Comparison of Different Strategies to Measure Medication Adherence via Claims Data in Patients With Chronic Heart Failure

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Medication adherence correlates with morbidity and mortality in patients with chronic heart failure (CHF), but is difficult to assess. We conducted a retrospective methodological cohort study in 3,808 CHF patients, calculating adherence as proportion of days covered (PDC) utilizing claims data from 2010 to 2015. We aimed to compare different parameters' influence on the PDC of elderly CHF patients exemplifying a complex chronic disease. Investigated parameters were the assumed prescribed daily dose (PDD), stockpiling, and periods of hospital stay. Thereby, we investigated a new approach using the PDD assigned to different percentiles. The different dose assumptions had the biggest influence on the PDC, with variations from 41.9% to 83.7%. Stockpiling and hospital stays increased the values slightly. These results queries that a reliable PDC can be calculated with an assumed PDD. Hence, results based on an assumed PDD have to be interpreted carefully and should be presented with sensitivity analyses to show the PDC's possible range.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ A common method to determine medication adherence is the analysis of claims data. These measures are noninvasive, economical, and relatively easy to analyze. A crucial point is the prescribed daily dose (PDD) but no gold standard exists, if assumptions on the PDD are needed.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The aim of our study was to measure the influence of different parameters, assumed PDD, stockpiling, and truncation because of hospitalizations on adherence measures in patients with heart failure exemplifying a complex chronic disease using claims data.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Our results show that it is not feasible to calculate a reliable proportion of days covered (PDC) and, consequently, determine medication adherence, with an assumed PDD.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Results based on an assumption of the daily doses have to be interpreted carefully. If this information is lacking, we recommend to present sensitivity analyses showing a possible range of the PDC.

Chronic heart failure (CHF) is associated with high hospitalization rates and mortality.[1–3] Good medication adherence to evidence-based pharmacotherapy is associated with fewer hospitalizations and higher patient survival.[4,5] However, irregular and inconsistent intake of medications is common.[4,6] A frequently used method to determine medication adherence is the analysis of claims data.[4,6–10] Claims data are based on billing data with additional information. They are characterized by long observations periods and lack recall bias or interviewer bias. They offer insurance-related pseudonymized information on the utilization of the health care system. Within the frame of this study, International Classification of Diseases, 10th revision (ICD-10) coded inpatient and outpatient diagnoses, drug prescriptions, and data of hospitalizations are of relevance.

There are different measures and related parameters for the calculation of medication adherence via claims data.[8,9] Even though there is no gold standard, the medication possession ratio (MPR) and the proportion of days covered (PDC) are most commonly used.[4,7,10,11] However, different definitions and related parameters within these methods are used in the literature, e.g., consideration

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Received August 30, 2018; accepted January 8, 2019. doi:10.1002/cpt.1378

Table 1 Characteristics of the study population (*N* = 3,808)

Characteristic	
Age mean, years (range)	80.3 (60–103)
Female, *n* (%)	2,144 (56.3)
Deceased, *n* (%)	880 (23.1)
NYHA stage, *n* (%)	
I	39 (1.0)
II	294 (7.7)
III	943 (24.8)
IV	1,088 (28.6)
Classification not coded	1,444 (37.9)
Comorbidities, Charlson score, mean ± SD (median)	3.7 ± 2.6 (3)
Mean number of ICD groups, mean ± SD (median)	14.7 ± 6.7 (14)
Mean number of hospitalizations, mean ± SD (median)	1.5 ± 1.6 (1)
Mean duration of hospitalization (days), mean ± SD (median)	14.9 ± 20.1 (8)
Mean number of ATC groups, mean ± SD (median)	13.7 ± 5.7 (13)
Diuretics, *n* (%)	3,808 (100.0)
Beta-blockers, *n* (%)	3,119 (81.9)
ACEi, *n* (%)	2,289 (60.1)
Statins, *n* (%)	1,687 (44.3)
MRA, *n* (%)	1,615 (42.4)
ARB, *n* (%)	1,131 (29.7)
Digitalis glycosides, *n* (%)	990 (26.0)

ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor antagonists; ATC, Anatomical Therapeutic Chemical Classification; ICD, International Statistical Classification of Diseases and Related Health Problems; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association.

of the duration of hospital stays and stockpiling (for an overview, see Andrade *et al.*,[8] Hess *et al.*,[9] and Vollmer *et al.*[12]). Prior to this methodological analysis, we performed a systematic literature review on methods and parameters to measure medication adherence via claims data in patients with CHF.[4] This systematic review discussed recommendations for a feasible method and the needed parameters. We identified the following parameters to be considered for adherence measures via claims data: measurement method, observation period, substances, dosing information, switches, stockpiling, truncations, statistical analysis, and cutoff for adherence. A crucial point for the adherence measure is the daily dosage a patient is advised to take—information not available in many claims data.[6,10,13–16]

Therefore, the aim of this investigation was to perform a methodological analysis to quantitate the influence of dose assumptions, stockpiling, and hospital stays on the calculation of the PDC.

