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Management of hypertension across the cardiovascular-renal continuum

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Abstract
A high incidence of cardiovascular risk misclassification and underestimation of high-risk patients prevails among primary care physicians. In addition, it has been observed that treatment goals of hypertension as recommended by guidelines are not followed in the primary healthcare setting. Therefore, there exists a large percentage of the population with uncontrolled hypertension in India. We aimed at developing a framework for the effective management of hypertension and cardiovascular-renal risk in the presence of comorbidities for clinicians/healthcare providers. An online advisory board meeting with eminent cardiologists from across India was conducted to understand their perspectives on the management of hypertension across the cardiovascular-renal continuum. The outcomes of the meeting were summarized following a literature review of cardiorenal disorders, stroke, and heart failure risk in hypertensive patients. Furthermore, optimal treatment of hypertension in patients with a high risk of coronary artery disease, stroke, and chronic kidney disease and the choice of angiotensin receptor blockers in these patients were suggested. The advisory board meeting provided management strategies for patients with hypertension across the cardiovascular-renal continuum considering the increased risk of heart failure and death in the Indian setting.

Keywords: Hypertension, cardiorenal continuum, heart failure, chronic kidney disease, stroke, telmisartan

Introduction

Cardiovascular diseases (CVDs) are a group of disorders usually caused by risk factors such as hypertension, diabetes mellitus, dyslipidemia, and visceral obesity. CVDs typically represent the final stage of progressive vascular damage. This process is called the cardiorenal continuum [1]. Early intervention to manage these risk factors is important to delay their progression to severe CVDs such as arterial sclerosis, coronary artery disease (CAD), myocardial infarction (MI), left ventricular hypertrophy, and left ventricular dysfunction; and eventually end-stage heart failure and death [2]. Several studies conducted in hypertensive patients suggest that high CVD risk is directly proportional to a high prevalence of chronic kidney disease (CKD). Cardiorenal diseases are also correlated to old age and high incidence of hypertension, type 2 diabetes mellitus (T2DM), obesity, and other CV risks [1].

CVDs are one of the leading causes of morbidity and mortality across the world [1]. In India, the prevalence of CVDs is increasing and has led to a major cause of mortality [3]. The Global Burden of Disease study reported that India has a higher CVD-associated death rate of 272 per 100,000 population compared to the global average of 235 per 100,000 population [4]. This might be due to the increasing prevalence of CVD risk factors in India [3]. Estimates suggest the prevalence of hypertension to be 30% of the Indian adult population. A study conducted by International Diabetes Federation (IDF) in 2013 reported that India has around 65.1 million people with T2DM. The Indian Council of Medical Research–India Diabetes (ICMR-INDIAB) study found that only 20% of individuals exhibited normal levels of all lipid parameters, suggesting that almost 80% had at least one lipid abnormality [4].Hypertension is a major risk factor for cardiovascular outcomes such as heart failure (HF), stroke, and coronary artery disease (CAD) [5, 6]. The Framingham heart study (FHS) reported a 2- to 4-fold increase in risks of major CV outcomes due to hypertension in men and women aged 36-64 years [6].

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Additionally, a prospective community-based cohort study reported that hypertensive patients had a 2.3-fold higher risk of death from a stroke after HF than those without stroke [7]. A strong continuous association between diastolic blood pressure (BP) and the risk of stroke has been observed in the Eastern Stroke and Coronary Heart Disease Collaborative Project. A decline in stroke can be achieved by lowering BP across a wider range of the population [8]. In addition, diastolic blood pressure is the strongest predictor of CAD in younger and middle-aged people, whereas systolic pressure is the most effective predictor for CAD in people aged >60 years [9]. Uncontrolled hypertension is one of the risk factors for developing CKD. Nearly, 85%-95% of patients with CKD (stages 3-5) suffer from hypertension. Conversely, worsening renal diseases can lead to uncontrolled hypertension due to volume expansion and increased systemic vascular resistance [10].

