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ORIGINAL ARTICLE

Not first-line antihypertensive agents, but still effective—The efficacy and safety of imidazoline receptor agonists: A network meta-analysis

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Abstract

Cardiovascular disorders are the leading cause of death in the world. Many organ diseases (kidney, heart, and brain) are substantially more prone to develop in people with hypertension. In the treatment of hypertension, first-line medications are recommended, while imidazoline receptor agonists are not first-line antihypertensives. Our goal was to conduct a network meta-analysis to assess the efficacy and safety of imidazoline receptor agonists. The meta-analysis was performed following the PRISMA guidelines using the PICOS format, considering the CONSORT recommendations. Studies were collected from four databases: PubMed, Cochrane Library, Web of Science, and Embase. A total of 5960 articles were found. After filtering, 27 studies remained eligible for network meta-analysis. Moxonidine reduced blood pressure in sitting position statistically significantly after 8 weeks of treatment (SBP MD: 23.80; 95% CI: 17.45–30.15; DBP MD: 10.90; 95% CI: 8.45–13.35) compared to placebo. Moreover, moxonidine reduced blood pressure more effectively than enalapril; however, this difference was not significant (SBP MD: 3.10; 95% CI: −2.60–8.80; DBP MD: 1.30; 95% CI: −1.25–3.85). Dry mouth was experienced as a side effect in the case of all imidazoline receptor agonists. After 8 weeks of treatment, the appearance of dry mouth was highest with clonidine (OR: 9.27 95% CI: 4.70–18.29) and lowest with rilmenidine (OR: 6.46 95% CI: 0.85–49.13) compared to placebo. Somnolence was less frequent with moxonidine compared to rilmenidine (OR: 0.63 95% CI: 0.17–2.31). Imidazoline receptor agonists were nearly as effective as the first-line drugs in the examined studies. However, their utility as antihypertensives is limited due to their side effects. As a result, they are not first-line antihypertensives and should not be used in

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ATE, atenolol; BP, blood pressure; CAP, captopril; CHL, chlortalidone; 95% CI, confidence interval 95%; CLO, clonidine; DBP, diastolic blood pressure; EMA, European Medicines Agency ENA, enalapril; ENA, Enalapril; EXMOX, extended-release moxonidine; FDA, Food and Drug Administration; GUA, guanfacine; GUB, guanabenz; HCT, hydrochlorothiazide; MD, mean difference; MET, methyldopa; MOX, moxonidine; NISR, sustained-release nifedipine; PRA, prazosin; PRO, propranolol; RIL, rilmenidine; SBP, systolic blood pressure; SD, standard deviation; SRD, sustained-release diltiazem; URA, urapidil.

monotherapy. However, in the case of resistant hypertension, they are a viable option. According to our findings, from the point of view of safety and efficacy, moxonidine appears to be the best choice among imidazoline receptor agonists.

KEYWORDS
clonidine, guanfacine, hypertension, imidazoline receptor agonists, moxonidine, rilmenidine

1 | BACKGROUND

Hypertension can not only increase the risk of many organ-related diseases but can also cause premature death. Approximately, 1.4 billion people suffer from this disease; however, only 14% of them keep it under control.[1] If the diagnosis of hypertension is confirmed, the WHO guideline strongly recommends starting pharmaceutical antihypertensive treatment. There is also a strong suggestion for the use of first-line antihypertensives. These medications include thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARB), and long-acting dihydropyridine calcium channel blockers. According to the previously mentioned WHO guideline, beta-blockers are also considered first-line agents.

Centrally acting agents are not recommended as first-line therapy, although they are an option in cases of resistant hypertension.[2] However, a group of centrally acting antiadrenergic agents (WHO ATC classification: C02A), the imidazoline receptor agonists (C02AC) are potent antihypertensive drugs. In addition, the prevalence of the less tolerated side effects (e.g., dry mouth and sedation) is less common in this group than in the case of other centrally acting antiadrenergic agents (e.g., methyldopa). Imidazoline receptor agonists should not be combined with beta-blockers, because they may increase the AV-blocking effect of beta-blockers.[3] Due to fluid retention, the effectiveness of sympatholytic antihypertensive medications are limited[4]; however, this can be avoided by combining it with an appropriate diuretic agent (thiazide diuretic).[5] Rilmenidine and moxonidine are considered selective imidazoline receptor agonists (SIRAs) and show low affinity to the alpha-2 adrenergic receptors.[6] These two active substances control blood pressure well and also have less side effects compared to other centrally acting antiadrenergic agents.[7] Rilmenidine and moxonidine may be especially beneficial, if hypertension is associated with diabetes, because they reduce microalbuminuria.[8,9] In 2017, moxonidine was available in 25 European countries, according to the European Medicines Agency (EMA) list of nationally authorized medicinal products. Guanfacine shows high affinity to the alpha-2 adrenergic receptors and low affinity to the imidazoline receptors.[10] Currently, guanfacine is less likely to be used as an antihypertensive medication; nonetheless, current studies reveal that this active ingredient has other applications such as in attention-deficit hyperactivity disorder (ADHD).[11,12] Clonidine shows high affinity to the imidazoline receptors and, however, has high affinity to the alpha-2 adrenergic receptors too.[10] Therefore, the use of clonidine is limited due to its main side effects (dry mouth, sedation, orthostatic hypotension, impotence, rebound hypertension).[13] Tolonidine's importance is limited; there is currently no antihypertensive drug containing tolonidine in the EMA or FDA databases.

This investigation aimed to conduct a network meta-analysis to compare the efficacy and safety of imidazoline receptor agonists with other antihypertensive medications and/or placebo to characterize the possible function and value of these drugs in modern therapy.

2 | METHODS

This network meta-analysis was performed following the PRISMA[14] and CONSORT[15] guidelines. The study protocol was prospectively registered in PROSPERO under the reference number CRD42023390680 (www.crd.york.ac.uk).

2.1 | Search strategy, selection criteria, and data extraction

The PICO format (Patient, Intervention, Comparison, Outcome) was used to define the selection criteria. Patients are hypertensive adults, intervention is imidazoline receptor agonists, comparison is placebo or antihypertensive agents, and outcomes are antihypertensive efficacy and side effects. In our study, only monotherapies were compared, and the indication of the use of imidazoline receptor agonists was hypertension. Comorbidities (e.g., hypertension associated with diabetes or renal disease) were not exclusion criteria. Only chronic and oral pharmacotherapy was considered. Double-blind randomized controlled trials were included exclusively.

According to the WHO's ATC system,[16] imidazoline receptor agonists are clonidine (CLO), guanfacine (GUA), tolonidine, moxonidine (MOX), and rilmenidine (RIL). Literature search was performed on May 12, 2023, in four databases: PubMed, Cochrane Library, Web of Science, and Embase. The search term was ((clonidine OR guanfacine OR tolonidine OR moxonidine OR rilmenidine) AND (hypert* OR blood)) AND random*. We applied no language restriction. Articles were filtered in the Zotero reference manager software (6.0.26). Two independent reviewers (AÉ, DC) screened the titles and abstracts of all identified articles for eligibility using the predefined inclusion and exclusion criteria. Any disagreements were resolved through

discussion and consensus. A third reviewer (RV) was involved to solve any disagreements during screening process.

