Hypertension Guidelines
More Challenges Highlighted by Europe

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The release of a new set of major international guidelines from an authoritative group commissioned jointly by the European Society of Cardiology and the European Society of Hypertension (ESH/ESC guidelines)[1] is cause for reflection both on the changing scene in hypertension and on the application of guidelines to improve outcomes in people with hypertension in their community.

At 76 pages long and supported by 735 references, this is a useful resource, but the question is: to whom? Guidelines should enable practitioners to follow best practice, establish standards of care, and provide balance in the face of many and varied influences experienced by busy clinicians. If it is the purpose of guidelines to enable practitioners, especially those at the front line of patient care, to follow best practice guided by the best available evidence, then these are too long and discursive to be used for everyday practice. A pocket guide is likely to become available in due course and clinicians might use this in their practice if it is user-friendly and can be easily found among the multitude of other disease-based guidelines made available to them.

Why Do Different Guidelines Sometimes Draw Different Conclusions?

Influences in Guideline Development

Guidelines are, of course, the product of their origins and of their audience (Figure 1). In this case, 2 learned societies provided nominees, and members of the panels were allocated tasks in relation to specific sections of the document. To write a guideline appropriate to the whole of Europe, let alone the whole world, is problematic. It is questionable that a 1-size-fits-all approach is appropriate. Patterns of development and the associated health burdens are changing at different rates and are at different stages even within Europe, let alone in Africa, Asia, Latin America, and elsewhere.[2] A useful resource must have a local flavor, and the more general guidelines become, the more adaptable, flexible, and culturally specific they must be in their implementation.

Disease Burden Varies

The prevalence of the disease and relationship to complications varies from population to population, particularly in the relative strength of the association of hypertension with stroke or coronary artery disease rates. Obesity and diabetes mellitus rates are increasing around the world, but at different rates.[3] Much of this is related to the state of transition from traditional disease burden to long-term conditions, such as hypertension, that are characteristic of contemporary high-income countries.[2] The pattern of comorbidities is another variable.

Within Europe, there is a very good example of local variation in population attributes that are pertinent to the diagnosis and management of cardiovascular risk. The Systematic Coronary Risk Evaluation model for determining absolute risk was based on large European cohort studies to estimate the risk of death from cardiovascular disease >10 years based on practice such as age, sex, smoking habits, cholesterol, and systolic blood pressure (BP).[4] However, this has to be calibrated for individual countries because of variation in both the prevalence of hypertension and other risk factors and the strength of their association with cardiovascular health.[5] For international use, this has been trimmed down to 2 sets of charts, 1 for high-risk and 1 for low-risk countries. Guidelines need a similar treatment.

Drug Responses Vary

There are clear examples around the world of ethnic variations in response to drug therapies epitomized by the benefits of thiazide diuretics and calcium channel blockers in lowering BP in blacks[6] and perhaps in older people of all races,[7] whereas blockers of the renin angiotensin system and β-adrenoceptor receptor blockers are just as effective in some other populations.

Urbanization

Urbanization is another factor that profoundly affects BP patterns. In developed countries, hypertension is more common in rural populations than in urban.[2] This pattern is reversed in developing, lower-, and middle-income countries where the first impact of rising rates of hypertension is seen in urban communities.[8]

Resource Availability

Recommendations for therapy must be realistic and, therefore, should take into account differing levels of access to care,

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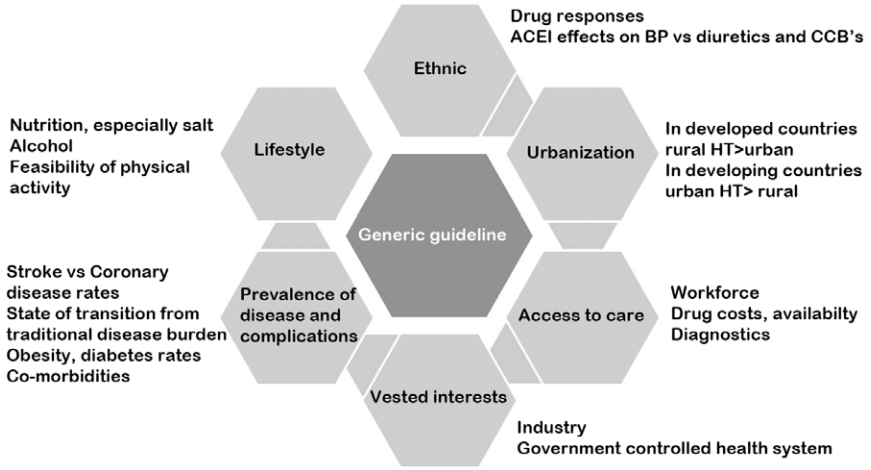

