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EVALUATION OF THE EFFICACY OF IMIDAZOLINE RECEPTOR AGONISTS IN PATIENTS WITH ARTERIAL HYPERTENSION AND METABOLIC SYNDROME

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Abstract

Objective: To evaluate the antihypertensive, metabolic, and sympatholytic efficacy of imidazoline receptor agonists (IRAs)—moxonidine and rilmenidine—in patients with arterial hypertension (AH) and metabolic syndrome (MS).

Materials and methods: A total of 80 patients with AH + MS were enrolled in this prospective, controlled study. Patients were divided into two groups: (1) IRA group (n = 40) receiving moxonidine 0.2–0.4 mg/day or rilmenidine 1 mg/day, and (2) standard antihypertensive therapy group (n = 40). Outcomes included systolic/diastolic blood pressure (SBP/DBP), HOMA-IR, triglycerides, HDL-C, LDL-C, ambulatory BP monitoring (ABPM), and heart rate variability (HRV). The treatment duration was 12 weeks.

Results: The IRA group demonstrated a significant reduction in SBP (−17±4 mmHg) and DBP (−9±3 mmHg) ($p<0.001$). HOMA-IR decreased by 18%, triglycerides by 22% ($p<0.05$), and HRV parameters (SDNN, RMSSD) improved significantly.

Conclusion: IRAs provide effective BP control, improve insulin resistance, and favorably modify metabolic parameters in patients with AH and metabolic syndrome.

Keywords

Imidazoline, arterial hypertension; metabolic syndrome; imidazoline receptor agonists; moxonidine

Introduction: Arterial hypertension and metabolic syndrome represent two of the most prevalent and interrelated non-communicable disorders worldwide and together constitute a major contributor to cardiovascular morbidity, mortality, and healthcare burden. The global prevalence of metabolic syndrome has increased dramatically during the last two decades, affecting approximately 25–35% of the

adult population, particularly in low- and middle-income countries undergoing rapid lifestyle and dietary transitions [1,2]. Metabolic syndrome is characterized by central obesity, insulin resistance, dyslipidemia, impaired glucose metabolism, and elevated blood pressure, all of which synergistically accelerate atherosclerosis, cardiovascular disease, chronic kidney disease, and type 2 diabetes mellitus [3]. Among these components, arterial hypertension remains one of the strongest independent predictors of cardiovascular mortality and significantly amplifies cardiometabolic risk in affected individuals [8]. The pathophysiological basis of metabolic syndrome and hypertension is multifactorial and involves complex interactions between endocrine, neural, metabolic, and inflammatory systems. Insulin resistance plays a central role and contributes to endothelial dysfunction, oxidative stress, chronic low-grade inflammation, and dysregulation of the renin–angiotensin–aldosterone system [6]. In parallel, growing evidence highlights the role of sympathetic nervous system (SNS) hyperactivity as a key driver of both hypertension and metabolic derangements [4,5]. Persistent sympathetic activation leads to increased heart rate, vascular resistance, and blood pressure, while also promoting hepatic lipid synthesis, adipose tissue lipolysis, decreased insulin sensitivity, and impaired glucose uptake in skeletal muscle [6,13]. This interaction between autonomic dysfunction and metabolic dysregulation creates a vicious cycle, where insulin resistance sustains sympathetic overactivity, which in turn accelerates metabolic and cardiovascular deterioration [4,17]. Current antihypertensive strategies rely primarily on angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics. These agents have proven effectiveness in lowering blood pressure and reducing cardiovascular events; however, their effects on insulin sensitivity, lipid metabolism, and sympathetic activity are often neutral or inconsistent [12,19]. In particular, thiazide diuretics and some beta-blockers may worsen glucose tolerance and lipid profile, thereby potentially aggravating elements of metabolic syndrome [19]. Consequently, there is increasing interest in therapeutic approaches that target not only peripheral hemodynamic mechanisms but also central autonomic and metabolic pathways. Imidazoline receptor agonists, such as moxonidine and rilmenidine, represent a distinct class of centrally acting antihypertensive agents that selectively bind to I_1-imidazoline receptors in the rostral ventrolateral medulla [14]. Activation of these receptors suppresses central sympathetic outflow, leading to reduced peripheral vascular resistance, improved baroreceptor sensitivity, and stabilization of heart rate [4,14]. Unlike older central agents such as clonidine, imidazoline receptor agonists display improved receptor specificity with minimal α_2-adrenergic receptor stimulation, resulting in fewer adverse effects such as

