, often overlooked in the heated debate around BP thresholds, targets, and treatment strategies. It is much less well appreciated that for primary prevention in patients with hypertension, the addition of a low-dose statin can further reduce the risk of coronary heart disease by about 35% and stroke by a further 25%, beyond the impact of controlling BP alone.[12,13] Indeed, in the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial), which randomized patients to both BP and lipid lowering, the patients receiving the most effective BP-lowering strategy (amlodipine ± perindopril) plus a statin (atorvastatin) experienced an approximately 80% reduction in CV risk from baseline *(Figure 2).*[14] In this regard, this is by far the most effective strategy to reduce CV risk beyond the benefits of BP lowering alone and optimize risk reduction in almost all hypertensive patients. It begs the question, why isn't this done more often?

Conclusion

There is undoubtedly a need to act to improve BP control globally and further reduce the risk of CV morbidity and mortality in hypertensive patients. The guideline developers have poured over masses of evidence and have provided a clear evidence-based template of how this can be done, the baton now passes to health care professionals across the world to deliver. ■

References

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71(6):1269-1324.
2. Williams B, Mancia G, Spiering W, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J.* 2018;39(33):3021-3104.
3. Whelton PK, Williams B. The 2018 European Society of Cardiology/European Society of Hypertension and 2017 American College of Cardiology/American Heart Association Blood Pressure Guidelines: more similar than different. *JAMA.* 2018;320(17):1749-1750.
4. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet.* 2018;392(10159):2052-2090.
5. Chow CK, Teo KK, Rangarajan S, et al; PURE (Prospective Urban Rural Epidemiology) Study Investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA.* 2013;310(9):959-968.
6. Gupta P, Patel P, Strauch B, et al. Biochemical screening for nonadherence is associated with blood pressure reduction and improvement in adherence. *Hypertension.* 2017;70(5):1042-1048.
7. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet.* 2016;387(10022):957-967.
8. Williams B, MacDonald TM, Morant S, et al; British Hypertension Society's PATHWAY Studies Group. 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(10008):2059-2068.
9. Williams B, MacDonald TM, Morant SV, et al; British Hypertension Society programme of Prevention Treatment of Hypertension With Algorithm based Therapy Study Group. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. *Lancet Diabetes Endocrinol.* 2018;6(6):464-475.
10. Bhatt DL, Steg PG, Ohman EM, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA.* 2006;295(2):180-189.
11. Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364(9438):937-952.
12. 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(9354):1149-1158.
13. Yusuf S, Lonn E, Pais P, et al; HOPE-3 Investigators. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. *N Engl J Med.* 2016;374(21):2032-2043.
14. Sever PS, Poulter NR, Mastorantonakis S, Chang CL, Dahlof B, Wedel H; ASCOT Investigators. Coronary heart disease benefits from blood pressure and lipid-lowering. *Int J Cardiol.* 2009;135(2):218-222.

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