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ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Effects of new drug interaction index on drug adherence in older patients with hypertension

Yaşlı hipertansiflerde yeni ilaç etkileşim indeksinin ilaç uyumuna etkisi

İbrahim Ersoy, M.D.[1], Pınar Ersoy, M.D.[2]

[1]Department of Cardiology, Afyonkarahisar University of Health Sciences, Afyonkarahisar, Turkey
[2]Department of Public Health, Afyonkarahisar Health Directorate, Afyonkarahisar, Turkey

ABSTRACT

Objective: Hypertension is a challenging problem in the older population because of poor drug adherence (DA). We aimed to determine the DA and examine the drug interaction index (DII) on DA in older patients with hypertension.

Methods: In this cross-sectional, observational study, we enrolled 418 eligible patients aged ≥ 65 years between 1 February 2020 and 30 September 2020 in a tertiary hospital outpatient cardiology clinic. We prepared a questionnaire to record sociodemographic characteristics, morbidities, and drugs used by the population. The Morisky Medication Adherence Scale-8 (MMAS-8) was used for DA assessment. We identified drug interactions using the Lexicomp application. We calculated the DII from a ratio of clinically relevant interaction to total interaction. Descriptive tests and multiple linear regression analyses were performed to find independent factors on DA.

Results: The mean age (± standard deviation [SD]) was 72.91 (±6.47), and 272/146 were female/male in the study population. The most frequent comorbid disease was diabetes mellitus (23.5%). The percentage of patients having polypharmacy was 39.5, and the mean daily drug (SD) use was 4.27 (±2.57). The most prescribed antihypertensive drugs were thiazide/derivates (29.8%) and angiotensin receptor blockers (24.8%). The mean MMAS-8 (±SD) was 4.55±0.98, and 321 (76.8%) participants had poor DA. A total of 33.4% of patients had significant drug interaction. The mean DII (±SD) was 0.345±0.017. The area under the receiver operating characteristic (ROC) curve for DII was 0.616 (95% confidence interval [CI]: 0.547-0.686).

Conclusion: We defined a new index for drug interaction intensity. Furthermore, the DII may be a useful tool to study aspects of DA in older patients with hypertension.

ÖZET

Amaç: Hipertansiyon, yaşlılarda tedaviye uyum düşük olduğu için yönetimi güç bir hastalıktır. Çalışmamızda yaşlı hipertansiflerde ilaç etkileşim indeksinin (İEE) ilaç uyum üzerine etkisini değerlendirmeyi amaçladık.

Yöntemler: Kesitsel gözlemsel çalışmamıza, 01.02.2020 ile 30.09.2020 tarihleri arasında üçüncü basamak hastanenin kardiyoloji polikliniğine başvuran 65 yaş ve üzeri, 418 hastayı dahil ettik. Hastaların sosyo-demografik özelliklerini, ek hastalıklarını ve aldıkları ilaçları sorgulayan bir anket hazırladık. İlaç uyumu için Morisky ilaç uyum skalası-8 (MMAS-8) kullanıldı. İlaç etkileşimleri, Lexicomp® uygulaması ile değerlendirildi. İlaç uyumunu etkileyen faktörlerin tespiti için tanımlayıcı testler ve çoklu lineer regresyon analizleri yapıldı. İlaç etkileşim indeksi, klinik ilişkili ilaç etkileşimlerinin toplam ilaç etkileşimlerine oranından hesaplanmıştır.

Bulgular: Araştırma popülasyonunun ortalama yaşı [± standart sapma (SS)] 72.91 (±6.47) idi ve 272/146'ü kadın/erkek. En sık eşlik eden hastalık diyabetes mellitustu (%23.5). Hastaların %39.5'inde polifarmasi mevcuttu, günlük ortalama (SS) 4.27 (±2.57) sayıda ilaç alıyordu. En sık reçete edilen anti-hipertansifler tiazid ve türevleri (%29.8), anjiyotensin reseptör blokerleri (24.8%), anjiyotensin dönüştürücü enzim inhibitörü (%14.9) idi. Ortalama MMAS-8 skoru (SS) 4.55±0.98 idi ve katılımcıların 321 (%76.8)'inin ilaç uyumu kötüydü. Hastalarının %33.4'ünde klinik ilişkili ilaç etkileşimi vardı. Yeni ilaç etkileşim indeksini ortalama (SS) 0.345±0.017 idi. MMAS-8 skorunu belirlemede İEE'nin tahmini için yapılan receiver operating characteristic (ROC) eğrisi analizinde eğri altı alanı 0.616 saptadık [95% güven aralığı (GA): 0.547- 0.686].

