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Effects of selective Imidazolin-1 (I1) receptor agonists *vs* ACE-Is/ARBs on metabolic parameters in patients of hypertension: A Meta-analysis of RCTs

Sharanabasayyaswamy B Hiremath[*1] and Srinivas LD[2]

[1]*Department of Pharmacology, SDM College of Medical Sciences and Hospital, Dharwad, Karnataka*
[2]*Department of Pharmacology, JJM Medical College, Davangere, Karnataka*

Corresponding author*

Dr. S. B Hiremath,
Department of Pharmacology,
SDM College of Medical Sciences and Hospital,
Dharwad-09, Karnataka
E-mail: dr.sharan83@yahoo.com

Abstract

Objectives: Co-existence of metabolic syndrome in hypertensive patients is associated with the higher risk for development of various complications including type 2 diabetes mellitus and hence highlights the need for selecting an anti-hypertensive with favorable effect on metabolic parameters. Present study aims at analyzing the efficacies of selective imidazolin-1 (I1) receptor agonists *vs* ACE-Is/ARBs on blood pressure, indicators of insulin resistance and plasma lipids concentration.

Methods: Electronic data search in PUBMED, Cochrane library and EMBASE was conducted. Eligible studies were analyzed by random and fixed effects model for the effect size measures. RevMan 5.2 software was used for statistical analysis

Results: There was significant difference in the level of decrease in total cholesterol and triglyceride in imidazolins group. However, the decrease in systolic and diastolic blood pressure was significantly more in ACE-Is/ARBs. However among these significant findings found in fixed effect model, the only significant change present in random effect model was the decrease in triglycerides by imidazolins.

Conclusion: Efficacy of I1-agonists on plasma lipids and decreasing blood pressure appears to be non-inferior to ACE-Is/ARBs at short term treatment.

Keywords: Imidazolin-1 receptor agonists, ACE-Is, ARBs, metabolic syndrome, hypertension.

1. Introduction

Metabolic syndrome or insulin resistance syndrome or cardiometabolic syndrome comprises of obesity, hyperglycemia, hypertention, dyslipidemia and hyperinsulinemia. Co-existence of metabolic syndrome in hypertensive patients is associated with the higher risk for development of type 2 diabetes mellitus.[1,2] Obesity plays a major and pivotal role in inducing the resistance to insulin and thus ultimately the sequences of complications that follow due to development of insulin resistance.[2] A higher insulin level in insulin resistance syndrome is responsible for sodium retention, sympathetic nervous system stimulation, vascular smooth muscle hypertrophy and oxidative stress.[3,4] Hence insulin resistance not only represents the mechanism or basis for development of type 2 diabetes mellitus but it is also the basis even for development of hypertension and oxidative stress induced low grade systemic inflammation. What is alarming is its onset at the early age with adolescent population becoming susceptible to obesity and thus insulin resistance syndrome.[5]

Need for search of a drug with favorable effect on metabolic parameters is relevant for two reasons. First, the drug should have the added benefits as seen with ACE-Is /ARBs without the major adverse effects or risks like hyperkelemia and acute kidney injury seen with ACE-Is/ARBs. Second, hypertensive patients with metabolic syndrome or insulin resistance may need add on drug in addition to ACE-Is/ARBs under the circumstances where target level blood pressure is not achieved and it preferably needs addition of a class of drug with favorable effects on metabolic profiles. Second line drugs found with either beneficial or neutral effect in metabolic syndrome or insulin resistance are third generation non-selective beta-blockers like carvedilol, alpha-1 blocker doxazosin, dihydropyridine calcium channel blockers (DHPs) and selective imidazolin-1 (I1) receptor agonists.[6-8] Major drawbacks of alpha-1 blockers in terms of safety were evident in the ALLHAT study and these drugs are obviously not preferable.[9] Hence the best second line anti-hypertensive drug to be added in the background of insulin resistance needs selection from either DHPs or carvedilol or I1-agonists as each classes of these drugs have either favorable or neutral effects against insulin resistance. We did not have

