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Medication adherence and persistence according to different antihypertensive drug classes: A retrospective cohort study of 255,500 patients

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ABSTRACT

Background: Suboptimal adherence to antihypertensives leads to adverse clinical outcomes. This study aims to determine and compare medication adherence and persistence to different first-line antihypertensive drug classes in a large cohort.
Methods: A cohort study was performed using claims data for prescriptions in the German statutory health insurance scheme that insures approximately 90% of the population. A total of 255,500 patients with a first prescription of an antihypertensive were included and followed for 24 months. Persistence was determined based on gaps in continuous dispensation. Adherence was analyzed by calculating the medication possession ratio (MPR).
Results: Within a 2-year period, 79.3% of all incident users of antihypertensive monotherapy met the classification of non-persistence (gap >0.5 times the number of days supplied with medication) and 56.3% of non-adherence (MPR < 0.8). Beta-blockers (42.5%) and angiotensin-converting enzyme inhibitors (31.9%) were the most widely prescribed drug classes. Non-persistence and non-adherence were highest for diuretics (85.4%, $n = 6149$ and 66.3%, $n = 4774$) and lowest for beta-blockers (77.6%, $n = 76{,}729$ and 55.2%, $n = 54{,}559$). The first gap of antihypertensive medication occurred in median 160–250 days after initiation, and the average medication possession ratio for all drug classes was less than 0.8. Fixed combinations with diuretics showed a 19.8% lower chance for non-adherence (OR = 0.802, 99.9% CI = [0.715–0.900], $p < 0.001$) and an 8.4% lower hazard for non-persistence (HR 0.916, 99.9% CI = [0.863–0.973], $p < 0.001$) compared with monotherapies.
Conclusions: This large cohort study reveals important differences in 2-year adherence and persistence between antihypertensives that were lowest for diuretics. Fixed-dose combinations with diuretics may facilitate adherence compared to single substance products. However, effective strategies to improve adherence to antihypertensives are needed regardless of drug class.

1. Introduction

Multiple randomized clinical trials demonstrate that blood pressure lowering is associated with major reductions in coronary events, strokes, and mortality [1,2]. In order to translate this robust evidence into clinical practice, long-term and continuous pharmacotherapy is required [3–5]. Non-adherence and even premature discontinuation of therapy or medication non-persistence are, however, major problems [6,7]. Improving patients' medication adherence reduces morbidity and mortality [8–10]. Medication adherence may differ in real-world patients when compared to closely monitored conditions in clinical trials [11–13]. Selection bias, run-in periods, and behavior reinforcement through close follow-up may contribute to this observation [12,14]. Previous studies found a relationship between adherence to antihypertensive (AHT) treatment and drug class but with inconsistent results [12,15–17].

Adherence according to the World Health Organization (WHO) is defined as “the extent to which a person's behavior – taking medication,

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following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider" [5]. Various methods have been described to measure medication adherence: direct methods like measurement of drug levels in blood samples, as well as indirect methods like self-reports, refill compliance or electronic medication monitors [18]. Despite some limitations (e.g., clinical data are usually unavailable), dispensation records, i.e., claims databases are a source of objective non-adherence information and often the only sources available for assessing adherence (synonym: compliance), particularly in large cohorts. It is recommended to evaluate both, persistence to medication and adherence, the latter most often as the medication possession ratio (MPR) [19,20].

The aims of this study were, therefore, (1) to estimate medication adherence and persistence to all first-line AHT drug classes using medication refill data in a large, nationwide German cohort covering all statutory health insurance (SHI) funds, and (2) to analyze the influence of covariates on adherence and persistence to AHTs.

2. Methods

2.1. Database

The database of the German Institute for Drug Use Evaluation (DAPI; www.dapi.de) comprises claims data of prescribed drugs, dispensed at community pharmacies at the expense of SHI funds. This insurance system includes nearly 90% of the German population [21]. The DAPI data cover more than 80% of all community pharmacies' claims data, without information on self medication (over-the-counter medication, OTC), dosing, hospitalizations, diagnosis/indications, or clinical data. A pseudonymized identification code allows for follow-up of insured persons.

Prescription data are linked to the ABDA database containing a complete inventory of German medicinal products and other items which are dispensed by pharmacies [22]. A linkage is possible via the product code "Pharmazentralnummer" (PZN). The PZN is a unique identifier for medicinal products that precisely defines each drug package and provides, e.g., information about the (brand) name, composition, active ingredient, strength, dosage form, package size, and pharmaceutical company [23].

2.2. Study design

We conducted a retrospective cohort study, using claims data of medications dispensed to patients at the expense of all SHI funds in Germany. We considered the recommendations on Good Practice for Secondary Data Analysis [24,25], and the checklist published by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) [19]. Medication persistence to AHTs was investigated using the gap method (GAP) and the MPR was calculated to assess adherence [20].

2.3. Study period

The study period includes prescriptions from January 1, 2004, to December 31, 2007, with a first prescription of an AHT between January 1 and June 30, 2005. Within 6 months following the first prescription, a second prescription of the same AHT was required and considered the index prescription. Each patient was followed for 24 months (Fig. 1).

