International Journal of Clinical Pharmacy (2019) 41:1166–1173
https://doi.org/10.1007/s11096-019-00894-4

RESEARCH ARTICLE

Pharmacists' influence on adverse reactions to warfarin: a randomised controlled trial in elderly rural patients

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Received: 18 November 2018 / Accepted: 22 August 2019 / Published online: 7 September 2019

Abstract

Background Adverse reactions to warfarin may be serious and can lead to hospitalisation or death. Minimising the risk of adverse drug reactions through the intervention of community pharmacists is important for patients receiving warfarin, especially for elderly (≥ 65 years) patients living in rural areas. *Objective* To evaluate the impact of an intervention by community pharmacists on the risk of adverse drug reactions in elderly rural patients receiving warfarin. Setting: A community pharmacy in a rural area of Croatia. *Method* We conducted a prospective randomised trial. Eligible patients were recruited at the pharmacy and randomised into one of two groups. The participants were followed up every month for 6 months. Main outcome measure: The incidence and type of adverse drug reactions caused by warfarin and the time-to-event. *Results* In total, 140 patients were randomized and 131 patients completed the study; 65 patients were in the intervention group. The median age of patients was 73 years of age. The cumulative incidence of adverse drug reactions was significantly lower in the intervention group (6-months rate 29% vs. 85% for intervention and control, respectively; hazard ratio = 0.17, $p < 0.001$) than in the control group. Factors multivariately associated with the development of adverse drug reactions related to warfarin ($p < 0.05$) were the absence of pharmaceutical intervention, higher time in therapeutic range, change of warfarin dose, changes in dietary vitamin K intake, and marital status other than married. *Conclusion* Overall, the pharmacist's intervention significantly prolonged the time to occurrence of adverse drug reactions and reduced their incidence.

Keywords Adverse drug reactions · Croatia · Elderly · Pharmacists' intervention · Rural population · Warfarin

Impacts on practice

- Community pharmacist's interventions reduce the risk of warfarin's adverse drug reactions in elderly rural patients in Croatia.
- Pharmacists—general practitioner collaborative care provides safer warfarin therapy in elderly patients.

Introduction

Warfarin-related adverse drug reactions (ADRs) are one of the most frequent causes of hospitalization and death [1, 2]. The mean expected hospitalization cost from a warfarin-related bleeding hospitalization is estimated as $835 per year per person [3]. The tight control of the international normalized ratio (INR) in the therapeutic range is very important to ensure safe and effective warfarin treatment. Concurrently, achieving a tight control of INR in therapeutic range is quite challenging because of the pharmacokinetic characteristics of warfarin and its narrow therapeutic index. INRs outside therapeutic range account for the majority of thromboembolic and haemorrhagic events in patients with atrial fibrillation [4]. Moreover, elderly patients are particularly sensitive to ADRs related to warfarin and taking warfarin in older age

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is recognized as a predictor of ADRs [5]. Previous research has shown that pharmacists' actions improve the quality of warfarin therapy [6, 7]. However, little is known about how pharmacists can influence the risk of ADRs in a specific subpopulation of patients taking warfarin, such as rural elderly patients. We performed a randomised controlled trial to investigate the influence of the pharmacist's intervention on the efficacy of warfarin use and showed that the pharmacist's interventions significantly improved the time in therapeutic range (TTR) in elderly rural patients [8]. Herein, we report secondary analyses on the effects of the pharmacist's interventions on the type and severity of warfarin-related ADRs.

Aim of the study

The aim was to explore the influence of the pharmacist's interventions on the incidence and type of warfarin-related ADRs in a subpopulation of elderly rural patients. We further explored other risk factors for the development of ADRs by using univariate and multivariate analyses.

Ethics approval

Ethical approval (Number 251-62-03-15-28) for this study was obtained on April 20th, 2015, from the Ethical Committee of the Faculty of Pharmacy and Biochemistry, University of Zagreb.

Method

The trial was conducted between May 2015 and January 2017 in a community pharmacy in Donji Miholjac, Croatia, and is registered at clinicaltrials.gov (NCT03212898).