2.2 | Data extraction and outcomes

Data on study characteristics (authors, year, country), patient characteristics (number, age, sex), drug information of intervention and comparator (dose, duration), time of measurements at each position, parameters of efficacy, and safety were extracted.

Blood pressure (BP), expressed in mmHg and measured in supine, sitting, and standing positions, is displayed as MDs with 95% confidence interval (95% CI). Side-effect results are presented as odds ratios with 95% CI. The significance of the differences was determined using *p*-values (<.05). Comparisons were made and illustrated with forest plots.

2.3 | Risk of bias analysis

The risk of bias was analysed by using the Cochrane Risk of Bias Tool (version 2.0). If the risk of bias was low in all domains, the overall risk of bias in each trial was considered low; if the risk of bias was high in at least one domain, the overall risk of bias in each trial was considered to be high. In any other context, the risk of bias was considered to show some concerns. Two authors (BT, AÉ) completed the bias risk assessment independently, and any differences were resolved by a consensus.[17]

2.4 | Statistical analysis

A frequentist network meta-analysis was performed using the netmeta package available in the R-4.2.2 software. To evaluate the inconsistency in our network model, net heat plot and net splitting methods were used. To test and quantify heterogeneity statistically, the I^2 and generalized Cochrane *Q* statistics are used. If $I^2 < 50\%$, the fixed-effect model was applied. If opposite results had been found, the random effect model was implemented. The network graph was provided to illustrate the overall structure of treatment comparisons in the network. To present the effect estimates for the treatment comparison, a net league table and forest plot were provided. The *p*-score is presented to describe the possibility of each treatment ranking. To detect publication bias, comparison-adjusted funnel plots and Egger's regression test were provided.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[18]

3 | RESULTS

3.1 | Study selection

A total of 5960 articles were found. After duplicate removal, 2986 studies remained. After selecting the title and abstract, 53 studies, and after selecting the full text, 27 studies remained eligible for meta-analysis (Figure 1). Out of 27 studies, 4 studies contained information only on BP values, 6 only on side effects, and 17 on both. Demographic data are presented in Table S1.

3.2 | Study characteristics

All 27 articles reported randomized controlled double-blind trials. The location of the studies was quite diverse; seven studies were carried out in Germany, five studies in France, four studies each in Italy and the United Kingdom, three studies in Belgium, two studies in the United States, and one study in Finland and the Netherlands, respectively. Clonidine and rilmenidine were used in eight studies, moxonidine in seven studies, and guanfacine in two studies. Placebo was used as a comparator in six studies, captopril, atenolol, hydrochlorothiazide in three studies, enalapril, chlortalidone, urapidil, propranolol, guanabenz, prazosin, sustained-release nifedipine, sustained-release diltiazem, and methyldopa in one study (Table S2). The applied doses varied from study to study, which are presented in Table S3. Sixteen out of 27 studies' inclusion criteria were essential hypertension. Out of the 11 studies, which did not indicate if essential hypertension was an inclusion criterion, five described secondary-, malignant-, or severe hypertension as exclusion criteria. Comorbidities as exclusion factors were varied from study to study; these criteria are in Table S4. In 15 studies, blood pressure was measured in supine position,[19–33] in 11 studies in standing position,[19–22,25–28,32,34,35] and in six studies in sitting position.[33,34,36–39] The antihypertensive efficacy of imidazoline receptor agonists could be meta-analysed based on 27 studies, in which blood pressure was measured in supine position in 15 studies: four studies at 2 weeks, two studies at 3 weeks, eight studies at 4 weeks, two studies at 6 weeks, six studies at 8 weeks, and one at 12 weeks. Eleven studies measured blood pressure in standing position, two studies at 2 weeks, six studies at 4 weeks, two studies at 6 weeks, and four studies at 8 weeks. Six studies measured blood pressure in sitting position, one study at 2 and 3 weeks, two studies at 4 and 8 weeks, two studies at 12 weeks, and one study at 26 weeks (Table S5).

3.3 | Risk of bias

The risk of bias for each trial is shown in Figure S1. The majority of the studies had low risk of bias or some concerns. Out of the included

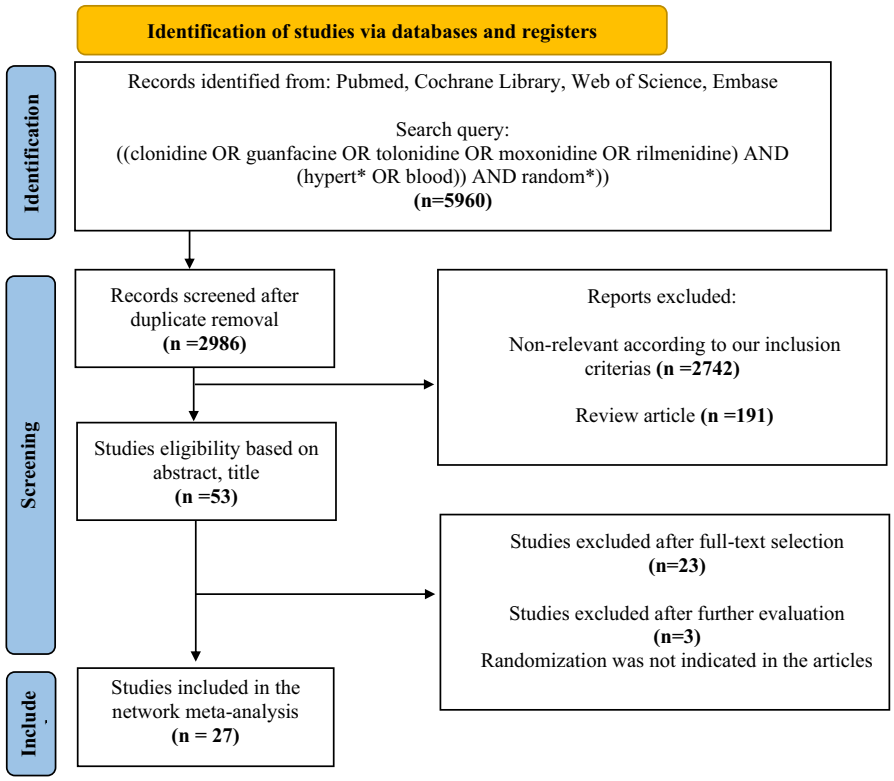

FIGURE 1 PRISMA flow diagram.

27 studies, in 18 studies (66.67%) there were some concerns linked to the random sequence generation. One study of[40] were judged to have high risk of randomization bias because detailed information was not provided about the randomization process and the number of patients enrolled in the intervention groups differed significantly and this could have influenced the results of the study. Regarding one study,[41] significant concerns were raised due to missing outcome data and there were some concerns linked to the selection of the reported results.