RESULTS

Study population

The final study population included 3,808 patients (**Table 1**). The mean age was 80.3 years, 56.3% (*n* = 2,144) were female, and 880 patients (23.1%) died during the observation period 2010–2015. At the time of coding, 8.7% (*n* = 333) were in New York Heart Association (NYHA) class I or II and 53.4% (*n* = 2,031) in NYHA class III or IV (37.9% had no information on the NYHA class). The mean Charlson Comorbidity Index was 3.7, indicating multimorbidity. Beside diuretics, the most commonly prescribed medications were angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), together 89.8% and beta-blockers (BB) 81.9%.

Summary of the main results

In relation to the method used, the average PDC varied from 41.9% to 87.6% for ACEi, 45.6% to 88.8% for ARB, 46.9% to 89.8% for BB, and 47.8% to 87.6% for mineralocorticoid receptor antagonists (MRAs). The different assumptions about the dose had a strong influence on PDC. The consideration of stockpiling increased the values of the PDC slightly. The consideration of hospital stays had only minor increasing effects.

Influence of the dosing assumptions

The larger the value of the assumed prescribed daily dose (PDD), the smaller the calculated PDC. The different assumptions (1.0 defined daily dose (DDD), one tablet per day, and PDD assigned to different percentiles) differ largely in size (**Figure 1**). This explains why these different assumptions result in a wide range of the PDC (**Figure 2**).

For example, the PDC for ACEi varied from 41.9% to 81.8% if stockpiling and hospital stays were excluded. Using the different PDD of the percentiles, the PDC for ACEi increased from 41.9% (20th percentile), to 63.4% (50th percentile), to 81.8% (80th percentile).

In addition, the different assumed PDD resulted in strongly varying values depending on drug class. For the frequently used dosing assumption of 1.0 DDD, the values of the PDC varied from 47.8% for MRA to 80.8% for ACEi, if stockpiling and hospital stays were not considered (**Table 2**). When using one tablet per day, the variations between the drug classes were a bit lower but still large from 65.6% for MRA to 81.4% for BB. Using the PDD assigned to different percentiles, we found very low variations between the drug classes' PDC.

Influence of stockpiling

The consideration of stockpiling increased the PDC values for all investigated drug classes. As an example with one tablet per day and without considering stockpiling and duration of hospital stays, the PDC for ACEi was 75.1%, 74.9% for ARB, 81.4% for BB, and 65.6% for MRA (**Table 2**). If stockpiling was considered, the PDC for ACEi was 80.9%, 81.4% for ARB, 87.3% for BB, and 69.7% for MRA (**Table 2**). The differences in value, caused by stockpiling, were similar within the results of the other dosing assumptions.

Influence of hospital stays

The consideration of hospital stays had the lowest influence on the PDC, regardless of the variation used. The following results refer to the PDC calculation without stockpiling. If the variations of hospitalization were considered, the PDC ranged between

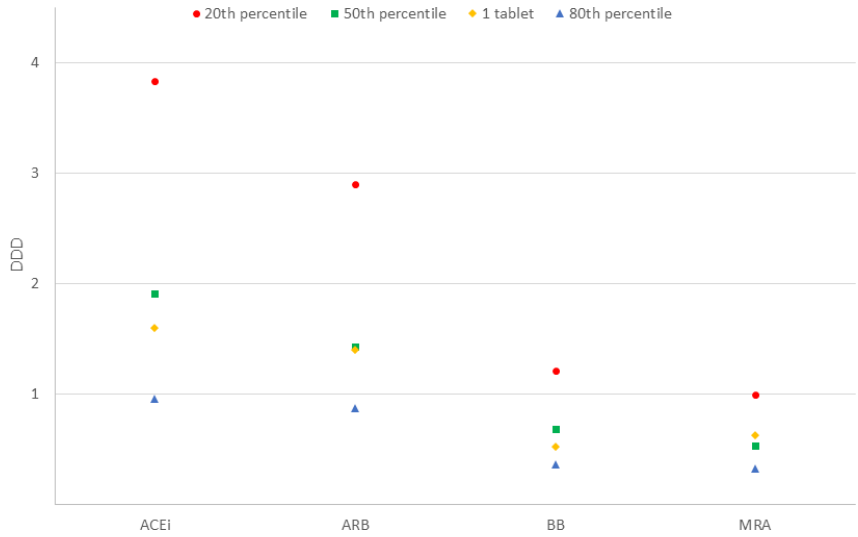

Figure 1 Dose assumptions. Resulted DDD assuming one tablet per day and 20th, 50th, 80th percentiles of the PDD (prescribed daily dose). The allocation of the percentiles varied between the drug classes. ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BB, beta-blockers; DDD, defined daily dose; MRA, mineralocorticoid receptor antagonists. [Colour figure can be viewed at wileyonlinelibrary.com]

