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RESEARCH ARTICLE

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Warfarin monitoring in nursing homes assessed by case histories. Do recommendations and electronic alerts affect judgements?

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ABSTRACT

Purpose: Older adults treated with warfarin are prone to complications, and high-quality monitoring is essential. The aim of this case history based study was to assess the quality of warfarin monitoring in a routine situation, and in a situation with an antibiotic–warfarin interaction, before and after receiving an electronic alert.

Materials and methods: In April 2014, a national web-based survey with two case histories was distributed among Norwegian nursing home physicians and general practitioners working part-time in nursing homes. Case A represented a patient on stable warfarin treatment, but with a substantial INR increase within the therapeutic interval. Case B represented a more challenging patient with trimethoprim sulfamethoxazole (TMS) treatment due to pyelonephritis. In both cases, the physicians were asked to state the next warfarin dose and the INR recall interval. In case B, the physicians could change their suggestions after receiving an electronic alert on the TMS-warfarin interaction.

Results: Three hundred and ninety eight physicians in 292 nursing homes responded. Suggested INR recall intervals and warfarin doses varied substantially in both cases. In case A, 61% gave acceptable answers according to published recommendations, while only 9% did so for case B. Regarding the TMS-warfarin interaction in case history B, the electronic alert increased the percentage of respondents correctly suggesting a dose reduction from 29% to 53%. Having an INR instrument in the nursing home was associated with shortened INR recall times.

Conclusions: Practical advice on handling of warfarin treatment and drug interactions is needed. Electronic alerts as presented in electronic medical records seem insufficient to change practice. Availability of INR instruments may be important regarding recall time.

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Introduction

Strict warfarin monitoring with regular INR measurements is necessary to avoid suboptimal anticoagulation [1], but studies have demonstrated large performance variations regarding warfarin monitoring in several countries irrespective of the level of care and type of health professionals involved [2–7]. In Norway, mainly general practitioners (GPs), and nursing home physicians, many of whom are GPs, monitor warfarin treatment based on clinical experience and without the support of computer software [2]. However, studies on the quality of warfarin monitoring in a nursing home population are scarce. Both thromboembolic and bleeding risks increase with age [8], and the number of older adults treated with anticoagulants is increasing [9–11]. High quality warfarin monitoring is essential for effective and safe treatment [4,7,12]. Although direct oral anticoagulants (DOACs) are increasingly used, warfarin will still be the anticoagulant of choice in many older adults, due to comorbidity and lack of studies on DOACs among these patients [13,14]. The aims of this case history based study were to assess the quality of warfarin monitoring by nursing home physicians in both a routine and a more challenging clinical situation, involving handling of an important drug interaction with possible patient safety consequences.

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Case A: A 86-year-old woman, on life-long treatment with warfarin due to recurrent deep venous thrombosis. Her therapeutic interval is INR 2.0-3.0 (target INR 2.5). She has dementia and osteoporosis, and has had a hip fracture. Her INR results have been stable for the last four months with a total weekly warfarin dose of 20 tablets (50 mg): 4 months ago: INR 2.3; 3 months ago: INR 2.0; 2 months ago: INR 2.2; and 1 month ago: INR 2.1. Her medical condition and treatment have remained unchanged during this period. Today her INR is 2.9.

A1. Would you adjust her total weekly warfarin dose?
❑ I would continue with the same dose? ❑ I would change the dosage
A2. If you have chosen to change the dose, please estimate the new total weekly warfarin dose
_____mg weekly (tick-off alternatives from 37.5 to 62.5 mg) or other dose: _____mg weekly
A3. When would you order the next INR measurement?
In _____days (alternatives from 1 to 13) In _____weeks (alternatives from 2 to 8) ❑ I do not know

Case B: A 81-year-old man with atrial fibrillation, prior stroke, benign prostatic hyperplasia and hypertension, who is treated with warfarin and antihypertensive drugs. His therapeutic interval is INR 2.0-3.0 (target INR 2.5). His weekly warfarin dose is 10 tablets (25 mg). Today a routine INR measurement is 2.7. He has not taken his daily dose of warfarin yet. However, he has had symptoms of urinary tract infection and fever (consistent with pyelonephritis), for 5 days. Since he is allergic to penicillin, you decide to treat him with trimethoprim-sulfamethoxazole (TMS) (80/400 mg): two tablets twice a day for one week.