Sonuç: Yaşlı hipertansiflerde ilaç etkileşim yoğunluğunu belirlemek için yeni bir endeks tanımladık. Bu endeks, ilaç uyumu tahmininde kullanışlı bir araç olabilir.

Hypertension is a common and challenging problem in older patients, reaching a prevalence as high as 70 to 80 percent.[1-3] Despite considerable improvements in the diagnosis and treatment of hypertension, control rates are lower in older adults than younger patients. According to published data in the National Health and Nutrition Examination Survey, blood pressure control rates were 46 and 33 percent among adults aged 65 to 74 and 75+, respectively.[1]

Poor adherence to treatment regimens contributes to the burden of uncontrolled hypertension. In literature, hypertensive older patients are 40 to

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Correspondence: İbrahim Ersoy, M.D., Department of Cardiology, Afyonkarahisar University of Health Sciences, Afyonkarahisar, Turkey
Tel: +90 506 493 58 05 e-mail: iersoytr@hotmail.com

77 percent nonadherent to drug therapy.[4,5] Drug adherence (DA) is generally defined as the consistency with which patients take their medications as prescribed by their healthcare providers.[6] According to the World Health Organization (WHO), there are 4 groups of factors that influence adherence: (1) healthcare-system-related, (2) disease-related, (3) therapy-related, and (4) patient-related components.[6] Therapy-related factors including polypharmacy and drug interactions are known barriers for DA in the older population. However, we believe that interaction intensity should be evaluated as the third dimension besides the drug quantities and interactions. Therefore, we designed a new, simple index called the drug interaction index (DII) to reflect intensity. This index measures the ratio of clinically relevant drug interaction to total drug interaction.

We hypothesized that a high drug interaction intensity and not merely drug interaction would decrease antihypertensive medication adherence. Based on this hypothesis, our study had 2 main objectives: (1) to determine DA rates and associated factors, and (2) to examine the influence of the DII on DA in older patients with hypertension.

METHODS

Patient population

The study was conducted with the cardiology outpatient clinic in Afyonkarahisar Health Sciences University, located in Turkey. The present study has a cross-sectional design. A total of 446 consecutive patients diagnosed with hypertension who were visiting the cardiology outpatient clinic for a follow-up about any complaint between 1 February 2020 and 30 September 2020 were examined in the study.

We included 418 eligible subjects in the study. The criteria for selecting the subjects were as follows: (1) age 65 and over; (2) diagnosed with hypertension; and (3) taking at least one antihypertensive medication for the previous 3 months. Most participants had scheduled a clinical appointments admission. Patients visiting the clinic because of exacerbation of acute cardiac problems (acute coronary syndromes, decompensated heart failure, malign arrhythmias) that might lead to hospitalization were excluded. As per the inclusion criteria, all the respondents in the study were outpatients who were previously on medications, and those patients seeking a physician's checkup as emergency care were excluded. The researchers filled in all the questionnaire data using a face-to-face interview. Verbal informed consent was obtained from participants after a brief explanation of the aim of the study.

