

ORIGINAL ARTICLE

Angiotensin-Converting Enzyme Inhibitors Evaluated by Office and Home Blood Pressure Measurements: TeleHBPM Study

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Abstract

Background: Angiotensin-converting enzyme inhibitors (ACEI) are a class of drugs fundamental to hypertension treatment; however, the individual medications within this class vary in their effectiveness at controlling Blood Pressure (BP).

Objectives: To analyze BP values obtained through casual measurements and home blood pressure monitoring (HBPM) in patients using ACEI as monotherapy or in dual combinations, focusing on BP control and goal achievement in a Brazilian population.

Methods: A cross-sectional study evaluating adult patients using ACEI between 2017 and 2020 included in the TeleHBPM platform. SBP and diastolic blood pressure (DBP) values were assessed by casual and home measurements. Those using three or more HBPMs were excluded. Paired t-tests, chi-square tests, and ANOVA were used, with a significance level of 5% ($p < 0.05$).

Results: 3,466 patients who met the criteria were selected, 54% in a dual drug combination. The mean BP values obtained via casual measurement and HBPM, respectively, were 131.6 ± 18.7 mmHg and 125.5 ± 14.8 mmHg for SBP ($p < 0.001$), and 83.4 ± 11.3 mmHg and 79.1 ± 9.4 mmHg for DBP ($p < 0.001$). The combination of ACEI with calcium channel antagonists prevailed (29%). Enalapril had similar BP means to ACEI with longer half-lives. Captopril monotherapy and in combinations had higher SBP and DBP means.

Conclusion: Enalapril was the most commonly used ACEI, demonstrating a similar BP-lowering effect, both as monotherapy and in combination, when compared to other drugs in the same class with longer half-lives.

Keywords: Hypertension; Angiotensin-Converting Enzyme Inhibitors; Enalapril.

Introduction

Arterial Hypertension (AH) is a highly prevalent disease with low control rates, resulting in significant costs related to its primary complications.^{1,2} Achieving BP control goals established by scientific evidence should be a clear priority for all healthcare professionals

managing this condition. It is well-established that using long half-life medications and fixed combinations improves hypertension control rates.³⁻⁸ Unfortunately, this antihypertensive (ATH) profile is not provided by the Brazilian Unified Health System (SUS) for treating hypertensive disease, making adherence difficult.

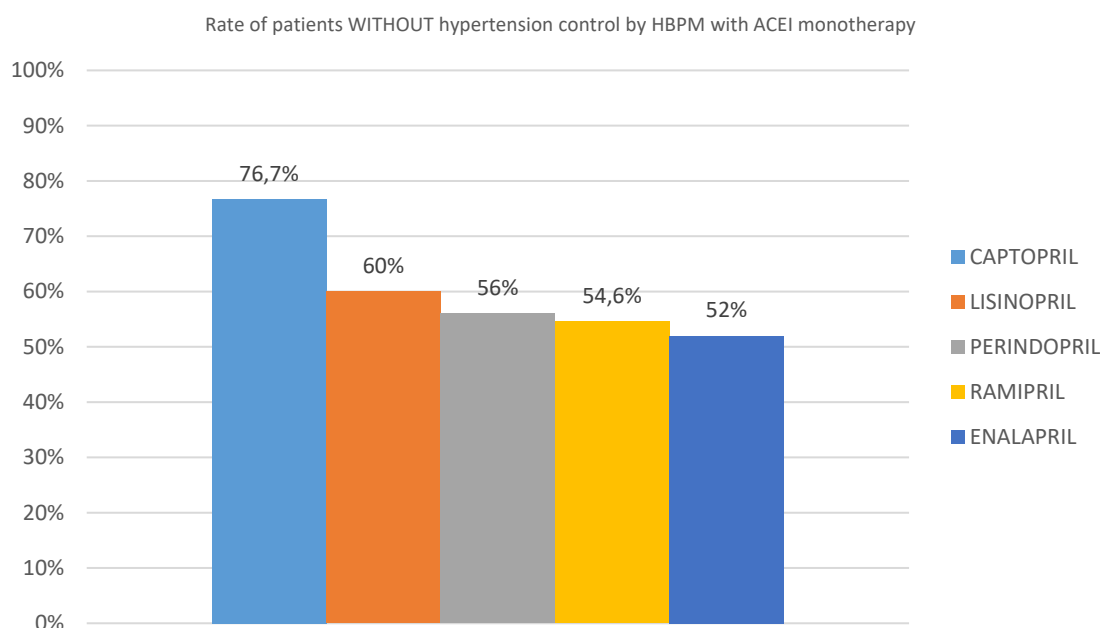
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Central Illustration: Angiotensin-Converting Enzyme Inhibitors Evaluated by Office and Home Blood Pressure Measurements: TeleHBPM Study

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Rate of patients without hypertension control by HBPM with ACEI monotherapy.