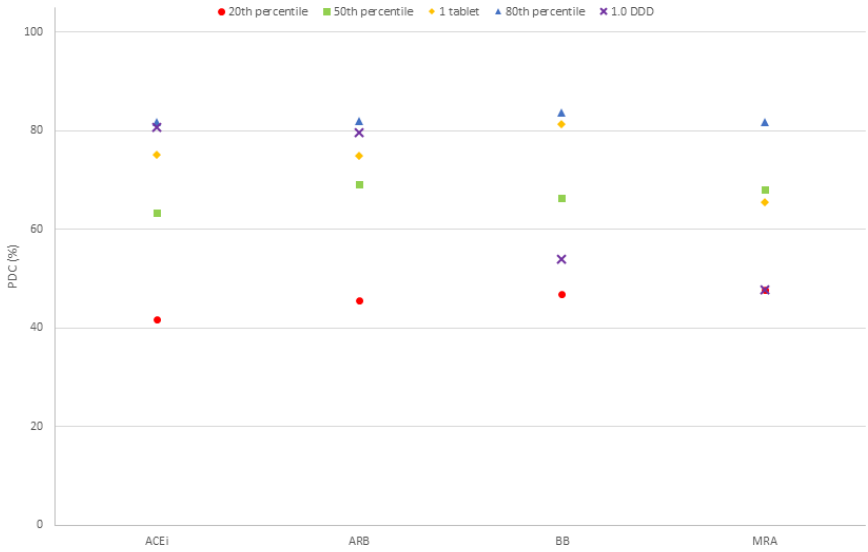

Figure 2 Values of the proportion of days covered (PDC) for the investigated drug classes in relation to the dosing assumptions. Proportion of PDC in percent (%) without considering stockpiling and hospital stays. ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BB, beta-blockers; DDD, defined daily dose; MRA, mineralocorticoid receptor antagonists. [Colour figure can be viewed at wileyonlinelibrary.com]

75.5% and 75.6% for ACEi using one tablet per day as daily dose (**Table 2**). In comparison, the PDC was 75.1% without consideration of hospital stays (H0). It differed between 75.3% and 75.5% for ARB (H0: 74.9%), between 81.8% and 82.1% for BB (H0: 81.4%), and between 66.2% and 66.47% for MRA (H0: 65.6%) (**Table 2**). The consideration of hospital stays changed the PDC between 0% and 2.8%, depending on the variation.

DISCUSSION

Methods and related parameters to assess medication adherence via claims data differ widely in the literature.[4,6,8–11] To the best of our knowledge, this is the first analysis comparing the influence of different strategies for the parameters assumed PDD, stockpiling, and truncations because of hospitalizations in patients with CHF.

We found wide variations in the adherence values, in relation to the method applied. The average PDC varied from 41.9% to 89.8%, depending on the method used and the considered drug class. The different assumptions about the daily dose had a strong influence on the calculated PDC. Stockpiling changed the calculated PDC values slightly. The duration of hospital stays had only a minor effect.

If available, studies used the individual prescribed doses to calculate the PDC.[17] If this dose is unknown, no gold standard exists for the assumption of the daily doses prescribed. Authors referred to the doses of major clinical trials,[18] the DDD,[13,14,19–21] the doses

Table 2 Average proportions of days under therapy for the investigated drug classes in relation to the dosing assumption, stockpiling, and hospital stays

			Dose assumption				
Drug class	Stockpiling	Hospital stay	20th percentile	50th percentile	1 tablet	1.0 DDD	80th percentile
ACEi	Without Stockpiling	H0	41.9	63.4	75.1	80.8	81.8
		H1	42.7	63.8	75.5	81.0	81.9
		H2	43.4	64.2	75.6	81.1	82.0
	With Stockpiling	H0	43.9	68.6	80.9	85.8	86.9
		H1	45.9	70.1	82.6	86.6	87.6
		H2	46.5	70.3	82.7	86.9	87.6
ARB	Without Stockpiling	H0	45.6	69.1	74.9	79.7	82.0
		H1	46.4	69.5	75.3	79.7	82.1
		H2	47.0	69.8	75.5	79.9	82.3
	With Stockpiling	H0	47.8	73.6	81.4	84.8	87.5
		H1	49.8	74.7	83.5	86.6	88.7
		H2	50.4	74.9	83.5	86.6	88.8
BB	Without Stockpiling	H0	46.9	66.5	81.4	53.9	83.7
		H1	47.8	67.3	81.8	54.8	84.2
		H2	48.6	67.7	82.1	55.5	84.3
	With Stockpiling	H0	49.3	71.6	87.3	57.4	88.7
		H1	51.4	73.4	88.7	59.7	89.7
		H2	52.1	73.7	88.8	60.2	89.8
MRA	Without Stockpiling	H0	47.8	68.1	65.6	47.8	81.9
		H1	48.6	68.7	66.2	48.6	82.0
		H2	49.0	68.9	66.4	49.0	82.0
	With Stockpiling	H0	49.6	72.2	69.7	49.6	86.5
		H1	51.2	73.7	71.5	51.2	87.6
		H2	51.6	73.9	71.7	51.6	87.5

Proportion of days covered (PDC) in percent (%). ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BB, beta-blockers; DDD, defined daily dose; MRA, mineralocorticoid receptor antagonists. H0 = PDC excluding information on hospital stays; H1 = In cases with a dispensing before and after discharge (within a period of seven days) the days of hospital stay were calculated as days of adherence; H2 = hospital stays were calculated as days of adherence, when a dispensing reaches the first day of hospital stay or starts within seven days after discharge.

recommended in each agent's product monograph,[22] or the assumption of one or one or two tablets per day.[10,23,24] As for many studies analyzing claims data,[6,11,13–16,25] the prescribed doses were not available in our study. Additionally, the dose recommendations by the drug's product monograph or summary of product characteristics are not explicitly provided for CHF and are incomplete for fixed-dosed combinations. Therefore, we made the following dose assumptions: 1.0 DDD, one tablet per day as well as a new approach by applying different percentiles (20th, 50th, and 80th) based on calculated PDD.

