EFFECT OF ORAL L-ARGININE SUPPLEMENTATION ON POST-EXERCISE BLOOD PRESSURE IN HYPERTENSIVE ADULTS: A SYSTEMATIC REVIEW WITH META-ANALYSIS OF RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES

Key words: L-arginine; Hypertension; Post-exercise; Heart; Systematic Review

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VEV supervised the study, draft the manuscript, and gave final approval for the version submitted for publication.

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The authors declare absence of financial and non-financial interests.

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SUMMARY AND KEYWORDS

Objectives: We studied the effects of oral L-arginine on post-exercise blood pressure (BP). **Update:** Throughout October 2020 and February 2021, the electronic databases Medline, Web of Science, CINAHL, Embase, Cochrane, Bireme, Open Gray, MedRxiv, Clinical Trials and Scopus were considered. The terms enforced to search randomized, double-blind and placebo-controlled clinical trials were, "Arginine" AND "Post-exercise". Three studies were involved in the meta-analysis, the original results of the three studies demonstrated a trend related to L-arginine intervention. The 95% CI ranged from -7.94 to -2.14 with a combined effect size of -5.04 for systolic BP and -4.96 to -0.97 with a combined effect size of -2.96 for diastolic BP. **Perspectives and projects:** Our meta-analysis revealed a combined effect size of 3.40 (p=0.0007) for systolic BP and 2.91 (p=0.004) for diastolic BP supportive of L-arginine intervention. **Conclusions:** Our review delivers evidence that oral L-arginine supplementation has the potential to reduce post-exercise systolic and diastolic BP in hypertensive patients.
Key-words: L-arginine; Hypertension; Post-exercise; Heart; Systematic Review

Objectifs: Nous avons évalué les effets de la L-arginine orale sur la tension artérielle après l'exercice. **Actualités**: Tout au long d'octobre 2020 et février 2021, les bases de données électroniques Medline, Web of Science, CINAHL, Embase, Cochrane, Bireme, Open Gray, MedRxiv, Clinical Trials et Scopus ont été étudiées. Les termes utilisés pour rechercher des essais cliniques randomisés, en double aveugle et contrôlés par placebo étaient «Arginine» ET «Post-exercice». Trois études ont été impliquées dans la méta-analyse, les résultats originaux des trois études ont démontré une tendance liée à l'intervention avec la L-arginine. L'IC à 95% variait de -7,94 à -2,14 avec une taille d'effet combiné de -5,04 pour la PA systolique et de -4,96 à -0,97 avec une taille d'effet combiné de -2, 96 pour la PA diastolique. **Perspectives et projets**: Notre méta-analyse a révélé une taille d'effet combiné de 3,40 (p = 0,0007) pour la tension artérielle systolique et de 2,91 (p = 0,004) pour la tension artérielle diastolique en faveur d'une intervention avec la L-arginine. **Conclusions**: Notre revue fournit des preuves que la supplémentation orale en L-arginine a le potentiel de réduire la tension artérielle systolique et diastolique post-exercice chez les patients hypertendus.

Mots clés: L-arginine, hypertension artérielle, post-exercice, cœur, revue systématique.

INTRODUCTION

Cardiovascular diseases are the primary cause of morbidity and premature death worldwide [1]. Amongst the adjustable factors, hypertension represents about 90% of myocardial infarction events [2]. Hypertension affects approximately 40% of adults globally [3] and has increased in the number of diagnoses in children and adolescents over the past few years [4]. It is well recognized that beneficial changes in lifestyle improve blood pressure (BP) and are commonly described as alternatives to the pharmacotherapies [5].

In this way, it is well recognized that dietary methods for hypertension (Dietary Approaches to Stop Hypertension - DASH) are effective in regulating BP [6]. It is hypothesized that this is by reason of the fact that the DASH diet is composed of proteins rich in L-arginine [7]. L-arginine is an amino acid converted directly from citrulline by the kidney; it was revealed over a century ago [8] and is the main substrate for the production of nitric oxide (NO). The low bioavailability of L-arginine as a substrate hinders the production of NO [9].

