

REVIEW ARTICLE

Hypertension treatment protocol for general physicians based on European society of cardiology and American heart association.

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ABSTRACT... The majority of our hypertension-related patients are treated by general physicians, not specialists. And trend of continuing medical education is lacking in Pakistan. In many countries, including India, Bangladesh, and Africa, general physicians are provided with a basic framework. This article is an attempt in this direction. A simple one-page, easy-to-read protocol based on recent and up-to-date guidelines from the European Society of Cardiology. It gives a basic framework for uniform treatment across the country and also gives them a basic diagnostic approach. How to assess on the first patient visit and what to do if the patient's follow-up is in doubt. It also gives them a basic guideline on when to refer the patient for specialist review.

Key words: Essential Hypertension.

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Article

Primary care is the cornerstone of any health system. United Nations and International goals of "Health for All" and "Sustainable Developmental Goals (SDG)" in health cannot be achieved without the involvement of general physicians.¹ In many remote areas of Pakistan, a general physician is the only source of medical care available to our population. In developed countries, there are programs for continuous medical education at all levels that equip all physicians with up-to-date knowledge.² In developing countries, including many countries of Asia and Africa, where such a program is lacking, physicians are provided with basic treatment protocols for the implementation of up-to-date recommendations.^{3,4} Pakistan is lacking in both. There is no compulsory program for continuous medical education, and there is no basic framework. We must provide our general physicians with a basic, up-to-date recommendation on which they can implement the international guideline-recommended therapy to patients. An example of this is Indian Hypertension Control Initiative, in which hypertension guidelines are implemented state-wise and programs are running to check efficacy at both state and national levels.^{5,6} A brief summary or chart to follow basic principles while giving them enough

freedom to practice on their own. This paper is a small effort in this direction.

This paper is an attempt to provide a basic framework based on the European Society of Cardiology guidelines for hypertension. It is recommended that the National societies of Pakistan should work on Local guidelines for the Pakistani population.

Step I – Checking Blood Pressure and Defining the Stage of Hypertension

The first step is checking the Blood pressure of the patient in the most optimal position with a standardized protocol.⁷

It has been emphasized that the best method is to get a home BP monitoring record or an ambulatory BP record of the patient; however, this is nearly impossible in rural areas where facilities are not available.⁸

For office monitoring, ideally, the patient should be sitting in a comfortable position with their back resting on a couch or chair, arms resting at the level of the heart, and both feet resting on the ground with uncrossed legs. It is recommended that the patient should be sitting in a controlled temperature,

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without any urge to pass stool /urine, and should not have consumed tea, coffee or energy drinks or smoked cigarettes in the past half hour.⁹

On the first visit, it is recommended to check blood pressure in both arms and use the arm with the higher readings for future reference. It is recommended to check for orthostatic hypotension before starting medicine.

It should be kept in mind that doing all these things is usually not possible for every physician who is checking the blood pressure of 100+ patients in some areas. Physicians are encouraged to reach as ideal an environment as possible, especially in patients with higher readings.

The next step is defining the stage of blood pressure. Multiple readings on at least two occasions or Ambulatory blood pressure monitoring (ABPM) is recommended before assigning a stage. ESC defined stages as follows

Normal: Systolic pressure lower than 120 mm Hg and diastolic pressure lower than 80 mm Hg.

Elevated: Systolic 120-129 mm Hg and diastolic lower than 80 mm Hg.

Stage 1: Systolic 130-139 mm Hg or diastolic 80-89 mm Hg.

