Pattern prescription drugs for systemic hypertension in primary health care: systematic review and meta-analysis

Padrão prescritivo de medicamentos para hipertensão arterial sistêmica na atenção primária em saúde: revisão sistemática e meta-análise

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RESUMO

Investigamos publicações científicas sobre o padrão prescritivo de medicamentos para hipertensão arterial sistêmica e uso de diretrizes na atenção primária em saúde por revisão sistemática e meta-análise. Os artigos foram selecionados nas bases de dados PubMed, Web of Science e LILACS, de acordo com as declarações PRISMA, de 2004 a 2020. A revisão sistemática mostrou um padrão de prescrição superior para terapia combinada (52,9%). A metanálise confirmou a superioridade para a terapia combinada (OR 1,76; IC 1,29 - 2,41). Foi observada maior prevalência de monoterapia no estudo Sueco (98%) e terapia combinada no Nigeriano (98%). Maior frequência prescritiva de inibidores da enzima de conversão da angiotensina em Trinidade (64%); diuréticos (64%), betabloqueadores (63%) e bloqueadores dos canais de cálcio (53%) na Nigéria; e bloqueadores dos receptores da angiotensina (43%) em Portugal. Quanto ao uso das diretrizes, 53% dos estudos relataram a sua utilização na prescrição de anti-hipertensivos na atenção primária em saúde.

Palavras-chave: Atenção primária em saúde. Diretrizes para prática. Hipertensão arterial sistêmica. Prescrição de medicamentos. Revisão sistemática.

ABSTRACT

We investigated scientific publications on the prescription pattern of systemic hypertension drugs and use of guidelines in primary health care by systematic review and meta-analysis. Articles were selected in the PubMed, Web of Science and LILACS databases, according to the PRISMA statements, from 2004 to 2020. The systematic review showed a higher prescription pattern for combination therapy (52,9%). The meta-analysis confirmed the superiority of prescription for combination therapy (OR 1.76, CI 1.29 - 2.41). Was observed higher monotherapy prevalence in the Swedish study (98%) and combined therapy in Nigerian (98%). Higher frequency prescriptive of angiotensin-converting enzyme inhibitors in Trinidad (64%); diuretics (64%), beta blockers (63%), and calcium channel blockers (53%) in Nigeria; and angiotensin-receptor blockers (43%) in Portugal. Regarding the use of guidelines, 50% the studies reported their use for the prescription of antihypertensive in primary health care.

Keywords: Prescription of drugs. Primary health care. Practice guideline. Systemic hypertension. Systematic review.

INTRODUCTION

Systemic hypertension is a common disease that affects multiple target organs, such as those of the cardiovascular system and the kidneys, with major morbidity and mortality,[1-4] being an important risk factor for cardiovascular disease.[3,5] The incidence and prevalence of hypertension are reaching epidemic proportions worldwide. Even though considerable progress has been made in the treatment of systemic hypertension, evidence shows that over 43% of the patients did not achieve the goal of controlling high blood pressure (BP) over the last two decades.[6]

The continued challenges in the management of hypertension still need special attention. It is important to take into account the specific barrier and action are necessary to promote the application of hypertension guidelines vary with each clinical action.[7] To be implementable in the everyday clinical setting, it is essential that guidelines harmonize with clinical and practical realities.[8] Many national and international guidelines for the management of hypertension have been published, highlighting mono-or combination therapy, according to the BP levels and associated comorbidity.[9]

The awareness of hypertension guidelines by primary-care physicians is associated with improved hypertension care. Consequently, continuing education of general practitioners in hypertension care is essential to connect both the actual and desired reality in the treatment of hypertension.[10]

The implementation of clinical guidelines, even strongly consensus, as in the case of the treatment of hypertension, it may occur in very low adherence of health professionals.[11] In parallel, a study developed in Italy shows that a sufficient degree of guidelines awareness is present in a minority of primary-care physicians.[12] Nonadherence to guidelines is common, and can affect the validity of readings obtained both in physicians' offices and at home, with significant and potentially harmful effects on treatment decisions.[13]

Scarce publications involving prescribing models of antihypertensive drugs in primary health care combined with the use of guidelines are described in the literature. In this sense, this study aimed to answer two suppositions: A) Do publish studies on antihypertensive prescription in primary health care follow the pattern of monotherapy or combination therapy? B) Do the prescriptive pattern follow the main national or international guidelines? To answer these questions, we investigated the scientific publications on prescription patterns of the antihypertensive drugs in patients with systemic hypertension in the primary health care by systematic review and meta-analysis.

