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Determining Drug Exposure Based on Medication Dispensing Data: A Validation Study of Vitamin K Antagonist Treatment Episodes Against INR Records

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ABSTRACT

Background: In pharmaco-epidemiological studies using vitamin K antagonist (VKA) exposure, constructing treatment episodes based on dispensed prescriptions is challenging, particularly due to the large variability in therapeutic dose.

Objectives: To validate different methods of constructing VKA treatment episodes based on dispensed prescriptions, using VKA exposure based on international normalized ratio (INR) measurements as a reference.

Methods: Data from five Dutch anticoagulation clinics were linked to VKA dispensing data from Statistics Netherlands. Three random samples of 10 000 VKA users between 2013 and 2019 were used to compare the construction of VKA treatment episodes based on dispensings, applying fixed or dynamic methods, against the reference of exposure based on INR measurements. A total of 60 different methods were validated by computing the percentage of INR measurements occurring outside dispensing-based VKA treatment episodes, the ratio of VKA-exposed person-time based on dispensings vs. INR measurements, and the number of dispensing-based episodes.

Results: Depending on the method used to construct treatment episodes, 14.8%–42.2% of the INR measurements were not covered by a dispensing-based episode. The VKA-exposed person-time ratio ranged between 0.73 and 1.13, and there was substantial

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variability in the number of dispensing-based episodes. Fixed methods resulted in a lower percentage of INR measurements outside the dispensing-based episodes, a VKA-exposed person-time ratio closer to 1.0, and a lower number of constructed episodes.
Conclusion: Fixed methods performed better than dynamic methods when classifying VKA exposure based on dispensing data. Our findings may guide other researchers working with VKA dispensing data, especially when the tablets dispensed or the prescribed dose are unavailable.

1 | Introduction

Pharmacy dispensing databases are frequently used in observational studies to collect information on medication exposure. A usual requirement for the use of these databases is the construction of individual-level treatment episodes over time from a sequence of dispensed prescriptions [1]. Different methods can be applied to construct drug treatment episodes, depending on whether information about the duration of drug exposure for a single dispensed prescription is available [2]. Challenges may arise when no data are available on the amount of drug dispensed nor the dose regimen, making it difficult to determine the end of medication exposure.

In essence, researchers need to decide which consecutive dispensed prescriptions belong to the same treatment episode and when a new episode has started. One approach is to assume that a dispensing lasts a fixed number of days [3]. Whenever the period between two subsequent dispensed prescriptions exceeds this fixed number of days, the next prescription is considered to belong to a new treatment episode. Several studies performed with anticoagulant dispensing data in the Netherlands have assumed that a dispensed prescription lasted for 90 or 100 days (allowing 10 days extra for flexibility) [4, 5], given that in the Netherlands drugs are prescribed for a maximum of 90 days [6].

This assumption may be valid for drugs with a fixed dosing regimen but is not appropriate for vitamin K antagonists (VKAs). VKAs, a type of oral anticoagulants, are characterized by a variable dosing requirement, that is, the daily dosage varies from patient to patient and within a patient over time [7, 8]. This variability is partly due to common polymorphisms affecting the pharmacokinetics and pharmacodynamics of VKAs [7, 9–14], but also dietary intake of vitamin K and concomitant medications [8, 15]. Other characteristics of VKAs include a slow onset of action and narrow therapeutic window [16–18], requiring specialized anticoagulation clinics to monitor the anticoagulation level and adjust the dose if necessary [7]. The anticoagulation level of VKAs is measured by the international normalized ratio (INR), a standardized version of the prothrombin time ratio [19, 20]. Patients with INR values below or above their therapeutic range are at increased risk of either thromboembolic events or bleeding, respectively [21–24].

These special properties of VKAs complicate the modeling of VKA exposure based on dispensing data. Even if information on days supplied or the amount of VKA dispensed is available, these measures may not be reliable if the variability in dose over time is not accounted for [25]. For example, if the dose is reduced based on a high INR result, the actual duration may last longer than estimated [26]. Consequently, the person-time exposed to VKAs may be misclassified and resulting inferences may be biased, if this exposure misclassification is not taken into account [27]. Our study aims to identify a method of constructing VKA treatment episodes based on dispensing data that minimizes misclassification of VKA exposure. We hypothesized that methods that incorporate variability of VKA dosing and resulting dispensed prescription duration would better classify VKA exposure than methods based on a fixed number of days. We used data from Dutch anticoagulation clinics linked to anticoagulant dispensing data from Statistics Netherlands to validate different methods of constructing VKA treatment episodes based on dispensed VKA prescriptions and compared them to VKA treatment episodes based on INR measurements.

2 | Methods

2.1 | Settings and Study Population

We used data on VKA treatment from five large Dutch anticoagulation clinics between January 1, 2013, and December 31, 2019. These clinics provided detailed data on VKA treatment, including registered treatment indications, start and end dates of VKA treatment, dates of INR measurements, and corresponding INR results. Data on VKA treatment were linked on an individual level to anticoagulant dispensing data from Statistics Netherlands covering 2012 until 2019. Linkage was performed by sex, date of birth, postal code, and last date known to be alive. Dispensing data from Statistics Netherlands contain dispensed outpatient medication prescriptions (excluding medications received during hospital stay and in nursing homes) [4, 5]. Outpatient dispensings of anticoagulants were identified by Anatomical Therapeutic Chemical (ATC) codes and included dispensing dates and types of anticoagulant (i.e., VKA, direct oral anticoagulant [DOAC], or heparin group). No information was available on the amount of medication collected or the prescribed dosages for each dispensing nor VKA subtypes. All data were anonymized, and each individual was assigned a unique identification code. A description of all data sources is provided in Supporting Information S1: Methods.