Stage 2: Systolic 140 mm Hg or greater or diastolic 90 mm Hg or greater

It is important to differentiate if it's a one-time reading associated with stress/white coat Hypertension or if there is a continuous trend of high blood pressure. Making a BP chart for few days (2 weeks) or getting an ABPM is the Gold standard. In peripheral areas, patients often come for a single visit where daily monitoring of BP or ABPM is not available. In such circumstances, looking for signs of end-organ damage associated with hypertension is the best way to establish the chronicity of the disease. This includes fundoscopy for hypertensive eye changes, ECG and Echocardiogram for left ventricular hypertrophy, and urine examination for proteinuria. In the presence of end-organ damage, initiation of anti-hypertensive medications along with lifestyle modification is recommended even on the first visit. As fundoscopy is a dying art and Echocardiography also has limited availability and cost issues, the

minimal requirement is an ECG and a urine dipstick. Their presence not only indicates end-organ damage but also predicts long-term prognosis.^{10,11}

Step II- Lifestyle Modifications

Treatment starts with patient education and counselling

Ideally, management of hypertension should start with non-pharmacological therapies.¹²

When it comes to hypertension, the best accepted intervention is weight loss.¹³

Weight loss of 1 kg is associated with a decrease in BP of 3-5mm of Hg. With adequate weight loss, a drop in blood pressure of up to 30mm is expected. These changes are more pronounced in patients who are overweight or obese, especially those with newly diagnosed hypertension and a recent gain in weight

Salt restriction to less than one-third of a tablespoon (5mg) reduces BP up to 5mm of Hg over all.¹⁴

Similarly, increased potassium intake (up to 3-4mm of Hg) and a healthy active lifestyle, including 30 min walk (3-4mm of Hg) and resistance exercise (3mm of Hg) is associated with a significant drop in BP without medicine.

Step-III and IV - Starting Anti-HTN

If lifestyle interventions fail and there are consistently high readings of Blood pressure, the next step is to start anti-hypertensive medicine

First-line drugs include calcium channel blockers, ACE/ARBs, and Diuretics.

The European Society of Cardiology recommends initiating with the drug that has the maximum benefit for the patient's comorbidities.

For example, if a 60-year-old gentleman who is a diagnosed patient of Stable angina presents to your clinic with High blood pressure readings, the best medicine to be started is the one that not only lowers blood pressure but also eases anginal symptoms. These include beta blockers and calcium channel blockers.¹⁵

Similarly, if a Diabetic patient presents with high blood pressure and proteinuria best medicine to be added is one that reduce proteinuria like ACE/ ARBS and ARNI.¹⁶

Depending upon age and co-morbidities, initiation therapy usually consists of either an ACE/ARB or a calcium channel blocker.

Calcium channel blockers are among the safest drugs, to start with limited side effects and excellent efficacy. Starting with calcium channel blockers also gives additional time in suspected cases of renal artery stenosis or nephropathy, in which starting ACE can lead to adverse outcomes. Because of these benefits, they are considered as the preferred first line.

Amlodipine has good efficacy and safety, in addition to strong evidence from large randomized controlled trials for cardiovascular event reduction, making it first-line anti-hypertensive.¹⁷

The Comparison of Amlodipine versus Enalapril to Limit Occurrence of Thrombosis (CAMELOT) trial, enrolled 1991 patients with angiographically documented coronary artery disease (CAD) and randomized them to amlodipine 10 mg, enalapril 20 mg, or placebo and followed them over 24 months. Atherosclerotic progression was also assessed. Amlodipine significantly reduced non-fatal myocardial infarction (MI) by 26% and stroke or transient ischemic attack by 50% (number needed to treat=16). Moreover, there was a statistically significant reduction in hospitalization rate for angina ($p=0.003$) with amlodipine. This study suggests that normotensive patients treated with amlodipine show reduced rates of CV events and hospitalizations.¹⁸

ACE Inhibitor	ARBS	Calcium Channel Blocker	Diuretics
Ramipril	Lorastan	Amlodipine	Chlorthalidone
Lisinopril	Telmi-Sartan	Nifedipine	Indapamide
Enalapril	Valsartan	Feldepine	Furosemide
Captopril	Irbesartan	Diltiazem	Spironolactone
		Verpamil	