METHODS

DATA SOURCE AND RESEARCH

A systematic review of the literature was carried out according to the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) statements.[14] (S-1. Supplementary file). The used databases were PubMed, Web of Knowledge and Latin American and Caribbean Health Sciences (LILACS), with publications from November 30, 2004 to June

15, 2020. The strategy used for the arrangement of this study is depicted in the flow chart (Figure 1).
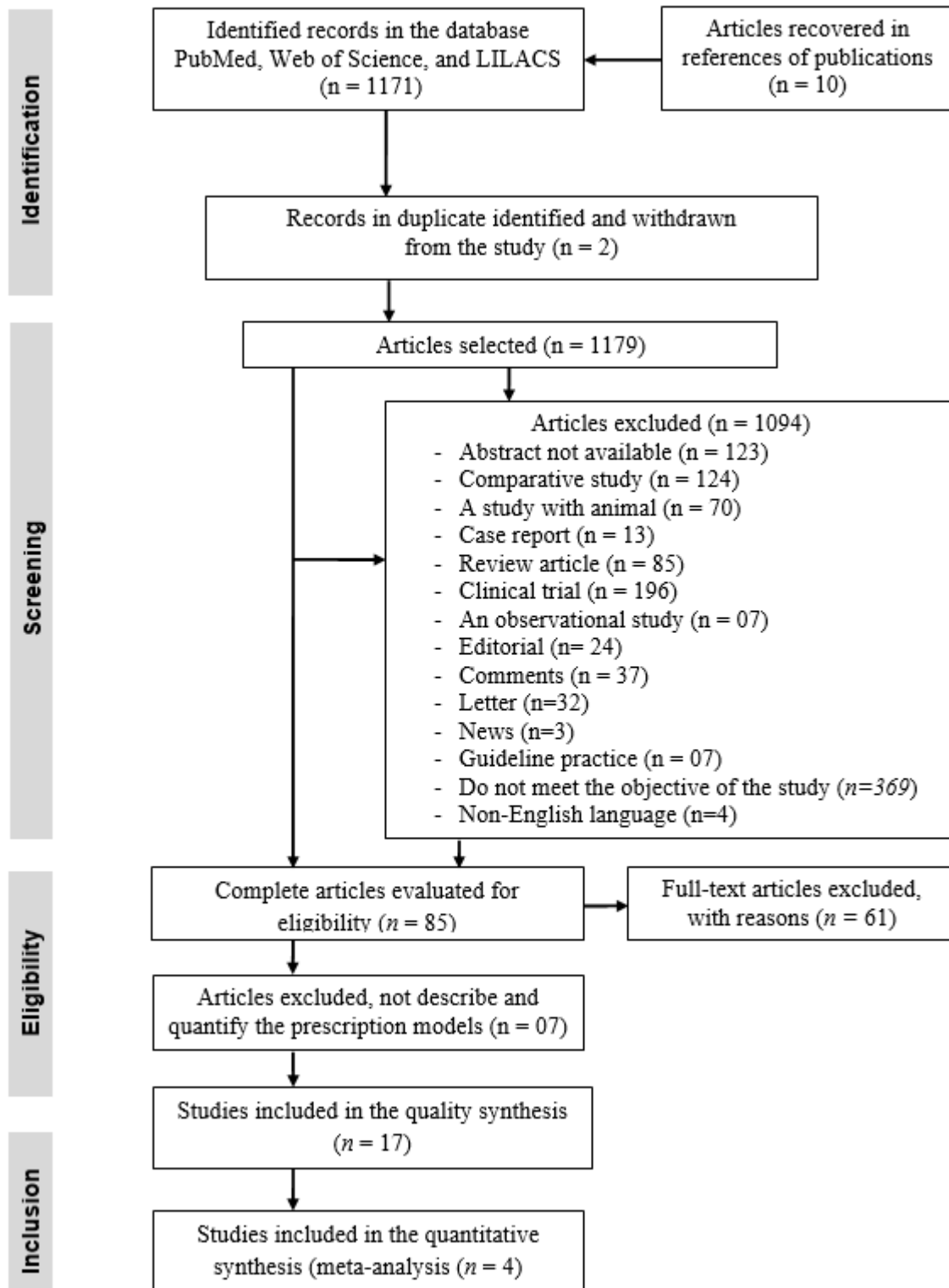
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┌─────────────────────────────────────────┐        ┌──────────────────────────────┐
│ Identified records in the database      │        │ Articles recovered in        │
│ PubMed, Web of Science, and LILACS      │◄───────│ references of publications   │
│ (n = 1171)                              │        │ (n = 10)                     │
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│ Records in duplicate identified and      │
│ withdrawn from the study (n = 2)         │
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│ Articles selected (n = 1179)             │
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┌───────────────────────────────────────────────────────┐
│ Articles excluded (n = 1094)                          │
│  - Abstract not available (n = 123)                   │
│  - Comparative study (n = 124)                        │
│  - A study with animal (n = 70)                       │
│  - Case report (n = 13)                               │
│  - Review article (n = 85)                            │
│  - Clinical trial (n = 196)                           │
│  - An observational study (n = 07)                    │
│  - Editorial (n= 24)                                  │
│  - Comments (n = 37)                                  │
│  - Letter (n=32)                                      │
│  - News (n=3)                                         │
│  - Guideline practice (n = 07)                        │
│  - Do not meet the objective of the study (n=369)     │
│  - Non-English language (n=4)                         │
└───────────────────────────────────────────────────────┘

