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ORIGINAL REPORT

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Empirical validation of the reverse parametric waiting time distribution and standard methods to estimate prescription durations for warfarin

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Abstract

Objectives: In many prescription databases, the duration of treatment for the single prescription is not recorded. This study aimed to validate 2 different types of approaches for estimating prescription durations, using the oral anticoagulant warfarin as a case.

Methods: The approaches undergoing empirical validation covered assumptions of a fixed daily intake of either 0.5 or 1.0 defined daily dose (DDD), as well as estimates based on the reverse parametric waiting time distribution (rWTD), with different sets of covariates. We converted estimates of prescription duration to daily dose and compared them to prescribed daily dose as recorded in a clinical registry (using Bland-Altman plots). Methods were compared based on their average prediction error (logarithmic scale) and their limit of agreement ratio (ratio of mean error ± 1.96 SD after transformation to original scale).

Results: Estimates of daily doses were underestimated by 19% or overestimated by 62% when assumptions of 0.5 or 1.0 DDD were applied. The limit of agreement ratio was 6.721 for both assumptions. The rWTD-based approaches performed better when using the estimated mean value of the inter-arrival density, yielding on average negligible bias (relative difference of 0 to 2%) and with limit of agreement ratios decreasing upon additional covariate adjustment (from 6.857 with no adjustment to 4.036 with the fully adjusted model).

Conclusions: Comparing the different methods, the rWTD algorithm performed best and led to unbiased estimates of prescribed doses and thus prescription durations and reduced misclassification on the individual level upon inclusion of covariates.

KEYWORDS

defined daily dose, Pharmacoepidemiology, prescription duration, validation, waiting time distribution, warfarin

1 | INTRODUCTION

A common challenge in pharmacoepidemiology is the lack of valid information from prescription registries on the duration of drug exposure that should be assigned to a single fill,[1] potentially affecting study validity due to exposure misclassification.[2]

A range of different methods have been applied in the attempt to assign durations to prescriptions. One approach is the assumption of patients using a fixed daily dose such as the defined daily dose (DDD), a standardized value assigned by the WHO.[3] In other cases, prescription durations are estimated based on clinical assumptions, eg, patients taking 1 tablet of statin therapy per day. Both approaches are especially problematic for drugs with large interindividual variation in daily dosages, such as the oral anticoagulant warfarin.[2]

We have recently proposed new methods to estimate prescription durations based on a reverse parametric waiting time distribution (rWTD)[4] and how this method allows inclusion of observed drug and patient characteristics as covariates.[5]

In this paper, we aimed to validate 2 different types of approaches for estimating prescription durations for warfarin: (1) assuming a daily intake of either 1.0 DDD or 0.5 DDD and (2) using the rWTD without covariates and with 3 different models of drug and patient characteristics as covariates. The empirical validation consisted of a comparison of the estimated daily doses to data on actual prescribed daily doses of warfarin obtained from a clinical anticoagulation registry, which we term the gold standard.[6] We assessed the performance of the methods with regards to relative error (bias) and variation in errors.

KEY POINTS

- We empirically validated 2 different approaches for estimating prescription durations, using warfarin as a case and data on prescribed dose from a clinical registry as "gold standard".
- The reverse parametric waiting time distribution (rWTD) approach showed less bias and higher precision compared to methods that assumed a fixed daily dose.
- The rWTD approach yielded virtually unbiased overall estimates when using the mean value of the inter-arrival density. Furthermore, misclassification on the individual level was reduced when covariates were included.
- Future use of the rWTD method in pharmacoepidemiological studies will prove its utility.

2 | MATERIAL AND METHODS

The study was an empirical validation of 2 different approaches for estimating the prescription duration of warfarin. We converted these estimates to daily doses and compared them to actual daily doses of warfarin collected from a clinical anticoagulation registry using Bland-Altman plots.