The results of the frequently used "DDD-approach" for calculating the PDC showed marked differences in comparison to the other dose assumptions. Many patients using BB or MRA take less than one DDD, whereas one DDD is a low dosage for ARB and ACEi. The discrepancy between the official DDD and the utilization in real life has also been described by Ude *et al.*[26] This is not surprising, since the DDD is a technical unit and not a recommendation for the therapeutic dose. Moreover, the main indication to calculate a DDD for these cardiovascular drugs is hypertension, instead of CHF.

The other common method is the assumption about one tablet per day, irrespective of the prescribed/dispensed drug strength. The variation of the PDC's value between the drug classes were lower when assuming one tablet per day than when assuming 1.0 DDD. The advantage of one tablet is that for each prescription an individual dose is used depending on the strength of the dispensed drug. One disadvantage of this method is that many patients split tablets, as it is often the case for spironolactone. Moreover, some drugs are dosed twice (e.g., carvedilol, metoprolol tartrate) or even three times a day (e.g., captopril).

We tested a new approach by applying percentiles calculated from the claims data per anatomical therapeutic chemical (ATC)-group. In contrast to the approaches of 1.0 DDD and one tablet per day, the PDD is based on real data of the analyzed population. Calculating the PDC with the PDD assigned to percentiles shall provide a possible range of the PDC. We decided to use the 20%

and 80% extremes of the percentiles as well as the middle 50%. It is highly likely that the "real" PDC lies within this range. We found very low variations in the values of the PDC of the same percentile between the drug classes. The PDC varied largely between the different percentiles, since the 20th and 80th percentiles represent extremes of the dosing assumption. One example of ACEi between the PDD of the 20th and 80th percentiles is the factor 4 (**Figure 1**). An advantage of this approach is the better comparability of results between drug classes compared with the DDD or one tablet per day.

By applying different assumptions of the PDD, we found a wide variation in the calculated PDC, both within and between drug classes. This holds true when the number of patients with a PDC ≥ 80% is determined, a commonly used cutoff for adherence (**Table S1**).

In conclusion, any calculated PDC based on an assumed PDD is a rough approximation. Without knowledge of the prescribed dosage, it is difficult to calculate a reliable PDC.[8,26–28] Most studies applied one DDD, a given dose recommendation by the product information, or one tablet per day. We demonstrated the uncertainty of these approaches and quantified the impact of different dosages on the adherence value by calculating the PDC. For the assumption of different dosages, we are proposing the new percentile approach in order to assess the effects quantitatively.

Real-life data support the wide range of daily doses. For example, Komajda *et al.*[29] showed that ACEi doses in patients with heart failure with reduced ejection fraction vary between 0.9 and 3 DDD. By assuming a single PDD for a cohort of patients, this variation is ignored.

We question that one method of assuming the PDD is the best in relation to the real PDD. That is why the results of a PDC based on dose assumptions have to be interpreted with great caution.

Studies often do not describe in detail which method and parameters (prescribed dose?) were used, or the dosing assumption is often not stated.[4,10,13–16,30–32] Out of 24 papers analyzed in our recent review,[4] 14 did not include information about the used daily dose.

If information on the PDD is unavailable, we recommend conducting sensitivity analyses by calculating the PDD based on different assumptions. The result is a possible range of the PDC. The reasons for the selection and the advantages and disadvantages of the different methods should be discussed.

Some studies allowed stockpiling, thus, the addition of overlapping dispensings.[20,21,23] This allows oversupply with the rationale that patients get new medication before they have used up their previous supply.[33] In line with other studies, we observed an increased PDC when allowing stockpiling.[9,34,35] Depending on the method used, this can lead to an overestimation of medication adherence. Therefore, we recommend a more conservative approach and suggest to exclude stockpiling to avoid misjudgments of medication adherence when using a comparable design. This recommendation is supported by the minor influence of stockpiling on the PDC.

During a hospital stay, the patient mostly receives the medication separately from ambulatory prescriptions. Therefore, many studies censored the duration of hospital stays.[22,36–42] Hospitalizations are frequent in patients with CHF,[3] but the length of stay is short in relation to the usual observation time of one year. In Germany, the average duration of hospitalization for patients with CHF was 10.4 days in 2015.[43] The average length of stay in our study population with at least one CHF-related hospitalization in the observation period up to 12 months was 14.9 days—indicating a sicker population. Thereby, we already investigated patients with a long hospital stay and found that the days of hospital stays had only a minor influence on the PDC. Thus, it seems to be acceptable to ignore the duration of hospital stays. However, censoring the duration of hospital stays increases the precision of the adherence calculation, and that could be important in other populations or for specific questions.