sufficient studies to compare carvedilol with other two classes of drugs. Considering the central mechanism of action of inhibiting the sympathetic stimulation by I1-agonist perhaps they might be having similar benefits as ACE-Is /ARBs. It's quite interesting to know whether this benefit of inhibition and its subsequent effects on blood vessels, metabolic parameters etc are extrapolated into better efficacy or are the identical to ACE-Is /ARBs. Hence the present study aims at analyzing the efficacies of I1-agonists *vs* ACE-inhibitors or ARBs on blood pressure, indicators of insulin resistance and plasma lipid concentrations.

2. Materials and Methods

2.1 Literature Search methodology:

Two authors independently conducted electronic database search in PUBMED, Cochrane library and EMBASE for the randomized trials or cross-over trials comparing I1-agonist vs ACE-Is/ARBs. Two authors conducted separate searches using search terms "rilmenidine" AND "hypertension" and "moxonidine" AND 'hypertension". Limits applied for the search in PUBMED were "randomized controlled studies", and "humans" while the limits applied for search in EMBASE were "randomized controlled trial" "conference paper" "article" "article in press" "embase" and "humans". No limits were applied in Cochrane library search. Search was limited to studies published upto 30th july 2015.

2.2 Eligibity Criteria:

Either cross-over studies or randomized trials with head-to-head comparison of I1-agonists with ACE-Is/ARBs in patients of either sex aged >18 yrs with hypertension and features of insulin resistance or metabolic syndrome or type 2 diabetes mellitus were eligible for inclusion. Studies with results of short duration of treatment (<1 month), studies published in language other than English and those with incomplete data required for statistical analysis or those published as abstracts were considered under exclusion criteria.

2.3 Data Extraction and synthesis:

Two authors are involved in independent extraction of all required data and it was planned to prepare final data only after reaching consensus between the two authors. Changes in systolic and diastolic blood pressure, changes indicators of insulin resistance: fasting plasma sugar, fasting insulin and plasma lipid levels were extracted.

2.4 Outcome measures:

Primary outcome measures were mean change in SBP & DBP, secondary outcome measures were mean differences indicators of insulin resistance: fasting plasma sugar, fasting insulin and plasma lipid levels between selective I1-agonists *vs* ACE-Is/ARBs.

2.5 Statistical methods:

Changes in the outcome measures between two groups were assessed by calculating the "mean difference'. Both fixed and random effect models were used in analysis. Sensitivity analysis of the results was conducted by comparing results of fixed effect model and random effects model. Heterogeneity between the studies was analyzed by using Cochrane Q test for heterogeneity and I^2 test. A chi square test with P value <0.10 and I^2 test value of >50% was considered as indicator of significant heterogeneity. Funnel plot method was used for assessment of publication bias. Statistical analysis was conducted by using RevMan software version 5.2. Un-blinded quality assessment of published data of eligible studies was done independently by two authors as described by Nancy *et al*.[10] Final score for the individual studies was allotted after arriving at consensus between the authors.

3. Results and discussion

3.1 Data search results:

Figure 1 shows the results of data search and the attrition diagram and number of studies excluded with reasons for exclusion. Excluded studies involved two studies published in language other than English. [11,12] Remaining two RCTs comparing I1-agonists *vs* ACE-Is/ARBs were eligible and included in the analysis.[13,14] One of the above excluded study was published in English language in another journal and was included as eligible study. Both the included studies were on rilmenidine as I1-agonist and none was on moxonidine. Among the ACE-Is/ARBs group, captopril was used in one study and lisinopril in another.