2.1 | Data sources

We collected prescribed daily doses of warfarin from the clinical registry Thrombobase and linked these to prescription fills obtained from the Odense University Pharmacoepidemiological Database (OPED).[7] The linkage was enabled by using the Danish Civil Registration Number System covering individual identification numbers on all residents in Denmark.[8] Thrombobase is a clinical anticoagulation database, which includes information about prescribed warfarin dose, international normalized ratio (INR) measurements, and treatment indication for patients receiving vitamin K-antagonist therapy from 3 outpatient clinics at Odense University Hospital and 50 general practitioners from the former county of Funen.[9] The prescribed warfarin dose is adjusted according to values of INR, which is measured at every patient visit and recorded in the database together with the dose. The prescription database OPED covers information on redeemed and reimbursed prescriptions from parts of Denmark, including Funen.[7] For every prescription, the number of redeemed packages, the date of redemption, and drug strength are recorded, among other variables. As with other Nordic prescription databases,[1] dosing instructions and prescription durations are not recorded in OPED.[7]

2.2 | The waiting time distribution

The WTD concept was initially suggested by Hallas et al in 1997[10] as a graphical approach based on a frequency distribution of each patient's first filling of a particular drug within a specific time interval. The WTD enables a distinction between 2 components corresponding to incident and prevalent users, respectively. In the absence of seasonal variation in incidence, incident users will redeem their first redemption uniformly throughout the study window, which results in a constant component of the WTD. By contrast, prevalent users will redeem new prescriptions in the beginning of the study period. In 2016, Støvring et al[11] proposed an algorithm based on a parametric model leading to the development of the parametric WTD model which enabled estimation of prescription durations for prevalent users. In brief, the model is based on renewal process theory which identifies the prevalent component of the WTD as a forward recurrence density (FRD), ie, the decreasing density of the distribution observed in the beginning of the time window. Based on an estimate of the FRD, it is possible by a simple mathematical transformation to estimate percentiles of the associated inter-arrival density (IAD).[11] Subsequently, Støvring et al[4] proposed a reversed model, in which the last (instead of the first) prescription fill of each patient within a time interval is considered, ie, the rWTD. The prevalent component of the rWTD is a backward recurrence density (BRD) resulting in a shape of the rWTD being mirrored compared with the ordinary WTD. In renewal processes, the BRD and the FRD coincide, and Støvring et al[4] showed that the theoretical agreement was also found in applications to real-world data. Percentiles of the IAD may be obtained using similar algorithms as for the original parametric WTD. Furthermore, an extension to the rWTD has been proposed to include in the estimation specific

patient and drug characteristics such as sex, age, or number of tablets filled as covariates.[5]

2.3 | Reference sample and dose (gold standard)

We identified all patients registered in Thrombobase from 1998 to 2010. We disregarded the first 4 months of follow-up for all treatment episodes (as recorded in Thrombobase), as INR values are known to be unstable early after treatment initiation.[12] From the remaining treatment episode, we chose a random prescription fill for each patient in OPED and identified the most recent previous patient visit recorded in Thrombobase. Data about the prescribed dose at this specific visit yielded the daily warfarin dose, which we considered as the reference value (ie, the gold standard) in the analysis.

2.4 | Estimation of drug duration

We examined 2 different types of approaches for the estimation of prescription durations for warfarin. These were based on DDD values (assuming either 1.0 DDD [7.5 mg] or 0.5 DDD [3.75 mg] per day) and the rWTD approach without covariates as with 3 different sets of drug and patient covariates. We did not include estimations based on the original parametric WTD, as this has been shown in a previous study to yield results similar to the rWTD.[4] All prescription durations obtained from the rWTD approach were converted into estimated daily doses to enable comparison with actual daily doses of warfarin collected from Thrombobase. We used the following equation for the conversion:

$$\frac{\text{Package size} \cdot \text{Number of packages} \cdot \text{drug strength (mg)}}{\text{prescription duration (days)}} = \text{daily dose (mg/day)}$$

In Denmark, warfarin is only available in packages of 100 tablets, each containing 2.5 mg. However, no restriction exists on the number of packages that can be obtained per prescription fill. For chronic treatments, an amount corresponding to approximately 3 months of treatment is usually prescribed. The number of packages redeemed is recorded in OPED.[13]

We implemented the DDD approach in this study by including assumptions of intake of 1.0 DDD, corresponding to 7.5 mg warfarin per day,[3] and intake of 0.5 DDD (3.75 mg), a value that has been applied in previous studies.[14] As this approach directly yields the daily dosage of warfarin, no further conversion was carried out before comparison with data from Thrombobase.

