Review

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Targeting the sympathetic nervous system with the selective imidazoline receptor agonist moxonidine for the management of hypertension: an international position statement

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Hypertension is often linked with metabolic risk factors that share common pathophysiological pathways. Despite widespread availability of multiple drug classes, optimal blood pressure (BP) control remains challenging. Increased central sympathetic outflow is frequently neglected as a critical regulator of both circulatory and metabolic pathways and often remains unopposed therapeutically. Selective imidazoline receptor agonists (SIRAs) effectively reduce BP with a favorable side effect profile compared with older centrally acting antihypertensive drugs. Hard outcome data in hypertension, such as prevention of stroke, heart and kidney diseases, are not available with SIRAs. However, in direct comparisons, SIRAs were as effective as angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers, and diuretics in lowering BP. Other beneficial effects on metabolic parameters in hypertensive patients with concomitant overweight and obesity have been documented with SIRAs. Here we review the existing evidence on the safety and efficacy of moxonidine, a widely available SIRA, compared with common antihypertensive agents and provide a consensus position statement based on inputs from 12 experts from Europe and Australia on SIRAs in hypertension management.

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Keywords: blood pressure, essential hypertension, moxonidine, stimulating central imidazoline (I1) receptors, sympathetic nervous system

Abbreviations: ACE, angiotensin-converting enzyme; ADR, adverse drug reaction; AHA/ACC, American Heart Association/American College of Cardiology; b.i.d., twice a day; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; ESH, European Society of Hypertension; FPG, fasting plasma glucose; HCTZ, hydrochlorothiazide; HDL, high-density lipoprotein; HOMA, Homeostatic Model Assessment of Insulin Resistance; IQR, interquartile range; ISH, International Society of Hypertension; ITT, intent to treat; LDL, low-density lipoprotein; LDL-C, LDL-cholesterol; MSNA, muscle sympathetic nerve activity; OSA, obstructive sleep apnea; PCOS, polycystic ovary syndrome; PICO, Population, Intervention, Comparison, and Outcome; PP, per protocol; PPG, postprandial plasma glucose; RAAS, renin–angiotensin–aldosterone system; REM, rapid eye movement; SD, standard deviation; SIRA, selective imidazoline receptor agonists; SNS, sympathetic nervous system

INTRODUCTION

Hypertension affects around one-third of the adult population worldwide, which translates to more than one billion individuals. According to a projection, the number of individuals with hypertension may rise by 15–20%, potentially approaching 1.5 billion by 2025 [1]. Although the global age-standardized prevalence of hypertension remained stable, the number of individuals between 30 and 79 years of age with hypertension has increased two-fold from 1990 to 2019 [2].

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Epidemiological studies over five decades have confirmed that hypertension is a significant factor in the development of major cardiovascular conditions such as coronary heart disease, stroke, peripheral artery disease, renal disease, and heart failure [3,4]. Epidemiological studies revealed that hypertension commonly coexists with other metabolic risk factors, and less than 20% of cases occur independently. These accompanying factors include glucose intolerance, low HDL cholesterol, high triglycerides, and obesity. When three or more of these risk factors co-exist, the metabolic syndromes may occur four times more frequently than would be expected by chance [3].

Randomized controlled trials have clearly demonstrated that lowering BP in patients with hypertension decreases the related cardiovascular risk and lowers overall mortality [5]. The recent European Society of Hypertension (ESH) hypertension guidelines (2023) emphasize the critical role of blood pressure (BP) reduction as the main mechanism leading to cardiovascular risk reduction in hypertensive patients [4]. Therefore, adequate management of BP is a global priority for cardiovascular health. However, the WHO reports that only ~21% of hypertensive adults have their BP under control, leaving many patients at unnecessarily increased cardiovascular risk [6].

Several factors have been identified to contribute to suboptimal BP control including unawareness of elevated BP, physician inertia, nonadherence with prescribed antihypertensive therapy and others [7]. Another likely explanation is that relevant pathophysiologic pathways known to play a crucial role in BP and metabolic control, such as the sympathetic nervous system are not or insufficiently opposed by current treatment strategies [8–17].

Hypertension pathophysiology

Several factors known to contribute to BP elevation have been extensively investigated, including sodium intake, overweight and obesity, insulin resistance, the renin–angiotensin–aldosterone system (RAAS), the sympathetic nervous system (SNS), endothelial dysfunction, poor prenatal nutrition, and others [8–18]. Increased activation of the SNS has been implicated in both the initiation and maintenance of elevated BP and was one of the earliest therapeutic target to lower BP through surgical sympathectomy and ganglion blockade. With the advent of other drug classes targeting relevant pathways, such as RAAS, calcium channels, volume homeostasis and others, the important role of an overactive sympathetic nervous system and directly targeting increased central sympathetic outflow has been somewhat neglected in clinical medicine [8–17]. Importantly, the well described links and interactions between the RAAS and the SNS further highlight the importance of targeting both systems when treating hypertension. However, except for beta blockers, the treatments targeting the SNS are not extensively included in international recommendations [19].

Hypertension in special populations with increased sympathetic nervous system activity

Metabolic disturbances (obesity, insulin resistance, etc.) are closely linked with uncontrolled hypertension as an independent factor [8–13,15–17,20]. Various pathophysiological mechanisms have been proposed to explain hypertension in metabolic syndrome, which include insulin resistance, obesity, activation of the SNS, and sodium retention [21].

Women with polycystic ovary syndrome (PCOS) [22] and menopausal women [23] have a higher likelihood of developing hypertensive disorders. The reasons for the increase in BP are complex and varied. The increased risk of hypertension in women with PCOS is linked to insulin resistance and hyperinsulinemia. These conditions affect the mechanism of vasodilation in the endothelium, leading to hypertrophy of the vascular muscle wall [22]. In contrast, the loss of estrogen, oxidative stress, endothelial dysfunction, changes in the RAAS system, and sympathetic activation could be responsible for the increase in BP in postmenopausal women [23,24]. Indeed, reducing sympathetic drive via modulation of the SNS has been suggested as a potential novel treatment modality for PCOS [25]. Furthermore, there is a shift to the right in pressure–natriuresis relation curve induced by loss of female sex hormones, which accounts for salt-sensitivity hypertension in postmenopausal women [26].

Strong evidence linking obstructive sleep apnea (OSA) and long-term hypertension was demonstrated by many studies. In one such study, it was observed that patients with OSA have elevated sympathetic nerve activity during wakefulness and persistent high BP throughout all sleep stages, peaking in stage II and rapid eye movement (REM) sleep stage. Sympathetic activity increases during sleep, especially in stage I and REM phases. Continuous positive airway pressure (CPAP) treatment reduces sympathetic activity and lowers BP during sleep in OSA patients. These findings emphasize the role of CPAP in mitigating sympathetic overactivity in OSA management [27]. Treatment of OSA with CPAP has been shown to reduce both daytime and nighttime BP, providing further evidence for a cause-and-effect relationship between OSA and chronic hypertension [28]. However, the SAVE study did not demonstrate a reduction in cardiovascular events by treating OSA with CPAP. The only benefit demonstrated was a reduction in daytime tiredness [29,30].

Chronic kidney disease (CKD) can both cause and result from hypertension, and hypertension can worsen CKD over time. In CKD, the deterioration of kidney function can cause an increase in sympathetic tone which contributes to the development of hypertension through afferent signaling [31]. Grassi *et al.* [32] have demonstrated a close relationship between the deterioration of kidney function and the increase in SNS activity. As kidney function declines, the RAAS system becomes more active, leading to retention of water and salt. Additionally, there is an increased sensitivity to salt, further exacerbating the issue [31]. Obesity aggravates the complex relationship between hypertension and kidney function by various mechanisms, including mechanical compression of the kidneys by visceral adiposity, SNS activation through leptin/proopiomelanocortin system, as well as RAAS and mineralocorticoid receptor activation [33].

Hypertension is the most common comorbidity in patients with heart failure with preserved ejection fraction and is involved in both the development and outcome of the disease. Improper secretion of aldosterone causes retention of sodium and water leading to hypertension, an

increase in urinary potassium excretion, and occasionally, hypokalemia. Furthermore, primary aldosteronism is the main cause of secondary hypertension [34].

Chronic systemic inflammation is a common feature of both chronic obstructive pulmonary disease (COPD) and cardiovascular disease, and this inflammation is a significant factor in the development of both the conditions. Moreover, patients with both COPD and hypertension may experience impaired endothelial function because of increased oxidative stress, caused by both internal and external factors [35].

Targeting sympathetic nervous system in the current hypertension management strategies

Activation of SNS is a common occurrence in individuals with essential hypertension, and it plays a significant role in initiation, maintenance, and progression of the disease. This activation is also responsible for the development of major complications [36]. In patients with resistant hypertension, SNS activity is even more pronounced, and this phenomenon can be caused by several factors, such as older age, kidney disease, obesity, metabolic syndrome, mental stress, and OSA [8–17]. Moreover, heightened sympathetic output seems to be a major mechanism involved in resistant and refractory hypertension. SNS overactivity is also a key factor in the development of heart failure, acute coronary syndrome, and arrhythmias [10,37,38]. Different approaches have been used to inhibit this overactivity, including central SNS blocking drugs, peripheral α-adrenergic and β-adrenergic receptor blockers, and novel approaches such as renal sympathetic denervation. These treatments have been beneficial in managing some of these conditions [36].

