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ORIGINAL ARTICLE

Effect of multidose drug dispensing on the time in therapeutic range in patients using vitamin-K antagonists: A randomized controlled trial

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Abstract

Background: A high number of vitamin K antagonist (VKA) users have a low proportion of time in therapeutic range (TTR) resulting in a high number of bleeding and thromboembolism events.

Objective: Can the quality of anticoagulation be improved by dispensing VKAs via multidose drug dispensing (MDD).

Method: A randomized controlled trial in the Netherlands. Patients who used VKAs, ≥65 years of age with a TTR <65% were eligible for inclusion. All oral drugs were dispensed via MDD. In MDD systems, all oral chronic medication intended for one dosing moment is packed in plastic disposable pouches. Controls received VKAs by manual dispensing. The difference in TTR between the 6 months after- and 6 months before the index date. A mixed-effects model with the intervention, TTR before the index date, MDD system at baseline as covariates, and pharmacy as random effect. A per-protocol analysis was performed with all patients who completed the study as intended.

Results: One hundred and seventy-nine patients were included. Mean age was 80.0 (SD 6.9) years. Mean TTR during the study was 79.2 ± 18.0% in the intervention group and 72.5 ± 20.1% in the control group. The intervention resulted in a 5.6% (95% CI: 0.1-11.1) increase in TTR compared to the control group. Per-protocol analysis resulted in an 8.3% (95% CI: 0.99-15.61) increase in TTR compared to the control group. No differences in reduction were observed between the intervention and control group.

Conclusion: The quality of anticoagulation can be improved with the use of MDD systems.

KEYWORDS
atrial fibrillation, community pharmacy, medication adherence, multidose drug dispensing, TTR

Trial registration: The trial is registered at the Dutch trial register (NTR5883). Registered 30 May 2016. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5883

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1 | INTRODUCTION

Despite the introduction of the non-vitamin K antagonist oral anticoagulants (NOACs), vitamin K antagonists (VKAs) are still used extensively.[1] VKAs are highly effective drugs to treat and prevent thromboembolism.[2,3] The management of VKA therapy differs between countries but always consists of assessment of the International Normalized Ratio (INR) followed by adjustment of dosing regimens. From consecutive INR values, the time in therapeutic range (TTR) can be calculated using the Rosendaal method.[4] The TTR is a measure for the quality of VKA therapy. A low TTR is correlated with an increased risk of bleeding and thromboembolism.[5-7] In the Netherlands, monitoring is performed by specialized anticoagulation clinics. Despite intensive support from these specialized anticoagulation clinics, around 20% of the patients have a TTR < 65%, which is considered inadequate.[5]

A low TTR can be caused by a variety of reasons that influence pharmacokinetics of VKAs like comorbidities, co-medication, alcohol, genetics, food, etc.[8,9] Another explanation is a reduced medication adherence to VKAs, possibly caused by the complexity of the VKA dosing regimens.[10] In particular, older persons frequently experience problems managing their medication. These problems can be due to a wide variety or combinations of reasons (eg, complex dosing regimens, polypharmacy, cognitive dysfunction, or impaired manual dexterity).[11-13]

Patients with a reduced medication management capacity may benefit from dosing aids.[14-16] In the Netherlands, the majority of patients in need of dosing aids receive their drugs via automated multidose drug dispensing (MDD).[15] In MDD systems all oral solid drugs are automatically robot-packed in disposable plastic sachets. These disposable sachets are labelled with patient data, content, date, and time of intake.[17] Not every drug is suitable to be dispensed via an MDD system due to practical packaging issues (eg, sachets, liquids, eye drops, suppositories) or fluctuating dosing regimens, like VKA. These drugs generally remain manually dispensed in their original packaging alongside the MDD system. It seems counterintuitive to dispense VKAs, which are one of the most complex drugs to manage, outside an MDD system. However, by dispensing the VKA via an MDD system, the medication adherence and consecutively the TTR might be improved.[18] For a number of patients, VKAs are already dispensed via an MDD system. However, it has never been shown that this method improves the TTR. Therefore, the aim of the study was to determine the effect of dispensing VKAs via an MDD system on the TTR.