The source population comprised patients treated with VKAs at one of the participating anticoagulation clinics between 2013 and 2019. From this population, we randomly sampled three groups of 10 000 VKA users each. Follow-up started on the first available INR record between January 1, 2013 and December 31, 2019 and lasted until the date of death or December 31, 2019, whichever occurred first.

2.2 | Study Design

We performed a cohort study to validate different methods of constructing VKA treatment episodes from VKA dispensed

Summary

- The variability in therapeutic dose of vitamin K antagonists (VKAs) complicates modeling of exposure based on dispensing data.
- We studied the validity of different definitions for VKA treatment episodes based on dispensed prescriptions, using exposure based on INR measurements as a reference.
- Three random samples of 10 000 VKA users treated by Dutch anticoagulation clinics between 2013 and 2019 were studied.
- Fixed methods generally showed less misclassification of VKA exposure than dynamic.
- Differences in the performance of the methods were observed between acenocoumarol and phenprocoumon.

prescriptions and compared those to VKA exposure based on INR measurements. VKA treatment episodes derived from INR records were considered as reference, based on the assumption that patients are exposed to VKA if their INR is measured regularly at an anticoagulation clinic. Treatment episodes based on dispensings were derived from either a single or a sequence of dispensed prescriptions. We studied different exposure times, defined as the period a patient was assumed to be exposed after the dispensing date, unless a refill, death, or end of follow-up occurred earlier. In other words, the exposure time was the allowed period between subsequent VKA dispensings within the same treatment episode. We studied both fixed exposure times and a combination of fixed and dynamic exposure times.

2.3 | VKA Treatment Episodes Based on INR Measurements (Reference)

VKA treatment episodes based on INR measurements were constructed applying a gap of 8 weeks between subsequent measurements. If the period between two subsequent INR measurements exceeded 8 weeks, a new VKA treatment episode was constructed. Dutch guidelines generally advise monitoring the INR at least once every 6 weeks [28]. Therefore, we assumed that regular INR measurements, with an allowable gap of 8 weeks between measurements to incorporate some flexibility, indicated VKA exposure. A treatment episode started on the date of the first INR measurement and ended 8 weeks after the last INR record. We applied the following exceptions in the construction of the end date: (1) if death or end of follow-up (December 31, 2019) occurred earlier than the constructed end date, the first occurring date of death or December 31, 2019, respectively, was used instead; (2) if the end date of VKA treatment originally registered by the anticoagulation clinic occurred within 8 weeks after the last INR record, the registered end date was used instead.

2.4 | VKA Treatment Episodes From Dispensed Prescriptions: Fixed Exposure Times

First, we studied fixed exposure times, that is, a predefined number of days, as a method to construct VKA treatment episodes from dispensed prescriptions. Each VKA treatment episode started on the first VKA dispensing date available between 2013 and 2019 and ended when there was no subsequent VKA dispensing within the defined exposure time starting on the preceding dispensing date. If the period between two subsequent dispensed VKA prescriptions exceeded the fixed number of days, a new VKA treatment episode was created (Figure 1A). We studied fixed exposure times of 60, 100, 120, 150, and 180 days. To construct the start date of the first

