



Tutorial

When blood pressure is not under control: Ten questions to ask and steps to take

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Introduction

“Hypertension may be an important compensatory mechanism which should not be tempered with even were it certain that we could control it” – Paul Dudley White, 1937

High blood pressure is the commonest risk factor for the commonest causes of death; cardiovascular disease. It remains a leading cardiovascular risk factor despite availability of highly effective interventions.

The number of people with raised blood pressure has risen worldwide, with the increase happening mainly in low-income and middle-income countries. In 2015, 874 million hypertensives, 7.8 million deaths and 140 million disability adjusted life years (DALYs) were estimated to be related to systolic blood pressure of 140 mmHg or higher ⁽¹⁾. Over 1.5 billion are expected to be affected by hypertension by 2025 ⁽²⁾. In a recently released analysis on life expectancy, the forecast for 2040 shows high blood pressure will remain a key health driver of premature mortality and the leading risk factor in 25 countries ⁽³⁾.

While cardiovascular mortality risk doubles with each 20/10 mmHg blood pressure increment, long-term antihypertensive therapy significantly reduces cardiovascular events ^(4,5). Despite undisputed benefit of blood pressure lowering, the rate of control remains disappointing in many populations with only around 40% of patients manage to achieve an adequate level of blood pressure control ⁽⁶⁾.

Unlike in clinical trials where treatment protocols are adhered rigorously and blood pressure control reaches 80%, in real-life setting the control is much poorer ^(7,8). Controlling blood pressure has been a challenging task.

Durability of blood pressure control over the long-term is a major contributor to CV disease reduction by antihypertensive therapy.

There is evidence that early achievement of control of blood pressure leads to better and sustained cardiovascular outcomes ⁽⁹⁾.

This article attempts to describe a stepwise approach to assess blood pressure control during encounters in the clinic with a patient already on treatment for hypertension.

1. Has the blood pressure been measured accurately? Check if the measurements are reliable.

A careful blood pressure measurement is an important preliminary step in determining if blood pressure is indeed at target levels. Doctors at busy clinics and outpatient departments where there is little time to spare are likely to overlook some of the recommended steps in the measurement.

At least two recordings should be made at every doctor-patient encounter and the mean taken. A third recording may be necessary if any one of the values are markedly different. Measurements taken by a nurse is preferred to minimize the white coat effect.

Pseudo hypertension should be suspected when the blood pressure is recorded high in an elderly patient due to a hardening of the brachial artery which makes it difficult to compress during the measurement. Typically, these patients do not have end-organ complications and run the risk of developing symptoms of hypotension due to overtreatment.

White coat hypertension should always be considered in the absence of target organ damage and is frequently seen in women, older persons and those with mild hypertension. This condition may have been overlooked when drug treatment was first initiated and some individual's blood pressure stabilizes only after several visits, inadequate blood pressure control should be cautiously interpreted.



White coat hypertension with high cardiovascular risk requires lifestyle advice but initiation of drug treatment lacks good evidence.

In the setting of inadequate control, ambulatory blood pressure monitoring (ABPM) is useful to distinguish white coat effect from poor control and to prevent stepping up of therapy unnecessarily. While the use of ABPM is the gold standard it is unlikely to be adopted widely in resource-poor setting due to several practical barriers.

Blood pressure targets have been established based on clinic blood pressure measurements. Furthermore, no recommendation is made for routine use of ambulatory blood pressure monitoring in the follow-up of patients on antihypertensive therapy. Repeated clinic measurements or home blood pressure monitoring is a feasible alternative.

As recording devices improve its accuracy and become widely available at reasonable cost, recourse to home blood pressure measurement values is practicable. Using the average of morning and evening readings, a minimum of three days are needed to reliably estimate out-of-office blood pressure and confirm a diagnosis of hypertension or to assess adequate control⁽¹⁰⁾. Use of validated automated oscillometric devices with proper instructions and training are required to take accurate measurements. It is important to point out that the normal mean value is lower than the average clinic reading. Self-monitoring of blood pressure can positively impact on medication adherence, improve control and a convenient way for individuals to check on the effectiveness of treatment.