Figure 1. Influences in guideline development that impact on universal recommendations for hypertension prevention, evaluation, and management. ACEI indicates angiotensin-converting enzyme inhibitors; BP, blood pressure; CCB, calcium channel blocker; and HT, hypertension.

drug costs and their availability, and the feasibility of recommendations made for the use of diagnostics. What is reasonable to recommend in wealthy European countries, such as the long list of laboratory investigations provided in the 2013 ESH/ESC guidelines, will be impossible in many resource-poor environments.

Vested Interests

Generic guideline development is also subject to vested interests. This could be pressure from industry, to include particular therapeutics or diagnostics, or a government-controlled health system, which is trying to moderate its costs, or even clinicians themselves wanting validation of their wishes to access new technology or therapies. Government-funded health systems have an interest in curbing costs. One way they may wish to influence guidelines is in the use of generic over branded drug preparations, an issue not taken up in the present guidelines.

Lifestyle

Finally, variations in lifestyle can be important in determining the weight given to various guideline recommendations. It is no value recommending alcohol moderation to a population that, for the most part, does not drink alcohol. The feasibility of physical activity varies considerably between communities and nutritional factors, such as the supply of the salt in the usual diet taken voluntarily or involuntarily through commercial foods.

An Evidence Base Like Swiss Cheese!

One reason that guideline committees dealing with ostensibly the same evidence base may draw different conclusions is that a physical form of the evidence base would look like Swiss cheese. There are many big issues not subject to randomized control trials or other requirements for consistent and strong recommendations. For the most part, randomized controlled trials focus on questions of interest to industry, so that matters pertaining to lifestyle, diagnostic algorithms, case finding, etc, miss the level of scrutiny that a new medication receives, and patient recommendations must be based on the personal opinions and group-think of well-meaning guideline committees.

Decision Support, Not Guidelines

We have too many guidelines. Clinicians want accessible support for their decision making. The time spent on large documents that eventually gather dust on a shelf would be better spent on decision support systems that work on easily available platforms and start with a patient, not a disease or risk factor. Given the capabilities, even in resource-poor environments, most clinicians carry in their pockets in the form of a smartphone or on their desktop, it is surprising that decision support algorithms tailored to the individual patient characteristics are not more widely available. There is no doubt, however, that this is the future of guideline implementation.[9]

Nevertheless, there are common messages found in the 2013 ESC/ESH guidelines and many others that precede it (Table).

What Is New?

BP Measurement

The previous version of the ESH/ESC guidelines was published in 2007.[10] Since then, the major advances relevant to clinical management include better support for the use of out-of-office measurement of BP, including home BP monitoring. The authors stop short of recommending home BP monitoring for all. While emphasizing the deficiencies of clinical BP measurement, it states the following: "It is now generally accepted that out-of-office BP is an important adjunct to conventional office BP measurement, but the latter currently remains the 'gold standard' for screening, diagnosis and management of hypertension."[11] Some would question whether the evidence supports this any more in places where out-of-office BP measurements are readily available, and the ESH/ESC guidelines offer a concession: "The time-honoured value of office BP, however, has to be balanced against its important limitations, which have led to the increasingly frequent suggestion that out-of-office BP measurements play an important role in hypertension management." Elsewhere, "It is recommended that the diagnosis of hypertension be based on at least two BP measurements per visit on at least two occasions."[11] Four clinical BP measurements will not be enough to sustain a diagnosis of hypertension and lifelong therapy for some hypertension experts.