Considering the various etiologies playing a role in the cardiovascular renal continuum, it becomes necessary for the timely management of underlying risk factors in hypertensive patients. However, risk-based management of hypertensive patients is far from satisfactory. Studies from different parts of the world have reported that the rates at which CV risk scores are used range from 17% to 65% [11]. According to a study conducted in the United States, 92% of physicians had knowledge about CV risk estimation tools; however, they used it in only 41% of patients. Out of the 41% of patients, the tools were used to make treatment-related decisions only in a fraction of patients [12]. Moreover, studies have reported inaccuracy in the subjective estimation of CV risk by physicians. Instead of absolute risk calculation, patients and physicians generally estimate risk by risk factor counting, which leads to underestimation of risk in those who may have slightly elevated levels of multiple risk factors that synergistically increase the overall absolute CV risk [11].

An online advisory board meeting including eminent cardiologists from India was conducted to understand their perspectives on the management of hypertension across the cardiovascular-renal continuum. This review aims to develop a framework for clinicians and healthcare providers on effective management and achievement of successful clinical outcomes in people with hypertension and cardiovascular-renal risk in the context of various comorbidities.

Need for CV risk evaluation
Evidence suggests approximately one-third of primary care physicians in Canada were unaware of the defining point for high CV risk [>20% 10-year Framingham risk score (FRS) CV risk]. This may have led to the misclassification of risk and undervaluation of truly high-risk patients [12]. Additionally, several discrepancies exist between different risk assessment tools. Various guidelines recommend the use of different risk score calculators to assess the 10-year CV risk that may vary the management depending on the risk score. There are differences in the methods used by various risk scores, and over time these have led to misunderstandings, confusion, and uncertainty by users. Therefore, the local applicability and modifiability of the risk model is important. For example, in a study on Asian Indians, only 5% of the population was found to be at high risk using the Framingham risk score (FRS) calculator (old

version), which appears to be an underestimation of CVD risk in this genetically predisposed population [13].

Hypertension management goals
The American guidelines are largely based on meta-analyses of major outcome trials such as Systolic Blood Pressure Intervention Trial (SPRINT), while the European guidelines are driven by population-based risk. However, the BP goal suggested by both guidelines is the same, i.e. <130/80 mmHg [14].
Treatment goals as per Indian Guidelines on Hypertension–IV 2019 suggest the following:
▪ The threshold for starting antihypertensive drugs should be 140/90 mmHg in most patients. In patients with CAD and HF, antihypertensive therapy may be started beyond the BP of 130/80 mmHg.
▪ Target BP of <130/80 mmHg should be achieved especially in those <60 years. In the elderly, the target can be between 130-140/80-90 mmHg, and it needs to be individualized.
▪ Patients with HF with preserved ejection fraction (HFpEF) derive significant benefits with good BP control and a target of <130/80 mmHg should be achieved just as in HF with reduced ejection fraction (HFrEF) [15].

Hiremath *et al.* reported that most of the physicians targeted a BP goal of <130/80 mmHg in patients with diabetes mellitus (n=161), CKD with proteinuria (n=179), and CKD without proteinuria (n=125). Overall, physicians followed a lower BP goal than the recommendations of various guidelines in patients with diabetes or CKD and those aged 60 years and above [16]. The percentage of the population with uncontrolled hypertension is too large with inevitable health consequences for the country. Therefore, it is wise for India to adopt and embrace the best features of both the American and European guidelines [17].

Uncontrolled hypertension, the most important risk factor in the CV-renal continuum
Uncontrolled BP is a driving factor for target organ damage such as the heart, brain, arterial blood vessels, and kidneys. Therefore, the evaluation of target organ damage becomes critical in people with hypertension [18]. Currently, FRS is the most popular scale used to access CV risk.

