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

Yaşlı hipertansiflerde yeni ilaç etkileşim indeksinin ilaç uyumuna etkisi

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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 a 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 endeksinin (İEE) ilaç uyumuzda etkisini değerlendirerek amaçladık.

Yöntemler: Kesitsel gözlem yöntemi uygulandı. 01.02.2020 ile 30.09.2020 arasında üçüncü basamak hastanenin kardiyoloji polikliniğine başvuran 65 yaş ve üzeri, 418 hasta dahil etti. Hastaların sosyo-demografik özellikleri, ek hastalıklarını ve aldıkları ilaçları sorgulayan bir anket hazırlanarak hastaların kadın/erkek oranını, yaş sapma [SS] 72.91 (±6.47) idi ve 272/146’sından kadın/hayırkerdi. En sık eşlik eden hastalik diyabetes mellitusü (%23.5). Hastaların %39.5’tinde polifarmasi mevcuttu, günlük otalama (SS) 4.27 (±2.57) sayıda ilaç alıyordu. En sık useHistory edilen anti-hipertansif tiazide ve türevleri (%29.8), anjiyotensin reseptör blokerleri (24.8%), anjiyotensin dönüştürücü enzim inhibitörü (%14.9) idi. Otalama MMAS-8 skoru (SS) 4.55±0.98 idi ve katılımcıların %76.8’inin ilaç uyumu kötüydü. Hastalarının %33.4’ünde ilaç etkileşimi vardı. Yeni ilaç etkileşimi indeksini otalama (SS) 0.345±0.017 idi. MMAS-8 skorunu belirlediğimiz 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 kullanılması bir araç olabilir.
77 percent nonadherent to drug therapy.\cite{4,5} Drug adherence (DA) is generally defined as the consistency with which patients take their medications as prescribed by their healthcare providers.\cite{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. \cite{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.

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.\cite{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.\cite{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,\cite{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). 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:

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

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).
The most commonly used antihypertensive drug classes in the study were thiazide and derivatives (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.

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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

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| 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                                        | 30 (6.1)                    |
| Arthropathies                                       | 39 (7.9)                    |
| Chronic renal disease                               | 3 (0.6)                     |
| 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)                        |
| 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.

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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
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 score; the structured model was significant (F=18.376, p<0.001). The model describes 33% of changes in the DA scale (R²=0.335), DII (p=0.001), and antihypertensive medication duration (p=0.002) and 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.\textsuperscript{[17]} Polypharmacy levels were consistent with previous findings of 30\% to 72\% in various studies.\textsuperscript{[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.\textsuperscript{[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,\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[14,24]} 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.\textsuperscript{[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.\textsuperscript{[27]} Additionally, concomitant use of thiazide with SSRIs may potentiate hyponatremic effects.\textsuperscript{[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.\textsuperscript{[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 comedinations 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.\textsuperscript{[22]} Additionally, the access to drugs could be affected during the pandemic.

In most of the trials about DA, sociodemographic properties were evaluated.\textsuperscript{[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.

**Peer-review:** Externally peer-reviewed.

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

Anahtar Kelimeler: Hipertansiyon; yaşlılık; ilaç uyumu; polyfarmasy; 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):** Definition and data collection

| Items                                                                 | No | Yes |
|-----------------------------------------------------------------------|----|-----|
| 1. Do you sometimes forget to take your high blood pressure pills?    |    |     |
| 2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your high blood pressure medication? |    |     |
| 3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it? |    |     |
| 4. When you travel or leave home, do you sometimes forget to bring along your high blood pressure medications? |    |     |
| 5. Did you take your high blood pressure medication yesterday?         |    |     |
| 6. When you feel like your blood pressure is under control, do you sometimes stop taking your medication? |    |     |
| 7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your blood pressure treatment plan? |    |     |
| 8. How often do you have difficulty remembering to take all your blood pressure medication? | Never/Rarely | 4 |
|                                                                       | Once in a while | 3 |
|                                                                       | Sometimes      | 2 |
|                                                                       | Usually        | 1 |
|                                                                       | All the time   | 0 |

**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) | n     | %     |
|---------------------------|-------|-------|
| Valsartan and hydrochlorothiazide | 63    | 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 |