2.4. Inclusion and exclusion criteria

All AHT which may be used as monotherapy in first-line treatment were included: angiotensin II receptor blockers (ARBs; anatomical therapeutic chemical (ATC) code C09CA), angiotensin-converting enzyme inhibitors (ACEi; C09AA), calcium channel blockers (CCBs; C08C, C08D, C08E), beta-blockers (BBs; C07AA, C07AB, C07AG), thiazide and sulfonamide diuretics (C03AA and C03BA), and fixed-dose combinations of ARBs, ACEi, CCBs, and BBs with a diuretic (C09DA, C09BA, C08G, C07BB, C07BA, C07CB, C07CA, C03EA) [26,27]. All dosage strengths of all products approved for hypertension were considered. The medicinal product at first prescription constituted the index product and, hence, the drug class.

Prescriptions of loop diuretics, mineralocorticoid receptor antagonists, or of any AHT, which was not approved for hypertension as single drug product (monotherapy) or fixed-dose combinations of loop diuretics or mineralocorticoid receptor antagonists, were excluded, as were patients with a prescription within 12 months prior to the first prescription of one of the AHT included. Parenteral or liquid formulations were also excluded. Patients with a prescription of a different AHT between first and index prescription were excluded. Switching the index AHT substance/fixed combination during the observation period was not allowed but claims for different brand products/generics of the index AHT were counted. Patients were excluded from the main analysis if they changed their insurance company or died during the study period, as well as if no prescription for any medication between 24 and 36 months following the index prescription has been claimed. These patients were included in the sensitivity analyses. Fig. 2 presents the selection process of the study cohort.

2.5. Definition of covariates

For each patient, the type of insured person (mandatory member, family member, retired), the medical specialty of the prescribing physician (e.g., general practitioner, internal medicine specialist), and the type of therapy (monotherapy or fixed-dose combination with a diuretic) was derived from the index prescription. Furthermore, the number of different drugs prescribed (ATC code 3rd level) was determined during 180 days prior to the index date.

2.6. Measurement of persistence

The gaps in continuous medication were quantitated to determine persistence [20]. The patient was classified as non-persistent when a gap exceeded 0.5 times the number of days supplied with medication. Persistence was determined for each prescription separately. Remaining medication units (tablets) from previous prescriptions at the time of the following prescription were not added to medication units of the following prescription [28]. Additionally, the duration of persistence until the first gap occurred was recorded.

The prescribed daily dose is unavailable in German claims data. Therefore, the number of days supplied with medication (DM) was determined for each prescription using the summary of product characteristics (SPC)—including the information about the mean number of doses/applications per day (MND) for the indication arterial hypertension and the number of medication units (e.g., one tablet) per single dose (UD). The calculation was performed as follows:

$$DM_{SPC}\,[\text{days}] = \frac{\text{number of medication units dispensed per prescription}}{(\text{MND} * \text{UD})}.$$

2.7. Measurement of adherence

To determine adherence, the MPR was calculated, which was defined as the number of doses dispensed in relation to the dispensing period [20]. The calculation of the MPR

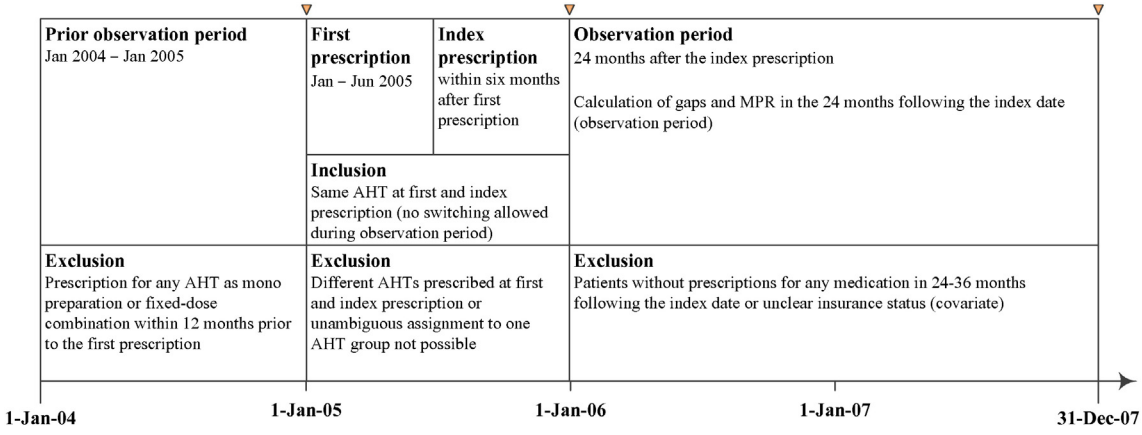

Fig. 1. Inclusion and exclusion criteria. AHT = antihypertensive.

