MAEDICA – a Journal of Clinical Medicine
2023; 18(4): 547-554
https://doi.org/10.26574/maedica.2023.18.4.547

MÆDICA - a Journal of Clinical Medicine

ORIGINAL PAPER

An Actual Perspective on I_1-Imidazoline Agonists in Blood Pressure Control. Results of a Multicentric Observational Prospective Study

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ABSTRACT

Background: *Despite the disadvantaged position of central adrenergic drugs (CAD) in the current therapeutic regimens of hypertensive patients, we hypothesized that the addition of the most recent representatives of this class – I_1-imidazoline agonists (CAD-I_1A) – to the usually recommended drugs might contribute to better blood pressure (BP) control.*

Method: *This multicentric observational prospective study included patients with BP ≥ 140/90 mm Hg who were using at least two antihypertensive drugs and were reassessed at three months apart in 44 urban medical centers. Patients with modifications in therapy were subsequently divided into two subgroups: one study group, with CAD-I_1A added to the initial therapeutic regimen, and one control group characterized by the addition of a drug from any other class of antihypertensives.*

Results: *The rate of BP normalization was 43% (144/333) after CAD-I_1A addition* vs *26% (15/58) following any other changes in treatment (p<0.01). The binomial logistic regression has validated the*

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Article received on the 24th of November 2023 and accepted for publication on the 13th of December 2023

presence of CAD-I_1A in the therapeutic regimen ($p<0.001$) and the stage of hypertension at baseline ($p<0.01$) as statistically significant predictors of a better BP control, while demographic, socio-economic, lifestyle factors and comorbidities were similarly distributed between the two groups. No differences in the rate of side effects were identified.

Conclusions: *The results of our study indicate a high probability of BP normalization when a CAD-I_1A is added to the therapeutic regimen of patients with uncontrolled hypertension under at least two drugs.*

Keywords: blood pressure control, central adrenergic inhibitors, I_1-imidazoline receptor agonists.

INTRODUCTION

Improvement of arterial hypertension (HTN) control is a worldwide priority, emphasized by many scientific societies and most recently by the World Health Organization in its first-ever report on the devastating global impact of high blood pressure (BP) (1-4). Accordingly, four out of five people with high BP are inadequately treated, despite extremely varied and relatively easily accessible therapeutic resources (4). In the last decades, the therapeutic control of HTN made a slow progress compared with awareness and the proportion of treated hypertensive patients (5, 6), reaching about 50% across Europe (7) and even less in Romania, an East-European country, where it only achieved 39% based on the latest available records (8). This problem requires vigorous actions if the persistence of high BP under treatment is associated with an augmented cardiovascular risk (9, 10). Along with measures addressing socio-economic conditions, adherence to treatment or correction of unhealthy lifestyle factors (11), the optimization of therapeutic regimens represents the cornerstone of HTN management.

The implication of the sympathetic nervous system in the pathogenesis of arterial HTN has been noticed since the early 20th century. In the late 1960s, powerful drugs were developed to block the adrenergic pathway. Still, many of them, such as central adrenergic drugs (CAD) represented by clonidine and methyldopa or alpha-blockers, not to mention ganglionic blockers or sympathetic neuronal blockers, were grafted with strong side effects (12-13). During the 1990s, the class of central I_1-imidazoline agonists (I_1A), including moxonidine and rilmenidine, became available (14). Despite their efficacy and high tolerability, they have been hit by the cone of shadow which progressively has covered the whole spectrum of drugs addressing directly the sympathetic pathways, also affecting the beta-blockers from a certain point (15). The entire class of CAD has been placed in the last lines of anti-hypertensive treatment (2, 16, 17). However, I_1-imidazoline agonists have been proven to be equally effective and safe when used in monotherapy (18, 19). That is why we conducted a multicentric observational prospective study to evaluate the impact of currently used CAD – in particular of I_1A – on BP control when added to the current antihypertensive therapeutic regimens. ❑