3.4 | Outcomes of meta-analysis

3.4.1 | Antihypertensive effect

Sitting position

The network meta-analysis of studies in which blood pressure was measured in sitting position is presented in detail, as this is the position in which blood pressure should be monitored according to WHO guidelines.[42] Blood pressure was measured in sitting position in six trials, as presented in the network graph in Figure 2. Two imidazoline receptor agonists, MOX (51 patients) and CLO (177 patients), were compared with first-line antihypertensives, like ENA (53 patients), HCT (188 patients), and other antihypertensive agents: ATE (176 patients), PRA (186 patients), SRD (182 patients), CAP (188 patients), and PLA (236 patients).

Two studies measured blood pressure after 8 weeks of treatment. However, we could not make an analysis with the other four studies,[34,35,37,38] because there was only one study at an exact time (2, 3, and 26 weeks). If there were at least two studies, which measured blood pressure at the same time (4 and 12 weeks), there was no common intervention between them. In case of studies that evaluated blood pressure after 8 weeks of treatment[33,36] the mean difference of SBP, compared to placebo was significantly lower in patients receiving imidazoline receptor agonists in the following order: MOX (MD: 23.80, 95% CI: 17.45–30.15; $p < .05$), ENA (MD: 20.70, 95% CI: 14.74–26.66; $p < .05$), CLO (MD: 13.00, 95% CI: 10.33–15.67; $p < .05$), HCT (MD: 11.00, 95% CI: 8.37–13.63; $p < .05$), SRD (MD: 10.00, 95% CI: 7.45–12.55; $p < .05$), PRA (MD: 9.00, 95% CI: 6.39–11.61; $p < .05$), ATE (MD: 8.00, 95% CI. 6.20–9.80; $p < .05$), and CAP (MD: 6.00, 95% CI: 3.37–8.63; $p < .05$; Figure 3A). In the case of DBP, the order of efficacy was slightly different: MOX (MD: 10.90 95% CI: 8.45–13.35; $p < .05$), ENA (MD: 9.60, 95% CI: 7.21–11.99; $p < .05$), SRD (MD: 9.00, 95% CI: 7.90–10.10; $p < .05$), CLO (MD: 7.00, 95% CI: 5.82–8.18; $p < .05$), ATE (MD: 7.00, 95% CI: 5.80–8.20; $p < .05$), PRA (MD: 6.00 95% CI: 4.75–7.25; $p < .05$), CAP (MD: 5.00, 95% CI: 3.73–6.27; $p < .05$), and HCT (MD: 5.00, 95% CI: 3.82–6.18; $p < .05$; Figure 3B). The p-scores show that moxonidine has the best potential to decrease SBP and DBP (Table 1). Furthermore, the netleauge table shows that moxonidine significantly reduced SBP and DBP compared to placebo and other pharmaceuticals, except enalapril and sustained-release diltiazem in DBP (Table 2). In summary, both imidazoline receptor agonists, clonidine and moxonidine, were significantly more effective than placebo in all cases (Figure 3A,B; Tables 1 and 2).

Publication bias was evaluated with the help of funnel plots. These refer to no significant publication bias; however, the number

of trials (2 studies) does not allow a reliable analysis, as it is below the Cochrane guidelines[43] (10 studies) (Figure S2a,b).

Standing position

Eleven studies measured patient blood pressure in standing position, two studies at 2 weeks, six studies at 4 weeks, two studies at 6 weeks, and four studies at 8 weeks after start of therapy. After 2 weeks, the mean difference of SBP between placebo and RIL and CLO was significant in favor of active therapies (RIL, MD: 10.00 95% CI: 1.69–18.31; $p < .05$; CLO, MD: 12.00 95% CI: 2.21–21.79; $p < .05$). Mean reduction was also significant in the case of DBP (RIL, MD: 7.00 95% CI: 3.08–10.92; $p < .05$; CLO, MD: 8.00 95% CI: 3.20–12.80; $p < .05$)[14,21] (Table 3, Figures S3–S5; Table S6).

In case of SBP, the mean differences from placebo after 4 weeks of treatment were significant, if GUA or CLO were used (GUA, MD: 23.60 95% CI: 8.53–38.67; $p < .05$; CLO, MD: 6.31 95% CI: 3.48–9.14; $p < .05$). Mean reduction was larger too in the RIL group too; however, this difference was not significant (RIL, MD: 4.18 95% CI: −0.66–9.02; $p > .05$). The same trend was observed for DBP as well, and all differences were significant (GUA, MD: 14.30 95% CI: 8.19–20.41; $p < .05$; CLO, MD: 10.98 95% CI: 7.73–14.23; $p < .05$ RIL, MD: 7.75 95% CI: 3.95–11.55; $p < .05$) (Table 4, Figures S6–S9; Table S7).[19,25–28,34]

The mean reduction of SBP after 6 weeks of treatment with RIL was less remarkable, compared to CLO, and this difference was not significant (RIL, MD: −1.00 95% CI: −6.17–4.17; $p > .05$). Similar results were obtained in the case of DBP too (RIL, MD: −1.00 95% CI: −3.76–1.76; $p > .05$; Figures S10–S12; Tables S8 and S9).[19,21]

After 8 weeks, HCT and ATE decreased SBP more efficiently than RIL, although these differences were not significant (HCT, MD: 5.50 95% CI: −5.42–16.42; $p > .05$; ATE, MD: 1.00 95% CI: −0.08–2.08; $p > .05$). ATE significantly decreased DBP, compared to RIL. HCT decreased DBP, compared to RIL also, although this difference was not significant (HCT, MD: 2.40 95% CI: −4.50–9.30; $p > .05$ ATE, MD: 1.40 95% CI: 0.81–1.99; $p < .05$) (Figures S13–S15; Tables S10 and S11).[22,27,32,33]

Supine position

Blood pressure was measured in supine position in 15 studies; in four studies after 2 weeks, in two studies after 3 weeks, in eight studies after 4 weeks, in two studies after 6 weeks, in six studies after 8 weeks, and in one study after 12 weeks.

The descending order of efficacy of antihypertensives in terms of SBP decrease after 2 weeks of therapy is the following: MOX (MD: 13.85 95% CI: 6.00–21.66; $p < .05$), CLO (MD: 13.85 95% CI: 6.65–21.01; $p < .05$), PRO (MD: 12.63 95% CI: 1.51–23.75; $p < .05$), and RIL (MD: 12.35 95% CI: 5.67–19.02; $p < .05$). The order is the same in mean reduction of DBP (MOX, MD: 11.93 95% CI: 7.46–16.39; $p < .05$; CLO, MD: 10.93 CI: 7.13–14.72; $p < .05$; PRO, MD:

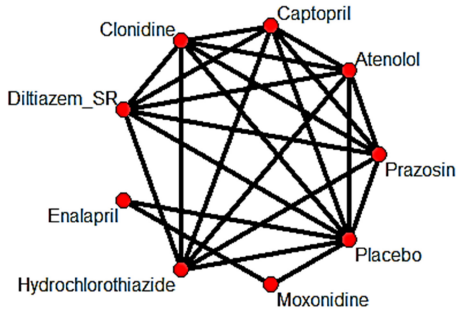

FIGURE 2 Network graph of studies in which antihypertensive agents were administered for 8 weeks and blood pressure was measured in sitting position.