┌─────────────────────────────┐        ┌──────────────────────────────┐
│ Complete articles evaluated  │        │ Full-text articles excluded, │
│ for eligibility (n = 85)     │───────►│ with reasons (n = 61)        │
└─────────────────────────────┘        └──────────────────────────────┘
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┌─────────────────────────────────────────┐
│ Articles excluded, not describe and      │
│ quantify the prescription models (n = 07)│
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│ Studies included in the quality synthesis│
│ (n = 17)                                 │
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│ Studies included in the quantitative     │
│ synthesis (meta-analysis (n = 4)         │
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Identification — Screening — Eligibility — Inclusion

Figure 1. Flow diagram of studies included in the systematic review and meta-analysis

Three independent researchers (EAO, IHPG and DCV - Group 1) carried out specific research to define the most suitable MeSH terms (Medical Subject Headings), in order to ensure high sensitivity for scientific publications (S-2. Supplementary file). Discrepancies or disagreements were resolved by consensus, with the support and validation of a specialist (JJVT). In the first phase of the study, the three researchers from Group 1 conducted the search with the exhibition of titles and summaries of the records found. In PubMed, aiming at the selection of articles, MeSH terms were organized in three blocks: Block 1, consisting of 4 MeSH terms: "Hypertension" OR "Blood Pressure" OR "Arterial Pressure" OR "Coronary Disease"; AND Block 2, made up of 08 MeSH terms: "Drug Therapy" OR "Drug Therapy, Combination" OR "Guideline Adherence" OR "Drug Utilization" OR "Drug Combinations" OR "Prescription Drugs" OR "Drug Prescriptions" OR "Therapeutic Use"; AND Block 3: "Primary Health Care". For the Web of Knowledge database, it was used articles search strategy by topic, which ensures a considerable sensitivity to research.

ARTICLES SELECTION

Initially, all publications that reported the prescription of antihypertensive drugs in primary health care, regardless of the language, were included in the study. With the use of databases filter and manual checking of summaries, the publications were selected and validated. Only original researches performed in primary health care, published in the period previously determined and that presented their abstract available in the database were maintained (S-3. Supplementary file). All articles relating to studies review, comparisons, case reports, clinical trials, editorials, comments to the editor, letters, news, guidelines and those performed with animals were excluded. Based on titles and abstracts of articles, those that did not discuss the theme of systemic hypertension or that did not address the prescription of antihypertensive drugs in primary health care in their abstracts were also excluded (S-4. Supplementary file). To develop

the meta-analysis, only publications that described BP values and use of guidelines were considered.

QUALITY EVALUATION

In the second phase, the selected articles were recovered in portable document format and randomly distributed to 3 independent researchers (EAO, IHPG and DCV - Group 1), in order to avoid bias and disagreements were resolved by consensus. Subsequently, to increase the sensitivity of the systematic review, a new investigation was carried out to identify original articles in the references of the selected publications in the qualitative synthesis.

In the third phase, the selected articles were randomized and distributed to two independent judges (RTPO and JJVT - Group 2). This step is critical, because it allows ensuring the validation, or not, of the articles selected by researchers from Group 1. The articles in which statistical method was used for data analysis and that described the prevalence of major classes of antihypertensive drugs remained in the sample, aligned with the purpose of this review. STROBE statement (Reporting of Observational Studies in Epidemiology) (S-5.Supplementary file) was applied to assess bias risk in the selected publications, according to the 22 items of the instrument (STROBE checklist),[15] composed of two cuts (≥75%, <75 %), respectively high and low-risk bias.[16,17]

DATA EXTRACTION

The fourth phase consisted of data extraction by three researchers from Group 1 (EAO, IHPG and DCV), with the support of two experts (RTPO and JJVT). The organization of the variables for tables' composition was performed in the following way: Table 1, characteristics of studies that comprised the systematic review (author/year, country, objective, design, sample (n), statistical analysis, prescription of the antihypertensive drugs classes); Table 2, characteristics of patients involved in the studies (source, age average/years, gender (%), race/ethnicity, type of therapy (monotherapy or combined therapy), systolic

arterial pressure (mmHg), diastolic arterial pressure (mmHg), guidelines used). The articles were once more randomly distributed among researchers from group 1, who reviewed the tables, in order to ensure the fidelity of the results, and any discrepancies were resolved by consensus. Subsequently, group 1 filled the tables and made them available to researchers from group 2 to validate the results of the selected articles in the form of tables.

