Quality of management of oral anticoagulation as assessed by time in therapeutic INR range in elderly and younger patients with low mean years of formal education: a prospective cohort study

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Abstract

Background: despite the overwhelming evidence of its effectiveness, oral anticoagulation continues to be underused in the elderly, presumably due to physicians’ misconceptions when estimating bleeding risk and ability to comply with treatment.

Objective: to investigate the quality of anticoagulation control among deprived elderly and younger patients.

Design: prospective observational study.

Setting: a public anticoagulation clinic in a developing country.

Subjects: all adult patients on intended long-term (>90 days) oral anticoagulation. We studied 171 patients (79 elderly and 92 non-elderly) with a mean follow-up of 273 ± 84.9 days.

Methods: the main outcome measure was the quality of anticoagulation management as measured by the time in therapeutic (TTR) international normalised ratio (INR) range. Elderly patients (≥60 years) were compared with younger patients with respect to the educational level and co-morbidities.

Results: the mean number of years of formal education was 4.37 ± 3.2 years. The mean TTR was 62.50 ± 17.9% in non-elderly and 62.10 ± 16.6% in elderly (P = 0.862) subjects, despite the higher prevalence of co-morbidities in the latter group: heart failure (46.3 versus 28.6%, P = 0.042), diabetes mellitus (22.8 versus 8.7%, P = 0.011), renal failure (estimated glomerular filtration rate <50 ml/min: 38.0 versus 7.1%, P < 0.001) and polypharmacy (84.8 versus 58.7%, P < 0.001).

Fifty elderly and 84 non-elderly subjects require little or no assistance in taking medications. Among them, the elderly had lower educational levels (3.42 ± 2.5 versus 5.55 ± 3.4 years of formal education, P < 0.001) and higher rates of cognitive impairment (34.0 versus 13.1%, P = 0.004), but a similar mean TTR (62.46 ± 16.1 versus 63.02 ± 17.8%, P = 0.856). The oldest (≥75 years) patients did as well as those aged ≤50 years (mean TTR: 62.54 ± 16.0 versus 62.23 ± 16.4%, respectively, P = 0.98).
Conclusions: good-quality management of oral anticoagulation is achievable in deprived populations attending an anticoagulation clinic. Elderly patients may experience similar quality of anticoagulation despite having higher levels of co-morbidities and polypharmacy. These results add evidence to the safety of such therapeutic interventions in the elderly.

Keywords: oral anticoagulation, warfarin, elderly, quality of health care, time in therapeutic range, elderly

Introduction

Large randomised trials have demonstrated that long-term oral anticoagulation therapy prevents recurrence in venous thromboembolism and cardioembolic events in atrial fibrillation [1]. Benefits and harms may increase with increasing age, and are largely dependent on achieving and maintaining the target intensity of anticoagulation, as guided by monitoring of the international normalised ratio (INR) [1]. Several reports [2, 3] have pointed out that elderly patients are often denied this intervention, presumably due to physicians’ misconceptions when estimating bleeding risk and ability to comply with treatment.

In a cohort [3] published in 1999 of ambulatory patients with atrial fibrillation who received care within a health maintenance organisation in the USA and who had no contraindication to anticoagulation, warfarin use was observed in 60.7% of those aged 65–74 years and in only 35.4% among those aged ≥85 years. A recent systematic review [4] enrolled only studies published after May 1997 and showed that anticoagulation underuse is still alarming. Only 52.3% of patients with atrial fibrillation patients at high risk for cardioembolism were on oral anticoagulation. High risk was defined as CHADS2 score ≥2. This is a simple risk stratification scheme in which the presence of congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, scores 1 point each, and prior history of stroke/transient ischaemic attack scores 2 points.

Despite extensive data from randomised trials demonstrating the efficacy and safety of oral anticoagulation for the prevention of thromboembolism, concerns persist about how these findings can be generalised if applied to ‘real world’ clinical settings [5, 6]. We believe that the answer is dependent upon the quality of anticoagulation management. Currently, the most highly recommended method to evaluate the quality of anticoagulation control is to estimate the time in therapeutic range (TTR) [1, 7, 8].

In the elderly, factors such as polypharmacy, cognitive impairment, insufficient social support and poor compliance with treatment could contribute to the fear of inadequate control of anticoagulation [9, 10]. However, few studies have compared the quality of anticoagulation control between elderly and non-elderly subjects [11–13].

We investigated the quality of anticoagulation control among deprived elderly and younger patients attending an anticoagulation clinic in a public hospital.