A Brazilian study involving 6,731 individuals who underwent home blood pressure monitoring (HBPM) revealed that angiotensin-converting enzyme inhibitors (ACEIs) accounted for 15.9% of the medications prescribed, whether as monotherapy or in combinations, making them the second most commonly prescribed drug class.⁹ Based on these findings and considering approximately 21.5 million hypertensive patients treated in Brazil,^{2,10} it is estimated that around 3.4 million Brazilians use ACEIs for AH management. Given these significant figures and the critical role of ACEI in reducing cardiovascular morbidity and mortality in hypertension treatment, we aimed to evaluate BP behavior through HBPM in a Brazilian population using various ACEI.¹¹⁻¹³

The objectives of this study were: (i) to verify the distribution of ACEI prescriptions among patients using ATH and by region; (ii) to compare the frequency of BP control according to casual measurement and HBPM for treatment strategies with ACEI; (iii) to compare the BP values of the drug strategies with each other by casual measurement and HBPM, observing the similarities and differences in the values achieved.

Method

A retrospective cross-sectional study that evaluated patients using ACEI who underwent tests on the TeleMRPA platform (www.telemrpa.com) between 2017 and 2020. This study received approval from the Research Ethics Committee of the Hospital das Clínicas at the Federal University of Goiás (CEP/UFG) under the Certificate of Presentation for Ethical Consideration (CAAE) 99691018.7.0000.5078.

HBPM is a validated, low-cost diagnostic method for monitoring BP at home. It was incorporated into the SUS system¹⁴ and added to the list of procedures covered by the National Health Agency (ANS) in 2023.¹⁵ The development of the TeleMRPA platform in 2017, an online tool for telemedicine-based test analysis, enabled remote HBPM reporting across different regions of the country. The test information is entered remotely and can be analyzed with the protection of the patient's personal data and health units (public and private institutions). The accumulated data on the TeleMRPA platform represent a significant database with features that allow filtering and analysis to address specific scientific research questions.

Data retrieved from the TeleMRPA platform included the following: sex (male/female); age (in years, based on birth date); number of valid HBPM measurements; SBP and diastolic blood pressure (DBP) obtained casually and via HBPM; and ATH medications used. The distribution of the sample by geographic regions of Brazil was also assessed.

The inclusion criteria were as follows: HBPM exams with at least 14 valid measurements, patients aged 18 or older, and those reporting the use of ACEI as monotherapy or in dual combinations with thiazide diuretics (DIUs), beta-blockers (BBs), or calcium channel blockers (CCBs). Exclusion criteria included patients using three or more ATH medications, combinations with ARBs, combinations with second-line ATH drugs (e.g., spironolactone, direct vasodilators, alpha2 agonists), or inappropriate combinations with another ACEI.

The devices provided for HBPM were automatic and validated, by the brands Omron®, Geratherm®, and Microlife®.

Statistical analysis

Data were exported from the TeleMRPA platform to Excel® (Microsoft) and then to the statistical analysis software Stata®, version 14.0. The drug classes described on the platform were coded and reviewed by two work teams and entered in duplicate with subsequent data cross-referencing to identify and correct any mistyping occurrences.

Continuous variables were presented with mean and standard deviation and categorical variables with absolute and relative frequencies. The Kolmogorov-Smirnov test was used to confirm the distribution of data for continuous variables.

For comparisons between mean SBP and DBP values obtained via casual measurements and HBPM, the paired Student's t-test was applied. The chi-square test or Fisher's exact test was used to compare the control rates obtained through casual measurement with those identified by HBPM, as well as to compare the blood pressure (BP) control and non-control rates according to each drug strategy, considering casual measurement and HBPM.

To compare BP measurements obtained via casual and home methods between ACEI monotherapy and combinations, one-way ANOVA followed by Tukey's *post-hoc* test was employed.