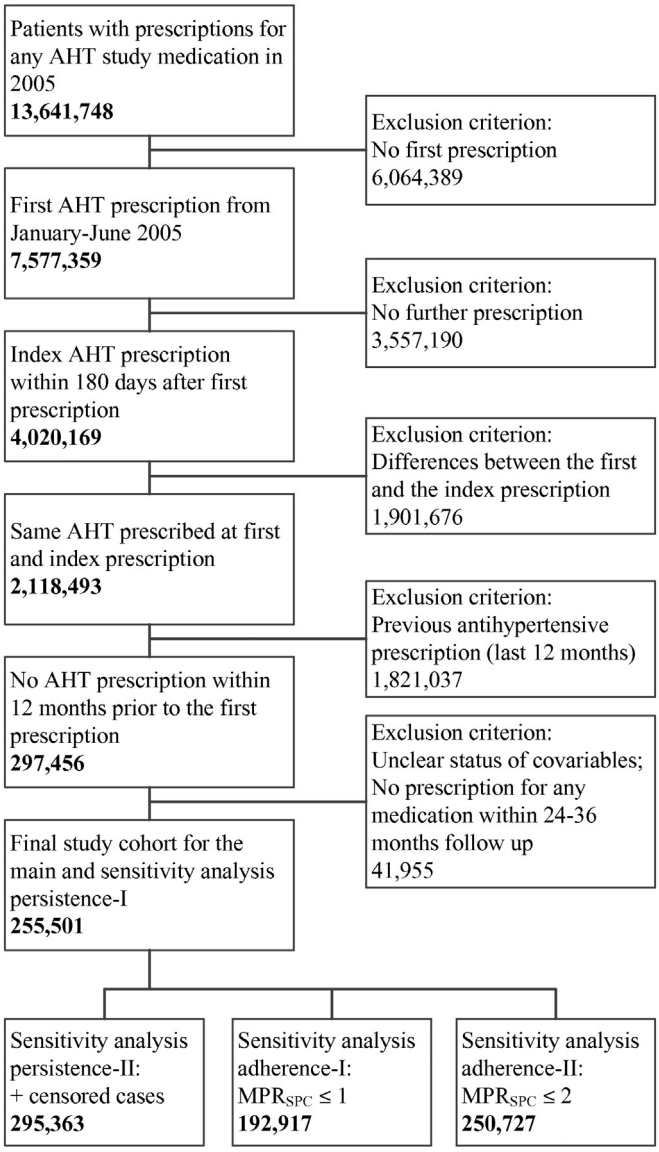

Fig. 2. Selection process. AHT = antihypertensive, MPR = medication possession ratio, SPC = summary of product characteristics.

was based on the calculation of the DM_{SPC} as described above, with x_i = ith dispensation and n = total number of prescriptions within 730 days after the index prescription:

$$MPR_{SPC} = \frac{\sum_{i=1}^{n} DM_{SPC}(x_i)}{730 \text{ days}}$$

Patients with MPR values ≥0.8 were classified as adherent, whereas MPR values <0.8 were rated as non-adherent [29–32]. This cutoff is widely used especially for AHTs and enables comparability with other published data [12,17,23,29,33–36].

2.8. Statistical analyses

2.8.1. General methods

Persistence and adherence were described for the different AHT groups using box plots to show the number of days until the first medication gap occurred (persistence) and the frequency distribution of the MPR (adherence). Categorical variables were analyzed using the chi-square test. Kaplan–Meier curves were used to present the cumulative probabilities of persistence, i.e., absence of gaps.

2.8.2. Influence of covariates on persistence and adherence

Cox-regression (persistence) and logistic regression (adherence; MPR <0.8 vs. MPR ≥0.8) were used to identify the influence of different AHT groups as well as covariates on persistence and adherence. The models were fitted unadjusted first, with diuretics (ATC codes C03AA and C03BA) as reference [37] and then adjusted for the following covariates: type of therapy, medical specialty of the prescribing physician, status of the insured person, and number of ATC 3rd level drugs and co-medication. The assumptions of proportional hazards were verified. Due to the very large cohorts, the level of significance was set at $p < 0.001$. Statistical analyses were performed using PASW Statistics 18 (version 18.0.0, released 30 July 2009, SPSS Inc., Chicago, Illinois, USA).

2.8.3. Sensitivity analyses

In total, four sensitivity analyses were performed (Fig. 2). To consider differences in dosing, e.g., splitting of tablets, persistence was determined allowing a 2-fold gap in the number of days supplied with medication (sensitivity analysis persistence-I). Additionally, patients without any prescription within 24 to 36 months after the index date where censored at their last prescription date during the observation time and included in a second sensitivity analysis (persistence-II).

For adherence, two additional sensitivity analyses were performed on excessive use of medication: excluding patients with either MPR values >1.0 (adherence-I) and >2.0 (adherence-II), due to the fact that stockpiling or medication overconsumption seems rather implausible [28].

3. Results

3.1. Study population

In the year 2005, 13,641,748 patients in our database received a prescription for any AHT of the study medication. Fig. 2 shows the selection process in relation to the inclusion and the exclusion criteria. Finally, 255,501 patients were included in the main analysis.

Table 1 presents the number of patients and analyzed variables according to the drug classes. BBs were most often prescribed (42.5%, $n = 108{,}590$), followed by ACEi (31.9%, $n = 81{,}512$). Diuretics were the AHT class with the least prescriptions (5.7%, $n = 14{,}475$). Fixed-dose combinations of ARBs and diuretics were prescribed approximately as frequent as monotherapies of these drug classes. Fixed-dose combinations of CCBs and diuretics were prescribed for 127 patients only. Therefore, this group was excluded from further evaluations. The other drug classes were more frequently prescribed as monotherapies. About 70% of the prescriptions of all AHTs were issued by general practitioners. CCBs and diuretics were predominantly prescribed for retired patients whereas mandatory, hence younger, members received particularly BBs. Approximately 75% of patients received up to six additional drug classes. 15.3% of the study population received lipid-lowering drugs (ATC code C10), 14.9% antidepressants (N06A), 13.6% oral antidiabetics or insulin (A10B or A10A), 10.9% additionally heart failure medications (cardiac glycosides (C01A), aldosterone antagonists (C03DA, C03E), or high-ceiling diuretics (C03C, C03EB)), 7.3% antiplatelet drugs (B01AC), 4.9% nitrates (C01DA), 3.5% vitamin K antagonists (B01AA), and 2.3% antiarrhythmics (C01B or C07AA07) (data not shown).