B1: Would you adjust his total weekly warfarin dose?
❑ No, I would continue with the same dosage ❑ Yes, I would change the dosage
B2. If you have chosen to adjust the dosage, please estimate the new total weekly dosage
_____ mg weekly (alternatives from 0 to 50 mg) or other dose: _____mg weekly
B3. When would you order the next INR measurement?
In _____days (alternatives from 1 to 13) In _____weeks (alternatives from 2 to 8) ❑ I do not know
B4. Would you have read some sources of information, such as guidelines or internet based information before you had decided on the new total weekly dose?
❑ Yes ❑ No ❑ I do not know
All the physicians then received (in the next window) this information from the Norwegian Medicines Agency:

Clinical consequences of TMS-warfarin interaction: increased concentration of warfarin (average 1.2 times in interaction study), increased risk for side effects (bleeding). **Interaction mechanism**: TMS inhibits warfarin metabolism, primarily through cytochrome P2C9. **Adjustment of dose**: about 20-40 % reduction of warfarin while on treatment with TMS. The degree of interaction varies widely, and it would be appropriate to consider other alternative antibiotics. INR should be monitored.

B5. Now that you have read the information from the Agency, would you like to reconsider your answer(s) regarding warfarin dosage and/or time until the next INR measurement?
❑ I will reconsider both ❑ I will only reconsider the warfarin dosage ❑ I will only reconsider the time until the next INR measurement ❑ I will not reconsider
Option only for those who would like to reconsider their answer:
B6. If you have chosen to change the dosage, please state the new total weekly dosage here:
_____ mg weekly (tick off alternatives from 0 to 50 mg) or other dose: _____mg weekly
B7. If you have chosen to change the time until a next INR measurement, please state the new answer here:
In _____days (alternatives from 1 to 13) In _____weeks (alternatives from 2 to 8) ❑ I do not know

Figure 1. Case histories and questionnaire.

Materials and methods

Two case histories cum questionnaire (Figure 1) were designed based on field experience, and pilot tested in a group of 19 nursing home physicians and GPs. Some minor changes were made, and in April 2014 an email with a link to an electronic survey (using Survey Monkey software) containing the case histories and questionnaire was sent to all nursing homes in Norway ($n = 950$), to be forwarded to affiliated physicians since personal email addresses were unavailable. The responding physicians were asked to provide background information especially with regard to clinical experience, i.e. using age, years as a nursing home physician and speciality as proxy. Further, respondents were offered a feedback report, and were informed that anonymous and aggregated data from the survey might be published. Approval by the Regional Ethical Committee is not necessary for this kind of research according to current Norwegian regulations.

Case history A described an 86-year-old female nursing home resident, who received warfarin due to a second episode of deep vein thrombosis. Her warfarin dosage had been stable in the last months, with INR values between 2.0 and 2.3. The INR result was

Table 1. Definition and number (%) of acceptable and unacceptable answers in case history A and B.

	n	%	*n*	%
Case history A				
Answered all questions in case A	378	100		
Acceptable answers				
Unchanged dose (50 mg) and INR within 3 weeks	231	61		
Unacceptable answers	147	39	147	100
Changed dose and/or inadequate INR recall interval				
Changed dose			55	37
Unchanged dose, but inadequate INR recall interval			92	63
Total	378	100	147	100
Case history B				
Answered all questions in case B	365	100		
Acceptable answers				
Dose reduction from 25 mg to 15–20 mg and INR in 2–4 days	33	9		
Unacceptable answers	332	91	332	100
Unacceptable dose and/or inadequate INR recall interval				
Dose of warfarin not in the 15–20 mg range			258	78
15–20 mg warfarin, but inadequate INR recall interval			74	22
Total	365	100	332	100

INR: Prothrombin Time International Normalized Ratio.

now increased, but was still within the therapeutic interval (INR 2.9), thus representing a routine clinical situation. The physicians were asked to state the further warfarin dosage and the number of days until they would measure a new INR.