Abbreviations:

ACEinh	*Angiotensin-converting enzyme inhibitors*
ARB	*Angiotensin receptor blockers*
AUC	*Area under the curve*
CI	*Confidence interval*
DA	*Drug adherence*
DII	*Drug interaction index*
IQR	*Interquartile range*
ROC	*Receiver operating characteristic*
SSRI	*Selective serotonin reuptake inhibitor*
WHO	*World Health Organization*

Patients taking acetylcholinesterase inhibitors and ginkgo biloba were also questioned about self-care capacity and cognitive status. Researchers made a simple cognitive assessment by 3 memory questions (testing recall of 3 random words) and 3 orientation questions (year, month, and day of the week). The patients included correctly answered ≥2 of the 6 questions and were classified as having only mild cognitive impairment.[7]

We excluded 28 patients based on communication problems that impacted our ability to obtain adequate data for the questionnaire. The problems included severe cognitive impairment (n=6) or advanced dementia (n=4), hearing difficulties (n=8), and missing pharmacy-identifying information (n=10).

We recorded the participants' sociodemographic characteristics (age, sex, marital status, and educational status), clinical parameters (height, weight, duration of treatment, number of tablets and number of doses per day, and number and types of comorbidities), and the level of adherence using the Morisky 8-item validated questionnaire.[8] Additionally, drug market names and active substrates were recorded in the dataset. Newly prescribed antihypertensive medications were not considered for drug interaction. Polypharmacy was defined as taking five or more different prescribed medications,[6] including antihypertensives. The comorbidities and their collection procedures are described in Appendix 1.

The study was approved by the Ethics Committee of the Afyonkarahisar Health Sciences University (no. 2020/12) on 2 January 2020. The study was conducted under the Declaration of Helsinki guidelines and the principles of Good Clinical Practice and with respect for the other parties' rights and dignity.

Drug interaction measurement

The risk scoring of each antihypertensive medication for potential drug-drug interactions was performed using the online Lexicomp® (Wolters Kluwer, Hudson, Ohio) program. The classification of this program is as follows:

A-No evidence of interactions in literature

B-Known interactions, but no action needed

C-Monitor therapy

D-Consider therapy modification

X-Avoid combination

Most of the studies evaluating drug interactions with the Lexicomp® application focus only on the clinically relevant part (C, D, X).[9-11] Classes A and B have not usually been considered by previous researchers. We believe that the drug interaction intensity could be substantial, and this term also includes the drug number and clinically relevant drug interactions together. However, there is no parameter for evaluating drug interaction intensity. Therefore, we developed a new index called the DII that is described as follows: first, drug interaction groups were determined as A, B, C, D, and X according to the Lexicomp classification. Then, we counted the sum of group C, D, and X interactions and the total interaction numbers. Finally, we calculated the ratio of groups C, D, and X to all groups (A, B, C, D, and X). The DII formula is shown below:

$$DII = \frac{\text{Class C+Class D+Class X}}{\text{Class A+Class B+Class C+Class D+Class X}}$$

Medications for concomitant diseases were classified according to the anatomical, therapeutic and chemical (ATC) system recommended by the WHO.

Measuring antihypertensive drug compliance

Medication adherence was measured by a validated Turkish version of the MMAS-8.[8] It is an eight-item questionnaire with high reliability and validity, and it is easy to use. Seven questionnaire items were answered with scores of 0 for yes and 1 for no, and one item had a 5-point Likert scale response option (see Appendix 1). The sum of the eight-item score indicates the level of DA. The minimum score obtained from the scale is 0, and the maximum score is 8. According to the scale, a score between 6 and 8 indicates good adherence, while a score below 6 indicates poor compliance.[12]

Statistical analysis

We calculated the sample size for multiple linear regression tests allowing 95% statistical power, 5% alpha error, and 0.15 effect size for a total of 32 predictors (including age, sex, height, weight, educational level, number of chronic medications taken daily, duration of antihypertensive use, and number and types of comorbidities) using G*power software v3.1.9.4 (Franz Faul, Universität Kiel, Germany). The estimated minimum sample size was 267.[13,14]

Study data were evaluated using the SPSS 22 software package (IBM Corp., Armonk, NY, USA). The descriptive data were summarized as the percentage frequency for categorical variables and the mean±standard deviations (SDs) or median 25-75 interquartile range (IQR) for continuous variables. The skewness and kurtosis tests were used to assess the normality of the distribution of the variables. A chi-square test was used to determine the difference in adherence by sample characteristics. Receiver operating characteristic (ROC) curve analysis was conducted on the predicted DII value for identification of the MMAS-8 score; the correspondent area under the curve (AUC) was calculated with its 95% confidence interval (CI). Multivariate linear regression analysis was performed to determine factors of the MMAS-8 score by using $p<0.5$ in univariate analysis. The relationships between DA and total drugs per day, antihypertensive medication duration, and the DII were calculated using multivariate regression analysis. Furthermore, the model was conducted with the enter method. $p<0.05$ was taken as the limit value for significance accompanied by 95% CI.