3.2 Characters of included studies:

Table 1 and 2. shows the baseline demographic, clinical features and characteristics of individual studies included in the analysis. Differences in the baseline demographic and clinical features between the two comparator groups in both studies were statistically insignificant. There was similarity in the doses of rilmenidine used in both studies and they did not varied significantly with regards to use of concomittent medications. However the duration of study was two months in one and three months in other. In study by Dimitri *et al*., 2005, only female patients were included and in study by scumama *et al.*, 1995 patients with type 2a or 2b hyperlipidemia were included and this could be a major reason for

inter-study heterogeneity. Quality score achieved by both studies was more than 75%. There was evidence of significant publication bias with most of the effect size measure estimated by random effect model.

Figure 1: Flow chart showing literature search result and attrition diagram

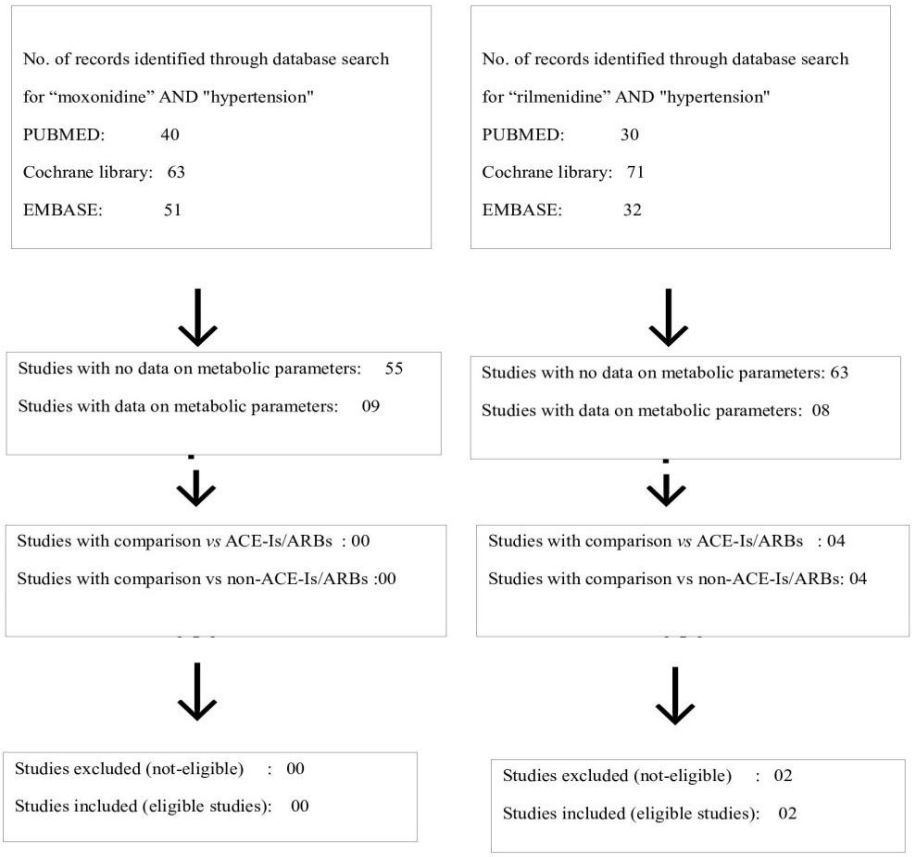


Table 1: Baseline demographic and clinical feature of patients included in eligible studies

Factors	Dimitri *et al*., 2005		Scemama *et al*., 1995	
	Lisinopril [N=27]	Rilmenidine [N=24]	Captopril [N=25]	Rilmenidine [N=26]
Age (Yrs)	54 ±9	53 ± 10	57.8 ±1.8	54.9 ±2 .3
BMI	35±5	35±5	N/A	N/A
Body weight (Kg)	N/A	N/A	72.8±2.2	70.5±2.0
Heart rate (bpm)	77±8	78±10	74.8±1.7	75.3±1.5
Sex Ratio (Male: Female)	00:27	00:24	15:10	12:14
SBP (mmHg)	171± 18	170± 16	166.7± 2.9	163.3± 2.3
DBP (mmHg)	100±6	97± 7	99.2±0.8	99.1± 0.4
Fasting glucose (mmlol/l)	6.48±1.89	6.82±1.27	N/A	N/A
Total Cholesterol (mmlol/l)	6.05±1.46	6.54±1.21	7.54±0.19	7.46±0.19
Triglycerides (mmlol/l)	1.56±0.59	2.23±0.94	1.61±0.12	1.67±0.17
HDL-cholesterol (mmlol/l)	1.12±0.23	1.25±0.29	1.32±0.07	1.43±0.08
LDL-cholesterol (mmlol/l)	4.15±1.26	4.27±1.20	5.48±0.16	5.28±0.16