Case history B was more challenging, dealing with drug interactions with warfarin. The 81-year-old male nursing home resident depicted was on warfarin due to atrial fibrillation. Antibiotic treatment (trimethoprim-sulfamethoxazole (TMS)) was started because of suspected acute pyelonephritis (Figure 1). First, questions on warfarin dosage and days until the next INR measurement were posed. Then, the physicians were asked whether they would have sought information on drug interactions before deciding upon dosage and INR recall intervals. Irrespective of their answers, all participants received pertinent information from the Norwegian Medicines Agency medicine database in the next window ('pop-up window' information) in SurveyMonkey, i.e. the advice actually presented automatically when using electronic journal systems (electronic alerts). Information in the electronic alert recommended to reduce the warfarin dose by 20–40%, and to monitor INR during TMS treatment [15]. After receiving the information, physicians were given the opportunity to reconsider the dose and number of days until measuring the next INR, and to state new answers if they had changed their mind. Physicians' perceived need for information, as well as the effect of short, pertinent electronic alerts could thus be explored.

The answers given by the physicians were categorized into clinically acceptable and unacceptable answers (Table 1), using information from published studies and recommendations as well as clinical experience [1,12,15–24]. In case history B, handling of the interaction was based on commonly used Norwegian drug databases; www.legemiddelsok.no/sider/Interaksjoner.aspx (The Norwegian Medicines Agency) [15], www.interaksjoner.no [17] and www.felleskatalogen.no [18].

Statistics

The Mann–Whitney *U* test was used to evaluate differences in INR recall intervals and in warfarin doses. Logistic regression was used to evaluate associations between answer categories (acceptable, unacceptable) and characteristics of the participants (gender, age, number of years working in nursing homes, whether part time or fully employees, main occupation, medical speciality, and availability of INR instrument in the nursing home). Likewise, in case B, associations between the need for information, the effect of information on drug interactions and participant characteristics were explored by logistic regression or Pearson Chi-square test. SPSS version 22.0 (SPSS Inc., Chicago, IL) was used, and statistical significance was set at $p < .05$.

Results

Altogether, 398 physicians working in 292 nursing homes responded. Physicians with incomplete answers for one or both case histories were excluded, leaving results from 378 physicians for case A and 365 for case B (Table 1). Fifty four percent had their main occupancy as GPs whereas 37% worked mostly in nursing homes. POCT for INR was available in 45% of the nursing homes (Table 2).

Management of a patient on stable anticoagulation (case history A)

Keeping the warfarin dose unchanged and measuring INR within 3 weeks (shortened interval) because of the

rather large INR increase, after months of very stable INR-values, were considered acceptable [1,12,16,24] and was stated by 61% of physicians. Among those with an *unacceptable* answer, 37% changed the warfarin dose, while 63% maintained the dose, but stated a too long INR recall interval (median 28 days vs. 14 days in the acceptable group, $p < .05$) (Tables 1 and 3).

Table 2. Characteristics of the responding physicians and nursing home settings.

Characteristics	Results	
Total number of physicians, *n*	378[a]	
	n	%
Gender		
Female	148	44
Male	185	56
Age		
25–35 years	103	31
36–50 years	113	34
>50 years	114	35
Main employment		
Nursing home physician	122	37
General practitioner	178	54
Other	28	9
Time employed as a nursing home physician		
≤3 years	152	46
>3 years	177	54
Type of employment in the nursing home		
Part-time (<20%)	63	19
Part-time (20–49%)	143	44
Part-time (≥50%) or full-time	119	37
INR instrument available in the nursing home		
No	184	55
Yes	153	45
Specialist status		
Specialist	161	51
Non-specialist	158	49

INR: Prothrombin Time International Normalized Ratio.
[a]42 (11%)–60 (16%) of the responders did not answer one or more questions about person and practice particulars.