MATERIALS AND METHODS

Hypertensive patients with uncontrolled BP (≥ 140/90 mm Hg) under at least two antihypertensive drugs were included in the present study after giving their written informed consent, and were reassessed three months apart. Patients were evaluated, enrolled and monitored by cardiologists in 44 urban medical centers. Patients' assessment consisted of a questionnaire including demographic data (age, gender, level of education); history of arterial hypertension; associated risk factors, including obesity (abdominal obesity defined by waist circumference ≥ 102 cm for males and ≥ 88 cm for females and obesity by a body mass index ≥ 30 kg/m^2), diabetes mellitus and smoking status (currently smoking at least one cigarette/day); history of overt cardiovascular disease (chest angina and myocardial infarction or stroke); lifestyle, including sedentarism (without any physical activity of at least 30 minutes/day ≤ once/month), duration and quality of sleep; self-declared adherence to therapy (taking regularly the medication or forgetting rarely the doses). At each study visit, BP, weight and waist circumference were measured. Whenever available, the plasmatic lipid

profile was also recorded. Classification of HTN was realized according to guidelines (ESH 2013, ESH 2023): I) 140-159/90-99 mm Hg; II) 160-179/100-109 mm Hg; III) ≥180/110 mm Hg (1, 20). Physicians were free to decide the therapeutic strategy after enrollment: to add any class of drug to the former antihypertensive treatment or to leave the previous treatment unchanged. Patients with modifications in therapy were subsequently divided into two subgroups: one study group with CAD added to the initial therapeutic regimen and one control group in which any other drugs from a different class were associated with the previous treatment of HTN.

The study was carried out respecting the rights of patients according to the Declaration of Helsinki and the European legislation on personal data protection.

For statistical analysis, IBM SPSS Statistics 20.0 software at a significance level of $p \leq 0.05$ was used by a company specializing in research.

Kolmogorov-Smirnov test was used to analyze continuous data distribution, according to which appropriate tests were further used in analysis: independent samples t-test or Mann-Whitney U test for differences between means of two independent groups, Chi-square

TABLE 1. Baseline characteristics for the entire study group and two subgroups: patients with *versus* without CAD-I_1A in treatment between study visits

Characteristics	Total n (%) 391	Patients with CAD-I_1A treatment between study visits		P
		No n (%) 58 (14.8)	Yes n (%) 333 (85.2)	
Mean age	63.01 (±9.28)	63.98 (±9.99)	62,84 (±9.16)	0.388 (p>0.05)
Gender				
▪ Males	164 (41.9)	25 (43.1)	139 (41.7)	0.886 (p>0.05)
▪ Females	227 (58.1)	33 (56.9)	194 (58.3)	
Level of education				
▪ Primary school	107 (27.4)	16 (27.6)	91 (27.3)	0.705 (p>0.05)
▪ Secondary school	201 (51.4)	32 (55.2)	169 (50.7)	
▪ High education	83 (21.2)	10 (17.2)	73 (22.0)	
Mean BMI (kg/m^2)	30.34 (±5.44)	29.58 (±4.02)	30.47 (±5.64)	0.525 (p>0.05)
Obesity (BMI)				
No	202 (51.7)	31 (53.4)	171 (51.4)	0.778 (p>0.05)
Yes	189 (48.3)	27 (46.6)	162 (48.6)	
Abdominal obesity				
No	145 (37.1)	23 (39.7)	122 (36.6)	0.661 (p>0.05)
Yes	246 (62.9)	35 (60.3)	211 (63.4)	
LDL cholesterol*	138.03 (±33.26)	130.80 (±34.90)	139.11 (±33.00)	0.299 (p>0.05)
Diabetes mellitus				
No	278 (71.1)	47 (81.1)	231 (69.4)	0.084 (p>0.05)
Yes	113 (28.9)	11 (18.9)	102 (30.6)	
Smoking status				
No	356 (91)	54 (93.1)	302 (90.7)	0.803 (p>0.05)
Yes	35 (9)	4 (6.9)	31 (9.3)	
History of CVD				
No	197 (50.4)	31 (53.4)	166 (49.8)	0.670 (p>0.05)
Yes	194 (49.6)	27 (46.6)	167 (50.2)	
Sedentary lifestyle				
No	128 (32.7)	26 (44.8)	102 (30.6)	0.051 (p>0.05)
Yes	263 (67.3)	32 (55.2)	231 (69.4)	
Duration of sleep				
≤ six hours	173 (44.2)	31 (53.4)	142 (42.6)	0.152 (p>0.05)
> six hours	218 (55.8)	27 (46.6)	191 (57.4)	
Adherence to treatment				
No	31 (7.9)	5 (8.6)	26 (7.8)	0.794 (p>0.05)
Yes	360 (92.1)	53 (91.4)	307 (92.2)	
Mean BP	171.93 (±18.26)	167.83 (±18.63)	172.64 (±18.12)	0.052 (p>0.05)
Hypertension severity				
▪ Stage I	69 (17.6)	14 (24.1)	55 (16.5)	0.181 (p>0.05)
▪ Stage II	192 (49.1)	30 (51.7)	162 (48.7)	
▪ Stage III	130 (33.3)	14 (24.2)	116 (34.8)	
Mean heart rate	78.58 (±12.09)	75.80 (±11.61)	79.06 (±12.12)	0.078 (p>0.05)

