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Scientific Research

Elderly Disabled Patients in Oral Anticoagulation Treatment: An Evaluation of a Bioanalyst-Led Management Program Reaching an Average of 72% of Time in Therapeutic Range

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Abstract

***Introduction*: The need for anticoagulation therapy increases with age, mainly due to the increased prevalence of atrial fibrillation. Time in therapeutic range (TTR) is a marker of the quality of the therapy as TTR is inversely correlated with adverse reactions. We developed a bioanalyst-led management program for control of warfarin treatment in elderly disabled patients in their own home and maintain a high TTR. *Material and Methods*: Residents in nursing home settings were included. Visiting nurses measured INR with a point of care testing device. If INR was within Therapeutic Range (TR), the nurse dosed warfarin unaltered. If INR was out of TR, the visiting nurse contacted a specially trained bioanalyst by phone. An explanation was sought, and a new dosage plan was made. *Results*: A total of 579 patients were included; 356 females (61%). Mean age was 79.6 years. Approximately 10% were residents in nursing home settings and the rest in domiciliary care. TTR was 72%. The subtherapeutic values were 15% and supratherapeutic values 13%. In total, 139 patients died during the study period. Ten deaths could be related to possible side effects of warfarin treatment. *Conclusions*: Our results indicate that a bioanalyst-led program is**

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able to simplify anticoagulation monitoring, while maintaining INR control similar to a specialized clinic. Furthermore, we avoided hospitalizations when INR was unacceptably high by treating the patient with oral vitamin-K at home. Our findings could be helpful when planning warfarin treatment in elderly, fragile patients.

Keywords

Warfarin, INR, Time in Therapeutic Range, Elderly, Nursery Care Setting

1. Introduction

A global challenge in the years to come is the increasing age of the population. The oldest-old (>85 years) have over the past decades been the most rapidly expanding segment of the population in the developed countries [1]. Currently, more than 1.6 million Americans are nursing home residents, and of these 12% are in long-term treatment with warfarin [2]. Also, data from statistics of Denmark show that anticoagulant treatment is frequent with approximately 6 individuals in 100 in the age group 65 - 79 years being treated with warfarin or phenprocoumon; this number increases to 1 in 10 in the 80+ year-olds (data from 2012 medstat.dk).

The need for anticoagulation therapy increases with age, mainly due to the increased prevalence of atrial fibrillation [3]. In patients with atrial fibrillation, advancing age is correlated with an increased risk of stroke [3]. Oral anticoagulation (OAC) therapy with warfarin or phenprocoumon is still the most common therapy in stroke prevention in patients with atrial fibrillation or prosthetic heart valves [4] and for venous tromboembolism [5].

Time in therapeutic range (TTR) can be used as a surrogate marker of the quality of the anticoagulant therapy, as TTR is inversely correlated with adverse reactions such as bleeding or thrombosis [6]. A register-based study aimed at determining the level of INR control associated with reduced stroke and mortality [7] concluded that in warfarin-treated moderate and high risk patients ($CHADS_2$ score ≥ 2) with non-valvular atrial fibrillation only those with a TTR > 70% had a significantly reduced risk of stroke, whereas survival was significantly improved for all warfarin-treated groups with TTR > 40% compared to treatment with non-warfarin [7]. $CHADS_2$ is a risk score for stroke that counts all relevant co morbidities (congestive heart failure, hypertension, age, diabetes and previous stroke) [8]. Hence, it is important to keep TTR high as stated in previous publications [9] [10]. The need for higher TTR in elderly in OAC therapy has been shown in several recent studies [11]-[13].

Whilst warfarin has been shown to be effective, it has a narrow therapeutic window and the treatment is furthermore complicated by several drug-drug [14] and drug-food interactions [15]. Furthermore, many diseases such as simple febrile episodes influence OAC treatment [16].

To keep a high TTR and to handle the problems regarding interactions in the frail elderly, we have developed a bioanalyst-led management program for control of OAC in elderly disabled patients in Region Zealand, Denmark.