Elderly patients were randomised into one of two groups (intervention and control) by using a computer-generated randomisation program (www.randomization.com) and were prospectively followed up for 6 months. Patients were defined as "elderly" if their chronological age was 65 years or older [9]. Other inclusion criteria were: (1); rural place of residence and (2) duration of warfarin therapy of at least 3 months before the study with an expected duration of at least a further 6 months. The exclusion criterion was: prescribed interacting drug with X degree of clinical significance based on the Lexi®-interact database. Lexi-interact database rates the risk of potential drug interactions in several risk categories (A; B; C; D; X), with the X category indicating two drugs should not be combined.

The study site Donji Miholjac in Croatia has a population of 9400 inhabitants, located in province Slavonia, qualifies as rural area based on the OECD (The Organisation for Economic Co-operation and Development) criteria [10] and has a surrounding rural population of around 13 000 inhabitants. The pharmacy is a part of a primary care medical centre that consists of nine general practitioner's out patient clinics, a laboratory, a paediatric and gynaecologist ambulance, radiology with X-ray and ultra sound and four stomatology ambulances. The centre provides healthcare to sparse surrounding population that is primarily elderly and limited in getting medical care due to the poor public transport.

The goal TTR was set to a minimum of 65%, to assure warfarin was superior to antiplatelet drugs [11].

The intervention group was repeatedly educated on all aspects of warfarin therapy, including potential ADRs, during monthly visits to the pharmacy and was provided with a follow-up plan and a pillbox. Interventions for warfarin dose change and the avoidance of drug interactions were made by contacting general practitioners (GPs). The control group had standard GP-managed care, and were not educated by the pharmacist.

At baseline, the CHA_2DS_2-VASc [12] and HAS-BLED [13] risk scores were calculated for each patient; sociodemographic data (age, gender, and marital status) and clinical data (warfarin indication, comorbidities, and medication and social history) were collected. Adherence, INR, complexity of dosing scheme, variability of vitamin K intake, and possible ADRs were assessed monthly for all the participants. Adherence was measured by the number of pills missing or removed and the complexity of the dosing scheme was categorised into three categories (simple: the same dose of warfarin every day of the week, without splitting pills; intermediate: two different doses of warfarin in a week, one of which required pill splitting; complex: two different doses of warfarin in a week, both of which required pill splitting. The only warfarin drug in Croatia is the 100X 3 mg generic tablet (Martefarin® 100X 3 mg, Orion Corporation, Orion Pharma, Espoo, Finland). The variability of vitamin K intake was reported by the patients and assessed by the investigator, as performed in the study of Franco et al. [14]. The participants were asked if they had eaten more, less, or the usual amount of vitamin K-rich vegetables over the week preceding the INR measurement. The duration of warfarin use before the study period was measured as number of years of continuous use.

To detect a potential ADR at the follow-up visit, the investigator interviewed patients about an experience of a new or worsening symptom or sign and asked if the patient had had an unplanned visit to the GP or the emergency department, or was hospitalized. Alternatively, patients unable to attend the follow-up visit were contacted by phone. If an event had occurred, the GP was contacted for additional data on laboratory findings, information from the discharge letter, or any relevant medical records. To assess the suspected ADR, a case report with the information from the interview, GP, laboratory,

or other available data was created. Each case report was discussed between the investigator, a clinical pharmacologist, and a clinical pharmacist. The probability of the ADRs was determined by the algorithm developed by Naranjo et al. [15]. The algorithm consists of 10 questions with different point values (−1, 0, +1, or +2) assigned to each answer and includes the usual features that are important for the assessment of causality. Based on the score of the algorithm, ADRs can be defined as doubtful, possible, probable, or definite; in this study, we only accepted ADRs scoring a minimum of 1 point.

If there were differences in judgments on the ADRs, these were resolved by discussion and a consensus was reached for each case.

We recorded the type of ADRs, the probability, incidence, and time-to-event of ADRs. All ADRs were assessed separately and reported to the Agency for Medicinal Products and Medical Devices (www.halmed.hr), the national legal entity for pharmacovigilance.

With regard to the severity of bleeding, ADRs were defined and classified in accordance with the Bleeding Academic Research Consortium definition of bleeding by Mehran et al. [16]: type 0, no evidence of bleeding; type 1, bleeding needing no medical intervention; type 2, bleeding that requires medical intervention, but that does not reach the criteria of severe bleeding; and types 3, 4, and 5, severe bleeding with clinical, laboratory, and/or imaging evidence of bleeding and one of the following: reduction in haemoglobin; need for transfusion; or need for surgical interventions or fatal bleeding.