Like so, physical exercise similarly performs an important role in BP regulation. Amongst the advantages that this promotes, we include the reduction in post-effort BP values. Physical exercise elevates blood flow and stimulates the production of NO [10-11]. Taking into consideration that low NO production is meticulously linked to the development and maintenance of hypertension, increasing levels of NO production can be crucial in the treatment and prevention of hypertension [8]. Moreover, physical activity was capable of lowering its values in a single post-exercise aerobic exercise session, promoting a condition known as post-exercise hypotension (PEH) [12]. Consequently, physical exercise has an important role in BP regulation.

With the number of hypertensive individuals increasing internationally, the number of pharmacotherapies for managing hypertension has similarly increased lately. This can cause other types of health problems for individuals, since those who take antihypertensive drugs are exposed to their side effects; for example, exacerbated electrolyte dysfunction, kidney damage, syncope, cerebral hyper-perfusion and exacerbated hypotensive effects [13-14]. The requirement to explain alternative new treatments for this disease is justified.

In recent decades, a series of randomized clinical trials have proposed to evaluate the effects of L-arginine on BP regulation. Yet, the small number of participants in the samples and the quality of these trials varied, bestowing a necessity for further analysis on the topic. Concerning the points discussed above, the following questions were raised: Does L-arginine ingested before exercise influence the cardiovascular system? Is there any interaction with hypertension? So, we anticipated to estimate the effect of oral L-arginine supplementation on BP in hypertensive individuals following physical exercise, by conducting an analysis of randomized, double-blind, placebo-controlled clinical trials.

METHOD

This systematic review was undertaken between October 2020 and February 2021, according to the protocol Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) [15]. The project for this review was registered in PROSPERO number CRD42021229813.

Search strategy

The searching and selection of these articles was reached via the acronym PICOS, where each letter represents a component: P – population; I - intervention/exposure; C -

comparison/control, O – outcome; and S - study design. After defining the components, the keywords were searched using the Medical Subject Headings (MeSH), with the terms "L-arginine" AND "Post-exercise". The electronic databases enforced in this research were Medline, Web of Science, CINAHL, Embase, Cochrane, Bireme. Searches were also achieved from other sources such as a database containing gray literature (Gray literature) Open Gray, MedRxiv, Clinical Trials and Scopus.

When the studies that made reference to the keywords were identified, a screening was achieved in the database itself via the filter: “study in humans.” These were then exported to the Rayyan QCRI program (Qatar Computing Research Institute, Qatar) [16], where, above and beyond the filters mentioned above, “Blood Pressure” was added, with duplicates being omitted.

The following data from the eligible studies were obtained and stored in a Microsoft Excel spreadsheet: title, author, year, objective, conclusion, sample and database. With this information, studies that were unable to complete the proposed theme for this review were omitted.

Articles approved in this final phase were read fully by two independent researchers, with a third researcher necessary for the decision, in case of disagreement about the inclusion or not of an article. After selecting the final articles [17,18,19], a table was designed with the following information: author and year, time of therapy, health status, gender, age, dosage of intervention, baseline blood pressure, antihypertensive drugs and adverse effects (Table 1).

Study Eligibility criteria

Population (subjects): The population comprised of studies performed on human subjects of either gender, Clinical diagnosis of pre-hypertension, arterial hypertension or

blood pressure measurements >120mmHg for systolic pressure and >80mmHg for diastolic pressure, of all ages and if they practiced physical activity or not. *Intervention:* The study intervention was based on the use of L-arginine supplementation prior to an exercise session. No criteria were established regarding the dose, the form wherein it was administered and the form of physical exercise. *Comparison/Control:* The comparison was accomplished with intake of placebo. *Outcome:* The main outcome was blood pressure (mmHg). *Study design***:** The references chosen included randomized trials, double blind and controlled designs.

Analysis of the risk of bias

The risk of bias analysis was executed under the guiding principles of the Cochrane organization [20], via the Review Manager program (RevMan 5.4.1) [21]. The approval for assessing the risk of bias in randomized clinical trials is a tool based on the assessment of domains, which is a critical assessment made discretely to different aspects of the risk of bias [22]. The evaluation is split into seven domains: “Random sequence generation”, “Allocation concealment”, “Blinding of participants and personnel”, “Outcome assessment blinding”, “Incomplete outcome data”, “Selective reporting” and “Other Bias”. At that point, classification is split into three direct responses, “Low risk” for low risk of bias, “Unclear risk” for questions not explained by the author of the original article and “High risk” for high risk of bias. Our verdict was based on the “Review author's judgment and criteria for judgment” table by Carvalho *et al.* [22].

