Introduction

Most individuals who receive warfarin therapy are elderly patients with atrial fibrillation and acute or recurrent venous thromboembolism. Anticoagulation in elderly people poses unique challenges because they are simultaneously at higher risk for recurrent thromboembolism and major bleeding, including catastrophic intracranial haemorrhage. The effectiveness of warfarin therapy is strongly linked to the proportion of time that patients spend in the target INR range (TTR).[1, 2] The risk of death, myocardial infarction, major bleeding and stroke or systemic embolism are all related to INR control.[3]

In Australia, the Department of Veterans' Affairs (DVA) introduced a system of providing formal medication reviews for Australian veterans in 1999, which was followed by the HMR program (available to all members of the Australian public) in 2001. For veterans taking warfarin, these reviews provide an opportunity for patient education and review of warfarin management in the community setting. General practitioners refer patients to an accredited pharmacist who undertakes a home visit, identifying any medication-related problems, including potential underuse, overuse, adverse effects, compliance and knowledge problems, or hoarding. The pharmacist provides a report to the doctor who has responsibility for follow-up with the patient. The potential benefits of patients receiving a pharmacist-conducted medication review were established in several large research projects performed in the late 1990s.[4, 5] These studies found that HMRs resulted in the resolution of medication-related problems and showed trends in reduced medication costs.

A study by Roughead et al. assessed the effect of HMRs in Australian veterans and war widows taking warfarin retrospectively using administrative claims data.[6] The study identified a 79% reduction in the likelihood of hospitalisation for bleeding between two and six months following the HMR (hazard ratio 0.21, 95% CI 0.05 - 0.87). This beneficial effort was not evident 6 to 12 months following review. As INR testing and TTR were not assessed

in the study, it is unclear whether improved INR control occurred as a result of the HMR, or whether the benefits occurred independently of improved INR control.

We aimed to determine whether HMRs are associated with improved INR control, and observe the degree of INR control in this population.

Materials and Methods

The DVA database

The Australian DVA claims databases contain details of all prescription medicines, medical and allied health services and hospitalisations provided for which DVA pay a subsidy. At the time of the study, the data file contained 140 million pharmacy records, 200 million medical and allied health service records and over 6 million hospital records for a treatment population of 310,000 veterans. The DVA maintain a client file, which includes data on gender, date of birth, date of death and family status. Medicines are coded in the dataset according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification[7] and the Schedule of Pharmaceutical Benefits item codes.[8] Hospitalisations are coded according to the WHO International Classification of Diseases (ICD) classification.[9]

Study design and data collection

A retrospective cohort study was undertaken to compare the degree of INR control in veterans taking warfarin who were exposed and not exposed to HMRs. Eligible veterans were initially identified and selected by the DVA based on data from their patient database. To be eligible for inclusion into this study, veterans were screened by the DVA to meet the following inclusion criteria: possess a Gold repatriation benefit card (eligibility for full entitlements), dispensed warfarin during the study period (1st January 2007 to 31st December 2009), and residing at home (as opposed to a residential aged-care facility).

The DVA identified a list of veterans who met the inclusion criteria and who had also had an HMR prior to 30th June 2009. This allowed for data to be available for at least 6 months of data following the HMR in the group exposed to HMRs. The DVA then randomly selected a matching number of veterans who met the inclusion criteria who had not been exposed to an HMR in the study period. The identified veterans were sent an information

sheet and consent form. A list of veterans who consented to be involved in the study was generated and sent to the DVA for data extraction.

Data provided by the DVA included age, sex, remoteness,[10] number of co-morbidities, dispensed medications, dates of HMR claims, and health services utilisation (hospitalisations (including diagnoses and procedures), general practitioner visits and specialist visits). The research team then contacted pathology laboratories that had claimed payment from DVA for measuring the veteran's INR.

Formation of HMR and control groups

The 'HMR' group were those who met the eligibility criteria, had received an HMR, and had at least two dispensings of warfarin in the six months prior to the HMR. The 'control' group was comprised of veterans who met the eligibility criteria and who had an average at least two dispensings of warfarin per six months between the first and final dispensing during the study period (to identify regular warfarin use), had at least three months between their first and final dispensing of warfarin (to identify long-term warfarin use) and had a first warfarin dispensing date before 1st January 2009 (to allow adequate time for a minimum of six months follow-up within the study period).

Eligible veterans in the control group were randomly allocated to an index month in the study period to match the time of the HMR in the HMR group. Control group veterans were only matched once in the study period.