3.2. Results for persistence

In total, 79% of all patients receiving AHT monotherapies, and 76% of all patients on combination therapies with diuretics were classified as non-persistent (gap exceeded 0.5 times the number of days supplied with medication). The proportion of non-persistent patients with monotherapy was highest for diuretics (85.4%, $n = 6149$), and lowest for BBs (77.6%, $n = 76{,}729$). The results for combination therapies of an ACEi, ARB, or BB with a diuretic were comparable (Table 2).

For the five AHT drug classes, the median of the first gap in medication available occurred between 150 days for diuretics and 236 days for ACEi monotherapy (Fig. 3). The median number of days for combinations with diuretics was between 187 days (diuretics as combination partner) and 287 days (ARBs as combination partner). The Kaplan–Meier curves (Fig. 4) indicate that half of the patients receiving ACEi, ARBs, and BBs were non-persistent after approximately 250 days. Half of the patients receiving CCBs and diuretics were non-persistent after approximately 160 days. In Germany, drug packages for chronic diseases are usually prescribed and dispensed in 3-month boxes representing the largest norm size (N3), containing approximately 100 tablets. This prescribing habit explains the pronounced decreases

of the probability of persistence at 3 and 6 months following the index prescription (Fig. 4).

Compared with diuretics, the unadjusted Cox-regression model (Table 3) resulted in a 17.6% lower hazard for non-persistence to BBs, 17.2% lower to ACEi, and 12.1% lower to ARBs (all $p < 0.001$). The results for the adjusted model, 22.7%, 17.9%, and 8.2%, respectively (all $p < 0.001$), are supportive of this order and magnitude. AHT/diuretic fixed-dose combinations showed a 8.4% lower likelihood for non-persistence (hazard ratio (HR) 0.916, 99.9% confidence interval (CI) [0.863–0.973], $p < 0.001$) compared with monotherapies (Table 4). All but one of the other covariates analyzed resulted in statistically significant differences in relation to the chosen reference group. For example, members (HR 1.157, 99.9% CI = [1.138–1.176], $p < 0.001$) and family members (HR 1.140, 99.9% CI = [1.110–1.170], $p < 0.001$) showed a statistically significant higher hazard for non-persistence with the retired group as reference.

The sensitivity analysis persistence-I resulted in comparable although more pronounced effects. Compared with diuretics, the unadjusted Cox-regression model resulted in a 32.8% lower hazard for non-persistence to BBs, 26.5% lower to ACEi, 25.1% lower to ARBs, and 11.8% lower to CCBs (all $p < 0.001$). The adjusted HR for CCBs became too significant: 0.882, 99% CI = [0.832–0.936], $p < 0.001$. AHT/diuretic fixed-dose combinations showed a 12.5% lower likelihood for non-persistence (HR 0.875, 99% CI = [0.813–0.942], $p < 0.001$) compared with monotherapies. The sensitivity analysis persistence-II didn't change the order and magnitude of the differences when compared to the main analysis (data not shown).

3.3. Results for adherence

Patients with MPR values ≥0.8 were defined as adherent, whereas MPR values <0.8 were rated as non-adherent [29–32]. Roughly 56% of all patients receiving AHT monotherapies and 50% of all patients with a diuretic combination therapy were classified as non-adherent (Table 2). The proportion of non-adherent patients receiving monotherapy (single drug products) as well as fixed-dose combinations was highest for diuretics (66.3%, $n = 4774$ and 61.0%, $n = 4438$, respectively), and lowest for BB monotherapy (55.2%, $n = 54{,}559$) and ARB/diuretic combinations (45.9%, $n = 6030$).

For the five AHT drug classes, the MPR for monotherapies ranged between 0.547 for diuretics and 0.684 for ACEi as well as for BBs (Fig. 5). The median MPR for combinations with diuretics was between 0.547 (diuretics as combination partner) and 0.821 (BB as combination partner).

The unadjusted logistic regression model resulted in statistically significant lower odds ratios (OR; chance for non-adherence) for ACEi, ARBs, CCBs, and BBs when compared to diuretics (all $p < 0.001$). The results for the adjusted logistic regression model were comparable to the results of the unadjusted model (Table 3). Combinations with a diuretic showed a statistically significant lower chance for non-adherence (OR = 0.802, 99.9% CI = [0.715–0.900], $p < 0.001$) compared with monotherapies (Table 4). The following covariates showed a statistically significant influence in relation to the corresponding reference group: type of prescriber, member status, and co-medication consisting of at least 7 drug classes. Co-medication of lipid-lowering drugs, antidiabetics, antiarrhythmics, vitamin K antagonists, or platelet aggregation inhibitors was associated with reduced odds for non-adherence, i.e., with better adherence (data not shown). Both sensitivity analyses resulted in comparable OR (data not shown).