The risk of bias analysis was finalized by two independent authors. A third author was required if there was a discrepancy in their judgments. We demonstrate below the result of the analysis of risk of bias in the studies (Figure 1 and Figure 2).

Data extraction and statistical analysis

For data extraction, the Web plot Digitizer program [23] (https://automeris.io/WebPlotDigitizer/) was enforced, where the datasets were removed from the graphs presented in the studies. If extraction via the software was impracticable, the authors of the appropriate article were contacted by e-mail. We adopted the criterion of extracting the data referring to 10 minutes following exercise, the mean and standard deviations were logged. After extraction, the data were organized in Microsoft Excel, and then handled in the Review Manager Program (RevMan 5.4.1) to develop Meta-analysis.

Heterogeneity was reached by the I^2 test, where a number >50% was considered to indicate substantial heterogeneity between the tests [24].

For the values of "CI" and "Test for overall effect size", values of $p < 0.01$ (or, <1%) were assumed as significant.

All data was created by the Review Manager Program (RevMan 5.4.1)

RESULTS

A total of 309 studies were identified through the searches in all the databases. Following removal of duplicates (*n*=164), 145 publications were screened for inclusion. Of these, 128 records were excluded after reviewing their title and/or abstract. The remaining 17 papers were selected for full text reading and 14 were excluded because of the characteristics of intervention and measurement procedures. Finally, three studies were included in the systematic review. A flowchart of the scientific research literature search and study selection is demonstrated in Figure 1 and the features of the selected studies are presented in Table 1.

We included studies published between 2012 and 2019. The sample size was 20 participants per study, for a total of 60 participants. All included studies are randomized, double-blind and placebo-controlled. Three studies have BP as the primary outcome. The

extent of the intervention varies from 1 day to 32 days, and the dose of L-arginine varies from 6 to 8 grams/day. No adverse effects from L-arginine consumption were detailed in any of the three studies. Our review endeavored to assess the effects of post-exercise L-arginine on the hypertensive population on either gender, nonetheless, only one of the three studies included had all male subjects. All studies demonstrate evaluations in hypertensive and pre-hypertensive individuals.

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Figure 3. Flowchart of study selection

Table 1. Characteristics of the studies included in the meta-analysis

Effects of Arginine on BP

Our search recognized three studies that achieved the inclusion criteria for our study and all were involved in the meta-analysis.

The net changes and 95% confidence intervals (CI) corresponding to systolic and diastolic BP in each trial are illustrated in Figure 4 and Figure 5. Compared to the placebo, the intervention with oral L-arginine was linked with a mean change ranging from -7.59 to -1.50 mmHg for systolic BP and from -4.17 to -2.83 mmHg for diastolic BP. The original results of the three studies presented a trend related to L-arginine intervention. The 95% CI ranged from -7.94 to -2.14 with a combined effect size of -5.04 for systolic BP and -4.96 to -0.97 with a combined effect size of -2.96 for diastolic BP. Our meta-analysis exhibited a combined effect size of 3.40 ($p=0.0007$) for systolic BP and 2.91 ($p=0.004$) for diastolic BP in favor of L-arginine intervention. We detected a heterogeneity of 21% considered trivial for diastolic BP and 0% for systolic BP. No sensitivity analysis was accomplished attributable to the low number of studies included.

Figure 4. Meta-analysis of the effect of oral arginine supplementation on post-exercise systolic BP in hypertensive patients compared to placebo.

Figure 5. Meta-analysis of the effect of oral arginine supplementation on post-exercise diastolic BP in hypertensive patients compared to placebo.

DISCUSSION

Our meta-analysis presented evidence, from a statistical point of view, that oral supplementation with L-arginine, in comparison with placebo, lessened BP in post-exercise in hypertensive patients.

L-arginine is a semi essential amino acid that assists as a substrate for the making of nitric oxide (NO), a vasodilator produced by the vascular endothelium. The reduction in NO production is meticulously linked to the increase in BP in humans and animals [25]. NO is a vasodilation regulator through the conversion of L-arginine to L-citrulline. Accordingly, the vascular endothelium has a central role in maintaining cardiovascular health [26] and the foremost regulator of BP [27].