The significance level adopted in the statistical analysis was 5% ($p=0,05$).

Results

The initial sample consisted of 57,603 HBPM exams performed between 2017 and 2020. After verifying the inclusion and exclusion criteria, 3,466 exams were maintained and were part of the final sample (Figure 1).

During the selected period, the platform contained data for 25,854 patients using ATH medications with documented details of the drugs used. When observing the sample distribution by region, ACEI were proportionally most used in the South (23.6%) and least used in the North (13%) among patients using AH on the platform during the selected period (Figure 2).

Among the 3,466 patients using ACEI, the majority were female (55%), with half residing in the Northeast region, and a mean age of 58.3 ± 14.6 years (18–96 years). The double combination strategy predominated in 54% of the sample, with the combination with CCBs being the most common (54%), followed by DIUs (24%) and BBs (22%). Monotherapy was used by 46% of participants.

The drugs that made up the ACEI class showed the following distribution (considering monotherapy and combinations): enalapril 1,212 (34.9%), perindopril 1,123 (32.4%), ramipril 737 (21.3%), benazepril 200 (5.8%), captopril 176 (5.1%), lisinopril 18 (0.5%). There were no patients using fosinopril. (Figure 3)

The averages of casual BP were higher for all treatment strategies when compared with the mean BP values in HBPM. The differences in the mean values between casual BP and HBPM for SBP and DBP in the total sample were 6.1 mmHg ($p < 0.001$) and 4.3 mmHg ($p < 0.001$), respectively. These differences configure the white coat effect and are maintained in all treatment strategies (Table 1).

Table 2 presents the percentage of BP control for monotherapy and combination strategies, based on casual measurements (less than 140/90 mmHg) and HBPM (less than 130/80 mmHg), according to current guidelines.^{3,16} ACEI monotherapy and ACEI combined with CCB achieved a higher percentage of control in the casual measurement with significance (60.3% and 54.1% respectively), which was not the case for the HBPM (Table 2). When analyzing the same parameter for the total number of patients in the sample, 2,015 patients (58.1%) had their BP controlled by the casual measurement and

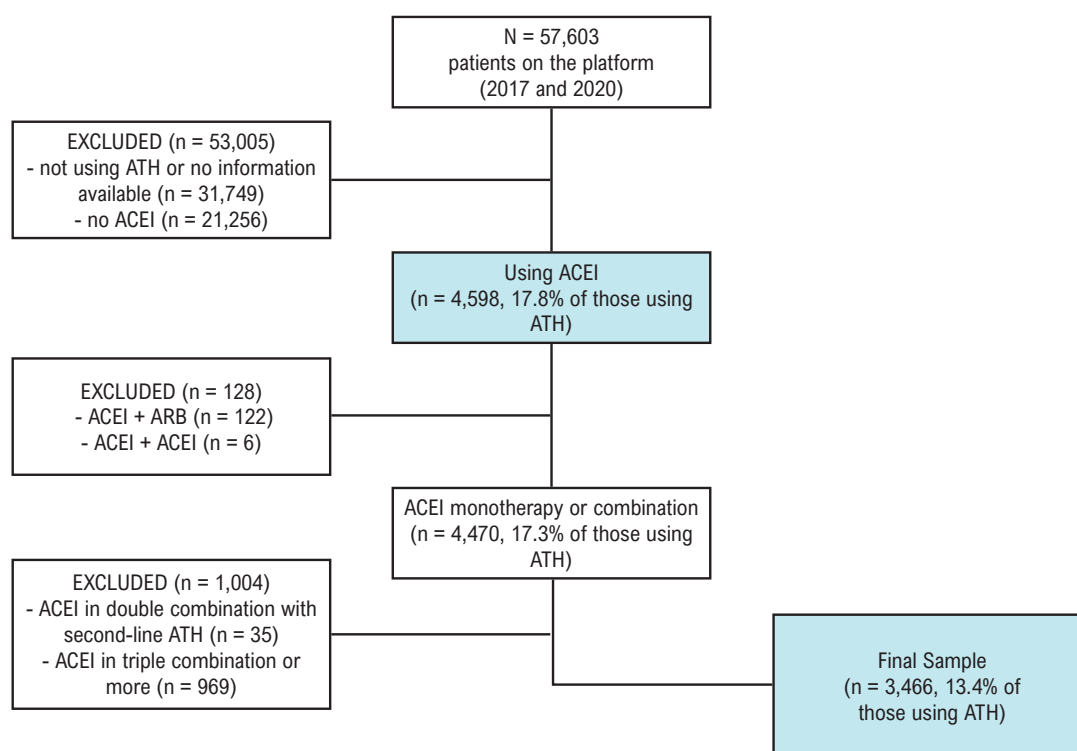


Figure 1 - Study sample selection flowchart.