Essentials

- Older patients frequently fail to adhere to the dosing regimens of Vitamin-K antagonists (VKAs)
- Dosing aids are an effective strategy to improve the quality of anticoagulation
- Collaboration between anticoagulation clinics and pharmacies is essential to dispense VKAs via dosing aids

2 | METHODS

2.1 | Design and setting

This was a randomized controlled trial with two study groups (allocation ratio 1:1) in 18 community pharmacies located in the catchment area of the Leiden Anticoagulation Clinic. The study was designed to conform to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement.[19]

2.2 | Intervention

Patients in the intervention group received all chronic solid oral drugs via an MDD system, including VKAs. Patients in the control group received VKAs via manual dispensing. Control patients were allowed to use an MDD system at baseline, but the VKA had to be dispensed manually. To enable community pharmacies to distribute VKAs via an MDD system, dosing schemes were sent both to the patient and the community pharmacy. If a patient receives the VKA via manual dispensing, the new VKA dosing scheme starts the day after the INR assessment. This short period of time hampers dispensing of VKAs via an MDD system because a pharmacist needs 3 days to order or produce the MDD system. Therefore, the shortest VKA dosing schemes for intervention patients were automatically extended by the Leiden Anticoagulation Clinic by 3 days (from 7 to 10 days). These three extra days enabled the community pharmacist to order or produce the MDD system, which included the VKA. If a dose adjustment of the VKA dosing regimen in intervention patients was needed, adjustment was deferred until the start of the new dosing scheme (4 days after the INR assessment). If a physician of the Leiden Anticoagulation Clinic considered deferred adjustment with 3 days inappropriate, the community pharmacy was informed by telephone and the MDD system was manually adjusted by the community pharmacy the same day.[20] If adjustment of the dosing regimen was necessary for patients in the control group, patients were directly contacted by telephone by the anticoagulation clinic the same day.

2.3 | Participants

Every 3 months the Leiden Anticoagulation Clinic selected patients ≥65 years of age with a chronic indication for VKAs and a low TTR (<65%) over the preceding 6 months.[7] Because of frequently fluctuating INR values during the first 3 months of VKA use, patients with VKA use of less than 9 months (3 + 6 months) were excluded. In addition, patients who performed INR measurements and dosing independently were excluded. Inclusion of a patient consisted of two steps: the first screening for eligibility was performed by the Leiden Anticoagulation Clinic. The list of potentially eligible

patients was then sent to the community pharmacy. The community pharmacy screened patients on additional inclusion and exclusion criteria and performed inclusion. Non-intentional non-adherent patients are willing to adhere to their medication regimen but fail (eg, because of cognitive problems, complex drug regimens, etc.). Dosing aids like an MDD system are more likely to affect non-intentional non-adherence. The chance of non-intentional non-adherence is larger when patients use more drugs as the medication regimens become more complex. Therefore, an inclusion criterion was the use of at least five chronic prescription drugs. Patients with home-care responsible for the administration of the patient's medication, or who already received their VKA via an MDD system or who received chemotherapy were excluded. As a consequence of the two steps, a lag time between the first screening and actual inclusion could be present. As a result, a patient's TTR could already be higher than 65% over the previous 6 months on the patient's index date.

2.4 | Patient inclusion

Eligible patients received an information letter by postal mail from the community pharmacist. Within 1 week after the information letter patients were invited by telephone to participate. If interested, patients were visited at home for written informed consent and study inclusion. At the start of the study, the patient's cognition and frailty were assessed with the Mini-Cog and the Groningen Frailty Indicator (GFI), respectively.[21,22]

2.5 | Randomization and blinding

Randomization (1:1) was stratified on MDD use at baseline, but the VKA had to be manually dispensed. Therefore, two randomization sequences containing 208 numbers, one for MDD use at baseline and one for manually dispensed drug use at baseline, were generated using SPSS (version 23.0, SPSS Inc.). After the community pharmacist obtained written informed consent, the principal investigator (BM) was contacted for group allocation. Group allocation was not blinded for patients, pharmacists, and investigators. Because the procedures of MDD patients differ from normal procedures, the physicians of the Leiden Anticoagulation Clinic were aware that a patient received the VKA via an MDD system but unaware of the patient's study participation. Study outcomes were analyzed by an independent statistician (SVB) who was blinded for group allocation.