Various classes of antihypertensive drugs can have different effects on sympathetic activation. For instance, some drugs such as RAAS blockers can reduce sympathetic activation, whereas others such as long-acting calcium channel blockers have no major net effect. However, some drugs like diuretics and short-acting calcium channel blockers increase sympathetic activation. Recent meta-analyses reported that β-blockers were less effective than other antihypertensive drug classes [37]. The use of β-blockers is related with side effects such as fatigue, depression, cold extremities, sexual dysfunction, and increase in low-density lipoprotein (LDL) cholesterol and blood glucose levels [39] that can limit their acceptance by patients often leading to discontinuation of the treatment. Due to the inherent heterogeneity of the β-blockers, including intrinsic sympathomimetic activity, adrenergic receptor selectivity and vasodilatory activity, the tolerability profile of these agents vary [40].

Centrally acting antihypertensive medications exhibit inequivalent efficacy in their therapeutic effects on hypertension. Those selectively stimulating central imidazoline (I1) receptors (SIRAs) cause peripheral sympathoinhibition that is similar to the effects produced by clonidine but with substantially less side effects commonly mediated through binding to the central α2-adrenoreceptor. SIRAs have been demonstrated to effectively lower elevated BP with a hemodynamic profile that is similar to that of clonidine and related drugs. However, SIRAs have a significantly lower affinity for central alpha-2 adrenoreceptors, resulting in fewer side effects than clonidine and α-methyl-DOPA and therefore better tolerability [41,42].

Moxonidine and rilmenidine are examples from this category of drugs. Both moxonidine and rilmenidine are second generation centrally acting antihypertensive drugs. They work by activating the I1-imidazoline receptors in the rostral ventrolateral medulla, which in turn reduces central sympathetic outflow.[41,42] These drugs act as arterial vasodilators, which help to reduce peripheral vascular resistance. However, it does not significantly affect the plasma concentrations of angiotensin II, adrenaline, aldosterone, or atrial natriuretic peptide [41]. In contrast to clonidine, moxonidine does not reduce heart rate to the extent clonidine does and has no withdrawal effects [43].

It has been almost two decades since the antihypertensive efficacy of moxonidine was established in a large number of patients with essential hypertension. Its efficacy was also studied in comparative controlled trials with most of the major classes of antihypertensive drugs including ACE-inhibitors, β-blockers, calcium antagonists, and diuretics. However, there are no recent updates on the comparative data on the safety and efficacy of moxonidine in the treatment of essential hypertension.

OBJECTIVE

This review was conducted to summarize existing evidence along with the recent data in literature on efficacy and safety of moxonidine when compared with other antihypertensive agents. The antihypertensive agents were analyzed for their effect on BP, insulin resistance, body weight, LDL levels, fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) levels along with the safety profile. Twelve experts from Europe and Australia reviewed the literature and developed the current consensus guidance for use of SIRAs in the current context of guideline-recommended hypertension treatment strategies.

METHODS

Literature search

A structured literature search was carried out using PubMed and Cochrane library databases to identify available evidence on the efficacy of moxonidine in reducing BP in comparison with other antihypertensive agents or relevant controls among patients with essential hypertension. No date restriction was followed for the literature search. The relevant articles were identified using the following keywords and their combinations (using Boolean operators AND/OR): essential hypertension, moxonidine, antihypertensive agents, metabolic syndrome, insulin, body weight, lipoproteins, LDL cholesterol, fasting plasma glucose, FPG, postprandial glucose, PPG, adverse effect, drug-related side effects and adverse reactions, and heart rate.

Eligibility criteria

Studies reporting the efficacy of moxonidine in comparison with other antihypertensive agents/controls among patients with essential hypertension were selected. The Population, Intervention, Comparison, and Outcome (PICO) framework with the eligibility criteria is illustrated in Table 1.

TABLE 1. Population, Intervention, Control, and Outcomes framework and eligibility criteria

Parameter	Inclusion	Exclusion
Population	Human	Animal, plants
	Adult (≥18 years)	Pediatric and neonates
	Patients with essential hypertension	Patients with comorbidities
Intervention	Moxonidine	
Comparator	Other antihypertensive agents/controls	
Outcomes	Efficacy – reduction in BP from baseline Reduction in insulin resistance from baseline Reduction of body weight from baseline Reduction in LDL cholesterol levels from baseline Reduction in FPG and PPG levels from baseline Safety: adverse events reported	
Language	English	
Study design	Randomized controlled trials Cohort studies Observational studies	Systematic reviews and/or meta-analysis Expert commentaries or review articles Case reports

BP, blood pressure; FPG, fasting plasma glucose; LDL, low-density lipoprotein; PICO, Population, Intervention, Control, and Outcomes.

The study selection was carried out by following abovementioned eligibility criteria. Eligible studies were identified based on: the study title and the abstract; and full text articles. The publications retrieved were screened by two independent reviewers.

Data extraction

Relevant data from the final list of eligible articles were extracted. Information including study details, population characteristics, reduction in BP from baseline (24 h SBP), reduction in insulin resistance from baseline, reduction of body weight from baseline, reduction in LDL cholesterol levels from baseline, reduction in FPG and PPG levels from baseline, and adverse effects associated with moxonidine were listed out (Table 2) [44–70]. The descriptive variables of the data extracted are presented in the Results section.

RESULTS

A structured literature search using PubMed and Cochrane library databases yielded 156 and 58 articles, respectively. After removing duplicates and review articles, 124 articles from PubMed and 27 Cochrane library articles were shortlisted for screening process. Out of total 151 articles, 124 articles were excluded as they did not meet the inclusion criteria. Thus, 27 articles were shortlisted. The results of the literature searches are summarized in the following sections (Fig. 1).

Effect on blood pressure

Moxonidine and 24 h ambulatory blood pressure monitoring

Of the 27 studies included in this article, 5 have used 24 h ambulatory blood pressure monitoring [44,52,54,55,62]. Lumb *et al.* [44] in 2004 observed a significant reduction of 10/5 mmHg in 24 h ambulatory blood pressure among patients with hypertension and type 2b Fredrickson hyperlipidemia, with SBP decreasing from 144 ± 18 to 134 ± 10 mmHg ($P = 0.01$). Wenzel *et al.* [52] in 1998 conducted a double-blind, placebo-controlled study, revealing that moxonidine significantly decreased both SBP (-10 ± 4 mmHg) and DBP (-5 ± 2 mmHg) profiles over the 24−h period. Schrover *et al.* [54] in 2017 focused on treatment response, indicating larger blood pressure reductions in women and participants aged 60 years or older during moxonidine use. Dorrestein *et al.* in 2013 compared moxonidine with other therapies, showing that aliskiren achieved the largest treatment effect, with a mean reduction of -9.8/-6.3 mmHg for 24-h blood pressure. Hydrochlorothiazide, but not moxonidine, resulted in a significant reduction of 24-h blood pressure (mean reduction −5.9/−2.6 mmHg)[55]. Saniuliani *et al.* in 2006 assessed the chronic effects of moxonidine on blood pressure, noting a significant reduction in both SBP and DBP over a 24-week period. Moxonidine therapy decreased SBP from 160.4 ± 2.4 to 142.1 ± 3.3 mmHg ($P < 0.005$) and DBP from 102.4 ± 1.3 to 89.7 ± 1.6 mmHg ($P < 0.005$) after 24 weeks of treatment [62].

Moxonidine as monotherapy

All of the studies reported the effect of moxonidine on SBP and DBP among different populations (Table 2). Patients with mild-to-moderate essential hypertension achieved a satisfactory lowering of BP with moxonidine at doses ranging from 0.2 to 0.6 mg (Fig. 2a and b). A post marketing surveillance study was conducted on 4005 obese patients with hypertension and/or metabolic syndrome. They received moxonidine treatment at doses of 0.3–0.6 mg. The study found that the mean BP for all patients decreased from 168/97 to 141/83 mmHg. Among patients with metabolic syndrome, the average BP dropped from 168/96 to 141/83 mmHg [48]. In another study on 10 hypertensive patients, moxonidine (0.4 mg) was given orally. It significantly reduced BP from 176/105 to 158/95 mmHg ($P < 0.01$) over 4 h. Systemic vascular resistance decreased, but cardiac output remained unchanged. The heart rate was slightly increased from 69 to 75 beats/min ($P < 0.01$), whereas pulmonary artery pressure and pulmonary vascular resistance did not demonstrate any significant changes [47].