Data handling and statistics

Data were analysed using SPSS 19.0 for Windows (IBM Corporation, New York, United States). Demographic variables were compared between the HMR and control groups using the following methods: paired and unpaired t-tests were used for normally distributed continuous variables; the non-parametric Mann-Whitney test was used for non-normal data. Categorical variables were analysed using the chi-square test. Fisher's exact test was used when at least one of the variables had fewer than five patients or events. Statistical significance was set at $p < 0.05$.

The primary outcome was the percentage TTR, calculated using Rosendaal's linear interpolation method,[11] for the six months prior to the HMR or index date, compared to the six months following the HMR or index date. An INR target range of 2.0 to 3.0 was assumed for this analysis as specific diagnoses for the condition requiring anticoagulation were not available for the majority of patients and a range of 2.0 to 3.0 was considered to be appropriate for most elderly patients. The literature suggests that patients in the community spend 50-60% of their time within the target range. At a power of 80% and statistical significance set at 0.05, a minimum of 75 patients analysed before and after HMR was required to detect a 10% difference in the percentage TTR.

The composite incidence of major bleeding and major thrombotic events resulting in hospitalisation occurring within six months of the HMR or index date was a secondary outcome. The ICD codes used to determine the primary diagnosis of hospitalisation associated with a bleeding event or thrombotic event are shown in Table 1.

Ethics

Ethical approval for this project was provided by the DVA Human Research Ethics Committee (Reference E009-010) and the Tasmanian Health and Medical Human Research Ethics Committee (Reference H0010963) prior to the commencement of the study.

Results

Figure 1 shows a flow diagram of recruitment of veterans into the study. The DVA selected 3,884 veterans according to the project methodology, from which the research team received 1,213 replies (31.2% response rate). A total of 1,029 veterans who replied provided their consent and were eligible for inclusion in the project. There were a total of 818 veterans who were allocated to the HMR (n = 281) or control groups (n = 537). INR data was available for a total of 344 of 818 (42.1%) veterans. At least two INR results were required to allow calculation of the TTR; veterans with only one INR result in the specified timeframe were excluded from the respective analyses. A total of 321 veterans had at least two INR results within the 12 month study period; 265 veterans had two or more INR results recorded in the six-month baseline period prior to their first HMR or index date, 279 veterans had two or more INR results recorded in the six-month period following their first HMR or index date and 229 veterans had two or more INR results in each six month period.

Characteristics of the groups are shown in Table 2. The groups were well matched with respect to gender, prior hospitalisations, prior bleeding and thrombotic events and region. The median number of co-morbidities was statistically significantly higher in the HMR group. The median age was also one year older in the HMR group, which was of marginal statistical significance.

In the overall study cohort, the median testing interval was approximately 16 days (range 1.0-65.7) and the mean TTR was 64.0 ± 27.3% (n=321). The proportion of veterans whose percentage TTR was > 60% and > 70% was 64.5% and 49.2%, respectively. The mean percentage TTR following HMR and index date was 63.0% ± 30.1% (n=98) and 67.0 ± 27.7% (n=181), respectively (p=0.27). There was no significant change in the TTR in either of the groups or the overall veteran cohort in the period following the HMR or index date from the six-month baseline period (Table 3).

Veterans living in outer regional and remote areas had significantly poorer INR control than those living in inner regional areas and major cities (mean TTR 49.9% ± 30.7% vs. 65.3% ± 30.7% for those living in outer regional/remote areas and those living in inner regional areas/major cities, respectively; $p < 0.01$).

There was no change in the combined number of bleeding and thrombotic events leading to hospitalisation (4/281 (1.4%) in the HMR group versus 6/537 (1.1%) compared to the control group; $p = 0.74$). In the HMR group, there was no significant change in the combined number of bleeding and thrombotic events leading to hospitalisation before and after the HMR (1/281 (0.4%) versus 3/281 (1.1%), respectively; $p = 0.62$).

Discussion

The mean percentage TTR for veterans included in the study was 64% and did not appear to be influenced by HMR. The degree of INR control in this study compares well with the mean TTR achieved in recent randomised trials comparing warfarin to the new anticoagulants dabigatran (64%), rivaroxaban (55%) and apixaban (62%)[12-14] in a much older population, and exceeds the usual level of INR control achieved in the primary care setting in many countries.[15]

A systematic review reported that INR control differed based on study site; in community-based studies, anticoagulation clinics and RCTs, mean TTR was 56.7%, 65.6% and 66.4%, respectively.[15] In the literature, appropriate TTR benchmarks for patients taking warfarin are suggested to be 60-70%.[16] In a study comparing the outcomes of patients randomised to dual antiplatelet therapy or warfarin, the benefits of warfarin were predicted to be lost using a population model when the TTR fell below 58%.[2] If we accept the TTR benchmarks that have emerged internationally since our study, a TTR of 60% as a lower benchmark for acceptable INR control, around 35% of veterans in our study were below this figure. If upper benchmark of 70% is used, 51% of veterans were below this mark.