Strengths and limitations

The major strength of this study is the characteristic of the routine data—above all, including a large number of patients. Information is available without interviewer bias or recall bias. A selection bias could occur due to the investigation of patients insured by only one, although large, health insurance fund. We investigated a fairly sick population of old (mean age 80 years) CHF patients only. For those with data available, more than 50% were coded with NYHA stage III or IV. The patients were suffering by a variety of comorbidities, and the inclusion criteria included both an acute decompensated heart failure hospitalization in the past 12 months and current use of a diuretic (ATC C03). Hence, the PDC data presented are specific for this cohort, although we identified in a previous systematic review[44] older age not to be associated with poorer medication adherence compared with younger (< 60–65 years) CHF patients. However, as the focus of this study is on methods, the CHF population is used to exemplify the methodology. Finally, within this study, we did not validate our percentiles approach for calculating a PDC against a gold-standard measure of adherence, which might be a combination of therapeutic drug or electronic monitoring and a self-report questionnaire.

CONCLUSIONS

The assessment of medication adherence is important for both research and clinical practice.[9,45] Claims data represent an often easily accessible source to assess medication adherence. By using the PDC method, we investigated the influence of different assumptions for the parameters dosing (expressed as DDD, number of daily tablets, or assumed PDDs), stockpiling, and truncations because of hospitalizations in CHF patients. It seems to be appropriate to exclude stockpiling and to ignore the duration of hospital stays calculating adherence for patients with CHF. The different methods of assuming the PDD leads to significant differences in the PDC. It seems impossible that a reliable PDC can be calculated without individual dosing instructions. If information on the individual PDD is lacking, we recommend to present sensitivity analyses showing a possible range of the PDC. The new approach by applying percentiles makes it possible to calculate such a range.

METHODS

Data set

We used a 10% sample of the Germany-wide pseudonymized data of a large statutory health insurance fund (Barmer GEK, insuring ~ 9.4

million persons in 2015), from 2010 to 2015. The data contained claims data of prescribed drugs, dispensed at community pharmacies, as well as data related to patients' sex and gender, ICD-10 German Modification coded outpatient and inpatient diagnoses, hospitalizations, and deaths. For prescribed drugs, the information on the ingredient (ATC code), the dosage per unit (strength), and the package size are available. In addition, the date of issuing the prescription and the date of dispensing at the pharmacy are available. For each dispensing, a new prescription has to be issued. The database contains no information on the number of drugs to be taken by the patient. Moreover, information on over-the-counter medication, medications dispensed at a hospital stay, and clinical data were not available.

Study design

Based on the findings of our systematic review for a feasible method and the needed parameters,[4] we conducted a retrospective methodological cohort study to compare the influence of different strategies regarding the assumed PDD, stockpiling, and truncations because of hospitalizations on the PDC. We considered the recommendations on Good Practice for Secondary Data Analyses,[46] and the checklist published by the International Society for Pharmacoeconomics and Outcome Research (ISPOR).[7]

Relevant parameters

We defined the following parameters for the operationalization of the adherence measurement: the PDC as the measurement method, 365 days as the observation period, and the consideration of typical CHF medications. We allowed switching within a therapeutic class. Deceased patients were censored and considered until death occurred. Different assumptions regarding the daily dose, stockpiling, and truncations due to hospitalizations were assessed.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were determined following the study population of major clinical trials on CHF.[47–49] We included patients with a discharge diagnosis of CHF (ICD-Code "I50") in the index quarter or an assured outpatient diagnosis, aged 60 years and older, and with a hospitalization for CHF in the last 12 months before inclusion. Additionally, patients had to have at least one dispensing of any diuretic (ATC C03) before inclusion but lasting into the index quarter by calculating the coverage with one defined daily dose (DDD).[19] Patients who died in the index quarter were excluded.

Drugs included in the analyses were ACEi (ATC codes C09A, C09B), ARB (C09C, C09D), BB (C07), and MRA (C03DA, C03EC, C03ED). All medications dispensed before the index quarter but extending into the observation period were included in the calculation.

Calculation of medication adherence

Adherence was calculated using the PDC, which is the ratio of number of days in the period covered by a medicine (numerator) to the total number of days in the observation period (denominator).[7]

Observation period. For every patient, the first day of therapy could be either the first day of the observation period (in cases with coverage of the drug from the preindex period) or the day of the first prescription in the observation period. The study period ended after 365 days or at the time of death. The observation period (denominator) was the number of days from the first day of therapy until the last day of the observation period.

Days covered. The calculation of the number of days covered with medication between the first and the last day of the observation period was determined (numerator) with different strategies regarding the assumed PDD, stockpiling, and the duration of hospital stays.

Finally, we used 30 different variations of these strategies to calculate the PDC: five dose assumptions, three considerations regarding hospital stays, and two regarding stockpiling.