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers.

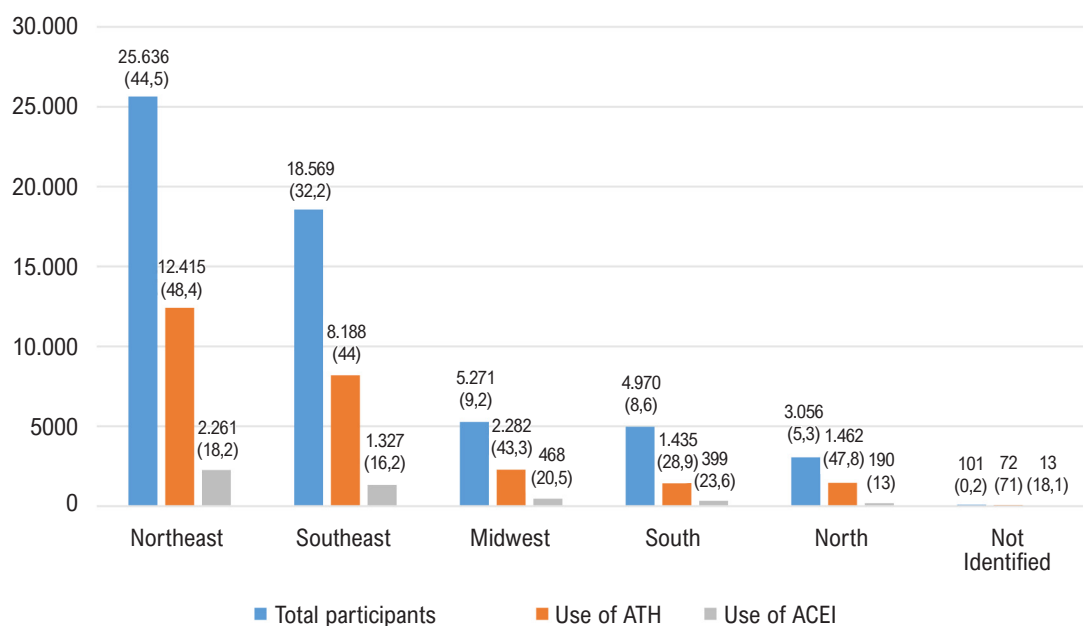


Figure 2 - Sample distribution – total number of participants (57,603 participants) and frequency of those using ATHs and ACEIs by region [n (%)]