The normality of distribution of numerical variables was examined by using Kolmogorov–Smirnov's test. The numerical variables were non-normally distributed and were presented as the median and inter-quartile range (IQR), with differences between the groups examined using Mann–Whitney's U test. Categorical variables were presented as percentages and the differences between groups were tested using the Chi squared (χ^2) test. The cumulative incidence over time/time-to-event analysis was based on the method by Kaplan and Meier, and differences between groups were tested using the Cox–Mantel version of the log-rank test [17]. The data were screened by using the custom-made MS Excel workbook [18]. The multivariate analyses were performed by using the logistic regression. p values of <0.05 were considered statistically significant. All reported analyses were performed using the MedCalc statistical software ver. 17.5 (MedCalc Software bvba, Ostend, Belgium).

Results

The study comprised a total of 131 patients; 66 in the control and 65 in the intervention group. The sociodemographic and clinical characteristics of the study participants are shown in Table 1. The median age of patients at the beginning of the study was 73 years of age, and 51% of them were male.

The median CHA_2DS_2-VASc risk score for thromboembolic events was 5, and the median HAS-BLED score was 3, which showed that a substantial proportion of the included patients were at high risk of both thromboembolic incidents and major bleeding.

At the end of the 6 month follow-up period, only bleeding ADRs were detected.

In total, 56 (85%) patients in the control and 19 (29%) patients in the intervention group [$p<0.001$] experienced an ADR. The patterns of observed ADRs are shown in Table 2.

The most frequent ADR was skin bruising, which occurred in 70% versus 29% of cases in the control and intervention group, respectively. More serious bleeding that required medical intervention (type 2) occurred only in the control group and was categorised as a definite ADR and all the other ADRs were defined as possible according to the Naranjo algorithm. The cumulative incidence curves for different types of ADRs are shown in Fig. 1.

The pharmacist's intervention significantly improved the cumulative incidence of overall ADRs [$p<0.001$, HR (hazard ratio) = 0.17] and type 1 ADRs [$p<0.001$, HR = 0.22]; the same tendency was observed for type 2 ADRs, but did not reach statistical significance pP = 0.083].

Factors univariately associated with the development of warfarin-related ADRs were the absence of pharmacist's intervention ($p<0.001$), older age ($p<0.001$), lower TTR ($p<0.001$), a higher number of warfarin dose changes ($p<0.001$), a higher complexity of dosing scheme ($p<0.001$), lower adherence to therapy ($p<0.001$), changes in dietary vitamin K intake ($p<0.001$), longer experience with warfarin therapy prior to study inclusion ($p<0.015$), and marital status other than single ($p=0.001$).

We also performed multivariate logistic regression analysis that investigated the independent contribution of parameters univariately associated with the development of warfarin-related ADRs while also controlling for HAS-BLED score. The results are shown in Table 3. The factors that remained significantly associated and therefore predictive of the development of ADRs independently of each other were the absence of pharmaceutical intervention, higher TTR, change of warfarin dose, changes in dietary vitamin K intake, and marital status other than married.

Discussion

To the best of our knowledge, this is the first randomised trial conducted in the subpopulation of elderly patients living in a rural area showing that the provision of interventions by a community pharmacist lowered the rate of ADRs related to warfarin.

Table 1 Sociodemographic and clinical characteristics of the study participants

Variable	Control group (n = 66)	Intervention group (n = 65)	*p* value
Age	75 (71–81)	72 (68–79)	0.053
Gender			
Female	32 (48%)	32 (49%)	0.793
Male	34 (52%)	33 (51%)	
Warfarin indication			
Atrial fibrillation	47 (71.2%)	50 (76.9%)	0.456
Thrombophlebitis	6 (9.1%)	6 (9.2%)	
Other	13 (19.7%)	9 (13.8%)	
CHA_2DS_2-VASc	5 (4–5)	5 (4–5)	0.533
HAS-BLED	3 (3–3)	3 (3–3)	0.838
Number of comorbidities	4 (4–5)	5 (3–5)	0.408
Number of drugs in therapy	6 (5–7)	6 (5–8)	0.187
Study INR	1.9 (1.8–2.1)	2.2 (2.1–2.4)	< 0.001*
Marital status			
Married	36	29	0.431
Single	2	4	
Widowed	28	32	
Time in therapeutic range	31.2 (0–50.2)	93 (71.7–100)	< 0.001*