Therefore, after a single session of exercise there is a reduction in BP, a mechanism acknowledged as post-exercise hypotension (PEH). This phenomenon triggered by the autonomic nervous system is closely linked to the withdrawal of the sympathetic nervous system [28]. Sympathetic nerve activity and the later release of norepinephrine mediate vasoconstriction and elevate vascular resistance [29], which is linked with the dilated effect of the exercised muscle. Consequently, the PEH is an important physiological mechanism [30] and can have a central role in regulating hypertension, as the extent of PEH is related to BP [31].

The study conducted by Lima *et al*. [18] specified that 7 grams of L-arginine prior to a single session of aerobic exercise was unable to influence systolic BP, but encouraged a moderate PEH in diastolic BP in hypertensive males and females with a mean age of 51 years.

Cassonato *et al.* [17] studied 20 pre-hypertensive and hypertensive adult, females where the participants ingested L-arginine pre isokinetic strength test. The authors revealed that 8 grams of L-arginine potentiated the hypotensive effects on systolic BP after exercise.

This result has been emphasized previously in the scientific research literature. L-arginine was demonstrated to be effective at reducing BP in a study wherein 61 pregnant women with a mean age of 29 years old. The sample was comprised of pregnant women with pre-eclampsia. The study population (that was included in the study) was from the 29^{th} week of gestation, following 3 grams of L-arginine, as a daily supplement for 3 weeks. It was revealed to be effective in lowering the systolic (134.2 ± 2.9 vs. 143.1 ± 2.8 mmHg) and diastolic (81.6 ± 1.7 vs. 86.5 ± 0.9 mmHg) BP, and reducing mean BP (101.8 ± 1.5 vs. 108.0 ± 1.2 mmHg) in relation to the placebo group. To finish, L-arginine was capable of increasing plasma levels of L-citrulline, an important amino acid in the control of BP [32].

Martina *et al.* [33], studied for 6 months some 24 type 2 Diabetes Mellitus and hypertensive males with a mean age of 64 years. They revealed that treatment with L-arginine (1200 mg once a day) and N-acetylcysteine (600 mg twice a day) were effective at reducing BP.

Figueroa *et al.* [27] assessed the effects of watermelon supplementation on 9 individuals of either gender and pre-hypertensive individuals. Subjects were randomly assigned to six weeks of watermelon supplementation (L-citrulline/L-arginine, 2.7 g/1.3

g/day, respectively) or placebo and, subsequently a four-week elimination period; then crossover. This study demonstrated that supplementation of these essential amino acids for the production of NO was capable of reducing systolic BP at rest (7 ± 2 mmHg), after the period of treatment.

Schwedhelm *et. al.* [34] and Waugh *et al.* [35] specified that this is since the oral intake of L-citrulline increases circulating levels of L-arginine in the plasma, on account of its conversion from L-citrulline to L-arginine. Besides, it has been reported in the scientific research literature that watermelon increased plasma L-arginine levels by up to 22% [36].

Since PEH is considered an important tool to decrease blood pressure levels in pre-hypertensive and hypertensive patients, the search for interventions that enhance these effects is important for blood pressure controls in the short, medium and long term [25].

Some studies contend that citrulline intake can be considered more advantageous to achieve the effects of PEH when compared to arginine intake. These aspects are chiefly related to the dose-effect complex of these interventions used. Of late, Agarwal *et al.* [37], demonstrated that when these two compounds are ingested in a similar dosage, citrulline is able to increase the levels of arginine concentration in plasma compared to only arginine intake [37]. The impact on the accessibility of arginine in plasma is mainly linked to its extraction in the intestine and then it is absorbed [25].

The ingestion of citrulline malate 6g before 40 minutes of submaximal aerobic exercise at 60% to 70% of HR, prolonged the reduction in systolic blood pressure after 60 minutes of exercise (−15.01 ± 2.57 mmHg vs. −6.30 ± 3.60 mmHg, p = 0.03). Additionally, it decreased diastolic blood pressure in the waking period (−13.93 ± 1.96 mmHg vs. −6.85 ± 2.57 mmHg, p = 0.027) and 24 hours after exercise (-13.83 ± 1.93 mmHg vs. −7.64 ± 2.58 mmHg, p = 0.047) [38].