* Significant difference, All Values in Mean±SD, N/A: Not Available

Table 2: Characteristics & quality scores of individual studies

Study	Dimitri *et al*., 2005	Scemama *et al*., 1995
Study Design & Duration	Randomized, Open-label Parallel group, 3 months	Randomized, Double-blind parallel group, 2 months
Centre & Country	Single centre Russia	Single centre France
Co-morbidity	Metabolic syndrome	Hyperlipidemia 2a or 2b
Intervention	Rilmenidine:1 to 2 mg/d Lisinopril: 10 to 20 mg/d	Rilmenidine:1 to 2 mg/d Captopril: 25 to 50 mg/d
Other interventions	None	None
Quality score	87.5%	78%

3.3 Outcome measures:

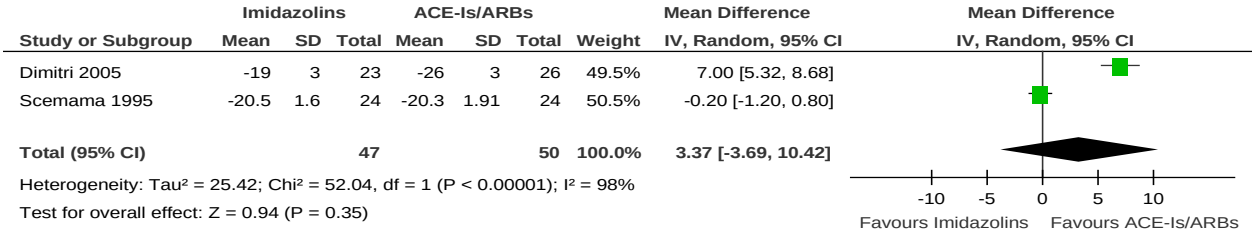
Data required to analyze the effect on fasting serum insulin level, fasting plasma glucose level, HOMA index could not be assessed as the data required was not available. Values of the mean changes in SBP and DBP at the end of the study period were not available in study by Scemama *et al.*, 1995. Hence we calculated the mean change and its standard deviation from the baseline and study end values published in the article. Considering the possibility of significant inter-study heterogenity, we present the results of random effects model as representatives of true effects. Figure 2 and Table.3 shows the effects size measures at short term (≈3 months) treatment. There was evidence of significant inter-study heterogeneity and publication bias in all the effect size measures calculated.

Table 3: Effect size measures of all outcome measures

Outcome measures	Mean Difference (Random effect model)	Mean Difference (Fixed effect model)	N
SBP (mm Hg):	3.37 [-3.69, 14.51]	1.67 [0.81, 2.53]*	97
DBP (mm Hg):	0.72 [-0.44, 1.87]	1.04 [0.64, 1.45]*	97
T. Cholesterol (mmol/L):	-0.21 [-0.72, 0.30]	-0.19 [-0.26, -0.12]*	97
Triglycerides (mmol/L):	-0.23 [-0.29, -0.17]*	-0.23 [-0.29, -0.17]*	97
HDL Cholesterol (mmol/L):	0.02 [-0.08, 0.12]	-0.00 [-0.02, 0.02]	97
LDL Cholesterol (mmol/L):	-0.11 [-0.70, 0.48]	-0.07 [-0.14, 0.01]	97

* Significant difference

Figure 2: Forest plot showing mean difference in SBP:



In fixed effect model the ammount of mean decrease in both SBP and DBP brought about by ACE-Is group was siginifcantly greater than rilmenidnie, was not seen in random effects model indicating lack of sensitivity in the results. The ammount of decrease in total cholesterol levels and triglyceride levels were significant in rilmenidine group than in ACE-Is group. The the significant difference with regard to triglycerides level was still present in fixed effect model, indicating possible strong effect of imidazolins in decreasing triglycerides level.