Table. Recommendations Common to All Contemporary Hypertension Guidelines

Blood pressure is a continuous variable but for practical purposes is broken down into grades
Measure blood pressure carefully
High blood pressure is bad for people
High blood pressure is especially bad for people who have extant vascular disease, multiple cardiovascular risk factors, diabetes mellitus, or renal disease
Assess vascular risk
Lifestyle measures come first when attempting to lower blood pressure, cardiovascular risk, and improving responses to antihypertensive drugs
Drugs come next, generally initial monotherapy followed by combinations
Combinations from different drug classes are generally good; combinations sharing similar actions are generally not advised

Cut-offs for diagnosis of hypertension are unchanged from the 2007 version and broadly consistent with the Joint National Committee[12] recommendations (JNC7). The terminology around normal and high BP is always challenged, and a table showing systolic BP of 120 to 129 mm Hg as normal and 130 to 139 mm Hg as high normal will not sit comfortably with everyone in the field. Some cut-offs introduced in the 2013 guidelines, which were not present in 2007, may appear quixotic, such as a pulse pressure >60 mm Hg as an indication of vascular organ damage and high risk. There is no doubt that wide pulse pressure indicates higher risk, but why this level?

There is a recognition that mercury sphygmomanometers are no longer widely available, and some support for repeated measurement at clinical visits with an automated device. A simple principle that is not articulated enough is that, assuming there is such a thing as a usual or baseline BP, the more measurements that are taken, the better the precision in estimating the mean (ie, methods that involve lots of measurements, such as ambulatory or home BP recording, will define BP better than those requiring a few).

These guidelines are at odds with the British guideline,[13] which firmly recommends ambulatory BP measurements based on a cost–effectiveness study performed by the National Institute of Clinical Excellence.

Attention in the new guideline then shifted to variations in BP as there are recent data on the importance of BP at particular times of the day, especially night time BP as an indicator of future outcome. White coat hypertension has been recognized for some time, but masked hypertension, whereby clinic BP is normal but ambulatory or home BP measurements reveal hypertension, has only recently emerged as a topic of interest in hypertension research. The implications for management are unclear for both white coat and masked hypertension as there have been no trials of intervention in either patient group. Both seem to be associated with worse prognosis and, perhaps, more organ damage than persistent normotension, and the frequency of masked hypertension in large studies brings into question the figures for the prevalence of hypertension in populations based on clinical BP surveys. The guidelines recommend lifestyle measures for all and drug treatment where there is a high cardiovascular risk for both masked and white coat hypertension.[11]

The authors consign measurement of BP during exercise or laboratory stress, techniques that estimate central BP or endothelial dysfunction, and analysis of visit-to-visit BP variability to clinical research as being not ready or not suitable for prime time in clinical management of hypertension.[11] This needs to be stressed because there are still no accepted, standardized clinical protocols, validated techniques, or criteria for interpretation of measurements. Nevertheless, there is significant discussion in the guidelines regarding central BP, endothelial dysfunction, and BP variability. The previous recommendation of carotid-femoral pulse wave velocity >12 m/s as an indicator of significant increase in stiffness of the proximal arterial tree in middle-aged hypertensive subjects was tightened up to include those with pulse wave velocity >10 m/s. Evidence was provided in support of ankle-brachial index as an indicator of peripheral arterial disease and future prognosis, but no recommendation was made.

Factors Influencing Prognosis and Work Up

The 2013 ESH/ESC guidelines list some 30 different factors, other than office BP, that influence prognosis and can be used to help stratify risk. These are listed under the headings of risk factors, asymptomatic organ damage, diabetes mellitus, and established cardiovascular or renal disease. Risk factors in people without cardiovascular disease or certain other comorbidities can be integrated using a model for determination of absolute risk, such as Systematic Coronary Risk Evaluation (see above).[4] The relative merits of various other findings and laboratory tests are discussed at length, but there is no clarity on the most useful of these, given the likely redundancy on the list. Clinicians need to know whether a dipstick assessment of microalbuminuria will tell them all they need to know about endothelial function and vascular damage to assess risk or guide treatment. Do they gain more by adding ultrasound of the heart, carotids, or other vascular assessment such as pulse wave velocity or ankle brachial index? It is stated that any of the 4 markers of organ damage—microalbuminuria, increased pulse wave velocity, left ventricular hypertrophy, and carotid plaques—can predict cardiovascular mortality independently of an absolute risk categorization using Systematic Coronary Risk Evaluation, but do we need all 4? Absolute risk algorithms such as Systematic Coronary Risk Evaluation are strongly driven by age. The committee has taken this into account by recommending relative risk assessment in younger hypertensives. In young people with high BP, absolute risk of an event >10 years may be quite small and apparently reassuring. Although they may not have a high likelihood of cardiovascular death or a major event <5 or 10 years, their longer-term risk, initially of organ damage and later of events, remains high. This is a reasonable suggestion, but clinicians may need more guidance on when they should use absolute or relative risk, what is the significance of a particular result, and when should they chase harder for evidence of organ damage in younger people. What is the best shortcut in resource-poor environments where the full range of tests is unaffordable or unavailable? What work up is most cost-effective?