Estimating cardiorenal risk in hypertensive patients
A continuous relationship exists between urinary albumin excretion (UAE) and cardiorenal risk, which is similar to the one that exists between BP and the risk of CV events. Kidney damage is indicated by the presence of microalbuminuria (MAU) in pathological conditions, such as CKD, diabetes, or hypertension, which is also a marker of progressive CKD, CV morbidity, and mortality. Under normal circumstances, UAE is less than 30 mg/day. If this value varies between 30 and 300 mg/day in a 24-hour urine sample or 30 to 300 mg/g of creatinine [urine albumin-to-creatinine ratio (UACR)] in the first-morning sample, it is termed as moderately increased albuminuria. Albuminuria of more than 300 mg/day is considered macroalbuminuria. The gold standard for MAU estimation is 24-hour urine collection, but the first-morning urine sample or a random sample at any time can also be tested for MAU [19].

Fibromuscular dysplasia or atherosclerosis commonly causes renal artery stenosis (RAS) and is often associated with hypertension, renal insufficiency (ischemic nephropathy), or both, or it may also occur alone. RAS can lead to hypertension and renal ischemia, often causing end-stage renal failure. RAS screening is advisable in patients suspected to have renovascular hypertension or ischemic nephropathy, so as to identify the need for endoluminal or surgical revascularization. There has been a considerable improvement in RAS screening since the end of the 20th century. Earlier techniques such as captopril renography are now replaced with well-advanced systems like Doppler ultrasound (US) of the renal arteries, computed tomography angiography (CTA), or magnetic resonance angiography (MRA), which have become the tests of choice for screening [20].

Glomerular filtration rate (GFR) along with albuminuria is another marker for estimating renal risk in patients with comorbidities. Widely recognized as the best assessment method for kidney function, a decline in estimated GFR (eGFR) indicates higher rates of acute kidney injury (AKI), CKD complications, CVD, and all-cause mortality [18]. According to Ninomiya et al., T2DM patients with UACR of 300 mg/g and eGFR <60 mL/min/1.73 m^2 were at a 3.2-fold increased risk for CV events and a 2.2-fold risk for renal events, as compared to patients having neither of these risks [19].

Estimating stroke risk in hypertensive patients

Ischemic stroke risk is indicated by the presence of left ventricular hypertrophy (LVH) on an electrocardiogram (ECG). Evidence suggests that baseline and serial changes on ECG in the presence of LVH separately predict subsequent cardiovascular events. A cohort study conducted in the Northern California Kaiser Permanente Medical Care Program involving 75,412 men and 107,954 women reported that LVH trajectories derived from ECG indicated coronary heart disease, stroke, and HF risk. These were independent of the level and difference in CVD risk factors and may have clinical utility [21].

Estimating heart failure risk in hypertensive patients

In routine clinical practice, amino-terminal pro-brain-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are the two main natriuretic peptides. Natriuretic peptide levels are correlated with HF prognosis and CV morbidities. The measurement of natriuretic peptides was hence recommended for the diagnosis of HF in previous guidelines by the National Institute for Health and Care Excellence (NICE) [22]. As per the 2016 European Society of Cardiology (ESC) guideline for acute and chronic HF, circulating levels of the biomarkers NT-proBNP and BNP can be used as primary diagnostic tests. For patients without acute HF, cut-off values of NT-proBNP and BNP are 125 and 35 pg/mL, respectively. ECG examination is suggested for patients with NT-proBNP/BNP values higher than the upper limit and for those having a medical history or symptoms suggesting HF. Relatively high negative predictive value of NT-proBNP/BNP (94%–98%) and low positive predictive value (44%–57% for nonacute HF and 66%–67% for acute HF) are considered as important screening indices of HF risk [23].

Management of hypertension with associated comorbidities

The International Society of Hypertension (ISH) global guideline recommends lifestyle modifications as the first-line intervention strategy when diagnosed with hypertension. For grade I hypertension (BP: 140-159 and/or 90-99 mmHg) in low to moderate-risk patients with persistent BP elevation, drug treatment should be initiated after 3-6 months of lifestyle intervention. In grade II hypertensive patients (BP ≥160/100 mmHg), there is a need to start drug treatment immediately along with lifestyle intervention [24].

A BP target of <130/80 mmHg may be reasonable for adults with confirmed hypertension, without additional markers of increased CVD risk. For initiation of antihypertensive drug therapy, American College of Cardiology (ACC) 2017 guidelines recommend the use of first-line agents including thiazide diuretics, calcium channel blockers (CCBs), and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) [25].