RESULTS

In our study, 418 patients were enrolled. The mean age (SD) was 72.91 (±6.47); 65% (n=272) were female and 35% (n=146) were male. The most frequent comorbid diseases were diabetes mellitus (27.8%), gastric and duodenal disturbances (19.4%), chronic obstructive pulmonary disease, and asthma (10.5%). Most patients had an educational level of primary school or below (n=359, 85.9%) (Table 1).

Table 1. Basal characteristics of the study population

Variables	Study population (n=418)
Age (years)*	72.9±6.47
Sex (F/M)	272/146
Body mass index (kg/m²)*	28.87±5.40
Hypertension duration (years) (IQR 25-75)	11 (5-15)
Antihypertensive drug duration (month) (IQR 25-75)	134 (60-180)
Education level, n (%)	
Illiterate	99 (23.7)
Literate	64 (15.3)
Primary school	196 (46.9)
Secondary school	14 (3.4)
High school	29 (6.9)
University	16 (3.8)
Concomitant Diseases, n (%)†	
Diabetes mellitus	116 (23.5)
Dementia	34 (6.9)
Coronary artery disease	43 (8.7)
Heart failure	4 (0.8)
Atrial fibrillation	74 (15.1)
Stroke/TIA	13 (2.6)
Epilepsy	3 (0.6)
Osteoporosis	6.1)
Arthropathies	39 (7.9)
Chronic renal disease	6)
Chronic hepatic disease	4 (0.8)
Chronic obstructive pulmonary disease/Asthma	44 (8.9)
Urinary incontinence	5 (1.0)
Gastric and duodenal disturbances	81 (16.5)

*Mean±standard deviation.
†Percentages were calculated according to cumulative disease numbers.
F: female; IQR: interquartile range; M: male, TIA: transient ischemic attack.

Table 2. Antihypertensive medication and drug interaction characteristics classes of study population

Variables	Value
Total drug number per day*	4.27±2.57
ATC Category of Antihypertensives, n (%)	
ARB	211 (24.8)
ACEinh	127 (14.9)
CCB	123 (14.5)
Thiazide and derivates	254 (29.8)
Beta-blockers	117 (13.7)
Mineralocorticoids	14 (1.6)
Alfa-blockers	4 (0.5)
Drug Interaction Class (%)	
A	769 (64.5)
B	15 (12.6)
C	369 (33.5)
D	7 (0.5)
X	2 (0.1)
Morisky Medication Adherence Score*	4.55±0.98
Poor drug adherence (%)	321 (76.8)
DII	0.345±0.017

*Mean±standard deviation.
ATC: Anatomical Therapeutic Chemical System; ARB: angiotensin receptor blockers; ACEinh: angiotensin-converting enzyme inhibitors; CCB: calcium channel blockers; DII: drug interaction index; IQR: interquartile range.

The most commonly used antihypertensive drug classes in the study were thiazide and derivates (29.8%), angiotensin receptor blockers (ARB) (24.8%), and angiotensin-converting enzyme inhibitors (ACEinh) (14.9%) (Table 2). There were 111 patients (26.5%) using dual antihypertensive drugs and 29 (6.9%) using 3 or more antihypertensive medications. The most commonly preferred combination (67.8%) was ARB with thiazide/thiazide-like diuretics. The most used active substrates were a combination with valsartan hydrochlorothiazide in the subgroup (see Appendix 1). The mean drug number per day was 4.27 (±2.57), and 39.5% of the patients were polypharmacal.

