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Hypertension guidelines: impact of blood pressure targets

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Abstract

There has been an abundance of hypertension guidelines in recent years. The purpose of these is to convey evidence-based findings from clinical trials to clinicians so that best medical choices can be made for the diagnosis and treatment of patients with hypertension. Over the past 3 years new hypertension guidelines have been published in the United States, Canada, Europe and elsewhere with new or refined recommendations made regarding diagnosis, therapy and intensity of treatment. Previous national guidelines were generally in alignment with each other. However, there are major differences in the current North American and European recommendations in terms of the classification of hypertension and treatment goals, with diagnosis of hypertension starting at 140/90 mmHg for the European guidelines and 130/80 mmHg for the United States and Canadian guidelines. An important controversial aspect in the updated guidelines relates to the lowered threshold (130/80 mmHg) at which hypertension is diagnosed and treated, because growing evidence indicates that those at low cardiovascular risk may be exposed to incremental harm due to overtreatment with antihypertensive drugs. However these concerns need to be weighed against the robust evidence from the landmark SPRINT study and numerous meta-analyses that clearly showed that intensive blood pressure lowering aimed at systolic blood pressure of 120-130 mmHg causes a significant reduction of over 25% in cardiovascular morbidity and mortality. This review highlights some of the important discrepancies between the major current guidelines focusing on definitions and treatment goals of hypertension. The impact of lower blood pressure targets and intensive antihypertensive treatment on cardiovascular benefit and risk is discussed.

Summary

Updated American and Canadian hypertension guidelines have redefined hypertension (130/80 mmHg) and treatment goals and advocate tighter blood pressure control at lower targets than previous guidelines. European guidelines are more conservative and maintain traditional definitions

of blood pressure (>140/90 mmHg). This review discusses the benefits and risks of stricter blood pressure control and the impact of different guidelines on the hypertension burden.

Introduction

Hypertension is the leading modifiable risk factor for disability and premature death from cardiovascular disease and accounts for $\approx 10\%$ of health care spending globally (1,2). Accordingly blood pressure reduction should be a priority in every health care system. Considering the availability of a wide range of effective antihypertensive drugs that are well tolerated and generally affordable, it is surprising that in our modern society hypertension is so poorly controlled, with recent data indicating that in treated patients only $\approx 30\%$ achieve adequate blood pressure control (2-4). Chobanian, in his Shattuck lecture described this as the ‘hypertension paradox’ where there is more uncontrolled disease despite improved therapy (5). Reasons for this are complex and multifactorial including poor adherence and compliance of drug treatment, therapeutic inertia, sub-optimal therapy and inadequate dosing (4,5). Further complicating these matters is the lack of clarity regarding optimal blood pressure targets, especially in hypertensive patients with co-morbidities, such as diabetes and kidney diseases and in the very elderly (2,6). The actual blood pressure thresholds at which treatment should be commenced and the target levels at which blood pressure should be maintained are a subject of intense discussion (7). To help address this, guidelines have been developed by experts to guide clinicians in the diagnosis and management of hypertension.

Most major hypertension guidelines are evidence-based and are usually dictated by randomized controlled trial data and observational clinical studies (8). Recommendations are made to enable busy practitioners to follow best practice, establish best standards of care and provide appropriate and balanced treatment to patients. Guidelines are usually written by experts in the field who scrutinize relevant published clinical studies and trials, resulting in evidence-based recommendations. However, despite the apparent rigor, not all guidelines are the same and this is most evident when comparing the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (9) with the current European hypertension guidelines (10). Main differences relate especially to definition of hypertension and blood pressure treatment targets.