BMI=body mass index; CAD-I_1A=central adrenergic drug selective on I_1-imidazoline receptors; CVD=cardiovascular disease; BP=blood pressure
*Data available from only 154 patients.

test (Fisher Exact Test) was used to analyze differences between categorical data.

Binary logistic regression using a stepwise likelihood ratio method (including multicollinearity testing and adjustments for major confounders) was employed for validation of predictors of BP control. ❑

RESULTS

In 391 patients with uncontrolled hypertension, therapeutic changes have been made as follows: 333 subjects received a CAD (intervention group) and for the remaining 58, drugs from any other therapeutic class were added (control group).

The CAD class was represented by rilmenidine in the vast majority of cases, alpha-methyl dopa in two cases and moxonidine in one case. The reality in the field led us to assimilate the study group with one that reflected the effects of an I_1A, and in particular of rilmenidine, on BP control, and has been renominated CAD-I_1A.

Baseline characteristics of the whole study group and the two study subgroups are summarized in Table I. No significant differences in baseline factors between the two subgroups have been noticed ($p>0.05$).

The total rate of BP normalization, following modifications in treatment between study visits, was 40.7% (159/391): 43% (144/333) after introduction of CAD-I_1A *versus* 26% (15/58) in the control group ($p<0.01$).

A binomial logistic regression was applied to test the association of BP normalization along with factors alleged to contribute to hypertension control such as gender, level of education, body mass index and abdominal obesity, diabetes mellitus, smoking status, history of cardiovascular disease, sedentary lifestyle, duration of sleep, self-declared adherence to treatment, HTN severity and presence of CAD-I_1A in the therapeutic regimen (Table 2). The binomial lo-

TABLE 2.
Binomial logistic regression for the association of BP normalization with baseline factors alleged to contribute to better control of hypertension