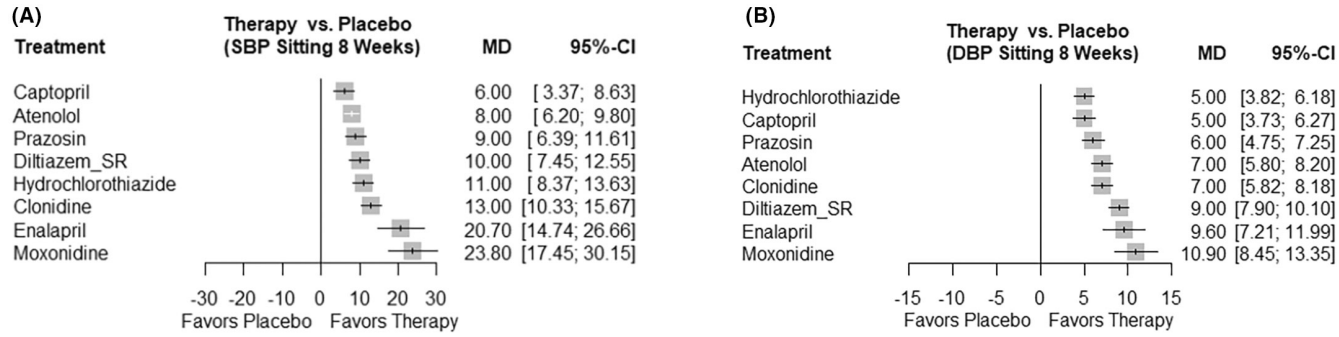

FIGURE 3 Antihypertensive efficacy of imidazoline receptor agonists compared to placebo based on their effect on SBP (A) and DBP (B) (measured in sitting) after 8 weeks of therapy.

TABLE 1 P ranking score SBP, DBP (measured in sitting stance) after 8 weeks of therapy.

Active substance		PLA	CLO	MOX	HCT	ENA	CAP	ATE	PRA	SRD
p-scores	SBP 8 weeks	0.0000	0.7400	0.9819	0.5951	0.8913	0.1368	0.2815	0.3808	0.4924
	DBP 8 weeks	0.0000	0.5602	0.9692	0.1936	0.8462	0.1954	0.5599	0.3742	0.8013

TABLE 2 Netleague table for the effect on SBP and DBP, measured in sitting stance, after 8 weeks of therapy. The figure presents all pairwise comparisons in the network for change in SBP (A) and DBP (B). In Tables 2–7, each point estimate represents the mean differences in blood pressure decrease, and the values in parentheses are the corresponding 95% confidence intervals. Yellow-colored cells represent significant ($p < .05$) comparisons; each cell compares the column against the row. For example, ATE significantly decreases SBP more effectively (2 mmHg greater SBP decreasing effect) than CAP.

ATE								
2.00 (−0.78; 4.78)	CAP							
−5.00 (−7.82; −2.18)	−7.00 (−9.72; −4.28)	CLO						
−2.00 (−4.72; 0.72)	−4.00 (−6.63; −1.37)	3.00 (0.33; 5.67)	SRD					
−12.70 (−18.93; −6.47)	−14.70 (−21.21; −8.19)	−7.70 (−14.23; −1.17)	−10.70 (−17.18; −4.22)	ENA				
−3.00 (−5.78; −0.22)	−5.00 (−7.69; −2.31)	2.00 (−0.72; 4.72)	−1.00 (−3.63; 1.63)	9.70 (3.19; 16.21)	HCT			
−15.80 (−22.40; −9.20)	−17.80 (−24.67; −10.93)	−10.80 (−17.69; −3.91)	−13.80 (−20.64; −6.96)	−3.10 (−8.80; 2.60)	−12.80 (−19.67; −5.93)	MOX		
8.00 (6.20; 9.80)	6.00 (3.37; 8.63)	13.00 (10.33; 15.67)	10.00 (7.45; 12.55)	20.70 (14.74; 26.66)	11.00 (8.37; 13.63)	23.80 (17.45; 30.15)	PLA	
−1.00 (−3.76; 1.76)	−3.00 (−5.67; −0.33)	4.00 (1.28; 6.72)	1.00 (−1.61; 3.61)	11.70 (5.20; 18.20)	2.00 (−0.67; 4.67)	14.80 (7.94; 21.66)	−9.00 (−11.61; −6.39)	PRA
ATE								
2.00 (0.78; 3.22)	CAP							
0.00 (−1.12; 1.12)	−2.00 (−3.20; −0.80)	CLO						
−2.00 (−3.04; −0.96)	−4.00 (−5.12; −2.88)	−2.00 (−3.00; −1.00)	SRD					
−2.60 (−5.27; 0.07)	−4.60 (−7.31; −1.89)	−2.60 (−5.26; 0.06)	−0.60 (−3.23; 2.03)	ENA				
2.00 (0.88; 3.12)	0.00 (−1.22; 1.22)	2.00 (0.90; 3.10)	4.00 (2.98; 5.02)	4.60 (1.94; 7.26)	HCT			
−3.90 (−6.63; −1.17)	−5.90 (−8.66; −3.14)	−3.90 (−6.62; −1.18)	−1.90 (−4.58; 0.78)	−1.30 (−3.85; 1.25)	−5.90 (−8.62; −3.18)	MOX		
7.00 (5.80; 8.20)	5.00 (3.73; 6.27)	7.00 (5.82; 8.18)	9.00 (7.90; 10.10)	9.60 (7.21; 11.99)	5.00 (3.82; 6.18)	10.90 (8.45; 13.35)	PLA	
1.00 (−0.20; 2.20)	−1.00 (−2.27; 0.27)	1.00 (−0.18; 2.18)	3.00 (1.90; 4.10)	3.60 (0.90; 6.30)	−1.00 (−2.18; 0.18)	4.90 (2.15; 7.65)	−6.00 (−7.25; −4.75)	PRA

9.48 95% CI: 4.02–14.94; $p < .05$ RIL, MD: 8.67 95% CI: 5.08–12.25; $p < .05$). In addition, all of these differences were significant (Table 5; Figures S16–S19; Table S12).[18,19,24,26]