Outcome with Nifedipine GITS (ACTION) study in which nifedipine GITS was compared with placebo, significant reductions of 28% and 27% were seen the incidence of any stroke or transient ischaemic attack (TIA) in both the total population and the hypertensive subgroup, respectively. 7665 randomized patients, 1732 patients were receiving RAS blockade at baseline, the addition of nifedipine GITS significantly reduced any cardiovascular (CV) event (-20% ; $P<0.05$), the composite of death, any CV event and revascularization (-16% ; $P<0.05$) and coronary angiography (-22% ; $P<0.01$).¹⁹ Similarly, comparison of Ace and nifedipine showed similar efficacy with different safety profiles.²⁰

Both of these studies prove the incremental benefit of starting calcium channel blockers as Anti-HTN in patients suffering from angina.

The recommended ACE inhibitor in patients with heart failure with reduced ejection fraction is Ramipril.²¹ In the landmark trial HOPE, RAMIPRIL reduced the risk of Death and stroke by 26 and 33% respectively. Otherwise, there is no superiority of one ACE over another.

ARBs commonly prescribed in Pakistan include Losartan, Valsartan, Telmisartan and Irbesartan. Telmisartan has been associated with potential additional benefits beyond blood pressure control. One of its unique properties is its activation of peroxisome proliferator-activated receptor gamma (PPAR- γ), which may have beneficial effects on insulin sensitivity, lipid metabolism, and reducing inflammation. This makes Telmisartan a potentially better choice in patients with metabolic syndrome or those at high risk for diabetes and heart disease.²¹ Telmisartan also has a longer half-life (24 hours) so it provides more uniform Blood pressure control compared to losartan, irbesartan, and valsartan. The elimination half-life of telmisartan is very long, about 24 h, and consequently has a long-lasting action and sustained reductions of blood pressure. More than 90% of telmisartan is excreted through feces, and therefore, telmisartan is different from other ARBs.

ARNI- is a new class of Anti-hypertensive and heart failure medications which basically include a

combination of an ARB(valsartan) with neprilysin inhibitor. Inhibition of neprilysin leads to persistent and prolonged action of naturally occurring peptides like BNP and ANP which in turn leads to increased natriuresis and diuresis. ESC and AHA both guidelines recommend ARNI in preference to ACE/ARBs and shifting to ARNI in patients who are already taking ACE/ARNI.

Sacubitril/valsartan significantly reduced the risk of cardiovascular death or hospitalization for heart failure compared to enalapril, as proven by the Landmark PARADIGM-HF trial. Among 13,194 participants in the PARADIGM-HF and PARAGON-HF trials, mean (SD) patient age was 67 (11) years, 8883 patients (67.3%) were male, and mean (SD) LVEF was 40% (15%). Sacubitril/valsartan significantly reduced the risk of all-cause hospitalization (ACH) compared with RASi over a median (IQR) follow-up period of 2.5 (1.8-3.1) years (hazard ratio [HR], 0.92; 95% CI, 0.88-0.97; $P = .002$).²²

Among diuretics, the recommended starting diuretic is a thiazide diuretic. Chlorthalidone is recommended in preference to hydrochlorothiazide, which is less studied.²³ Thiazide-like diuretics, including Indapamide and Metaxone, are also better than Hydrochlorthiazide.

In resistant cases, it is recommended to add spironolactone (Aldactone antagonist in preference to other anti-hypertensives).

It's important to remember that there is no fixed formula that will work in every patient. Remembering beneficial effects in certain conditions and looking for side effects is the best policy for reaching optimal control. In stage II with end-organ damage, it is recommended to start with combination therapy (at least 2 drugs). It is recommended to add drugs based on proven benefits and guidelines instead of "Gut feeling".

Once a medicine is started, it's taken to the maximum tolerated dose, and if still an optimal effect is absent, then the 2nd anti-hypertensive is added.