Some insight into the committee's views on this can be obtained from a table on laboratory investigations. Hemoglobin (or hematocrit), fasting plasma glucose, lipids,

electrolytes, uric acid, creatinine, and urine analysis, including a test for microalbuminuria, are listed as routine tests. Some additional tests are recommended if plasma glucose is elevated or dipstick tests are positive. A muted enthusiasm for out-of-office BP measurements is suggested by the inclusion of home or ambulatory BP monitoring as additional tests along with echocardiogram, carotid, peripheral artery, abdominal ultrasound, pulse wave velocity, and ankle brachial index. Classicists may be alarmed to see fundoscopy listed as an additional test.

Cardiac magnetic resonance, the gold standard for noninvasive assessment of cardiac structure and tissue characterization, is dealt with peremptorily as being of value when echocardiography is technically not feasible, perhaps a reasonable conclusion based on feasibility, availability, and cost, but other tests that are no more freely available get more favorable treatment.

Having said that these guidelines are too long, secondary hypertension deserves more attention than the single paragraph on this subject in the ESH/ESC guidelines. It is rightly pointed out that although a relatively small proportion of those presenting with hypertension have a secondary cause, it is a small proportion of ≈1 billion people worldwide and, therefore, a significant health burden in itself. The routine work up recommended in the guidelines will pick up many people with hypertension related to renal disease and perhaps vascular cause such as coarctation or renal artery stenosis, but unless there is significant hypokalemia or characteristic symptoms of people with hyperaldosteronism or pheochromocytoma, respectively, they may be missed at least in the first instance.[14] These guidelines will not inform practitioners of further evaluation when preliminary signs of a secondary cause are present beyond a table that includes a firstline test for each condition and referral to a specialist. This underlines an inconsistency within these guidelines. For the most part, they are comprehensive and pitched at hypertension experts, yet when things get tough such as the work up of secondary hypertension, the advice is referral to a specialist.

Treatment and Targets

These new guidelines include a reappraisal of the target BP with therapy. These were previously <140/90 mm Hg in low–moderate-risk hypertensives and <130/80 mm Hg in those at higher risk as a result of diabetes mellitus, cerebrovascular, cardiovascular, or renal disease. The authors rightly make the point that in many instances these targets were not met in randomized controlled trials and the evidence supporting them is scant or absent, especially in people with diabetes mellitus or renal disease. They no longer support the contention that lower is better for everyone with hypertension, citing subgroup analysis of a number of recent trials, including the Felodipine Event Reduction study performed in Chinese patients with hypertension.[15]

The recommendation adopted by the committee was a systolic BP goal of <140 mm Hg for most hypertensives. In those aged >80 years with systolic BP >160 mm Hg, a modest reduction to 140 to 150 mm Hg was recommended, with adjustment according to tolerability in the fragile elderly. A diastolic BP target <90 mm Hg was recommended for all but diabetic hypertensives, where it is 85 mm Hg.

The treatment recommendations are not new and the lifestyle measures—salt restriction, alcohol moderation, high consumption of vegetables, fruits, low fat intake, weight reduction, physical exercise, and cessation of cigarette smoking—are generally consistent with other international hypertension guidelines. There is some discussion on whether regular isometric exercise lowers BP (perhaps)[16] and on what is an ideal body mass index—22.5 to 25, or >25 kg/m^2.[17]

Drug classes recommended for firstline therapy are unchanged from previous ESH/ESC guidelines. It is recommended that diuretics (including thiazides, chlorthalidone, and indapamide), β-adrenoceptor blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are all suitable for the initiation and maintenance of antihypertensive therapy either as monotherapy or in some combinations. This is at odds with a number of other guidelines—for example, JNC7, where diuretics were preferred for initial therapy over other classes,[12] and British guidelines, which excluded β-blockers from firstline use except in people with angina or heart failure.[13] The British guidelines also had specific recommendations and a hierarchy of drug classes for younger or older people with hypertension. Recent data suggesting that diuretics such as chlorthalidone and indapamide have better evidence for reduced cardiovascular mortality in hypertension than conventional thiazide diuretics was not supported.[18] There is strong support for the use of single-pill combinations, even as initial therapy for some patients.[7]

The authors noted the results of Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension ,whereby benazepril plus amlodipine showed a mortality benefit over benazepril plus hydrochlorothiazide[19] but did not make a firm recommendation on the best secondline drug class after angiotensin-converting enzyme inhibition. They did take into account experience in Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial,[20] with a combination of telmisartan and ramipril, and Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints Including 12 Month Safety Follow-up Off-treatment,[21] where aliskiren was added to background blockade of the renin angiotensin system to reiterate the importance of not combining drugs with similar actions.