Moxonidine versus placebo

Wenzel *et al.* in 1998 conducted two studies on the effects of 0.4 mg moxonidine. In healthy volunteers and hypertensive

TABLE 2. Patients details included in shortlisted studies

S. No.	Study	Patient characteristics	Sample Size	Age (years)	Type of BP monitoring	Interventions
1	Lumb *et al.*, 2004 [44]	Hypertension and type 2b Fredrickson hyperlipidemia	12	Mean ± SD 55.7 ± 7.0	24 h ABPM	Moxonidine 0.2 mg
2	Abellan *et al.*, 2005 [45]	Hypertension with type 2 diabetes	112	Mean ± SD 61.2 ± 10.6	As per international guidelines	Moxonidine 0.4 mg
3	Elisaf *et al.*, 1999 [46]	Hypertension	20	38–61	Triplicate measurements with a calibrated sphygmomanometer	Moxonidine 0.4 mg
4	Mitrovic *et al.*, 1991 [47]	Essential hypertension	10	Mean 52	Triplicate measurements with a calibrated sphygmomanometer	Moxonidine 0.4 mg
5	Sharma *et al.*, 2004 [48]	Hypertension	4005	Median (IQR) 61 (20–93)	Blood pressure measured at baseline, 4th week and 8th week (type not specified)	Moxonidine 0.3–0.6 mg
6	Ebinc *et al.*, 2008 [49]	Women with essential hypertension	55	Mean ± SD 44.7 ± 10.7	Supine Patient Measurement by sphygmomanometer (triplicate)	Moxonidine 0.4–0.6 mg
7	Greenwood *et al.*, 2000 [50]	Essential hypertension	14	Mean ± SD 58 ± 2.1	Average of three readings (type not specified)	Moxonidine 0.2 mg, moxonidine 0.4 mg
8	Chazova *et al.*, 2013 [51]	Uncontrolled essential hypertension	ITT 5603 PP 4916	ITT 41–65	Measured 1–3 months and six months (type not specified)	Moxonidine 0.2–0.4 mg (monotherapy or adjunct therapy)
9	Wenzel *et al.*, 1998 [52]	Hypertension	26	Mean 55.26	24 h ABPM	Moxonidine 0.4 mg, placebo
10	Kirch *et al.*, 1990 [53]	Hypertension	8	Mean ± SD 49 ± 15.7	Supine and erect position (zero sphygmomanometer)	Moxonidine 0.25 mg, placebo
11	Schrover *et al.*, 2017 [54]	Obesity-related hypertension	31	Median (IQR) 60 (55–63)	24 h ABPM	Moxonidine 0.4 mg, aliskiren 300 mg, hydrochlorothiazide 25 mg, placebo
12	Dorresteijn *et al.*, 2013 [55]	Obesity-related hypertension	31	Median (IQR) 60 (55–63)	24 h ABPM	Moxonidine 0.4 mg, aliskiren 300 mg, hydrochlorothiazide 25 mg, placebo
13	Kaaja *et al.*, 2007 [56]	Hypertensive obese postmenopausal women	98	Mean 53.4 (45–58)	Type not specified	Moxonidine 0.6 mg, atenolol 50 mg, placebo
14	Frei *et al.*, 1994 [57]	Essential hypertension	161	Mean 55.1	Weekly blood pressure measurements (until week eight)	Moxonidine 0.4 mg, hydrochlorothiazide 25 mg, placebo
15	Kujala *et al.*, 2014 [58]	Hypertensive obese postmenopausal women	98	Mean 53.4	Type not specified	Moxonidine 0.6 mg, atenolol 50 mg
16	Pöyhönen-Alho *et al.*, 2008 [59]	Hypertensive obese postmenopausal women	87	Mean ± SD 53.4 ± 3.1[a] 53.4 ± 2.8[b]	Type not specified	Moxonidine 0.6 mg, atenolol 50 mg
17	Prichard *et al.*, 1992 [60]	Essential hypertension	63	Mean ± SD 55 ± 10	Three readings at 3 min intervals	Moxonidine 0.2–0.4 mg, atenolol 50 mg
18	Masajtis-Zagajewska *et al.*, 2010 [61]	Arterial hypertension and insulin resistance	15	Mean ± SD 48.3 ± 14.3	Official BP recordings before and after treatment (mercury sphygmomanometer)	Moxonidine 0.4 mg, amlodipine 10 mg
19	Sanjuliani *et al.*, 2006 [62]	Hypertension with obesity	40	Mean ± SD 48.7 ± 2.1[a] 46.5 ± 1.8[b]	24 h ABPM	Moxonidine 0.2 or 0.4 mg, amlodipine 5 or 10 mg
20	Planitz, 1987 [63]	Hypertension	152	Mean 58[a] 57[b]	Morning and late afternoon BP recordings	Moxonidine 0.2–1.0 mg, clonidine 0.2–1.0 mg
21	Planitz, 1984 [64]	Uncomplicated essential hypertension	20	Mean ± SD 41 ± 5.8[a] 39 ± 7.5[b]	Multiple daily measurements during treatment periods	Moxonidine 0.2–0.4 mg, clonidine 0.2–0.4 mg
22	Pichard *et al.*, 2002 [65]	Mild-to-moderate essential hypertension	154	Mean ± SD 51.2 ± 9.3[a] 52.2 ± 10.3[b]	Triplicate measurements based on Korotkoff phase V sounds	Moxonidine 0.2 mg, enalapril 5 mg
23	Kuppers *et al.*, 1997 [66]	Mild-to-moderate essential hypertension	140	Mean ± SD 54.9 ± 8.6[a] 51.2 ± 10.9[b]	Weekly measurements during placebo run, bi-weekly in active phase	Moxonidine 0.2 mg, enalapril 5 mg
24	Martina *et al.*, 1998 [67]	Mild-to-moderate essential hypertension	14	Mean ± SD 50 ± 14	Three times in sitting position (5 min intervals)	Moxonidine 0.2–0.4 mg, cilazapril 2.5–5.0 mg

TABLE 2 (*Continued*)

S. No.	Study	Patient characteristics	Sample Size	Age (years)	Type of BP monitoring	Interventions
25	Derosa *et al.*, 2007 [68]	Mild hypertension with type 2 diabetes	99	Mean ± SD 55 ± 7	Right arm measurements with standard sphygmomanometer	Moxonidine 0.2 mg, moxonidine 0.4 mg, moxonidine 0.2 mg plus irbesartan 150 mg
26	Jacob *et al.*, 2004 [69]	Hypertension with type 2 diabetes	200	Mean ± SD[c] 62.4 ± 8.2[a] 61.7 ± 8.4[b]	Type not specified	Moxonidine 0.2–0.6 mg, metoprolol 50–150 mg
27	Wolf, 1992 [70]	Hypertension	229	Mean ± SD 55.6 ± 9.5[a] 55.8 ± 9.5[b]	Postdrug intake blood pressure measurements (12 or 24 h)	Moxonidine 0.2 mg, nifedipine 20 mg

ABPM, ambulatory blood pressure monitoring; IQR, interquartile range; ITT, intent to treat; PP, per protocol; SD, standard deviation.
[a]Age of patients in moxonidine group.
[b]Age of patients in comparative group.
[c]Per protocol group.

patients, moxonidine decreased muscle sympathetic nerve activity (MSNA; $P < 0.05$) and plasma norepinephrine levels ($P < 0.01$). Among hypertensive patients, moxonidine significantly reduced SBP ($P < 0.0001$) and DBP ($P < 0.001$). The BP at baseline was $153 \pm 3/95 \pm 2$ mmHg and after 150 min of moxonidine intake, the reduction in SBP was -10 ± 4 mmHg and DBP was -5 ± 2 mmHg, whereas it remained unchanged in the placebo group. In healthy participants, the heart rate was lowered ($P < 0.05$); however, in hypertensive patients, a decrease was noted during nighttime ($P < 0.05$) and not during the daytime (not significant). Moxonidine acts by inhibiting central nervous sympathetic activity to achieve these effects [52]. An intraindividual comparative study was conducted on eight hypertensive patients to assess the impact of moxonidine 0.25 mg and placebo on multiple parameters. There was a notable reduction in elevated SBP/DBP from $153 \pm 6.5/98 \pm 10.4$ mmHg at baseline to mean of individual maximum SBP reduction of 23.1 mmHg and DBP reduction of 17.5 mmHg within 2–5 h of administration. Moxonidine significantly reduced BP, with the maximum antihypertensive effect occurring after a delay compared with peak plasma levels. No significant differences in heart rate, sedation, and salivary flow were noted between moxonidine and placebo-treated groups [53].

Moxonidine monotherapy versus multidrug therapy or as adjunct with antihypertensive medications

Chazova *et al.* in 2013 conducted a study on the effects of moxonidine on BP and metabolic syndrome in patients with uncontrolled essential hypertension. Patient response to hypertension treatment increased from 24.2% ($n = 1345$) initially to 41.3% ($n = 2314$) at the 6-month mark. This included nondiabetic patients with SBP greater than 140 mmHg and diabetic patients with SBP greater than 130 mmHg. The BP-lowering effect with moxonidine was more pronounced in those on monotherapy (55.7 versus 37.8% in those on multidrug therapy). Blood pressure changes showed an average decrease of 24.5 ± 14.3 mmHg in SBP, 12.6 ± 9.1 mmHg in DBP, and a mean pulse pressure change of -11.8 ± 12.8 mmHg, with notable variations in different patient subgroups [51].

In another study, Derosa *et al.* in 2007 investigated the antihypertensive and metabolic effects of moxonidine in patients with type 2 diabetes and mild hypertension. The mean SBP and DBP at baseline was 145 ± 4 and 94 ± 3 mmHg, respectively. At the 3-month mark, patients receiving moxonidine 0.2 mg showed significant improvements in SBP and DBP (140 ± 3 and 89 ± 3 mmHg, $P < 0.05$ versus baseline). Additionally, when moxonidine 0.2 mg was combined with irbesartan 150 mg, significant reduction in both SBP and DBP were observed (132 ± 4 and 81 ± 3 mmHg, $P < 0.01$ versus baseline) [68].