ACEI: angiotensin-converting enzyme inhibitors; ATH: antihypertensives

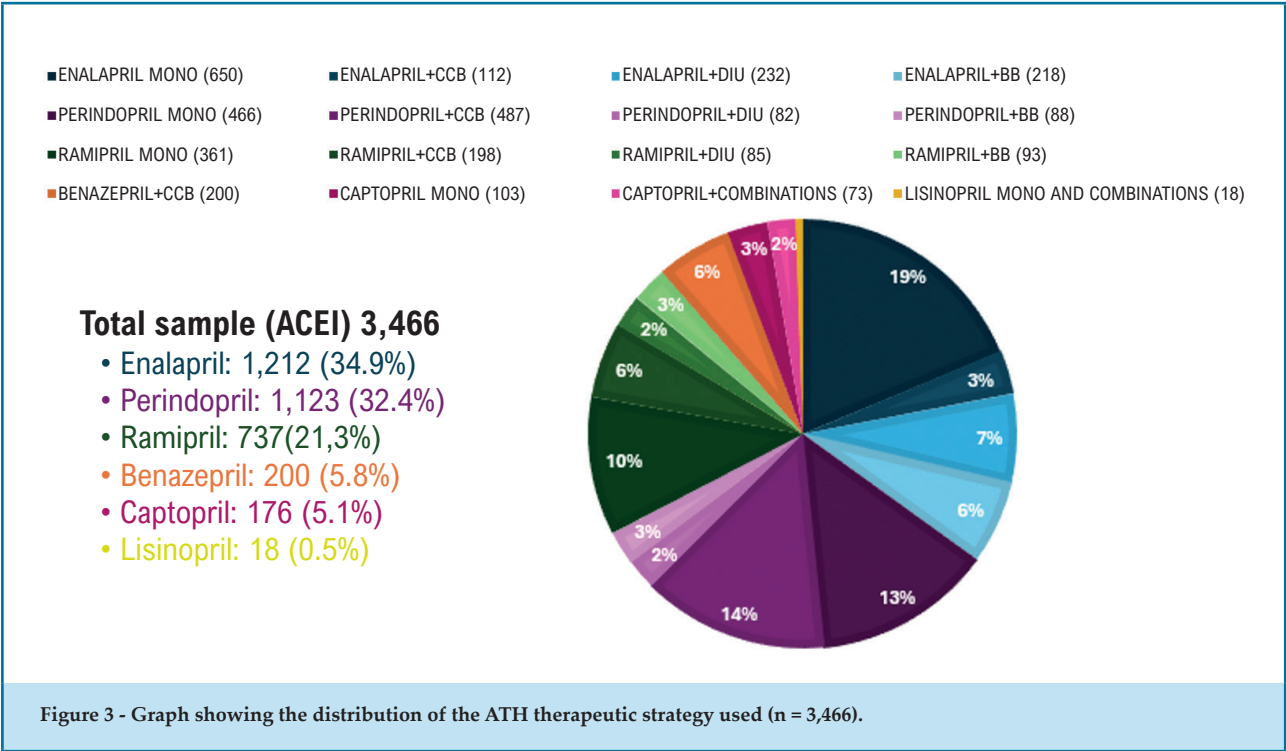


Table 1 - Comparison between mean systolic and diastolic BP obtained by casual measurement and HBPM			
Variable	Casual Measurement	HBPM	p*
Total (n = 3,466)			
SBP	131.6 ± 18.7	125.5 ± 14.8	< 0.001
DBP	83.4 ± 11.3	79.1 ± 9.4	< 0.001
ACEI monotherapy (n = 1,595)			
SBP	130.7 ± 18.9	125.1 ± 14.7	< 0.001
DBP	83.0 ± 11.1	78.9 ± 9.5	< 0.001
ACEI + CCB (n = 1,009)			
SBP	132.6 ± 16.8	125.8 ± 13.1	< 0.001
DBP	84.8 ± 10.9	80.1 ± 8.9	< 0.001
ACEI + DIU (n = 451)			
SBP	131.3 ± 20.5	124.2 ± 15.5	< 0.001
DBP	83.2 ± 11.9	78.5 ± 9.3	< 0.001
ACEI + BB (n = 411)			
SBP	133.0 ± 21.0	127.9 ± 17.8	< 0.001
DBP	81.5 ± 12.2	77.9 ± 10.1	< 0.001
* Paired t-test; ** Chi-square test. ACEI: angiotensin-converting enzyme inhibitors; CCB: calcium channel blockers; DIU: diuretics; BB: beta-blockers; HBPM: home blood pressure measurement; SBP: systolic blood pressure; DBP: diastolic blood pressure.			

Table 2 - Comparison of the frequency of controlled and uncontrolled BP by casual measurement and HBPM according to the use of ACEI in monotherapy (n = 1,595) and combinations with CCB (n = 1,009), DIU (n = 451) and BB (n = 411).

Variable	Controlled	Uncontrolled	p*
ACEI monotherapy (n = 1,595)			
Casual Measurement	962 (60.3%)	633 (39.7%)	0.016
HBPM	706 (44.3%)	89 (55.7%)	0.056
ACEI + CCB (n = 1,009)			
Casual Measurement	546 (54.1%)	463 (45.9%)	0.002
HBPM	384 (38.1%)	625 (61.9%)	0.001
ACEI + DIU (n = 451)			
Casual Measurement	265 (58.8%)	186 (41.2%)	0.774
HBPM	209 (46.3%)	242 (53.7%)	0.079
ACEI+ BB (n = 411)			
Casual Measurement	242 (58.9%)	169 (41.1%)	0.744
HBPM	175 (42.6%)	236 (57.4%)	0.982
* Paired t-test; * Chi-square test. ACEI: angiotensin-converting enzyme inhibitors; CCB: calcium channel blockers; DIU: diuretics; BB: beta-blockers; HBPM: home blood pressure measurement.			

