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GUIDELINES

RSSDI Guidelines for the management of hypertension in patients with diabetes mellitus

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Abstract

Hypertension and diabetes mellitus (DM) are two of the leading lifestyle diseases in the Indian and South Asian populations that often co-exist due to overlapping pathophysiological factors. Obesity, insulin resistance, inflammation, and oxidative stress are thought to be some common pathways. Up to 50% of hypertensive cases in India are diagnosed with type 2 diabetes mellitus (T2DM), which defines the need for a comprehensive guideline for managing hypertension in diabetic patients. These RSSDI guidelines have been formulated based on consultation with expert endocrinologists in India and Southeast Asia, acknowledging the needs of the Indian population. Ambulatory blood pressure monitoring and office and home-based blood pressure (BP) monitoring are recommended for the early analysis of risks. Cardiovascular risks, end-organ damage, and renal disorders are the primary complications associated with diabetic hypertension that needs to be managed with the help of non-pharmacological and pharmacological interventions. The non-pharmacological interventions include the nutrition education of the patient to reduce the intake of salt, sodium, and trans fats and increase the consumption of nuts, fresh fruits, vegetables, and potassium-rich foods. It is also recommended to initiate 50 to 60 min of exercise three to four times a week since physical activity has shown to be more beneficial for hypertension control in Indian patients than dietary modulation. For the pharmacological management of hypertension in patients with T2DM, angiotensin II receptor blockers (ARBs) are recommended as the first line of therapy, demonstrating their superiority over other antihypertensive agents such as ACEi. However, most of the global hypertension guidelines recommend initiation with combination therapy to achieve better BP control in most patients and to reduce the risk of adverse events. For combination therapy, calcium channel blockers (CCBs) are recommended to be administered along with ARBs instead of beta-blockers or diuretics to avoid the risk of cardiovascular events and hyperglycaemia. Among the CCBs, novel molecules (e.g. cilnidipine) are recommended in combination with ARBs for better cardiovascular and reno-protection in diabetic hypertensive patients.

Keywords Diabetes mellitus · Hypertension · Macrovascular complication · Treatment

Abbreviations

ABPM	Ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACEi	Angiotensin-converting enzyme inhibitors
AD	Alzheimer's disease
ADA	American Diabetes Association
AHA	American Heart Association
ALDO ANT	Aldosterone antagonist
ARBs	Angiotensin II receptor blockers
ASCVD	Atherosclerotic cardiovascular disease
BB	Beta-blockers
BP	Blood pressure
CAD	Coronary artery disease
CCB	Calcium channel blockers
CKD	Chronic kidney disease
CVD	Cardiovascular disorders
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ED	Erectile dysfunction

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eGFR	Estimated glomerular filtration rate
eNOS	Endothelial nitric oxide synthase
HBPM	Home blood pressure monitoring
HFrEF	Heart failure with reduced ejection fraction
HMOD	Hypertension-mediated organ damage
HTN	Hypertension
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LMIC	Low- and middle-income countries
LV	Left ventricular
MACCE	Major adverse cardiac and cerebrovascular events
MHSBP	Morning home systolic blood pressure
MI	Myocardial infarction
OSA	Obstructive sleep apnoea
PAD	Peripheral arterial disease
PE	Preeclampsia
RAAS	Renin–angiotensin–aldosterone system
RAS	Renin–angiotensin system
RCT	Randomized controlled trial
ROS	Reactive oxygen species
RSSDI	Research Society for the Study of Diabetes in India
SBP	Systolic blood pressure
SGLT2 inhibitors	Sodium–glucose cotransporter 2 inhibitors
SNA	Sympathetic nerve activity
SPC	Single-pill combination
SUA	Serum uric acid
T2DM	Type 2 diabetes mellitus
TIA	Transient ischaemic attack
UACR	Urine albumin–creatinine ratio
UPCR	Urine protein–creatinine ratio
VSM	Vascular smooth muscle
WHO	World Health Organization

Introduction

Currently, hypertension is a major public health issue in India, causing over 1.6 million annual deaths accounting for 10.8% of the total mortalities and 4.6% of the disability-adjusted life years [1]. Both conditions' co-existence is common in the middle and older age groups across all geographic and socio-demographic groups in India [2]. A crucial consideration for the management of hypertension in Indian subjects is the management of risk factors, which can be achieved through a combination of treatment approaches [3]. To manage the co-existing diseases, there is a need for detailed guidelines that consider the safety and efficacies of various treatment agents in patients with DM. This guideline by the Research Society for the Study of Diabetes in India (RSSDI) provides a detailed account of the standard, approved, and novel treatment agents to be used in India for controlling hypertension in patients with DM and for managing and reducing the risks of associated complications and organ damage. It also will describe lifestyle modification strategies and dietary approaches recommended for patient education, which is a pressing need for the Indian population [4]. This guideline focusses only on the management of hypertension in diabetic patients. Discussion on the non-pharmacological or pharmacological management of diabetes and special populations like pregnancy may not be in the purview of this guideline.

Definition of hypertension

Hypertension or systemic arterial hypertension refers to persistently high blood pressure in the systemic arteries beyond 140 mmHg [5]. ACC/AHA guidelines have changed the range to 130/80; however, Indian Guideline of Hypertension IV (IGH IV) guideline defines hypertension as systolic blood pressure (SBP) of ≥ 140 mmHg and/or diastolic blood pressure (DBP) of ≥ 90 mmHg [6].

Classification of blood pressure

Blood pressure is defined as the pressure exerted on the blood vessels due to blood flow. Measurement of systolic pressure refers the pressure in arteries when the heart beats while the diastolic pressure refers the pressure in arteries when the heart rests between beats. A pressure below 120/80 mmHg is normal for all age groups. Table 1 shows a classification of normal and elevated blood pressure. When the BP levels of the patient are far beyond the normal and range higher than 180/120 mmHg, they are in a state of hypertensive crisis (as referred by AHA) requiring immediate medical attention [6].

Other criteria based on office, ambulatory (ABPM), and home blood pressure (HBPM) measurements are shown in Table 2.

Types of hypertension

Based on causative factors

Primary or essential hypertension

- Primary hypertension is mostly asymptomatic and is diagnosed based on repeated BP measurements or community screening [5].

Table 1 Various blood pressure categories and definitions of hypertension grade [6]

Blood pressure category	Systolic mmHg (upper number)		Diastolic mmHg (lower number)
Normal	Less than 120	and	Less than 80
Elevated	120–129	and	Less than 80
High blood pressure (hypertension) stage 1	130–139	or	80–89
High blood pressure (hypertension) stage 2	140 or higher	or	90 or higher
High blood pressure (hypertension) stage 3 OR hypertensive crisis	Higher than 180	and/or	Higher than 120

Table 2 Office, ambulatory (ABPM), and home blood pressure (HBPM) measurements [6]

	SBP/DBP, mmHg
Office BP	≥ 140 and/or ≥ 90
ABPM	
24-h average	≥ 130 and/or ≥ 80
Daytime (or awake) average	≥ 135 and/or ≥ 85
Nighttime (or asleep) average	≥ 120 and/or ≥ 70
HBPM	≥ 135 and/or ≥ 85

- Positive family history because of involvement of multiple genes and their allelic variants [5]
- Up to 60% of the population above 60 years of age is more susceptible to primary hypertension [7].
- Indian patients with primary hypertension are mostly unaware of their status and remain undetected. Hence, the Ministry of Health and Family Welfare Guidelines have advised that patients with positive risk factors such as obesity, diabetes mellitus, previous history of cardiovascular disease, patients above 60 years, and current smokers must be screened regularly [8].

Salt-sensitive hypertension

- Patients' response to salt due to the genetic build-up is one of the described factors for the development of essential hypertension. Not all individuals demonstrate a rise in BP due to the intake of a salt-rich diet.
- Salt sensitivity is a crucial element in the pathophysiology of hypertension. It is involved in both mechanisms of hypertension: (a) increased pulse volume and inability to excrete sodium in the urine and (b) endothelial dysfunction and increased peripheral resistance.
- Salt-sensitive hypertension is presented by a significant increase or decrease in the BP levels of the patient depending on the salt content of the diet [9].
- In Indian patients, salt intake has been a significant barrier to managing hypertension, as the average intake is as high as 13.8 g per day [4].
- Approximately 17–30% of cases of hypertension and associated cardiovascular conditions have been attributed to high salt consumption in India [4]. It also increases the risk of endothelial dysfunction and renal function decline [9]

  The possible mechanism by which excess salt intake contributes to hypertension involves its effects on cardiac output. Excessive salt intake leads to an expansion of extracellular volume in the presence of sodium, which causes an increase in the cardiac output, increasing the cardiac workload. Reduction of dietary salt intake, thus, has a positive effect and is thus recommended in Indian patients [10].

Secondary hypertension

- Secondary hypertension is often due to an identifiable reason showing sudden worsening of BP. It is secondary to other diagnoses such as aldosteronism, reno-vascular hypertension, renal disease, and obstructive sleep apnea (OSA) [5].
- The prevalence of secondary hypertension is about 5–10% of hypertensive cases, wherein 2–3% cases are reno-parenchymal hypertension, and 1–2% are reno-vascular [11].
- As per the International Society of Hypertension, the following signs and symptoms should suggest the possibility of secondary hypertension [12]:

  Muscle weakness/tetany
  Cramps, arrhythmias
  Hypokalemia
  Pulmonary edema
  Sweating
  Palpitations
  Frequent headaches (pheochromocytoma)
  Snoring, daytime sleepiness (obstructive sleep apnea)

- Across all adult ages, renal disease, reno-vascular hypertension, aldosteronism, and OSA represent the most common causes of secondary hypertension.
- In patients with secondary hypertension, besides blood pressure assessment, further investigations should include blood investigations for the sodium, potassium, serum creatinine, estimated glomerular filtration rate

(eGFR), lipid profile, and fasting glucose levels, along with urinalysis.
- Clinical recommendations in practice for the evaluation of hypertension are for early detection of secondary hypertension, for prevention of hypertension-mediated organ damage (HMOD) and associated cardiovascular complications [13].
- Young adults prone to secondary hypertension should be assessed for renal parenchymal disease [14].