4. Discussion

As medication adherence (synonym: compliance) and medication persistence are two different constructs, we distinguished between adherence and persistence to characterize medication taking behavior comprehensively, as recommended by Cramer et al. [20] Within a 2-year period, 79.3% of all incident users of antihypertensive medication as monotherapy were classified as non-persistent (gap exceeded 0.5 times the number of days supplied with medication) and 56.3% as non-adherent (medication possession ratio (MPR) < 0.8). Beta-blockers (BBs; 42.5%) and angiotensin-converting enzyme inhibitors (ACEi; 31.9%) were the most widely prescribed drug classes. Both non-persistence and non-adherence were highest for diuretics and lowest for BBs. The first gap of antihypertensive (AHT) medication occurred in median as early as 160–250 days after initiation and the average MPR for all drug classes was less than 0.8. Fixed combinations with a diuretic showed roughly a 20% lower chance for non-adherence and an 8% lower hazard for non-persistence compared with monotherapies.

Our findings of real-world patients add to the existing body of literature that non-adherence to AHTs is not only common but cannot be overestimated. Especially worrying are the very low rates of persistence, independent of the AHT class chosen as first-line pharmacotherapy,

Table 1
Characteristics of the analyzed variables according to AHT drug class.*

Analyzed variables	ACE inhibitors	Angiotensin II receptor antagonists	Beta-Blockers	Calcium channel blockers	Diuretics	Total
Number of patients (%)	81,512 (31.9)	27,830 (10.9)	108,590 (42.5)	23,094 (9.0)	14,475 (5.7)	255,501 (100.0)
Therapy						
Monotherapy	57,105 (70.1)	14,684 (52.8)	98,828 (91.0)	22,967 (99.5)	7203 (49.8)	200,787 (78.6)
Combination	24,407 (29.9)	13,146 (47.2)	9762 (9.0)	127 (0.5)	7272 (50.2)	54,714 (21.4)
Prescriber						
GP	58,888 (72.2)	19,953 (71.7)	76,004 (70.0)	16,138 (69.9)	10,257 (70.9)	181,240 (70.9)
IMS	21,426 (26.3)	7512 (27.0)	29,079 (26.8)	6489 (28.1)	3924 (27.1)	68,430 (26.8)
Other	1198 (1.5)	365 (1.3)	3507 (3.2)	467 (2.0)	294 (2.0)	5831 (2.3)
Status[a]						
Retired	45,419 (55.7)	13,513 (48.6)	43,371 (39.9)	15,272 (66.1)	9113 (63.0)	126,688 (49.6)
Member	3002 (36.8)	11,997 (43.1)	51,940 (47.8)	6378 (27.6)	4206 (29.1)	77,523 (30.3)
Family member	6072 (7.4)	2320 (8.3)	13,279 (12.2)	1444 (6.3)	1156 (8.0)	24,271 (9.5)
Co-medication						
0–1 drug class	19,320 (23.7)	7093 (25.5)	28,406 (26.2)	5798 (25.1)	2361 (16.3)	62,978 (24.6)
2–3 drug classes	22,076 (27.1)	7608 (27.3)	28,944 (26.7)	6228 (27.0)	3655 (25.3)	68,511 (26.8)
4–6 drug classes	21,191 (26.0)	7006 (25.2)	26,583 (24.5)	5952 (25.8)	4145 (28.6)	64,877 (25.4)
≥ 7 drug classes	18,925 (23.2)	6123 (22.0)	24,657 (22.7)	5116 (22.2)	4314 (29.8)	59,135 (23.1)

Table 1 includes the number of patients per drug class of a total of 255,501 patients; *n* (%).
AHT = antihypertensive; GP = general practitioner, IMS = internal medicine specialist.
* Significant differences of the analyzed variables between the five study cohorts ($p < 0.001$; chi-square test).
[a] Data available for 228,482 patients.

Table 2
Number (%) of non-persistent and non-adherent patients.

	ACEi	ARB	BB	CCB	Diuretics	Total
Non-persistent patients (GAP)						
Monotherapy	45,510 (79.7)	12,049 (82.1)	76,729 (77.6)	18,722 (81.5)	6149 (85.4)	159,159 (79.3)
Combination	18,646 (76.4)	9938 (75.6)	7187 (73.6)	80 (63.0)	5862 (80.6)	41,713 (76.2)
Non-adherent patients (MPR <0.8)						
Monotherapy	31,867 (55.8)	8462 (57.6)	54,559 (55.2)	13,474 (58.7)	4774 (66.3)	113,136 (56.3)
Combination	12,268 (50.3)	6030 (45.9)	4808 (49.3)	43 (33.9)	4438 (61.0)	27,587 (50.4)

Table 2 includes 200,787 (78.6%) patients with monotherapy, and 54,714 (21.4%) patients with fixed-dose combination therapy.
ACEi = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor antagonists, BB = beta-blockers, CCB = calcium channel blockers, GAP = gaps in continuous medication, MPR = medication possession ratio. Note: The total number of combinations of calcium channel blockers was very small ($n = 127$) in relation to other medications.

within the 2-year period of observation. Persistence and adherence are far from optimal for all patients in this huge nationwide cohort of incident users.

The DAPI database covers data from over 80% of community pharmacies and thus is expected to be representative for the entire SHI scheme, insuring approximately 90% of the German population. Due to the objectivity of claims data [20], reporting bias – which may be present in studies using adherence questionnaires for patients or health care providers – can be ruled out. Another strength of this study is the evaluation of all relevant AHT classes over 2 years.