2.6 | Sample size calculation

To demonstrate an absolute difference in TTR of 10% for the primary outcome with an alpha of 0.05, a standard deviation of 23 and a power of 80%, a total number of 83 patients in both the intervention and the control group were needed. To compensate for loss to follow-up we aimed at an additional 25% extra patients in both study groups, which resulted in a total aim of 208 patients.

2.7 | Primary outcomes

The primary outcome was the difference in TTR improvement between the intervention and control group. TTR was calculated over a period of 6 months, both before the index date and after the index date. The index date for the intervention was the first day a VKA was dispensed via an MDD system. The index date for control patients was the date that the patient signed informed consent.

2.8 | Secondary outcomes

A secondary outcome was the number of patients with an adequate quality of anticoagulation (TTR ≥ 65%) over the 6 months after the index date. Patients with an inadequate TTR can be under- or overanticoagulated. Therefore, both the time under (TuTR) and time above the therapeutic range (TaTR) were calculated. Other secondary outcomes were the number of high INR assessments (>4.0), the number of vitamin K doses for an uncontrolled INR, and the mean number of INR control visits.

2.9 | Safety monitoring

For safety reasons, thromboembolic events, all bleedings (minor and major), and hospital admissions were recorded. Recording was performed by staff of the anticoagulation clinic and occurred according to the guidelines of the Federation of Dutch Anticoagulation clinics.[23]

2.10 | Statistical analyses

Data were analyzed using statistical software packages SPSS (version 23.0, SPSS Inc.) and R (version 3.4.4). Based on the data reported by the statistician, the investigators wrote the final report. Information on treatment indications, target INR ranges, INR measurements, bleeding, thrombosis, and hospital admissions were obtained from the Leiden Anticoagulation Clinic. TTR calculation was performed conforming to the linear method described by Rosendaal et al.[4] The time during hospitalization, including the first 2 weeks after discharge, were excluded from the analyses. A two-sided *P*-value <.05 was considered statistically significant. Mean values are presented with standard deviations (SD) or 95%-confidence intervals (95% CI).

Primary outcomes were analyzed using a linear mixed-effects model (intervention, MDD use at baseline, the TTR before the index date as covariates, and the participating pharmacies as random effect). MDD use at baseline was included in the model as randomization was stratified on MDD use. TTR before the index date was included in the model to compensate for any baseline differences. A TTR cannot be higher than 100%; thereby, the higher a patient's TTR is at baseline, the less likely an improvement becomes. Last, community pharmacies were included as random effects to compensate for potential differences in procedures between the community pharmacies. Intention-to-treat analyses were performed with all patients who had at least two INR assessments after the index date. A per-protocol analysis was

performed with patients with a TTR < 65% in the 6 months before the index date and who completed the study period as intended.

Categorical values were calculated using a mixed-effects logistic regression model (intervention, MDD use at baseline, the TTR before the index date as covariate, and the participating pharmacies as random effect). Non-normally distributed secondary continuous outcomes were analyzed with a linear quantile mixed-effects model (intervention, MDD use at baseline, TaTR or TuTR before index date as covariates, and participating pharmacies as random effect). Countable secondary outcomes were analyzed using mixed-effects Poisson regression model (intervention, MDD use at baseline as covariate, participating pharmacies and study number as random effect, and number of control visits as off-set parameter). Safety outcomes were analyzed using a quasi-Poisson regression model (intervention and MDD use at baseline as covariates).

2.11 | Predefined subgroup analyses

Subgroup analyses were performed for patients using an MDD system or manually dispensed medication at baseline.