1,474 (42.5%) by HBPM. When analyzing BP control by HBPM using the previous guideline's thresholds¹⁷ (SBP less than 135 mmHg or DBP less than 85 mmHg), 63% of the sample (2,184 patients) achieved controlled BP.

Table 3 describes the percentages of control of the different ACEI in monotherapy combined with CCB, DIU, or BB. A higher rate of non-control was observed for enalapril and captopril, both as monotherapy (by HBPM) and in combinations (by HBPM and casual measurement, respectively). Notably, 76.7% of patients on captopril monotherapy did not meet the target of less than 130/80 mmHg (Table 3, Central Illustration).

Perindopril combinations had the highest frequency of BP control in casual measurements but paradoxically showed higher non-control rates in HBPM, emphasizing the importance of home monitoring to assess BP targets in treated hypertensive patients (Table 3).

Ramipril + combinations achieved control by casual measurement in 63.6% of patients (Table 3).

Table 4 compares BP control rates between monotherapy and combination strategies, presenting average BP values from casual measurements and HBPM for ACEI (Table 4).

Captopril monotherapy had higher BP means in casual SBP ($p = 0.002$), MRPA SBP ($p < 0.01$), and MRPA DBP

($p < 0.01$) when compared to other ACEI monotherapy. Also, captopril + combinations showed worse means in HBPM SBP when compared to all other ACEI evaluated ($p = 0.001$) (Table 4).

Enalapril monotherapy had SBP and DBP means in both casual measurement and HBPM similar to perindopril, ramipril, and lisinopril, which are ACEI with longer half-lives. Enalapril + combinations also behaved similarly in HBPM SBP than ACEI with longer half-lives (Table 4).

Discussion

ACEI are a first-line drug class for hypertension treatment.^{3,6,8} A 2012 meta-analysis demonstrated their importance, showing a 10% reduction in all-cause mortality among hypertensive patients.¹³ This study extends the 2020 analysis, which found ACEI to be the second most frequently used hypertension treatment in this database.⁹ We evaluated aspects related to BP behavior both in-office and at home with the various drugs that make up the ACEI class.

Enalapril and captopril were shown antagonistically in the results. Enalapril and captopril are the only ACEI provided free of charge by the public health

Table 3 - A comparison of BP control rates by casual measurement and HBPM was conducted for patients using ACEI in monotherapy (n = 1,595) and combinations with CCBs, DIUs, or BBs (n = 1,868).

Variable	Controlled	Uncontrolled	p*
Enalapril monotherapy (n = 650)			
Casual Measurement	385 (59.2%)	265 (40.8%)	0.530
HBPM	307 (47.2%)	343 (52.8%)	0.007
Perindopril monotherapy (n = 466)			
Casual Measurement	287 (61.6%)	179 (38.4%)	0.104
HBPM	205 (44.0%)	261 (56.0%)	0.492
Ramipril monotherapy (n = 361)			
Casual Measurement	226 (62.6%)	135 (37.4%)	0.069
HBPM	164 (45.4%)	197 (54.6%)	0.239
Captopril monotherapy (n = 103)			
Casual Measurement	55 (53.4%)	48 (46.6%)	0.322
HBPM	24 (23.3%)	79 (76.7%)	< 0.01
Lisinopril monotherapy (n = 15)			
Casual Measurement	9 (60.0%)	6 (40.0%)	0.883
HBPM	4 (40.0%)	9 (60.0%)	0.843
Perindopril + combinations (n = 657)			
Casual Measurement	350 (53.3%)	307 (46.7%)	0.005
HBPM	240 (36.5%)	417 (63.5%)	0.001
Enalapril + combinations (n = 562)			
Casual Measurement	319 (56.8%)	243 (43.2%)	0.471
HBPM	261 (46.4%)	301 (53.6%)	0.040
Ramipril + combinations (n = 376)			
Casual Measurement	239 (63.6%)	137 (36.4%)	0.024
HBPM	158 (42.0%)	218 (58.0%)	0.833
Benazepril + combinations (n = 200)			
Casual Measurement	110 (55.0%)	90 (45.0%)	0.354
HBPM	81 (40.5%)	119 (59.5%)	0.550
Captopril + combinations (n = 73)			
Casual Measurement	33 (45.2%)	40 (54.8%)	0.024
HBPM	25 (34.2%)	48 (65.8%)	0.148

* Paired t-test; * Chi-square or Fisher's exact test. ACEI: angiotensin-converting enzyme inhibitors; CCB: calcium channel blockers; DIU: diuretics; BB: beta-blockers; HBPM: home blood pressure measurement.