STATISTICAL ANALYSIS

All statistical analyses for the meta-analysis were developed in Stata 9.0® software (Stata Corporation, College Station, TX, USA), using the Metan Command, with significance for p <0.05 with a two-tailed approach. The data extracted from the publications for the elaboration of the forest plot are described in supplementary file (S-6.Supplementary file). The estimated effect measure grouped for the variability between and among the groups of the dichotomous variables was performed by the Odds Ratio (OR), with a confidence interval of 95%. Fixed-effects models and random effects models were initially tested. The split between the subgroups' monotherapy and combined therapy percentages was calculated for each study to determine the consistency of the results. The selected publications differ in variables, study design, age group, race/ethnicity and type of therapy. The Pooled used for analysis of the antihypertensive prescription model, considering the proportions between monotherapy and combined therapy, was of random effects,[18] with 95% confidence interval.

SUBGROUP ANALYSIS

The subgroups were analyzed according to the model of treatment to hypertensive patients (monotherapy/combined therapy).

HETEROGENEITY AND PUBLICATION BIAS

Heterogeneity between the studies was performed using Cochran's Q statistical test (p <0.10) as indicative of significance. For the evaluation of publication bias, Begg's[19] and Egger's[20] method was used, as well as funnel plots, with significance p<0.05, for symmetry analysis. The analysis of the inconsistency of publications' findings was performed by Higgins and Thompson I^2 statistic, according to the following classification: low (25%), moderate (50%) and high (75%).[21]

RESULTS

Our searches selected 1171 records in the database. In the references of the selected publications, another 10 publications were identified, two of which were repeated, totaling 1179 abstracts. There was an exclusion of 1094 records from the screening process, according to the exclusion criteria. Thus, remained 85 articles that had their titles and abstracts analyzed by three independent reviewers. Regarding the eligibility criterion, 68 Complete articles excluded because they do not describe the main classes of the antihypertensive drugs in systemic hypertension treatment in primary health care and also did not meet the objectives of the study. Therefore, 17 articles[22-38] met all the criteria for inclusion in this review (Figure 1).

The sample size (n), considering the 17 studies included in the synthesis quality, was of 141,920 patients with hypertension. The mean age of the patients involved in the studies ranged between 45-99 years and most were female. All studies presented statistical analyses and reported the prescription prevalence of the main classes of antihypertensive drugs used in the pharmacotherapeutic systemic hypertension treatment, except one article.[24] Eight studies,[24,27,28,30-32,35,37] describing and analyzing the prescription of antihypertensive drugs in systemic hypertension patients in primary health care, and nine presented cross-sectional delineation[24,27,28,30-32,35-37] and come from countries in Europe,[23,25,29-33] and Asia.[26,27,36,38] (Table 1)

Table 1. Characteristics of the patients of systematic review and meta-analysis on systemic hypertension in primary health care (2004-2020)

| Source | Age Average/ Years (SD) | Gender | | Race or Ethnicity | Therapy pattern | | BP Systolic (mmHg) | BP Diastolic (mmHg) | Guidelines Used |
		Female (%)	Male (%)		Monotherapy (%)	Combined Therapy (%)			
Novello et al[22]	45 to 99	69.0	31.0	Brazilian	34.6	65.4	NR	NR	VI Brazilian Guidelines
Ponte Márquez et al[23]	85.0	56.6	43.4	Spanish	21.6	78.4	NR	NR	Standard European
Bakare et al[24]	58.4(± 12.7)	65.0	35.0	Nigerian	2,5	97.5	130,6 (± 17.3)	80.0 (± 12.3)	JNC-7
Qvarnström et al[25]	61.5(± 12.5)	55.1	44.9	Swedish	98.0	2.0	166.4 (± 19.6)	93.6 (± 11.6)	NR
Cheong et al[26]	53.7(± 16.2)	52.8	47.2	Chinese, Malayan Indian	69.7	5.1	NR	NR	NR
Limet al[27]	68.6(± 6.4)	56.6	42.4	Chinese, Malayan Indian	53.1	46.9	NR	NR	NR
Clement et al[28]	62.0(± 11)	71.1	29.9	Asian Indian descent (54.1%)	54.8	39.3	NR	NR	JNC-7 CHRC
Chmiel et al[29]	64.0	50.0	50.0	Switzerland	41.8	46.7	157.3 (± 15.3)	91.9 (± 11.1)	Switzerland and ESH/ESC
Kuehlein et al[30]	64.5	58.4	41.6	German	30.6	69.4	NR	NR	NR
Buckley et al[31]	64.7(± 11.9)	53.8	46.2	Irish	40.5	59.5	139.4 (± 17.5)	81.1 (± 10.0)	BHS, ESH/ESC, JNC-7
Cortez-Dias et al[32]	58.1(± 15.1)	61.3	38.7	Portuguese	47.6	52.4	136.0 (± 19.0)	79.0 (± 11.0)	NR
Jeschke et al[33]	64.2(± 14.5)	63.5	36.5	German	64.0	36.0	NR	NR	NR
Akici et al[34]	61.5(± 10.5)	60.6	39.4	Turkish	93.4	6.6	NR	NR	WHO (1999)
Abaci et al[35]	60.0(± 11.0)	60.2	39.8	Euro-Asian (Turkish)	75.7	24.3	NR	NR	NR
Chiang et al[36]	64.7	56.7	43.3	Taiwanese	47,1	52.9	NR	NR	NR
Igho-Pemu et al[37]	47.0(± 13.0)	68.0	32.0	Afro-American (≥30%)	58.0	42.0	NR	NR	JNC-7
Al Khaja et al[38]	67.3(± 5.9)	33.1	66.9	Asian	47.4	48.8	151 (± 19.0)	85 (± 8.5)	WHO/ISH