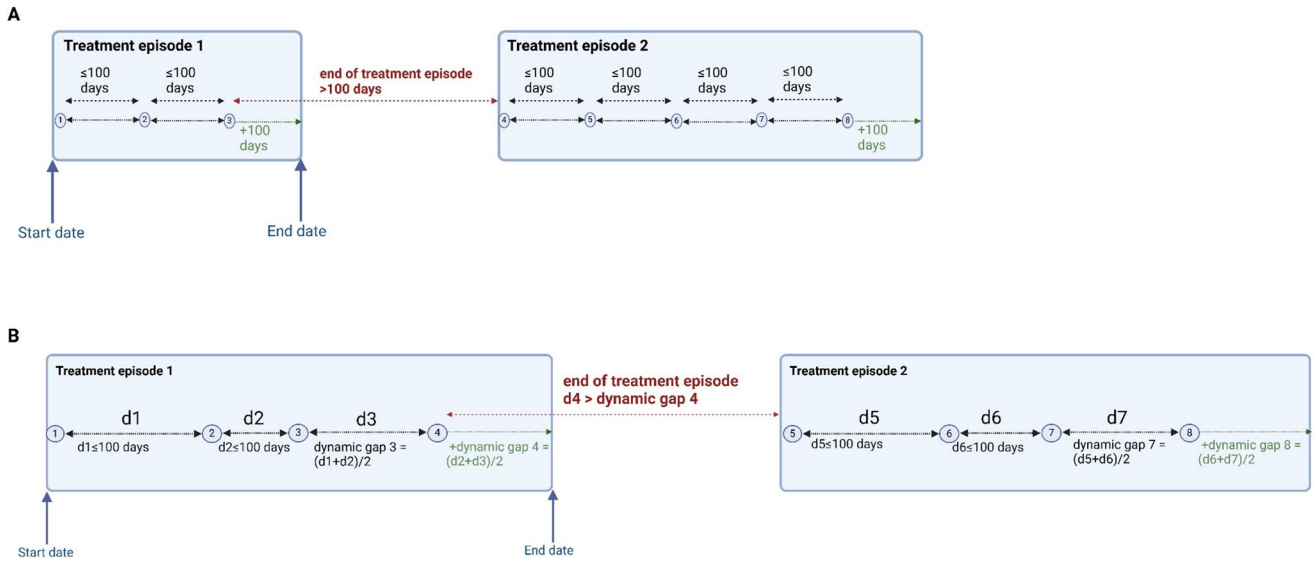

FIGURE 1 | Illustration of fixed and dynamic exposure times used to construct VKA treatment episodes. (A) This figure illustrates an example of applying a fixed exposure time of 100 days between subsequent dispensed VKA prescriptions (numbered 1–8) and the addition of 100 days to the date of last VKA dispensing within the treatment episode. (B) This figure illustrates the use of a dynamic method. The dynamic exposure time is calculated as the average period between the preceding two dispensed VKA prescriptions, with a fixed exposure time of 100 days for the first two dispensings. The dynamic exposure time was added to the date of last VKA dispensing within the treatment episode to construct the end date. This figure was created in BioRender. Kruip (2024). https://BioRender.com/z70g565.

episode, we identified the last VKA dispensing available in 2012. If the first VKA dispensing in 2013 occurred within the defined fixed exposure time after the last VKA dispensing in 2012, the start date of the first VKA treatment episode was set as January 1, 2013. The end date of each treatment episode was constructed by adding a fixed number of days (60, 100, or 120 days) to the last VKA dispensing date within the treatment episode.

2.5 | VKA Treatment Episodes From Dispensed Prescriptions: Dynamic Exposure Times

For our second approach, we constructed dynamic exposure times to capture better the large inter- and intra-individual variability in VKA dosing. These dynamic exposure times differ from patient to patient and over time because they are calculated based on the most recent redeemed prescription history of each patient. We adopted two methods: calculating the dynamic exposure time as the average period between the preceding two or the preceding three VKA dispensing dates. Since dynamic exposure times cannot be calculated without dispensing history, we applied a fixed exposure time for the first two or three dispensings of the treatment episode (100, 120, 150, or 180 days) (Figure 1B).

Similar to the fixed methods, each VKA treatment episode started on the first VKA dispensing date available between 2013 and 2019 and ended when there was no subsequent dispensed VKA prescription within the dynamic or fixed (for the first two or three dispensings) exposure time from the preceding dispensing. For patients exposed on January 1, 2013, the period between the last 2012 VKA dispensing and the first 2013 VKA dispensing was also included in the calculation of the patient's first dynamic exposure time. The end date of a treatment episode was constructed by adding the dynamic exposure time to the last VKA dispensing date within the treatment episode. If the treatment episode ended before the first two or three dispensings, we added a fixed number of days to the last VKA dispensing within the episode.

Furthermore, we studied an extension of the dynamic method to incorporate additional flexibility. This involved increasing the dynamic exposure time by adding a percentage of its length (10%, 25%, 50%, 75%, or 100%). A treatment episode ended in this definition when there was no subsequent dispensed VKA prescription within the defined fixed (for the first two or three dispensings) or dynamic exposure time + x% from the preceding dispensing date.

For both fixed and dynamic methods, we applied the following exceptions in the construction of the end date: if death or end of follow-up occurred earlier than the constructed end date, the date of death or December 31, 2019, respectively, was used as the end date of the treatment episode. An overview of all studied methods is provided in Table S1.

2.6 | Data Analysis

Methods for constructing treatment episodes based on VKA dispensings were validated against episodes based on INR measurements with the following parameters: (1) the percentage of the total number of INR measurements that was not covered by a dispensing-based treatment episode and (2) the ratio of person-time a patient was exposed to VKA based on dispensings vs. INR measurements. Each method was assessed and ranked based on these criteria from 1 to 60, as we studied 60 methods in total, with the lowest rank assigned to the best-performing method for each criterion (Table 1). The overall best method was defined as the method with the lowest sum of ranks for both criteria. In addition, we computed the median number of dispensing-based episodes during follow-up and their duration. Subgroup analyses were performed to assess differences in the results between acenocoumarol and phenprocoumon users, in which patients who switched from VKA type were excluded. All analyses were performed in R version 4.2.3 with the packages dplyr, tidyverse, and lubridate [29–32].

2.7 | Sensitivity Analyses

Sensitivity analyses were conducted in the second and third random samples of 10,000 VKA users. Additionally, we varied the construction of INR-based treatment episodes: (1) if the last INR value of the episode was ≤ 1.5, the date of the last INR measurement was used as the end date instead of adding 8 weeks; (2) either 4 or 6 weeks were added to the last INR record within the treatment episode to construct the end date; (3) the end date was set as the last INR record within the treatment episode; and (4) an allowable gap of 6 weeks instead of 8 weeks between subsequent INR measurements was applied. We also examined INR values that were measured either inside or outside dispensing-based treatment episodes.

3 | Results

3.1 | Baseline Characteristics

Baseline characteristics of the 10000 randomly sampled VKA users are displayed in Table 2. At the start of follow-up, the median age of the cohort was 73.9 years (IQR: 65.0–81.9), 45.6% were female, and 77.3% used acenocoumarol. The most common registered indications for VKA therapy were atrial fibrillation and other

TABLE 1 | Criteria for assessing fixed and dynamic exposure times.