Data are presented as n (%) or median; IQR = interquartile range. P values were obtained by the Mann–Whitney U test for numerical data or the Chi squared for categorical variables

CHA_2DS_2-VASc Congestive heart failure or left ventricular dysfunction, Diabetes, Stroke (doubled)-Vascular disease, function Hypertension, Age ≥ 75 (doubled), Age 65–74, Sex category (female)

HAS-BLED Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly

Table 2 Adverse drug reactions after 6 months in the control and intervention group

Adverse drug reaction	Control group (n = 66)	Intervention group (n = 65)	Bleeding type*	*p* value
Bruising (n, %)	46 (70%)	19 (29%)	Type 1	< 0.001**
Bleeding from nose or gums (n, %)	7 (10%)	0	Type 1	0.006**
Bleeding requiring medical intervention (n, %)	3 (5%)	0	Type 2	0.244
Overall incidence (n, %)	56 (85%)	19 (29%)	–	< 0.001**

*Ref. [6] **Chi squared of Fisher's exact test for categorical data

Our study sample comprised of elderly patients at a high risk of thromboembolic events, as well as a high risk of bleeding events with median CHA_2DS_2-VASc C and HAS-BLED scores of 5 and 3, respectively. The participants were also characterised by specific sociocultural habits, such as the frequent use of self-grown food and poor education. The overall incidence of ADRs was high, but the majority of these ADRs were not serious and the probability of most ADRs was categorised as possible according to the Naranjo's algorithm. Unexpectedly, no patients experienced a thromboembolic incident, despite suboptimal TTR and INR values below the range in the control group of patients. The INR values of patients assigned to either intervention or control group had a general tendency towards lower values of the therapeutic range (below 2.5), but significantly lower INR values were observed in patients managed by GPs (control group), although no thromboembolic event was recorded during the follow up period. We would assume that a longer follow-up period as well as a bigger sample size could have produced different results in terms of thromboembolic events. Meta-analysis from Saokaew and colleagues [19] suggested that a follow-up time of 6 months would be required to capture all dimensions of pharmacist managed warfarin therapy effects on clinical outcomes. They found that the effects of pharmacist warfarin therapy management on bleeding were largely observed in the trials with short follow-up time while these effects were not evident