2.12 | Ethics approval

The Medical Ethics Review Committee (METC) of the Leiden University Medical Centre (LUMC) concluded the Dutch Medical Research Involving Human Subjects Act (WMO) wasnot applicable. The trial is registered at the Dutch National Trial Register (www.trialregister.nl) under the identifier NTR 5883. In addition, the study protocol was approved by the institutional review board of UPPER, division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University. To protect patients' privacy, only age, gender, and study number were documented.

3 | RESULTS

Of 528 invited patients, 179 (34%) gave informed consent (Figure 1). Forty-eight percent were female and mean age was 80.0 years (SD = 5.9). Study enrolment lasted from June 2016 to September 2017. The last patient completed the study in January 2018. The number of included patients per pharmacy ranged from 1 to 28 (mean 9, SD = 5). The mean number of days between the selection by the anticoagulation clinic and the start of the intervention was 67 days for the intervention group and 57 days for the control group ($P = .054$). As a consequence of this delay, 57 (32%) patients had a TTR in the 6 months before the index date, which was higher than the predefined 65%. The study groups were similar at baseline with the exception of the target INR range (Table 1). As all patients had at least two INR assessments after the index date, all patients were included in the intention-to-treat analysis. Fourteen patients (7.8%) did not complete the 6-month study period as intended (five patients died, five patients switched to an NOAC, and four patients returned to manual dispensing). No dropout differences were observed ($P = .53$). The study flow is depicted in Figure 1.

3.1 | Primary outcomes

The TTR improved for both the intervention and the control group during the 6-month study period (Table 2). In the intervention group