Criterion	Rank
Total percentage of INR measurements outside dispensing-based VKA treatment episode	Lowest % was assigned rank 1 Total rank 1–60
$\frac{\text{abs(Total PT exposed based on VKA dispensings} - \text{Total PT exposed based on INR records)}}{\text{Total PT exposed based on INR records}} * 100\,\%$	Lowest % was assigned rank 1 Total rank 1–60
Sum of ranks	Best-performing method had the lowest sum of ranks

TABLE 2 | Baseline characteristics.

	Total ($N = 10\,000$)
Demographics	
Sex, female, No. (%)	4558 (45.6)
Age at start of follow-up in years, median [Q1, Q3]	73.9 [65.0, 81.9]
Registered indications for VKA therapy,[a] No. (%)	
Mechanical heart valve	556 (5.6)
Biological valve and other heart surgery	207 (2.1)
Atrial fibrillation and other arrhythmias	6520 (65.2)
Valvular heart disease/ decompensation cordis	133 (1.3)
Cardiomyopathy	427 (4.3)
Cerebral vascular disease	155 (1.6)
Arterial embolism	118 (1.2)
Peripheral arterial disease	99 (1.0)
Coronary syndrome and interventions	188 (1.9)
Vascular surgery	249 (2.5)
VTE	1728 (17.3)
Cerebral embolism	36 (0.4)
Venous prophylaxis	38 (0.4)
Pulmonary hypertension	25 (0.3)
Other	115 (1.2)
INR therapeutic range, No. (%)	
2.0–2.5	35 (0.4)
2.0–3.0	2272 (22.7)
2.5–3.5	5596 (56.0)
3.0–4.0	815 (8.2)
Other	17 (0.2)
Unknown	1265 (12.7)
Type of VKA,[b] No. (%)	
Acenocoumarol	7726 (77.3)
Phenprocoumon	2264 (22.6)
Other/Unknown	10 (0.1)

Abbreviations: INR, international normalized ratio; VKA, vitamin K antagonist; VTE, venous thrombotic event.
[a]All treatment indications for VKA treatment that have been registered until the date of data export and were identified from the Dutch anticoagulation clinics. One or more indications can be present.
[b]Registered at the start of follow-up.

arrhythmias (65.2%), venous thromboembolism (17.3%), and mechanical heart valves (5.6%).

3.2 | Treatment Episodes Based on INR Measurements (Reference)

Based on INR measurements and an 8-week allowable gap, a median of 1 VKA treatment episode (IQR: 1–1) occurred during follow-up, with a median estimated duration of 5.1 years (IQR 3.2–7.0). Only 1155 (11.6%) patients had multiple INR-based treatment episodes. A 6-week allowable gap resulted in 2 INR-based treatment episodes during follow-up (IQR: 1–4) with a median estimated duration of 3.1 years.

3.3 | Fixed Exposure Times vs. INR Measurements

The percentage of INR measurements that was not covered by a dispensing-based treatment episode for the different fixed methods ranged from 14.8% to 42.2%, while the VKA-exposed person-time ratio based on dispensed prescriptions vs. INR measurements ranged between 0.73 and 1.12 (Figure 2). Based on the assigned ranks, the fixed exposure time of 100 + 100 days was the best-performing method for classifying VKA exposure with a sum of ranks of 33 (Table S2). This method resulted in 22.5% of INR measurements occurring outside the dispensing-based treatment episode, a VKA-exposed person-time ratio of 1.01, and a median of 4 dispensing-based episodes (IQR: 1–9) during follow-up. The median estimated length of these treatment episodes was 101 days (IQR: 101–200). The shortest fixed exposure time of 60 + 60 days resulted in the highest amount of misclassification (sum of ranks 120).

3.4 | Dynamic Exposure Times vs. INR Measurements

Dynamic methods generally performed worse than fixed methods for classifying VKA exposure, with a higher percentage of INR measurements occurring outside dispensing-based VKA treatment episodes, a VKA-exposed person-time ratio more often above 1.0, and a higher number of dispensing-based episodes during follow-up. The percentage of INR measurements occurring outside the dispensing-based episodes ranged from 16.1% to 33.7%, and the VKA-exposed person-time ratio ranged between 0.95 and 1.13 (Figure 3). The median number of dispensing-based episodes ranged between 2 and 6 (Figure 4). According to the assigned ranks, the dynamic exposure time based on the preceding three dispensed prescriptions +100% combined with a fixed exposure time of 100 days for the first three dispensings was the best-performing dynamic method with a sum of ranks of 47 (Table S2).

3.5 | Sensitivity Analyses

Similar results were found in the second and third random samples of 10 000 VKA users (Tables S2 and S3). In these sensitivity