Resistant Hypertension

Perhaps the most striking change between 2007 and 2013 in the field of clinical hypertension has been in the study and treatment of resistant hypertension. There are recommendations mostly based on consensus that resistant hypertensive patients should withdraw drugs that are shown not to lower BP; consider adding mineralocorticoid antagonist, amiloride, or doxazosin to the regimen; and consider renal denervation or baroreceptor stimulation if optimal drug therapy is ineffective, but only in truly resistant patients after ambulatory BP recording and only by teams experienced in the procedure and its follow-up. However, such recommendations fall short in giving practical guidance when the busy clinician is faced with the challenges of managing

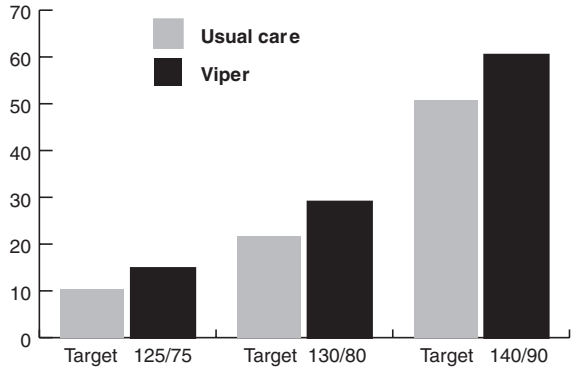

Figure 2. Achieving individual blood pressure (BP) goals (125/75 for people with hypertension and >1 g/d of proteinuria; 130/80 for people with hypertension and a history of coronary heart disease, stroke, chronic kidney disease, or <1 g/d of proteinuria; and 140/90 for all other hypertensives) in a randomized clinical trial with (dark colums) and without (light colums) a decision support system and fixed drug titration (VIPER-BP study).[9] The rate of achieving a target of 140/90 was ≈4× higher than the rate of achieving a BP target of 125/75.

a patient with resistant hypertension. We are not informed how treatment should be withdrawn and it is unclear when and which alternative drugs should be used. Moreover, suggesting renal denervation or baroreceptor stimulation as alternative strategies is correct, but these procedures are not available in most centers, are not yet used as routine clinical therapeutic strategies, and randomized controlled studies are scant.

Conclusions

Beyond the above, it will not be very helpful to a busy clinician managing large numbers of people with hypertension to provide a blow-by-blow assessment of the hundreds of recommendations and conclusions new and old in the 2013 ESC/ESH guidelines. Clearly, not everyone will agree with the new clinical BP targets for therapy, although the differences are marginal. The new targets for therapy are about as solidly based as the old ones were, as they are mainly based on retrospective analysis of large trials designed for other purposes. This is a clear example of an important gap in the evidence base. The problem with the old targets, particularly the more aggressive ones for people with vascular renal disease or diabetes mellitus, is it was not so much that they were wrong but that they were rarely met in real life (Figure 2).[9]

Another area in which guideline recommendations are likely to vary because of lack of evidence is in the extent to which absolute risk is used as a determinant or even a target for therapy. The advantage of treating only people with high absolute risk is that fewer people need treatment to prevent an end point. The disadvantage is that the data that lie behind them are based on short-term observations, and waiting until absolute risk is high may delay action until target organ damage has occurred and irreversible changes in the circulation.

In conclusion, guidelines are inevitably flawed. There can only be a distillation of what is known at a particular time, yet the evidence keeps flowing in. At any given time, value judgments must be drawn. The evidence base will never be complete, and using smoking cessation as an example, some recommendations that are clearly important will never have support of randomized control trials. Better registries and the availability of real-life big datasets and better public support for trials for public good interventions that have no interest to industry will improve the precision of guideline development in the future along with vigorous evaluation and categorization of the existing evidence. In the meantime, these useful new guidelines will be the subject of vigorous debate.

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Disclosures

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