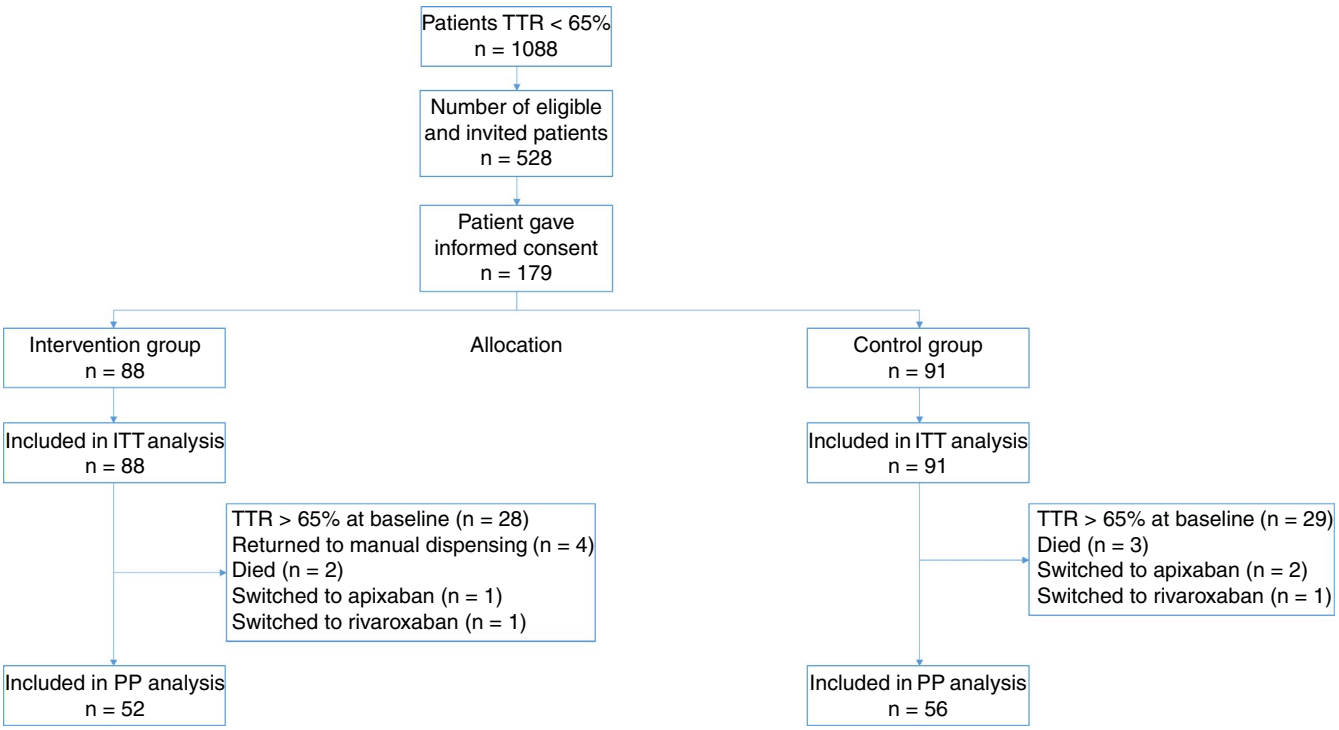

FIGURE 1 Study flow. ITT, intention to treat; n, number; PP, per protocol; TTR, time in therapeutic range

TABLE 1 Baseline characteristics over the 6 months before the index date

	Intervention (n = 88)	Control (n = 91)
Age mean (±SD)	79.8 (7.1)	80.2 (6.7)
Female n (%)	42 (48)	43 (47)
MDD system in use n (%)	35 (40)	32 (35)
Frail n (%)	46 (54)	43 (53)
Cognition impaired n (%)	29 (34)	22 (25)
Treatment indication atrial fibrillation n (%)	80 (91)	75 (82)
INR target range 2.0-3.0, n (%)	85 (97)	78 (86)
INR target range 2.5-3.5, n (%)	3 (3)	13 (14)
TTR mean (±SD)	60.8 (16.4)	55.9 (18.0)
TuTR median (IQR)	13.8 (0; 29.8)	11.6 (0; 30.9)
TaTR median (IQR)	21.0 (4.1; 30.4)	22.7 (11.1; 38.1)
Number of INR control visits mean (±SD)	9.42 (3.7)	10.0 (4.0)
Number of INR assessments >4.0 (n)	40	63
Number of bleedings (n)	26	14
Number of thromboembolic events (n)	2	2
Number of hospital admissions (n)	11	15
	(n = 83)	**(n = 83)**
Number of drugs mean (±SD)	10.4 (4.1)	10.6 (4.2)
Number of vitamin K doses (n)	8	10
Most-used drugs		
Beta blocking agents n (%)	63 (76)	69 (83)
Proton pump inhibitor n (%)	55 (66)	56 (67)
HMG CoA reductase inhibitors n (%)	59 (71)	52 (63)
High-ceiling diuretics n (%)	33 (40)	35 (42)
ACE inhibitors n (%)	25 (30)	30 (36)
Drugs for constipation n (%)	25 (30)	29 (35)
Vitamin D n (%)	23 (28)	29 (35)
Dihydropyridine calcium channel blockers n (%)	24 (29)	22 (27)
Angiotensin II antagonists n (%)	17 (20)	27 (33)
Oral blood glucose lowering drugs n (%)	24 (29)	18 (22)

Abbreviations: ATC, anatomical therapeutic chemical; INR, international normalized ratio; IQR, interquartile range; MDD, multidose drug dispensing; SD, standard deviation; TaTR, time above therapeutic range; TTR, time in therapeutic range; TuTR, time under therapeutic range.

an additional increase in TTR of 5.6% (95% CI: 0.1; 11.1) was observed compared with the control group. For the per-protocol analysis, 71 patients were excluded (see Figure 1). The mean TTR at baseline in the intervention group (n = 52) was 50.7% (SD ± 10.6%) and the mean TTR in the control group (n = 56) was 47.6% (SD ± 12.4%; P = .16). In the per-protocol analysis, an additional increase in TTR of 8.3% (95% CI: 1.0; 15.6) was observed.