Frei *et al.* in 1994 compared moxonidine 0.4 mg, HCTZ 25 mg, and their combination with placebo in patients with mild-to-moderate hypertension. Moxonidine 0.4 mg once daily was found to be effective in significantly lowering BP compared with placebo. Furthermore, the combination of moxonidine and HCTZ showed enhanced efficacy without additional safety concerns. The overall response rate to the different treatments was calculated, with monotherapy with

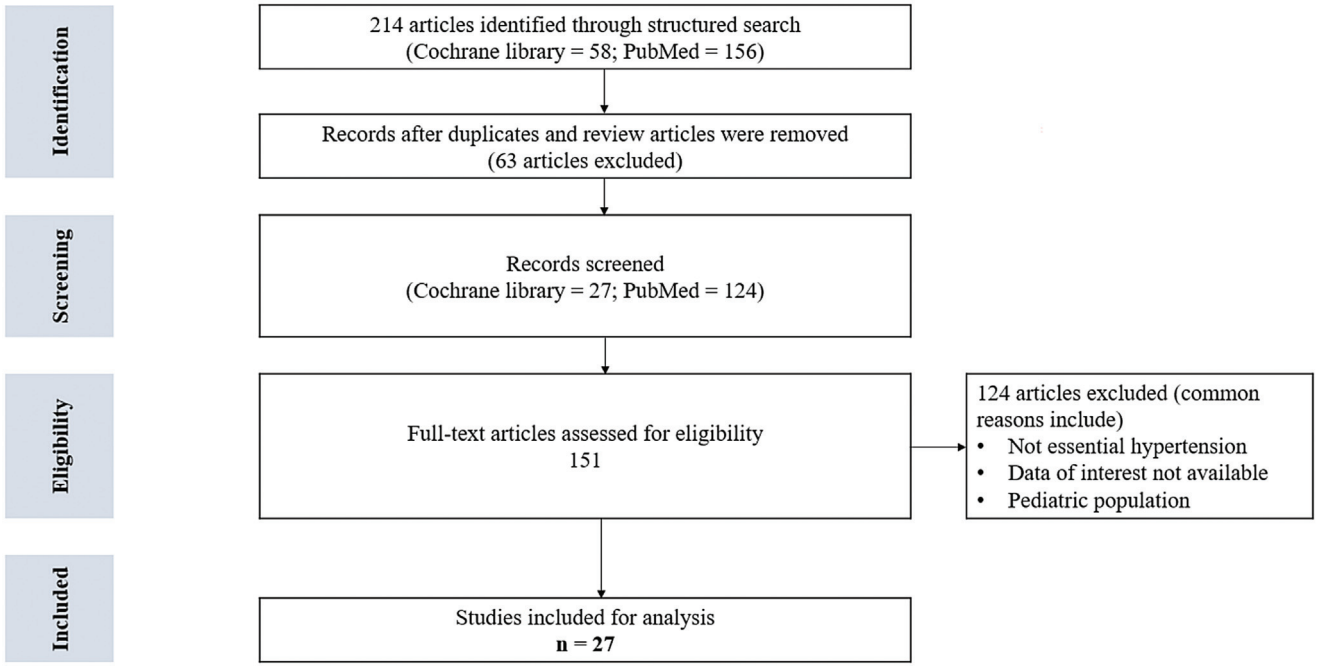

FIGURE 1 Study selection process.

moxonidine and HCTZ achieving response rates of 70.3 and 70.0% respectively, while the combination treatment yielded a response rate of 87.8% in all patients in the treatment group [57].

Moxonidine versus other antihypertensive agents

The antihypertensive efficacy of moxonidine against other antihypertensive agents has been investigated in several comparative clinical trials. Hard outcome data in hypertension, such as prevention of stroke, heart and kidney diseases, are not available with SIRAs. However, in terms of BP-lowering, the efficacy of moxonidine was equivalent to atenolol [56,58,61,62,65], metoprolol [69], enalapril [65,66], nifedipine [70], clonidine [63], and HCTZ [57]. Three studies reported that the efficacy of moxonidine was less than atenolol [59], aliskiren [55], and cilazapril [67] (Table 3).

Studies by Kujala *et al.* (2013) and Poyhönen-Alho *et al.* (2008) showed that treating hypertensive postmenopausal women with moxonidine (0.6 mg/day) or atenolol (50 mg/day) for 8 weeks resulted in significant reduction in DBP. Moxonidine reduced DBP by 6.2 mmHg, whereas atenolol reduced it by 9.5 mmHg [58]. In another study, Masajtis-Zagajewska *et al.* [61] in 2010 found that both moxonidine and amlodipine led to reductions in mean BP (9.8 ± 7.6 and 10.4 ± 7.3 mmHg, respectively) in patients with arterial hypertension and insulin resistance.

In a study comparing moxonidine and clonidine, Plänitz (1984) determined that both drugs had equivalent antihypertensive efficacy. However, moxonidine resulted in fewer side effects and a lower likelihood of causing withdrawal symptoms [64]. Plänitz (1987) conducted a 6-week multicenter, double-blind comparison study and observed that both moxonidine ($n = 122$) and clonidine ($n = 30$) significantly reduced SBP and DBP to a similar extent. Moxonidine reduced SBP and DBP by 25.4 and 12.4 mmHg, respectively, while clonidine reduced them by 25.3 and 10.0 mmHg, respectively. The average individually titrated dose of moxonidine and clonidine HCI was noted to be 0.36 mg/day. Additionally, clonidine slightly decreased heart rate by 3 beats/min during dose titration, whereas moxonidine had no effect on heart rate [63].

Dorresteijn *et al.* in 2013 conducted a study in patients with previously untreated obesity-related hypertension (Table 4). The median (interquartile range) office BP during the second screening visit at baseline was 153 (145–167)/88 (84–96). Aliskiren showed the most significant reduction in mean 24 h BP (−9.8/−6.3 mmHg) compared with placebo. Hydrochlorothiazide also lowered BP, but to a lesser extent (−5.9/−2.6 mmHg). Moxonidine, despite reducing MSNA, did not significantly affect BP in this study [55]. Prichard *et al.* (2002) conducted a placebo-controlled study comparing moxonidine and enalapril in mild-to-moderate essential hypertension. Moxonidine demonstrated a similar average reduction in sitting BP as enalapril (24.9 ± 20.7/13.2 ± 8.4 versus 21.9 ± 17.1/11.9 ± 7.5 mmHg, respectively) and was significantly superior to placebo (1.2 ± 14.4/2.3 ± 7.0 mmHg; $P < 0.001$) [65].

Effect of moxonidine on hypertensive postmenopausal women

Three studies examined the impact of moxonidine on hypertensive postmenopausal women. Over the course of an 8-week treatment period, women receiving atenolol and moxonidine experienced significant reductions in mean DBP. In the atenolol group, the average decrease was 9.5 ± 8.13 mmHg whereas in the moxonidine group, it was 6.2 ± 9.22 mmHg. These decreases were found to be statistically significant within each group ($P < 0.001$), although the difference between the atenolol and moxonidine group was not statistically significant ($P = 0.097$) [56,58,59].