2. Is the blood pressure on target - What is the blood pressure target to achieve?

After many years of recommending a treatment goal of <140/90 mmHg, of recent, blood pressure goals to aim at has been a moving target. The lack of conclusive benefit of recent clinical trials on hypertension and the latest guidelines have added to the confusion with blood pressure targets dialled upwards and back again to the lower values. With the publication of the controversial JNC 8, the blood pressure targets were made less aggressive particularly for patients ≥ 60 years old⁽¹¹⁾.

The recent guidelines from both ESC/ESH and from the American College of Cardiology (ACC), the American Heart Association (AHA) have recommended lower targets⁽¹²⁻¹³⁾. The ESC/ESH guidelines recommends a target range of blood pressures depending on the age and not a target level: a lower range of 120-129 mmHg for those under 65 years and 130-139 mmHg for 65 years and over. The US guidelines advises a target of 130/80 mmHg for all adults including those with comorbidities such as diabetes mellitus, chronic renal disease and cardiovascular disease or those at higher risk.

In the absence of an updated local guideline on hypertension and a lack of harmonisation of the two major guideline documents, for a practising clinician, this can be confusing. It may be reasonable to assume suboptimal blood pressure control when blood pressure is higher than 130/80 mmHg in the under 65 and 140/80 mmHg in those 65 years and older.

3. Are lifestyle measures adequately adhered to? Encourage adopting a healthy lifestyle. Give practical advice.

This is another challenging assessment to make during a patient review in the clinic. Lifestyle factors are important determinants of blood pressure control. Adoption of exercise, smoking cessation, weight loss, healthy eating, and reduced sodium intake have a significant impact on blood pressure.

While advice is often directed at avoiding high salt containing food and added salt, it is important to note that most of it comes from processed food and in items that you least expect such as bread, cereals, sauces and sausages. The effect of modest salt reduction has a greater effect on those with hypertension compared to normal persons⁽¹⁴⁾. The size of the reduction is greater in those with higher levels of baseline blood pressure, increased age and also significant in certain ethnic groups such as South Asian and blacks⁽¹⁵⁾. The effects are also substantial in those with chronic renal disease and diabetes mellitus. If effectively adhered to, the number and dose of antihypertensives can be reduced.



Encourage the patient to have a healthy balanced diet rich in fruits, vegetables, whole grains, and low-fat dairy products as these have a blood pressure lowering effect.

An intake of 3-4 drinks per day or more can contribute to poor blood pressure control. Checking on current excess use is a vital assessment to identify a key modifiable factor of poor control. A recent systemic review and meta-analysis shows that a reduction in alcohol consumption in people with a baseline intake of more than two drinks per day is associated with a significant blood pressure reduction that increases with higher baseline alcohol intake comparable in magnitude seen with other lifestyle changes such as increased physical activity and weight loss⁽¹⁶⁾. If excess drinking is encountered, it is advisable to limit alcohol intake to less than two drinks per day for men and no more than one drink for women.

Physical activity levels are infrequently discussed during patient encounters. The benefits of regular aerobic type of physical activity on blood pressure and cardiovascular risks are clear. Most guidelines recommend at least 30 min of moderate-intensity dynamic aerobic exercise (walking, jogging, cycling, or swimming) on 5–7 days per week. Performance of resistance exercises on 2 – 3 days per week can also be advised.

4. Is there non-adherence to medications? Find out what the problems are.

“Drugs don’t work in patients who don’t take them” – C Everett Koop, Former Surgeon General of United States, 1985

This is another important step to check before proceeding further. Detecting non-adherence and then probing further the underlying reasons in those at risk is a daunting task for a busy physician. Good adherence not only improves better blood pressure control but also leads to greater reduction of their cardiovascular risk⁽¹⁷⁾. Non adherence is characterised by non-initiation, short persistence and poor execution resulting in treatment interruptions. At one year, about 50% are non-persistence with their medications⁽¹⁸⁾. Medication taking behaviour improves around a scheduled visit and decreases after a doctor’s consultation.

Find out in a non-threatening manner about taking drugs, counting remaining pills and examining the heart rate (if on beta blockers or on non-dihydropyridine calcium channel blockers) as it may indicate objective evidence of poor adherence.