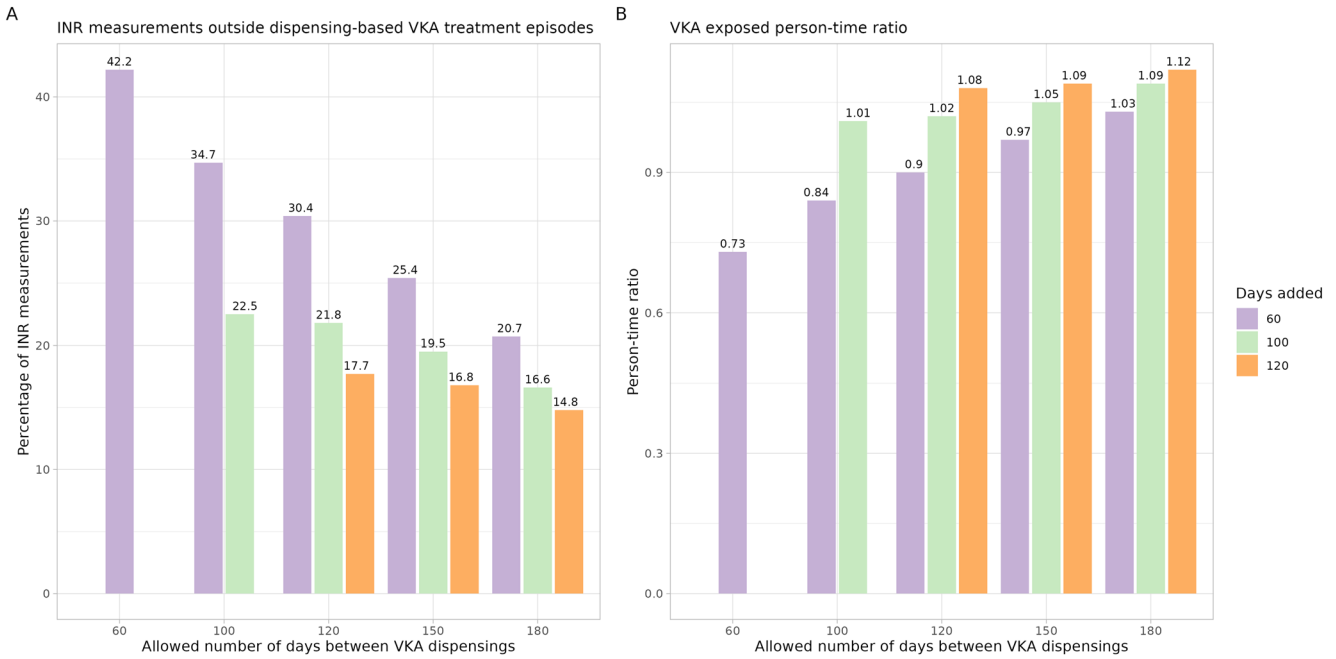

FIGURE 2 | Results of fixed exposure times. (A) The percentage of INR measurements outside dispensing-based VKA treatment episodes was calculated by dividing the number of INR measurements that occurred outside the VKA treatment episode by the total number of INR measurements. (B) The VKA-exposed person-time ratio was calculated by dividing the person-time exposed to VKA according to dispensing-based treatment episodes vs. INR-based treatment episodes. In both panels, the x-axis displays the fixed exposure time, that is, the number of days allowed between subsequent dispensed VKA prescriptions within the same treatment episode. The different colors represent the number of days added to the date of last VKA dispensing within the treatment episode.

analyses, fixed methods also performed better than dynamic with the fixed exposure time of 120 + 100 days in Sample 2 and 100 + 100 days in Sample 3 as the best-performing method for classifying VKA exposure. For these methods, the percentages of INR measurements occurring outside dispensing-based treatment episodes were 22.4% in Sample 2% and 22.9% in Sample 3, with a VKA-exposed person-time ratio of 1.00. Changing the construction of INR-based treatment episodes did not affect the ranking results (Table S2). In addition, INR values were similar with a median of 2.6 for all methods, regardless of whether they were measured inside or outside dispensing-based treatment episodes (Table S4).

3.6 | Subgroup Analysis

Our subgroup analysis demonstrated that the performance of the methods differed between acenocoumarol and phenprocoumon, with generally better performance in acenocoumarol users (Table S2). Phenprocoumon users had longer INR-based than dispensing-based VKA treatment episodes, resulting in a higher percentage of INR measurements outside the dispensing-based treatment episodes compared with acenocoumarol users, while the VKA-exposed person-time ratio was more often below 1.0 (Table S2). In addition, more dispensing-based treatment episodes were constructed among phenprocoumon users. Nonetheless, in both subgroups, the lowest rank was assigned to a fixed method, with fixed exposure times of 150 + 60 days having the lowest rank in acenocoumarol users and 180 + 120 days in phenprocoumon users. The best-performing method of 100 + 100 days in the total cohort had a sum of ranks of 47 in acenocoumarol users, while this method performed worse in phenprocoumon users with a sum of ranks of 77.

4 | Discussion

In this cohort study, we validated and compared different methods to construct VKA treatment episodes from dispensed VKA prescriptions against treatment episodes based on INR measurements. We hypothesized that dynamic methods would better capture the inter- and intra-individual variability in VKA dosing and, therefore, better classify VKA exposure than fixed methods. However, according to our predefined criteria, fixed methods performed better in accurately classifying VKA exposure. The best method to construct treatment episodes from a sequence of VKA dispensing dates was to use a fixed exposure time of 100 days between subsequent dispensed prescriptions, adding 100 days after the last dispensing date to construct the end date. This method showed the lowest amount of misclassification in VKA exposure among all validated methods. Still, over 20% of INR measurements occurred outside the dispensing-based VKA treatment episode, leaving room for improvement.