BHS, British Hypertension Society; **NR**, Not Reported; **CHRC**, Caribbean Health Research Council; **WHO**, World Health Organization; **ESH/ESC**, European Society of Hypertension/ European Society of Cardiology; **ISH**, International Society of Hypertension; **JNC7**, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, **VI Brazilian Guidelines** on Hypertension and the blood pressure control rate in primary care.**SD**, Standard Deviation

Antihypertensive drugs monotherapy[25-28,33-35,37] had a prevalence of 47.1%, while the combined therapy[23,24,29-32,36,38] was 52.9%. Monotherapy reached 98.0% in Sweden,[25] 93.4% in the Turkish study[34] and 75.7% in Euro-Asia,[35] followed by the Malaysian research, with 69.7%.[26] As for combined therapy, the prevalence was of 97.5% in Nigeria,[24] 78.4% in Spain[23] and 69.4% in Germany.[30] The majority of studies did not present data on the systolic and diastolic BP (64.7%)[22,23,26-28,30,33-37] and, among those who reported this parameter, the systolic BP average ranged from 130.6 to 166.4mmHg, whereas the diastolic from 79 to 93.6mmHg. Regarding the use of guidelines, 52,9% of the studies reported their use,[23,24,28,29,31,34,37,38] being the seventh report of the joint national committee on prevention and treatment of high blood pressure used in 25% of them (Table 1).

The prescription of the angiotensin-converting enzyme inhibitors was more prevalent in Trinidad (63.6%)[28] and Brazil (57.8%),[22] followed by Spain and Bahrain (both with 41%),[23,38] with lower prescriptive prevalence in Malaysia (14.9%).[27] Angiotensin-receptor blockers had a higher prescriptive prevalence in Portugal (43.0%),[32] Spain (29.7%)[23] and Switzerland (29.4%),[29] and lower in Trinidad (2.3%),[28] while it was not reported in Malaysia,[26] Turkey[34] and Bahrain.[38] The use of beta blockers was higher in Nigeria (63.0%)[24] and Bahrain (50.4)[38] and lower in Turkey (7.5%)[34] (Table 2).

Table 2. Characteristics of the studies of systematic review and meta-analysis on systemic hypertension in primary health care (2004-2020)

(Continua)

Author/ year	Country	Goal	Design	Sample	Statistic	Antihypertensive classes (%)					
						Diuretics	BB	CCBs	ACE-I	ARBs	Other
Novello et al, 2017[22]	Brazil	Avaliar o grau de conformidade das prescrições anti-hipertensivas com as VI Diretrizes Brasileiras	Cross-sectional	332	Yes	63.0	26.8	25.3	57.8	18.4	4.2
Ponte Márquez et al, 2016[23]	Spain	Describe the prescription of antihypertensive drugs classifying them in five pharmacological groups. Assess in appropriate antihypertensive prescriptions to older patients.	Multicentre prospective observationalstudy	532	Yes	53.5	29.7	32.2	41.0	29.7	-
Bakare et al, 2016[24]	Nigeria	Identify the most prescribed antihypertensive drugs and its prescription patterns comorbidities, cost of medications, and laboratory investigations.	Cross-sectional	200	No	64.0	63.0	53.0	51.5	16.5	1.0
Qvarnström et al, 2015[25]	Sweden	Study patterns of switching between antihypertensive drug classes and to determine factors associated with poor persistence.	Cohort	4.997	Yes	27,5	21.2	7.8	37.5	4.1	-
Cheong et al, 2015[26]	Malaysia	Analyze the duration of the first control of the BP after the diagnosis of hypertension	Retrospective Cohort	195	Yes	33.8	9.6	25.0	31.6	-	-
Lim et al, 2012[27]	Malaysia	Determine the trend of antihypertensive prescription in elderly patient	Cross-sectional	21.868	Yes	23.3	25.5	27.1	14.9	6.3	2.9
Clement et al, 2012[28]	Trinidad	Describe the prescription of antihypertensive drugs in primary health care	Cross-sectional	442	Yes	25.8	29.2	12.0	63.6	2.3	6.8
Chmiel et al, 2011[29]	Switzerland	Evaluate the characteristics of patients with not controlled systemic hypertension and determinants associated	Cross-sectional, prospective	122	Yes	9.8	17.7	6.9	39.2	29.4	-