Factors	Category	B	Wald	P	OR	95% CI
Gender	Female	-0.211	0.764	0.382	0.809	0.504–1.3
Level of education	Primary school	0.344	1.087	0.297	1.41	0.739–2.69
	Secondary school	0.146	0.258	0.611	1.157	0.66–2.029
	High education		1.124	0.57		–
Obesity (BMI)	YES	0.069	0.077	0.781	1.072	0.657–1.749
Abdominal obesity	YES	-0.085	0.102	0.75	0.918	0.543–1.552
Diabetes mellitus	YES	-0.09	0.126	0.722	0.914	0.556–1.503
Smoking status	YES	-0.007	0	0.985	0.993	0.448–2.197
History of CVD	YES	-0.22	0.937	0.333	0.803	0.514–1.253
Sedentary lifestyle	YES	0.039	0.027	0.87	1.04	0.649–1.668
Duration of sleep	> six hours	-0.092	0.159	0.69	0.912	0.579–1.435
Adherence to treatment	YES	0.283	0.428	0.513	1.327	0.568–3.1
Hypertension severity	Stage I	2.063	33.72	0**	7.87	3.922–15.79
	Stage II	0.912	11.637	0.001**	2.49	1.474–4.205
	Stage III		33.873	0**		
Treatment with CAD – I_1A	YES	1.1	9.974	0.002**	3.003	1.518–5.942

BMI=body mass index; CAD-I_1A=central adrenergic drug selective on I_1-imidazoline receptors; CVD=cardiovascular disease; BP=blood pressure
**p< 0,01

TABLE 3.
Validation of hypertension severity and treatment regimen as predictors of blood pressure normalization according to the regression equation

Factors	Category	B	Wald	P	OR	95% CI
Hypertension severity	Stage I	1.961	33.755	0	7.107	3.667–13.771
	Stage II	0.863	11.592	0.001	2.371	1.443–3.898
	Stage III		34.057	0		
Treatment with CAD-I_1A	YES	1.046	9.454	0.002	2.847	1.461–5.547

Regression equation:
Ln ODDS (Normal BP) = -2.080 + (+1.046 x Treatment) + (+1.961x Stage I hypertension at baseline) + (+0.863 x Stage II hypertension at baseline),
where every variable can have values between 0 and 1
Stages of hypertension: I=140-159/90-99 mm Hg; II=160-179/100-109 mm Hg; III=≥180/110 mm Hg
CAD-I_1A=central adrenergic drug selective on I_1-imidazoline receptors

Evolution of symptoms between study visits	Treatment with CAI	Treatment without CAI	P
Variation of headaches (%)	**-52.6**	**-39.7**	**< 0.05****
Variation of fatigue (%)	-34.5	-25.9	> 0.05
Variation of dizziness (%)	-37.2	-31	> 0.05
Variation of facial hyperemia (%)	**-17.1**	**-5.2%**	**< 0.01****
Variation of tachycardia (%)	-14.4	-1.7	> 0.05
Variation of palpitations (%)	-11.1	-3.4	> 0.05
Variation of insomnia	-1.2	-5.2	0.05

CAD-I1A=central adrenergic inhibitors selective on I1-imidazoline receptors.
*Statistically significant, P < 0.01

TABLE 4. Tolerability of CAD selective on I_1-imidazoline receptors in comparison with other therapeutic regimens not including CAD-I_1A

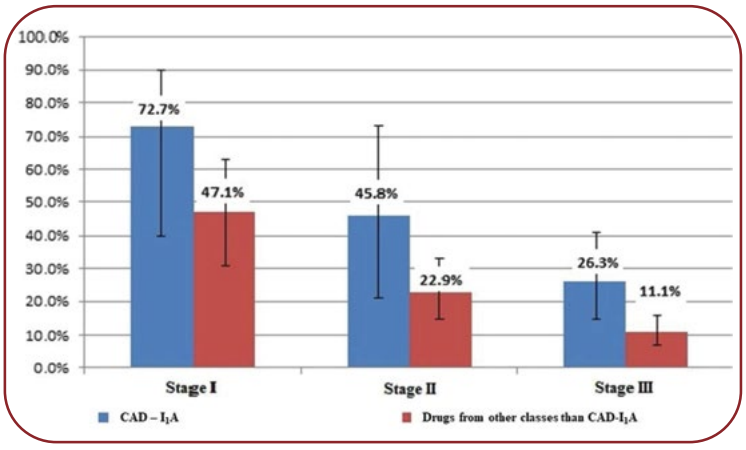

FIGURE 1. The probability of blood pressure normalization according to the severity of hypertension at baseline and the presence of CAD-I_1A in the therapeutic regimen (CAD-I_1A=central adrenergic drugs selective on I1-imidazoline receptors)