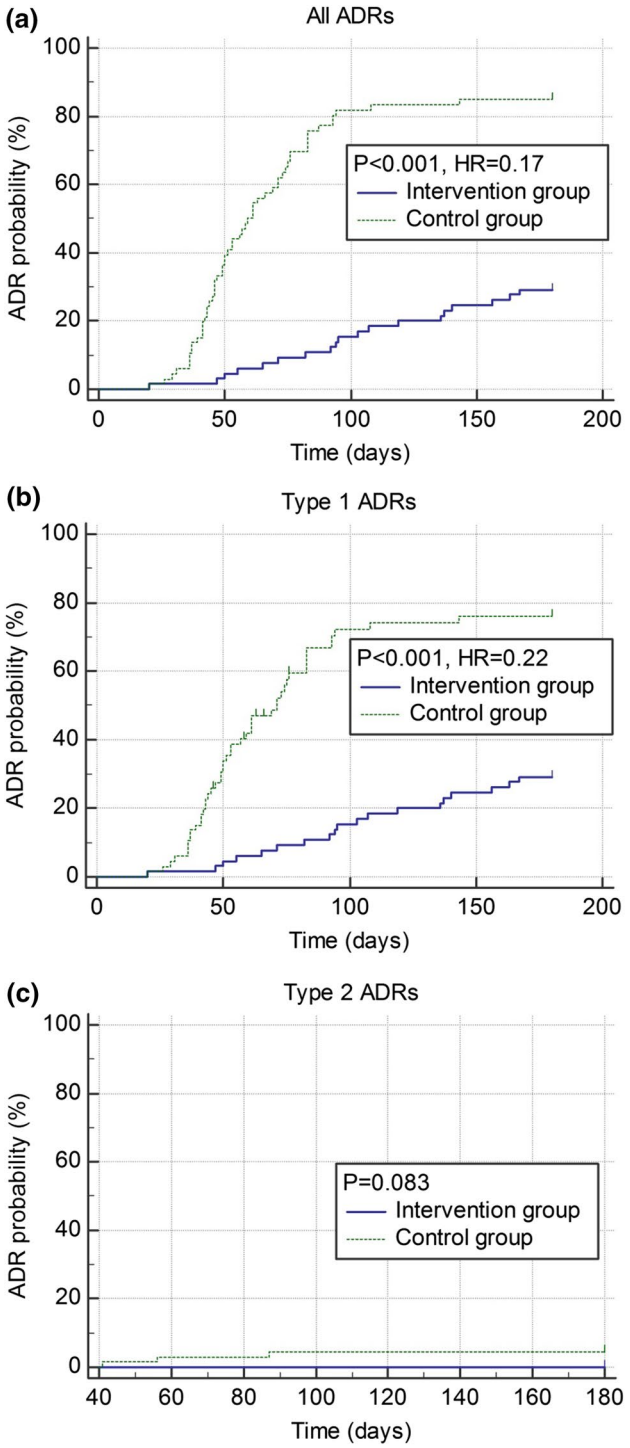

Fig. 1 Cumulative incidence curves for the development of warfarin-related ADRs in the intervention and control groups: **a** all ADRs; **b** type 1 ADRs; **c** type 2 ADRs

in studies with longer follow-up time. On the contrary, the effects of the pharmacist warfarin therapy management on thromboembolic events were clearly shown in studies with a longer follow-up time.

Table 3 Multivariate logistic regression model showing the independent contribution of different factors to the development of ADRs

Variable	OR and 95% CI	*p* value
Pharmacist's intervention	0.08 (0.02–0.41)	0.002*
Age	1.04 (0.96–1.12)	0.340
TTR ≥ 65%	5.54 (1.01–30.5)	0.049*
1 dose change	2.98 (1–8.83)	0.049*
> 1 dose change	1.45 (0.27–7.81)	0.666
Complex dosing scheme	1.59 (0.45–5.59)	0.473
Adherence < 80%	1.51 (0.48–4.72)	0.479
Change in vitamin K intake	3.22 (1.16–8.96)	0.025*
Longer warfarin use	0.8 (0.28–2.26)	0.672
Non-married marital status	4.67 (1.53–14.28)	0.007*
HAS-BLED score	1.23 (0.65–2.33)	0.527

Overall $p < 0001$ Nagelkerke R^2 0.75

*Statistically significant at $p < 0.05$

Furthermore, the difference between the groups in our study concerning the incidence (85% vs. 29% in the control and intervention group, respectively) and severity of ADRs was significant. Only three bleeds were recorded that required medical intervention, but were not categorized as major bleeding; all three cases occurred in the control group. These bleeds were categorized as a definite ADR, with documented elevation of INR above the therapeutic range.

Published data on the related topic originates mainly from studies conducted in hospital setting, or studies involving patients starting warfarin during hospitalisation and transferring to primary care, which is very different from our study sample [20, 21]. Most studies reported a non-significant trend toward fewer bleeding episodes [22, 23] or no differences between groups [24–28]. Moreover, no difference was seen in bleeding, or thrombosis rates, between patients receiving pharmacist-recommended doses and those receiving traditional care, although sample sizes of the studies were small and none of the studies were powered to detect differences in the rates of adverse effects [21]. Manzoor et al. [29] performed a systematic review to evaluate the quality of warfarin anticoagulation control in outpatient pharmacist-managed anticoagulation services compared with routine medical care. Compared with routine care, pharmacist-managed outpatient-based anticoagulation services attained better quality of anticoagulation control, lower bleeding and thromboembolic events, and resulted in lower health care utilization. However, only three randomized trials were included in this systematic review with non-significant results on bleeding.

There is little data on this topic originating from the community pharmacy setting. Harper et al. performed a prospective audit, providing Community Pharmacy-Based Anticoagulation Management Service in New Zealand

[30], and reported similar results to ours: 82.3% minor bleeds and 15.6% moderate bleeds. Another prospective, non-randomised, controlled cohort trial, involving community pharmacists in Australia in a home-based post-discharge warfarin management service, reported reduced adverse events and improved persistence in patients taking warfarin following hospital discharge [31]. Manji and colleagues performed a retrospective study and reported the incidence of 1.25% major bleeding in patients receiving anticoagulation care provided by pharmacists in a rural area of Kenya but no data on minor ADRs. To our knowledge our study is the only randomized study evaluating a community pharmacist anticoagulation service in rural area and therefore our results add to the existing evidence on the topic.