The rWTD approach without covariates was implemented in the study as estimated prescription durations by using the calendar year 2004 (mid-study period) as time window. From users of warfarin within 2004, we identified the latest redeemed prescription using dispensing information from OPED. We used a Log-Normal BRD, which implies that the corresponding IAD is a Log-Normal distribution with parameters μ and σ, which are the mean and standard deviation (SD) of the time to next prescription redemption for prevalent users on the log-scale. This implies that the k'th percentile of the IAD is given by $\exp(\Phi^{-1}(k)\sigma + \mu)$, where $\Phi(\cdot)$ is the standard normal cumulative distribution function. Similarly, the mean of the IAD is given by $\exp\left(\mu + \frac{1}{2}\sigma^2\right)$. From these expressions, we calculated the 50th, 60th, 70th, 80th, 90th percentile and the mean of the IAD.[4,5]

For the rWTD with covariates, we used a similar time window as for the rWTD without covariates. We again used a Log-Normal BRD, and the 50th, 60th, 70th, 80th, 90th percentiles and mean of the IAD were consequently estimated from similar expressions, except that the parameters μ and σ now depended on individual covariates. We included 3 sets of covariates leading to 3 different models of the rWTD. The first model included sex and continuous age, the second further included number of packages, while the third and final model also included "time since last redemption" (continuous in days).

2.5 | Analysis

We compared the daily doses of warfarin estimated from the 2 approaches outlined above with actual daily doses from Thrombobase using Bland-Altman plots.[15,16] These plots provide a graphical presentation of the difference between the estimated dose and actual dose on a logarithmic scale plotted against mean values of the estimated dose and actual dose on a logarithmic scale. For each method, we computed the average difference between predicted and actual dose on the logarithmic scale and reported it in percentage as the relative difference is on the original scale. If we, eg, find a difference of 0.5 on the logarithmic scale, we report this as a (exp(0.5) − 1) = 64.8% relative difference. As customary for Bland-Altman analyses, we also computed the so-called limits of agreement, which are defined as the average difference $\delta \pm 1.96$ SD, also computed on the logarithmic scale. To facilitate comparisons of methods, we summarized variation by reporting of the ratio of the upper limit of agreement to the lower limit, both back-transformed to the original scale. A smaller ratio indicates a more precise prediction of dose on the individual level.

$$\text{Limit of agreement ratio} = \exp(\delta + 1.96 \cdot SD - (\delta - 1.96 \cdot SD)) = \exp(3.92 \cdot SD)$$

2.6 | Sensitivity analysis

As sensitivity analyses, we first changed the method used for determining actual daily warfarin doses in the reference sample. This was

carried out by calculating the mean value of dosages within a time interval of 6 months for each patient (instead of using the dose from the randomly selected dispensing). Second, we applied a different sampling approach redefining the index date to the first prescription within the treatment episode (instead of a random prescription) while still disregarding the first 4 months of each treatment episode.

2.7 | Other

All analyses were performed using STATA Release 14.2 (StataCorp, College Station, TX, USA). According to Danish law, ethical approval is not required for registry-based studies.

3 | RESULTS

In the reference sample, we included 2848 warfarin users, which were registered in Thrombobase from 1998 to 2010. Of these, 62% (*n* = 1778) were males, the median age was 69 years (interquartile range (IQR), 58-77), and the main indication for warfarin treatment was atrial fibrillation (59%) followed by venous thromboembolism (18%) and heart valve disorder (16%). The daily doses of warfarin among the users in the reference sample, as recorded in Thrombobase, displayed a right-skewed distribution (Figure 1) with a median dose of 4.82 mg (IQR: 3.39-6.43) and a mean dose of 5.17 (SD 2.46).