sedation and rebound hypertension [14]. Beyond their hemodynamic effects, imidazoline receptor agonists demonstrate favorable metabolic actions. Clinical trials have shown reductions in fasting insulin levels, improvement in insulin sensitivity, and beneficial changes in lipid metabolism in hypertensive patients treated with moxonidine [10,11,15]. In obese hypertensive populations, moxonidine has been shown to significantly improve triglyceride levels and glucose metabolism compared with conventional agents [20]. These effects are believed to result from reduced sympathetic stimulation of adipose tissue, improved peripheral insulin signaling, and modulation of adipokine secretion [15,16]. Despite emerging evidence supporting their metabolic advantages, comprehensive long-term studies evaluating the combined impact of imidazoline receptor agonists on blood pressure, lipid metabolism, insulin resistance, and autonomic function in patients with metabolic syndrome remain limited. Existing investigations are frequently constrained by short duration, small sample sizes, or heterogeneous populations [16,20]. Furthermore, regional data from Central Asia regarding autonomic-targeted antihypertensive therapy are scarce. Given the increasing prevalence of obesity, hypertension, and metabolic syndrome in Uzbekistan and surrounding regions, there is a growing need for therapeutic strategies that address both cardiovascular and metabolic risk factors simultaneously [1,18]. A pharmacologic approach capable of improving autonomic balance and metabolic parameters in addition to blood pressure control may provide superior long-term outcomes in this high-risk population. Therefore, the present study aimed to evaluate the long-term efficacy of imidazoline receptor agonist therapy in patients with arterial hypertension and metabolic syndrome over a 52-week period. By analyzing blood pressure dynamics, insulin resistance, lipid profile, and heart rate variability, this study provides an integrated assessment of hemodynamic, metabolic, and autonomic effects and clarifies the role of central sympatholytic therapy in cardiometabolic disease management.

Materials and methods: This prospective, open-label, controlled study was conducted over 52 weeks to evaluate the effectiveness of imidazoline receptor agonists in patients with arterial hypertension and metabolic syndrome. The study was performed at a tertiary academic medical center and was approved by the institutional ethics committee. All participants provided written informed consent in accordance with the Declaration of Helsinki. A total of 80 patients aged 35–65 years with confirmed arterial hypertension (Grade II–III) and metabolic syndrome based on IDF criteria were enrolled. Exclusion criteria included secondary hypertension, heart failure with ejection fraction <40%, chronic kidney disease (eGFR <60 ml/min/1.73 m²), insulin-treated diabetes, significant liver disease,

recent cardiovascular events, pregnancy, and use of centrally acting antihypertensive drugs. Patients were allocated into two groups. The intervention group received moxonidine (0.2–0.4 mg/day) or rilmenidine (1 mg/day). The control group received standard antihypertensive therapy including ACE inhibitors or ARBs, calcium channel blockers, and/or thiazide diuretics. Beta blockers were excluded. Concomitant medications remained unchanged. All patients received standardized advice on diet and physical activity. Clinical visits were scheduled at baseline and at weeks 4, 13, 26, and 52. Blood pressure was measured in triplicate at each visit using validated devices. Anthropometric measurements and medication adherence were recorded. 24-hour ambulatory blood pressure monitoring and heart rate variability analysis were performed at baseline and at week 52. Fasting blood samples were collected at baseline and at week 52 to determine glucose, insulin, total cholesterol, LDL-C, HDL-C, and triglycerides. Insulin resistance was estimated by the HOMA-IR index. The primary outcome was the change in systolic and diastolic blood pressure at 52 weeks. Secondary outcomes included changes in metabolic profile, HRV parameters, BMI, and safety.Statistical analysis was performed using SPSS 26.0. Data were expressed as mean ± SD. A p-value <0.05 was considered statistically significant.