Methods

Study population and design

The study protocol was approved by the ethics committee of the Federal University of Minas Gerais and ‘Hospital Odilon Behrens’. From December 2006 to January 2008, we conducted a prospective observational study in the anticoagulation clinic of the Hospital Odilon Behrens, a public hospital in Belo Horizonte, Brazil. We enrolled all adult patients on oral anticoagulation that was expected to be continuous or at least for 90 days. We included both patients at the beginning of anticoagulation and patients already on chronic anticoagulation. Written informed consent was obtained from all patients (or caregivers) enrolled in the study.

Baseline investigations

At the beginning of the follow-up period, we obtained the demographic and clinical data of patients by reviewing medical records and conducting an interview with a structured questionnaire. The latter included the indication for anticoagulation; beginning and proposed duration of anticoagulation; presence of caregivers (responsible for the administration of medications); co-morbidities; currently used medications; use of painkillers and anti-inflammatory drugs; consumption of tea, coffee and alcoholic beverages; smoking status; and recent (previous 12 months) hospitalisations. Patients (or caregivers) also completed a 3-week dietary questionnaire from which we calculated the daily intake of vitamin K. Polypharmacy was defined as the long-term daily use of four or more medications. Family support was assessed by patient perception of support from his/her family.

We carried out some additional tests among patients who need little or no assistance in taking medications. The Primary Care Evaluation of Mental Disorders (PRIME-MD) [14] was used for the screening of depression and the Mini-Mental State Examination (MMSE) for the screening of cognitive status. For the definition of cognitive deficit, we used the cut-off points in the MMSE proposed in our country by Almeida [15]: ≤23 for people with schooling and ≤19 for people without formal education. Compliance was assessed by a four-item Morisky Test [16]. This test consists of four questions which have yes/no answers. It aims to evaluate patient behaviour regarding use of their standard medications. The patient is classified as a ‘good complier’ if the answers to
all questions are negative. Medication management capacity (MMC) was assessed by the Drug Regimen Unassisted Grading Scale (DRUGS) [17]. This tool correlates the physician’s prescription and the actual dosages reported by the patient. Patients must carry out the following four tasks with each one of their medications: identify the appropriate medication; open the container; select the correct dose and report the appropriate timing of doses. Scores on the DRUGS can range from 0 to 100%, with equal weighting of each of the four tasks.

Follow-up
At each consultation during the follow-up, blood samples were collected by venipuncture and the INR was obtained. We checked the dose of warfarin in use and, if necessary, made adjustments in warfarin doses guided by a manual nomogram protocol based on international guidelines [1].

At the end of the follow-up period, we assessed the quality of anticoagulation management by calculating the TTR using the linear interpolation method of Rosendaal et al. [18]. The TTR was calculated based on the strict INR target range (2.0–3.0 for most cases or 2.5–3.5 for patients with mechanical prosthetic heart valves). We also evaluated the number of INRs that were <1.5, <1.8, >4 and >5 per year. We excluded from these analyses the first 3 weeks of anticoagulation, when there is greater variability in the INR.

Statistical analysis
Statistical analyses were carried out using the software Statistical Package for Social Sciences, version 13.0. (SPSS Incorporated, Chicago, IL, USA). Categorical variables were expressed as percentages and analysed by Chi-square test (or the Fisher exact test as appropriate). In the analysis of continuous variables, we used the Kolmogorov–Smirnov test to verify the normality of distribution, and the Levene test for homogeneity of variance. Normal continuous variables were expressed by mean ± standard deviation (SD) and compared with Student’s t-test. Non-normal values were expressed as median and inter-quartile range (IQR) and compared using the Mann–Whitney U test. A two-sided P-value of <0.05 was considered significant.

Additionally, we constructed a multiple linear regression analysis to adjust results for baseline differences between the two study groups and examine the influence of age in the TTR. Lastly, we made a post hoc analysis to determine the study power to detect differences in the TTR between the groups compared.

Results
We requested participation from all 233 patients followed at our anticoagulation clinic, 41 of whom were excluded due to intended anticoagulation duration <90 days. A total of 192 patients were enrolled, of whom 21 (10.9%) were lost to follow-up before 90 days. Even patients who died were included if sufficient data were available. The final analysis included 171 patients aged 19–93 years (mean age, 58 ± 15 years). The mean duration of follow-up was 273 ± 84.9 days, equalling 127.9 patient-years.

The mean number of years of formal education was 4.37 ± 3.2 years. Patients were allocated into two groups according to age: elderly, i.e. those aged ≥60 years (79 patients) and non-elderly (92 patients). Table 1 shows the baseline data of these groups.