There is a strong correlation between TTR and clinical outcomes for patients taking warfarin.[3, 17-19] The generalisability of the results of trials comparing new anticoagulants to warfarin depends to a large extent on the TTR achieved in the trials, as it has been established that the efficacy, safety and cost-effectiveness of comparators to warfarin changes depending on the quality of INR control.[20, 21] In the RE-LY trial, a 10% increase in TTR independently predicted a 20% lower rate ($p < 0.001$) of the composite clinical outcome (stroke, systemic embolism, or major haemorrhage).[19] The number of clinical events in this study was too low to enable a statistical comparison of the clinical event rate and the degree of INR control.

Noting that the study was underpowered to detect differences in hospitalisation for major bleeding and thrombosis, we did not identify any effect of HMRs on hospital admission resulting from complications associated with warfarin therapy in veterans who had been taking warfarin for a period of at least six months.

Two studies in Australia involving a combination of a series of medication review and point-of-care (POC) INR monitoring have found that this combination reduces the risk of complications with warfarin therapy in the early post-discharge period.[22, 23] However, most of the beneficial effect of these interventions was due to a reduction in minor bleeding, and not events that resulted in hospitalisation. In the more recent study,[23] the intervention was associated with significantly decreased rates of combined major and minor haemorrhagic events to day 90 compared to usual care. However, there were no significant differences in readmission and death rates, or in INR control between the groups. Furthermore, significant reductions in complications associated with warfarin therapy only occurred in the group of patients newly initiating, rather than continuing, warfarin therapy.

It is therefore difficult to extrapolate the benefits of these interventions involving multiple home-visits to the effectiveness of a single HMR on people who are relatively stable on warfarin therapy (versus those recently discharged from hospital and/or recently initiated on warfarin). Additionally, the focus of the medication review in the studies was directly on warfarin, while this may often not be the reason for the initiation of an HMR in people who are stabilised on warfarin therapy. In a retrospective study by Roughead et al, using administrative claims data from the DVA, the effect of a single HMR on Australian veterans and war widows 65 years and older who were taking warfarin was investigated.[6] The study identified a 79% reduction in the likelihood of hospitalisation for bleeding between two and six months following the HMR. This analysis did not include INR data, so it is unclear whether the HMR influenced INR control. The results of the present study, albeit in a smaller

subset of the veteran population, suggest that this reduction in hospitalisation occurred independently of improved INR control. However, it remains possible that if INR data were available to examine TTR in the larger cohort investigated in Roughead et al's study, an improvement in both INR and warfarin-related hospitalisations may have been detected.

In order to obtain INR histories for included patients in the present study, the investigators were required to obtain consent from veterans. This meant that it was not possible to obtain information from veterans who had died either during the study period or in the time following the study period prior to the DVA mail-out, and excluded veterans who were readmitted to hospital with a major bleeding or thrombotic event and subsequently died. Therefore, we were not able to investigate the data of the entire veteran cohort who were taking warfarin during the study period. It is possible that the more seriously ill veterans, and perhaps those most likely to suffer from adverse events related to warfarin were not included as a result of this methodology. This may have underestimated any influence that HMRs may have had on the clinical outcomes of warfarin therapy or on INR control. The low rate of major bleeding in this study (equivalent to 2% p.a.) might be explained by careful selection of veterans who are candidates for warfarin by prescribers, the relatively high standard of INR control, the exclusion of veterans who suffered major bleeding events and subsequently died (due to the nature study methodology) or a combination of these factors.

Limitations

There were several methodological limitations to the study, which have largely been previously discussed. It should be acknowledged that while the percentage TTR is strongly associated with bleeding and thromboembolism in people taking warfarin, the absence of a change in TTR as a result of an HMR in this study does not rule out the possibility that HMRs may improve these outcomes through alternative means. Additionally, the data available from

the DVA was limited in respect to the documentation of co-morbidities, which meant that it was impossible to determine the indication for warfarin from the data available. Therefore, a target INR of 2.0 to 3.0 was assumed for all veterans. It is likely that this would have resulted in an under-estimation of the TTR rather than an over-estimation of the degree of INR control. INR data were only available for approximately 40% of the included veterans. In some cases, the pathology provider did not comply with the joint request from the research team, the DVA and the veteran for the data to be released. In some cases the pathology provider only held a proportion of the INR data available; the veteran may have changed provider or office-based INR testing was used (in which case it was not available to the pathology provider). It was not possible to identify which veterans may have received office-based point of care INR testing during the study period and it is therefore unknown whether their INR control is comparable to that of the veterans included in this study.