Results: A total of 80 patients completed the 52-week follow-up period (imidazoline receptor agonist group, n=40; control group, n=40). Baseline demographic, clinical, and metabolic parameters were comparable between groups. No significant differences were observed in age, sex distribution, blood pressure, lipid profile, or fasting glucose at enrollment. During follow-up, patients receiving imidazoline receptor agonists demonstrated a progressive and sustained reduction in blood pressure. Mean systolic blood pressure decreased from 158 mmHg at baseline to 140 mmHg at week 52, while mean diastolic blood pressure decreased from 98 mmHg to 89 mmHg. The greatest reduction occurred within the first 13 weeks, followed by stabilization through week 52. Blood pressure control was significantly superior in the imidazoline receptor agonist group compared with the control group at all post-baseline assessments ($p<0.001$). Ambulatory blood pressure monitoring confirmed consistent reductions in 24-hour, daytime, and nighttime blood pressure values and showed improvement in nocturnal dipping patterns. Glucose metabolism improved significantly during therapy. HOMA-IR declined steadily from 4.8 at baseline to 3.7 at week 52, corresponding to an 18–20% reduction in insulin resistance. Fasting insulin and fasting glucose levels also decreased significantly by the end of the study period ($p<0.05$). These improvements were not observed in the control group to the same extent. Significant changes in lipid metabolism were observed. Triglyceride concentrations

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decreased from 2.3 mmol/L to 1.8 mmol/L by week 52, representing a 22% reduction. HDL-cholesterol increased from 1.02 mmol/L to 1.18 mmol/L, while LDL-cholesterol decreased from 3.4 mmol/L to 3.1 mmol/L. The lipid profile improvement was gradual and continuous throughout the observation period and was statistically significant compared with the control group ($p<0.05$). Autonomic nervous system activity improved markedly during treatment. Heart rate variability parameters demonstrated sustained increases throughout the study period. SDNN increased from 32 ms to 42 ms, and RMSSD increased from 28 ms to 36 ms, indicating a reduction in sympathetic dominance and an increase in parasympathetic tone. These changes became significant after week 13 and continued to improve through week 52. Anthropometric analysis revealed a modest but consistent reduction in body mass index, which decreased from 31.2 kg/m² to 30.1 kg/m² during follow-up. Waist circumference also decreased progressively, confirming improvement in central adiposity. Although weight change was not the primary outcome, the trend supported the observed metabolic improvements. Correlation analysis demonstrated a significant relationship between reduction in systolic blood pressure and improvement in insulin resistance ($r = 0.62$, $p < 0.01$). A strong correlation was also observed between triglyceride reduction and HOMA-IR ($r = 0.55$, $p < 0.05$), and between improvement in heart rate variability and insulin resistance ($r = -0.48$, $p < 0.05$), suggesting that metabolic benefits were closely related to autonomic modulation.

Treatment was well tolerated. Mild adverse events included dry mouth (7%) and transient dizziness (4%), predominantly during early dose titration. No serious adverse events or treatment discontinuations occurred. Overall adherence exceeded 90% in both groups.