Based on disease severity

Resistant hypertension

- Patients in whom hypertension remains unmanaged despite being treated with 3 or more antihypertensive medications, including diuretics, are classified to have treatment-resistant hypertension after ruling out non-adherence to treatment and sub-optimal choices in antihypertensive therapy [5].
- It affects about 10% of the population and is associated with a high risk of cardiovascular disorders, end-organ damage, and all-cause mortality [12].
- Patients with resistant hypertension must be screened for secondary causes with the help of lab investigations that have been outlined above as per guidelines by the International Society of Hypertension.

Hypertension in special populations

Isolated systolic hypertension

- In elderly patients, isolated systolic hypertension is the predominant type that carries a significant cardiovascular or cerebrovascular risks, leading to significant morbidity and mortality [15].
- Approximately 60% of individuals above the age of 60 years have isolated systolic hypertension, and its prevalence is expected to rise substantially in the future [15].
- The incidence of isolated systolic hypertension is lower among generalized adult age groups in India, with 5.1% of men and 3.6% of women being diagnosed in North India as per the findings of a community cross-sectional survey conducted in the year 2010 [16]. However, isolated diastolic hypertension has also been identified in parts of rural India, which has a much higher prevalence of 70%, according to another cross-sectional survey of 3148 adults [17].
- Overall, Asian populations have been identified to be at a greater risk of systolic hypertension when compared with Western counterparts putting, which increases the risk of cardiovascular disorders, renal functional decline, and mortality [18].

Gestational hypertension: In pregnant women, hypertension with or without the diagnosis of preeclampsia is termed gestational hypertension, which increases the risk of maternal mortality and fetal abnormalities [19].

Refer to Table 3 for the diagnosis and blood pressure range for various types of hypertension [20].

Other sub-types of hypertension

White coat hypertension

- White coat hypertension, also called isolated clinic hypertension, is characterized by elevated office BP readings but normal out-of-the-office values [1].
- Ambulatory blood pressure monitoring is recommended for the diagnosis of white coat hypertension. Patients with office BP values at least 20/10 mmHg higher when compared with their ambulatory values are positive for white coat hypertension [21].
- In Indian patients, the risk of white coat hypertension is higher among younger populations compared to the elderly [21].

Table 3 Types of hypertension with a blood pressure range [20]

Type of hypertension	Description	Blood pressure range
Essential hypertension (most common type)	Chronic elevation in blood pressure with no underlying disease	Both systolic and diastolic blood pressures are elevated at more than 140/90 mmHg
Secondary hypertension (second most common type)	Chronic elevation in blood pressure due to underlying pathology (mostly due to renal problems)	Both systolic and diastolic blood pressure are elevated at more than 140/90 mmHg
Isolated systolic hypertension	Common in the elderly due to the loss of elasticity of major arteries	The systolic blood pressure is higher than 140 mmHg, while the diastolic blood pressure is close to the normal range
Resistant hypertension	When more than three different antihypertensive agents are prescribed, including a diuretic, and blood pressure remains elevated	Both systolic and diastolic blood pressures are elevated at more than 140/90 mmHg

Masked hypertension

- Masked hypertension, or isolated ambulatory hypertension, refers to a state where the patient has normal office readings but elevated out-of-the-office BP levels [5, 22].
- It is diagnosed with the help of office blood pressure monitoring and ambulatory monitoring.
- The risk of masked hypertension is not related to the age group of patients in the Indian population.
- Overall, patients who are receiving appropriate treatment for the management of hypertension are at a lower risk of masked hypertension [23].

Refer to Table 4 for the diagnosis of masked and white coat hypertension.

Table 4 Criteria for the diagnosis of white coat hypertension and masked hypertension in clinical practice [21]

- White-coat hypertension (isolated clinical hypertension)
  - Untreated patients with elevated office BP ≥ 140/90 mmHg and 24-h ambulatory BP < 130/80 mmHg and
    Awake ambulatory BP < 135/85 mmHg and
    Sleep ambulatory BP < 120/70 mmHg
- Masked hypertension
  - Untreated patients with office BP < 140/90 mmHg and
    24-h ambulatory BP ≥ 130/80 mmHg and/or
    Awake ambulatory BP ≥ 135/85 mmHg and/or
    Sleep ambulatory BP ≥ 120/70 mmHg
- Pseudo- or false-resistant hypertension because of the white-coat effect
  - Treated patients with elevated office BP ≥ 140/90 mmHg and
    24-h ambulatory BP < 130/80 mmHg and
    Awake ambulatory BP < 135/85 mmHg and
    Sleep ambulatory BP < 120/70 mmHg
- Masked uncontrolled hypertension
  - Treated patients with office BP < 140/90 mmHg and
    24-h ambulatory BP ≥ 130/80 mmHg and/or
    Awake ambulatory BP ≥ 135/85 mmHg and/or
    Sleep ambulatory BP ≥ 120/70 mmHg

Global and Indian scenarios of hypertension

- As per WHO, worldwide, about 1.13 billion people have hypertension. Among them, two thirds are from low- and middle-income countries (LMICs). The percentage of adults having hypertension is higher in LMICs (31.5%) than in high-income countries (28.5%) [24].
- A systemic analysis of population-based studies from 90 countries showed the age-standardized prevalence of hypertension was slightly higher in men (31.9%) than in women (30.1%) [25].
- As the Global Burden of Diseases 2016, 1.63 million deaths in India were attributed to hypertension. This was 108% higher than in 1990 [26].
- The fourth National Family Health Survey reported hypertension in 13.8% of men vs. 8.8% of women aged 15–49 and 15–54, respectively [26].
- In India, about 33% and 25% of urban and rural residents, respectively, are hypertensive. Among them, over 50–75% are unaware of their hypertensive state [27].

Prevalence of hypertension in patients with diabetes

- The prevalence of hypertension is higher in patients with diabetes mellitus (DM), with 50% of cases of hypertension also being diagnosed with type 2 diabetes mellitus (T2DM) [28].
- This risk is marked in the elderly population, who are at a greater risk of complications, including macro- and microvascular diseases due to the co-existence of DM and hypertension [29].
- In India, an increase in the coexistence of diabetes and hypertension is being reported. Patients with diabetes showed 1.5–2.0 times higher prevalence of hypertension than those without diabetes [30].

Good blood pressure measurement and its significance

Office blood pressure measurement

Blood pressure measurement in the office or clinic is a standard diagnostic test for hypertension and follow-up. A minimum of 2–3 office visits at 1–4-week intervals (depending on the BP level) is required to confirm the diagnosis of hypertension. Diagnosis must be performed in the first visit if BP is ≥ 180/110 mmHg with an evidence of cardiovascular disease (CVD). Figure 1 shows recommendations for Office BP measurement.

An automated oscillometric upper-arm cuff device (validated) is recommended for BP measurement. To measure BP, the cuff bladder must be wrapped so that it covers 80% of the arm circumference of the patient and 40% of the width. Accurate positioning of the patient is most crucial for precisely monitoring his/her BP levels. AHA recommends measuring blood pressure while the patient sits upright with legs uncrossed and arms supported. The centre of the cuff on the upper arm must be at the level of the right atrium of the patient, which lies at the midpoint of the

sternum. Chair positioning and pillows as support must be made to achieve the desired level.

Ambulatory blood pressure and home BP measurement

Ambulatory BP monitoring (ABPM) provides a 24-h account of the patient's state and is useful for diagnosing primary and secondary hypertension and differentiating it from the white coat and masked subtypes [31]. ABPM is accurate in predicting the risk of cardiovascular disease and mortality [31]. BP level measurement using home or ambulatory BP monitoring is recommended in patients with office BP classified as high-normal BP or grade 1 hypertension (systolic 130–159 mmHg and/or diastolic 85–99 mmHg) (Table 5).

Blood pressure monitoring in patients with diabetes

- ABPM is recommended for patients with DM and hypertension to reduce the risk of post-treatment complications and improve BP control [36]. In elderly patients, it is recommended to opt for a standing position during blood pressure monitoring [37].
- In a systematic review of 95 randomized control trials (RCTs), it was stated that for patients with hypertension and diabetes mellitus, the blood pressure target must be kept close to 120 to 130 mmHg to reduce the risk of stroke [38].
- In a clinical trial of 244 subjects with uncontrolled SBP and DM, it was found that home blood pressure monitoring alleviated the risk of cardiovascular disorders due to the reduction of BP by 9 mmHg and better control of BP fluctuations during the day [39]. More than half of the patients achieved better adjustment of antihypertensives with the help of home blood pressure monitoring [39].
- As per the American Diabetes Association (ADA) recommendations, blood pressure must be monitored at every office visit in patients with DM [40]. In patients with elevated BP, multiple readings must be taken to diagnose hypertension [36].
- If automated devices are used during office measurement of BP, the machine must be calibrated and validated regularly. Generally, a 5- to 10-mmHg variation from a traditional sphygmomanometer is expected [36].

Digital mediums being used for blood pressure measurement in India

Digital semiautomatic and fully automatic devices have been introduced in India for ABPM [40]. While it has the advantage of reducing the risk of human errors, especially in busy clinics, there is a mistrust related to the use of digital monitoring devices among the clinicians, primarily because they are not formally validated and, thus, have a range of error [40]. Population-based studies in India