Logistic regression did not reveal associations between answering acceptable and participant characteristics.

Management of a drug interaction with warfarin (case history B)

Reducing the warfarin dose by 20–40% (from 25 mg to 15–20 mg) when initiating TMS treatment, and monitoring INR within 2–4 days (treatment period seven days), were considered an acceptable action [15,17–23]. This management was suggested by only 9% of the physicians. Among the other physicians giving an unacceptable response, 78% did not reduce the warfarin dose, while 22% stated a too long INR recall interval, but reduced the dose adequately (Table 1). The recall interval was significantly longer (median 7 vs. 3 days) and the dose higher (median 25 vs. 17.5 mg) when comparing unacceptable and acceptable answers (Table 3). In the 'unacceptable' group, 49% stated that they would have sought information by themselves before adjusting the dose, compared to 67% in the 'acceptable' group ($p = .054$). No characteristics of the physicians were associated with seeking information or with providing acceptable answers.

Impact of receiving information from a drug interaction database (case history B)

After presenting the electronic alert (Figure 1) on management of the TMS-warfarin interaction, 162 out of 332 physicians with unacceptable answers (49%),

Table 3. Warfarin doses and INR recall intervals given by the physicians in case history A and B.

	Warfarin dose (mg) Median (10–90 percentile)	Recall interval (days) Median (10–90 percentile)
Case history A ($n = 378$)		
Acceptable answers; $n = 231$ (61%)	50 (50–50)	14 (7–21)
Unacceptable answers; $n = 147$ (39%)	50 (46.7–50)[a]	28 (7–28)[a]
Case history B ($n = 365$)		
Before reading the electronic alert ($n = 365$)		
Acceptable answers; $n = 33$ (9%)	17.5 (17.5–20)	3 (2–4)
Unacceptable answers; $n = 332$ (91%; 74 respondents with correct dose reduction only, of whom 58 chose not to change their answers after the alert)	25 (17.5–25)[a]	7 (3–14)[a]
Changes in the unacceptable answers in response to the electronic alert ($n = 162$)		
Now acceptable; $n = 47$ (29%; all with correct dose reduction)		
Answer *before* the alert	25 (17.5–25)	4 (2–7)
Answer *after* the alert	17.5 (17.5–20)	3 (3–4)
Still unacceptable; $n = 115$ (71%; 54 with correct dose reduction)[b]		
Answer *before* the alert	25 (22.5–25)	7 (3–21)
Answer *after* the alert	20 (15–25)	7 (3–8)

INR: Prothrombin Time International Normalized Ratio.
[a]Statistical significant difference ($p < .05$).
[b]Overall, the number of respondents with correct dose reduction in case B increased from $33 + 74 = 107$ (29%) before the alert to $33 + 58 + 47 + 54 = 192$ (53%) after reading the alert.

compared to three (9%) with acceptable answers changed their response ($p < .05$). However, only 47 of these 162 participants (29%) changed into acceptable answers (Table 3), 36 of them by reducing the warfarin dose adequately. The few changes in the 'acceptable group' were still acceptable. Among the 115 participants whose answers were still unacceptable, 80 (70%) reduced the dose, but only 54 as recommended. The electronic alert thus increased the percentage of acceptable dose reduction from 29% to 53% overall (Table 3).

Choosing to make a change was associated with having an INR instrument in the nursing home laboratory, but not with other participant characteristics. Those with an INR instrument in the nursing home reduced the time until the next INR measurement significantly more than those with no instrument (median from 7 to 4 days), whereas dose reductions were similar in the group with and without INR instrument (data not shown).

Discussion

Statement of principal findings

Three main findings of this study should be emphasized: 39% of the physicians did not consider a large INR deviation within the therapeutic interval as a probable real change requiring a shorter recall interval; the important interaction between TMS and warfarin with possible patient safety consequences was not recognized by 91% of physicians; and an electronic alert was not as effective in influencing practice as could be expected.