Obs.1: Benazepril monotherapy was not analyzed as no patients in the sample used this drug alone. This substance was only found in association with CCB.

Obs.2: Data on lisinopril in combination were excluded, as only three patients were recorded using it.

Table 4 - Comparison of BP measurements obtained by casual measurement and HBPM between ACEI monotherapy and in combinations.

Monotherapy	Enalapril (n = 650)	Captopril (n = 103)	Perindopril (n = 466)	Ramipril (n = 361)	Lisinopril (n = 15)	P-value
Casual SBP	131.0 ± 19.6 ^a	137.6 ± 22.4 ^{b,c}	129.4 ± 16.8 ^a	130.0 ± 18.8 ^a	133.4 ± 14.4 ^{a,c}	0.002
Casual DBP	82.6 ± 11.4	85.5 ± 11.1	83.5 ± 10.9	82.3 ± 11.0	81.7 ± 7.1	0.071
HBPM SBP	124.9 ± 15.0 ^a	132.2 ± 17.3 ^{b,c}	124.0 ± 13.3 ^a	124.6 ± 14.5 ^a	131.1 ± 13.1 ^{a,c}	< 0.001
HBPM DBP	78.5 ± 9.9 ^a	82.6 ± 10.2 ^{b,c}	79.3 ± 8.7 ^a	78.1 ± 9.2 ^a	80.1 ± 8.2 ^{a,c}	< 0.001
Combinations (CCB/DIU/BB)	Enalapril (n = 562)	Captopril (n = 73)	Perindopril (n = 657)	Ramipril (n = 376)	Benazepril (n = 200)	P-value
Casual SBP	133.2 ± 21.1 ^{a,c}	139.3 ± 19.9 ^a	132.0 ± 17.6 ^{b,c}	130.3 ± 16.9 ^{b,c}	132.7 ± 17.2 ^{a,c}	0.003
Casual DBP	82.2 ± 12.0 ^a	85.7 ± 13.8 ^{a,b,d}	84.9 ± 11.1 ^{b,c,d}	82.6 ± 10.9 ^a	85.5 ± 11.2 ^{c,d}	<0.001
HBPM SBP	126.3 ± 16.6 ^b	132.5 ± 16.9 ^a	125.0 ± 13.2 ^b	125.9 ± 14.3 ^b	125.3 ± 14.7 ^b	0.001
HBPM DBP	77.8 ± 10.0 ^a	80.9 ± 9.3 ^{a,b}	80.0 ± 8.7 ^b	79.2 ± 9.0 ^{a,b}	80.2 ± 9.5 ^b	<0.001

**One-way ANOVA with Tukey post-hoc. Equal letters correspond to similar means and different letters correspond to different means between columns (comparison of BP means between different medications). ACEI: angiotensin-converting enzyme inhibitors; CCB: calcium channel blockers; DIU: diuretics; BB: beta-blockers; HBPM: home blood pressure measurement; SBP: systolic blood pressure; DBP: diastolic blood pressure.*

system in Brazil. Enalapril was the most widely used ACEI and despite not having a long half-life, and requiring two doses per day, it presented similar results in reducing BP both as monotherapy and in combinations compared to other ACEI with long half-lives. It is noteworthy that more than 75% of patients using captopril monotherapy did not reach the goals recommended by the MRPA. When the average BP levels achieved were assessed, captopril again showed worse averages in several scenarios, both in monotherapy and in combinations.

For optimal efficacy, a drug's half-life and trough-to-peak ratio must be considered. Only drugs with a trough/peak ratio above 50% can be used in a single daily dose. Among ACEIs, these ratios vary: captopril 25%; enalapril 40–64%; perindopril 75–100%; benazepril 50%; lisinopril 30–70%; ramipril 50–63%.¹⁸ The low frequency of captopril use in this sample (5.1%) despite its accessibility in the public health system suggests that prescribers are aware of the impact of dosing frequency on adherence and BP control. Captopril requires at least three doses per day for effectiveness. The similar BP control results observed with enalapril and longer half-life ACEI are attributed to proper adherence to the recommended twice-daily dosing for enalapril. It is important to note that the data analyzed did not specify the

number of daily doses for each drug, only the drug names. Based on the results, it can be inferred that enalapril was appropriately used, whereas captopril was underutilized.

