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REVIEW

Aiming for improved blood pressure control

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Although hypertension is common, it is inadequately controlled in the vast majority. The benefits of treating high blood pressure (BP ≥ 140/90 mmHg) include significantly reducing cardiovascular events and mortality. This review discusses several evidence-based practical approaches to optimising high blood pressure treatments with angiotensin converting enzyme inhibitors (ACE-i) or angiotensin receptor blockers (ARBs), calcium-channel blockers (CCBs) and diuretics, often in fixed-dose or flexible single pill combinations.

Keywords: hypertension, blood pressure control, antihypertensive drugs, fixed-dose combination, single pill combination

Introduction

In 2010 the global burden of hypertension (HT) was estimated at 1.4 billion, a figure that is predicted to rise to more than 1.6 billion by 2025.[1] In 2019, the Global Burden of Disease Study of data from 204 countries showed that high systolic blood pressure (BP) was the leading risk factor for death globally.[2] It is a disturbing statistic that only one in seven patients has their high BP treated successfully and adequately controlled.[3] That means that approximately 1.2 billion are not benefiting from evidence-based BP lowering strategies.

This narrative review aims to raise awareness of the importance of BP control in the management of HT. In this regard several pertinent questions are raised about controlling BP to optimise HT treatment.

Are there benefits in treating hypertension?

Several meta-analyses of large randomised controlled trials (RCTs) have shown significant clinical benefit. Highlights of two pivotal meta-analyses are highlighted here:

Thomopoulos et al.[4]

In this meta-analysis of 68 RCTs comprising a total of 245 885 individuals treated with anti-hypertensive drugs, the standardised effect of reducing systolic BP by 10 mmHg and diastolic BP by 5 mmHg was evaluated. The relative risk reduction of stroke was 36% (95% CI 29–43%), and heart failure, 43% (95% CI 28–54%). Myocardial infarction and mortality were also significantly reduced, although to a lesser extent.[4]

Ettehad et al.[5]

This large meta-analysis involving 123 RCTs and more than 600 000 participants showed that for every 10 mmHg systolic BP reduction, the risk of stroke was reduced by 27% (95% CI 23–32%) and the risk of heart failure was reduced by 28% (95% CI 22–33%). The risk of coronary artery disease and mortality was also reduced.[5]

Thus, it is concluded that lowering BP significantly and consistently reduces the risk of cardiovascular disease (CVD) and mortality attributed to HT, irrespective of the baseline BP, or age, gender or ethnicity, and irrespective of the presence of comorbidities. However, it should be noted that many of the HT RCTs included in the meta-analyses were conducted in older individuals or people with high cardiovascular risk. It should also be noted that the duration of many RCTs was limited to typically only five years.[6] HT is a lifelong condition and needs treatment over extended periods of time. Therefore, it is essential to appreciate that the recommendation for treating younger patients with HT and life-long treatment is not wholly based on evidence from a specific RCT, but rather on the extrapolation of data from existing RCTs.[6] Observational studies have provided compelling evidence that the benefits of treating HT continue for decades.[6]

When should drug treatment be started in hypertension once the diagnosis is made using repeated measurements including at least one out-of-office measurement?

Most major HT guidelines recommend treatment when BP remains elevated at ≥ 140/90 mmHg after repeated measurements in the clinic, which are preferably accompanied by an out-of-office measurement.[6-8] There are some differences of opinion around this BP level: for instance, the American guidelines suggest initiating treatment at a BP threshold of 130/80 mmHg.[7] This lower cut-off is a significant change from previous guidelines.

How should stage 1 hypertension (BP 140–159/90–99 mmHg) with a low overall cardiovascular risk be treated?

While some recommend initiating monotherapy, many advocate fixed-dose combinations (FDCs) of two drugs. Although there is clinical benefit in treating low-risk people with Stage 1 HT, more studies are probably needed for greater clarity.

What about those patients with blood pressure below 140/90 mmHg, typically 130/80 mmHg or higher, but who are at a high cardiovascular risk?

Based on their overall cardiovascular risk, it is argued that these patients require treatment as they benefit from BP lowering therapies. Individualising treatment decisions is recommended in these individuals.

When considering the very elderly above the age of 80 years, it is important to note that they too could benefit from treatment but that their frailty may limit their options. One RCT, the HYVET, assessed the thiazide-like diuretic, indapamide, with add-on perindopril, an ACE inhibitor, if needed, to control BP. Significant clinical benefit was shown in this group of very elderly hypertensive patients.

The USA guidelines recommend starting treatment in all people with a BP > 130/80 mmHg.[7] Much of this argument comes from one RCT, the SPRINT, where methods of BP measurement differed significantly from most other RCTs, making comparisons difficult. BP levels requiring treatment initiation remain somewhat disparate between the major guidelines. Calculating the cardiovascular risk using a risk engine such as Framingham does, however, help one to decide who to treat and when to initiate drug treatment.

Which drug(s) should be used to initiate hypertension treatment?

The European Society[6] advocates starting with an FDC of two drugs, preferably an **(A)** ACE inhibitor or ARB + **(C)** calcium-channel blocker, or alternately (A) + (**D**) diuretic, i.e. A+C or A+D. The next step, if not reaching target BP, is to prescribe three drugs, i.e. A+C+D. The latter implies two pills, i.e. an FDC plus a third drug. Alternatively, a single pill combination (SPC) of various dosage forms of three drugs such as perindopril, amlodipine and the thiazide-like diuretic, indapamide, i.e. A+C+D, may simplify the treatment regimen which is associated with better adherence to treatment and better control of BP.