Strengths and weaknesses of the study

A limitation of the study is that it is based on two case histories presented to the physicians in a questionnaire, and not on real life results covering a wider range of decisions. However, specific aspects of warfarin monitoring are well suited for case histories, since clinical situations in which INR is used are well defined, and there is no need for additional laboratory results. 'Patients' can be 'standardized', facilitating comparison of responses, and electronic surveys allow for sequential presentation of information with follow-up questions. Further, Noklus has considerable experience in formulating and pilot-testing case histories to ensure face validity (i.e. that the case histories and questions posed are recognized as plausible by physicians) [2,3,25–27]. Similarities concerning some of our findings and experiences from field studies indicate that the case histories reflect real-life practice [2,3,5,28–30], e.g. our finding that electronic alerts seem inadequate (case history B).

Even though we consider the response sufficient, the denominator cannot be adequately determined since the number of doctors attending nursing homes was not available. However, we received responses from a large number of physicians and nursing homes, representing a variety of clinical experience and nursing home settings. Probably responding physicians were among those more interested and knowledgeable of the topic, which is rather frequently encountered in primary care [11], and most respondents also work as GPs. Thus, the real-life responses in such scenarios may be less adequate than we report, also due to the fact that real life imposes time constraints which should be less prominent in such a short survey. The 'exam effect' could be countered by the fact that answers to case histories are easily made, with no real clinical consequences.

Findings compared to other studies

Management of a patient with stable anticoagulation (case history A)

This patient displayed a long period of very stable anticoagulation. Most physicians, probably by intuition, recognized the rather large change within the therapeutic interval as a real change, since there is less than 5% probability for analytic and biologic variation to be the reason for this change [2,3]. However, according to recommendations, the dose should remain unchanged [16,24,31], while the recall interval should be shortened [1,12,32]. Still, about 15% of the physicians changed the dose, which may lead to unstable anticoagulation [12]. A substantial percentage did not shorten the recall interval, allowing a possible further increase in INR to go undetected, although in most cases the next INR would often be within the therapeutic range [12,32]. The case history demonstrates that even in this familiar situation, handling of the patient varies. Our findings are concordant with findings in several field studies [2,3,5], and may indicate that dosing is based more on experience and personal routines than on guidelines.

Management of a drug interaction with warfarin (case history B)

Antibiotic guidelines in Norway prescribe the use of either TMS or ciprofloxacin to treat pyelonephritis [33], and both drugs have a potential for increasing the INRs when combined with coumarin derivatives [19,20,34–37]. It should be well known that drug

interactions abound for patients on coumarins [16,31,36,38], and it is therefore of concern that only half of the physicians would use easily available internet resources on drug interactions before starting treatment. We are not aware that this has been shown in other studies. In a real-world situation, the percentage that would seek – or read – information is probably even lower both because of time constraints, but also because of selection bias with regard to participants in our study.

Almost all the physicians, irrespective of years of clinical experience and speciality, seemed to be unaware of the drug interaction, and associations with physician characteristics may therefore not be anticipated. A recent study regarding interaction between warfarin and carbamazepine showed that the prescribers' awareness of the interaction was limited [28]. As the interaction between TMS and coumarin has been shown to lead to supra-therapeutic INRs in 30–69% of patients [21,22], dose reduction should be pre-emptive. Most authors recommend a reduction of 20–40% [15,17,18,39]. Pre-emptive dose reduction is also recommended for other antibiotics, for example, fluoroquinolones and macrolides, and it is especially concerning that common interactions seem unknown to physicians caring for frail patients [17,18,40].