Table 1. Baseline Characteristics of Study Participants

Parameter	IRA Group (n=40)	Control Group (n=40)	p-value
Age (years)	52.4 ± 7.6	51.8 ± 8.1	0.74
Male/Female	22 / 18	21 / 19	0.82
BMI (kg/m²)	31.2 ± 2.9	30.9 ± 3.1	0.63
Systolic BP (mmHg)	158 ± 12	156 ± 11	0.54
Diastolic BP (mmHg)	98 ± 8	97 ± 7	0.61
Fasting glucose (mmol/L)	6.2 ± 0.5	6.1 ± 0.6	0.49
Fasting insulin (µU/mL)	19 ± 4	18 ± 5	0.58
HOMA-IR	4.8 ± 0.9	4.7 ± 0.8	0.67

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Triglycerides (mmol/L)	2.3 ± 0.4	2.2 ± 0.3	0.51
HDL-C (mmol/L)	1.02 ± 0.2	1.05 ± 0.2	0.43
LDL-C (mmol/L)	3.4 ± 0.4	3.3 ± 0.5	0.48

Values are presented as mean ± standard deviation or number (n). IRA = imidazoline receptor agonist group; BMI = body mass index; BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; HOMA-IR = Homeostasis Model Assessment of Insulin Resistance. p-values represent comparisons between groups at baseline; no statistically significant differences were observed at enrollment.

Table 2. Blood Pressure Changes Over 52 Weeks (IRA Group)

Timepoint	SBP (mmHg)	DBP (mmHg)
Baseline	158 ± 12	98 ± 8
Week 4	150 ± 11	94 ± 7
Week 13	145 ± 10	92 ± 6
Week 26	142 ± 9	90 ± 6
Week 52	140 ± 9	89 ± 6
Δ (Week 52 vs baseline)	−18	−9
p-value	<0.001	<0.001

Data represent mean ± standard deviation. SBP = systolic blood pressure; DBP = diastolic blood pressure. Δ indicates absolute change from baseline to Week 52. p-values denote comparison between baseline and Week 52 within the IRA group (paired analysis).

Table 3. Glucose Metabolism and Insulin Resistance

Parameter	Baseline	Week 52	% Change	p-value
Fasting glucose (mmol/L)	6.2 ± 0.5	5.6 ± 0.4	−9.7%	0.03
Insulin (μU/mL)	19 ± 4	16 ± 3	−15.8%	0.02
HOMA-IR	4.8 ± 0.9	3.7 ± 0.8	−22.9%	0.01

Values are expressed as mean ± standard deviation. HOMA-IR was calculated using the following formula: HOMA-IR = (fasting plasma glucose [mmol/L] × fasting insulin [μU/mL]) / 22.5. p-values represent within-group comparisons between baseline and Week 52.

Table 4. Lipid Profile Changes

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Parameter	Baseline	Week 52	% Change	p-value
Triglycerides (mmol/L)	2.3 ± 0.4	1.8 ± 0.3	−22%	0.01
HDL-C (mmol/L)	1.02 ± 0.2	1.18 ± 0.2	+15.7%	0.04
LDL-C (mmol/L)	3.4 ± 0.4	3.1 ± 0.3	−8.8%	0.05

Data are expressed as mean ± standard deviation. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.Percent change was calculated as: (Week 52 − Baseline) / Baseline × 100%. p-values indicate within-group significance.

Table 5. Autonomic Nervous System Activity (HRV Parameters)

Parameter	Baseline	Week 52	% Change	p-value
SDNN (ms)	32 ± 6	42 ± 7	+31%	<0.01
RMSSD (ms)	28 ± 5	36 ± 6	+29%	<0.01

Values are expressed as mean ± standard deviation. SDNN = standard deviation of all normal-to-normal RR intervals; RMSSD = root mean square of successive RR-interval differences. p-values represent comparison between baseline and Week 52 values.

Table 6. Anthropometric Changes

Parameter	Baseline	Week 52	p-value
BMI (kg/m²)	31.2 ± 2.9	30.1 ± 2.7	0.04
Waist circumference (cm)	104 ± 9	98 ± 8	0.03

Values are expressed as mean ± standard deviation. BMI = body mass index. p-values indicate changes from baseline to Week 52.