There were clear differences between the two groups regarding the indication for anticoagulation. Among the elderly, the main indication for anticoagulation was non-valvular atrial fibrillation (70.9%). Among the non-elderly, the main indications were valve disorders (31.5%) and venous thromboembolism (30.4%). The prevalence of the following co-morbidities was also higher in the elderly: heart failure (46.3 versus 28.6%, P = 0.042), diabetes mellitus (22.8 versus 8.7% P = 0.011) and renal failure (38.0 versus 7.1%, P < 0.001), the latter being defined by creatinine clearance <50 ml/min (estimated by the Cockcroft–Gault equation). There were no significant differences between the groups regarding regular use of acetaminophen (paracetamol), dipyrone (an analgesic and antipyretic drug), anti-inflammatory drugs, and regular consumption of coffee, tea, tobacco and alcoholic beverages. Only regular use of antacids was higher among the elderly (5.1 versus 0%, P = 0.044). The number of medicines for long-term use (in addition to warfarin) was also higher in the elderly group [5.0 (IQR 3–5) versus 3.0 (IQR 2–5), P < 0.001], as well as the presence of polypharmacy (84.8 versus 58.7%, P < 0.001). The number of hospitalisations in the 12 months preceding the study and the pattern of intake of vitamin K were similar in both groups.

Table 2 shows additional baseline data of the 134 patients who need little or no assistance in taking medications. The elderly group had: fewer years of formal education [3.5 (2–5) versus 5.0 (4–8) years, P < 0.001] and a greater proportion of patients with cognitive impairment (26.0 versus 7.1%, P = 0.002). Compliance as assessed by the Morisky Test was similar between the groups, but MMC for long-term medications as assessed by DRUGS was higher in the non-elderly group (95.24 ± 11.8 versus 93.60 ± 9.9%, P = 0.018). Depression screening was also similar between non-elderly and elderly (20.2 versus 18.0%, respectively, P = 0.751).

Analysis of the anticoagulation pattern at the end of the follow-up period showed that the quality of anticoagulation control between the two groups was very similar (Table 3). The mean TTR was 62.10% among the elderly group and 62.50% among the non-elderly group. Extreme INR values, i.e. below 1.5 or above 5, were similar between the two groups. Warfarin was the only anticoagulant used. Its mean daily dose was higher in the non-elderly group (5.65 ± 3.4 versus 4.44 ± 1.9 mg, P = 0.020).
In the subgroup of 134 patients (50 elderly and 84 non-elderly) who need little or no assistance in taking medications, the quality of anticoagulation management was also similar between groups. The mean TTR was 63.02% in the non-elderly group and 62.46% in the elderly group (P = 0.882).

We also compared two even more distinct subgroups with respect to age: ≤50 versus ≥75 years. Again, there was no significant difference in the quality of anticoagulation control between these two groups (TTR of 62.23 versus 62.54%, respectively, P = 0.994).

In multiple linear regression analysis, elderly status was not a predictor of the TTR, as it accounts for a small and non-significant change in the TTR of −0.26% (95% CI, −6.68% to +6.62%, P = 0.994). Our study had power of 80% to detect a difference in TTR of 6.5% and a power of 99% to detect a difference of 10%.
Discussion

In ‘developing’ countries, the World Health Organisation (WHO) defines elderly subjects as those aged ≥60 years. The population of this age group is increasing worldwide. Nevertheless, older people are less likely to receive some drug treatments that have proven efficacy [19]. In this context, long-term anticoagulation is sometimes denied to elderly patients due to fear of inadequate control of anticoagulation and the risk of bleeding [2, 20, 21].

In the present study, the quality of anticoagulation was similar in elderly and non-elderly subjects even though these two groups had different levels of education, cognitive deficits, co-morbidities and polypharmacy. Moreover, these similarities were also found in the subgroup analysis among these groups [22, 23].

75 and >75%) and found no differences in mean age oagulants on three groups according to the TTR (<60, 60 – strovibrillation using antic-

Few studies have compared the TTR of elderly and non-elderly subjects. Abdelhaﬁz and Wheeldon[11] found equivalent TTRs (58%) in patients aged <75 and >75 years. However, even the younger group had a considerable proportion of elderly subjects (mean age, 64.3 years). A Chinese study [12] used the same age cut-off, and also found no differences in the quality of anticoagulation among groups. In a recent study in Veterans Health Administration anticoagulation clinics, multivariable analysis pointed out that older patients actually had better anticoagulation control than younger patients [13]. Moreover, two studies allocated patients with atrial ﬁbrillation using anticoagulants on three groups according to the TTR (<60, 60–75 and >75%) and found no differences in mean age among these groups [22, 23].