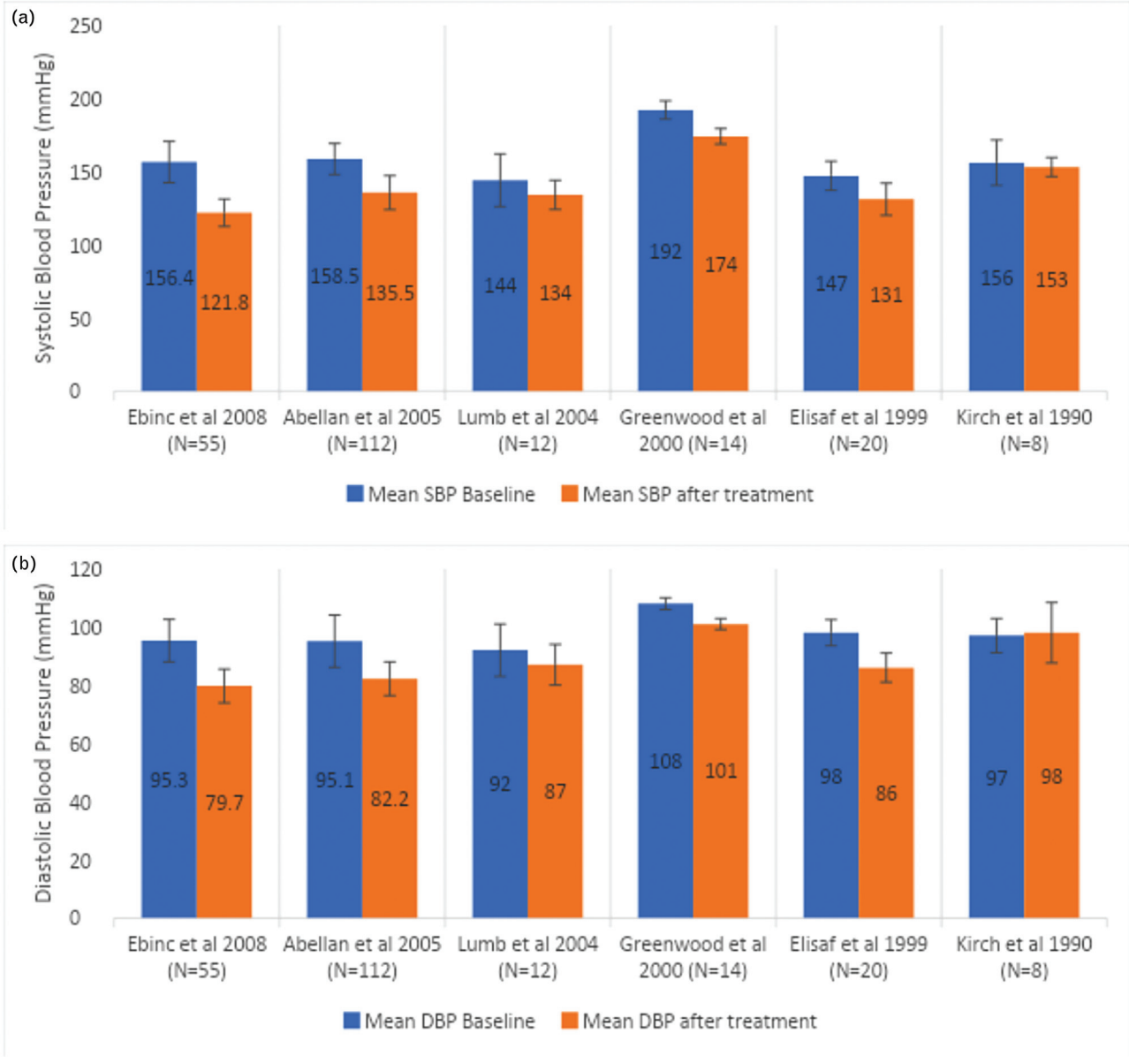

FIGURE 2 (a) Change in SBP when moxonidine was administered as monotherapy. (b) Change in DBP when moxonidine was administered as monotherapy. The bars represent the mean SBP and DBP of patient population and the error bars denote the standard deviation. The graph presents results from studies with uniform set of data.

Chazova *et al.* (2013) conducted a separate study to assess the long-term effectiveness and safety of moxonidine in hypertensive patients who had metabolic syndrome. In a subgroup analysis, the study results indicated that nonpostmenopausal women had approximately 1 mmHg lower mean SBP and DBP levels (SBP 157.8 ± 13.7 versus 158.9 ± 14.1 mmHg; $P < 0.001$). The mean SBP and DBP at baseline was $158.3 \pm 13.8/94.1 \pm 8.7$ mmHg and after treatment, the mean SBP and DBP for nonpostmenopausal female and postmenopausal female patients was 157.8 ± 13.7 and 158.9 ± 14.1 mmHg; $P < 0.001$, respectively (Table 4) [51].

Effect on insulin resistance

Metabolic syndrome involves interconnected factors – sympathetic overactivity and insulin resistance. Insulin serves as an important link between dietary intake and the sympathetic nervous system. Fasting is hypothesized to alleviate insulin resistance and reduce sympathetic activity. Conversely, in insulin resistance or high carbohydrate intake, increased insulin triggers glucose metabolism in hypothalamic neurons, boosting sympathetic outflow. Despite evidence of insulin's impact on central nervous system activity, precise links to sympathetic overactivity in insulin resistance remain unclear [56].

Ten studies reported the effect of moxonidine on insulin resistance. When moxonidine was compared with amlodipine in patients with arterial hypertension and insulin resistance, no significant changes in the Homeostatic Model Assessment of Insulin Resistance (HOMA) index were observed with either moxonidine (4.5 ± 2.0 versus 5.2 ± 3.0 pretreatment and posttreatment, respectively; $P = 0.27$) or amlodipine (7.1 ± 3.6 vs. 7.9 ± 4.1, respectively; $P = 0.32$)

TABLE 3. Efficacy of moxonidine versus other antihypertensive drugs on SBP and DBP

S. No.	Study	Interventions	Sample Size	Moxonidine			Antihypertensive agent		
				Mean SBP/DBP at baseline (mmHg)	SBP after treatment (mmHg)	DBP after treatment (mmHg)	Mean SBP/DBP at baseline (mmHg)	SBP after treatment (mmHg)	DBP after treatment (mmHg)
1	Kujala *et al.*, 2014[a] [58]	Moxonidine 0.6 mg Atenolol 50 mg	112	159.55 ± 15.96/102.28 ± 4.7	Mean change in SBP: 3.2 ± 14.46 NS	Mean change in DBP: 6.2 ± 9.22*	159.96 ± 18.32/101.07 ± 4.7	Mean change in SBP: 12.9 ± 17.18*	Mean change in DBP: 9.5 ± 8.13*
2	Kaaja *et al.*, 2007[a] [56]	Moxonidine 0.6 mg Atenolol 50 mg	98	159.96 ± 18.32/102.28 ± 4.7	Mean change in SBP: 3.2 ± 14.46 NS	Mean change in DBP: 6.2 ± 9.22	159.55 ± 15.96/101.07 ± 4.7	Mean change in SBP: 12.9 ± 17.18*	Mean change in DBP: 9.5 ± 8.13
3	Sanjuliani *et al.*, 2006[b] [62]	Moxonidine 0.2 or 0.4 mg Amlodipine 5 or 10 mg	40	Average 24 h blood pressure 143.1 ± 4.2/86.1 ± 2.6	Mean SBP: 131.8 ± 4.0	Mean DBP: 79.7 ± 3.0	Average 24 h blood pressure 143.3 ± 4.3/88.3 ± 2.7	Mean SBP: 127.2 ± 1.9	Mean DBP: 78.5 ± 1.6
4	Jacob *et al.*, 2004 [69]	Moxonidine 0.2 - 0.6 mg Metoprolol 50–150 mg	200[c]	154 ± 12/91 ± 9	Mean SBP: 142 ± 17	Mean DBP: 83 ± 9	152 ± 13/90 ± 8	Mean SBP: 140 ± 15	Mean DBP: 84 ± 10
5	Martina *et al.*, 1998 [67]	Moxonidine 0.2–0.4mg Cilazapril 2.5–5.0 mg	14	151 ± 8/101 ± 5	Mean SBP: 147 ± 6	Mean DBP: 98 ± 7	164 ± 12/102 ± 6	Mean SBP: 140 ± 9	Mean DBP: 93 ± 9
6	Kuppers *et al.*, 1997[a] [66]	Moxonidine 0.2 mg Enalapril 5 mg	140	163.5 ± 12.5/101.5 ± 3.2	Mean change in SBP: 13.8 ± 14.4	Mean change in DBP: 10.1 ± 9.8	163.5 ± 11.9/101.5 ± 4.3	Mean change in SBP: 14.0 ± 16.2	Mean change in DBP: 12.6 ± 10.5
7	Prichard *et al.*, 1992[b] [60]	Moxonidine 0.2–0.4 mg Atenolol 50 mg	63[c]	167 ± 8/101 ± 3	Mean SBP: 148 ± 22	Mean DBP: 89 ± 10	169 ± 12/102 ± 4	Mean SBP: 145 ± 17	Mean DBP: 87 ± 8
8	Wolf, 1992 [70]	Moxonidine 0.2 mg Nifedipine 20 mg	229	168.4 ± 14.9/102.3 ± 7.2	Mean SBP: 144.6 ± 18.9	Mean DBP: 86.0 ± 11.5	167.6 ± 15.2/102.1 ± 6.5	Mean SBP: 139.8 ± 15.4	Mean DBP: 83.1 ± 9.1

NS, nonsignificant with $P = 0.1740$.
[a]For some studies mean reduction in SBP/DBP values are given.
[b]For others, absolute BP levels after treatment are given.
[c]Per protocol.
*$P < 0.0001$.

[61]. Another study compared the effects of HCTZ, aliskiren, and moxonidine on insulin sensitivity in patients with obesity-related hypertension after treatment for 8 weeks. Hydrochlorothiazide treatment worsened insulin sensitivity, whereas aliskiren and moxonidine had no significant effect [55]. However, extended treatment with moxonidine for 24 weeks showed a notable reduction in the HOMA index compared with amlodipine [62]. In patients with type 2 diabetes, it was observed that moxonidine tended to improve insulin sensitivity, whereas metoprolol worsened it [69]. Slight improvements in insulin resistance were observed with moxonidine in patients with hypertensive type 2b Fredrickson hyperlipidemia, but it was not statistically significant [44].

Ebinc *et al.* (2008) examined the effect of moxonidine treatment on insulin resistance in women diagnosed with essential hypertension. The results indicated that moxonidine treatment has the potential to ameliorate the unfavorable metabolic condition associated with insulin resistance. This improvement may be attributed to the increase in adiponectin levels and a potential reduction in the risk of developing type 2 diabetes among patients with essential hypertension [49].

In a study conducted by Kaaja *et al.* (2007), the impact of moxonidine on insulin resistance was investigated in hypertensive postmenopausal women. The findings revealed that atenolol resulted in decreased insulin sensitivity in noninsulin-resistant women, whereas moxonidine showed no significant change. However, moxonidine treatment proved beneficial for insulin-resistant women, leading to a notable improvement in insulin sensitivity, whereas atenolol did not yield statistically significant results [56]. When same population was studied to understand correlation between improvements in insulin sensitivity and postmenopausal symptoms, no significant associations were found [58].

Pöyhönen-Alho *et al.* (2008) examined the effects of moxonidine and atenolol on hypertensive postmenopausal women. They reported an increase in insulin sensitivity, as measured by the Insulin Sensitivity Index (ISI), in both the moxonidine group (from 4.71 ± 2.14 to 4.85 ± 2.34, $P = 0.613$) and the atenolol group (from 4.24 ± 2.14 to 4.42 ± 2.67, $P = 0.804$) over an 8-week period [59].