A recent review study endeavored to accumulate some meta-analyzes and discuss the effects on reducing blood pressure levels by comparing the two interventions (arginine versus citrulline) [25]. A recent meta-analysis [39] established that citrulline supplementation may have a greater effect in reducing blood pressure levels (4.1 / 2.08 to 7.54 / 3.77 mmHg) [39] when compared to arginine (5.39 / 2.66 mmHg) [9]. Yet, the study [39] was retracted since the authors considered that the data were unreliable. Against this background, the discussion about the potential of these interventions still requires investigations that are more robust.

Dong *et al*. [9] completed a study on the performance of L-arginine intake in hypertensive patients. The cited systematic review and meta-analysis included 11 studies and verifies the studies presented up until now. The study assessed a sample of 387 subjects, of both genders aged 21 to 66 years. It was detected that L-arginine positively influences BP. The meta-analysis of 11 studies stated that this constituent reduced the values of systolic and diastolic BP.

Like this, the studies revealed that L-arginine directly influenced BP values, both by way of treatment [9,27,32,33] and during post-exercise, potentiating PEH [17,18], in hypertensive patients. Then again, the third study in our systematic review, Lima *et al*. [19], assessed 20 hypertensive females and reported that L-arginine improved baseline BP values, increased baseline NO production but was unable to influence the improvement in PEH. The author stated the lack of improvement in BP values after exercise as a result of the low production of NO and justified the low production of NO after exercise with the low intensity of the proposed activity, based on a study that evaluated low intensity exercise and found no change in the NO production. It is imperative to highlight that, unlike low intensity exercise, high intensity exercise exhibited an increase in its production [40].

Lima *et al*. [18] justified the absence of improvement in post-exercise values with the possibility of a clearance throughout exercise. Low intensity exercise may well contribute to this hypothesis. Still, since they collected blood only 10 minutes after the termination of exercise, this prevents an incisive concluding statement.

Our review had strict inclusion criteria. All studies included were randomized, double-blind and placebo-controlled clinical trials, that minimized bias and suggested high internal validity. We only undertook studies with L-arginine for post-exercise intervention in hypertensive patients, so the BP effects were largely because of the L-arginine.

Study limitations

The quality of the outcome of a systematic review is meticulously connected to the quality of the studies accessible on the proposed subject. Our study has a number of restrictions, arising from the original studies, so caution is required when interpreting the data. The scientific research literature regarding L-arginine is scarce, and we evaluated its influences on a specific population, which gave us a small sample, limiting the randomization process and, increasing the potential influences of confounding factors. The heterogeneity of the sample is another factor that requires careful consideration in this study. A reference examined included males and females with a mean age between 50 and 70 years old, practitioners and non-practitioners of physical exercise, hypertensive and pre-hypertensive. Hereafter, caution must be applied when interpreting their results.

Cassonato *et al.* [17] analyzed subjects with a body mass index (BMI) greater than 26, considered as pre-obese by the World Health Organization (W.H.O.) [41]. Furthermore, we emphasize the nonappearance of nitrite and nitrate bioavailability markers in that study, without these markers we can only assume that L-arginine positively influenced PEH.

A restriction of the study conducted by Lima *et al.* [18] was the inclusion of males and females. We assume that mixing genders may have influenced their outcomes.

Lima *et al*. [19] presented an experimental group with total cholesterol values of 258 mg/dl, well above the model values of 190 mg/dl as considered by the Brazilian Society of Cardiology [42]. The quoted study intended to evaluate the acute effects of L-arginine on post-exercise, but then the results of the exercise sessions were recorded in 32 days, and with the usage of L-arginine throughout this period. We conceived that an adaptation of the organism to the substance may have arisen and the extent of the acute effect of L-arginine has been compromised.

CONCLUSION

This review of randomized, double-blind and placebo-controlled clinical trials with meta-analysis offers evidence that oral L-arginine supplementation has the potential to reduce post-exercise systolic and diastolic BP in hypertensive patients. Nevertheless, we conclude that extra randomized clinical trials are required to better understand the effects of L-arginine on cardiovascular parameters in general and the necessity for larger samples.