As per ESC 2018 guidelines, BP should be targeted to 140/90 mmHg or lower if tolerated. Preferred two-drug combinations are a RAS blocker (either ACE inhibitor or ARB) with a CCB or a diuretic. A beta-blocker in combination with a diuretic or any drug from the other major classes is an alternative when there is a specific indication for a beta-blocker, such as angina, post-MI, HF, or heart rate control. The use of a three-drug single-pill combination is advised, comprising of a RAS blocker, a CCB, and a diuretic if BP is not controlled by a two-drug combination [26].

Coexistence of certain comorbidities along with hypertension may affect clinical decision-making. These include ischemic heart disease, HFrEF, HFpEF, CKD, cerebrovascular disease, atrial fibrillation, peripheral artery disease, diabetes mellitus, and metabolic syndrome [25]. The ISH global guideline recommends initiating drug therapy immediately in high-risk hypertensive patients with comorbidities [24].

Optimal treatment of hypertension and prevention of HF

For the prevention of HF in patients with hypertension, ACC 2017 guidelines recommend an optimal BP of <130/80 mmHg in adults with an increased risk of HF [25].

Individuals with T2DM have a 2-fold risk of incident HF than in people without diabetes. This is partly due to the presence of all major risk factors for HF such as obesity, advanced age, sleep apnea, dyslipidemia, hypertension, CKD, and CAD in patients with T2DM [27]. The ACC 2017 guidelines recommend initiation of antihypertensive drug treatment in hypertensive patients with DM and a BP of 130/80 mmHg or higher. The treatment goal of these patients should be less than 130/80 mmHg. First-line classes of antihypertensive agents such as diuretics, ACE inhibitors, ARBs, and CCBs are useful and effective [25].

The ESC 2018 guidelines recommend that the target systolic BP should be 130 mmHg or lower if tolerated, but not <120 mmHg, and the target diastolic BP should be <80 mmHg, but not <70 mmHg. Treatment with a combination of a RAS blocker with a CCB or thiazide/thiazide-like diuretic is recommended [26].

Hypertension and patients at high risk of HF

For adults with confirmed hypertension and known CVD or 10-year Atherosclerotic Cardiovascular Disease (ASCVD) event risk of 10% or higher, a BP target of <130/80 mmHg is recommended [25].

Optimal treatment of hypertension in patients at high risk of CAD

In adults with stable ischemic heart disease (IHD) and hypertension, a BP target of less than 130/80 mmHg is recommended.

First-line therapy in patients with hypertension and previous MI or stable angina is beta blockers, ACE inhibitors, or ARBs, with the addition of other drugs (for example dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists [MRAs]) as needed to further control hypertension [25].

In patients with CAD, the target systolic BP should be 130 mmHg or lower if tolerated, but not <120 mmHg, and the target diastolic BP should be <80 mmHg, but not <70 mmHg. Initial therapy should be a dual combination of (i) ACE inhibitor or ARB plus beta-blocker or CCB; or (ii) CCB + diuretic or beta-blocker; or (iii) beta-blocker + diuretic. The second step is a triple combination of the above agents, while the third step is a triple combination plus spironolactone or other diuretic, alpha-blocker, or beta-blocker [26].

Optimal treatment of hypertension in patients at high risk of stroke

In hypertensive patients with a history of stroke or transient ischemic attack (TIA) and those who experience a stroke or TIA, a BP goal of <130/80 mmHg may be reasonable. Treatment with a thiazide diuretic, ACE inhibitor, or ARB, or combination treatment consisting of a thiazide diuretic + ACE inhibitor, is beneficial [25].

According to the ESC 2018 guidelines, the recommended antihypertensive drug treatment strategy for stroke prevention is a RAS blocker + a CCB or a thiazide-like diuretic [26].

Optimal treatment of hypertension in patients with CKD

Adults with hypertension and CKD should be treated to achieve a BP goal of <130/80 mmHg. To stop the progression of kidney disease, treatment with an ACE inhibitor is reasonable. In patients with hypertension and CKD, treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated [25].