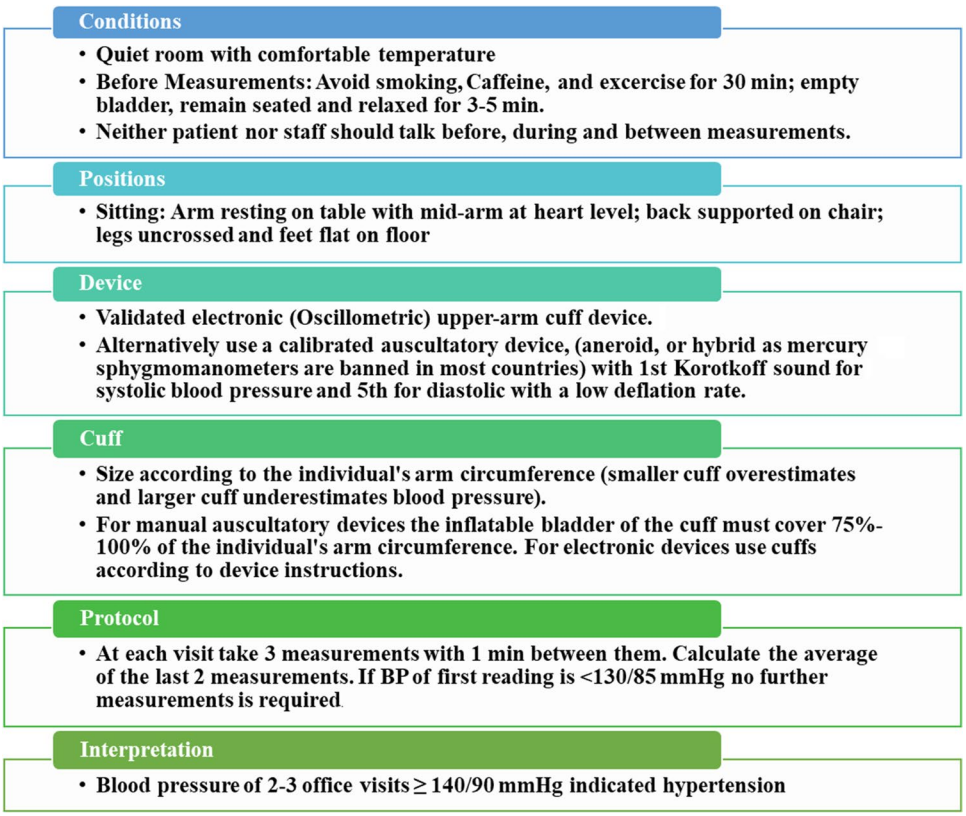

Fig. 1 Recommendations for office blood pressure measurement [12]

Table 5 Home and ambulatory blood pressure (BP) measurement [32–35]

	Condition	Position	Device	Cuff	Measurement protocol	Interpretation
Home blood pressure monitoring	As for office blood pressure	As for office blood pressure	Validated electronic (oscillometric) upper-arm cuff device	Size according to the individual's arm circumference	Before each visit to the health professional: • 3–7-day monitoring in the morning (before drug intake if treated and the evening) • Two measurements on each occasion after 5 min sitting rest and 1 min between measurements Long term follow-up of treated hypertension: • 1–2 measurements per week or month	• 24-h monitoring at 15–30 min intervals during daytime and night-time • At least 20 valid daytime and 7 nighttime BP readings are required. If less, the test should be repeated
24-h ambulatory blood pressure monitoring	Routine working day	Avoid strenuous activity. Arm still and relaxed during each measurement			• Average home blood pressure after excluding readings of the first day ≥ 135 or 85 mmHg indicates hypertension	• 24-h ambulatory blood pressure after ≥ 130/80 mmHg indicates hypertension. (Primary criterion) • Daytime (awake) ambulatory blood pressure ≥ 135/85 mmHg and night-time (asleep) ≥ 120/70 mmHg indicated hypertension

indicate that an aneroid sphygmomanometer must be preferred over digital devices since their readings are more like a traditional mercury-based sphygmomanometer, the most reliable device. However, digital mediums can be preferred for home-based measurement for higher patient comfort, which has a specificity of 80% and a sensitivity of 67.7% in the Indian population [41].

Hypertension and diabetes: the relationship

A complex cause–effect relationship between hypertension and diabetes involves obesity, visceral adiposity, and insulin resistance as the probable main pathogenic factors [42] (Fig. 1). Hypertension and diabetes are the consequence of metabolic syndrome. Inflammatory markers such as C-reactive protein are elevated in patients with DM or hypertension, indicating that both the conditions are associated with low-grade inflammation and genetic factors such as single nucleotide polymorphisms [43]. Insulin being a pleiotropic hormone has a role in developing hypertension, diabetes, and metabolic syndrome [44].

In patients with DM and hypertension, the risk of isolated systolic hypertension is the highest due to autonomic neuropathy (Fig. 2) [38]. They have a higher baseline heart rate and are at an increased risk of cardiovascular disorders (CVDs) [37]. Furthermore, nocturnal BP elevation is not significant in these patients, but they face greater day fluctuations [37].

The incidence of resistant hypertension (RH) is higher among people with diabetes than in the general or hypertensive population.

The peculiar presentation of hypertensive patients with DM reflects the need for specific guidelines. Indian guidelines need to be more comprehensive in terms of patient education and consideration of dietary factors so that the overall risk and burden of hypertensive disorders is reduced in patients with DM. This objective is addressed in present guideline, which provides recommendations related to the use of various antihypertensive combinations and treatments in patients with DM along with dietary and lifestyle changes as well as the need for monitoring.

Hypertension-mediated/related conditions

Hypertension, diabetes, and cardiovascular disorders

Hypertension is common among patients with diabetes mellitus and so is the risk of cardiovascular complications (Fig. 3). Hypertension alleviates the risk of atherosclerotic cardiovascular disease (ASCVD), heart failure, and microvascular complications. In subjects with diabetes, ACSVD significantly increases the morbidity and mortality [36].

It has been observed that the management of hypertension in patients with DM lowers the risk of ASCVD events. With every 10 mmHg decrease in systolic BP, the risk of complications of DM is reduced by 12%, and the associated mortality is reduced by 15%. The risk of MI in these patients is reduced by 11%, and microvascular complications are reduced by 13% [46]. This states the significance of good blood pressure management in patients with DM, especially those at a high risk of cardiovascular complications.

Hypertension-mediated organ damage

Undesired changes in the structure and function of arteries or organs lead to hypertension-mediated organ damage, a critical marker of cardiovascular (CV) disease. Higher incidences of all-cause death and CV events including ischemic heart disease, ischemic stroke, hemorrhagic stroke, cardiac death, and major adverse cardiac and cerebrovascular events (MACCE) may be observed. Nephropathy is the

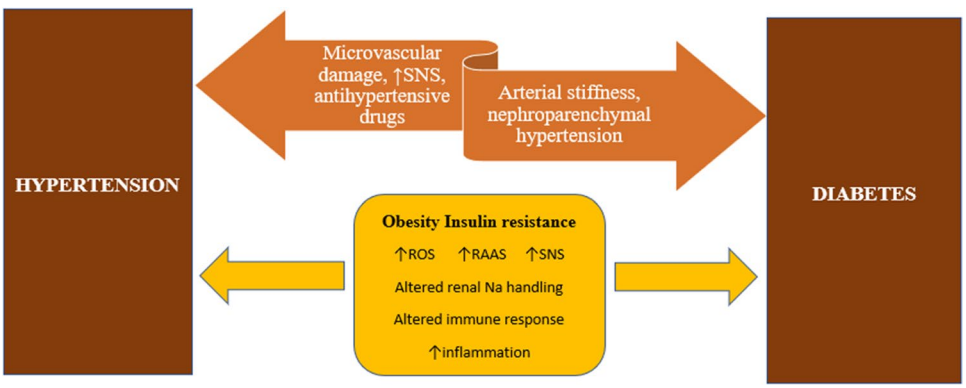

Fig. 2 Relationship between hypertension and diabetes

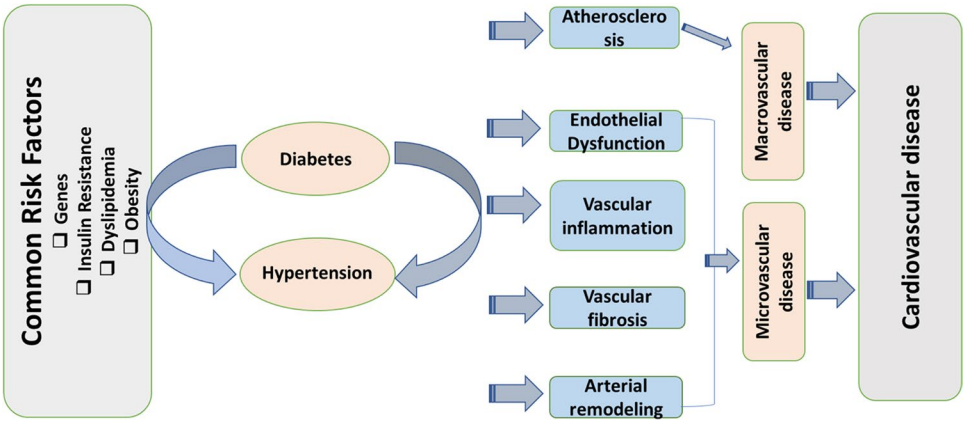

Fig. 3 Diabetes and hypertension predispose to cardiovascular disease [45]

most common form of organ damage seen in hypertensive patients. European Society of Cardiology guidelines for hypertension recommend basic screening of HMOD in all hypertensive patients [47].

Hypertension and chronic kidney disease

Hypertension is closely linked with chronic kidney disease because a sustained state of elevated BP worsens kidney function (Fig. 4) [48]. The pathophysiology of CKD and hypertension is complex. A loss of kidney function worsens blood pressure or vice versa.

Tight control of BP reduces the risk of chronic kidney disease by attenuating the pathophysiological pathways that contribute to eGFR progression and loss of kidney function [49]. Along with antihypertensive medications, dietary management, including salt restriction, forms the mainstay in the management of BP in CKD patients [50], which has been discussed in the dietary recommendations made by RSSDI ahead.

Proteinuria/microalbuminuria and end-organ damage

- Microalbuminuria or proteinuria is a major risk factor for renal disease progression, and it is also a powerful marker of cardiovascular disease and all-cause mortality [51]. For early diagnosis and better management of albuminuria with the help of sensitive tests such as albumin-to-creatinine ratio (UACR) is recommended for the avoidance of these complications [52].
- UACR is the key to early diagnosis of chronic kidney disease (CKD) in patients with diabetes mellitus because the patient is generally asymptomatic at this

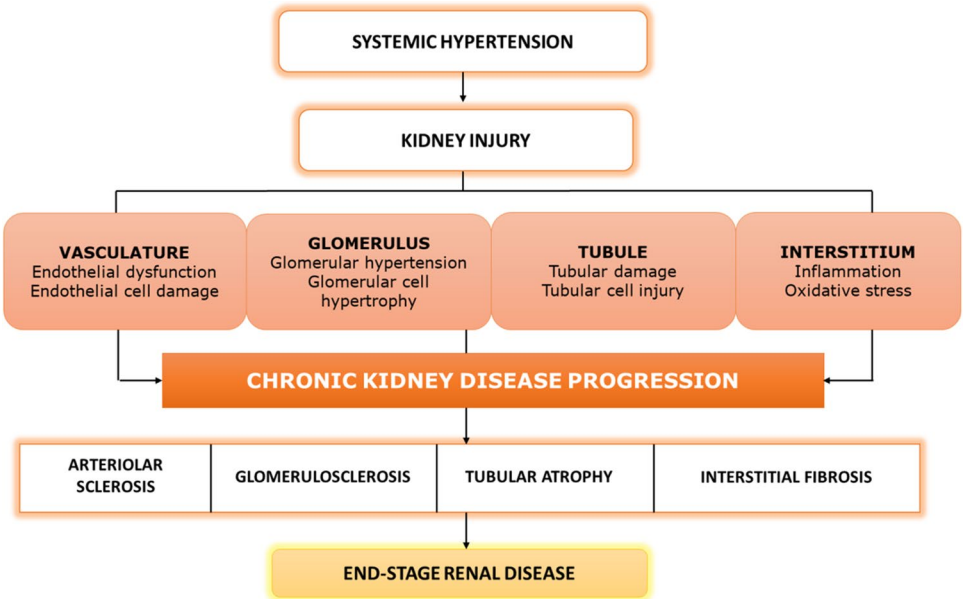

Fig. 4 Pathophysiological relationship between hypertension and chronic kidney disease [49]

stage, and their glomerular filtration rate (GFR) is also close to normal [52].