3.2 | Secondary and safety outcomes

Eighty-one percent (n = 71) of the patients in the intervention group had a TTR > 65% during the study period compared with 65% (n = 59) of the patients in the control group (relative risk [RR] = 1.44; 95% CI: 1.09-1.90). The distribution of patients per 10%-TTR range is graphically presented in Figure 2. The largest increase in number of patients was observed in the group of patients with a TTR between 90% and 100% during the 6-month study period (RR = 1.48; 95% CI: 1.02-2.14). Individual TTR values are shown in Appendix S1 in supporting information. An overview of the other secondary and safety outcomes is given in Table 3. No difference was seen in the average dose of VKA between the intervention and control group (P = .13). The intervention resulted in a lower median TuTR in the intervention group compared with the control group.

A subgroup analysis in patients with an MDD system at baseline resulted in an additional increase in TTR of 6.2% (95% CI: −3.13 to 15.48). Among patients who used manually dispensed drugs at

TABLE 2 Main outcomes for intervention and control patients in TTR during the 6 months after the index date

Analysis		Intervention	Control	Effect of intervention mean (95% CI)	*P*-value
Intention to treat: Intervention (n = 88); Control (n = 91)	TTR after index date mean (±SD)	79.2 (±18.0)	72.5 (±20.1)	+ 5.6% (0.1; 11.1)	.048
	Estimated TTR after index date mean (95% CI)	78.0 (73.9; 82.0)	71.4 (67.3; 75.5)		
Per protocol: Intervention (n = 52); Control (n = 56)	TTR after index date mean (±SD)	79.4 (±18.6)	69.9 (±20.3)	+ 8.3% (1.0; 15.6)	.026
	Estimated TTR after index date mean (95% CI)	81.4 (75.8; 86.9)	73.1 (66.7; 79.6)		

Note: Effect of intervention with 95% CI (adjusted for TTR before index date, MDD at inclusion and pharmacy).
Abbreviations: CI, confidence interval; n, number; SD, standard deviation; TTR, time in therapeutic range.

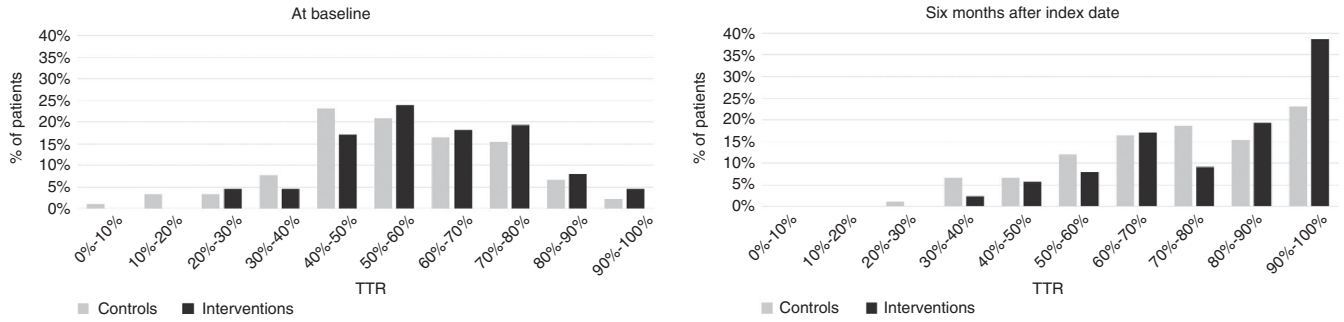

FIGURE 2 **Distribution of intervention and control patients in the 6 months before the index date and the 6 months after the index date**

baseline, an additional increase in TTR of 5.1% (−2.01 to 12.24) was observed (*P*-value for interaction = .86).

4 | DISCUSSION

This study shows that dispensing VKAs via an MDD system can improve the patient's quality of anticoagulation compared to manual dispensing of VKAs. The intervention resulted not only in an increase in TTR but also in a higher number of patients with a TTR between 90% and 100%. The higher TTR was reflected by a lower time under the therapeutic range in the intervention group compared to the control group, which may result in a lower number of thromboembolic events. This was not observed on the safety outcomes as the study was not powered on safety outcomes. The intervention was well accepted as only four patients (5%) returned to manual dispensing of the VKA.