2. Material and Methods

The anticoagulation centre (AC-centre), Naestved, consists of physicians and bioanalysts with a special interest in OAC treatment. The inclusion period, of this Bioanalyst-led program, was from 1st June 2010 to 31st December 2013. Eligible patients were residents in nursing home settings in Region Zealand, Denmark, as well as patients requiring domiciliary care by a nurse. Domiciliary care consisted of a visiting nurse who helps patients still living at home with daily living, *i.e.* help with medication, assistance with personal hygiene et cetera. The patients were referred to the AC-centre by the patient's GP. Prior to study entry, informed consent was obtained from the patient or legal guardian and the GP. Indication for AC-treatment and the INR ranges were set by the referring attending physician. The AC-treatment was performed according to standardized treatment algorithms [17].

The AC-centre provided the visiting nurses with a point of care testing INR device, CoaguChek® (Roche Diagnostics, Schwitzerland). INR was measured by the nurse in the home of the patient or in the nursing home setting. Prior to entry, each nurse was trained in sampling and measuring INR by a bioanalyst from the AC-centre, and it was endeavoured to have 2 - 4 nurses at each nursing home setting to take care of the measurements. If the value obtained was within Therapeutic Range (TR), which usually is between 2 - 3 INR, the nurse was in-

structed to dose the warfarin for the next week unaltered. Afterwards, the nurse would send a fax with the plan to the AC-centre, where the bioanalysts would reply by fax with a reconfirmation of the dosage plan and a date for the next INR measurement. If the INR value was out of TR, the visiting nurse contacted a bioanalyst at the AC-centre by phone. An explanation was sought: Alteration in daily living, food, medical changes, infectious diseases, or alcohol consumption guided by a written chart with the most common conditions of INR deviations. The treatment was then adjusted by the trained bioanalyst, resulting in an individual plan for the patient's OAC treatment. If needed, the plan could include pause with warfarin or administration of Vitamin K. When a high INR value (>8) was obtained, the nurse would make sure that the patient was not bleeding, had no headache, and that the patient's condition was unaltered. The case was then conferred with a bioanalyst and a doctor at the AC-centre. In most cases, it was possible to keep the patient at home and treat with an appropriate Vitamin K dose-normally 2.5 mg. The nurse would then return to the patient later the same day to verify that the INR value was decreasing.

In case of subtherapeutic INR levels *i.e.* below 1.5 with therapeutic levels of 2.0 - 3.0 or below 2.0 with therapeutic level 2.5 - 3.5, low molecular weight heparin (LMWH) was considered. Contact to the local pharmacy was made by phone to make sure that the medication was available and that it would be delivered to the patient's home the same day. The nurse would then return to the patient to administer LMWH.

TTR was estimated by the Rosendaal method [18], which is based on the principle that two measurements are linked with a straight line. Given two following INR measurements, were the first measurement was within and the following was outside the TR, the Rosendaal method estimate the time the patient has spent in therapeutic range. The sub- and the supratherapeutic range is the proportion of that line that is either below or above the respective therapeutic level.

3. Results

A total of 579 patients were included. Initially all 17 counties in Region Zealand were invited and 13 accepted to participate. The reasons for non-participation were not further specified, but 2 counties feared that participation would need an increase in staff. All public nursing home settings in the participating 13 counties were included, giving a total of 35. Each centre had an average of 12 patients (range 1 - 56 patients).

The majority of the patients were treated with warfarin. Less than 1% was treated with phenprocoumon. The indications for OAC treatment are listed in **Table 1**, and data regarding TTR are provided in **Table 2**. The TTR was almost constant during time of study. The numbers of patients were graduately increasing from initially 18 to 239 at evaluation. Time between measurements' showed a decreasing tendency from 2.5 weeks between measurements to 2.0 weeks between measurements. The sex distribution was 356 females (61%) and 223 males (39%). Mean age was 79.6 years. TTR remained high, despite an increase in active patients from 18 to 239 and with more frequent measurements.

Approximately 10% were residents in nursing home settings, and the remaining 90% were in domiciliary care.

Of the included 579 patients, 139 patients died during the study period. Mean age at death was 81.4 years. The patient records were evaluated, when the patient were reported dead. It was considered a possible fatal adverse reaction, if the patient had a diagnosis of hemorrhage at any anatomical location or stroke on admission to hospital prior to death. The first INR value after hospitalization was recorded. Ten deaths could be related to possible side effects of warfarin treatment and of these 6 were intracranial hemorrhages (**Table 3**). Data of non fatal strokes were obtained from the national Patient Registry of Denmark (LPR) giving a total of 19, of whom

Table 1. Indications for OAC treatment.