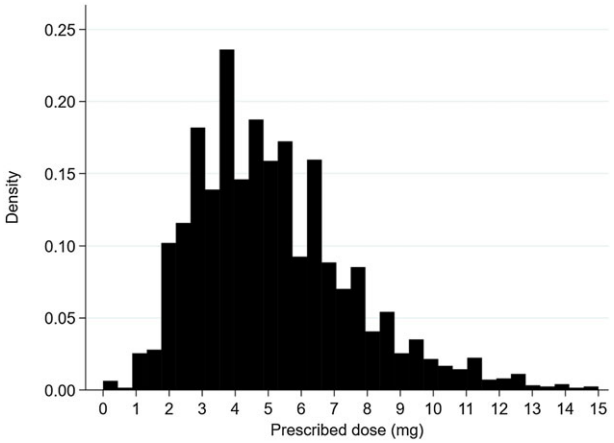

FIGURE 1 Distribution of prescribed daily doses (mg) of warfarin among 2848 included patients in the reference sample, as recorded in Thrombobase

Bland-Altman plots from the validation of the DDD approaches showed a straight line, due to the fixed assumption of either 1 DDD (7.5 mg) or 0.5 DDD (3.75 mg) as daily dose (Figure 2). The assumption of 0.5 DDD showed a relative difference of −19%, indicating that the warfarin dose was underestimated, corresponding to an overestimation of the exposure duration. Similarly, the assumption of 1.0 DDD led to a relative difference of 62%. Both DDD assumptions showed a limit of agreement ratio of 6.721 (see footnote to Table 1).

Results from the validation of the rWTD approach without and with 3 models of covariates are presented in Table 1. For each model, we applied the 50th, 60th, 70th, 80th, 90th or the mean of IAD for estimating the daily dose of warfarin. Estimations based on the 60th percentile and the mean of IAD showed the lowest relative difference of 0% to 2%. When the 50th percentile of the IAD was applied, the relative difference increased indicating an overestimation of the warfarin dose, thus underestimating the drug exposure duration. Conversely, the exposure duration became overestimated when the 70th, 80th, and 90th percentiles were applied. The limit of agreement ratio decreased from the rWTD without covariates (6.867) to the final model of full covariate adjustment of rWTD (4.036), indicating a reduced variability of predictions on the individual level when covariates were included in the prediction model.

We present only Bland-Altman plots from the estimations based on the mean of IAD (Figure 3), with plots from the 50th and 80th percentile presented in the supplementary appendix. The plot for the rWTD without covariates displayed a relative difference of 0% (−62% to 162%) and parallel lines, which correspond to warfarin users redeeming different numbers of packages. In the basic model of the rWTD, the relative difference was 1% (−60% to 155%), and, although some variation was seen (from age and sex), some banded stripes remained reflecting the small number of different prediction values. When we additionally adjusted for the number of packages filled in the rWTD medio model, the clustered pattern was nearly eliminated. This model showed a relative difference of 2% (−57% to 146%). The final model had an almost similar pattern, but with a more horizontal spread which indicates that bias in predictions did not depend on the size of the daily dose. The relative difference was 2% (−49% to 104%).

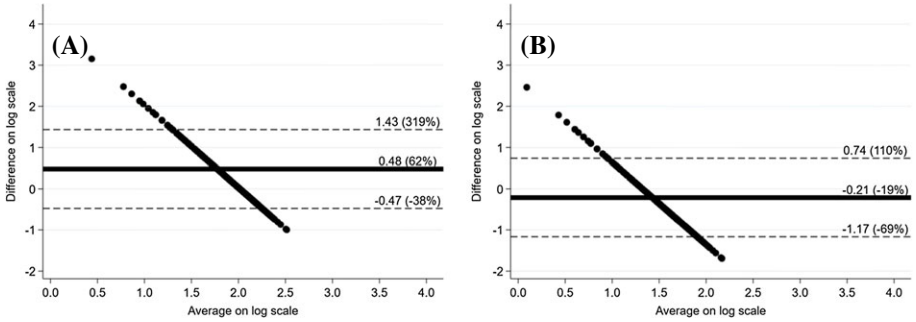

FIGURE 2 Bland-Altman plots comparing estimated daily dose of warfarin using the assumption of either 1.0 DDD (7.5 mg; part A) or 0.5 DDD (3.75 mg; part B) to prescribed daily doses as recorded in Thrombobase (gold standard). The black lines denote the average difference on the log scale, which, when back-transformed corresponds to the median relative difference (provided in the parenthesis). The dashed lines denote the upper and lower limit of agreement