(Conclusão)

Author/year	Country	Goal	Design	Sample	Statistic	Anti-hypertensive classes (%)	Author/year	Country	Goal	Design	Sample
Kuehlein et al, 2009[30]	Germany	Contribute, through clinical practice, for the academic discussion on the diuretics as a therapy of 1st. choice	Cross-sectional	58.825	Yes	8.6	41.0	8.6	31.7	9.5	-
Buckley et al, 2009[31]	Ireland	Determine the proportion of hypertensive patients that do not reach the targeted BP	Cross-sectional	1.534	Yes	29.7	39.8	27.9	32.2	22.0	-
Cortez-Dias et al, 2009[32]	Portugal	Check the prevalence and treatment of systemic hypertension in the primary health care	Cross-sectional	9.964	Yes	47.4	16.2	18.9	39.2	43.0	-
Jeschke et al, 2007[33]	Germany	Investigate the strategies of treatment of systemic hypertension in complementary and alternative medicine, comparing them with the guidelines	Multicenter, Observational	1.320	Yes	15.7	30.7	16.7	24.0	11.7	1.2
Akici et al, 2007[34]	Turkey	Analyze the prescription of antihypertensive drugs in health centers	Intervention	297	Yes	16.2	7.5	28.8	31.7	-	15.8
Abaci et al, 2007[35]	Turkey	Investigate the practice of prescribed medications antihypertensive drugs at primary health care	Cross-sectional	12.897	Yes	15.4	20.6	17.9	30.1	14	2.0
Chiang et al, 2007[36]	Taiwan	Analyze trends in antihypertensive drugs-use by diabetic patients comparing them with the guidelines	Cross-sectional	27.460	Yes	9.5	16.7	16.9	19.6	13.7	3.2
Igho-Pemu et al, 2005[37]	USA	Identify the prescription antihypertensive drugs, barriers at the care and, also, opportunities of intervention in the control of systemic hypertension	Descriptive epidemiological	710	Yes	43.0	20.4	28.0	24.6	15.9	-
Al Khaja et al, 2004[38]	Bahrain	Determine the adherence of physicians to guidelines for the drug management of hypertension	Multicenter	225	Yes	31.8	50.4	30.2	41.1	-	3.2

ACE-I, Angiotensin-converting enzyme inhibitors; **BB**, Beta blockers; **ARBs**, Angiotensin-receptor blockers; **CCBs**, Calcium channel blockers.

Calcium channel blockers were more used in antihypertensive therapy treatment in Nigeria (53%),[24] followed by Spain (32.2%)[23,38] and less in Switzerland (6.9%)[29] and Sweden (7.8%).[25] As for diuretic drugs, the countries which had the highest prescription were Nigeria (64.0%),[24] Brazil (63.0%)[22] Spain (53.5%)[23] and Portugal (47.4%)[32], while the countries that used them the least were Germany (8.6%),[30] and Taiwan (9.5%).[36] The prescription of other antihypertensive drugs, a parameter reported only in half the studies (52.9%),[22,24,27,28,33-36,38] had higher prevalence in Turkey (15.8%)[31] {Chmiel, 2012, Uncontrolled arterial hypertension in primary care--patient characteristics and associated factors} and Trinidad (6.8%).[28] (Table 2)

SUBGROUP ANALYSIS AND PUBLICATIONS BIAS

Only four publications met the criteria for conducting the meta-analysis.[24,29,31,38] were considered. Data pooled by random effect model shows the summary OR of 1.76 (IC 1.29-2.41), with high prevalence for combined therapy pattern. We analyzed the heterogeneity among the 4 publications with statistical test Chi-square. The I^2 statistic test showed consistent heterogeneity of publications ($I^2 = 93.9\%$, $p < 0.001$) (S-6. Supplementary file). Begg's rank-correlation test was used to identify distortions in studies and it did not show any significant evidence of bias publication ($p = 1.00$), while Egger's test ($p = 0.026$) confirmed the presence of publication bias (S-7. Supplementary file).