gistic regression has been validated as a statistically significant predictor of BP normalization: the type of treatment (presence or absence of CAD-I_1A in the therapeutic regimen) (Wald=34.057; p<0.001) and the stage of hypertension at baseline, with better improvement for less severe hypertension at baseline (Wald=9.454; p<0.01), but not the comorbidities, lifestyle or socio-economic factors (Table 3).

Prediction of BP normalization was calculated for each hypertension stage at baseline after adding CAD-A1I compared with other therapeutic changes between study visits. The probability of BP normalization was significantly higher in the group with added CAD-A1I to treatment than the control group (CI 95%): 72.66% (40%–91%) for stage I hypertension, 45.77% (21%–73%) for stage II hypertension and 26.25% (15%-41%) for stage III hypertension (Figure 1).

Tolerability of CAD-A1I was very good in comparison with other therapeutic regimens not including them, with a significant advantage in reducing headaches and facial hyperemia (Table 4). ❑

DISCUSSIONS

Moxonidine and rilmenidine act primarily on the central I_1-imidazoline receptors, with little impact on alpha-2 receptors which are mainly responsible for the side effects of the first generation of CAD (21). The antihypertensive effect of CAD-I_1A consists in the reduction of vascular resistance while sparing heart rate and cardiac output (22-27). A complementary mechanism of their action could be the presynaptic inhibition of transmitter release from postganglionic sympathetic neurons (25). The efficiency of moxonidine and rilmenidine in lowering BP was tested in comparative studies with many other antihypertensives such as clonidine, alpha-methyldopa, diuretics, alpha-blockers, beta-blockers, calcium antagonists and angiotensin-converting enzyme inhibitors (18, 19, 29), but very few studies have questioned their effects in combination with other classes of antihypertensives with the CAD-I_1A initiation of therapy (13, 30).

In our observational prospective study, we followed patients with uncontrolled HTN under at least two antihypertensives after their physicians modified their therapeutic regimen to improve BP control. In most cases, the background treatment consisted of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, and thiazide-like diuretics, in variable combinations. The addition of a new drug was done in step 3 of treatment, but also in step 2 when one of the three classes of drugs generally recommended proved to not be well tolerated. In patients for whom the intervention consisted of addition of a new class of drug, we compared the benefits of introducing a CAD with adding a drug from any other classes.

One of the most surprising findings of our study was that medical practitioners preferred to introduce CAD-I_1A instead of spironolactone

when a better control of HTN was needed. It was an unexpected result as long as, in ESH guidelines from the time the study was conducted, this particular class of drugs was excluded from the main therapeutic recommendations and spironolactone was considered a first-line drug for the upgrade of a therapeutic regimen that failed to control HTN (17). The PATHVWAY-2 study showed the superiority of spironolactone compared to bisoprolol, doxazosin, or placebo by introducing it into the fourth line of treatment in patients with apparently resistant HTN (31). However, spironolactone has an inadequate tolerability profile (mastodynia or gynecomastia and sexual dysfunction in men, hyperpotassemia) and must be avoided in patients with advanced chronic kidney disease with an estimated glomerular filtration rate of less than 30 mL/min/1.73 m^2 (1). This may be an explanation for the reluctance of doctors toward spironolactone, as other real-life studies have shown. In a survey conducted in the USA, only 9% of patients with apparent resistant hypertension were treated with spironolactone (32). On the other hand, CAD-I_1A have the advantage of optimal cardiac and renal tolerability (29, 33, 34) and are metabolically neutral (28). In our study, the old CAD did not constitute an option due to their known side effects, nor the moxonidine which belongs to the CAD-I_1A class, but it was much less promoted and distributed in our country than rilmenidine. Last but not least, we must take into account the fact that our study has not addressed patients with resistant HTN but those with therapeutically uncontrolled HTN. The effect of pharmacological treatment changes was not biased by other factors recognized for their influence on BP control as long as the distribution of demographic or socio-economic factors, some lifestyle factors or comorbidities was similar between study groups. However, it is worth mentioning that we did not evaluate the impact of salt or alcohol consumption more precisely, and the treatment adherence was assessed by the self-declaration of the patients. Also, due to the non-interventional nature of the study, we were not able to evaluate the contribution of changes in therapy after optimization of antihypertensive drug doses.