According to the ESC 2018 guidelines, initial treatment should be (i) ACE inhibitor or ARB plus CCB or (ii) ACE inhibitor or ARB or diuretic. Second-line treatment should be a triple combination of ACE inhibitor or ARB plus CCB plus diuretic. The third step is a triple combination plus spironolactone or other diuretic, alpha-blocker, or beta-blocker [26].

Hypertension and patients with HF

As per the ACC 2017 guidelines, patients with HFrEF and hypertension should be prescribed medical therapy to attain a BP goal of less than 130/80 mmHg. In adults with HFpEF who present with symptoms of volume overload, ACC recommended the use of diuretics to control hypertension. Post-management of volume overload, the patient should be prescribed ACE inhibitors or ARBs and beta blockers titrated to attain systolic BP of <130 mmHg [25].

According to ESC 2018 guidelines, initial therapy should be ACE inhibitor or ARB plus diuretic plus beta blocker. Second-line treatment should be ACE inhibitor or ARB plus diuretic plus beta-blocker plus MRA [26].

When antihypertensive therapy is not required, treatment should be prescribed according to the ESC HF guidelines.

ESC HF consensus 2019 recommends the most effective combinations for HFrEF as (i) sacubitril/valsartan + beta-blocker + MRA, and (ii) ACE inhibitor + beta-blocker + MRA + ivabradine, leading to reductions in all-cause mortality and in all-cause hospitalizations for each combination [28].

The 2016 ESC Heart Failure guidelines have also focused on the role of ivabradine to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with a reduced LVEF ≤35% and sinus rhythm ≥70 beats per minute (bpm) despite treatment with an evidence-based dose of beta-blocker or a dose below the recommended dose [29].

Selecting appropriate pharmacological agents for the management of hypertension with comorbidity

Selecting appropriate ARBs in management of hypertension

ARBs were a milestone in the history of hypertension treatment amongst the available therapeutic options. They further widened the range of therapy, especially for patients unable to tolerate ACE inhibitors. ARBs are safe in terms of absence of negative metabolic effects and no accumulation of bradykinin. They also have additional cardiac and renal protective effect by virtue of the ability to activate the angiotensin II type 2 (AT2) receptors, which causes vasodilatation in the small vessels.

Each ARB is important in the treatment of hypertension, according to recent findings. There is no guidance available with respect to the preference of which ARB should be administered in case of different co-morbid conditions. However, several studies have reported that certain ARBs have shown additional beneficial effects [30].

Telmisartan: ARB of choice in the management of hypertension in different comorbid conditions

A detailed review of the available literature has helped in treatment selection for individual patients. Telmisartan is primarily the ARB of choice in patients with high CV risk for preventing CV events [30].

Numerous clinical trials have evaluated the effects of telmisartan at different stages of the cardiovascular and renal disease continuum, along with its effects on various risk factors, regression of organ damage, and the delay of cardiovascular outcomes. In a 1-year randomized controlled trial (RCT) evaluating the effects of telmisartan on atherosclerosis, telmisartan significantly inhibited the progression of intima-media thickness of the common carotid artery relative to losartan without significant between-group differences in BP. A small study evaluated the effects of telmisartan on the coronary plaque component and local inflammatory cytokines in patients with hypertension. Levels of inflammatory cytokines [matrix metalloproteinase 3 and 9, tumor necrosis factor (TNF)-α, and high-sensitivity C-reactive protein (hsCRP)] in the coronary sinus were reduced only in the telmisartan-

receiving group, but not in the control group. A meta-analysis of nine RCTs demonstrated that telmisartan had favorable effects as compared to other antihypertensives with regard to left ventricular mass regression in hypertensive patients [31].

As per the Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial, telmisartan reduced risk of the composite outcome of cardiovascular death, MI, or stroke [32].