These "real-life" data exhibit important differences in both, adherence and persistence to AHT of separate classes. The differences by drug class may be related to different profiles in dosage and side effects [38,39]. Our results, related to the high non-persistence and non-adherence rates for diuretics, correspond to the existing literature [12, 15,16,29,35,38,40–54]. The mean overall persistence at 12 months with antihypertensives, available from 12 studies in the meta-analysis by Kronish et al., ranged from 35% to 84% [12]. Patients with prescription of ARBs were approximately twice as likely to have a higher adherence than patients with prescription of diuretics which is consistent with the results of our adjusted regression analyses. In contrast to most previous studies [12,15,48,50–52,54,55], we found the highest persistence and adherence rates for BBs, followed by ACEi and ARBs. But, one may question whether these significant differences are of clinical importance. However, our finding is in agreement with Lachaine et al. who report the highest persistence rate after a two-year period for BBs [29]. With more recent guidelines and the availability of cheaper generics of renin–angiotensin–aldosterone system (RAAS) inhibitors, i.e., ACEi and ARBs, BBs are probably prescribed less frequently first-line for hypertension nowadays.

The fact that persistence to AHTs is generally low and independent of drug class could be explained by the lack of symptoms in patients with hypertension. Probably, patients try to use the first prescription correctly, take the following prescription, but stop the therapy before achieving daily routine. This illustrates the importance of assisting patients with newly prescribed medication [56–58].

Converting continuous data (MPR) into categorical data and defining a cutoff distinguishing poor from good adherence (usually as MPR < vs. ≥0.8) is more often than not supported by appropriate research [19]. Although the evidence that patients having been dispensed at least 80% of AHTs have a better outcome than patients taking less is not overwhelming, the evidence of this cutoff for AHTs/hypertension is the best known to us: High adherence to AHTs (defined as MPR ≥0.8–1.0) was associated with higher odds (odds ratio (OR) 1.45, 95%

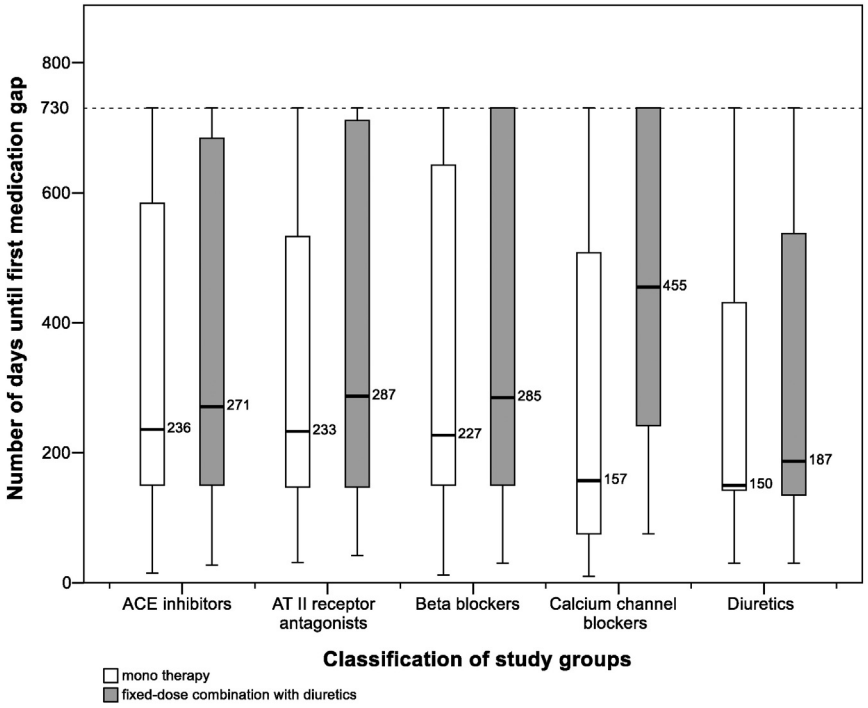

Fig. 3. Persistence of the five antihypertensive drug classes determined as number of days until the first gap in medication occurred (box plot). Note: The total number of combinations of calcium channel blockers was very small ($n = 127$) in relation to other medications.

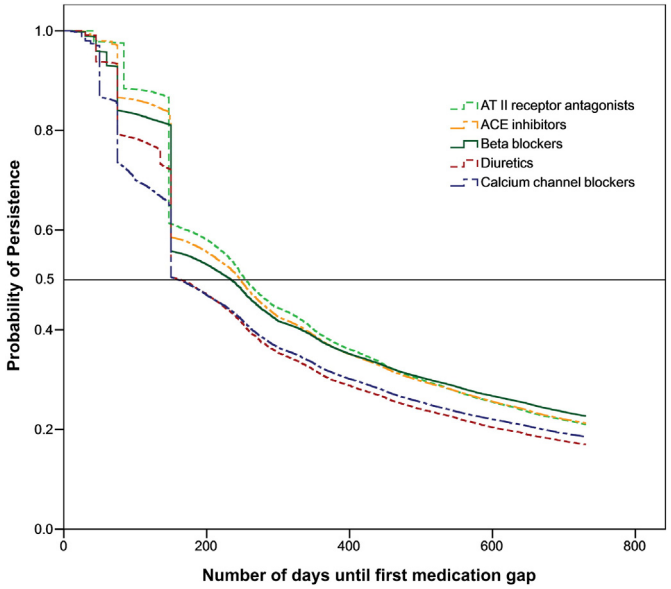

Fig. 4. Probability of persistence of the five antihypertensive drug classes determined as number of days until the first gap in medication occurred over the study period of 730 days (Kaplan–Meier curves).