The intervention resulted in a TTR increase of 5.6%. Among patients who still fulfilled the inclusion criterion of a TTR < 65% at index date, the increase was even higher. As dispensing VKAs via an MDD system is costly and time consuming, it should only be applied when a clinically relevant effect can be expected (eg, low TTR). The correlation between the TTR and clinical outcomes like bleeding and thromboses is strong. Also in our study, a reduction in the number of bleedings was observed, both in the intervention and control group. However, the difference was not statistically different between intervention and control group. The interpretation of the magnitude of TTR increase can be debated as no minimal clinical effect on TTR is defined. The effect of the TTR on the number of bleedings has been shown to be linear; the higher the TTR, the lower the number of complications.[7,24] The TTR is a surrogate endpoint; however, an increase in TTR of 5% will reduce the number of thromboembolic events, major bleeding events, and deaths in a large population.[24,25] Ideally, a cost-effectiveness analysis would be performed including the additional costs of the MDD systems and potential health savings. The start of an MDD system seems especially interesting for patients with a low TTR not provoked by an explanatory cause (eg, long-lasting flu, hospital admission for surgery). In addition, unintentional non-adherence must be suspected as MDD systems are unlikely to improve intentional non-adherence.[15,17,26]

A previous retrospective database study by Van Rein et al[18] reported that dispensing VKAs via an MDD system could temporarily improve the patient's TTR compared to users of manually dispensed VKAs. The effect in this retrospective study was present after 1 month but not after 4 or 6 months. The effect of an MDD system on the patient's TTR was lower in the study by Van Rein et al compared to our study. A major limitation in the study by Van Rein et al was that MDD systems were not specifically initiated to improve the TTR. Finding identical control patients is almost impossible as MDD systems are initiated for patients with a reduced medication management capacity.[14] For example, if patients receive home care who are responsible for the medication administration, legislation obligates that the patient's medication is dispensed via an MDD system to reduce dispensing errors. To eliminate potential confounders,

TABLE 3 Secondary and safety outcomes for intervention and control patients in the 6 months before the study period and during the 6-month study period. Before and after the index date comparisons within the study group and between group comparisons

	Intervention (n = 88)	Control (n = 91)	Effect of intervention (95% CI)	*P*-value
TuTR median (IQR)				
Value	0.6 (0; 13.3)	7.2 (0; 23.9)	−5.9 (−11.0; −0.86)	.02[a]
Estimated value (95% CI)	7.2 (3.2; 11.1)	13.5 (8.7; 18.3)		
TaTR median (IQR)				
Value	5.3 (0; 17.8)	6.7 (0; 21.4)	−0.8 (−4.2; 2.6)	.65[a]
Estimated value (95% CI)	10.0 (6.3; 13.7)	11.4 (6.9; 15.9)		
Number of control visits mean (±SD)				
Value	7.8 (3.3)	8.3 (3.7)	−0.3 (−1.3; 0.6)	.50[b]
Estimated value (95% CI)	8.1 (7.4; 8.5)	8.3 (7.6; 9.1)		
INR assessments >4% (n/total INR assessments)				
Value	2.2 (15/685)	4.4 (33/756)	0.7 (0.3; 1.34)	.29[c]
Estimated value (95% CI)	1.3 (0.6; 2.4)	3.2 (2.0; 4.9)		
Vitamin K doses[e]% (n/total INR assessments)				
Value	1.7 (11/651)	1.4 (10/708)	1.4 (0.4; 5.2)	.61[c]
Estimated value (95% CI)	0.77 (0.18; 2.14)	0.38 (0.01; 1.45)		
Bleedings (n)				
Value	17	10	1.7 (0.6; 5.6)	.33[d]
Estimated value (95% CI)	16.6 (7.8; 30.0)	9.6 (2.4; 23.6)		
Thromboembolic events (n)				
Value	1	0	n.a.	n.a.
Estimated value (95% CI)	n.a.	n.a.		
Hospital admissions (n)				
Value	14	12	1.2 (0.5; 3.0)	.67[d]
Estimated value (95% CI)	13.7 (5.8; 26.3)	11.8 (6.1; 19.8)		

Note: n.a. due to small number of observations.