Until fairly recently hypertension was generally diagnosed as a sustained office blood pressure greater than 140/90 mmHg, with clinical guidelines suggesting commencement of pharmacologic treatment when blood pressure is above this level. However in 2017 the ACC/AHA reclassified hypertension by lowering the threshold for treatment from 140/90 mmHg to 130/80 mmHg (9). Moreover these guidelines recommended that pharmacologic treatment should be initiated in patients with a blood pressure >130/80 mmHg and who are at high risk, defined as individuals with existing cardiovascular disease, a calculated 10-year cardiovascular risk of > 10% or those who have other risk factors (eg kidney disease or diabetes). In all patients with a blood pressure of > 140/90 mmHg independent of risk factors, ACC/AHA guidelines suggest that treatment should be initiated. Similar recommendations were soon adopted by many other major national guidelines including the Canadian Hypertension Education Program (CHEP) (11) and the International Society of Hypertension/American Society of Hypertension (12). The evidence underpinning the lower blood pressure targets was driven in large part by the Systolic Blood Pressure Intervention Trial (SPRINT), which demonstrated that intensive treatment to lower blood pressure targets is cardiovascular protective (13). Various meta-analyses also showed benefit of intensive blood pressure lowering. In a meta-analysis of over 44,000 patients, intensive blood pressure lowering below 140 mmHg was associated with improved cardiovascular and renal outcomes (14). In another study of over 613,000 participants lowering blood pressure to a systolic blood pressure of less than 130 mmHg was associated with significantly reduced cardiovascular events and mortality (15).

Systolic Blood Pressure Intervention Trial (SPRINT)

The SPRINT study was a ground breaking trial that investigated effects of intensive blood pressure therapy on risk of cardiovascular disease and events in patients with hypertension (13). The primary outcome was a composite of heart failure, acute coronary syndrome, myocardial infarction and stroke. The trial enrolled 9,361 patients. Patients at least 50 years of age with at least one cardiovascular risk factor were randomly assigned to intensive treatment with a systolic blood pressure goal of <120

mmHg or standard treatment with a systolic blood pressure goal of <140 mmHg. The 5 year trial was terminated prematurely after 3.26 years because the primary composite outcome in the intensive treatment group showed a significant reduction, with a 25% relative risk reduction versus standard therapy. These findings underscored the implementation of intensive treatment of blood pressure to lower targets in the ACC/AHA and CHEP guidelines. It has been estimated that implementing such approaches could prevent 107,500 premature deaths from cardiovascular death annually (16).

Hypertension guidelines in North America and Europe

Following the 2017 ACC/AHA recommendations, the 2018 European Society of Cardiology and the European Society of Hypertension (ESC/ESH) guidelines on the diagnosis and management of hypertension were published (10). While both reports were developed using similar evidence-based clinical data, the recommendations differ with respect to two main points, 1) the classification of hypertension and 2) treatment goals. The ACC/AHA guidelines in the USA (9) and the CHEP guidelines in Canada (10) lowered the threshold for hypertension to 130/80 mmHg, while guidelines in Europe, UK and other regions such as Australia (16-18) have largely maintained traditional blood pressure categories, with grade 1 hypertension defined as an office blood pressure >140/90 mmHg. The ESC/ESH also introduced the concept of ‘safety boundaries’, defined as treated systolic blood pressure not below 130 mmHg in people >65 years and not below 120 mmHg in people <65 years. This cautious strategy is based on concerns of potential adverse events associated with overtreatment with antihypertensive drugs and is supported by the findings of Bress et al (19) who reported that over a 10 year period the number of cardiovascular events that would be prevented by intense blood pressure management would be similar to the number of serious adverse events. In response to these concerns, the American College of Physicians and the American Academy of Family Physicians (ACP/AAFP) developed their own guidelines for hypertension management in the USA for adults older than 60 years, suggesting a blood pressure target of 150 mmHg at which level treatment should be started (20). Similar to the ESC/ESH guidelines and ACP/AAFP guidelines, the 2019 National Institute for Health

and Clinical Excellence (NICE) guidelines also maintained a conservative approach (21). Current recommendations of NICE have not changed the definition of hypertension of 140/90 mmHg from the previous 201 iteration (17).

The impact of lower diagnostic thresholds on the global hypertension burden.