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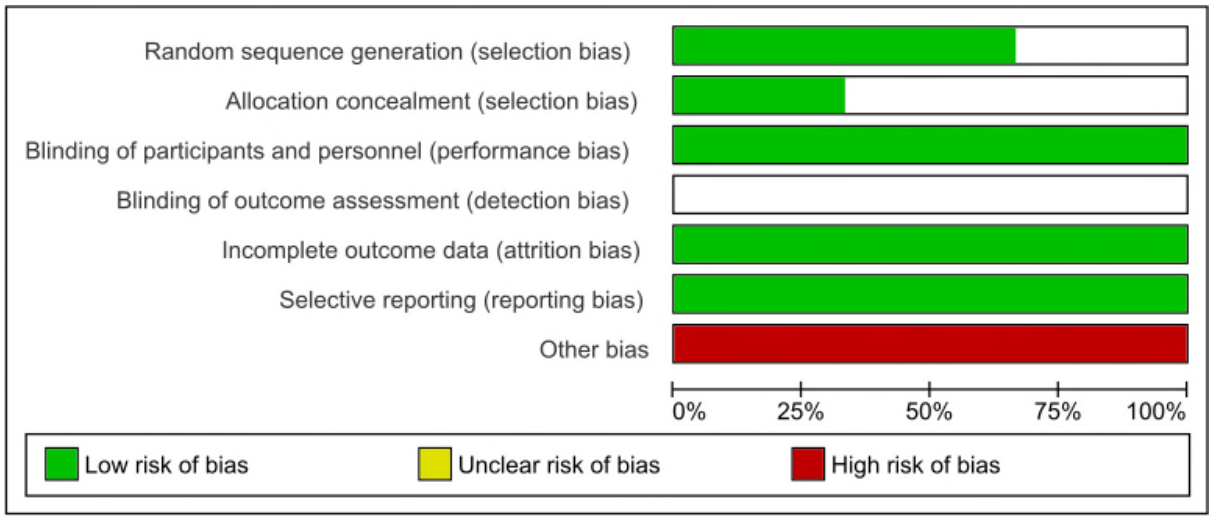
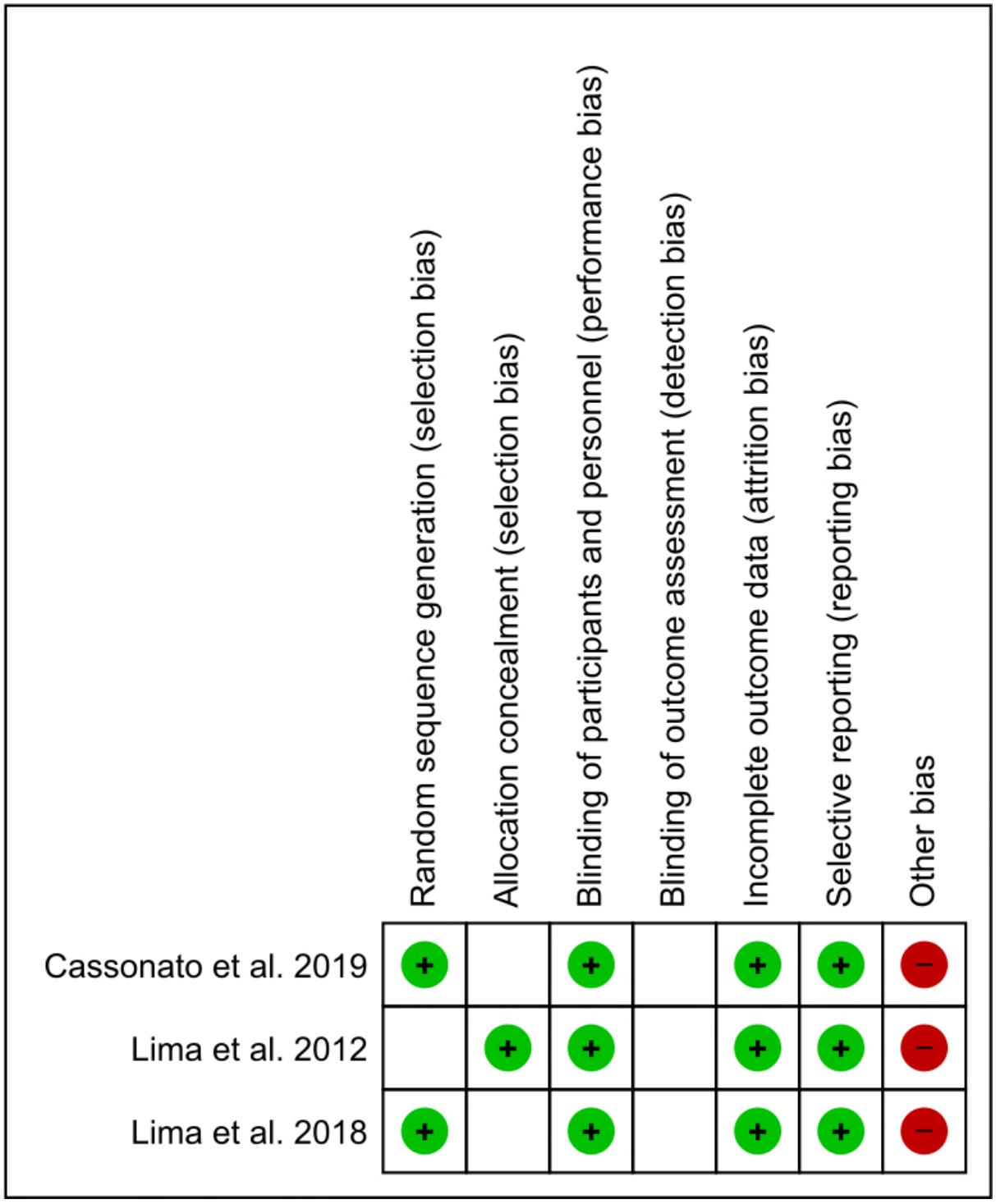