Furthermore, Derosa *et al.* (2007) investigated the impact of different doses of moxonidine on insulin sensitivity in patients with mild hypertension and type 2 diabetes. They found that the group receiving moxonidine 0.4 mg showed significantly greater changes in the HOMA-S compared with the group receiving a combination of moxonidine 0.2 mg and irbesartan 150 mg ($P < 0.05$). The HOMA-S value for patients receiving moxonidine 0.2 mg as monotherapy was 8.9 ± 2.0, whereas the baseline HOMA-S was 9.0 ± 2.1 [68].

Effect on body weight

Figure 3 illustrates results from the studies that noted the effect of moxonidine on body weight. Of the available articles, seven studies reported a significant reduction in body weight with moxonidine treatment. In a postmarket surveillance study, Sharma *et al.* (2004) observed an average reduction in weight of 1.4 kg after 8 weeks of treatment in patients who were administered moxonidine 0.3–0.4 mg. This effect was particularly noticeable in obese patients [48].

TABLE 4. Effect of moxonidine on blood pressure based on various parameters

Parameter	Study	Effect on blood pressure		
Age	Schrover *et al.*, 2017 [54]	Individuals ≤60 years showed greater decreases in SBP (−4 mmHg, 95% CI −9 to 1 mmHg) compared with individuals >60 years (−2 mmHg, 95% CI −7 to 3 mmHg; $P = 0.09$).		
	Chazova *et al.*, 2013 [51]	The average SBP and DBP were approximately 4 mmHg lower in patients <65 years old (157.6 ± 13.5/95.1 ± 8.4 mmHg) compared with older patients (160.3 ± 14.4/91.6 ± 9.1 mmHg; $P < 0.001$). The average SBP and DBP at baseline was 158.3 ± 13.8/94.1 ± 8.7 mmHg.		
Sex	Schrover *et al.*, 2017 [54]	Female participants exhibited greater reductions in blood pressure (−4 mmHg SBP, 95% CI −7 to −1 mmHg) compared with male participants (−3 mmHg SBP, 95% CI −8 to 3 mmHg; $P = 0.06$).		
		Baseline	0.2 mg Moxonidine	0.4 mg Moxonidine
Dose	Derosa *et al.*, 2007 [68]	145 ± 4/94 ± 3 mmHg	140 ± 3/89 ± 3 mmHg $P < 0.05$	134 ± 3/84 ± 2 mmHg $P < 0.02$
	Greenwood *et al.*, 2000 [50]	192 ± 7.3/108 ± 2.2 mmHg	174 ± 5.3/101 ± 1.9 mmHg	164 ± 4.6/96 ± 2.0 mmHg
Metabolic disorders	Dorresteijn *et al.*, 2013 [55]	Aliskiren and moxonidine had no impact on glucose metabolism. Moxonidine led to a decrease in all lipid particles, whereas no changes in lipid levels were observed during treatment with aliskiren and HCTZ compared with placebo. There were no noticeable changes in leptin and adiponectin concentrations during any of the treatments in comparison to the placebo.		
		BMI	Change in SBP mmHg	*P* value
Obesity	Schrover *et al.*, 2017 [54]	>30.7 kg/m^2	−4 (−11 to 3)	0.91
		≤30.7 kg/m^2	−3 (−8 to 2)	

HCTZ, hydrochlorothiazide.

Masajtis-Zagajewska *et al.* (2010) observed that insulin-resistant hypertensive patients who received moxonidine experienced a significant reduction in body weight (from 84.0 ± 20.6 to 83.1 ± 20.4 kg; $P = 0.001$). Conversely, the administration of amlodipine led to a significant increase in body weight (83.5 ± 20.4–84.3 ± 20.5 kg; $P = 0.01$) [61]. Similarly, in a crossover comparison of moxonidine and clonidine, Plãntiz (1984) also reported a slight decrease in body weight in both treatment arms [64]. On the contrary, Pöyhönen-Alho *et al.* (2008) found no significant changes in weight during a study comparing the effectiveness of moxonidine (0.6 mg) with atenolol (50 mg) [59].

Effect on low-density lipoprotein levels

A total of nine studies reported the effect of moxonidine on LDL-C levels (Table 5). Overall, moxonidine showed no effect on LDL-C levels except in patients with hypertension and type 2b Fredrickson hyperlipidemia.

Dorresteijn *et al.* (2013) examined the individual impact of aliskiren (300 mg), moxonidine (0.4 mg), HCTZ (25 mg), and placebo on patients with obesity-related hypertension over an 8-week treatment period. Additionally, the authors investigated the effect of these medications on LDL-C levels. The placebo group exhibited a median change in LDL-C of 3.7 (IQR = 3.1–4.1, $N = 30$), whereas the aliskiren group showed a minimal change of −0.02 (−0.19 to 0.15, $N = 28$). Moxonidine demonstrated a slight decrease of −0.14 (−0.30 to 0.03, $N = 30$) in LDL-C, and HCTZ exhibited a small increase of 0.08 (−0.08 to 0.26, $N = 29$) [55]. Derosa *et al.* (2007) found that in patients with type 2 diabetes and mild hypertension, neither moxonidine monotherapy (0.2–0.4 mg) nor moxonidine combined with irbesartan (150 mg) caused a significant change in LDL cholesterol levels throughout the study. The baseline LDL-C level was 114 ± 8 mg/dl, and after 3 months of moxonidine 0.2 mg treatment, it was 113 ± 7 mg/dl. After an additional 3 months of treatment with moxonidine 0.2 mg

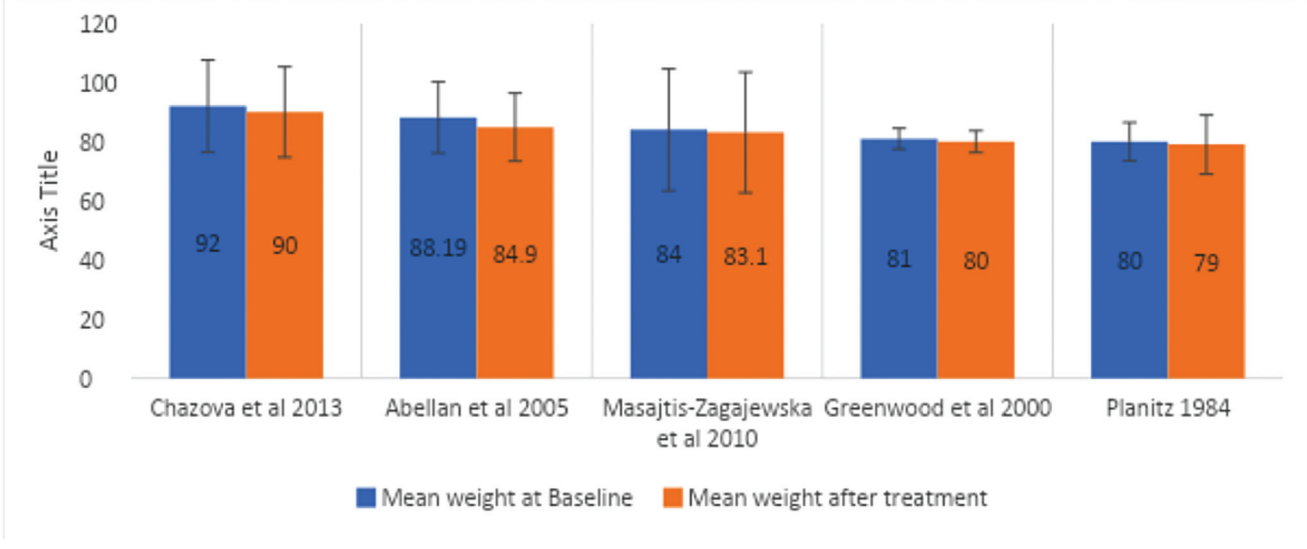

FIGURE 3 Effect of moxonidine on body weight. The bars represent mean of the body weight of patient population and the error bars denote standard deviation. This graph presents results from studies where uniform data is reported.