Redefining hypertension from 140/90 mmHg to 130/80 mmHg classifies previously 'normotensive/prehypertensive' individuals as being 'hypertensive' who may require treatment. The impact of this on the hypertension burden nationally and globally is enormous, both in terms of the prevalence of hypertension and the number of individuals requiring healthcare and antihypertensive therapy (22). By applying the new definitions, the prevalence of hypertension in adults younger than 45 years triples for men and doubles for women in the United States (23). Numerous large studies further confirmed this in the general adult population. The Reasons for Geographic And Racial Differences in Stroke (REGARDS) study reported that adopting the 2017 ACC/AHA definitions would double the prevalence of hypertension worldwide (24). Similar findings were demonstrated in the US National Health and Nutrition Examination Survey (NHANES) and the China Health and Retirement Longitudinal Study (CHARLS) (25). Based on diagnostic criteria of 140/90 mmHg, the global prevalence of hypertension in adults is currently 30-35%. However applying the 2017 ACC/AHA or CHEP guidelines, increases the global prevalence of hypertension in adults to > 60%. Associated with this, the number of patients requiring treatment would be doubled and those already on treatment would require intensification of pharmacotherapy. Hence the potential impact of the hypertension burden on healthcare systems is significant.

Another important consideration with the lower threshold for diagnosing hypertension using the ACC/AHA or CHEP criteria, is at the individual patient level, where people will be labeled as being hypertensive and unwell, even though they may be at low risk of disease (26,27). This may impact adversely on their sense of well-being and could have negative implications on personal health

insurance and other situations (eg jobs) if they are considered to have a preexisting medical condition (28).

Impact of guidelines on benefits and risks- effects of intensive treatment

Collaborative meta-analysis of individual participant data from separate prospective studies clearly indicates that the relative risk of mortality due to cardiovascular disease in adults doubles with every 20 mmHg increase in systolic blood pressure or 10 mmHg increase in diastolic blood pressure (29). This positive relationship holds true for systolic blood pressures from as low as 115 mmHg, below which there is little evidence. In adults 40-69 years, each difference of 20 mmHg systolic blood pressure is associated with more than a twofold difference in the rate of death due to stroke, ischaemic heart disease and other vascular causes (29). Hence aggressive efforts at reducing blood pressure should be a priority to ensure good cardiovascular health and prevention of premature death due to cardiovascular disease. However, the level of blood pressure at which such treatment efforts should be initiated is currently a matter of deliberation (7,30).

It is predicted that implementing, achieving and maintaining the ACC/AHA guideline goals could prevent 3.0 million cardiovascular disease events over 10 years compared with the number of events prevented using prior guidelines (19). However, these benefits may be associated with potential risks, especially related to serious adverse events of overtreatment with antihypertensive drugs. The forecast is that implementation of the 2017 ACC/AHA guidelines would not only prevent cardiovascular events but would also lead to about 3 million more treatment-related serious adverse events (19).

Concerns have also been raised regarding the ACC/AHA recommendations in patients with mild hypertension and low cardiovascular risk and questions are being raised as to whether these individuals should be treated with antihypertensive drugs since since there is a lack of supporting clinical evidence (31,32). This was recently addressed in a longitudinal cohort study using electronic health records from 38 286 low risk patients with mild hypertension. Data were extracted from the

Clinical Practice Research Datalink (33). The study failed to show an association between exposure to antihypertensive treatment and mortality or cardiovascular disease. On the other hand, there was evidence that treatment may be associated with an increased risk of adverse events including hypotension, syncope and acute kidney disease. Hence antihypertensive treatment in low risk patients with mild hypertension may have little benefit and may actually be associated with some harm (27,31).

Taken together these recent provocative studies emphasize the importance of weighing benefit versus risk and harm in treating patients aggressively to lower blood pressure targets, especially in those who have no or few risk factors. Guidelines simply provide recommendations and that clinical judgement and the need to individualize antihypertensive treatment taking into account comorbidities and associated cardiovascular risk factors, should remain the basis of hypertension management.

Impact of lower blood pressure targets on dementia and chronic kidney disease.

i) Dementia and cognitive impairment.