3.4 Discussion:

Overview of the results of the study give impressions that the imidazolin, rilmenidine appears to have identical effects as that of ACE-Is on blood pressure levels and the effect on plasma lipid levels, especially triglyceride levels is better than the ACE-Is at around three months. However, we should consider the major limitations of our study before making the strong conclusion on these observations. Including only two studies of short duration and of small sample size is a major drawback. The possibility of significant heterogeneity and publication bias with the two different types of patients included in each study, extrapolating these results to general population needs cautiona and further studies.

References

[1] Zhou MS, Wang A, Yu H. Link between insulin resistance and hypertension: what is the evidence from evolutionary biology?. *Diabetology & Metabolic Syndrome* 2014; 6(12):1-8.

[2] Rizos CV, Elisaf MS. Antihypertensive drugs and glucose metabolism. *World J Cardiol* 2014; 6(7): 517-30.

[3] Abel ED, O'shea KM, Ramasamy R. Insulin resistance: metabolic mechanisms and consequences in the heart. *Arterioscler Thromb Vasc Biol* 2012; 32:2068-76.

[4] Jia G, Aroor AR, Demarco VG, Martinez-Lemus LA, Meininger GA, Sowers JR. Vascular stiffness in insulin resistance and obesity. *Front. Physiol* 2015; 6 (231):1-8.

[5] Steinberger J, Daniels SR. Obesity, insulin resistance, diabetes, and cardiovascular risk in children. *Circulation* 2003; 107:1448-53.

[6] Schachter M. Metabolic effects of moxonidine and other centrally acting antihypertensives. *Diabetes Obes Metab* 1999; 1(6):317-22.

[7] Torres YC, Katholi RE. Novel treatment approaches in hypertensive type 2 diabetic Patients. *World J Diabetes* 2014; 5(4): 536-45.

[8] Hansson L. Therapy of hypertension and metabolic syndrome: today's standard and tomorrow's perspectives. *Blood Press suppl*. 1998; 3:20-2.

[9] Furberg CD, Wright JT, Davis BR, Cuttler JA, Alderman M, Black H, *et al*. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker *vs* diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2002; 288(23):2981-97.

[10] Nancy GB, Robert AP**.** Meta-analysis: neither quick nor easy. *BMC medical research methodology* 2002, 2:10.

[11] Miczke A, Pupek-Musialik D, Cymerys M, Bryl W, Kujawska-Łuczak M, Bogdański P. The effect of analysed hypotensive drugs on certain metabolic parameters. *Polskie Archiwum Medycyny Wewnętrznej* 2003; 109(3):237-42.

[12] Scemama M, Fevrier B, Beucler I, Dairou F. Effects of rilmenidine (Hyperium) on the lipid balance of hyperlipidaemic hypertensive patients. randomized, controlled, double-blind 8-week study in parallel groups versus captopril. *Annales De Cardiologie Et D'Angeiologie* 1996; 45(10):595-601.

[13] Anichkov DA, Shostak NA, Schastnaya OV. Comparison of rilmenidine and lisinopril on ambulatory blood pressure and plasma lipid and glucose levels in hypertensive women with metabolic syndrome. *Current medical research and opinion* 2005; 21(1):113-9.

[14] Scemama M, Février B, Beucler I, Dairou F. Lipid profile and antihypertensive efficacy in hyperlipidemic hypertensive patients: comparison of rilmenidine and captopril. *Journal of cardiovascular pharmacology* 1995; 26(2):S34-9.