The effectiveness of CAD-I_1A might reside in the fact that it counteracts a strong pathogenic link of HTN. The sympathetic nervous system activation was objectified in 40-65% of hypertensive patients, increased with the severity of high BP, and characterize some important clinical forms of HTN, such as those associated with obesity and diabetes mellitus (35), chronic kidney disease (36), sleep apnea syndrome (37) or stress and anxiety (38-40) and for some of these conditions, the benefit of rilmenidine administration has been already proven (30, 41).

The results of our observational study should be taken into consideration with caution, but they can constitute a working hypothesis for a randomized prospective study to test the utility of CAD-I_1A compared to other classes of antihypertensives for a better BP control in treatment step 2 or 3. ❑

CONCLUSIONS

Until present CAD-A1I has been analyzed mostly in monotherapy, regardless of other antihypertensive drugs. The novelty of our study is that it evaluates the effects of this class in complementarity with the commonly used antihypertensives. Its results indicate the benefit of reconsidering the place of central I_1-imidazoline agonists in the treatment regimen of patients with uncontrolled hypertension based on their efficiency and safety in association with the main classes of antihypertensive drugs recommended by current guidelines. They could represent a good therapeutic option in any stage of hypertension if one of the recommended classes is not tolerated or in addition to them, especially in clinical forms of hypertension with high adrenergic drive such as those associated with obesity, diabetes mellitus, chronic kidney disease, sleep apnea or stress. ❑

Conflicts of interest: The corresponding article of this article, Oana Florentina Gheorghe-Fronea (OF G-F), on behalf of all authors of this work, declares that two of the authors – ROD and OF G-F – had, at various times in the last 10 years, conference contracts with Servier Pharma Laboratories – Romanian Division.

Financial support: OF G-F, the corresponding author of the current article, on behalf of all authors of this work, declares that the study the present article refers to was realized with the financial support of Servier Pharma Laboratories – Romanian Division.

Aknowledgments: We are expressing our gratitude to all physicians who participated as investigators in this study, without whose efforts this work would not have been accomplished.

List of investigators: ANTON Florin; ARAMA Laura; BANICA Luminita; BELADAN Carmen; BENGUS Cristina; BIRZU Raluca; BISOC Alina; BOB Flaviu-Raul; BOERU George; CHISCANEANU Teodor; COLTUC Valentin Radu; COZMA Alexandru; DARABANTIU Dan; DIACONESCU Sabina; DOBRIN Ruxandra; DUMITRASCIUC Mihaela; GOLDA Flavius; GRINEI Florentin; GUTU Alina; HAIDUCU Lenuta; HOROVITZ Monica; IOSIPESCU Laura; LUCA Elena; MAGHERU Sorina; MALAI Adina; MITRE Adriana; MOGA Rodica; MOLFEA Vlad Alexandru; NEICONI Iliana; NICA Aura; NICOLIN Mihaela; PODOLEANU Cristian; POP Ligia; POPESCU Monica; RANCEA Raluca; RAU Marcela; RUSU Ramona; SCARLATESCU Simona; STATESCU Cristian; STEFAN Liliana; STOIAN Florian; TRONARU Violeta; TUDOR Cecilia; UNGUREANU Anda Laura

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