TABLE 1 Comparison of the recorded daily dose (reference sample) and the estimated daily doses. The results are displayed as relative differences (on original scale) in percentage including the 95% CI of the limit of agreement

	Relative Difference	Limit of Agreements	Limit of Agreement Ratio[a]
DDD assumptions			
1.0 DDD	62%	−38% to 319%	6.721
0.5 DDD	−19%	−69% to 110%	6.721
rWTD (without covariates)			
50th percentile of IAD	15%	−56% to 200%	6.857
60th percentile of IAD	0%	−62% to 163%	6.857
70th percentile of IAD	−13%	−67% to 128%	6.857
80th percentile of IAD	−26%	−72% to 93%	6.857
90th percentile of IAD	−41%	−78% to 53%	6.857
Mean of IAD	−0%	−62% to 162%	6.857
Basic rWTD-model including sex and continuous age as covariates			
50th percentile of IAD	15%	−54% to 191%	6.394
60th percentile of IAD	1%	−60% to 155%	6.388
70th percentile of IAD	−12%	−65% to 122%	6.382
80th percentile of IAD	−25%	−70% to 88%	6.375
90th percentile of IAD	−41%	−76% to 50%	6.365
Mean of IAD	1%	−60% to 155%	6.382
Medio rWTD-model including sex, continuous age, and number of redeemed packages as covariates			
50th percentile of IAD	15%	−52% to 176%	5.787
60th percentile of IAD	2%	−58% to 145%	5.781
70th percentile of IAD	−11%	−63% to 115%	5.777
80th percentile of IAD	−23%	−68% to 84%	5.775
90th percentile of IAD	−38%	−74% to 49%	5.776
Mean of IAD	2%	−57% to 146%	5.778
Final rWTD-model including sex, continuous age, number of redeemed packages, and "time since last redemption" (continuous in days) as covariates			
50th percentile of IAD	12%	−44% to 122%	3.952
60th percentile of IAD	0%	−50% to 100%	3.996
70th percentile of IAD	−11%	−56% to 79%	4.059
80th percentile of IAD	−22%	−62% to 58%	4.153
90th percentile of IAD	−36%	−69% to 34%	4.321
Mean of IAD	2%	−49% to 104%	4.036

Abbreviations: IAD, inter-arrival density; rWTD, reverse waiting time distribution.

[a]When a method predicts the same dose for all individuals, it can be shown that the limit of agreement ratio is constant irrespective of the value of the prediction. This is the reason that the 2 DDD methods have identical limit of agreement ratios. The reason that the rWTD model without covariates does not return the same limit of agreement ratio is that the rWTD model estimates a fixed duration of a prescription, thereby yielding different estimates of daily dose when different number of packages are filled.

The results of the sensitivity analysis using a weighted average prescribed dose for comparison (Supplementary Figure 1) or using the first eligible prescription instead of a random prescription (Supplementary Figure 2) yielded estimates comparable to the main analysis.

4 | DISCUSSION

The study demonstrated that using the rWTD approach to estimate prescription durations by the mean of the IAD resulted in estimates of daily dose which had on average negligible bias relative to the prescribed daily dose. This was in contrast to conventional approaches based on a fixed daily intake of, eg, 0.5 or 1.0 DDD of warfarin which both showed substantial bias. When we further incorporated covariates to the rWTD approach, the precision of the estimated daily doses on the individual level improved markedly, as seen from the decreasing limit of agreement ratio obtained with increasing covariate adjustment.