- American Diabetes Association (ADA), Kidney Disease Improving Global Outcomes (KDIGO), and US Kidney Disease Outcomes Quality Initiative (KDOQI) recommend at least annual screening for UACR in patients with diabetes mellitus [52].
- Indian guidelines recommend that all patients with hypertension must be screened for the presence of kidney disease at the time of their diagnosis and regularly thereafter [53]. Along with UACR, serum creatinine measurement and calculation of eGFR are also recommended [54].
- Urine protein-to-creatinine ratio (UPCR) is an accurate method to quantify proteinuria for the diagnosis of preeclampsia (PE), the onset of hypertension accompanied by significant proteinuria after 20 weeks of gestation [55].

Hypertension and coronary/peripheral artery disease

Globally, peripheral arterial disease (PAD), coronary artery disease (CAD), and cerebrovascular disease (CVD) are leading causes of morbidity and mortality [56]. Patients with cerebrovascular complications, including ischemic and hemorrhagic stroke, observed increased systolic hypertension more frequently. Post hoc analysis of the INternational VErapamil-SR/Trandolapril STudy (INVEST) demonstrated that among hypertensive CAD patients, concomitant PAD indicates a worse prognosis for adverse cardiovascular outcomes than CAD over a mean follow-up of 2.7 years [57].

Hypertension-associated erectile dysfunction

Hypertension and erectile dysfunction (ED) are related diseases with a common denominator, i.e. endothelial dysfunction. Changes in the endothelium-derived factors can lead to an increase in vascular smooth muscle (VSM) contraction [58]. Hypertension induces vascular changes that affect pudendal arteries and penile vasculature leading to reduced blood circulation to the penis [59]. High blood pressure or antihypertensive treatment can also lead to ED. Antihypertensive drugs like diuretics, beta-blockers, and centrally acting agents negatively affect erectile function. At the same time, calcium antagonists and ACE inhibitors are neutral [60].

Hypertension and heart failure

There is a direct correlation between increased blood pressure and the risk of developing heart failure. Patients with blood pressure greater than or equal to 160/100 mmHg have a doubled risk of heart failure than those with blood pressure less than 140/90 mmHg [61]. High blood pressure can also lead to high prevalence of atrial fibrillation [62], ventricular arrhythmias [63], and a sixfold greater risk of myocardial infarction [64], and subsequent heart failure with reduced ejection fraction (HFrEF). High BP increases the left ventricular (LV) afterload and peripheral vascular resistance, which causes diastolic dysfunction followed by concentric or eccentric LV hypertrophy (Fig. 5) [65].

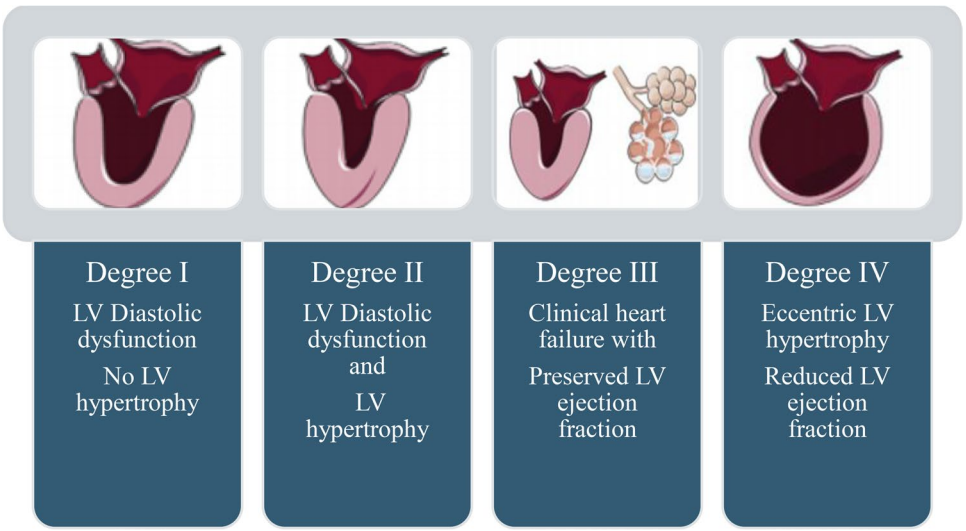

Fig. 5 Different stages of hypertensive heart disease

Hypertensive retinopathy

Choroidopathy, retinopathy, and optic neuropathy are hypertension-related ocular diseases [66]. Hypertensive retinopathy occurs because the retinal vessels are damaged due to elevated blood pressure. Angiotensin-converting enzyme allele deletion increases the risk of hypertensive retinopathy [67]. Higher plasma leptin level was reported to be associated with hypertensive retinopathy and vascular endothelium damage [68]. A study showed that serum uric acid (SUA) concentration and hypertensive retinopathy are significantly associated. For every 1 mg/dL increase in SUA, there was a significant 6% higher probability of hypertensive retinopathy [69].

Communities study of atherosclerosis risk showed that the incidence of stroke was two- to fourfold higher in patients with moderate hypertensive retinopathy, independent long-term hypertension, cigarette smoking, and dyslipidemia [70].

Long-term effects of hypertension

Patient with hypertension having abnormal BP is at high risk of transient ischemic attack (TIA) [71]. Not only first TIA, but hypertension is also a risk factor for recurrent TIA and stroke. A study in TIA patients ($N=1707$) showed that 58% of patients had a history hypertension while 75% of them had SBP > 140 mmHg following the onset of TIA [72, 73].

Normotensive people after stroke can have high blood pressure—acute hypertensive response perhaps due to autonomic nervous system dysfunction and/or abnormal cerebrovascular reactivity [74].

Hypertension might increase the risk of Alzheimer's disease (AD). The pathology linking hypertension to Alzheimer's disease is intracranial atherosclerosis, possibly limiting cerebral blood flow and/or dampening perivascular clearance [75]. A cross-sectional study in < 60 years of age group individuals showed all-cause dementia, mixed Alzheimer's/vascular dementia, and Alzheimer's disease with elevated SBP and those on antihypertensive medication [76].

For all the above disease situations, recommended BP thresholds for treatment are shown in Table 6.

Hypertension: risk factors

Several factors predisposing hypertension vary from country to country and between urban and rural region of same place. An Indian community-based cross-sectional study reported tobacco and alcohol consumption, overweight, obesity, and abdominal obesity as risk factors associated with HTN [78]. Old age and physical inactivity are independent risk factors for hypertension. Different epidemiologic and clinical studies showed sleep-related breathing disorders (SRBD) (obstructive sleep apnea (OSA) and habitual snoring) as independent risk factors for essential hypertension [79].

Table 7 [80] shows the cardiovascular risk assessment based on risk factors. Patient with grade 1 hypertension can be at low risk to high risk depending upon risk factors. Men above 50 years, non-smoking, and non-obese with grade 1 HTN may be at low risk, whereas smoking men are at moderately to higher risk of HTN. Diabetic patients irrespective of other factors are at high risk of HTN.

Table 6 Summary of office blood pressure thresholds for treatment [32]

Age group	Office SBP treatment threshold (mmHg)					Office DBP treatment threshold (mmHg
	Hypertension	+diabetes	+CKD	+CAD	+Stroke/TIA	
18-65years	≥140	≥140	≥140	≥140	≥140	≥90
65-79 years	≥140	≥140	≥140	≥140	≥140	≥90
≥80 years	≥160*	≥160	≥160	≥160	≥160	≥90
Office DBP treatment threshold (mmHg	≥90	≥90	≥90	≥90	≥90	

*As per NICE guideline (2019) ≥ 150 mmHg [77]

Table 7 Assessment of cardiovascular risk in patients with hypertension based on the number of risk factors

Hypertension disease staging	Other riskfactors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1 (uncomplicated)	No other risk factor	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥ 3 risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (Established disease)	Established CVD, CKD grade ≥ 4, or diabetes mellitus with organ damage	Very High Risk	Very High Risk	Very High Risk	Very High Risk

Methodology

The RSSDI guidelines for the management of hypertension in diabetics have been formulated in consultation with expert endocrinologists and diabetologists in India and Southeast Asia for making recommendations for the management of hypertension, along with strategies to reduce the risks for HMOD and cardiovascular complications. These recommendations were supported by literature evidence and clinical overview obtained from existing Indian and international guidelines. Literature evidence included data and recommendations from Indian, international, and South Asian journals, gathered based on extensive literature research, primarily conducted in PubMed and Cochrane libraries. After a thorough quality assessment, published RCTs, systematic reviews, meta-analysis papers, cross-sectional studies, cohort studies, and expert opinion papers were considered and included. The first draft having recommendations was

prepared and circulated among RSSDI panellists to gather suggestions for improvements. All the authors provided written recommendations for improvements in each section following the rigorous review of the document based on their expertise in the field (Tables 8 and 9). The draft was revised to address the identified gaps and was sent out to the authors for further review and feedback. Since all the expert authors approved the recommendations made in the second draft, it was finalized and sent out for publication.

Management/treatment

RSSDI recommendations for the management of hypertension in patients with diabetes mellitus

Summary of evidence

Dietary and lifestyle recommendations A nutrition education program is recommended for patients with DM and hypertension to reduce the risk of metabolic syndrome complications [81].