CI = 1.04–2.02) of blood pressure control compared with those with medium or low levels of adherence [30,31]. Moreover, Krousel-Wood et al. [32] showed that the hazard ratio (HR) for cardiovascular disease (CVD) events (stroke, myocardial infarction, congestive heart failure, or CVD death) associated with medium (MPR 0.5 to <0.8) and low (MPR < 0.5) adherence were 1.17 (95% CI = 0.87–1.56) and 1.87 (95% CI = 1.06–3.30), respectively, compared to high adherence (MPR ≥0.8). Pharmacy-refill but not self-report AHT medication adherence was associated with incident CVD. Moreover, this cutoff enables the comparison of our results with other published data using the same cut-off [12,17,23,29,33–36,59].

Only half of the patients achieved a MPR ≥0.8, with little differences in relation to the drug class. Wang et al. showed that only 19% of a total of 896 patients achieve a MPR ≥0.8 in the preindex period [60]. Potential reasons should be identified within daily practice, to counteract premature and unintended early discontinuation of medication intake by patients and eventual subsequent prescribing.

Additionally, our results suggest that retired, hence, older patients have a lower likelihood for non-persistence and non-adherence for AHTs than younger patients (status “member” or “family member”). This is similar to the results of other studies finding a higher risk of medication non-adherence in younger patients [61,62]. Probably, newly diagnosed patients with the first prescription of AHT are in particular need for enhanced care provided by healthcare professionals.

We found a moderately lower likelihood for non-persistence and non-adherence in fixed-dose combinations of AHTs with diuretics compared with monotherapies. It could be assumed that the change from mono to combination therapies could improve medication adherence [60,63,64]. But, not all individual therapies could be combined, and not any cause of non-adherence can be addressed by this approach [65,66].

Patients with co-medication of lipid-lowering drugs, antidiabetics, antiarrhythmics, Vitamin K antagonists, or platelet aggregation inhibitors representing an increased cardiovascular risk, showed better persistence and adherence.

4.1. Limitations

Main limitations arise from the unavailability of (hypertension) diagnosis, physicians' prescriptions, and actual amount of doses taken by the patient. In Germany, it is not obligatory for physicians to note the diagnosis and prescribed dose on the prescription. The absence of clinical and demographic data is further limiting the assessment of potential covariates.

To minimize the potential impact of these limitations on our results, we included only incident users of antihypertensive medication approved for hypertension so that all patients were AHT-naïve for at least 12 months. Although we cannot exclude the possibility that BBs were prescribed for patients without hypertension, significant differences according to the clinical diagnosis between AHT drug classes studied are not to be expected. Apart from BBs, the first use of RAAS inhibitors or CCBs might be for other indications than hypertension. Nevertheless, residual confounding resulting from missing information regarding diagnoses (of hypertension) or prescribed daily doses may have affected the results.

We cannot fully exclude the possibility that BB were prescribed for more symptomatic indications or more severe hypertension, potentially resulting in better persistence and adherence compared to other AHTs. But only including incident users with the same drug at first and index prescription, excluded both patients with a change in medication and de-prescribing, e.g., due to successful changes in lifestyle during this period; 21.4% of the patients received a combination therapy. The percentage of combination therapies, usually prescribed as first therapy in more severe hypertension, was much lower in the BB group (9.0%) compared to ARBs (47.2%) or ACEi (29.9%). Moreover, the percentages of number of drug classes as co-medication were quite similar in all AHT classes.

Table 3
Cox-regression (non-persistence determined according to gaps in continuous medication) and logistic regression (non-adherence determined according to the MPR).

Study group	HR	99.9% CI	*P* value	OR	99.9% CI	*P* value
	Non-persistence			Non-adherence		
Unadjusted						
Diuretics	Reference			Reference	.	
ACEi	0.828	0.802–0.856	<0.001	0.675	0.634–0.717	<0.001
ARB	0.879	0.847–0.913	<0.001	0.621	0.579–0.665	<0.001
BB	0.824	0.798–0.851	<0.001	0.689	0.649–0.732	<0.001
CCB	1.017	0.979–1.057	0.150	0.806	0.750–0.866	<0.001
Adjusted[*]						
Diuretics	Reference			Reference		
ACEi	0.821	0.785–0.859	<0.001	0.643	0.589–0.702	<0.001
ARB	0.918	0.871–0.967	<0.001	0.670	0.606–0.741	<0.001
BB	0.773	0.740–0.807	<0.001	0.576	0.529–0.628	<0.001
CCB	0.988	0.941–1.037	0.397	0.742	0.675–0.815	<0.001

ACEi = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor antagonists, BB = beta-blockers, CCB = calcium channel blockers, CI = confidence interval, HR = hazard ratio, MPR = medication possession ratio, OR = odds ratio.

[*] Adjusted for the following covariates: type of therapy, medical specialty of the prescribing physician, status of the insured person, number of ATC 3rd level drugs, and co-medication.