The mean MMAS-8 score was 4.55 (±0.98) (Table 2). A total of 321 participants (76.8%) scored below 6 and were classified as having low DA.

The drug interaction analyses showed that 65.8% of the older patients with hypertension in the study were not at risk in terms of potential interaction, and 33.4% of patients should be followed to monitor interaction (group C interaction risk score). Furthermore, 9 patients had clinically significant interactions, and they should be consulted about medication change (group D and X interaction risk scores). Two of these patients were detected as having a group X interaction risk (see Appendix 1).

We found a mean DII of 0.345 (±0.017). The ROC curve analysis was conducted to identify the DII value for MMAS-8 score prediction; the AUC was

Table 3. Univariate and multivariate linear regression analysis of predictors and adherence to antihypertensive medications using Morisky Medication Adherence Scale-8

	Univariate				Multivariate			
		95% CI				95% CI		
Variables	Beta	Lower bound	Upper bound	*P*	Beta	Lower bound	Upper bound	*P*
Constant					4,810	2,676	6,945	<0.001
Age	0.014	-0.022	0.049	0.450	-	-	-	-
Sex	-0.256	-0.740	0.229	0.300	-	-	-	-
Education level	-0.191	-0.259	0.024	0.250	-	-	-	-
Total drug number	-0.167	-0.968	-0.270	0.001	-0.115	-0.188	-0.042	0.002
Drug interaction index	-1.055	-1.630	-0.446	<0.001	-1.013	-1.604	-0.422	0.001
Antihypertensive medication duration (years)	-0.005	-0.007	-0.002	<0.001	-0.00[illegible]	-0.005	-0.001	0.001

R^2=0.335, F=18.376, *p*<0.001.

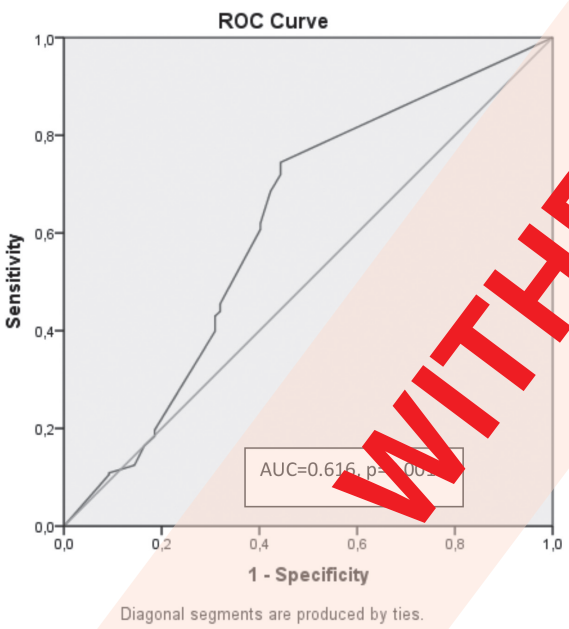

Figure 1. The Receiver-Operator Curve analyses for the ability of drug interaction index to drug adherence score identification.
AUC: area under the curve.

0.616, and a cut-off value of 0.127 with 80% sensitivity and 67% specificity (2.37 positive likelihood ratio) for the DII could predict DA with 95% CI: 0.547 to 0.686 (p<0.001) (Figure 1).

As a result of the multivariable linear regression analysis using the enter method, variables such as age, sex, educational level, drug numbers, DII, and hypertension duration were thought to affect the MMAS-8 [illegible]e; the structured model was significant (F=[illegible] p<0.001). The model describes 33% of chang[illegible] in the DA scale (R^2=0.335). DII (p=0.001), an[illegible]ntihypertensive medication duration (p=0.002) [illegible]d total drug number per day (p=0.001) have statistically significant effects on the DA level (Table 3).

DISCUSSION

Hypertension is the most common chronic disease in the geriatric population. Moreover, older hypertensives are at a higher risk of drug-drug interaction because of their high polypharmacy rates and decreased drug metabolism capacity. It is generally agreed that low DA and polypharmacy are an increasing trend among older patients with hypertension.[15,16] However, to date, little attention has been paid to drug interaction intensity in this population.