STROBE checklist showed the following concordances for the selected publications: title and abstract (87.3%), introduction (100.0%), methods (60.5%), results (23.5%), discussion (60.3%) and other information (68.8%). Only 6 (35.3%) of the selected studies[22,23,25-27,32] were concordant with 75% or more of the checklist and 11 (64,7%)[24,28-31,33-38] {Bakare, 2016, Antihypertensive use`, prescription patterns`, and cost of medications in a Teaching Hospital in Lagos`, Nigeria;Clement, 2012, Drug prescribing for hypertension at primary healthcare facilities in Trinidad;Chmiel, 2012, Uncontrolled arterial hypertension in primary care--patient characteristics and associated factors;Kuehlein, 2011, Diuretics for hypertension--an inconsistency in primary care prescribing behaviour;Buckley, 2009, Blood pressure control in

hypertensive patients in Irish primary care practices} had a percentage of less than 75.0%. The mean STROBE checklist score was 68.4% (range 17.5 to 100.0%) and the agreement among the researchers was 98.2% (S5. Supplementary file). Another relevant point was that none of the authors reported the employment of STROBE statement in individual publications.

DISCUSSION

The findings of this systematic review showed higher proportions for the pattern combination therapy for systemic arterial hypertension in primary health care. The meta-analysis confirmed the findings of systematic review through the greater pooled effect values for combined therapy pattern in comparison to monotherapy. The findings also highlighted that, in most studies, there is no report of the use of guideline by prescribers for the prescription of antihypertensive in primary health care. This review included numerous publications and approximately 150,000 patients with systemic hypertension, from several countries, mostly Euro-Asian, showing the existence of a large variability in the prescription of antihypertensive drugs for systemic hypertension in primary health care. We observed a large predominance of the female gender for systemic arterial hypertension, since in 154 of the 17 studies women were more frequent. These findings contradict data from the 2013 update on hypertension in the United States, which pointed out that, among 20-year-old or older women, there was the lower prevalence of hypertension ranging from 30.7% for non-Hispanic white women and of 47.0% for non-Hispanic black women.[39] Study have shown different prevalence for hypertension arterial between genders, as a higher prevalence for the male[40,41] and similar prevalence for both sexes.[42] Despite the immediately plausible notion that men and women are different, contemporary hypertension guidelines do not recommend sex-specific treatment strategies.[43]

Observational clinical studies have demonstrated that only 30-40% of patients with systemic hypertension reached the recommended goal of BP $\leq 140/90$ mmHg.[44] These data indicate the necessity of action to better control this disease, such as the application of padronized procedures, defined in guideli-

nes, what could guide towards more effective results. However, in many situations, this seems to not occur, since our study detected the lack of guidelines use by prescribers in the majority of the studies. In parallel, a research conducted in the United Kingdom reported that 36-53% of patients with known or calculated cardiovascular risk are not being treated according to national guidelines.[45]

Walther et al. report that several practical challenges arise in aligning pharmacotherapy to guidelines. Guidelines differ worldwide, and several documents potentially influence practitioners in a given country. Even within one document, conflicting recommendations may apply to the same individual. Also, drug choice is influenced by efficacy, tolerance, security and price.[46] In parallel, Labeit *et al.* report that the selection of drugs is influenced by many factors, such as socio-economic and cardiovascular risk factors, co-existing diseases, patient response, interactions, and evidence strength.[46] A false-positive diagnosis of hypertension exposes patients and the health care system to the unnecessary costs of antihypertension medications and office visits.[48] The degree of adherence in the clinical setting to the guidelines for measuring BP both in the physician's office and at home is largely unknown.[13]

Research on the control of BP and the patterns of pharmacotherapy in the USA indicated that BP control is progressing, not only in global aspects but also in patients with diabetes mellitus. However, the need of improvement is still significant. It also provides evidence to suggest that there was a consistent and significant trend towards a greater control of arterial BP and more aggressive forms of treatment.[49]

While there are differences between countries in terms of the most frequently used antihypertensive class, an international trend in the choice of drug groups can be discerned.[50] Analysis of antihypertensive drugs prescription conducted in an outpatient care unit in a tertiary hospital in Bangalore, India, revealed that monotherapy was consistently more recommended in the early stages of hypertension to reach BP goals, and calcium channel blockers were the drugs chosen for hypertensive patients as single medication therapy and for overall use.[51] In parallel, a research conducted at 3,362 primary health-care sites in China showed a higher frequency for the prescriptive model of monotherapy and calcium channel blockers for BP control.[51]

The high rate of monotherapy and a decrease in incremental gain over BP control when more antihypertensive drugs agents were used highlight the importance of the adequate pharmacological treatment, as well as of the control of risk factors.[29] This review, therefore, highlights the need for improvement in the control of systemic arterial pressure in primary health care, which is absent in most studies, and also for greater use of guidelines, which were not described in most of articles.