- In the RCT of 51 participants, it was found that the knowledge of food portion control for weight reduction, education about healthier food choices, individualized meal planning, understanding of the glycemic index and glycemic loads of different food items and their importance in blood glucose control, recognition of the food pyramid, and its use in meal planning for BP control assisted in the improvement of metabolic factors in patients with DM [81].
- In a systematic review of 198 studies for BP management in diabetic patients in low- and middle-income countries, it was stated that self-management and control through patient education are crucial for managing CVD risk factors [82]. Nutritional interventions that facilitate glycaemic and blood pressure control are recommended [81, 82].
- In the RCT of 40 patients with DM and hypertension, it was noted that Dietary Approaches to Stop Hypertension (DASH) diet and increased walking duration helped reduce ABPM values [83]. This dietary plan promotes

Table 8 Levels of recommendation based on the type of literature evidence

Level	Type of evidence
I	Systematic review (with homogeneity) of RCTs OR RCTs with a large sample size depicting significant results
II	Systematic review (with homogeneity) of cohort studies OR small-scale RCTs with unclear results OR consistent recommendations from multiple consensus guidelines (more than 2 national/international guidelines) OR randomized observational studies
III	Individual cohort studies or clinical studies without randomization OR "outcomes" research OR cross-sectional studies OR evidence gathered from existing consensus guidelines
IV	Systematic review (with homogeneity) of case–control studies OR individual case–control studies OR guidelines with improper evidence/lack of consensus OR retrospective analysis of patient data
V	Case series OR independent case study observations OR expert opinion without explicit critical appraisal based on standard principles or narrative reviews or literature reviews without systematic analysis

Table 9 Grades of recommendation for guiding practice implications for the physicians

Grade	Descriptor	Quantifying evidence	Implications for practice
A	Strong recommendation	Level I evidence with consistent findings from multiple studies of levels II, III, and IV	Clinicians should follow grade A recommendations unless a clear and compelling rationale for an alternative approach is defined
B	Recommendation	Levels II, III, and IV evidence with consistent findings but lack of level I evidence	Clinicians should follow grade B recommendation while remaining alert to newly published evidence and sensitive to patient preferences
C	Option	Levels II, III, and IV evidence with inconsistent findings	While considering grade C evidence for individual practice, clinicians should be flexible in their decision-making approach, patient preferences and peer opinions should have a substantial influencing role
D	Option	Level V evidence: little or no systematic empirical evidence	For grade D evidence, the physician must consider all options in their decision making and be alert to newly published evidence that clarifies the benefit versus harm of the selected approach; patient preference should have a substantial influencing role

higher consumption of whole grains, fat-free or low-fat dairy products, fruits, vegetables, poultry, fish, and nuts, along with reduced intake of saturated fat, total fat, cholesterol, and sodium and high intake of potassium, calcium, magnesium, fibre, and protein [79, 84]. DASH diet, in consideration of the taste preferences of Indian patients, is recommended for hypertensive control in DM patients.

- For the prevention of CVDs in patients with DM and hypertension, it is recommended that physicians must work closely with the patients to identify potential barriers and support them in reaching their target BP and HbA1c goals [84].
- Regular exercise or walking is recommended along with dietary control in patients with hypertension and DM [83, 85]. In the RCT of 94 Indian participants, it was affirmed that physical activity had a greater impact on BP control when compared with dietary salt restriction [86]. Therefore, brisk walking for 50 to 60 min, three to four times a week was recommended for effective BP management [86]. Yoga and salt restriction were also effective for Indian patients but had a lower impact than physical activity [86]. Alcohol intake was to be decreased or avoided [54]. Smoking cessation should be advised to all patients. Cessation therapies should be provided for patients who wish to quit smoking [54]. Combining these approaches would achieve maximal benefits for patients with co-existing disease [86].
- Worksite interventions are effective for reducing SBP, diastolic blood pressure (DBP), and blood glucose levels in obese Asian subjects at risk of metabolic conditions [87]. These interventions must be planned in the form of multidisciplinary sessions by including physicians, nutritionists, and physical trainers to guide the patient [87].

Recommendations

- Pharmacological therapy with lifestyle modifications should be initiated in patients with confirmed office-based BP > 140/90 mmHg
- A target value of 120 to 130 mmHg must be achieved in patients with co-existing DM and hypertension through a combination of dietary and lifestyle interventions, including a low sodium diet, plenty of fresh fruits, vegetables, and whole grains along with regular physical activity (grade A)
- Brisk walking as a physical form of activity, having sessions for 50–60 min three to four times a week, is more effective than dietary salt restriction and yoga and must be recommended in patients (grade B)
- Nutrition education about the role of diet and knowledge of healthy food choices is crucial for self-management of BP in diabetic patients (grade A)

Overview of treatment options for the management of hypertension in patients with diabetes mellitus

- Initial treatment for diabetes depends on the severity of hypertension with a regimen that includes calcium channel blockers (CCBs), angiotensin II receptor blocker (ARB)/ACE inhibitors, and diuretics, beta-blockers for compelling indications [54]. Real-world studies consider ACE inhibitors or ARBs as the first-line treatment agents for diabetic hypertensive patients depending on their treatment response and tolerance profiles [88].
- Clinical evidence suggests that single-pill combination (SPC) containing two or more antihypertensive agents (with complementary MOA) offers potential advantages over free drug combinations [89].
- Thiazides may also be used for the first-line treatment, but these must be administered alongside ACEi or ARBs [90].
- The drug's clinical effects must be evaluated before the selection of any treatment agents, particularly ARBs [91]. The selection of treatment agents must be based on the patient's profile, especially in those at the risk of end organ damage due to multiple comorbidities [91].

Antihypertensive drug therapy for the management of hypertension in diabetic patients

1. Blockers of the renin–angiotensin–aldosterone system (RAAS): angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs)

    - ARBs and ACEi are the most widely used antihypertensive drugs because of their similar effects on cardiovascular outcomes.
    - ARBs help in reducing the cardiovascular and cerebrovascular risks and renal complications, hence minimizing the morbidity and mortality risks in patients with hypertension [92].
    - ARBs are safer, tolerant, and more efficacious than ACEi for BP control [89, 92, 93]. In the RCT of 1600 patients, telmisartan facilitated greater BP reduction than ramipril [92]. ARBs have been found to have maximal reno-protective effects when compared with other classes of drugs [26]. The risk towards side effects is also lower with these agents compared with ACEi that induce cough [89]. Therapy having a combination of an ARB and an ACE inhibitor is not recommended as it is associated with an excess of adverse renal events [93].

- ARBs are administered in combination with other agents such as calcium channel blockers (CCBs) or thiazide diuretics to reduce the risk of CVDs and renal disorders in patients with DM [89, 93].
- In diabetic hypertensive patients, telmisartan and losartan are the most effective choice of ARBs to reduce cardiovascular risk factors [91]. Telmisartan must be selected as the first-line ARB agent in diabetic patients because of its beneficial impacts on fasting blood glucose and insulin levels [91]. In those at a higher risk of stroke, losartan must be preferred, whereas telmisartan is recommended in patients having a history of atrial fibrillation [91].
- German registry "EARLY" reported that a significantly greater proportion of patients in the azilsartan group achieved the target blood pressure of < 140/90 mmHg compared to ACEi [94].
- In RCT of 204 Indian patients, it was found that the efficacy and safety of azilsartan are like telmisartan. Thus, it can be selected as an alternative drug in patients based on its availability [92].
- ACEi may be preferred as first-line treatment agents in patients with diabetic hypertension as an alternative to ARBs [95]. Both these agents effectively reduce the risk of CVDs in high-risk patients, although ARBs are more efficacious [92–96].
- Both ARBs and ACEi effectively reduce the risk of end-stage renal disease [97].
- Azilsartan is a suitable agent for antihypertensive therapy in CKD patients. A 20-mg dose of azilsartan has demonstrated potent antiproteinuric effects compared with other agents such as candesartan [98]. An 80-mg dose is effective for controlling SBP and DBP in office and ambulatory settings [99]. Azilsartan improved diastolic function of the left ventricle in patients with heart failure with preserved ejection fraction (HFpEF) [100].
- While ACEi also achieved this clinical benefit, a more beneficial impact was observed with ARBs [101].
- A single-centre study including 133 hypertensive subjects diagnosed with COVID-19 infection showed a lower rate of admission to semi-intensive/intensive care units when patients were treated with RAAS inhibitor (32% using ARBs and 30% using ACEi) [102]. Suppose target blood pressure values are not achieved with either of the therapies. In that case, the addition of a thiazide diuretic is indicated as a second-line agent [95].
- A meta-analysis containing 7 studies compared ACEi/ARB alone and in combination therapy with sodium–glucose cotransporter 2 (SGLT2) inhibitors in T2DM patients. The analysis reported that combination therapy with SGLT2 inhibitors could achieve better control of blood pressure and estimated glomerular filtration rate (eGFR) [103].

2. Beta-blockers

- Beta-blockers are used for the initial management of BP in diabetic patients in cases with a previous history of CVDs such as myocardial infarction, heart failure, coronary artery disease, or stable angina [95].
- Beta-blockers and CCBs are not used independently. They are only indicated as a part of combination therapy with ARBs or ACEi in patients with DM [95].
- Recent clinical trial showed that the use of beta-blockers increases the risk of cardiovascular events in patients with DM due to the promotion of a hypoglycemic state. Hence, its use is not recommended in patients with co-existing DM and hypertension unless absolutely indicated [104].
- Beta-blockers are combined with other classes of antihypertensive drugs for treating hypertension in specific situations like heart rate control, symptomatic angina, post-myocardial infarction, HFrEF, and as an alternative to RAAS in young hypertensive women with a pregnancy plan or of child-bearing potential [105].

3. Calcium channel blockers

- Several RCTs have confirmed that CCBs can reduce cardiovascular morbidity and mortality.
- CCBs are potent, first-line blood pressure-lowering drugs with minimal contraindications [106].
- A meta-analysis including 147 RCTs involving 464,164 participants confirmed a significant reduction in risk of coronary events (20–25%) and stroke (30–45%) with all the five BP lowering agents. CCBs had a more pronounced preventive effect on stroke [107].
- CCBs can be used alongside ARBs as a part of combination therapy for the management of hypertension in diabetic patients.
- The vasodilatory effect of CCBs on vascular smooth muscle cells is attributed to their inhibitory effect on calcium entry through L-type calcium channels. Recently, novel CCBs are preferred due to their added pleiotropic benefits above their antihypertensive action. Certain CCBs block the activity on N- and L-type calcium channels and hence show additional benefits of lowering cardiovascular events and renal injury [106].