Abbreviations: CI, confidence interval; INR, international normalized ratio; n, number; n.a., not applicable; SD, standard deviation; TaTR, time above therapeutic range; TuTR, time under therapeutic range.

[a]Linear quantile mixed-effects model.

[b]Linear mixed-effects model.

[c]Mixed-effects Poisson regression model. Number of control visits in 6 months before index date as off-set parameter.

[d]Quasi-Poisson regression model.

[e]Data available for 83 intervention and 83 control patients.

a randomized control trial is more appropriate. A second study by Dumas et al[27] evaluated the effect of a different dosing aid, a pill-box, on the quality of anticoagulation in naïve VKA users. No differences were seen between the three study arms in this prospective observational cohort study. The study differed on some important aspects from our study. First, our study focused on patients with a low quality of anticoagulation despite long-term use of VKAs and not on naïve VKA users. Second, as a result of the non-randomized study design of Dumas et al, large differences in age, gender, and education were observed between the study groups, which hampers conclusions.

An improvement of the TTR was observed not only in the intervention group, but also in the control group. This might be explained by two known phenomena. First, all patients received written information about their low quality of anticoagulation and were visited at home for written informed consent and inclusion. Thus, awareness on the importance of therapy adherence may also have risen in the control group. Second, regression to the mean may have been stronger in the control group as the mean TTR before the index date was lower compared to the intervention group. Ideally, a third group who did not receive any information about the study or their low quality of anticoagulation would incorporated in the study. However, without informed consent, no patient data can be used under the Dutch Medical Research Involving Human Subjects Act.

Our study had some particular strengths. First, the only introduced difference between the intervention and control group was the dispensing of the VKA via an MDD system. By using an existing

network of care with regular patient follow-up, the effect of dispensing VKAs via an MDD system was specifically determined. All patients continued to receive standard care from the anticoagulation clinic. Second, the TTR is an objective outcome measure strongly correlated with clinical outcomes.[7,24,25] Last, included patients were representative for the type of patients that are eligible for MDD as comparable patient characteristics were found in an observational study among new MDD users.[14]

Besides the strengths, our study has some potential limitations. First, the protocols used to adjust VKA regimens during the study differed between users of MDD systems and manually dispensed medication. VKA dose regimens were automatically prolonged 3 days for patients allocated to the intervention. Theoretically, this can lead to a slightly lower TTR for MDD patients, which could have reduced the positive effect of the intervention. Second, we did not include the intended number of patients. During the trial, lower loss to follow-up percentages were observed than anticipated. Therefore, inclusion was ceased at the moment that the required number of patients with sufficient follow-up were included. Last, despite randomization, more patients in the control group had a target INR range of 2.5-3.5. A higher target INR range is associated with a lower TTR, which might explain the lower TTR preceding the index date in the control group. As mentioned before, this may also imply that control patients were more likely to regress to the mean.

5 | CONCLUSION

The quality of anticoagulation can be improved by dispensing VKAs via an MDD system, especially in patients with a TTR < 65%. The improved quality of anticoagulation was reflected by an improved TTR and a lower TuTR. No differences in reduction of number of bleedings or thromboembolic events between the intervention and control were found.

CONFLICT OF INTEREST

B. Mertens received an unconditional grant for the PhD project about MDD to conduct this research. The other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

BJ Mertens had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. BJ Mertens, H-F Kwint, FJM van der Meer, RJ van Marum, and ML Bouvy were responsible for the concept and design of the study. The statistical analysis was performed by SV Belitser. BJ Mertens, H-F Kwint, FJM van der Meer, RJ van Marum, and ML Bouvy interpreted study results. BJ Mertens drafted the first version of the manuscript and all authors contributed to the revision of the manuscript. All authors approve the final version of the manuscript. We thank research assistants F Boutkourt and MC Baltus for their help during the study.

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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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