Indication	Numbers (%)
Atrial fibrillation	401 (70)
Venous thromboembolism	70 (12)
Pulmonary thrombosis	44 (8)
Prosthetic heart valve	29 (5)
Others	35 (6)
Total	579

Table 2. Data from the study: Number of active patients in the end of each time period, time in therapeutic interval (TTR), time above (>TR) and below (<TR) therapeutic interval and the mean time between INR measurements in 12-month period. The first period (June-December 2010) consists of 7 months.

Year	2010	2011	2012	2013
Period	1	2	3	4
Numbers	18	82	154	239
TTR (%)	75	72	73	72
>TR (%)	13	13	13	15
<TR (%)	12	16	14	13
Time interval (week)	2.4	2.4	2.2	2.0

Table 3. Cause of hospitalization and INR on admission in the 10 patients, where an evaluation of the hospitalization in relation to their death provided bleeding-related diagnosis.

Patient	Age	Cause of hospitalization	INR
1	87.9	Intracerebral hemorrhage	N/A
2	88.1	Intracerebral hemorrhage	2.4
3	85.4	Intracerebral hematoma	2.5
4	80.6	Bleeding from rectum	5.8
5	82.5	Brainstem hemorrhage	5.4
6	85.0	Ventricular and enterostomy bleeding	2.2
7	86.7	Subdural hematoma	2.4
8	74.1	Gastric ulcer	3.8
9	83.0	Gastric ulcer	1.1
10	81.9	Subdural hematoma	2.9

15 patients had the atrial fibrillation.

At the end of the study, 239 patients were still active. The remaining patients (201 patients) had either stopped warfarin/phenprocoumon, shifted to other antithrombotic agents or moved out of the region.

TTR using the Rosendaal method [18] for the 239 patients active at the end of the study period was 72%. The subtherapeutic values were 15% and supratherapeutic values 13%. The results are compared to previous publications in **Table 4**.

4. Discussion

Our study was targeted frail elderly and includes both residents in nursing home settings and patients in domiciliary care *i.e.* patients who are too fragile to administer their own medication, but still living at home. In this study, we have obtained TTR comparable to or even higher than in previous studies [11] [19]-[31]. There are differences in TTR between the several studies listed in **Table 4** ranging from 48.6% - 76.7%. Our study is among the studies with the highest TTR, only surpassed by two studies. However, the comparison should not be overestimated, as there are several differences between the studies with regard to age, sex ratio and calculation of TTR.

There have been previous reports of AC-treatment in nurse or pharmacist led clinics showing a comparable high TTR as can be seen from **Table 4** [32] [33]. But in these settings, the patients attend the clinic at a weekly basis. Our approach aimed at keeping the patient at home and letting the nurses visit and monitor INR in the patients home. And our study show, that this design can obtain equally high TTR.

A continuous problem in warfarin treatment is the numerous medical and food interactions [34]. Very often the patients have numerous medical conditions, and polypharmacy is common among the elderly [35]. Beside

Table 4. Comparison of TTR between our study and previous publications.

Study	Numbers	Age, Median or Mean ±SD	TTR	% Males	Country
Our Results (Total)	579	79.6 ± 10.04	69	39	Denmark
Our Results (Active)	239	78.71 ± 9.52	72	37	Denmark
Aristotle (Granger) 21	9081	70 (Range 63 - 76)	62[1]	65	Multicenter
RE-LY (Connolly) 20	6022	71.6 ± 8.6	64[1]	63.3	Multicenter
Rocket (Patel) 29	7133	73 (Range 65 - 78)	55[1]	60.3	Multicenter
Plichart 30	2633	87.7 ± 4.4	57.9	27.1	France
Papaioannou 28	128	85.9 ± 8.0	69	25	Canada
Nelson 27	23,425	74.8 ± 9.7	67.3 ± 14.4		USA
Wieloch 31	18,391	70 ± 12	76.7	60.3	Sweden
Hassan 24	146	≥75	63.73[1]	34	USA
Gurwitz 22	490	82.3 ± 10.0	49.6[1]	30	USA
Han 23	392	72.7	56.7	25	USA
Melamed 26	906	71.7 ± 9.0	48.6	40.1	Israel
Verhovsek 11	105	83.6 (Range 54.7 - 98.0)	54.1	28	Canada
Aspinall 19	160	71 ± 11.7	55[1]	98	USA
Gallagher 10	27,458	73 ± 9.8	63	55.2	UK
McCormick 25	174	N/A	51	N/A	USA