Performance differed between acenocoumarol and phenprocoumon, but regardless of VKA type, the use of a fixed method resulted in the lowest amount of misclassification of VKA exposure. In general, we observed more misclassification of VKA exposure in phenprocoumon users. According to INR measurements, the VKA-exposed person-time was longer among phenprocoumon than acenocoumarol users, which aligns with phenprocoumon's longer half-life [33]. Because of its longer

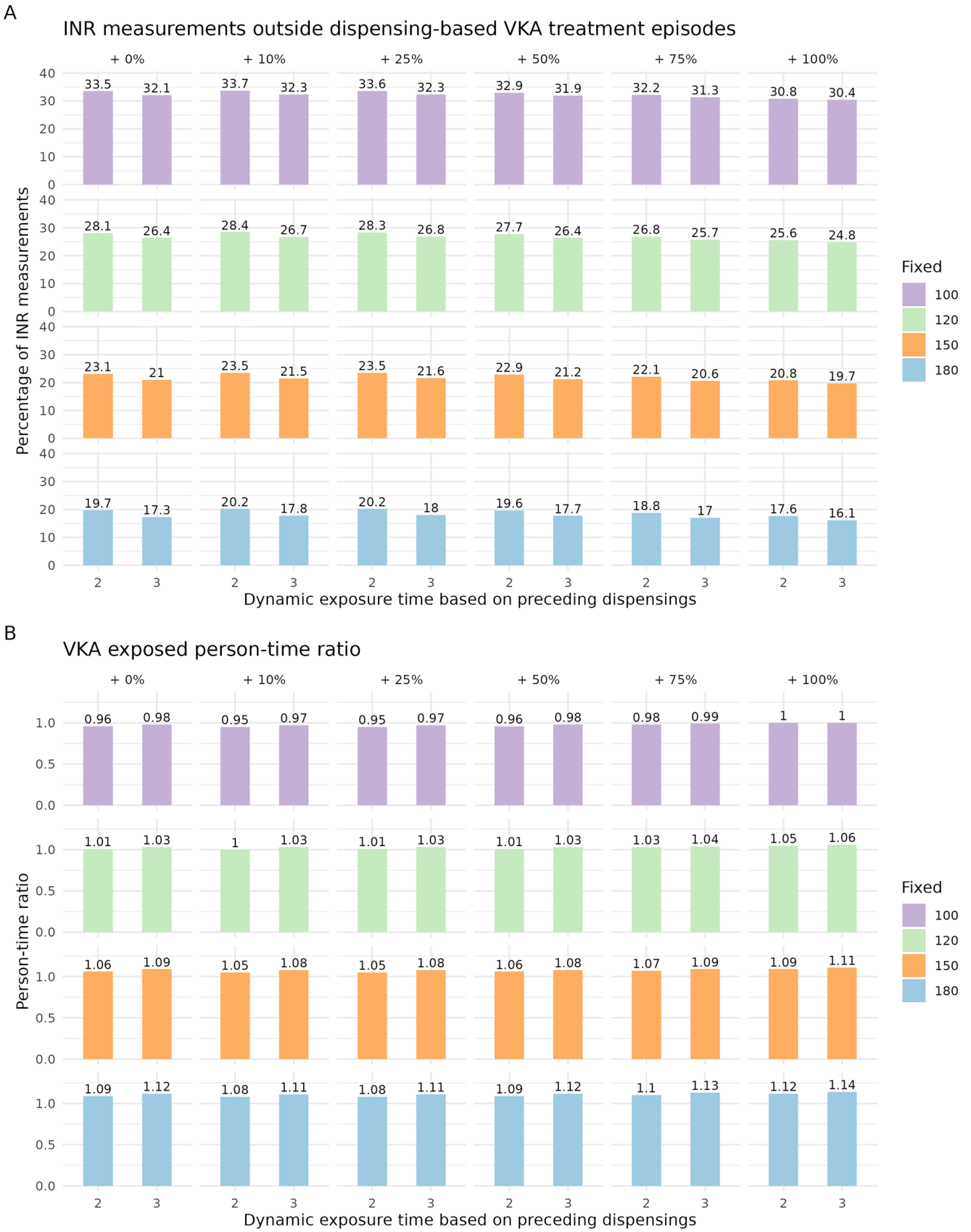

FIGURE 3 | Legend on next page.

FIGURE 3 | Results of dynamic exposure times. (A) The percentage of INR measurements outside dispensing-based VKA treatment episodes was calculated by dividing the number of INR measurements that occurred outside the VKA treatment episode by the total number of INR measurements. (B) The VKA-exposed person-time ratio was calculated by dividing the person-time exposed to VKA according to dispensing-based treatment episodes vs. INR-based treatment episodes. In both panels, the *x*-axis displays whether the dynamic exposure time was calculated based on the preceding two or three dispensed prescriptions. The different colors represent the fixed exposure time that was applied for the first two or three dispensings of the treatment episode. The upper panels display the percentage by which the dynamic exposure time was increased.

half-life and the higher dose per single tablet, the prescribed number of tablets of phenprocoumon is often lower [28, 34, 35], and patients may less frequently collect their dispensed tablets from the pharmacy. Consequently, the period between two subsequent phenprocoumon prescription fills may be longer, thereby exceeding the allowed period between dispensings when estimating treatment duration, potentially resulting in the construction of more dispensing-based treatment episodes. These findings underscore the importance of considering VKA-type specific characteristics when constructing treatment episodes.

Our findings contribute to the literature about assigning exposure durations to dispensed prescriptions when information on prescribed dose and dispensed amount of drug is lacking. One established approach is the waiting time distribution (WTD), in which the exposure period for a single dispensing is estimated by the moment prevalent drug users first redeem their prescription inside a particular time window [36, 37]. Similar to our dynamic method, this approach also uses patients' dispensing history, but only the first dispensing within a certain calendar year. The estimated exposure period is subsequently applied as a fixed exposure time to construct treatment episodes. Based on the cumulative WTD described by Pottegård and Hallas [37], the estimated exposure period for a single dispensed VKA prescription ranged between 99 and 104 days during our study period. These estimates closely align with the fixed exposure time of 100 days found as the best method in our study, and these similarities strengthen our conclusions.