The primary aim of this study was to find out the impacts of drug interaction intensity on DA in older patients with hypertension. We found that a higher DII value was an independent risk factor for low DA. The regression analysis showed that daily medication number and treatment duration also have negative effects on drug compliance. Moreover, we saw that 33.4% of the patients had clinically relevant drug interactions. Finally, most of our patients had polypharmacy, low DA, and long-term hypertension.

In our study, the daily drug number average was 4.27, and 39.5% of patients were taking 5 or more drugs per day (polypharmacy). The main contribu-

tors to polypharmacy were diabetes mellitus, gastric and duodenal disturbances, and atrial fibrillation.[17] Polypharmacy levels were consistent with previous findings of 30% to 72% in various studies.[18,19] The higher number of chronic prescription drugs in the study group may be explained by the older age and multiple morbidities. Polypharmacy alone was an independent risk factor for poor DA.[15]

Another important finding was that 76.8% of our study population had low DA, and the mean MMAS-8 score (SD) was only 4.55 (±0.98). Compared with the values (22.7% to 67.7%) in the literature in different countries,[20,21] our DA rates were much lower. This result may be influenced by the fact that many of our study participants had a low literacy rate. Also, it can be argued that the low DA is caused by the study population's inherent nature. For example, 11.2% of the study group had mild cognitive dysfunction. Additionally, our cross-section period was during the coronavirus (COVID-19) pandemic. At the beginning of the pandemic, there was some speculative information that renin-angiotensin receptor blockers could increase the risk of COVID-19 in hypertensives.[22,23] Thus, patients could be hesitant to take this drug from a critical group. Moreover, pandemic-related conditions such as low hospital admission could have decreased DA levels.

Antihypertensive treatment duration was another independent risk factor for low DA. The median duration of antihypertensive treatment (the IQR) was 134 months (60-180). This finding is in line with previous studies.[4,24] A plausible explanation is that DA may decrease as new morbidities requiring medication, such as cardiovascular diseases and diabetes, develop over the years.

Consistent with literature, we showed that the daily medications involved in drug interactions were 33.4% prevalent in the geriatric population.[19,25,26] Antidiabetic drugs and selective serotonin reuptake inhibitors (SSRIs) have the most frequent drug interactions in the present study. A possible explanation for this finding might be that thiazides have adverse effects on glucose metabolism, which is regulated by anti-diabetics.[27] Additionally, concomitant use of thiazide with SSRIs may potentiate hyponatremic effects.[28,29] In our study population, the most frequent combination was valsartan and thiazide. It should be noted that recent findings indicate increased serum thiazide levels with valsartan interaction.[30] Thus, this combination may enhance thiazide side effects.

We proposed a new index evaluating interaction intensity. As mentioned above, we define DII as a ratio of action-required drug interactions to total drug interactions. Furthermore, for the first time, the present data shows that a 0.127 cut-off value with 80% sensitivity and 67% specificity (2.37 positive likelihood ratio) for DII could predict adherence level. The observed association between DII and DA might be explained in the following way: more intense interactions could cause significant alterations in drug plasma levels, impair metabolic and electrolyte levels, and influence central nervous system function. These situations could cause discomfort and discontinuation of drugs for older patients with complex comedications and comorbidity.

This study provides an insight into the underlying barriers to medication adherence in older hypertensives. Although there are many drug interaction studies in older patients with hypertension, no previous research has investigated drug interaction intensity. This is the first study in literature to examine the influence of drug interaction intensity on medication adherence among geriatric hypertensive patients. There is still a great deal of work to be done in this area. Our study also extends knowledge about drug prescription habits, interactions, and useful features of older patients with hypertension in a tertiary hospital.

Limitations

The results of this study should be interpreted with some caution because of the limitations of data collection. The Berksonian type bias cannot be eliminated as the patients were enrolled in an outpatient clinic. Therefore, behaviors observed against drug and concomitant medication use cannot be generalized to the general population. Another important limitation of the study is that the study was conducted during the COVID-19 pandemic. A pandemic, as a well-known and significant stress factor, could have increased the DA in the older population, whereas the speculations even in the media coverage against the use of ACEinh could have decreased the use of these agents during the pandemic.[22] Additionally, the access to drugs could be affected during the pandemic.