The results are in accordance with the published data and meta-analysis showing pharmacist's interventions can optimise quality and safety of warfarin use in the primary care [29]. The study involved comprehensive interventions provided by clinical pharmacists in the community pharmacy involving patient education and counselling on warfarin, medication/drug interactions review, recommendations to GP's on warfarin dose adjustments based on INR, assessment of medication adherence, ADRs and diet related to warfarin therapy. In this randomised designed study we demonstrated that such a complex intervention resulted in better safety profile as evidenced by lower minor bleeding occurrence. This is of importance for countries and areas not having outpatient anticoagulation services established, especially in the rural areas. In Croatia, there are no widely accessible coagulation clinics (for outpatients), no national, regional or institutional patient registries, and the Croatian Health Insurance Fund does not reimburse the use of portable coagulometers [32]. A properly trained community pharmacist can fill in this gap, although such an intervention requires a dedicated time and effort.

In addition, the regression model detecting factors attributing to the development of warfarin related ADRs highlighted some factors that were not reported in previous randomised trials, such as the number of dose changes, and marital status; these were mainly consistent with the reports from observational studies [33]. The relationship between higher TTR and ADRs in the model is surprising but, Vestergaard et al., reported in their systematic review that an increase in the mean TTR was associated with a decrease in the rate of major bleeding, and that the association was markedly weakened when the differences in the relevant clinical characteristics of the included patient cohorts were accounted for [34]. Despite being illustrative our results need to be interpreted with caution due to the explorative nature of analysis, wide confidence intervals and Nagelkerke R^2 of 0.75. Nonetheless, the log-rank analysis showed that the pharmacist's interventions in the trial significantly prolonged the time to an adverse drug reaction and reduced the risk of ADRs.

The described educational and clinical interventions should be an important part of patient follow-up due to the significant health costs associated with ADRs associated with warfarin. Marušić et al. showed that the ADRs related to warfarin were common in a cohort of patients discharged from a clinic in Croatia [35]. Study of Urbonas et al. in Lithuania showed rural patients had lower TTR and fewer INR measurements than urban patients managing warfarin therapy in primary care [36].

Pharmacists can help bridge these gaps in healthcare especially using novel technologies as reported by Zhang et al. [37], where chat platforms were used to adjust warfarin doses and communicate with patients in rural areas; this resulted in a minor bleeding incidence of 8%.

Our study has several limitations. The study was performed at a single site so the results cannot be generalised. Our patients had a specific lifestyle, defined by culture, socio-economic status, and GP anticoagulation care specific for Croatia. The low probability of ADR scores may have been a result of the lack of laboratory monitoring that was under the control of GPs, or it is possible that some ADRs were not detected because the patient did not recognise them or forgot to report them, or due to incomplete patient's records. The change of intake of vitamin K was measured by reliance on patients' memory that could cause bias. The goal TTR of 65% set in our study is lower than the one recommended in the guidelines as high quality TTR of 70% [38] but the difference in TTR between study groups shows that this probably had no effect on the outcomes. In addition, the study was conducted for only a 6-month period, and had a small sample size that was not powered for the detection of major ADRs, especially thromboembolic events.

Conclusion

Our study shows that the pharmacist's intervention resulted in the reduction of ADRs in the intervention group compared with the control group. The pharmacist's intervention affected the risk of bleeding by affecting several variables, but contributed to the lower risk of bleeding, independently of other analysed factors. As our data provides the evidence that this type of intervention provided by community pharmacist reduces the risk for elderly rural patients receiving warfarin therapy, this type of intervention should be applied and investigated in a broader patient population. Further research in this area is needed to confirm our results.

Acknowledgements This study is a part of the Ph.D. thesis of the first author. The authors would like to acknowledge all the general

practitioners responsible for the study participants for the provision of the required data.

Funding This study was self-funded.

Conflicts of interest The authors declare that they have no conflicts of interest.

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