Similar to previous studies, our findings demonstrate that rates of treatment discontinuation or non-persistence are affected by the method applied when constructing treatment episodes (i.e., shorter gap lengths will lead to higher rates of non-persistence or discontinuation and an increase in the number of treatment episodes) [1, 25]. We observed a large variability in the number of dispensing-based VKA treatment episodes during follow-up, with a median of 1 when applying exposure times of 180 days between subsequent dispensings and a median of 11 with exposure times of 60 days. Therefore, when studying drug persistence as an outcome, the method used to construct treatment episodes from dispensed prescriptions should be carefully considered and preferably standardized, especially when comparing multiple drug types or classes. This is particularly relevant for comparisons between VKAs and DOACs, since constructing treatment episodes for DOACs is generally easier due to their standard dosing schemes, especially when information on the prescribed dose and number of tablets dispensed is available. For VKAs, information on the dose regimen is often unavailable [38] or the days-supply data are unreliable due to dose adjustments over time [25]. Similarly, these considerations apply to studies investigating outcomes during drug-exposed vs. unexposed periods or studies in which survival analyses are performed [1, 27].

A previous study evaluating the impact of different gap periods between dispensed warfarin prescriptions on the misclassification of warfarin discontinuation also observed that shorter time periods allowed between subsequent warfarin prescriptions resulted in more misclassification (i.e., overestimation of the incidence of discontinuation) [25]. That study, which used warfarin pharmacy claims with information on days' supply linked to INR records from anticoagulation clinics, suggested the combined use of dispensing data and INR records for constructing treatment episodes. However, this approach is only feasible when both data on dispensed prescriptions with days' supply and INR records are available.

The strengths of our study include the combined use of two data sources on VKA exposure, making it possible to validate different methods for constructing dispensing-based VKA treatment episodes against reference exposure periods based on INR measurements. Dutch anticoagulation clinics provide high-quality and detailed data on VKA treatment, which made VKA exposure according to INR measurements suitable as a reference in this validation study. We studied large and unselected samples of VKA users, including both acenocoumarol and phenprocoumon users, and allowed for switching between VKA types during follow-up, increasing the generalizability of our results.

Despite these strengths, several limitations should be considered when interpreting our results. First, non-adherence of patients to both VKA use as well as INR monitoring could not be taken into account. Nevertheless, we could reasonably assume that patients were at least to a certain extent exposed to VKAs when the INR was monitored regularly. Moreover, the median (IQR) INR value of 2.6 (2.1–3.2) and a median of 14 days (7–22) between subsequent INR measurements during our study follow-up suggest a therapeutic anticoagulant effect in most patients. Second, we only had data on outpatient medication dispensings, potentially leading to misclassification of VKA exposure during hospitalizations. However, INR measurements during hospitalizations were also missing, so this may not have affected our comparisons on a relative scale, and hospital admissions are typically shorter than the studied exposure times. Third, when constructing INR-based VKA treatment episodes, the start and end dates of VKA treatment provided by anticoagulation clinics may contain some misclassification. We applied a gap of 8 weeks between subsequent INR measurements to define INR-based treatment episodes, in alignment with the guidelines used by Dutch anticoagulation clinics [28]. Moreover, reducing the allowable gap between INR measurements to 6 weeks did not affect our ranking results. Fourth, we used data from five anticoagulation clinics, which introduces a possibility for misclassification of INR-based treatment episodes if patients moved to an anticoagulation clinic not included in the study. This would result in missing INR