Among the pharmacological groups, diuretics are among the drugs most commonly prescribed, and their effectiveness in reducing BP and preventing cardiovascular adverse events in patients with hypertension varies considerably among their classes.[53] In spite of this, the percentage of diuretics prescription, in our study, was 16% or less in 6 of the 16 articles included. This demonstrates the lack of use of diuretics, contradicting the recommendations of the seventh report of the joint national committee on prevention and treatment of high blood pressure, the most cited guideline in the studies included in this review (25%), which indicates them as the drug of first choice for the treatment of systemic arterial hypertension.

Hypertensive patients with risk factors were more likely to receive antihypertensive medications and a higher rate of adequate BP control was obtained in patients with obesity and coronary artery disease, but not in those patients with diabetes mellitus or dyslipidemia.[54] Results of a study conducted at the University Hospital indicate that many treated hypertensive patients do not reach the control of their BP and only 37% of hypertensive patients had their BP controlled.[55] More worrying, however, is the extremely low control of BP by hypertensive patients with diabetes mellitus or chronic kidney disease, that is, the control of BP is worse among the patients who are at higher risk.[46] Nevertheless, it could be verified in this study that the control of BP was not a consensual goal in the studies, since the parameters of systolic and diastolic BP were not measured in the majority of them (64.7%).

There is moderate evidence to support the beginning of the treatment with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers or diuretics in the white hyper-

tensive population, including those with diabetes mellitus. In the black hypertensive population, including diabetics, calcium channel blockers or diuretics are recommended as initial therapy. However, these recommendations are not a substitute for clinical judgment and decisions about hypertension care should consider and incorporate the clinical characteristics and circumstances of each patient.[2] In part, clinical judgment and decisions about patient care performed by the prescriber may contribute to justify the great variability in the prescription of antihypertensives found here. Nevertheless, the use of calcium channel blockers in the studies included in this systematic review is below that of the other antihypertensive classes in most of the studies, with a lower prescription when compared to angiotensin-converting enzyme inhibitors in 14 of the studies (82.4%). This shows the low use of calcium channel blockers, despite their relevance in the pharmacotherapy of systemic arterial hypertension. In this study, a greater tendency in the prescription of angiotensin-converting enzyme inhibitors, followed by diuretics, beta-blockers and calcium channel blockers.

The meta-analysis was evaluated by random effect model, with significant heterogeneity, but the results pointed to, concomitantly, the lack and the presence of publication bias. In parallel, systematic review and meta-analysis published on first-line combination therapy versus first-line monotherapy for primary hypertension, involving only clinical trials published until June 15, 2020, showed that the data were not sufficient for a conclusion on the topic.[56] It is highly relevant to note that combined therapy with two antihypertensive drugs has been suggested by international guidelines for proper management of hypertension.[2]

STRENGTHS AND LIMITATIONS OF THE STUDY

Our systematic review and meta-analysis have several strengths. First, it is largest review provided by bases the electronic databases (PubMed, Web of Science, and LILACS). Second, numerous independent searches with the MeSH terms and research strategies were carried out and agreed upon by consensus. The findings available by the selected articles were organized and detailed in tables, maintaining a consistent and correct representation of the results.   Third, the systematic review showed a higher prescription pattern

for combination therapy for systemic hypertension in primary health care. The meta-analysis confirmed the evidence of systematic review indicating the superiority of prescription for the pattern of combined therapy. The findings also highlighted that, in most studies, there is no report on the use of prescribers' guidelines for the prescription of antihypertensive in Primary Health Care. Several publications did not present the mean values and standard deviation of blood pressure. The high heterogeneity between scientific publications and the small number of citations included in the meta-analysis were other limitations of the study. Although the meta-analysis facilitates the measurement of the pooled data, if the studies involve present distortions, it does not allow their correction. The observational epidemiological studies analyzed in this review evidenced poor agreement with STROBE Statement, with 1/3 of the publications in line with the 22 items in the checklist. Thus, both the limitations and the biases of the studies were not sufficiently valued by the authors of the selected papers. Clear and transparent reporting in research paper helps clinicians and researchers, who can evaluate the validity of articles.[57] The studies included in this research were different from their design; in spite of that, the majority of them were cross type-sectional. Also, many of them did not report the systolic and diastolic BP parameters nor made references to the guidelines/recommendations used in the treatment of systemic arterial hypertension.

CONCLUSIONS

In summary, the systematic review and meta-analysis identified a higher prescription pattern for combination therapy for systemic hypertension in primary health care. The findings also highlighted that, in most studies, there is no report of the use of guideline by prescribers for the prescription of antihypertensive in primary health care. Other evidence shown in this study was the high frequency of the prescription of angiotensin-converting enzyme inhibitors, followed by diuretics, beta-blockers and calcium channel blockers. Therefore, further studies are required, especially controlled randomized multicenter clinical trials.

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