In most of the trials about DA, sociodemographic properties were evaluated.[12,20,31] This analysis ex-

amines only the educational levels and therefore, the results are limited to drug properties. Another critical limitation lies in the fact that we did not consider achieving target blood pressure, which could be a reason for patients to discontinue their medications.

Additionally, the DII is structured to measure antihypertensives' interaction, but we do not know the comedications' interactions with each other. We examined drug interactions only from one online application. It is not a full pharmacokinetic and pharmacodynamic assessment. So, this approach does not fully consider the problems that can appear in complex situations. But it does demonstrate the need for further research.

Conclusion

This study found that most older patients with hypertension have low drug compliance, long-term hypertension, and polypharmacy. The findings from this study make several contributions to the current literature. First, we defined a new index for drug interaction intensity. Moreover, this index can be used to predict DA in hypertensive patients. Second, we found that drug numbers and therapy duration have negative effects on DA.

To increase adherence, practitioners should evaluate older patients more meticulously in follow-up visits. The ability to predict adherence levels based on DII values can help providers identify patients who need additional monitoring. Also, patients and caregivers could be given the information in drug interaction applications. In future work, the DII may be a useful tool to study aspects of DA.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Afyonkarahisar Health Sciences University (Approval Date: January 2, 2020; Approval Number: 2020/12).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

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Authorship Contributions: Concept - İ.E., P.E.; Design - İ.E.; Supervision - İ.E., P.E.; Resources - İ.E.; Materials - İ.E., P.E.; Data Collection and/or Processing - İ.E., P.E.; Analysis and/or Interpretation - İ.E., P.E.; Literature Search - İ.E., P.E.; Writing - İ.E., P.E.; Critical Revision - İ.E., P.E.

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Keywords: Hypertension; elderly; drug adherence; polypharmacy; drug interactions

Anahtar Kelimeler: Hipertansiyon; yaşlılık; ilaç uyumu; polifarmasi; ilaç etkileşimi

Appendix 1. Supplementary Methods and Data

Supplemental Method. Comorbidities: Definition and data collection.

Variables	Definition and data collection
Body mass index	Calculation based on weight/size:Clinical examination
Ischemic heart disease	History of cardiac disease involving coronary artery disease: Clinical examination and extraction from medical records
Heart failure	History of systolic or diastolic heart failure: Clinical examination and extraction from medical records
Atrial fibrillation	History of atrial fibrillation, regardless of the pattern status:Clinical examination and extraction from medical records
Epilepsy	Defined by at least 2 unprovoked seizures occurring more than 24 hours apart, clinical examination and extraction from medical records
Osteoporosis	Defined by T-score ≤-2.5 SDs at any site based upon BMD measurement by DXA: Clinical examination and extraction from medical records
Arthropathies	History of Rheumatoid arthritis, Inflammatory osteoarthritis and degenerative osteoarthritis: Clinical examination and extraction from medical records
Urinary incontinence	History of urge urinary incontinence, stress urinary incontinence, overflow incontinence, urethral hypermobility and bladder outlet obstruction: Clinical examination and extraction from medical records
Gastric and duodenal disturbances	History of gastritis, peptic ulcers, duodenal ulcers and dyspepsia: Clinical examination and extraction from medical records
Kidney failure	Defined by a creatinine clearance rate <60 mL/min/1.73 m2, as calculated with the MDRD equation: Clinical examination and extraction from medical records
Diabetes mellitus	Defined by a fasting glucose level >1.26 g/L confirmed twice, or active treatment for diabetes mellitus: Clinical examination and extraction from medical records
Chronic hepatic disease	History of chronic hepatitis B, C, steatohepatitis: Clinical examination and extraction from medical records
Chronic obstructive pulmonary disease	Defined by the need for long-term oxygen therapy for a lung condition: Clinical examination and extraction from medical records
Dementia	Defined by the criteria for dementia according to DSM-5:Clinical examination and extraction from medical records
Stroke/Transient ischemic attack	Defined by transient or permanent brain hypoperfusion due to thrombosis or hemorrhage: Clinical examination and extraction from medical records

BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; MDRD: modification of diet in renal disease.