[1]TTR is computed by the Rosendaal method.

their daily medication, elderly patients very often receive various short-term medical treatments, such as antibiotics or antifungal treatment as well as different pain relievers. In a survey of the most common drug-drug interactions leading to excessive anticoagulation, tramadol and paracetamol were involved. However, an even more frequent cause of adverse reactions was illness [36]. As the health visitor is actually at the patient's home in this program, it is possible to focus on the reason why INR is out of range. This information is then reported to the AC-centre, who takes it in account, when dosing the patients OAC treatment.

Previous studies have found preventable errors to occur in 29% of the adverse reactions, whereas 57% of severe adverse events were considered preventable [22]. The errors included monitoring and prescription, the latter including wrong warfarin dose and known drug interactions. In our study we have seen TTR similarly or perhaps even slightly improved in comparison to other studies. A part of this could be explained by an increased focus on preventable errors.

One major problem in OAC treatment is the adverse effects mainly in the form of minor bleeding episodes such as epistaxis. These adverse effects were not recorded in our study. When evaluating all causes of dead in hospitalized patients, we found that 6 patients died from intracerebral hemorrhage/hematoma. This finding is consistent with previous publications [37]. However, INR on admission was above the therapeutic interval in only one case and not measured in another case. It is impossible to determine the exact frequency of fatal adverse effects, as most of the patients were not hospitalized in relation to their death. We can only estimate that 7.2% of the causes of dead were possibly warfarin-related. A recent publication reported an incident rate of intracranial hemorrhage of 74/10,000 years in patients with warfarin treatment, compared to 5/10,000 non-warfarin treated [38]. The unadjusted hazard ratio (HR) for fatal intracranial hemorrhage was 1.64 for warfarin patients compared to non-warfarin patients. However, the HR was no longer significant after adjustment for confounding variables. In that context, it does not seem unlikely or alarming that we observe 6 fatal cases of intracranial hemorrhage in 579 patients included over 3 years. We observed at total of 15 non fatal strokes in the patients with atral fibrillation. Giving that the total number of patients treated with warfarin due to atrial fibrillation were 401 we found complications comparable with previous publications [20].

Underuse of warfarin is common. In a study of 13,289 subjects with non-valvular atrial fibrillation and a

$CHADS_2$ score ≥ 2, a total of 47% were unexposed to warfarin [39]. This finding is consistent with other papers [40]. These studies also argue that the underuse of warfarin might be due to a fear among the prescribing physicians of complications such as bleeding episodes. A review assessed this subject and found that advancing age, risk of falls and bleeding were a significant barrier to prescribing anticoagulant treatment, despite the fact that the patients may benefit from anticoagulant treatment [41]. We found that it is possible to get acceptable results with oral anticoagulant therapy in the elderly which hopefully could lead to more patients receiving warfarin treatment, by lowering the fear of complications among the prescribing physicians.

A high INR level usually leads to hospitalization. In our study, we kept the patients at home after vitamin K treatment, unless symptoms were present. This approach had numerous advantages: The vitamin K treatment is started sooner than if admitted to a hospital and admission to hospital is avoided. So far no side effects to this approach had been observed. The results are consistent with previously reports [42].

We aimed to simplify treatment with OAC in elderly disabled patients by keeping the patients at home. We conclude that this bioanalyst-led programme reveals results comparable to specialized clinics, and we have obtained these results in a group of patients with sparse or no selection at all. Thus the study describes a very true patient-like population with common indications for prescribing of OAC in the elderly. These results are therefore interesting for everyone facing the challenges of treating elderly patients with warfarin.

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