The role of the novel CCB — cilnidipine in diabetic hypertension:

- Cilnidipine is a novel and unique dihydropyridine calcium channel blocker that has inhibitory actions on both L-type and N-type calcium channels. Intracellular Ca^{2+} overload is associated with atrial fibrillation. Cilnidipine restricts this overload and activates eNOS which regulates cardiac function [108].
- CCBs are used alongside ARBs as a part of combination therapy for the management of hypertension in diabetic patients.
- As per a prospective observational trial, single-pill combination treatment with ARB plus cilnidipine helps in reducing morning home systolic blood pressure (MHSBP), in elderly patients [109].
- Cilnidipine is preferred in hypertensive patients with DM because it improves insulin sensitivity through its vasodilator effects [110]. Besides its antihypertensive effect, cilnidipine has improved insulin sensitivity along with various reno-protective and cardioprotective benefits, thus making it the choice of DHP-CCB in hypertension with DM [111]. Refer to Fig. 6 for the mechanism of action of cilnidipine.
- Amlodipine and cilnidipine are equally efficacious in reducing blood pressure; however, the incidences of pedal edema are lower with cilnidipine associated than amlodipine [112].
- When administered at a dosage of 5–20 mg/day, based on the patient's clinical profile, cilnidipine facilitates BP reduction and helps reduce heart rate and serum triglyceride levels in Indian patients, suggestive of cardioprotective benefit [113].
- Independent of blood pressure reduction, 8-week treatment with cilnidipine 5–10 mg/day improved left-ventricular systolic function [114].
- Cilnidipine is more tolerable in Indian patients and must be preferred in those with proteinuria or pedal edema [115, 116].

Thus, cilnidipine should be the preferred CCB in diabetic hypertensives due to its reno-protective and cardioprotective benefits and better safety and tolerability profile (pedal edema) over other CCBs.

4. Diuretics

- Low-dose thiazides have demonstrated their success in mild to moderate cases of hypertension, but its function is depleted if the sodium intake of the patient is above 8 g/day, indicating the relevance of dietary salt restriction and its use [118].
- Low doses, i.e. 12.5 to 25 mg/day of chlorthalidone or hydrochlorothiazide, or 1.25 mg/day of indapamide, minimize metabolic complications and their antihypertensive effects [119].
- Hydrochlorothiazide lowers pulse pressure by 4 to 6 mmHg due to the greater effect on systolic than on diastolic blood pressure [120].
- Thiazide-like diuretics such as chlorthalidone demonstrated superior blood pressure reduction in patients with resistant hypertension [121, 122].
- Diuretics such as hydrochlorothiazide are not recommended in patients with diabetic hypertension

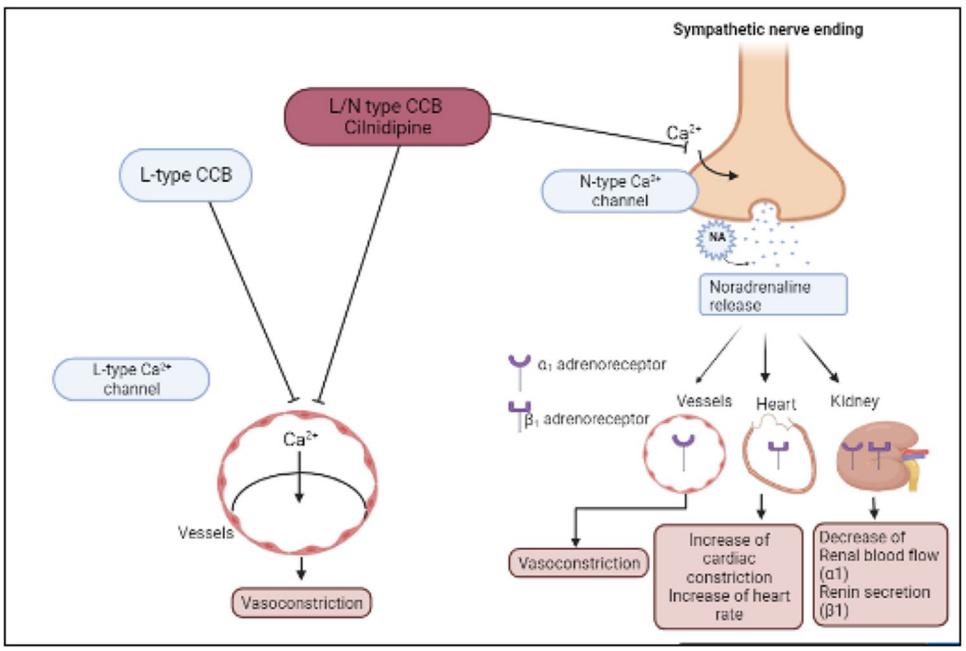

Fig. 6 Mechanism of action of cilnidipine in the lowering of blood pressure in hypertensive patients [117]

Table 10 Guideline comparison for hypertension treatment [129]

Guideline	Population	Goal BP mmHg	Initial management
2014 hypertension guideline	Diabetes	< 140/90	ACEi, ARB or CCB, thiazide-type diuretics
	CKD	< 140/90	ACEi or ARB
ESH/ESC 2013	Diabetes	< 140/85	ACEi or ARB
	CKD no proteinuria	< 140/90	
	CKD + proteinuria	< 130/90	
CHEP 2013	Diabetes	< 130/80	ACEi or ARB with additional CVD risk, ACEi, ARB, thiazide
	CKD	< 140/90	ACEi or ARB
ADA 2013	Diabetes	< 140/80	ACEi or ARB
ESC/ESH 2018	CAD, CKD, diabetes	≤ 140/90	ACEi or ARB + CCB or diuretic-dual combination for CAD) ACEi/ARB + CCB OR ACEi/ARB + diuretic (or loop diuretic-dual combination for CKD) ACEi/ARB + CCB/diuretic-dual combination for diabetes
ISH 2020	CKD	< 130/80 mmHg (< 140/80 in elderly patients)	RAS inhibitors as first line; CCBs and diuretics can be added
KDIGO 2012	CKD no proteinuria	≤ 140/90	ACEi or ARB
	CKD + proteinuria	≤ 130/80	
KDIGO 2021	RRT (CKD G1T-G5T)	≤ 130/80	CCB or ARB

because of its potential to elevate fasting blood glucose and HbA1c levels [123].

- A systematic review of 26 RCTs indicated that low doses of thiazide might avoid glycemic changes [124]. However, the strength of this finding is low since evidence against low-dose hydrochlorothiazide has been stated by another meta-analysis of 368 studies [125].
- While diuretics are not commonly used to manage hypertension in patients with DM, their use is indicated in certain specialized cases [126], such as elderly patients with existing CVDs [118].
- In a crossover trial, the use of potassium-sparing diuretics such as spironolactone reduced BP by − 8.7 mmHg for reaching the target levels in patients with resistant hypertension, compared to other two treatments, i.e. doxazosin and bisoprolol [127].
- A low dose of spironolactone is recommended in those whose serum potassium is < 4.5 mmol/L and

Table 11 Major drug combinations with efficacy results

Combination	Type of patients	% Change in relative risk
Two RAS blockers/ACE inhibitor 1 ARB or RAS blocker 1 renin inhibitor [131]	High-risk diabetic patients	More renal events
ACE inhibitor and diuretic	Stroke or TIA [132]	− 28% strokes ($p < 0.001$)
	Diabetes [133]	− 9% micro-/macrovascular events ($p = 0.04$)
	Hypertensive; > 80 years [134]	− 34% CV events ($p < 0.001$)
ARB and diuretic	Hypertensive; ≥ 70 years [135]	− 28% non-fatal strokes ($p = 0.04$)
CCB and diuretic	Hypertensive [136]	− 27% CV events ($p < 0.001$)
ACE inhibitor and CCB	Older with isolated systolic hypertension (ISH) [137]	− 37% CV events ($p < 0.004$)
Beta-blocker and diuretic	Older with ISH [138]	− 36% strokes ($p < 0.001$)
	Older hypertensive [139]	− 40% CV events ($p = 0.003$)
ARB and CCB	Older with ISH [140]	14% reduction in BP
	Hypertensive [141]	Lower incidences of CV events (risk ratio [RR], 0.80; 95% confidence interval [CI], 0.70–0.91; $p < .001$)

eGFR is > 45 mL/min/1.73 m^2 to achieve BP targets [127, 128].

Guideline comparison of blood pressure goals and recommended drug options in different populations has been mentioned in Table 10.

5. Combination therapies

- Drug combinations including ARB plus cilnidipine or ARB plus hydrochlorothiazide effectively reduce nocturnal BP fluctuations [125]. However, due to the risk of glycemic variability, ARB plus cilnidipine must be considered even in patients with nighttime BP fluctuations, rarer in patients with co-existing diabetes and hypertension [123–125].
- A combination of ARB and CCB must also be preferred over beta-blockers because of the potential of the latter to cause adverse cardiovascular events (Table 11) [105].

Safety considerations for hypertensive management in diabetic patients

- When treatment agents such as blockers of the renin–angiotensin–aldosterone system (RAAS) are being used to manage BP in patients with DM, close monitoring of kidney functions and the levels of electrolytes are recommended [38].
- Frequent monitoring of potassium and creatinine is recommended in patients treated with aldosterone antagonists, such as spironolactone. Monitoring of serum potassium levels in patients on combination therapy is stated to reduce the risk of hyperkalemia [38].
- An observational study in diabetes patients concluded that CCB, when added to ACEi/ARBs, is associated with reno-protective and cardioprotective outcomes compared to thiazide diuretics [130].