Supplemental Method. **Morisky Medical Adherence Scale (MMAS-8-TR):[8] Definition and data collection**

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Supplementary data. **The main medications involved in grade D and X potential drug interactions**

Serious interaction group	Antihypertensive drug	Interacting drug	Interacting mechanism*
Group X interactions	Trandolapril and verapamil	Pimozide	CYP3A4 inhibitors
	Perindopril and indapamide	Olmesartan and hydrochlorothiazide	Angiotensin-converting enzyme inhibitors/ Angiotensin II receptor blockers
Group D interactions	Trandolapril and verapamil	Colchicine	CYP3A4 inhibitors
	Nebivolol	Brimonidine (Ophthalmic)	Beta-blockers/Alpha2-agonists
	Diltiazem	Atorvastatin	CYP3A4-mediated metabolism
	Amlodipine	Phenytoin	Phenytoin/Calcium channel blockers
	Amlodipine	Erythromycin (Systemic)	Calcium channel blockers/ Macrolide antibiotics
	Amlodipine	Phenytoin	Phenytoin/Calcium channel blockers
	Ramipril	Lithium	Lithium/Angiotensin-converting enzyme inhibitors

*Data from Lexicomp® Drug Interactions application

Supplemental data. Drug interactions according to the ATC system of non-antihypertensive medications

ATC Category of non-antihypertensive therapy	Drug interactions (C,D,X) (n=408)
Cardiovascular system	49
Genito urinary system and sex hormones	18
Systemic hormonal preparations, excl. sex hormones and insulins	159
Musculo-skeletal system	24
Nervous system	104
Respiratory system	74

ATC: Anatomical, therapeutic chemical system.

Supplemental data. Antihypertensive combination characteristics

Total combination (n=260)		%
Valsartan and hydrochlorothiazide	65	25.2
Candesartan and hydrochlorothiazide	35	14
Valsartan and amlodipine	27	10.8
Perindopril and indapamide	22	8.8
Losartan and hydrochlorothiazide	22	8.8
Ramipril and hydrochlorothiazide	18	7.2
Telmisartan and hydrochlorothiazide	14	5.6
Irbesartan and hydrochlorothiazide	14	5.6
Olmesartan and hydrochlorothiazide	13	5.2
Verapamil and trandolapril	12	4.8
Zofenopril and hydrochlorothiazide	9	3.6
Cilazapril and hydrochlorothiazide	7	2.8
Quinapril and hydrochlorothiazide	5	2
Perindopril and amlodipine	5	2
Lisinopril and hydrochlorothiazide	4	1.6
Fosinopril and hydrochlorothiazide	4	1.6
Enalapril ad nitrendipine	4	1.6
Benazepril and hydrochlorothiazide	3	1.2

Supplementary data. Antihypertensive substrate characteristics

Antihypertensive substrates	n	%
Valsartan	99	11.9
Candesartan	37	4.4
Amlodipine	81	9.7
Perindopril	34	4
Losartan	26	3.1
Ramipril	43	5.1
Telmisartan	16	1.9
Irbesartan	14	1.7
Olmesartan	7	0.8
Verapamil	14	1.7
Zofenopril	8	1
Cilazapril	8	1
Quinapril	6	0.7
Nifedipine	8	1
Lisinopril	5	0.6
Fosinopril	5	0.6
Enalapril	3	0.3
Benazepril	2	0.2
Trandolapril	15	1.8
Benazaepril	2	0.2
Nitrendipine	6	0.7
Lercanidipine	9	1
Phelodipine	3	0.3
Hydrochlorothiazide	213	25.5
Metoprolol	63	7.5
Nebivolol	25	3
Carvedilol	18	2.1
Spironolactone	15	1.8