TABLE 5. Effect of moxonidine on change in low-density lipoprotein cholesterol levels

a. Effect of moxonidine on change in LDL cholesterol levels when given as monotherapy

S. No.	Study Sample size	Dose	Before treatment	After treatment	*P* value
1.	Chazova *et al.*, 2013 [51] $N=1421$	0.2–0.4 mg	3.5 ± 1.1 mmol/l	3.0 ± 0.9 mmol/l	$P=0.007$
2.	Ebinc *et al.*, 2008 [49] $N=51$	0.4–0.6 mg	3.02 ± 0.8 mmol/l	3.47 ± 1.01 mmol/l	–
3.	Lumb *et al.*, 2004 [44] $N=12$	0.2 mg	4.01 ± 1.05 mmol/l	3.64 ± 1.09 mmol/l	$P<0.05$
4.	Elisaf *et al.*, 1999 [46] $N=20$	0.4 mg	98 ± 28 mg/dl	92 ± 25 mg/dl	–

b. Effect of moxonidine and other antihypertensive agents on LDL levels of patients with essential hypertension

S. No.	Study Sample size	Dose	Moxonidine		Comparative drug	
			Before treatment	After treatment	Before treatment	After treatment
1.	Masajtis-Zagajewska *et al*,. 2010 [61] ($N=15$)	Moxonidine 0.4 mg Amlodipine 10 mg	135.0 ± 39 mg/dl	138.0 ± 31 mg/dl	138.0 ± 27 mg/dl	149.0 ± 27 mg/dl
2.	Sanjuliani *et al.*, 2006 [62] Moxonidine ($N=19$) Amlodipine ($N=21$)	Moxonidine 0.2 or 0.4 mg Amlodipine 5 or 10 mg	144.9 ± 12.6 mg/dl	158.0 ± 9.9 mg/dl	145.5 ± 8.8 mg/dl	156.7 ± 8.9 mg/dl
3.	Jacob *et al.* 2004[a] [69] Moxonidine ($N=66$)	Moxonidine 0.2 or 0.6 mg Metoprolol 50 or 150 mg	123 mg/dl	132.5 mg/dl	135.0 mg/dl	135.0 mg/dl

[a]Per protocol.

twice daily and moxonidine (0.2 mg) + irbesartan (150 mg), the LDL-C levels were 110 ± 6 and 111 ± 7 mg/dL, respectively [68].

Effect on FPG and PPG levels

Eight studies reported the effect of moxonidine on FPG levels and one study reported the effect of moxonidine on PPG levels (Table 6). Overall, a significant reduction in FPG levels was observed with moxonidine treatment when compared with amlodipine, metoprolol, and moxonidine in combination with irbesartan.

Safety profile

Of the 27 studies, 14 studies reported on side effects associated with moxonidine. Fig. 4 illustrates the total number of events reported in these studies. The most frequent adverse drug reaction (ADR) associated with moxonidine was dry mouth sensation (1.51%), followed by drowsiness (0.42%), headaches (0.40%), nausea (0.39%), vertigo (0.38%), dizziness (0.26%), and fatigue (0.06%). Other ADRs reported were muscle ache, knee pain, slight worsening of COPD, gastroenteritis, diarrhea, bronchitis, back pain, vomiting, abdominal pain, vasodilation, hypotension, edema. Küppers *et al.* (1997) classified the reported ADRs as per the body systems and reported ADRs under digestive, metabolic/nutritional, nervous, and respiratory [66].

DISCUSSION AND RECOMMENDATIONS

The SNS plays a crucial role in regulating BP, sodium and water balance, and maintaining metabolic homeostasis. Assessing sympathetic nerve activity in an individual patient

TABLE 6. Change in FPG (mmol/l) after treatment with moxonidine

S. No.	Study Sample size	Dose	Before treatment	After treatment	*P* value
Monotherapy					
1.	Chazova *et al.*, 2013 [51] ($N=5603$)	0.2–0.4 mg	6.8 ± 2.1 mmol/l	6.2 ± 1.6 mmol/l	$P=0.001$
2.	Ebinc *et al.*, 2008 [49] ($N=51$)	0.4–0.6 mg	5.47 ± 0.7 mmol/l	5.29 ± 0.7 mmol/l	$P<0.05$
3.	Lumb *et al.*, 2004 [44] ($N=12$)	0.2 mg	6.08 ± 1.14 mmol/l	5.37 ± 0.21 mmol/l	-
Comparative studies[b]					
4.	Dorresteijn *et al.*, 2013 [55] ($N=30$)	0.4 mg	5.1 (4.9–5.5) mmol/l	delta vs placebo 0.24 (0.03–0.45) mmol/l	$P<0.05$
5.	Masajtis-Zagajewska *et al.*, 2010 [61] ($N=15$)	0.4 mg	111.7 ± 29.1 mg/dl	delta vs placebo 3.4 ± 15.9 mg/dl	$P=0.42$
6.	Derosa *et al.*, 2007 [68] ($N=97$)	0.2 mg	146 ± 10 m/dl	142 ± 9 mg/dl	
		0.4 mg	NA	135 ± 8 mg/dl	$P<0.05$
7.	Sanjuliani *et al.*, 2006 [62] ($N=19$)	0.2–0.4 mg	99.4 ± 3.4 mg/dl	102.2 ± 4.6 mg/dl	$P=0.96$
8.	Jacob *et al.*, 2004 [69] ($N=66$)[a]	0.2–0.6 mg	206 mg/dl	186.8 mg/dl	–

NA, not available.
[a]Per protocol.
[b]Pertaining only to moxonidine has been presented in the comparative studies table.

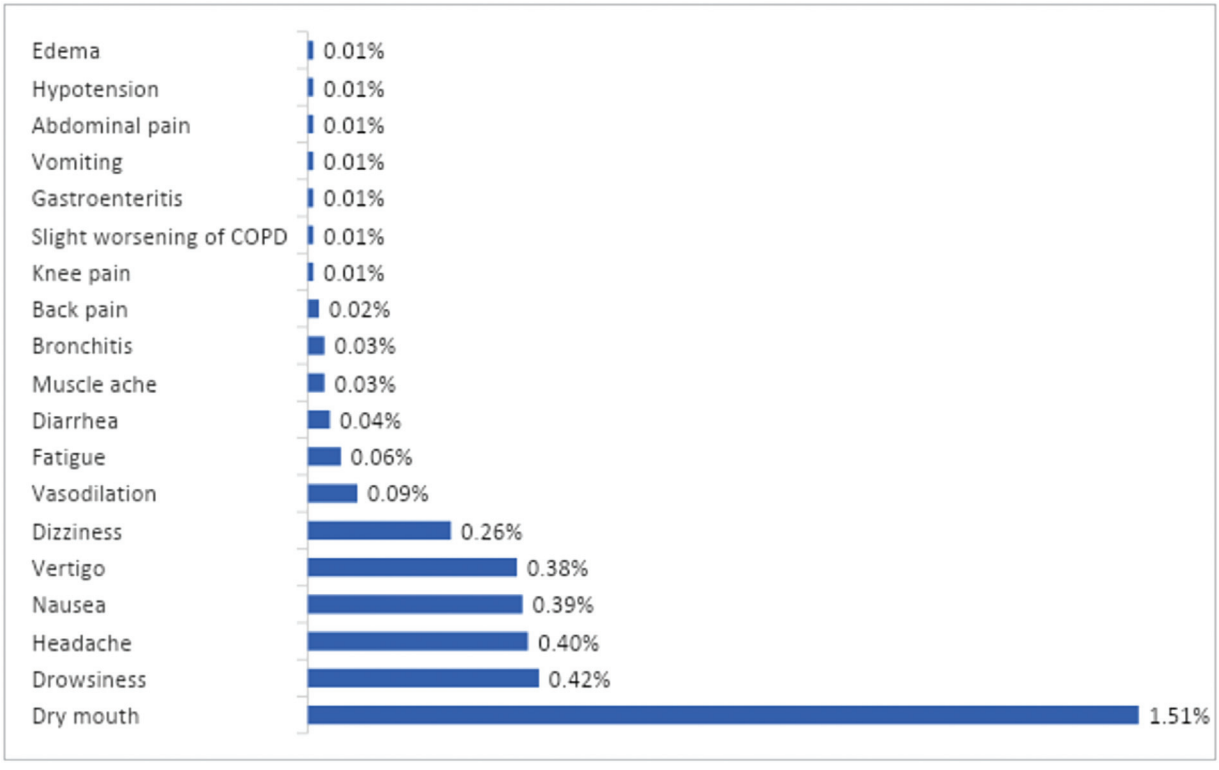

FIGURE 4 Total number of adverse events reported in 14 studies (total sample size $n = 10\,908$).

is challenging and there are currently no reliable methods available to measure SNS activity clinically. An elevated heart rate may indicate increased sympathetic outflow to the heart but can have many other contributing causes. Research methods such as direct recording of MSNA derived from postganglionic sympathetic fibers of the peroneal nerve (microneurography) [71] or, more invasively, assessment of the spillover of released noradrenaline from sympathetic nerve terminals into the venous outflow from relevant organs such as the heart and kidneys (noradrenaline spillover) [72], have unequivocally demonstrated that hypertension is commonly neurogenic in nature, and that other frequent comorbidities of hypertension including overweight, obesity, metabolic syndrome, diabetes, CKD, heart failure, and OSA are characterized by substantially elevated sympathetic drive [8–17]. Targeting sympathetic overactivity, therefore, represents an obvious therapeutic strategy to reduce BP and potentially impact other relevant pathways beneficially. Leaving increased sympathetic drive unopposed, as is common with current guideline recommended first-line therapies, may well represent a contributing factor to the low rate of BP control achieved in contemporary large cohort studies.

There are currently over 125 drugs available for the treatment hypertension, and many of them are effective. However, despite this, controlling BP remains a challenge. When following a stepped-care approach, increasing the dosage of a particular drug can enhance its effectiveness, as per the respective dose–response curves. However, for most drugs, this approach is also associated with higher rates of side effects as these are commonly, although not uniformly, dose-dependent. Consequently, recent international guidelines including AHA/ACC, ISH 2020, and most recently ESH 2023 guidelines recommend initiation of antihypertensive pharmacotherapy with initial low/moderate dose of combination therapy. Indeed, combining two different antihypertensive agents at a moderate dose results in more pronounced BP lowering than using a high dose of a single medication [73].