Dosing assumptions. The PDD of a drug is required to determine the number of days covered out of a drug's dispensing. This information is not available in many claims databases.[6,10,13–16]

We made the following assumptions about the PDD:

1. One DDD is the "average maintenance dose per day for a drug used for its main indication in adults."[50] Assuming the DDD as PDD, the days covered were calculated by using the DDD's specified amount in mg as daily dose.
2. Assuming one tablet per day as PDD, the days covered were calculated by using the number of tablets prescribed/dispensed. Thereby, one tablet prescribed/dispensed resulted in one day covered.
3. A calculated PDD assigned to the 20th, 50th, and 80th percentiles. The 20th, 50th, and 80th percentiles represent the total dispensings' portion that shows a coverage until the next prescription/dispensing or beyond using this respective PDD. To calculate the PDD for a dispensing with a given dispensing date as starting point, we needed an ending date which is the date of the following dispensing event. Defining that the total drug's amount of the first dispensing was sufficient until the second dispensing, the PDD was calculated as the drug's amount of the respective dispensing event divided by the number of days until the second dispensing. For example, there was a dispensing of 50 tablets with a dosage strength of 25 mg and a second dispensing of that drug after 60 days. We then divided the total drug amount of that dispensing (50 tablets × 25 mg = 1,250 mg) by 60 days, which would result in a PDD of 20.83 mg. After calculating the PDD of every dispensing with a following dispensing, the PDD's percentiles were depicted per ATC group and by sorting the dispensing periods by PDD downward and percentile ranked. The PDD values of the 20th, 50th, and 80th percentiles were used for further analyses.

When using the PDD of a corresponding percentile to calculate the coverage of a dispensing, the corresponding percentile represents the total dispensings' portion that shows a coverage until the next dispensing or beyond. The result is that the smaller the PDD used for the calculation of coverage, the higher the number of days covered by a dispensing, and the bigger the total dispensings' portion with coverage until the next dispensing or beyond. Therefore, the bigger the percentile, the smaller the corresponding PDD. We used the PDD of the 20th, 50th, and 80th percentiles. The 80th percentile represents the daily dose's lower range, the 20th percentile the upper range, respectively.

In order to compare the different dose assumptions, they each were converted into the corresponding DDD (**Figure 1**). For converting the assumption about one tablet per day in a corresponding DDD, the mean strength of all prescribed tablets of one ATC group was calculated.

Consideration of stockpiling. With each dose assumption, the number of days covered for each dispensing was calculated. If the subsequent dispensing occurred before the end of coverage by the previous dispensing, adherence calculation was performed with and without stockpiling. Stockpiling describes the extension of a dispensing if there were residues of the last dispensing, thus the addition of overlapping dispensings. In the scenario without stockpiling we censored residues. We extended the residues of a dispensing in the scenario with stockpiling i.e., we moved the start of the subsequent dispensing until the end of the previous.

Consideration of hospital stays. Regarding the influence of hospital stays on the PDC, we applied different scenarios, whether days in hospital were taken into account as days covered:

Scenario "H1": Days in hospital are considered as days covered, if the coverage of a dispensing reached the first day of the hospital stay, and a subsequent dispensing within seven days after hospital discharge was detected.
Scenario "H2": Days in hospital are considered as days covered, if the coverage reached the first day of the hospital stay or a dispensing started within seven days after discharge.

Additionally, we calculated adherence ignoring days in hospital (H0), resulting in three different variations of consideration regarding hospital stays.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Table S1. Proportions of patients with a PDC ≥ 80% for the investigated drug classes in relation to the dosing assumptions, stockpiling, and hospital stays.

ACKNOWLEDGMENTS

The authors would like to thank the statutory health insurance fund BARMER for the supply of the data. We would also thank Lea Botermann, ABDA, Department of Medicine, Berlin, Germany, for her support.

FUNDING

No funding was received for this work.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

P.I., K.K., N.G.-M., N.P., U.L., and M.S. wrote the article; P.I., K.K., I.S., and M.S. designed the research; P.I., K.K., I.S., and M.S. performed the research; P.I., K.K., I.S., N.G.-M., N.P., and M.S. analyzed the data.