Role of calcium channel blockers in CV risk reduction

According to a meta-analysis conducted by Chi *et al.*, ARB plus CCB lowered the incidence of CV events (risk ratio 0.80 [0.70, 0.91]) and yielded a 4.21 mL/min/1.73 m^2 lower eGFR reduction than other combinations (p<0.001; Table 1 and Table 2) [33]. Another systematic review and meta-analysis of 18 long-term RCTs showed that treatment with a diuretic was significantly more effective than placebo in preventing stroke, HF, ischemic heart disease, and mortality [34].

Table 1: Cardiovascular composite outcomes, including cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke

Trial name, year	A+C		Other			Risk ratio M-H, Random 95% CI
	Events	Total	Events	Total	Weight	
ACCOMPLISH 2008	288	5762	364	5744		0.79 [0.68, 0.92]
COPE 2011	25	1110	29	1089	6.1%	0.85 [0.50, 1.43]
COLM 2014	75	2568	88	2573	18.2%	0.82 [0.60, 1.11]
Total events	385	-	481	-	-	-
Total (95% CI)	-	9440		9406	100.0%	0.80 [0.70, 0.91]

A+C, angiotensin converting enzyme inhibitor/angiotensin receptor blocker plus calcium channel blocker; ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension; CI, confidence interval; COLM, Comparison of Olmesartan Combined with a Calcium Channel Blocker or a Diuretic in Elderly Hypertensive Patients study;; COPE, Combination Therapy of Hypertension to Prevent Cardiovascular Events study; M-H, Mantel-Haenszel method

Table 2: Renal function (the reduction of estimated glomerular filtration rate)

Trial name, year	A+C Events			Other Events				Mean difference IV, Random 95% CI
	Mean	SD	Total	Mean	SD	Total	Weight	
ACCOMPLISH 2008	0.88	15.6	5762	4.22	16.3	5744	21.8%	−3.34 [−3.92, −2.76]
GUARD 2008	2.03	1.42	153	13.6	16.1	151	13.5%	−11.57 [−14.98, −8.16]
J-CORE 2009	1.2	1.9	103	6.9	1.9	104	21.9%	−5.70 [−6.22, −5.18]
COPE 2011	2.5	12	1110	2.8	12	1089	21.1%	−0.30 [−1.30, 0.70]
COLM 2014	3.2	13	2568	6	13	2573	21.6%	−2.80 [−3.51, −2.09]
Total (95% CI)	-	-	9696	-	-	9661	100.0%	−4.2 [-6.21, −2.21]

A+C, Angiotensin converting enzyme inhibitor/angiotensin receptor blocker plus calcium channel blocker; ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension; CI, confidence interval; COLM, Comparison of Olmesartan Combined with a Calcium Channel Blocker or a Diuretic in Elderly Hypertensive Patients study; COPE, Combination Therapy of Hypertension to Prevent Cardiovascular Events study; GUARD, Gauging Albuminuria Reduction with Lotrel in Diabetic Patients with Hypertension; IV, weighted mean difference; J-CORE, Japan-Combined Treatment with Olmesartan and a Calcium Channel Blocker Versus Olmesartan and Diuretics Randomized Efficacy

Conclusion

Hypertensive patients with comorbidities need to be managed on a regular basis to reduce the risk across cardiovascular and renal disease continuum. There is a lack of clear guidelines regarding the management of hypertension associated comorbidities like CVD, CKD, stroke, and heart failure for the Indian population. A consensus of BP treatment goals and use of combination of antihypertensive agents needs to be set for the management of such patients. This review aims to provide the basis for the formation of these guidelines considering the increasing risks of hypertension ultimately leading to heart failure and death in India.

Acknowledgments

Conflict of interest

Jabir Abdullakutty is a member of the Cardiological Society of India, Indian Medical Association, and Society for Heart Failure and Transplantation. Both authors received speakers' honoraria from Abbott for participating in the advisory board meetings.

Declarations

The expert group discussion was conducted in association with Abbott Healthcare Pvt. Ltd. This article is based on the views expressed during the expert group discussion. The views expressed and discussed in the meetings and stated in this article are the independent views of the authors and not of Abbott Healthcare Pvt. Ltd.

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