Another important principle of hypertension management is identification, wherever possible, of relevant pathophysiologic pathways underpinning the BP rise. Preferential use of diuretics in the context of overt fluid overload, or aldosterone antagonists in patients diagnosed with primary aldosteronism not treatable by surgery are clinical examples of pathophysiology-informed BP management.

Renin–angiotensin system inhibitors, diuretics, and calcium channel blockers are typically recommended as the first line of treatment for high blood pressure. However, sympathetic activation is an important contributor to hypertension and is not always effectively treated with these drugs, some of them being known for even increasing it. SIRAs are often suggested as add-on therapy because of their ability to reduce central sympathetic outflow. They are highly specific for the imidazoline I1 receptor and have little affinity for α2-adrenergic receptors, which was demonstrated by several studies that have shown their superior affinity for I1 receptors compared with α2-adrenergic receptors in the rostral ventrolateral medulla [74].

SIRAs reduce BP to a similar degree as other first-line antihypertensive agents with fewer side effects compared with other centrally acting antihypertensive effects including sedation, dry mouth, headache, dizziness, diarrhea, and others [74]. SIRAs are usually well tolerated and can be

combined with any of the other drug classes, making them attractive combination drugs.

However, there are no clinical trials with composite cardiovascular outcome parameters available to compare their effectiveness to standard treatments. Although the Food and Drug Administration accepts BP lowering as a surrogate for cardiovascular risk reduction and studies have shown that SIRAs are as effective as ACE inhibitors, β-blockers, calcium channel blockers, or diuretics in lowering BP, international guidelines rely on the availability of relevant outcome trials to provide respective recommendations. Given that molecules that target SNS have been used for many years, conducting large-scale studies to investigate their impact on cardiovascular risk may not be an economically viable option.

SIRAs are typically considered when BP is not effectively controlled by the three major drug classes, yet they may be effective in specific patient groups, such as obese patients with metabolic syndrome or postmenopausal women, because of their beneficial effects on metabolic homeostasis. Additionally, SIRAs have been associated with improved metabolic parameters, such as body weight, triglycerides, insulin resistance, impaired glucose tolerance, and hyperlipidemia, which results in a lower overall cardiovascular risk. Despite these potential benefits, the SIRA drug class is not widely mentioned in international hypertension management guidelines [74]. Recently, 2023 ESH guidelines have indicated that moxonidine can be employed as an add-on therapy in the rare cases of resistant hypertension, when alternative approaches have been proven ineffective. Additionally, it may be used in certain situations, such as during pregnancy, as a substitute for methyldopa [4].

While acknowledging the lack of outcome data for moxonidine, its BP-lowering efficacy paired with potentially beneficial effects on several metabolic factors makes it a useful treatment option for patients with mild-to-moderate hypertension, particularly in the presence of metabolic disturbances. Furthermore, it can be combined with any other antihypertensive agents without the need for any specific monitoring. Moxonidine is generally well tolerated, exhibits a minimal potential for drug interactions, and can be administered once daily for the majority of patients [75].

Frei *et al*. [76] have reported that moxonidine combined with HCTZ has an additional antihypertensive effect. Moxonidine in combination with a calcium antagonist or an ACE-inhibitor is effective in treating hypertension [77]. These findings are aligned with the recent report from the Hypertension Optimal Treatment study, which suggests that up to 72% of patients may need combination therapy to achieve adequate BP control [78].

In spite of the known benefits of moxonidine with respect to its BP-lowering efficacy, it is essential to acknowledge that moxonidine has been shown to be associated with increased mortality in patients with established heart failure [79]. However, it is noteworthy that in this study (the MOXCON trial), moxonidine was given at a very high dose (3.0 mg daily; sustained-release preparation) that was several-fold greater than the recommended dose for the treatment of hypertension (0.2–0.6 mg daily; immediate release formulation) with forced up-titration [79]. Furthermore, enrolment included heart failure patients without a substantial sympathetic activation at baseline, in whom no benefit from aggressive sympathoinhibition would be expected. Nevertheless, moxonidine is, therefore, contraindicated in moderate-to-severe heart failure. There is no data to suggest that moxonidine would have similar adverse effects in patients with hypertension.

Future guidelines are unlikely to further define the potential role of targeting SNS overdrive by SIRAs in general or in specific patient groups without further evidence from appropriately designed clinical trials in relevant patient cohorts. In the meantime, this expert consensus statement may provide some much-needed guidance for clinical practitioners to inform on the best use of SIRAs in the current environment and taking the available real-world data into account.

Recommendations

1. Targeting the SNS especially in obese individuals and patients with the metabolic syndrome could be an important strategy in the management of hypertension. However, there is a need to create awareness among physicians on SNS modulation.
2. In view of these benefits of SIRAs, the experts recommend moxonidine in the proposed subset of population where SNS overactivation is evident and can be considered as an add-on to the existing combination to treat uncontrolled hypertension.
3. Sympathoinhibition with moxonidine can be considered in combination with first-line therapies in various other populations that are frequently characterized by substantial SNS activation. These include patients with hypertension and any of the following co-morbidities: CKD/OSA/diabetes.
4. The ideal patient profile to be considered for treatment with moxonidine is uncontrolled hypertension without severe cardiovascular disease or heart failure, especially in proposed special patient groups. It can also be considered in young patients having early-onset of mild–moderate hypertension as SNS activation plays a major role in this population.

Addressing knowledge gaps

Although moxonidine treatment has demonstrated positive effects on surrogate measures, there is a lack of outcome trials confirming a reduction in cardiovascular events. This gap may stem from the fact that measurable impacts often require longer observation periods than typical clinical trials provide.

Clinical trials, aiming for sufficient event rates, frequently recruit patients aged 55 and above, leading to limited representation of younger patients in outcome trials.

Limitations

The lack of sufficient number of studies, data, and statistical analysis are limitations of this review. Due to lack of studies exploring benefits on cardiovascular outcomes, we conclude that further research is required in the field. Also, only those articles published in English language were considered in this review.

CLINICAL IMPLICATIONS

Blood pressure can be controlled by targeting different pathophysiological mechanisms. Targeting the adrenergic system with beta blockers has its own limitations, such as tolerability issues and adverse metabolic effects. Targeting the SNS especially in the obese and patients with metabolic syndromes and other relevant co-morbidities highlighted above could be an important strategy. However, there is a need to create awareness among treating physicians on SNS modulation.

Although hard outcome data in hypertension are not available, Moxonidine lowers high BP, and studies have been conducted in the past to compare it with various other drugs used to treat hypertension, including clonidine, diuretics, drugs that block both α receptors and β receptors, calcium antagonists, and ACE inhibitors. The study results demonstrated that the effectiveness of moxonidine in reducing BP was similar to other drugs. Moreover, moxonidine has a favorable side effect profile and is generally well tolerated. Owing to the potentially relevant additional metabolic benefits of SIRAs, the experts recommend moxonidine to be considered as part of a therapeutic combination regimen for special populations where SNS overactivation is evident and its inclusion in standard algorithms for treating uncontrolled hypertension, as an add-on therapy, along with first-line antihypertensives.

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Conflicts of interest

M.S. is/has been a consultant for Viatris and Abbott and has received consulting fees and/or travel and research support from Medtronic, Abbott, ReCor, Novartis, Servier, Pfizer, and Boehringer-Ingelheim. K.T. has no conflict of interest to declare. S.T. is/has been a consultant for Servier; a speaker for Servier, Sandoz, Neopharmed Gentili, and Scharper; and has received research grants from Novartis, Idorsia, Boehringer Ingelheim. C.F. has no conflict of interest to declare. M.C. is/has been a consultant for Boehringer Ingelheim and a speaker for Astra Zeneca. A. S. has received honoraria, speaker fees, consultancy fees, is a member of advisory boards or has appeared on expert panels for: Abbott, Alphapharm, Amgen, Aspen, Astra Zeneca, Bayer, Biotronik, Boehringer Ingelheim, Bristol Myers Squibb, CSL, Edwards, Eli Lilly, Glaxo Smith Kline, HealthEd, Jansen Cilag, Medtronic, Menarini, Merck Sharp and Dohm, Mylan, Novartis, Otsuka, Pfizer, Roche, Sanofi, Servier, St Jude, and Vifor. C.B. is/has been a member of advisory board for Servier, Novartis, Alfasigma, Amarin, Novo Nordisk, Recordati, Menarini Corporate and/or a speaker for Servier, Menarini, Astra-Zeneca, Recordati, Novartis, Novo Nordisk, Gilead. J.P. is/has a speaker for Pfizer, Novartis, AstraZeneca, and Roche Diagnostics and/or has received research grants from Orion Pharma Finland, and Pfizer. M.M. has no conflict of interest to declare. A.-M. V. has received speaker fees, consultancy fees, is a member of advisory boards or has appeared on expert panels for: Amgen, Astra Zeneca, Bayer, Berlin Chemie Menarini, Boehringer Ingelheim, Egis, KRKA, Merck, Novartis, Pfizer, Sanofi, Servier, Terapia, Viatris, Vifor Pharma, Zentiva. A.F. has been a consultant for Viatris and a speaker for Astra Zeneca, Servier Pharma SRL, Zentiva, Novartis, NovoNordisk, Boehringer Ingelheim, Vifor, Berlin Chemie. K.M.G.K. has received consulting fees and/or travel and research support from Medtronic and Abbott. S.C. is an employee of Viatris Inc, Bangalore, India.

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