After 4 weeks of treatment, the mean difference of SBP reduction between GUA and placebo was 26.70 mmHg, which is a significant difference (95% CI: 12.86–40.54; $p < .05$). Additionally, CLO and RIL also significantly decreased SBP, compared to placebo (CLO, MD: 6.80 95% CI: 4.10–9.51; $p < .05$ RIL, MD: 5.84 95% CI: 1.72–9.96; $p < .05$). GUA was the most potent in the mean reduction of DBP (MD: 12.50 95% CI: 3.65–21.35; $p < .05$). CLO significantly decreased DBP by 7.49 mmHg, compared to placebo (95% CI: 2.29–12.69; $p < .05$). RIL decreased DBP compared to placebo too after 4 weeks, although this difference was not significant (RIL, MD: 5.72 95% CI: −0.71–12.15; $p > .05$) (Table 6; Figures S20–S23; Table S13).[18,19,25–28,30,31]

RIL and CLO appeared to be more potent than URA in reducing SBP after 6 weeks of pharmacotherapy (RIL, 95% CI: −10.30–34.30; $p > .05$; CLO, 95% CI: −9.95–33.95; $p > .05$). If we look at the mean reduction of DBP after 6 weeks, it is greater in case of CLO and RIL than in the URA groups (CLO, MD: 6.00 95% CI: −4.66–16.66; $p > .05$ RIL, MD: 5.00 95% CI: −6.01–16.01; $p > .05$), but these differences were not significant (Figures S24–S26; Tables S14 and 15).[19,21]

RIL, MOX, and MET had similar potential in mean reduction of SBP after 8 weeks of therapy (MET, MD: 0.00 95% CI: −5.82–5.82; $p > .05$; MOX, MD: 0.30 CI: −3.64–4.24; $p > .05$). In DBP, the mean RIL was slightly more effective than MOX and MET (MOX, MD: −0.70 95% CI: −3.19–1.79; $p > .05$ MET, MD: −0.60 CI: −3.23–2.03; $p > .05$); however, none of these differences was significant (Table 7; Figures S27–S29; Table S16).[18,22,23,27,29,32]

TABLE 3 Netleague table for the effect on SBP and DBP, measured in standing stance, after 2 weeks of therapy.

CLO		
12.00 (2.21; 21.79)	PLA	
2.00 (−3.17; 7.17)	−10.00 (−18.31; −1.69)	RIL
CLO		
8.00 (3.20; 12.80)	PLA	
1.00 (−1.76; 3.76)	−7.00 (−10.92; −3.08)	RIL

Yellow shades mean, the difference is significant ($p < .05$)

3.5 | Side effects

3.5.1 | Dry mouth

The frequency of dry mouth, one of the most common side effects of imidazoline receptor agonists, was reported in 20 studies. After 3 weeks of pharmacotherapy, two studies were eligible for analysis. Dry mouth appearance was more frequent, if CLO or GUA (CLO, OR: 6.05 95% CI: 0.26–142.04; $p > .05$ GUA, OR: 3.63 95% CI: 0.11–115.06;

TABLE 4 Netleague table for the effect on SBP and DBP, measured in standing stance, after 4 weeks of therapy.

CHL					
13.00 (0.46; 25.54)	CLO				
−4.29 (−24.10; 15.52)	−17.29 (−32.62; −1.95)	GUA			
13.33 (−2.43; 29.09)	0.33 (−9.21; 9.87)	17.62 (−0.31; 35.55)	HCT		
19.31 (6.45; 32.17)	6.31 (3.48; 9.14)	23.60 (8.53; 38.67)	5.98 (−3.74; 15.70)	PLA	
15.13 (1.82; 28.45)	2.13 (−2.33; 6.59)	19.42 (3.59; 35.25)	1.80 (−6.63; 10.23)	−4.18 (−9.02; 0.66)	RIL
CHL					
7.00 (1.45; 12.55)	CLO				
4.14 (−3.60; 11.89)	−2.86 (−8.26; 2.55)	GUA			
9.84 (1.88; 17.80)	2.84 (−2.86; 8.55)	5.70 (−2.05; 13.45)	HCT		
18.44 (12.66; 24.23)	11.44 (9.81; 13.08)	14.30 (9.15; 19.45)	8.60 (2.81; 14.39)	PLA	
10.14 (4.13; 16.16)	3.14 (0.82; 5.47)	6.00 (0.27; 11.73)	0.30 (−4.91; 5.51)	−8.30 (−10.81; −5.79)	RIL

Yellow shades mean, the difference is significant ($p < .05$)

TABLE 5 Netleague table for the effect on SBP and DBP, measured in supine position, following 2 weeks of the start of the therapy.

CLO				
0.00 (−3.14; 3.14)	MOX			
13.83 (6.65; 21.01)	13.83 (6.00; 21.66)	PLA		
1.20 (−10.26; 12.66)	1.20 (−10.68; 13.08)	−12.63 (−23.75; −1.51)	PRO	
1.48 (−2.71; 5.68)	1.48 (−3.76; 6.72)	−12.35 (−19.02; −5.67)	0.28 (−11.33; 11.89)	RIL
CLO				
−1.00 (−3.35; 1.35)	MOX			
10.93 (7.13; 14.72)	11.93 (7.46; 16.39)	PLA		
1.45 (−4.06; 6.95)	2.45 (−3.54; 8.43)	−9.48 (−14.94; −4.02)	PRO	
2.26 (−0.31; 4.84)	3.26 (−0.22; 6.75)	−8.67 (−12.25; −5.08)	0.82 (−4.90; 6.54)	RIL

Yellow shades mean, the difference is significant ($p < .05$)

TABLE 6 Netleague table for the effect on SBP and DBP, measured in supine stance, after 4 weeks of therapy.

CLO					
−19.90 (−33.99; −5.80)	GUA				
−0.72 (−8.31; 6.87)	19.17 (3.25; 35.09)	HCT			
6.80 (4.10; 9.51)	26.70 (12.86; 40.54)	7.53 (−0.35; 15.40)	PLA		
−5.36 (−14.16; 3.44)	14.53 (−1.85; 30.91)	−4.64 (−16.19; 6.91)	−12.17 (−20.93; −3.41)	PRO	
0.96 (−2.59; 4.51)	20.86 (6.42; 35.29)	1.68 (−5.03; 8.40)	−5.84 (−9.96; −1.72)	6.33 (−3.08; 15.73)	RIL
CLO					
−7.85 (−13.03; −2.67)	GUA				
1.95 (−2.83; 6.73)	9.80 (2.85; 16.76)	HCT			
4.65 (3.15; 6.14)	12.50 (7.54; 17.46)	2.70 (−2.18; 7.58)	PLA		
−6.88 (−10.98; −2.78)	0.97 (−5.39; 7.34)	−8.83 (−15.06; −2.60)	−11.53 (−15.52; −7.54)	PRO	
1.05 (−1.33; 3.43)	8.90 (3.31; 14.49)	−0.90 (−5.05; 3.24)	−3.60 (−6.17; −1.03)	7.93 (3.28; 12.58)	RIL

Yellow shades mean, the difference is significant ($p < .05$)

TABLE 7 Netleague table for the effect on SBP and DBP, measured in supine stance, after 8 weeks of therapy.