The complexity of the drug regimen, medication costs or its adverse effects may be reasons to abandon treatment. Simplifying the dosage regimen and minimising the number of pills by using fixed combination meds may improve adherence. Socioeconomic factors such as poor health literacy or social support may contribute. Patient factors such as cognitive impairment, depression, visual problems should be probed.

Health system issues such as hospital-patient relationship, lack of access to healthcare or continuity of care are major issues that impact on poor adherence.

Being an asymptomatic condition, motivation is key. Communicating effectively to patients that elevated blood pressure often occurs without symptoms and treatment is generally lifelong is challenging. Emphasising the need to continue medication despite the blood pressure values returning to normal is vital. Providing written instructions additionally help improve adherence.

5. Are the medication combinations appropriate?

It is not uncommon to find poor selection of two antihypertensive therapies resulting in inadequate blood pressure control. Suboptimal treatment regimens are when rational drug combinations are not used or not using drugs in maximum tolerable doses. The main guidelines now recommended that persons with hypertension be commenced with combination of two drugs to improve the chances of better control and better still if it is in a single pill^(12, 13).

Ideal and preferred combinations include thiazide diuretics or calcium channel blockers with either angiotensin converting inhibitors or angiotensin receptor blockers or beta-blockers with dihydropyridine calcium channel blockers.



These combinations have been proved in controlled intervention trials such as LIFE, ONTARGET, VALUE, ASCOT, ACCOMPLISH and HYVET^(19, 20, 21, 22, 23, 24).

Although, dihydropyridine calcium channel blockers (CCB) and beta-blockers combine well, the same is not true for non-dihydropyridine CCBs (verapamil and diltiazem) and beta-blockers. There is a high risk of atrioventricular block and bradycardia with this combination. ACEI/ARB and beta-blockers also do not show good blood pressure lowering effect.

Combining an ACE inhibitor with a beta-blocker is not recommended due to a lack of antihypertensive efficacy as shown in the ALLHAT study⁽²⁵⁾. However, third generation beta-blockers such as nebivolol produce significant additive effect. Although a combination of ACEI/ARB+ diuretic is additive, there is an increased risk of developing diabetes mellitus with the beta-blockers and diuretic combination.

6. Are there any substances used regularly raising blood pressure or interfering with the action of the medications?

A number of drugs interfere with the actions of antihypertensives and reduces its effectiveness. Drugs such as decongestants, herbal medicines, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids can contribute to raising blood pressure. Except for CCBs, NSAIDs blunts the antihypertensive effect of most classes of drugs through volume expansion following the inhibition of vasodilatory and natriuretic prostaglandins. Consider alternative analgesics such as acetaminophen or topical NSAIDs depending on indication and risk. Lowering the dose of steroids or if feasible changing the route of administration may help. Uncommonly, cyclosporine and erythropoietin and its analogues may interact with antihypertensive medications. Alternative drugs associated with less effects on blood pressure should be considered (e.g. tacrolimus).

In women, it is important to check if she is on the oral contraceptive pills, in particular the combined oestrogen-progesterone preparation. Alternative form of contraception should be suggested such as a progesterone-only form of contraception or barrier method if appropriate.

7. Are there any comorbid conditions affecting good control?

The presence of co-morbid conditions makes blood pressure control more difficult notwithstanding the lower blood pressure targets to achieve. Furthermore, cardiovascular outcomes might be influenced by the choice of anti-hypertensive medications. Additional medications and cost burden on the patient adds to the complexity. These conditions also enhance cardiovascular risk. Failure to meet optimal targets for each of these conditions impacts on the overall control. Obesity, excessive alcohol use, obstructive sleep apnoea, diabetes mellitus and chronic renal disease are important comorbid conditions that are associated with poor blood pressure control. While obesity, diabetes mellitus and renal disease are easy to identify, others are more challenging.

Obesity is linked to hypertension with a three-fold risk than a normal-weight person. In many studies, obesity is linked to reduced likelihood of achieving blood pressure targets despite the use of increased number of medications. Weight loss is an important strategy to improve blood pressure control in those who are obese or overweight.