In general, INR recall time when introducing a new drug should be 3–8 days, but in the case of TMS, it should be shorter (2–4 days) due to the possibility of early onset of supra-therapeutic INRs [19–23,31]. In a study including four anticoagulation clinics in the Netherlands, three of the clinics had an established protocol for pre-emptive dose reduction and one would monitor INR within 3–5 days after TMS initiation [37]. This could indicate that the specialists in these anticoagulation clinics were more aware of handling of interactions than Norwegian nursing home physicians. However, the results from Norwegian GPs align well with a finding that 46% of patients still had no INR measurement after 1 week of co-treatment with carbamazepine in a Swedish study [28]. Our findings probably also extend to general practice, since the nursing home physicians were mainly GPs, and the clinical scenarios should be familiar also to them. Of note, the recommendation only specified the recall time to be during TMS treatment, and was more precise regarding the size of the dose reduction [1,19,23,34,36,39].

Electronic alerts (case history B)

The simplest form of alerts, and the ones most prone to be followed, would be pertinent, short [29,41], automatically displayed texts [42], which are used in several electronic patient record systems in general practices, although not yet used in nursing homes in Norway. However, we aimed to mimic such electronic alerts by presenting the information actually used in record systems together with the case history in a separate window in SurveyMonkey. The recommendation was detailed regarding the 20–40% pre-emptive dose reduction, but the number of physicians who reduced the dose accordingly increased only from 29% to 53% after receiving the information. This is in accordance with a study showing a low effectiveness of a computerized warning to physicians ordering TMS in a warfarin treated patient [30] and a study on electronic clinical alerts in the care of cardiovascular disease where only one-third of the physicians even noticed them [29]. That 47% of physicians in our study did not follow advice about pre-emptive dose reduction may affect patient safety.

Recommendation regarding reduced INR recall interval when using TMS was much less acted on, as could be expected since this recommendation was not explicit. Reasons for the low adherence may be that physicians in primary care rarely experience patients with bleeding complications due to interactions, but also to the fact that the advice was somewhat embedded within theoretical considerations (Figure 1). We did not find associations between making changes and physician characteristics, and in case history B most replies were unacceptable, so information strategies to improve knowledge would probably have to be general and targeted on actions. Still, availability of laboratory results on demand by having an INR instrument may lead to a more acceptable recall time.

Meaning of the study

Warfarin monitoring and improvements of practice is still important, especially when the general knowledge of warfarin monitoring probably decreases because of many patients switching from warfarin to the new DOACs [11]. The patients remaining on warfarin will probably be the high-risk patients (e.g. older adults and patients with mechanical heart valves). Implementation of electronic alerts to improve quality management may therefore be important, especially if the experience with warfarin monitoring decreases. However, as this study shows, electronic alerts do not automatically mean increased quality of care. Their length and their way to present advice should be optimized in close collaboration with physicians for whom they are intended to make them understandable and useful in practice. Furthermore, nursing home

physicians may be encouraged to use different kinds of dosing algorithms [4]. However, regarding changes in medication, the use of updated drug interaction databases should be preferred since dosing algorithms cannot cover a variety of specific scenarios. The use of dedicated computer software for INR-dosing may improve performance, but will have to be rather sophisticated to include large changes within the therapeutic interval and especially influence of drug interactions. Direct and to-the-point recommendations would probably be as good in these circumstances. Nursing homes should have routines for rapid analysis of INR (INR instruments if possible or close cooperation with a hospital or emergency room laboratory nearby) to be able to act on changes immediately if necessary [7]. Finally, the case histories should be familiar to GPs as well, and findings should therefore also be applicable to general practice.

Conclusions

Monitoring of warfarin as assessed by case histories, is still suboptimal, especially when handling drug interactions. Electronic alerts as presented in electronic medical records seem insufficient to change practice. Availability of INR instruments may be important regarding recall time in situations when rapid INR analysis is needed.

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All authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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Reyes Serrano Teruel contributed to the statistical calculations and drafted and revised the manuscript.

Geir Thue contributed to the trial design, drafted and revised the manuscript.

Svein Ivar Fylkesnes contributed to the trial design, drafted and revised the manuscript.

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Ann Helen Kristoffersen contributed to the trial design and the statistical calculations, drafted and revised the manuscript.

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