ATE				
−10.80 (−21.67; 0.07)	HCT			
2.20 (−3.72; 8.12)	13.00 (0.71; 25.29)	MET		
1.90 (−2.18; 5.98)	12.70 (1.19; 24.21)	−0.30 (−7.33; 6.73)	MOX	
2.20 (1.12; 3.28)	13.00 (2.18; 23.82)	0.00 (−5.82; 5.82)	0.30 (−3.64; 4.24)	RIL
ATE				
1.40 (−5.92; 8.72)	HCT			
3.10 (−2.20; 8.40)	1.70 (−4.56; 7.96)	MET		
3.20 (−2.04; 8.44)	1.80 (−4.41; 8.01)	0.10 (−3.52; 3.72)	MOX	
2.50 (−2.11; 7.11)	1.10 (−4.58; 6.78)	−0.60 (−3.23; 2.03)	−0.70 (−3.19; 1.79)	RIL

Yellow shades mean, the difference is significant ($p < .05$)

TABLE 8 Netleague table for the risk of dry mouth, after 4 weeks of therapy. The figure presents all pairwise comparisons in the network for change in dry mouth. In Tables 8–13, each point estimate represents the odds ratios for the risk of the side effect, and the values in parentheses are the corresponding 95% confidence intervals. Yellow-colored cells represent significant ($p < .05$) comparisons; each cell compares the column against the row. For example, CLO significantly increases the risk of dry mouth 2.31 times, compared to PLA.

CLO				
1.45 (0.10; 20.98)	HCT			
0.35 (0.06; 2.19)	0.24 (0.01; 5.71)	EXMOX		
2.31 (1.40; 3.81)	1.59 (0.12; 22.02)	6.61 (1.13; 38.70)	PLA	
0.50 (0.05; 5.04)	0.35 (0.09; 1.34)	1.44 (0.08; 25.18)	0.22 (0.02; 2.07)	RIL

$p > .05$) was used, compared to URA, although these differences were not significant (Figures S30–S32; Tables S17 and S18).[20,21]

Following 4 weeks of therapy, four studies were eligible for analysis. EXMOX and CLO significantly increased the risk of dry mouth, compared to placebo (EXMOX, OR: 6.61 95% CI: 1.13–38.70; $p < .05$; CLO, OR: 2.31 95% CI: 1.40–3.81; $p < .05$). RIL also increased the risk of dry mouth; however, this difference was not significant (RIL, OR: 4.59 95% CI: 0.48–43.63; $p > .05$) (Table 8; Figures S33–S35; Table S19).[26–28,41]

After 6 weeks of pharmacotherapy, two studies were eligible for analysis. Compared to MOX, CLO significantly increased the risk of dry mouth (OR: 3.57 95% CI: 1.54–8.32; $p < .05$) (Table 9; Figures S36–S38; Table S20).[21,44]

Following 8 weeks of pharmacotherapy, nine studies were eligible for analysis. The use of MOX, CLO, and MET was associated with a significantly increased risk of dry mouth compared to placebo (MET, OR: 11.60 95% CI: 1.40–95.92; $p < .05$; CLO, OR: 9.27 95% CI: 4.70–18.29; $p < .05$; MOX, OR: 7.11 95% CI: 1.21–41.64; $p < .05$). RIL, ATE, GUB, and HCT also increased the risk of dry mouth; however, these differences were not significant compared to placebo (RIL, OR: 6.46 95% CI: 0.85–49.13; $p > .05$; ATE, OR: 3.57 95% CI: 0.15–85.29; $p > .05$; GUB, OR: 2.83 95% CI: 0.23–34.52; $p > .05$; HCT, OR: 2.15

TABLE 9 Netleague table for the risk of dry mouth, after 6 weeks of therapy.

CLO		
3.57 (1.54; 8.32)	MOX	
3.29 (0.12; 89.81)	0.92 (0.03; 27.95)	URA

Yellow shades mean, the difference is significant ($p < .05$)

TABLE 10 P ranking score of dry mouth at 8 weeks.

Active substance	PLA	CLO	MOX	RIL	HCT	ENA	ATE	MET	GUB
p-scores	0.8072	0.248	0.3257	0.3779	0.6283	0.9132	0.5095	0.1407	0.5494

Yellow shades mean, the difference is significant (p<0.05)

95% CI: 0.10–46.47; $p > .05$). On the other hand, the risk of dry mouth was lower in ENA users than in the placebo group after 8 weeks of therapy, although this difference was not significant (OR: 0.42, 95% CI: 0.03–5.65; $p > .05$; Figures 4 and 5; Table 10). Imidazoline receptor agonists significantly increased the risk of dry mouth, except for RIL; however, there were no significant differences between them (Table 11). The risk of publication bias is considered low, based on the funnel plot (Figure S39).[22,23,29,32,33,36,44–46]

3.5.2 | Vertigo

Thirteen studies reported the appearance of vertigo. After 8 weeks of pharmacotherapy, two studies were eligible for analysis. MOX and CLO increased the risk of vertigo; however, these differences were not significant (MOX, OR: 5.00 95% CI: 0.23–106.89; $p > .05$ CLO, OR: 1.77 95% CI: 0.75–4.15; $p > .05$) (Figures S40–S42; Tables S21; S22).[33,36]

3.5.3 | Headache

Thirteen studies reported headache as a side effect. After 6 weeks, three studies were eligible for the analysis. The risk of headache was lower, if CLO or MOX was used, compared to RIL, although these differences were not significant (CLO, OR: 0.94 95% CI: 0.54–1.65; $p > .05$; MOX, OR: 0.23 95% CI: 0.01–3.93; $p > .05$) (Figures S43–S45; Tables S23; 24).[19,21,39]

After 8 weeks, three studies were eligible for analysis. MET significantly increased the risk of headache, compared to RIL after 8 weeks of therapy (OR: 2.79, 95% CI: 1.37–5.70; $p < .05$) (Table 12; Figures S46–S48; Table S25).[29,32,41]

3.5.4 | Somnolence

Nine studies reported somnolence. After 8 weeks, three studies were eligible for analysis. The appearance of somnolence was lower, if MOX was used, compared to RIL, but the difference was not significant (MOX, OR: 0.63 95% CI: 0.17–2.31; $p > .05$) (Table 13; Figures S49–S51; Table S26).[23,29,46]

3.5.5 | Reduced libido, asthenia, anxiety

Forty-four studies reported, if reduced libido or asthenia was experienced, and six reported, if anxiety was experienced in the observed population. Of the four studies, only two were eligible to analyse the risk of reduced libido. When CLO was used, the risk of reduced libido was 10 times higher, compared to placebo (OR: 10.98 95% CI: 0.65–184.61; $p > .05$). If RIL was used, the occurrence of reduced libido was more than three times more likely than in the placebo group (OR: 3.20 95% CI: 0.13–81.50; $p > .05$). However, none of these differences was significant (Figures S52–S54; Tables S27 and S28).[26,28]