1. van Riet Evelien, E.S., Hoes, A.W., Wagenaar, K.P., Limburg, A., Landman Marcel, A.J. & Rutten, F.H. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur. J. Heart Fail.* **18**, 242–252 (2016).
2. Chioncel, O. *et al.* Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction. An analysis of the ESC Heart Failure Long-Term Registry. *Eur. J. Heart Fail.* **19**, 1574–1585 (2017).
3. Ponikowski, P. *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. Heart J.* **37**, 2129–2200 (2016).
4. Krueger, K. *et al.* In search of a standard when analyzing medication adherence in patients with heart failure using claims data: a systematic review. *Heart Fail. Rev.* **23**, 63–71 (2018).
5. Fitzgerald, A.A. *et al.* Impact of medication nonadherence on hospitalizations and mortality in heart failure. *J. Card Fail.* **17**, 664–669 (2011).
6. Schulz, M. *et al.* Medication adherence and persistence according to different antihypertensive drug classes: a retrospective cohort study of 255,500 patients. *Int. J. Cardiol.* **220**, 668–676 (2016).
7. Peterson, A.M., Nau, D.P., Cramer, J.A., Benner, J., Gwadry-Sridhar, F. & Nichol, M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health* **10**, 3–12 (2007).
8. Andrade, S.E., Kahler, K.H., Frech, F. & Chan, K.A. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol. Drug Saf.* **15**, 565–574 (2006).
9. Hess, L.M., Raebel, M.A., Conner, D.A. & Malone, D.C. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann. Pharmacother.* **40**, 1280–1288 (2006).
10. Arnet, I. *et al.* Operationalization and validation of a novel method to calculate adherence to polypharmacy with refill data from the Australian pharmaceutical benefits scheme (PBS) database. *Clin. Epidemiol.* **10**, 1181–1194 (2018).
11. Gwadry-Sridhar, F.H. *et al.* A framework for planning and critiquing medication compliance and persistence research using prospective study designs. *Clin. Ther.* **31**, 421–435 (2009).
12. Vollmer, W.M., Xu, M., Feldstein, A., Smith, D., Waterbury, A. & Rand, C. Comparison of pharmacy-based measures of medication adherence. *BMC Health Serv. Res.* **12**, 155 (2012).
13. Qin, X., Teng, T.-H.K., Hung, J., Briffa, T. & Sanfilippo, F.M. Long-term use of secondary prevention medications for heart failure in Western Australia. A protocol for a population-based cohort study. *BMJ Open* **6**, e014397 (2016).
14. Menditto, E. *et al.* Adherence to chronic medication in older populations. Application of a common protocol among three European cohorts. *Patient Prefer. Adherence* **12**, 1975–1987 (2018).
15. Ofori-Asenso, R. *et al.* Patterns of statin use and long-term adherence and persistence among older adults with diabetes. *J. Diabetes* **10**, 699–707 (2018).
16. Bartlett, L.E., Pratt, N. & Roughead, E.E. Does tablet formulation alone improve adherence and persistence. A comparison of ezetimibe fixed dose combination versus ezetimibe separate pill combination?. *Br. J. Clin. Pharmacol.* **83**, 202–210 (2017).
17. Dunlay, S.M., Eveleth, J.M., Shah, N.D., McNallan, S.M. & Roger, V.L. Medication adherence among community-dwelling patients with heart failure. *Mayo Clin. Proc.* **86**, 273–281 (2011).
18. Roe, C.M., Motheral, B.R., Teitelbaum, F. & Rich, M.W. Angiotensin-converting enzyme inhibitor compliance and dosing among patients with heart failure. *Am. Heart J.* **138**, 818–825 (1999).
19. Deutsches Institut für medizinische Dokumentation und Information (DIMDI). Anatomisch-therapeutisch-chemische Klassifikation mit Tagesdosen <https://dimdi.de/static/de/amg/atcddd/index.htm>. Accessed October 31, 2018.
20. Corrao, G., Rea, F., Ghirardi, A., Soranna, D., Merlino, L. & Mancia, G. Adherence with antihypertensive drug therapy and the risk of heart failure in clinical practice. *Hypertension* **66**, 742–749 (2015).
21. Vegter, S., Nguyen, N.H., Visser, S.T., de Jong-van den Berg Lolkje, T.W., Postma, M.J. & Boersma, C. Compliance, persistence, and switching patterns for ACE inhibitors and ARBs. *Am. J. Manag. Care* **17**, 609–616 (2011).
22. Lamb, D.A. *et al.* Changes in adherence to evidence-based medications in the first year after initial hospitalization for heart failure: observational cohort study from 1994 to 2003. *Circ. Cardiovasc. Qual. Outcomes* **2**, 228–235 (2009).
23. Corrao, G., Conti, V., Merlino, L., Catapano, A.L. & Mancia, G. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. *Clin. Ther.* **32**, 300–310 (2010).
24. Schaffer, A.L., Buckley, N.A. & Pearson, S.-A. Who benefits from fixed-dose combinations? Two-year statin adherence trajectories in initiators of combined amlodipine/atorvastatin therapy. *Pharmacoepidemiol. Drug Saf.* **26**, 1465–1473 (2017).