Although is generally accepted that increasing age is associated with higher risk of bleeding there are controvers-

dial data from several reports either supporting [24, 25] or rejecting [11, 26] this association. Establishing a causal association between advanced age per se and increased risk of anticoagulant-associated bleeding is difﬁcult because age may be associated with other factors that increase the risk of bleeding, such as cognitive impairment, risk of falls, co-morbidities and polypharmacy [1, 27]. Furthermore, it has been suggested that older patients who have high-quality management of anticoagulation have the same risk of bleeding than younger patients [28, 29] Nonetheless, age has been a barrier to the use of oral anticoagulation [2, 20]. This is of concern because older patients receive the greatest absolute beneﬁt from warfarin in terms of reduction in the risk of stroke due to the high absolute risk of thromboembolic events in such patients. This undertreatment can be deleterious considering the signiﬁcant number of thromboembolic events that could be avoided [30].

A limitation of the present study was to analyse an intermediate outcome (TTR) and not a clinical outcome such as bleeding and thromboembolic complications. However, anticoagulation control based on the INR was shown to be a good predictor of clinical outcomes. A strong relationship between TTR and adverse events (haemorrhagic and thromboembolic) was observed in several studies [22, 31–36]. Jones et al. [33] showed that a reduction of 10% in the TTR was associated with signiﬁcant increases in mortality (29%) and prevalence of ischaemic stroke (10%). Combined data from the SPORTIF III and IV trials [22] showed that patients with atrial ﬁbrillation on warfarin with TTR <60% had higher rates of annual mortality (4.20%), stroke or systemic embolism events (2.10%) and major bleeding (3.85%) compared with those with TTR >75% (1.69, 1.07 and 1.58%, respectively, P<0.05 for all). Furthermore, Veeger et al. [32] demonstrated a closer relationship of bleeding and thromboembolic events with the TTR than with sporadic INRs outside the therapeutic range. As in any single -centre, another shortcoming is the potentially limited external validity. However, our ﬁndings support the generalisability of controlled trials results to the ‘real world’. In this study, we were interested in comparing young and elderly subjects. Analysis of the effect of the studied variables (such as educational level, vitamin K intake, MMSE and others) on the quality of anticoagulation control, i.e. as predictors of the TTR, will be addressed in a separate study.

Overall, the quality of anticoagulation was very good in this cohort, with a comparable TTR to those reported in international publications. A systematic review [37] found a TTR of 62.1% in anticoagulation clinics using warfarin. Most of the studies included were conducted in wealthy nations in Europe or North America. Our study provides evidence that similar results may be achieved in developing countries, despite low education levels and lower socio-economic status.

In conclusion, good-quality management of oral anticoagulation is achievable in deprived populations attending an anticoagulation clinic. Elderly patients can experience a similar proportion of TTR, despite higher levels of co-morbidities and polypharmacy. If similar compliance and vitamin K intake is achieved, similar TTR may be achieved regardless of age. Our results add evidence to the safety of such therapeutic intervention in the elderly.

Key points

- Good-quality management of oral anticoagulation is achievable in deprived populations attending an anticoagulation clinic.
- Elderly patients may experience a similar proportion of TTR.
- This seems to occur irrespective of co-morbidities, old age or polypharmacy.

Conflicts of interest

All authors have completed the Unified Competing Interest form at www.icmje.org (available on request from the corresponding author) and declare that all authors had: (i) no
financial support for the submitted work from anyone other than their employer; (ii) no financial relationships with commercial entities that might have an interest in the submitted work; (iii) no spouses, partners, children or other family/personal relationship have relationships with commercial entities that might have an interest in the submitted work; (iv) no non-financial interests or potential conflicts that may be relevant to the submitted work.

**Author contributions**

G.L.B.C.: study concept and design, acquisition of subjects and data, analysis and interpretation of data and preparation of manuscript.

D.C.F.: acquisition of subjects and data, analysis and interpretation of data and preparation of manuscript.

R.A.V.: study concept and design, statistical analysis and interpretation of data and preparation of manuscript.

M.C.V.M.: study concept and design, analysis and interpretation of data and preparation of manuscript. It is also assured that there is no one else who has contributed significantly to the work.

**References**


Impairment of kidney function and reduced quality-of-life in older people: a cross-sectional study

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Abstract

Objective: to assess the association of kidney function with quality-of-life in community-dwelling older adults aged 75 years or more in the UK.
Design: cross-sectional study.
Setting: primary care; 12 UK general practices participating in a cluster trial of health screening.
Subjects: estimated glomerular filtration rate (eGFR, ml/min/1.73 m²) using the four-variable modified diet in renal disease equation was derived in 1,195 men and 1,772 women with available bloods, these were 92% of 3,211 study participants who consented to interviews and 73% of those invited into the original cluster trial of health screening.
Main outcome measures: interviews by trained fieldworker using the Sickness Impact Profile (home management, mobility, self-care, social interaction), and the Philadelphia Geriatric Morale Scale. Higher scores imply worse quality-of-life in a given domain.


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