Three studies were eligible for the analysis of the risk of asthenia. Asthenia was more likely than in the placebo group if RIL was used; however, this difference was not significant (RIL, OR: 2.59 95% CI: 0.10–66.49; $p > .05$) (Figures S55–S57; Tables S29 and S30).[26,30,41]

Two studies were eligible to analyse the risk of anxiety. Anxiety was more common, if HCT or ATE was used, compared to RIL after 8 weeks of therapy; however, these differences were not significant (HCT, OR: 3.23 95% CI: 0.13–81.58; $p > .05$; ATE, OR: 1.14 95% CI: 0.15–8.46; $p > .05$) (Figures S58–S60; Tables S31 and S32).[32,46]

3.5.6 | Fatigue, constipation

Eight studies reported if fatigue was experienced and six reported if constipation was experienced in the observed population. After 6 weeks of pharmacotherapy, two studies were eligible for analysis. Fatigue was more than two times more frequent, if MOX or CLO was used compared to RIL; however, these differences were not significant (MOX, OR: 2.07 95% CI: 0.41–10.36; $p > .05$; CLO, OR: 2.74 95% CI: 0.84–8.94; $p > .05$) (Figures S61–S63; Tables S33 and S34).[19,44]

After 8 weeks of pharmacotherapy, three studies were eligible for analysis. The risk of constipation is five times greater if HCT was used compared to RIL (OR: 5.52 95% CI: 0.25–118.61; $p > .05$) (Figures S64–S66; Tables S35 and S36).[32,42,46]

3.6 | Classification of treatment

The p-scores of the different treatments' effectiveness and the side effects are presented in Tables S37 and S38. If we evaluate the effectiveness of active substances by the mean *p*-score, independently from the measurement position and the length of therapy, the five most potent antihypertensive agents are CHL (0.8987 ± 0.0684), GUA (0.8817 ± 0.0921), ENA (0.8688 ± 0.0319), MOX (0.6918 ± 0.3149), and CLO (0.6859 ± 0.1411). By the mean *p*-score, the least effective imidazoline receptor agonist is RIL (0.4175 ± 0.1741).

The evaluation of safety yielded a different conclusion than the effectiveness results. The five active substances, which have the best side-effect profiles among the studied agents, ranked by their overall mean p-scores as follows: URA (0.7191 ± 0.1709), ENA (0.6849 ± 0.3229), ATE (0.6085 ± 0.1866), GUB (0.5494 ± 0), and MOX (0.5459 ± 0.2375). EXMOX had the lowest p-score, among imidazoline receptor agonists (0.1849 ± 0), and only dry mouth was

TABLE 11 Netleague table for the risk of dry mouth, after 8 weeks of therapy.

ATE								
0.39 (0.02; 9.89)	CLO							
8.60 (0.31; 242.33)	22.32 (1.50; 331.56)	ENA						
1.26 (0.02; 71.66)	3.27 (0.29; 36.31)	0.15 (0.00; 5.45)	GUA					
1.66 (0.06; 47.62)	4.30 (0.19; 100.01)	0.19 (0.01; 4.93)	1.31 (0.03; 69.03)	HCT				
0.31 (0.03; 3.79)	0.80 (0.09; 7.35)	0.04 (0.00; 0.38)	0.24 (0.01; 6.44)	0.19 (0.02; 2.01)	MET			
0.50 (0.04; 7.01)	1.30 (0.20; 8.66)	0.06 (0.01; 0.45)	0.40 (0.02; 8.51)	0.30 (0.02; 3.73)	1.63 (0.51; 5.19)	MOX		
3.57 (0.15; 85.29)	9.27 (4.70; 18.29)	0.42 (0.03; 5.65)	2.83 (0.23; 34.52)	2.15 (0.10; 46.47)	11.60 (1.40; 95.92)	7.11 (1.21; 41.64)	PLA	
0.55 (0.05; 6.34)	1.43 (0.17; 12.19)	0.06 (0.01; 0.63)	0.44 (0.02; 10.97)	0.33 (0.03; 3.35)	1.80 (1.00; 3.23)	1.10 (0.41; 2.98)	0.15 (0.02; 1.18)	RIL

Yellow shades mean, the difference is significant ($p < 0.05$)

TABLE 12 Netleague table for the risk of headache, after 8 weeks of therapy.

ATE		
0.13 (0.01; 1.44)	MET	
0.36 (0.04; 3.61)	2.79 (1.37; 5.70)	RIL

Yellow shades mean, the difference is significant ($p < .05$)

TABLE 13 Netleague table for the risk of somnolence, after 8 weeks of therapy.

HCT			
0.03 (0.00; 0.74)	MET		
0.22 (0.01; 5.76)	7.36 (1.30; 41.83)	MOX	
0.14 (0.01; 2.79)	4.66 (1.47; 14.79)	0.63 (0.17; 2.31)	RIL

Yellow shades mean, the difference is significant ($p < .05$)

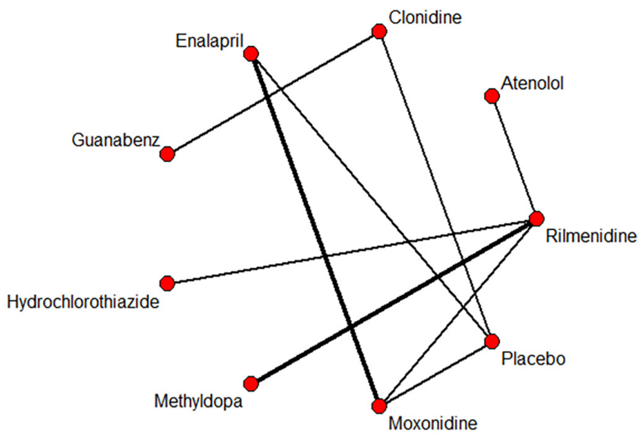

FIGURE 4 Network graph of studies in which dry mouth was reported as side effect (8 weeks of treatment).

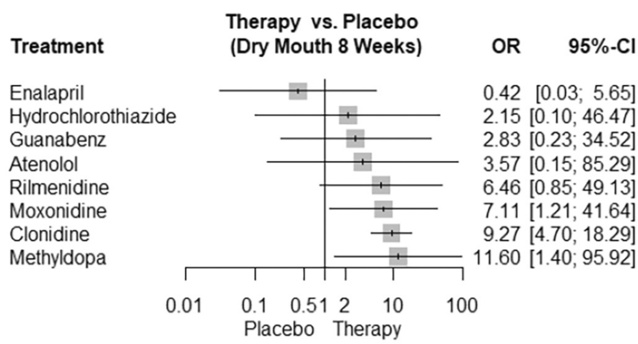

FIGURE 5 Forest plot of the occurrence of dry mouth after 8 weeks of therapy.

experienced with the use of this active substance. However, based on the side effects CLO has the lowest mean p-score value among the imidazoline receptor agonists (0.3319 ± 0.2135).