It is estimated that for every 1kg of weight loss, there is 1 mmHg reduction in blood pressure⁽²⁶⁾. However, these are estimates are based on short term studies. In the longer term, blood pressure reduction is approximately 50% of that seen in short term studies⁽²⁷⁾. Successful weight loss requires dietary intervention and regular physical activity. Motivation counselling is helpful. Anti-obesity drugs and bariatric surgery should be reserved when other measures have failed.

Obstructive sleep apnoea is an important reversible cause of secondary hypertension. History of snoring may require further evaluation to exclude obstructive sleep apnoea, initially with a clinical scoring tool like Epworth Sleepiness Scale and night-time pulse oximetry and followed up with polysomnography for confirmation.



Hypertension is 1.5–3 times more prevalent among the diabetic subjects than among the non-diabetic population⁽²⁸⁾. Diabetes mellitus can also contribute to the difficulty in controlling blood pressure with conventional doses of antihypertensive agents due to sodium retention caused by hyperinsulinaemia. The benefits of blood pressure lowering in diabetes mellitus may even exceed those of glycaemic control for the prevention of cardiovascular complications.

For many of the cor-morbid conditions that are usually encountered in clinical practice such as diabetes mellitus, chronic renal disease, stable ischaemic heart disease, heart failure and secondary prevention after ischemic stroke, the recommended treatment goal for blood pressure by the US guidelines is below 130/80 mmHg⁽¹²⁾.

8. Is there a secondary cause? Check for clinical and laboratory clues.

An occult or overlooked secondary cause of hypertension should always be excluded, notably endocrine disorders such as primary aldosteronism (Conn's syndrome), pheochromocytoma, renovascular disease or rare genetic disorders. Patients with these conditions often do not respond readily to conventional antihypertensive agents.

Suspicion of secondary hypertension should be high when hypertension occurs in the young or of late-onset, blood pressure values are markedly high or rises acutely after good control.

A revisit to the history and physical examination may reveal clinical clues of an underlying secondary cause. Investigation may herald a clue such as an abnormal blood (low serum potassium) or urine test (e.g. red cells) or renal ultrasound (unilateral small kidney). A systematic approach and careful clinical evaluation using simple algorithms help avoid unnecessary investigations but additional confirmatory tests may be required. Correcting the cause of secondary hypertension can lead to improved blood pressure control if not a cure, avoiding the need for long-term medical therapy.

9. Should additional medication be added or dose optimised?

If the patient blood pressure control is inadequate despite optimal use of at least three drugs, there are few additional measures than be taken. Maximising diuretic therapy is one option. There is increasing evidence that adding a low dose of mineralocorticoid receptor antagonist such spironolactone is effective^(29,30). However, there should not be significant renal impairment or hyperkalemia. If spironolactone is contraindicated, amiloride or the long acting alpha blocker, doxazosin could be alternative choices. Spironolactone appears to counteract the salt retention due to inappropriate aldosterone secretion.

10. Does the patient need a specialist referral?

If the patient has not attained the new strict blood pressure target levels of 130/80 mmHg despite all the above measures, it is very likely that the patient is on more than three antihypertensive medications at tolerable doses of drugs. The patient is at significant cardiovascular risk and renal failure. Make sure that the patient is willing to take additional medications or undergo further testing. If so, there is a strong case for a referral to a specialist or cardiologist with special interest in hypertension. Device based therapy such as renal denervation and baroreflex activation therapy are niche procedures that are still evolving and may be locally available in the future.



	Checklist of steps and actions
Step 1	Assess if blood pressure is off target? – Determine the blood pressure level
Step 2	Check if blood pressure measurements are reliable? Improve accuracy
Step 3	Note if lifestyle measures are adequately adhered to – Encourage to adopt a healthy lifestyle and provide practical help
Step 4	Is there non-adherence to medications? Find out why
Step 5	Check if the medication combinations are appropriate - use rational combinations
Step 6	Evaluate for interfering substances – exclude these items
Step 7	Identify co morbid conditions – optimise the management of these conditions
Step 8	Exclude a secondary cause – reassess and investigate
Step 9	Consider additional medication and optimise existing therapy
Step 10	Refer to specialist with special interest in hypertension - consider renal denervation

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