A potential risk and clinical concern of overtreatment of hypertension is hypotension and cerebral hypoperfusion with consequent negative impact on the brain and cognition. The recent SPRINT MIND study, a substudy of SPRINT, specifically questioned whether intensive blood pressure control reduces the occurrence of dementia (34). Results showed that unlike beneficial effects on cardiovascular events, intensive BP aimed at < 120 mmHg compared with <140 mmHg did not significantly decrease the incidence of probable dementia. However intensive blood pressure control was associated with a significant reduction in mild cognitive impairment, a risk factor for dementia. It should be highlighted that although dementia rates were not altered in SPRINT MIND, there was no evidence of cerebral hypoperfusion and no harm to cognition in patients treated to lower blood pressure levels. SPRINT was terminated early because of significant cardiovascular benefit, and accordingly the trial may have been underpowered to evaluate the primary adjudicated cognitive outcome of probable dementia. Perhaps had the trial extended beyond the 3.26 years, significance on probable dementia rates may have been evident. Whether the outcomes would be beneficial or harmful is unknown, but hopefully

SPRINT patients will be followed long term to gain better insights into dementia outcomes over time in this patient cohort. Although lower blood pressure was not associated with cognitive harm in SPRINT, it should be emphasized that the trial did not focus on mean arterial pressure and pulse pressure, which are primary drivers of cerebral blood flow (35).

ii). Chronic kidney disease.

Hypertension and chronic kidney disease are common comorbidities, with high mortality risk. Blood pressure lowering is associated with reduced cardiovascular events in these patients (36). However there is still deliberation about the optimal blood pressure and therapeutic goal. Guidelines differ on blood pressure targets with the 2017 ACC/AHA recommending a goal of <130/80 mmHg in patients with chronic kidney disease while the European guidelines favor a higher systolic blood pressure goal of 130-140 mmHg. Numerous trials have examined effects of intensive blood pressure control on cardiovascular events and all-cause mortality in patients with hypertension and chronic kidney disease. Data from large meta-analyses have not been consistent with some studies showing benefit only in patients with proteinuria (36) and others reporting clear benefit of more intensive blood pressure control in patients with stage 3-5 chronic kidney disease (37). Some studies have reported worsening of renal disease with tighter blood pressure control, especially in patients with diabetes (38-40). In a case control study, incident chronic kidney disease in the setting of intensive systolic blood pressure lowering was accompanied by decreases, rather than elevations, in levels of kidney damage biomarkers (41). A recent meta-analysis comprising four major trials (Modification of Diet in Renal Disease (MDRD); African American Study of Kidney Disease and Hypertension (AASK); Action to Control Cardiovascular Risk in Diabetes (ACCORD) and SPRINT) compared intensive versus standard blood pressure approaches. Results clearly showed that intensive blood pressure management improves survival of patients with hypertension and chronic kidney disease, supporting the lower targets suggested by some current guidelines (42). Nevertheless, within the context of high risk patients

with chronic kidney disease, treatment of hypertension should be adapted to each individual patient, taking into consideration associated risk factors.

Conclusions

Hypertension guidelines all have the same overall objective of communicating evidence-based data from clinical trials to practitioners providing recommendations for best clinical practice and best care for patients with hypertension. Despite the plethora of international, national and regional guidelines, the prevalence of hypertension is high and control rates remain disappointingly low worldwide, due to many complex factors. This is likely to worsen with changing definitions of hypertension and lower blood pressure targets for treatment. The updated recommendations in Europe and the UK, together with the guidelines of the ACP/AAFP are in general alignment that treatment of patients should aim at lowering blood pressure to 140/90 mmHg (43). However these guidelines are at odds with the current ACC/AHA and CHEP guidelines, which have lowered the threshold to 130/80 mmHg. These disparities in the recommendations likely reflect a lack of consistent evidence from clinical trials and studies. The more conservative approach of the EU and NICE guidelines is based in large part on the potential risks and harm associated with intensive antihypertensive treatment to lower BP targets while the ACC/AHA guidelines are driven by the proven benefit of intensive treatment shown by SPRINT, which unambiguously showed a 25% reduction of morbidity and death associated with cardiovascular disease, despite some risk of adverse events. Such discrepancies add confusion and challenges to diagnostic and treatment choices for the busy clinician managing patients with hypertension. From a pragmatic viewpoint, it should be underscored that guidelines are merely recommendations based on the best available evidence aimed at guiding decisions and criteria regarding diagnosis and that the central element in decision-making for our hypertensive patients depends on good clinical judgment. Moreover, clinicians should strongly advocate and actively prescribe healthy lifestyle choices for all hypertensive patients independently of whether the systolic blood pressure is greater or less than 130 mmHg and whether or not they are on antihypertensive medication.

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Conflicts

Nothing to declare

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