3.7 | Withdrawals, mortality

Withdrawal rates are listed in Table S39. Only three studies[36,39,46] reported deaths. In[36] three patients died during the study, which was

reported not related to the study drugs. In[39] one patient died during the study, which happened in the EXMOX group. In one study,[46] two patient died during the trial; one participant died in the RIL group due to pulmonary edema.

3.8 | Effectiveness with time

Based on p-scores, RIL effectiveness changed from 2 to 8 weeks, measured in supine and standing position. From 2 to 4 weeks the efficacy decreased, however, it increased at week six, and then decreased again at 8 weeks. CLO followed the same trend as RIL in supine and standing position, although there was no data available on SBP and DBP at 8 weeks. The effectiveness of MOX decreased from 2 to 8 weeks in supine position. GUA was measured only at week four; therefore, effectiveness cannot be measured in time in this active substance. Figures X and Y demonstrate the above-mentioned effectiveness change on SBP and DBP of the pharmaceuticals (Figure S68).

4 | DISCUSSION

This is the first network meta-analysis that evaluates the effectiveness and safety of imidazoline receptor agonists. A total of 27 studies were included to analyse the effectiveness and safety of imidazoline receptor agonists. Except tolonidine, all imidazoline receptor agonists were used in at least two studies. Following the WHO guideline, BP should be measured in sitting position. In this position, MOX reduced SBP and DBP more significantly than the first-line antihypertensives used in these studies (ENA, HCT), which means that MOX is as, or even more effective than these first-line antihypertensives. Taking into account p-scores too, GUA, MOX, and CLO have the best potential to reduce SBP and DBP among the imidazoline receptor agonists.

Despite the remarkable number of included studies, all of them are at least 20 years old. The longest study was 8 weeks long; therefore, the long-term efficacy and safety of imidazoline receptor agonists are not sufficiently supported. Since only studies that used monotherapies were included, the efficacy of combinations (e.g., imidazoline receptor agonist with diuretic) was not assessed.

Overall, most of the withdrawals due to side effects were related to CLO use. RIL increases the risk of dry mouth, asthenia, and reduced libido after 8 weeks of therapy, compared to placebo, although these differences are not significant. CLO and MOX significantly increase the risk of dry mouth after 8 weeks and do not significantly increase the risk of vertigo, compared to placebo. However, CLO caused fatigue and somnolence more frequently compared to MOX, but these differences were not significant either. These side effects limit the use of these active substances for long-term use as antihypertensive agents. In case of GUA, the only side effect experienced was dry mouth after 3 weeks of treatment. CLO and GUA seem to have more and more common side effects than selective imidazoline receptor agonists (rilmenidine, moxonidine), possibly due to their high affinity to alpha-2 adrenergic receptors. It should be noted that only two studies used GUA (in comparison, CLO, RIL: 8 studies; MOX: 7 studies). Moreover, some studies reported the decrease of dry mouth overtime.[18–20]

After 8 weeks of therapy, the efficacy of RIL, CLO, and MOX decreased, when blood pressure was measured in supine and standing position. The studies that measured blood pressure in the standing position did not explicitly indicate that they monitored the occurrence of orthostatic hypotension, but the method used did.[47] According to our analysis, MOX did not cause excessive deaths in patients with hypertension, which was presented in the MOXCON trial in patients with heart failure, although only two studies reported death cases.[36,39] In the MOXCON trial, sustained-release MOX was used and doses were titrated to 1.0–2.0–3.0 mg/day, which is extensively higher than the maximum recommended dose of MOX (0.6 mg daily).[48–50] However, the MOXCON trial lasted for 10 months, when it was terminated due to excessive death cases, the actually analysed studies' longest duration was 8 weeks.

In a four-month randomized double-blind, parallel group study[51] on patients with obesity, hypertension, hypertriglyceridemia (> or =2.3 mmol/L), and impaired glucose tolerance, rilmenidine was proved to have toward its potent antihypertensive effect and ability to improve lipid risk factors, glucose tolerance, and insulin sensitivity. In a recent pilot report in non–insulin-dependent diabetic patients with microalbuminuria, rilmenidine was as effective as captopril, both in lowering blood pressure and also in reducing microalbuminuria.[52] In a large open study, but with blinded echo analysis, the effects of rilmenidine on the reduction of left ventricular mass have been confirmed.[53] Moxonidine significantly decreased blood pressure, fasting glucose, triglycerides, total cholesterol, HOMA-IR, and albumin excretion in a study of 55 non-diabetic hypertensive patients and 53 normotensive women.[54]

In a randomized controlled trial on 42 patients with hypertension with cardiovascular magnetic resonance was proven that after one of two equipotent antihypertensive regimens for 6 months, the reduction in left ventricular mass was significantly greater in the valsartan and moxonidine group compared with bendroflumethiazide and amlodipine.[55]

In a randomized comparative study in 36 postmenopausal women with arterial hypertension, after 6 months of treatment with moxonidine, the left ventricular myocardial mass was significantly reduced, and also a positive effect of moxonidine on the variables of lipid exchange variables was revealed.[56]

Thus, based on the literature, moxonidine appears to have similar beneficial characteristics on glucose and lipid metabolism and on target organs, as rilmenidine. According to the National Health Insurance Fund of Hungary database, in 2022, following perindopril, amlodipine, allopurinol containing medications, the fourth most prescribed and dispensed medications active substance in Hungary was rilmenidine.[57] This fact indicates that the use of rilmenidine is frequent in Hungary; however, moxonidine seems to have a better side effect profile and has better efficacy, according to our findings.

5 | CONCLUSIONS

In summary, imidazoline receptor agonists are as potent as first-line antihypertensives, although their side effect profile is worse than that of first-line antihypertensives. These pharmacons are not used in monotherapy and are not considered first-line antihypertensive agents.[58] On the contrary, when first-line antihypertensive agents fail to control hypertension, imidazoline receptor agonists are useful options.[59] Caution is needed when they are combined with beta-blockers. Moreover, they might need to be combined with a diuretic to avoid the decrease of efficacy. According to our analysis, in monotherapy MOX is more effective in reducing blood pressure (SBP and DBP) after 8 weeks of therapy than enalapril, a first-line antihypertensive agent. Due to the short duration (up to 8 weeks) and age (at least 20 years old) of the included studies, the available evidence does not support that imidazoline receptor agonists are a good choice for long-term treatment of hypertension. However, MOX seems to be the best choice to treat hypertension among imidazoline receptor agonists, when first-line antihypertensives fail to control hypertension.

AUTHOR CONTRIBUTIONS

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by András Érszegi, Muh. Akbar Bahar, and Dezső Csupor. The first draft of the manuscript was written by András Érszegi and all authors commented on later versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

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