Single drug	Either ACE/ARB or Calcium Channel or A Thiazide Diuretic Preference for One Drug is Based on Patient's Comorbidities
2 drug	A Combination Single Pill is Recommended to Ensure Compliance Recommended Combinations Are ACE or ARBS+Calcium Channel Or ACE/ARB + Thiazide Diuretics
3 drug	Combination of All 3- Ideally in a Single Pill ACE/ARB + Calcium Channel + Thiazide Diuretics
4 th drug	Aldosterone antagonist- Spironolactone Or Eplerenone
5 th drug	Referral to a Specialist, cardiologist, or endocrinologist is recommended for further medical care if still uncontrolled

For stage 2 hypertension, it is recommended to start with 2-drug therapy. The best combination based on research is either a combination of ACE/ARB with calcium channel or diuretics. This combination counters the side effects of other drugs and is more effective compared to a single drug.

Single pill combination*

In a multicenter trial conducted across Italy, China, Russia, Mexico, and South Korea, the benefits of a single pill combination were proven to be superior to multiple separate pills. It improves compliance and reduces economic burden, too.²⁴ The most common cause of uncontrolled blood pressure is non-compliance, and a major factor is the multiple pills required per day. That poses difficulty in both understanding, and there is an added financial element too. SPC reduced mortality by 5.4% in Italy, 4.9% in Russia, 4.5% in China, 2.3% in South Korea, and 3.6% in Mexico versus CTP and showed greater reductions in mortality than SLGS and FCC. The projected incidence of clinical events was reduced by 11.5% in Italy, 9.2% in Russia, 8.4% in China, 4.9% in South Korea and 6.7% in Mexico for SPC versus CTP

Hypertension Treatment Protocol

For General Physicians

- **Normal:** Systolic lower than 120 mm Hg and diastolic lower than 80 mm Hg.
- **Elevated:** Systolic 120-129 mm Hg and diastolic lower than 80 mm Hg.
- **Stage 1:** Systolic 130-139 mm Hg or diastolic 80-89 mm

Hg.

- **Stage 2:** Systolic 140 mm Hg or greater or diastolic 90 mm Hg or greater
- END ORGAN DAMAGE
- Heart (left ventricular hypertrophy)
- Kidneys (Micro-albuminuria + eGFR)
- Brain (stroke/microinfarcts+haemorrhages)
- Eyes (Retinopathy)
- Vascular system (increased vascular wall thickness and arterial stiffness)

Step-I Check Blood Pressure + Define Stage and Assess for End-Organ Damage

1. WEIGHT LOSS (1-KG WEIGHT loss associated 1-5mm Hg drop in blood pressure in various studies)
2. Decrease salt intake
3. Get moving- daily brisk walk decrease blood pressure independent of its weight loss effect
4. Avoid smoking, alcohol, recreational drugs and stress

Step-II Assess Patients' Motivation and Advice
Life Style Modifications for Non-Pharmacological Control of Hypertension

Step-III Medical Treatment- DUAL Rx

First Line Drug Class- Calcium Channel Blockers, ACE/ARBs/ARNI, Diuretics,

IF STAGE 2, with end-organ damage, start with a 2-drug regimen, ideally a combination of ACE/ARB/ARNI with a diuretic or calcium channel blocker

Step IV- Triple Rx

If Uncontrolled After 2 Weeks of Double Therapy
Shift OT Triple Regime (A +C+ D)

First line diuretic recommended are thiazide-like diuretics

Note: ideally, chlorthalidone or indapamide are recommended in preference to hydrochlorthiazide

Step V- ADD Aldosterone Antagonist- Consider Beta Blockers

No specific recommendation on beta blockers- in heart failure, anginal, or tachycardiac patient, nebivolol is recommended in preference to other beta blockers.

Beta blockers can be added at any step with no specific recommendation in a patient without

comorbidities.

STEP –VI

If still uncontrolled, label as refractory hypertension and refer to cardiologist, endocrinologist, or hypertension specialist for further workup and treatment

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Rizwan Ahmed: Data analysis.
3	Tooba Iqbal: Research editing.
4	Aimen Iqbal: Review.