Conclusions

The overall level of INR control in the veterans participating in the study was good, and comparable to that achieved in RCTs, which generally involve a younger, healthier cohort. However, there appear to be a relatively large group of patients who would benefit from interventions to improve their INR control. HMRs did not appear to influence the INR control of veterans whose pathology data was available for analysis. The previously reported effect of pharmacist-led medication review on reducing hospital admission is likely to be due to other factors. It is clear there is an ongoing need to regularly audit INR control in veterans taking warfarin and intervene as appropriate to maximise the benefits and minimise the risks of warfarin therapy.

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Figure 1. Patient recruitment flow diagram

Table 1. ICD-10 primary diagnosis codes used to identify hospitalisation due to haemorrhagic and thromboembolic events

ICD-10 code	Description	ICD-10 code	Description
Haemorrhagic events		*Thromboembolic events*	
D683	Bleed due to anticoagulant	G450,G451, G452, G453, G454, G458, G459	Transient cerebral ischaemic attacks and related syndromes
D698, D699	Haemorrhagic condition unspecified	G460, G461, G462, G463, G464, G465, G466, G467, G468	Vascular syndromes of brain in cerebrovascular diseases
I60 I61 I62	Cerebral haemorrhage	I260, I269	Pulmonary embolism
K250, K252, K254,K259, K260, K262, K264, K266, K270, K272, K272, K276	GI ulcer with haemorrhage	I630, I631, I632, I633, I634, I635, I636, I638, I639	Cerebral infarction
K290	Acute haemorrhagic gastritis	I64	Stroke, not specified as haemorrhage or infarction
K280, K284, K286, K5701, K5703, K5711, K5713, K5721, K5723, K5731, K5733, K5743, K5751, K5783, K5791, K5793, K625, K661	Other intestinal bleed	I81	Portal vein thrombosis
K920	Haematemesis	I820, I821, I822, I823, I828,I829	Other venous embolism and thrombosis
K922	GI haemorrhage		

	unspecified
H113, H313, H356, H431	Eye bleeds
M2501, M2502, M2503, M2504, M2505, M2506, M2509	Haemarthrosis
R040, R042, R048, R049	Epistaxis
R58	Other haemorrhage unspecified
R31	Unspecified haematuria

Table 2. Patient characteristics

	HMR group **n = 281**	**Control group** **n = 537**	***p*-value**
Male gender (%)	181 (64.4)	349 (65.0)	0.87
Median age (range)	84.0 (56.0-93.0) years	83.0 (41.0-94.0) years	0.047
Median number of co-morbidities (range)	9.0 (1.0 - 28.0)	7.0 (1.0 - 30.0)	0.003
Prior hospitalisations*			0.24
0 (%)	200 (71.2)	390 (72.6)	
1 (%)	44 (15.7)	96 (17.8)	
2 or more (%)	37 (13.2)	51 (9.5)	
Prior hospitalisation for a bleeding or thrombotic event (%)*	3 (1.1)	8 (1.5)	0.76
Prior hospitalisation for a bleeding event (%)*	1 (0.4)	2 (0.4)	0.99
Prior hospitalisation for a thrombotic event (%)*	2 (0.7)	6 (1.1)	0.72
Region†			0.56
Major city (%)	175 (62.3)	347 (64.6)	
Inner regional (%)	79 (28.1)	142 (26.4)	
Outer Regional (%)	23 (8.2)	39 (7.3)	
Remote (%)	3 (1.1)	6 (1.1)	
Mean percentage TTR (SD) ‡	64.8 (25.2)	68.3 (28.4)	0.32
Median number of tests (range) ‡	8.0 (2.0-30.0)	7.0 (2.0-52.0)	0.33
Median testing interval in days (range) ‡	12.6 (1.0-76.0) days	17.4 (1.0-70.5) days	0.002

* In the six months prior to the HMR (HMR group) or index date (control group).

† The region was unknown for four veterans.

‡ Veterans with only one INR value recorded for the six months prior to the HMR or index date were excluded (n = 94 for the HMR group and n = 171 for the control group).

Table 3. Percentage TTR following HMR or index date*

	Before	**After**	**Mean difference**	***p*-value**
HMR group (n = 78)	67.9 ± 23.3	69.6 ± 25.2	+1.7	0.63
Control group (n = 151)	70.4 ± 26.1	68.5 ± 26.1	- 1.9	0.40
Overall (n = 229)	69.6 ± 25.1	68.9 ± 25.8	+ 0.7	0.72

*Only veterans with more than one INR value available for both the six months before and the six months following the HMR or index date were included.