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Figure 1


Random sequence generation (selection bias)
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Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Cassonato et al. 2019
Lima et al. 2012
Lima et al. 2018

Figure 2

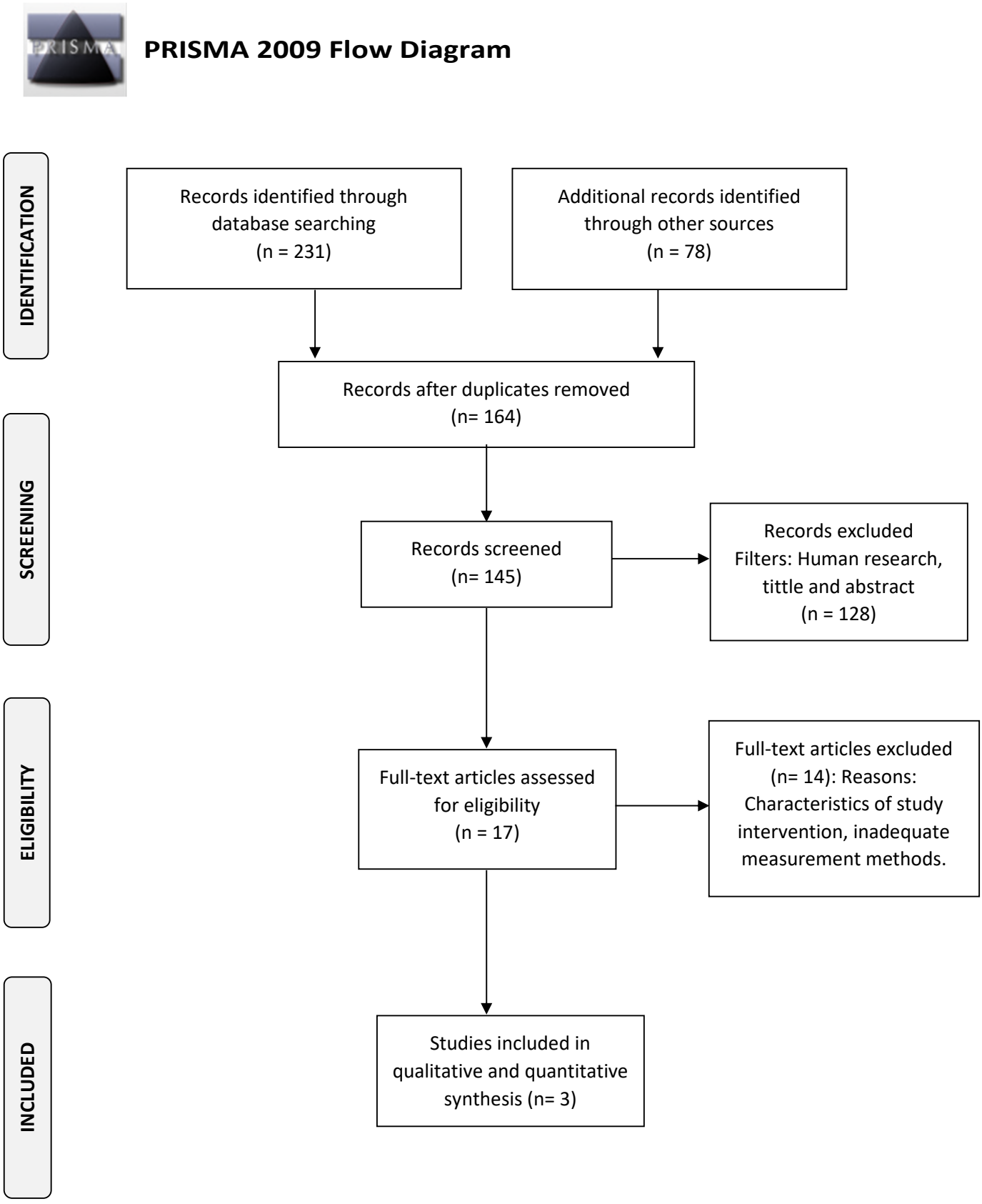
PRISMA 2009 Flow Diagram
IDENTIFICATION
SCREENING
ELIGIBILITY
INCLUDED
Records identified through database searching (n = 231)
Additional records identified through other sources (n = 78)
Records after duplicates removed (n= 164)
Records screened (n= 145)
Records excluded Filters: Human research, tittle and abstract (n = 128)
Full-text articles assessed for eligibility (n = 17)
Full-text articles excluded (n= 14): Reasons: Characteristics of study intervention, inadequate measurement methods.
Studies included in qualitative and quantitative synthesis (n= 3)