Recommendations: which treatment therapy to use and when

- Individual profile of the patient and their response to the treatment must be evaluated for the selection of the most suitable treatment agent for hypertensive management (grade A)
- ARBs, either alone or in combination with CCBs, can be used for BP control in diabetic patients (grade A)
- Combination therapy of ARB and CCB is recommended to be initiated in hypertensive patients for better BP control, reducing risks of complications, and better patient adherence (grade B)
- ARBs must be preferred over ACEi in diabetic patients with hypertension, telmisartan or azilsartan being selected as the first-line agent (grade B)
- In patients at the risk of CVDs, renal disorders, or cerebrovascular disorders, combination therapy must be preferred for the reduction of patient mortality (grade B)
- Calcium channel blockers must be preferred over beta-blockers and thiazides in combination therapy with ARBs. Cilnidipine is a comparatively more effective and safer novel molecule as compared to conventional CCBs for Indian diabetic hypertensive patients (grade A)
- The use of beta-blockers and thiazide diuretics must be avoided in patients with DM and hypertension because of their potential to cause cardiovascular events and hyperglycaemia, respectively (grade A)
- Monitoring of electrolyte levels, serum potassium, and creatinine levels, as well as regular evaluation of kidney function, is recommended for patients with diabetic hypertension based on the choice of treatment agents and their risk profile (grade B)

Data on the global approvals of molecules of each class For the selection of the treatment agent necessary on the individual clinical profile of the patient, it is essential to understand the treatment indications of various FDA-approved drug labels, which have been summarized in Tables 11 and 12.

Management of hypertension in patients with CKD

- In patients at the risk of CKD, it is recommended to maintain blood pressure values below 130/80 mmHg for renal and cardioprotection in patients under 60 years [52].
- National Institute for Health 2014 and Care Excellence guideline recommends a goal blood pressure of < 140/90 in a patient with CKD while < 130/80 mmHg in patients with an albumin creatinine ratio of ≥ 70 mg/mmol [146].
- 2012 KDIGO guideline recommendation for blood pressure goals in diabetic and non-diabetic patients with non-dialysis dependent CKD is mentioned in Fig. 7 [147].

  Combination therapy is mostly recommended for achieving these target BP levels in these patients [115]. It is useful for managing patients who are unresponsive to the use of a single drug agent [148].
- SPC with cilnidipine (10 mg) and ARB (80 mg) was seen to be effective in reducing BP values in patients with sympathetic hyperactivity [39]. Control of sympathetic activity is one of the treatment goals in hypertensive patients with DM and CKD to reduce cardiovascular risks. This SPC was also effective in reducing diurnal and nocturnal blood pressure fluctuations in patients with DM. Thus, SPCs are recommended [109, 125]. Cilnidipine has been clinically proven effective for morning hypertension and white-coat hypertension, closely associated with sympathetic overdrive.

Table 12 FDA- and DCGI-approved drug labels for hypertension management in diabetic patients

	Indications
FDA-approved drug	
Telmisartan	For hypertensive management in patients with CVD risk factors and diabetes patients with end-organ damage [142]
Azilsartan	In patients with DM and hypertension for BP control [93]
Olmesartan	Management of hypertension in diabetic patients with other comorbidities such as chronic kidney disease, cerebrovascular events, heart failure, and ischaemic heart disease [143]
Captopril	Management of hypertension in patients with impaired renal function, presence of diabetic nephropathy, myocardial infarction, and left ventricular dysfunction [144]
DGCI-approved drug [145]	
Cilnidipine tabs. 5 mg, 10 mg	For treatment of mild to moderate hypertension
Amlodipine besylate IP Eq. to amlodipine 10 mg + indapamide SR 1.5 mg tablet	For the treatment of mild to moderate hypertension
Combination drug containing - Cilnidipine:10 mg Olmesartan medoxomil IP (20 mg/40 mg) Chlorthalidone IP (12.5 mg)	For the treatment of essential hypertension
Combination drug containing - Losartan potassium IP (50 mg) Amlodipine besylate IP Eq. to amlodipine (5 mg) Hydrochlorothiazide IP (12 mg)	For the treatment of hypertension in patients who are not managed with the help of dual therapy
Combination drug containing - Olmesartan medoxomil (20 mg) Amlodipine besylate (5 mg)	For mild to moderate hypertension
Combination drug containing - Olmesartan medoxomil (20 mg) Ramipril (5 mg)	For treatment of essential hypertension

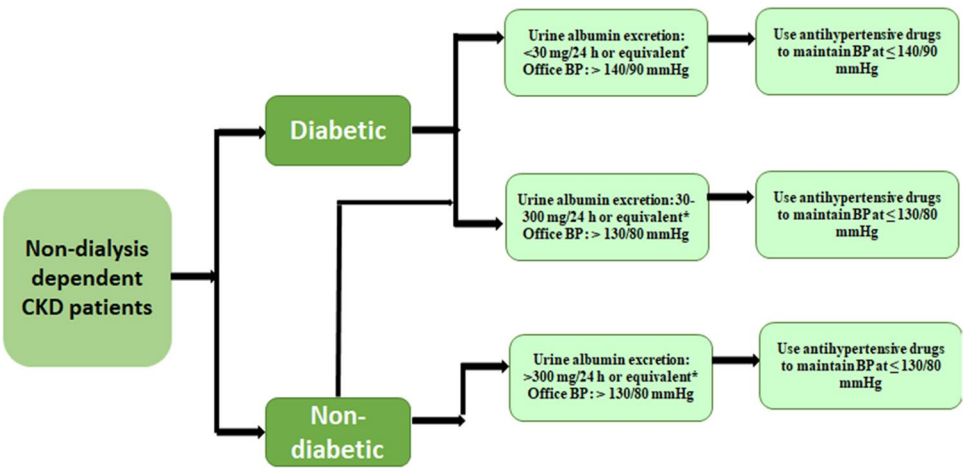

Fig. 7 2012 KDIGO guidelines on the management of hypertension in diabetic/non-diabetic CKD patients

- Due to its N-type calcium channel blockade and unique sympatholytic activity, cilnidipine offers cardiovascular benefits apart from its antihypertensive action. In a study involving hypertensive patients ($n = 2920$), treatment with cilnidipine and angiotensin receptor blocker showed significant reductions in heart rate, particularly in those with a higher baseline heart rate [149] (Tables 13 and 14).
- In patients with microalbuminuria/proteinuria, treatment with cilnidipine is recommended when CCBs are used in combination therapy [150, 151]. Compared to other drugs, such as amlodipine, cilnidipine facilitates UACR reduction and helps in decreasing albumin excretion in hypertensive patients [149, 150]. It is a preferred agent in patients with proteinuria, sympathetic overactivity, and pedal edema. It is a better treatment agent than amlodipine for hypertensive patients [109, 150].
- In a clinical trial of 50 patients with diabetic nephropathy, it was found that 12-week treatment with cilnidipine

Table 13 Indications of individual drug classes based on guidelines and clinical studies [6]

Compelling indication*	Recommended drugs^						Clinical trials basis#
	Diuretic	BB	ACEI	ARB	CCB	ALDO ANT	
Heart failure	■	■	■	■		■	ACC/AHA Heart failure Guidelines, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES
Postmyocardial infraction		■	■	■[2]	■[1]	■	ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHESUS
High coronary disease risk	■	■	■		■		ALLHAT, HOPE, ANBP$_2$, LIFE, CONVINCE
Diabetes	■	■	■	■	■		NKF-ADA, Guideline, UKPDS, ALLHAT
Chronic kidney disease			■	■	■[3]		KDIGO 2021, NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK
Recurrent stroke prevention	■		■		■[4]		PROGRESS

[1]Option for patients without heart failure or impaired LV function in patients with contraindications to beta-blockers (Danish Verapamil Infarction Trial II–DAVIT)[153]

[2]If ACEi not tolerated

[3]First-line antihypertensive agent in adult kidney transplant recipients

[4]A meta-analysis of 13 studies with 1789 subjects randomized to CCBs

*Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP

^Drug abbreviations: *ACEI* angiotensin-converting enzyme inhibitor, *BB* beta-blockers, *ARB* angiotensin receptor blocker, *Aldo ANT* aldosterone antagonist, *CCB* calcium channel blocker

#Conditions for which clinical trials demonstrate the benefit of specific classes of antihypertensive drugs

led to a significant reduction in estimated GFR values and serum creatinine levels [125]. Six months of treatment with the drug helped significantly control albumin excretion [150, 151].

- Thiazide diuretics can be used if GFR is greater than or equal to 40 mL per minute per 1.73 m^2, while loop diuretics are used in GFR ≤ 40 to 50 mL per minute per 1.73 m^2 [115].
- A combination of ACEi and ARBs reduces urinary albumin excretion compared to monotherapy; however, they are associated with a further risk to the kidney and hence are not recommended [152].

Oral antidiabetic agents that exert reno-protection:

- Combining SGLT2 with ACEi + ARB inhibitor reduced composite kidney outcome (CKO) among T2DM patients with CKD [161].
- Evidence suggests that DPP-4 inhibitors and SGLT2 inhibitors exert reno-protective effects in patients with diabetes.

Management of resistant hypertension

- Early diagnosis of resistant hypertension with the help of ABPM is recommended to avoid end-organ damage in patients [32, 126].
- Initial treatment with ARBs along with CCBs is recommended [126]. In patients with resistant hypertension, additional treatment agents such as diuretics are recommended since patients may be unresponsive to standard combination therapies [5, 126]. Refer to Fig. 8 for treatment selection and management in patients with resistant hypertension.

Novel concepts in hypertension and future treatment molecules

- Growing significance of central aortic blood pressure:

In the pathogenesis of cardiovascular disease, central (aortic and carotid) pressures are gaining more relevance than peripheral pressures. The left ventricle encounters the aortic systolic pressure during systole (afterload), while the aortic pressure during diastole determines coronary perfusion. Ideally, central aortic pressures should be measured directly using invasive devices, but there are numerous methods available currently to derive the central pressures by analysing the applanated radial and carotid pulses or carotid distension waves. Higher augmentation index (AI) is linked with coronary artery disease (CAD).