Table 4
Adjusted Cox-regression (non-persistence) and adjusted logistic regression (non-adherence) in relation to covariates.*

Study group	HR	99.9% CI	*P* value	OR	99.9% CI	*P* value
	Non-persistence			Non-adherence		
Therapy						
Mono therapy	Reference			Reference		
Combinations	0.916	0.863–0.973	<0.001	0.802	0.715–0.900	<0.001
Prescriber						
GP	Reference			Reference		
IMS	1.028	1.011–1.046	<0.001	1.037	1.006–1.068	<0.001
Other	1.478	1.410–1.550	<0.001	1.651	1.501–1.817	<0.001
Status						
Retired	Reference			Reference		
Member	1.157	1.138–1.176	<0.001	1.339	1.300–1.379	<0.001
Family member	1.140	1.110–1.170	<0.001	1.286	1.226–1.350	<0.001
Co-medication						
0–1 drug class	Reference			Reference		
2–3 drug classes	1.012	0.992–1.033	0.052	1.002	0.966–1.040	0.842
4–6 drug classes	1.022	1.001–1.044	<0.001	1.024	0.986–1.064	0.039
≥7 drug classes	1.062	1.038–1.086	<0.001	1.114	1.069–1.160	<0.001

CI = confidence interval, OR = odds ratio, GP = general practitioner, HR = hazard ratio, IMS = internal medicine specialist.
* Adjusted for the following covariates: type of therapy, medical specialty of the prescribing physician, status of the insured person, number of ATC 3rd level drugs, and co-medication.

Taken together, these findings do not support an increase in adherence and persistence (to BBs) with increasing severity of hypertension. The vast majority of patients with atrial fibrillation (AF) or coronary artery disease (CAD), potential indications for BBs, have hypertension and the analyses included only BB-containing products approved for hypertension. In addition, co-medication with drugs indicative for AF (vitamin K antagonists), heart failure (HF, i.e., cardiac glycosides, aldosterone antagonists, high-ceiling diuretics), or CAD (i.e., nitrates) was small in relation to the study cohort. In general, persistence and adherence to all cardiovascular drugs independently of the diagnosis is warranted to improve clinical outcomes.

Furthermore, data indicating age and gender are missing in our database. However, the insurance membership status (e.g., retired person) may be an indicator for the patients' age. In total, 50% of the patients (40% in the BB cohort) referred to the "retired" status. Defining retirement as 65 years of age or older, our results of better adherence and persistence to AHTs when compared to younger patients, i.e., family members or members, are consistent with other findings [40,50,61,62,67]. To the best of our knowledge, there is no evidence for a significant gender difference in adherence or persistence to AHTs [49].

Not allowing switching the AHT, identified as the same substance/fixed combination at first and index prescription, during the observation period might have overestimated non-persistence. This approach, however, allowed a more robust comparison of different drug classes. Of note, any claims for different brand products/generics of the index AHT during the observation period were considered. Hence, a change of product within the same antihypertensive class may not explain the observed non-adherence/non-persistence.

Finally, we were unable to consider hospitalizations, i.e., time when medication might have been provided outside primary care. However,

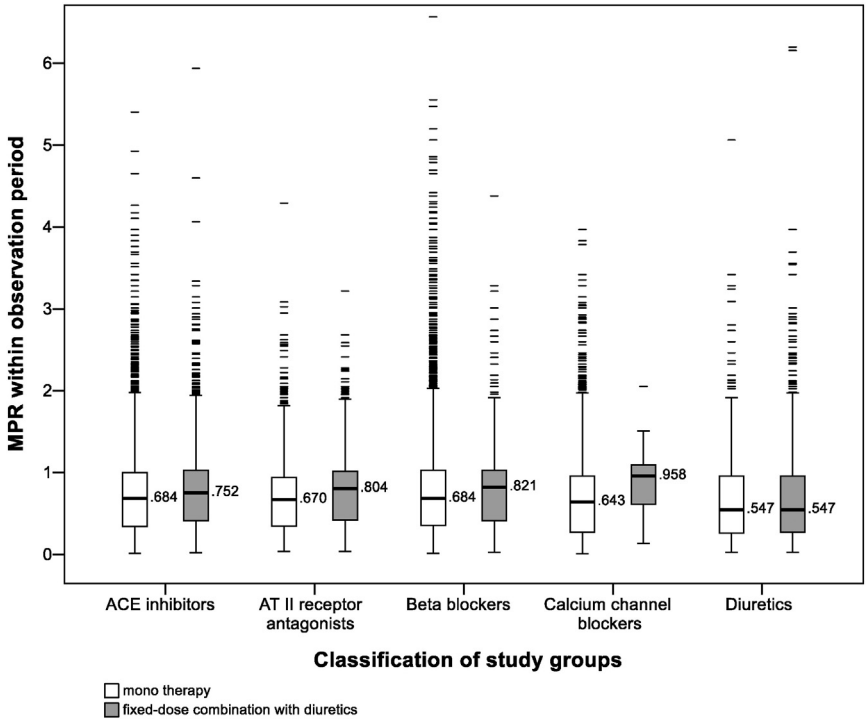

Fig. 5. Medication adherence to the five antihypertensive drug classes determined as medication possession ratio (MPR, box plot). Note: The total number of combinations of calcium channel blockers was very small ($n = 127$) in relation to other medications.

we assume that periods of hospitalizations are usually too short to explain the pronounced differences we observed between AHT drug classes in this study.

5. Conclusions

This large contemporary analysis reveals important differences in adherence and persistence to AHTs in separate classes, with lowest for diuretics. Fixed-dose combinations, e.g., of an ACEi or ARB with a diuretic may facilitate adherence and persistence compared to single substance products. However, both persistence and adherence was suboptimal regardless of drug class. More research is needed to develop suitable methods to identify unintended discontinuation (non-persistence) in a timely manner, to explore patient-related reasons, and to develop effective interventions.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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