Figure 3

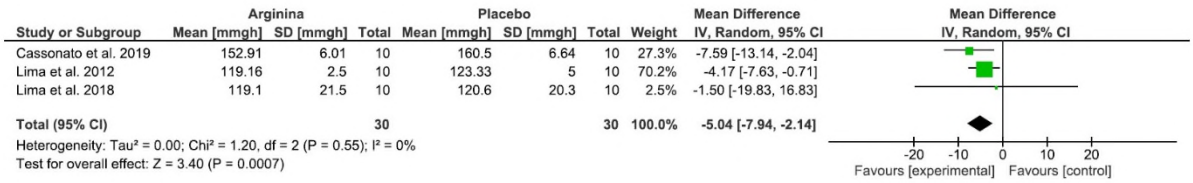

Figure 4

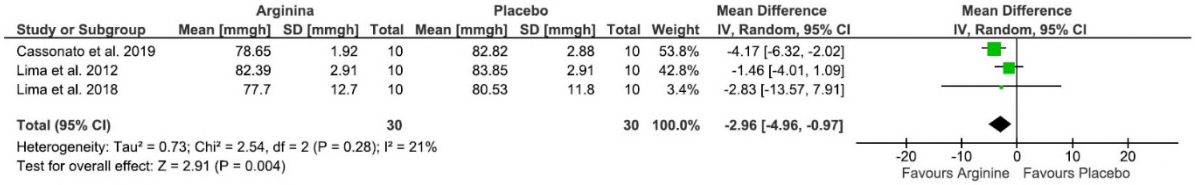

Figure 5

Table I - Characteristics of the included trials in the meta-analysis.

Authors and years	Therapy Duration (weeks)	Healthy Status	Sex (M or F)	Mean age (y)	L-arginine dose (g/day)	Baseline BP (mmHg)	Antihypertensive drug use	Adverse effects
Casonatto et al. 2019	1 day	Pre hypertension and hypertensive	0/20	Arg: 70,6 ± 2,2 PLA: 72,5 ± 1,6	8	Arg: 121,5/73,8 vs. Pla: 124,3/75,8	Have not to use medicines that increase blood flow	Without evidence of damage to patients' health
Lima F.F et al. 2018	2 days	Hypertensive	5/15	51.47 ± 1.24	7	Arg: 124,1/80,3 vs. Pla: 120,2/78,0	Not use beta blockers and calcium channel blockers	Without evidence of damage to patients' health
Lima J.M et al. 2012	32 days	Hypertensive	0/20	Arg: 50.0 ± 1.8 PLA: 51.5 ± 1.6	6	Arg: 137,0/ 87,2 vs. Pla: 134,8/84.8	All volunteers used medication antihypertensive class of angiotensin-converting enzyme inhibitors	Without evidence of damage to patients' health