Regarding prescription frequency, lisinopril was the least prescribed ACEI in this sample (approximately 0.5%), despite being reported as the most prescribed AH medication globally, according to Messerli *et al.*¹⁹

BP control was observed in 60.3% of cases for ACEI monotherapy in the casual measurement. It is inferred that the higher percentage of control observed in monotherapy is associated with the fact that patients using a single class of ATH usually have stage 1 hypertension.

For combinations, a stronger association was observed with CCBs, in contrast to a similar study on ARBs, which showed a greater association with DIUs.²⁰ Notably, the ACEI + CCB combination was highlighted in the ACOMPLISH trial (2008), which demonstrated that benazepril + amlodipine was superior to benazepril + thiazide in achieving the same BP control while reducing cardiovascular outcomes and mortality in hypertensive patients, reporting a 21.5% reduction in AMI and a 13.9% reduction in myocardial revascularization in the ACEI + CCB group.²¹ The predominance of double combination strategies aligns

with current guidelines, which recommend limiting monotherapy to patients with stage 1 hypertension and low CV risk, BP between 130–139/85–89 mmHg with high CV risk, or elderly and/or frail individuals.³ It is worth noting that combinations with CCBs or DIUs (rather than other combinations) should be prioritized, reflecting adherence to national recommendations.^{5,22} The association with BBs is typically reserved for specific cases, such as patients with CAD or arrhythmias. Unfortunately, it is not possible to state from this analysis whether such identified associations were fixed combinations, which has also been proven to be more effective in controlling BP.⁴

Less than half of the study population (42.5%) had BP controlled by HBPM, which is concerning given the direct relationship between BP control and a reduced risk of death and cardiovascular diseases.^{23,24}

BP control was more frequently observed with casual measurements than with HBPM, likely due to the higher reference threshold for casual measurement (140x90 mmHg) compared to HBPM (130x80 mmHg), making the target easier to achieve. This highlights the importance of home measurement methods in terms of detecting real BP control and identifying, in this case, the white coat effect.^{16,25} It is important to note that patients on combination therapies are typically at moderate to high risk, meaning their casual measurement goal would be even stricter (SBP < 130 mmHg and DBP < 80 mmHg).

This study has limitations, as it is observational and lacks details about the dosages, number of daily doses, or whether medications were provided as combination pills. Additionally, the risk profiles of patients and their hypertension stages, which influence BP goals, are not available. It is unclear whether the centers where the tests were conducted are public or private. A recent national study has shown that patients in public healthcare settings use almost twice as many hypertension medications but achieve lower BP control compared to those in private care.²⁶ It is also not possible to know whether the prescriptions are predominantly written by cardiologists or doctors from other areas. While we assume that patients using ACEI and undergoing HBPM are hypertensive, it is acknowledged that this class of drugs is also used for other conditions, such as heart failure. Despite its large size, the sample is not statistically representative of the Brazilian population – there was a discrepant predominance of exams from the Northeast region in relation to the others. However, the study includes patients from all five regions

of the country, providing valuable insights into the use of ACEI and the BP behavior associated with these drugs, whether in monotherapy or combination.

Conclusion

In the large sample of Brazilian adults treated with ACEI, a preference for the use of enalapril was observed. Although enalapril has a shorter half-life compared to other ACEI with longer half-lives, it achieved similar BP control outcomes. This is a significant advantage, as enalapril is distributed free of charge through the national public healthcare system. In contrast, captopril showed notably poorer BP control and performance compared to other drugs in the same class.

Author Contributions

Conception and design of the research, writing of the manuscript and critical revision of the manuscript for intellectual content: Colombo T, Vitorino PVO, Feitosa A, Brandao A, Barbosa ECD, Miranda RD, Gomes MM, Sousa ALL, Souza WKS; acquisition of data and obtaining financing: Colombo T, Souza WKS; analysis and interpretation of the data and statistical analysis: Colombo T, Vitorino PVO, Sousa ALL, Souza WKS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This article is part of the thesis of master submitted by Tariane Colombo, from Universidade Federal de Goiás.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Hospital das Clínicas da Universidade Federal de Goiás under the protocol number 4.504.756. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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