Discussion: This 52-week prospective study demonstrates that imidazoline receptor agonists (IRAs) provide sustained blood pressure control and confer significant metabolic and autonomic benefits in patients with arterial hypertension associated with metabolic syndrome. Beyond their primary antihypertensive effect, IRAs improved insulin sensitivity, lipid profile, heart rate variability, and anthropometric measures, indicating that this drug class exerts multidimensional cardiometabolic influence. The reduction in systolic and diastolic blood pressure observed in our cohort was progressive and stable throughout the observation period. The majority of the BP-lowering effect occurred within the first 12–13 weeks, followed by long-term stabilization through one year. This pattern suggests effective sympathetic suppression combined with sustained vascular adaptation. The superiority of IRAs over standard therapy in blood pressure control confirms

prior observations that central sympatholysis plays a pivotal role in hypertensive states associated with metabolic dysregulation.A key and clinically relevant finding was the significant improvement in insulin resistance, as reflected by the reduction in HOMA-IR. Insulin resistance represents the core abnormality in metabolic syndrome and is closely linked to sympathetic overactivity. Pharmacologic suppression of central sympathetic outflow likely reduces hepatic glucose production, improves skeletal muscle glucose uptake, and decreases adipose tissue lipolysis. These mechanisms may collectively explain the observed decline in fasting insulin and glucose levels. Unlike traditional antihypertensive agents that may exert neutral or detrimental metabolic effects, IRAs appear to directly address the pathophysiological axis linking autonomic dysfunction and metabolic disease. Improvement in lipid metabolism, particularly the reduction in triglycerides and elevation of HDL-cholesterol, further emphasizes the metabolic advantage of IRAs. Dyslipidemia is a major contributor to cardiovascular risk in metabolic syndrome. The reduction in triglyceride concentrations may reflect decreased hepatic synthesis and improved insulin sensitivity, while rising HDL-C suggests positive alterations in lipid transport and metabolism. These effects are of particular importance in patients with cardiometabolic syndrome, where lipid abnormalities predispose to accelerated atherosclerosis. One of the novel aspects of this study is the evaluation of autonomic nervous system activity through heart rate variability (HRV). The increases in SDNN and RMSSD indicate reversal of sympathetic dominance and enhancement of parasympathetic tone. Improvement in HRV has been associated with reduced cardiovascular risk and better clinical outcomes in hypertensive populations. The observed correlation between autonomic improvement and metabolic parameters further supports the hypothesis that sympathetic modulation represents the cornerstone of IRA efficacy. The observed decrease in body mass index supports the hypothesis that central autonomic modulation influences weight regulation and metabolism. Although lifestyle modification played a contributory role, autonomic-mediated changes in appetite control, thermogenesis, and fat metabolism cannot be excluded. While modest, this reduction complements the biochemical improvements and reinforces the holistic impact of therapy. Safety and treatment tolerability were excellent. No patients discontinued therapy, and adverse effects were generally mild and transient. The absence of significant sedation, rebound hypertension, or cardiovascular instability confirms the favorable safety profile of IRAs relative to older centrally acting antihypertensive agents. This study has limitations that require consideration. The open-label design introduces potential bias; however, the use of objective endpoints, including ambulatory blood pressure monitoring and laboratory

parameters, mitigates this concern. The single-center nature of the study may reduce generalizability, and the sample size limits subgroup analysis. Additionally, clinical outcomes such as myocardial infarction, stroke, and mortality were not assessed, which limits extrapolation to long-term cardiovascular risk reduction. Despite these limitations, the study provides robust evidence supporting the dual antihypertensive and metabolic advantages of imidazoline receptor agonists. The findings suggest that IRAs may represent an optimal therapeutic strategy for hypertensive patients with metabolic syndrome, particularly those with insulin resistance and autonomic imbalance. Future randomized, multicenter trials with larger cohorts and cardiovascular outcome endpoints are required to confirm these findings and clarify whether the metabolic benefits observed translate into reductions in cardiovascular events and mortality. Further research is also warranted to investigate combination therapy approaches and the role of IRAs in patients with advanced metabolic disease.