The main strength of our study is the use of real-world prescription data coupled to a useful gold standard of prescribed daily doses recorded in Thrombobase, which allows us to validate the usefulness of the DDD and rWTD-based approaches in a realistic epidemiological setting. Both Thrombobase and OPED provide nearly complete follow-up of all relevant subjects over extended periods of time.[7,9]

The study also has limitations. The primary limitation is the reliance on prescribed daily dose as gold standard, because patients may not accurately follow the prescribed dose regime. However, any method based solely on observations in a prescription database cannot be expected to yield absolutely accurate information at the level of individual patients. Rather, the objective when using this type of data must be to obtain estimates of prescription duration unbiased

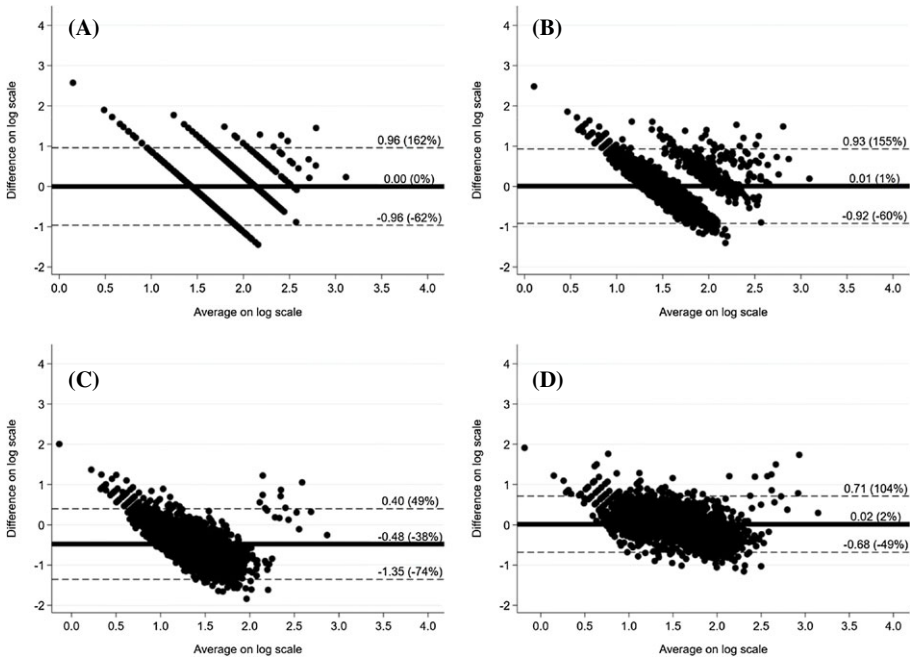

FIGURE 3 Bland-Altman plots comparing daily doses estimated using the rWTD approach to prescribed daily doses as recorded in Thrombobase (gold standard). The first model (A) did not include covariates. The basic model (B) included sex and age (continuous) as covariates. The medio model (C) included sex, age, and number of redeemed packages as covariates. The full model (D) included sex, age, number of redeemed packages, and "time since last redemption" (continuous in days) as covariates. rWTD estimates were predicted using the mean of the interarrival density (IAD). The black lines denote the average difference on the log scale, which, when back-transformed corresponds to the median relative difference (provided in the parenthesis). The dashed lines denote the upper and lower limit of agreement

at the population level and with the smallest possible error variation. From this perspective, we would anticipate that if a method could provide an unbiased estimate of the average duration of a prescription among patients in active treatment, such a method would likewise provide unbiased estimates of daily doses. Reassuringly, this is indeed what we find when using the rWTD-based mean estimates, even though predictions suffer from error at the individual level. Of note, this study specifically excluded the first 4 months of each patients' treatment episode, to ensure that a stable phase of warfarin treatment had been reached.[12] Thereby, the results do not necessarily reflect recently initiated treatment. A further limitation is that we only have access to prescriptions redeemed at pharmacies, which implies that medication obtained from and during hospitalizations are not recorded. However, in-hospital use of warfarin is very limited,[17] and we thus expect this misclassification to be minor.