25. Wilke, T. *et al.* How to use pharmacy claims data to measure patient nonadherence? The example of oral diabetics in therapy of type 2 diabetes mellitus. *Eur. J. Health Econ.* **14**, 551–568 (2013).
26. Ude, M. *et al.* Comparison of different ways of calculation (DDD vs. SPC) to determine persistence and compliance with beta blockers in the DAPI database <http://www.egms.de/static/en/meetings/dkvf2011/11dkvf039.shtml>. Accessed October 31, 2018.
27. Höer, A., Gothe, H., Khan, Z.M., Schiffhorst, G., Vincze, G. & Häussler, B. Persistence and adherence with antihypertensive drug therapy in a German sickness fund population. *J. Hum. Hypertens.* **21**, 744–746 (2007).
28. Williams, A.B., Amico, K.R., Bova, C. & Womack, J.A. A proposal for quality standards for measuring medication adherence in research. *AIDS Behav.* **17**, 284–297 (2013).
29. Komajda, M., Cowie, M.R., Tavazzi, L., Ponikowski, P., Anker, S.D. & Filippatos, G.S. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction. The QUALIFY international registry. *Eur. J. Heart Fail.* **19**, 1414–1423 (2017).
30. Tang, K.L., Quan, H. & Rabi, D.M. Measuring medication adherence in patients with incident hypertension. A retrospective cohort study. *BMC Health Serv. Res.* **17**, 135 (2017).
31. Bansilal, S. *et al.* Assessing the impact of medication adherence on long-term cardiovascular outcomes. *J. Am. Coll. Cardiol.* **68**, 789–801 (2016).
32. Choudhry, N.K. *et al.* Effect of a remotely delivered tailored multicomponent approach to enhance medication taking for patients with hyperlipidemia, hypertension, and diabetes. The STIC2IT cluster randomized clinical trial. *JAMA Intern. Med.* **178**, 1182–1189 (2018).
33. Arnet, I., Kooij, M.J., Messerli, M., Hersberger, K.E., Heerdink, E.R. & Bouvy, M. Proposal of standardization to assess adherence with medication records: methodology matters. *Ann. Pharmacother.* **50**, 360–368 (2016).
34. Greevy, R.A. *et al.* Comparisons of persistence and durability among three oral antidiabetic therapies using electronic prescription-fill data: the impact of adherence requirements and stockpiling. *Clin. Pharmacol. Ther.* **90**, 813–819 (2011).
35. Martin, B.C., Wiley-Exley, E.K., Richards, S., Domino, M.E., Carey, T.S. & Sleath, B.L. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. *Ann. Pharmacother.* **43**, 36–44 (2009).
36. Bagchi, A.D., Esposito, D., Kim, M., Verdier, J. & Bencio, D. Utilization of, and adherence to, drug therapy among medicaid beneficiaries with congestive heart failure. *Clin. Ther.* **29**, 1771–1783 (2007).
37. Karve, S., Cleves, M.A., Helm, M., Hudson, T.J., West, D.S. & Martin, B.C. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Curr. Med. Res. Opin.* **25**, 2303–2310 (2009).
38. Zhang, Y. & Baik, S.H. Race/ethnicity, disability, and medication adherence among medicare beneficiaries with heart failure. *J. Gen. Intern. Med.* **29**, 602–607 (2014).
39. Ho, P.M. *et al.* Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial. *JAMA Intern. Med.* **174**, 186–193 (2014).
40. Setoguchi, S., Choudhry, N.K., Levin, R., Shrank, W.H. & Winkelmayer, W.C. Temporal trends in adherence to cardiovascular medications in elderly patients after hospitalization for heart failure. *Clin. Pharmacol. Ther.* **88**, 548–554 (2010).
41. Sueta, C.A. *et al.* Medication adherence based on Part D claims for patients with heart failure after hospitalization (from the atherosclerosis risk in communities study). *Am. J. Cardiol.* **116**, 413–419 (2015).
42. Lemstra, M. & Blackburn, D. Nonadherence to statin therapy: discontinuation after a single fill. *Can. J. Cardiol.* **28**, 567–573 (2012).
43. Krankenhausstatistik - Diagnosedaten der Patienten und Patientinnen in Krankenhäusern <https://www-genesis.destatis.de/genesis/online/logon?language=de&sequenz=tabellen&selectionname=231*>. Accessed October 31, 2018.
44. Krueger, K., Botermann, L., Schorr, S.G., Griese-Mammen, N., Laufs, U. & Schulz, M. Age-related medication adherence in patients with chronic heart failure. A systematic literature review. *Int. J. Cardiol.* **184**, 728–735 (2015).
45. Lam, W.Y. & Fresco, P. Medication adherence measures: an overview. *Biomed. Res. Int.* **2015**, 217047 (2015).
46. Arbeitsgruppen 'Erhebung und Nutzung von Sekundärdaten' und 'Epidemiologische Methoden' der DGSMP/DGEpi/GMDS. GPS – Gute Praxis Sekundärdatenanalyse: revision nach grundlegender Überarbeitung. *Gesundheitswesen* **70**, 54–60 (2008).
47. Kelly, J.P. *et al.* Patient selection in heart failure with preserved ejection fraction clinical trials. *J. Am. Coll. Cardiol.* **65**, 1668–1682 (2015).
48. McMurray, J.J. *et al.* Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur. J. Heart Fail.* **15**, 1062–1073 (2013).
49. Cannon, J.A. *et al.* Clinical outcomes according to QRS duration and morphology in the Eplerenone in Mild Patients: Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). *Eur. J. Heart Fail.* **17**, 707–716 (2015).
50. WHO Collaborating Centre for Drug Statistics Methodology. Definition and general considerations <https://www.whocc.no/ddd/definition_and_general_considera/>. Accessed October 31, 2018.