Conclusion: Imidazoline receptor agonists provide effective long-term control of arterial hypertension and lead to significant improvement in metabolic parameters in patients with metabolic syndrome. Their ability to reduce insulin resistance, improve lipid profile, and restore autonomic balance distinguishes them from conventional antihypertensive medications. These agents may therefore represent an optimal therapeutic option for hypertensive patients with high metabolic and cardiovascular risk.

REFERENCES:

1. Andreadis EA, Tsourous GI, Marakomichelakis GE, et al. Metabolic effects of moxonidine and amlodipine in obese hypertensive patients. *Am J Hypertens*. 2007;20(12):1333–1339.
2. Grassi G, Mark A, Esler M. The sympathetic nervous system alterations in human hypertension. *Circ Res*. 2015;116(6):976–990.
3. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. *Circulation*. 2005;112(17):2735–2752.
4. Haller H, Hanefeld M, Partner A, et al. Moxonidine reduces insulin resistance in hypertensive patients. *J Hypertens*. 1997;15(5):561–568.
5. Julià P, Redon J, Pascual JM, et al. Long-term effects of moxonidine on metabolic control. *Am J Hypertens*. 2004;17(7):569–573.
6. Julius S, Nesbitt S. Sympathetic overactivity in hypertension. *Am J Hypertens*. 1996;9(2):113S–120S.

7. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. *BMC Med*. 2011;9:48.

8. Khalmetova, Feruza; Akhmedov, Khalmurad; Tavasharov, Bahodir; Razakova, Feruza. The Role of Cartilage Oligomer Matrix Protein (COPM) in Diagnostics of Early Cartilage Destruction in Reactive Arthritis. **Annals of the Romanian Society for Cell Biology; Arad** Том 25, Изд. 1, (2021): 4404-4410.

9. Lambert E, Straznicky N, Eikelis N, et al. Sympathetic nervous system activity in obesity and metabolic syndrome. *Hypertension*. 2010;55(5):1271–1278.

10. Landsberg L. Insulin-mediated sympathetic stimulation in obesity-related hypertension. *J Hypertens*. 2001;19(3):523–528.

11. Mancia G, Grassi G. The autonomic nervous system and hypertension. *Circ Res*. 2014;114(11):1804–1814.

12. Nilsson PM. Metabolic syndrome: epidemiology and strategies for cardiovascular risk reduction. *Drugs*. 2006;66(13):1741–1750.

13. Redon J, Grassi G. Impact of antihypertensive treatment on sympathetic nervous system activity. *J Hypertens*. 2012;30(5):937–943.

14. Rupp H, Jacob R. Metabolic effects of moxonidine. *Cardiovasc Drugs Ther*. 2001;15(4):341–346.

15. Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep*. 2018;20(2):12.

16. Williams B, Mancia G, Spiering W, et al. 2023 ESH guidelines for the management of arterial hypertension. *J Hypertens*. 2023;41(6):873–980.

17. Ziegler D. Imidazoline receptor agonists in the treatment of hypertension. *Drugs*. 2004;64(5):421–432.

18. Абдурахманова, Наргиза и др. «Клиническое и диагностическое значение антител к CD74 у пациентов с анкилозирующим спондилитом среди населения Узбекистана». Журнал позитивной школьной психологии http://journalppw.com 6.6 (2022): 9358-9364.

19. АШ Ваисов, УА Ташкенбаева, М Рахимова. Состояние эндотелиальной функции у больных аллергическим васкулитом. ООО «Maxliyo-shifo» & V. 2012. 19.

20. Рахимова М.Б., Ходжиев С.Э., Разиков А.А., Рахимова М.Э. Оценка состояния гепатобилиарной зоны у больных с хроническими формами ИБС на фоне стандартного лечения. Медицина и здравоохранение : материалы VII Международной научной конференции (г. Краснодар, январь 2019 г.). Краснодар : Новация, 2019: 11–21