USA guidelines[7] recommend starting with an FDC of two drugs A+C or A+D when the initial BP is ≥ 140/90 mmHg. This may be escalated to three drugs (A+C+D) to reach goal BP if a two-drug combination is inadequate.

The International Society of Hypertension (ISH) guidelines[8] recommend as Step 1, initiating A+C, each at half-dose, and as Step 2, escalating both A+C components to full dose. The half-dose suggestion may ease many doctors' concerns about starting two-drug combinations and reducing BP precipitately. Escalating to three drugs (A+C+D) is also recommended to reach goal BP.

Should a two-drug regimen be the new foundational treatment for hypertension?

An FDC of two drugs offers an alternative. The FDC provides optimal adherence to prescribed treatment, overcomes doctors' treatment inertia, attains earlier BP control (especially in high-risk people) and has the potential of better long-term BP control.[6] The use of a three-drug regimen is recommended as the next step in all the BP guidelines. An SPC of three anti-hypertensives allows titration as the doses of the individual components range from ultra-low to higher doses. Two possible exceptions to starting with anti-hypertensive combination therapy and rather initiating monotherapy include (i) the very elderly, especially the frail, and (ii) the Stage 1 low-risk hypertensive patient.

What is the goal (or target) blood pressure on treatment?

ISH offers a pragmatic recommendation:[8] Step 1 for all people with HT is to aim for a BP < 140/90 mmHg. If this is not possible, reduce the systolic BP by 20 mmHg and the diastolic BP by 10 mmHg as this has been shown in observational studies to relatively halve CVD events. Step 2 for people younger than 65 years, is to aim for 130/80 mmHg if they can tolerate it. Meanwhile, Step 2 for people older than 65 years, is to decrease BP to below 140/90 mmHg.

ISH also states that individualising treatment should be considered in most people. Achieving a lower goal of treated BP also depends on the tolerability of the treatment. The systolic BP should not be lowered below 120 mmHg as at this level, the harm outweighs the benefit.[6] In general, although there are no good data, diastolic BP should not be lowered below 60 mmHg as that is the diastolic pressure required for coronary artery perfusion of the myocardium.

How important is blood pressure control?

The concept of BP control has several related aspects. Control is viewed as reaching target BP and keeping it there consistently. However, globally the control of BP is poor. The Prospective Urban Rural Epidemiology (PURE) study examined a cross-sectional sample of 142 042 participants from high-income countries and middle-income and low-income countries.[9] Only a 32.5% (95% CI 31.9–33.1%) minority of those participants, known to have HT and receiving drug treatment, had a controlled BP. Consistent sustained control of BP over time is important in preventing adverse clinical outcomes,[10,11] and control should be achieved rapidly. Mancia et al.[10] argued in the VALUE trial of valsartan + HCTZ vs amlodipine + HCTZ, that participants achieving rapid control within a few months had fewer adverse cardiovascular outcomes than those who achieved control over a longer period. Similar post hoc evidence was noted in the ALLHAT (monotherapy) and ASCOT-BPLA (amlodipine + perindopril) trials.

European guidelines recommend that BP control should be achieved within three months. Start with an FDC of two drugs which controls about two-thirds of hypertensive people. If control is not achieved, move to a three-drug combination of

A+C+D, preferably in an SPC, which may be able to control BP in more than 80% of hypertensive patients.[6]

Achieving BP control rapidly is more protective than achieving control later and this can more easily be achieved by initiating combination therapy. This strategy of combination therapy from the start not only improves adherence but can overcome treatment inertia.

What can we as doctors do to improve the control of blood pressure?[12]

Various strategies may improve BP control. Prescribing long-acting agents that have 24-hour duration of action is preferred as nocturnal high BP and the absence of BP dipping are important predictors of future cardiovascular events. Drugs that act for 24 or more hours can prevent nocturnal high-risk episodes.

Long-acting drugs also reduce BP variability, especially in systolic BP, which has been associated with an increased cardiovascular risk, especially of stroke.

As far as possible, prescribe combination drug treatment. Consider combination pills (either fixed-dose or flexible SPCs) to improve adherence, and therefore outcomes: if patients remain hypertensive after two-drug combinations, escalate to three, typically A+C+D.

Measure and note in how many instances the BP is below the target BP. In a post hoc study of the ALLHAT RCT it was noted that, if during visits to the doctor, BP was recorded below the target of 140/90 mmHg on every occasion over five years, the maximum benefit was seen in the reduction of cardiovascular events. As this percentage dropped, the event rate went up.

If possible, do a 24-hour ambulatory BP measurement to evaluate control of BP over the day and night periods. Make sure that nocturnal BP is reduced (normal dipping).

Encourage the use of home BP measurements to enable evaluation of BP control using more measurements spaced over a longer time. The use of home measurements of BP also involves patients in their own management of HT and can be associated with improved adherence.

Establishing a good patient-doctor relationship does improve adherence and could improve HT management overall.

Summary and conclusion

Treatment of HT is associated with reduced cardiovascular events and mortality which is the primary aim of treatment.

Reaching goal BP remains problematic as this goal has been lowered by the major HT guidelines. This lowering of the goal BP implies more individual pills are required that complicate treatment regimens and increase the risk of reduced adherence to therapy. The new paradigm is to use multi-drug therapy and an improvement is to use either two-drug fixed-dose combinations, or three-drug flexible single pill combinations as these simplify treatment, improve adherence and improve BP control. Constant and persistent BP control at goal BP should be evaluated by 24-hour ambulatory BP monitoring and home BP monitoring as they are both valuable tools to achieve BP control. Individualising the management of HT is often necessary.

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