The use of warfarin as a case needs to be discussed. The close monitoring and documentation hereof is a property of warfarin treatment that permits us to use these data to assess the validity of the rWTD estimates of prescription durations. However, such monitoring also means that the contribution from non-compliance to prescription durations is likely smaller for this drug than for other drugs. Regardless, the large interindividual variation in daily dose of warfarin makes it particularly challenging to estimate durations for this drug. The fact that the rWTD algorithm performs well under such difficult circumstances suggests that it can be useful for a wide range of drug classes.

The substantial bias revealed for the 1.0 DDD assumption is most likely explained by the known discrepancy between the DDD value for warfarin as determined by the WHO (ie, 7.5 mg) and the actual average daily dose of warfarin as used in clinical practice,[2] which in this study was found to be 4.8 mg. The DDD approach is expected to perform better for drugs with better concordance between the DDD value and the actual daily dose.

Other studies have attempted to validate methods for estimating prescription duration or, more or less equivalently, daily dose. Recently, Taipale et al[18] compared treatment status derived with the "prescription drug purchases to drug use periods" (PRE2DUP) method in a cohort of older persons and found good agreement.[19] Meid et al[20,21] compared an individual estimation of drug coverage (COV), in which estimations are based on averaged fraction of prescribed doses from longitudinal prescription history, to real data and found it preferable over the DDD approach. It should, however, be noticed that estimation of treatment status is to a certain extent a simpler task than obtaining an unbiased estimate of daily dose.

At its core, modern pharmacoepidemiology often relies on observations of prescription as recorded in large-scale databases, and thus it remains a fundamental problem to infer how a drug is used based on such data. Ideally, we would for each patient like to know on any given day the dose that was taken. As this is unrealistic, the objective must be to provide optimal predictions based on observed data, ie, predictions with minimal bias and error variation. Improved precision in predictions can be expected to confer improved statistical precision and validity in studies where drug use is the exposure of interest.[4,5] Most methods to estimate drug use have been based on decision rules with clinical input or elaborate algorithms, whereas methods based on an explicit statistical model are scarce. Our validation study shows that in a setting where most users of the drug continue treatment and can be expected to comply with dose instructions, the rWTD method estimates what it would be expected to from a theoretical perspective.[4] The distinctive feature of the different WTD approaches is that they all rely on

identifying the forward or backward recurrence distribution which corresponds to users in continued treatment.[4,11] With the addition of covariates in the rWTD, this distribution can be made more specific to improve precision in predictions.[5] Still, the present study shows that precision at an individual level is low with the covariates used here (age, sex, number of packages, and time since last redemption). We are not aware of covariates which could be expected to have substantial predictive power apart from these. Future research could both focus on identifying important predictors to be included in the model and perform similar validation studies for other drug classes and patient groups. Such validation studies should also include comparisons with other recent suggestions such as the PRE2DUP algorithm and the COV approach,[18,20] although this is complicated by the fact that these approaches require some expert input. By contrast, the WTD approach only relies on standard statistical modeling techniques, and its fit can therefore be assessed with standard diagnostic techniques.

The validity of these algorithms relates to the subject of exposure misclassification. Having specified too long treatment periods to single prescription will have little effect on most treatment episodes, as the overlap between consecutive prescriptions is usually disregarded. Too short durations, on the other hand, will lead to unduly segmented treatment episodes with frequent artificial gaps.[22] Misclassification is likely to be non-differential, usually generating a weak or moderate bias towards the null. In self-controlled designs, however, such bias can be substantial, even with low degrees of misclassification,[23] and drug survival analyses are also highly sensitive to assumptions about prescription durations.[24]

In summation, we have provided an empirical validation of WTD-based approaches to estimate prescription durations using warfarin as case. We found that the rWTD-based approaches outperformed the simple approaches assuming a fixed daily intake, with negligible bias at the aggregate level and improved precision at the individual level. However, even when including covariates in the rWTD model, substantial variation in predictions remained. The use of these new methods in future pharmacoepidemiological studies, facilitated by available STATA implementations of the algorithm, will show how best to utilize them and, ultimately, how they will fit into the pharmacoepidemiological methods armamentarium.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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