Central pressure correlates with cardiovascular risk in apparently healthy subjects as well. Carotid systolic BP is an independent determinant of left-ventricular wall thickness, and late systolic augmentation of the central pressure

Table 14 Indian evidence on the use of antihypertensive agents [154–160]

Drug	Efficacy data	Safety data	Indications	Adverse events/contraindications	Corresponding Indian study
Azilsartan	• Effective for lowering BP levels by 26–29 mmHg as per a 6-week RCT of 303 patients • Non-inferior to telmisartan	• Non-inferior to telmisartan in terms of safety in Indian patients • Well-tolerated with only mild treatment-related side effects	First-line therapy in essential hypertension	Headache and dizziness	[154]
Telmisartan	• Telmisartan 40 mg is efficacious in reducing DBP by 18.1% compared to Losartan (14.3%) as reported in adult hypertensive male and non-pregnant female patients between 18 and 65 years of age	No serious adverse events were reported in this study	Patients with clinic blood pressure (BP) levels of systolic BP (SBP) of 140–200 mmHg and diastolic BP (DBP) of 95–114 mmHg	No reports	[155]
	• Telmisartan reduces proteinuria in hypertensive patients with chronic kidney disease	Well tolerated with no adverse events	Patients with CKD (96.36% hypertensive; 63.61% diabetic)	No reports	[156]
Olmesartan	Olmesartan 20/40 mg helped in reducing by 34/18 mmHg in 6 months as per the results of an open-label observational study of 8940 Indian patients	No serious adverse events were reported in this study	Patients with BP values above 140/99 mmHg	Few patients complained of dizziness, vertigo, and oedema	[157]
Cilnidipine	Comparable efficacy to amlodipine in lowering BP levels as per the results of an Indian cross-sectional study of 140 mild to moderate hypertensive patients	• Superior safety profile than amlodipine • No significant impacts on the heart rate	Patients with CVDs	No adverse events Previous studies have reported headache, dizziness, and GI symptoms as adverse events	[158]
	Cilnidipine helped in lowering the heart rate and uric acid levels of the patient in addition to their BP management over 24 weeks as per a clinical study of 100 Indian patients	Higher safety profile than amlodipine No reflex tachycardia	Patients with high uric acid levels and those with CVDs/tachycardia	Not reported	[159]
	Cilnidipine helps in reducing the heart rate along with lowering BP levels of patients, as depicted by an Indian RCT of 63 participants Amlodipine also lowered BP but significantly increased heart rate	Higher safety over amlodipine due to cardiovascular benefit through heart rate reduction	Patients with proteinuria, pedal oedema, and sympathetic overactivity	Nausea, decreased appetite, headache, insomnia, and palpitation	[160]

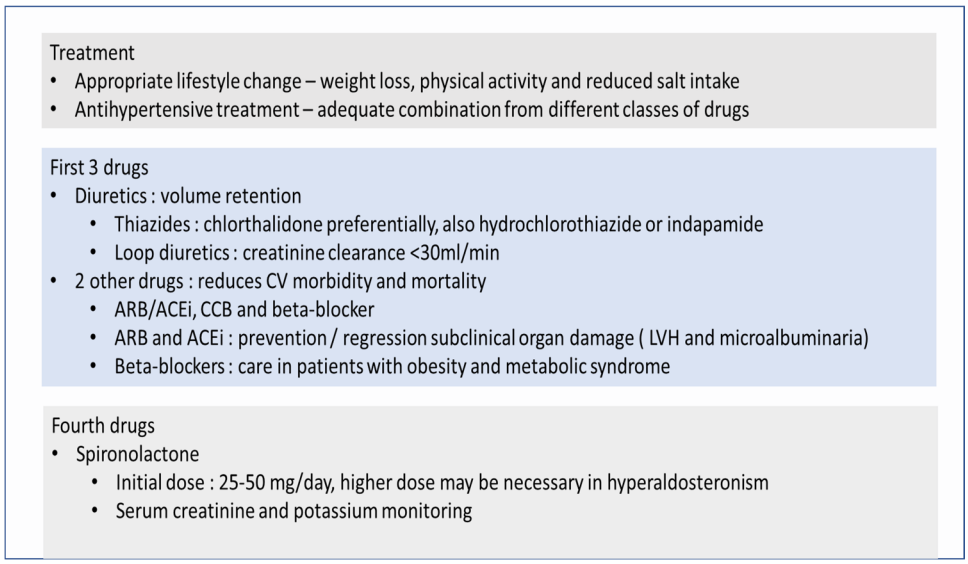

Fig. 8 Therapeutic approach in resistant hypertension [162]

waveform may denote an increase in left ventricular mass index, independent of age and BP.

Study suggests that non-invasively determined central pulse pressure is a better predictor of incident cardiovascular disease than does the corresponding brachial pulse pressure, which may be because of a more accurate representation of the vascular load on the left ventricle. There is growing evidence that central BP may provide incremental value over and above peripheral BP in firmly confirming the cardiovascular risk. The CAFE Study was the first randomized, prospective event-based study which mentioned that central BP and related indices may be a useful guide to treatment [163].

- Future treatment molecules:

Several novel drugs such as peptide- and non-peptide-based therapeutic agents that may function as RAAS inhibitors have been emerging to manage hypertension in diabetic patients. For personalized treatment of hypertension in patients with DM, the use of artificial intelligence technologies such as gene sequencing mechanisms, genomics, transcriptomics, proteomics, and metabolomics is increasing in clinical practice towards understanding the disease pathogenesis for early recognition of possible end-organ damage, detection of the treatment response of the patient, and their monitoring [164, 165].

Currently, among the existing CCBs, cilnidipine is a promising molecule, effective in BP reduction and its multiple pleiotropic benefits, and a good choice for use as a combination therapy for hypertension management in patients with DM [150, 151, 166–168]. As anticipated in the future, the use of other conventional CVD risk reduction drugs such as statins and immunosuppressants such as mycophenolate mofetil may also expand in clinical practice [169]. While new drugs shall continue to emerge, the use of CCBs, ARBs, and ACEi will persist in the future. At the same time, beta-blockers and thiazide agents may need more studies to understand their usage in this sub-set of patients [170].

Summary

Key messages: For the management of hypertension in patients with DM (Fig. 9), it is essential to understand the clinical profile of the patient to select the most suitable treatment agents that do not add to any risks.

1. Definition of hypertension. As per the Indian Guideline of Hypertension IV (IGH IV), hypertension is defined as systolic blood pressure (SBP) of ≥ 140 mmHg and/or diastolic blood pressure (DBP) of ≥ 90 mmHg.
2. Type of hypertension. Primary hypertension is mostly asymptomatic, while secondary hypertension is due to various underlying pathologies. Uncontrolled BP, despite the usage of 3 antihypertensive drugs, is referred to as "resistant hypertension".
3. Epidemiology and risks. Over 1 billion people suffer from hypertension globally, which is expected to rise up to 1.5 billion by 2025. Up to 50% of cases of hypertension are also diagnosed with type 2 diabetes mellitus (T2DM). Hypertension presents as a major risk factor for heart failure, CVD, CKD, PAD, ED, and end-organ damage.
4. Blood pressure measurement. For patients with DM and hypertension, 24-h ambulatory blood pressure monitoring is recommended to maintain BP targets of ~ 120–130 mmHg.

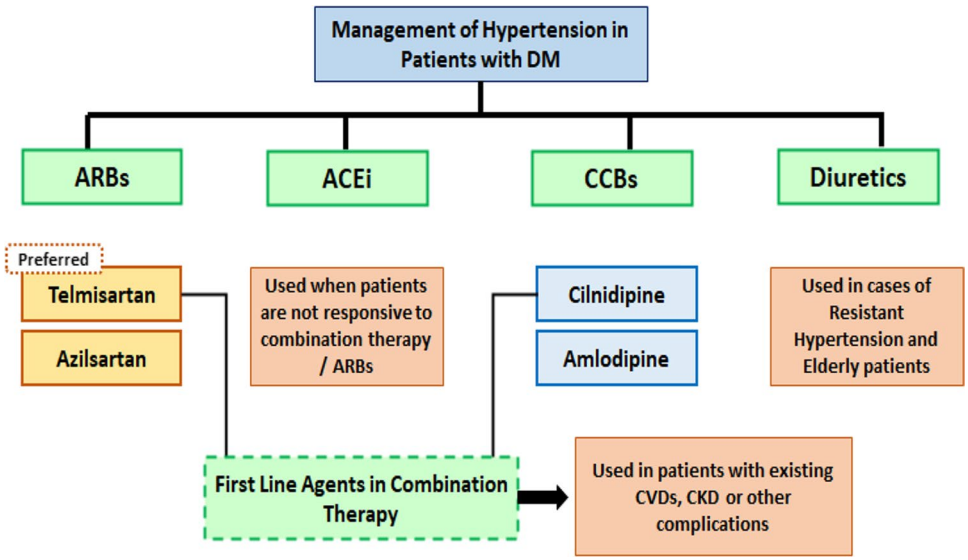

Fig. 9 Summary of guideline

The use of an aneroid sphygmomanometer must be preferred over digital devices; however, digital machines may be preferred for home-based measurement. Blood pressure thresholds vary with age and comorbid conditions.

5. Hypertension and diabetes: the relationship. There is a complex cause–effect relationship between hypertension and diabetes, which predisposes the patients to increased risks of cardiovascular complications.
6. Non-pharmacological management of hypertension in diabetic patients. Lifestyle modifications may delay the need for pharmacological interventions or can complement the BP lowering effect of drugs. A low sodium diet, a physical activity, and a healthy diet are recommended to manage hypertension in diabetic patients.
7. Pharmacological management of hypertension in diabetic patients. ARBs are recommended as the choice of therapy preferably in combination with CCBs to manage hypertension and its resulting complications. For combination therapy, newer CCBs (e.g. cilnidipine) along with ARBs are recommended. Cilnidipine is a novel, effective, and safe CCB, which is established for its reno-protective benefits. Combination therapy of ARBs with thiazide-like diuretics also reduces the risk of renal disorders. While telmisartan can be the first-line ARB for treatment of diabetic hypertensives due to its beneficial effects on fasting blood glucose and insulin levels, alternatively, azilsartan, with a similar safety and efficacy profile, is also recommended. Thiazide-like diuretics can be preferred in elderly patients with existing CVDs. ACE inhibitors may be used as an alternative to ARBs for CVD risk reduction in high-risk patients. Beta-blockers may be preferred in patients with a previous history of CVDs and as an alternative to RAS blockers in pregnant women. Hypertension is a strong, modifiable risk factor for the macrovascular and microvascular complications of diabetes. Strong evidence from clinical trials and meta-analyses supports targeting blood pressure reduction to at least140/90 mmHg in most adults with diabetes. Lower blood pressure targets may be beneficial for selected patients with high cardiovascular disease risk if they can be achieved without undue burden, and such lower targets may be considered on an individual basis. In addition to lifestyle modifications, multiple medication classes are often needed to attain blood pressure goals.

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