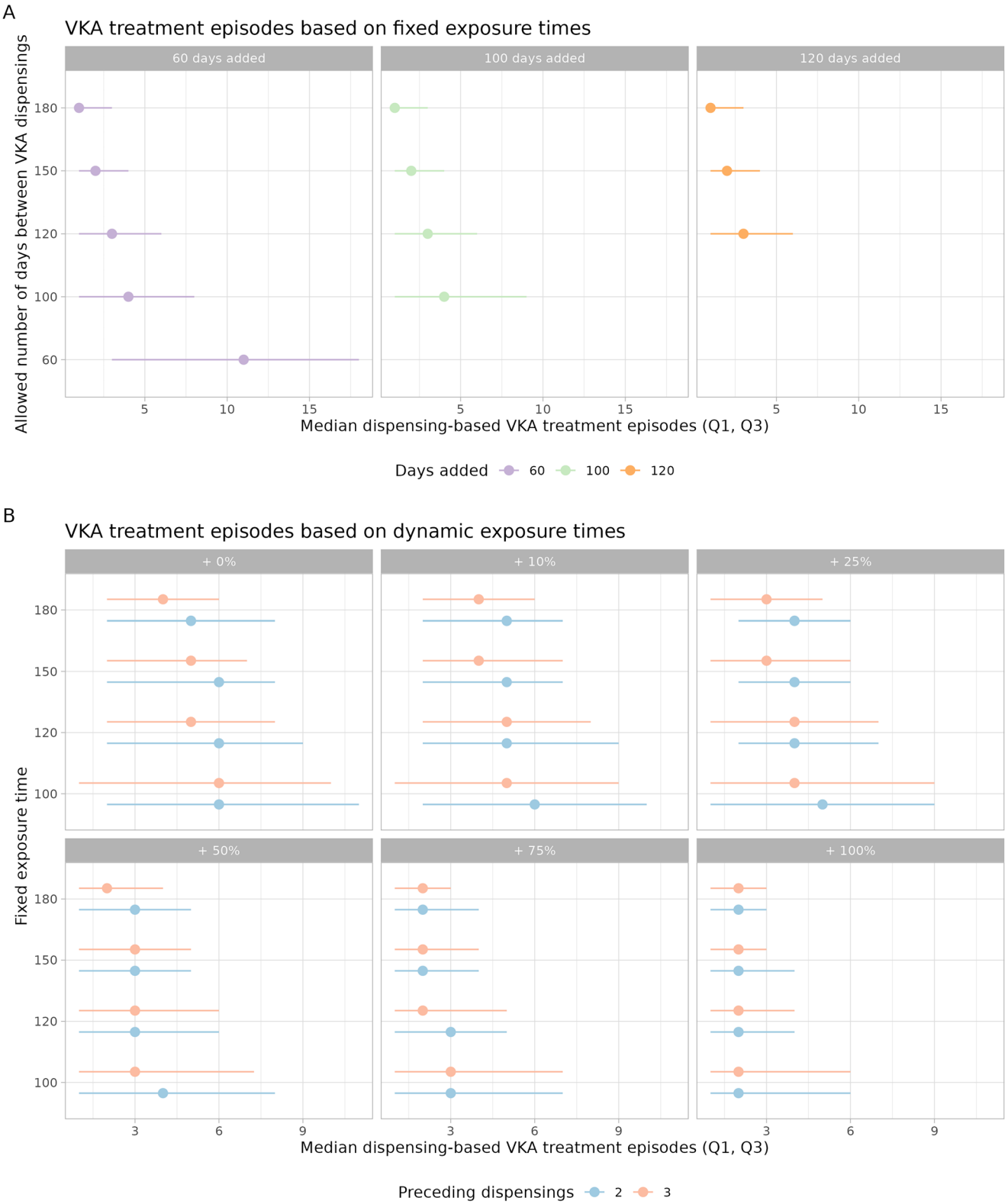

FIGURE 4 | Median number of dispensing-based VKA treatment episodes. Median number of dispensing-based VKA treatment episodes with first and third quartiles are displayed for both fixed (A) and dynamic (B) methods. (A) The *y*-axis displays the fixed exposure time, that is, the number of days allowed between subsequent dispensed VKA prescriptions within the same treatment episode. The different colors represent the number of days added to the date of last VKA dispensing within the treatment episode. (B) The two colors indicate whether the dynamic exposure time was calculated based on the preceding two or three dispensings. The *x*-axis displays the fixed exposure time that was applied for the first two or three dispensed prescriptions of the treatment episode. The upper panels display the percentage by which the dynamic exposure time was increased.

information and an overestimation of the VKA-exposed person-time ratio. Nevertheless, a switch to a different clinic primarily occurs when patients move to a different geographic area in the Netherlands, which would only concern a very small proportion of patients. Finally, our findings may not be directly generalizable to countries where warfarin is most commonly used, as only 0.1% of our study population used another VKA type other than acenocoumarol or phenprocoumon.

4.1 | Conclusion

In conclusion, our validation study demonstrated that fixed methods result in less misclassification of VKA exposure than dynamic methods. In our cohort, a fixed exposure time of 100 days between subsequent dispensed VKA prescriptions was associated with the least misclassification when compared with INR-based episodes. These findings can guide other researchers working with VKA dispensing data, especially when information on the number of dispensed tablets or the prescribed dose is unavailable. However, differences in characteristics and drug-taking behaviors between VKA types should be accounted for when constructing treatment episodes.

4.2 | Plain Language Summary

In many research settings, researchers rely on pharmacy records to determine whether a patient used medication during the study period. These records typically contain the date of medication dispensing and the type of drug dispensed. However, accurately determining how long a patient has used a drug can be challenging, especially for medications like VKAs, a commonly used group of blood thinners that require frequent dose adjustments and close monitoring. In the current study, we used two data sources: detailed information of VKAs from specialized clinics, considered the best available source, and pharmacy records of dispensed medicines. We compared different methods of estimating VKA use from the pharmacy records against the more detailed information from the specialized clinics. We found substantial differences between the methods and identified the best method for constructing periods of VKA use. Our findings can help other researchers who use pharmacy records to determine VKA exposure.

Author Contributions

E.K.K., C.V., J.G., and S.C.C. designed the study. E.K.K. and C.V. had full access to all data in the study and performed the analysis of the data. E.K.K. drafted the initial version of the manuscript. C.V., J.G., Q.C., M.S., A.G.O., C.D., D.A., S.J.A., K.J.L., J.E.A.P., M.C.N., A.B.D., S.J.C.M.L., F.A.K., E.C.T.G., M.J.H.A.K., and S.C.C. contributed to the interpretation of the data and critically revised the manuscript. All authors approved the final version of the manuscript.

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Ethics Statement

This study received approval from the Science Committee of the department of Clinical Epidemiology at Leiden University Medical Center with a waiver for participant consent due to the use of pre-existing, de-identified data (#A0178).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

This study used non-public microdata from Statistics Netherlands and the Federation of Dutch Anticoagulation Clinics. These data cannot be shared directly by the authors. Under certain conditions, these data are accessible for statistical and scientific research. For additional information: microdata@cbs.nl and fnt@fnt.nl.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.