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International normalised ratio stability in patients aged 80 years and over taking warfarin for non-valvular atrial fibrillation

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ABSTRACT

Background: A large proportion of the older population with non-valvular atrial fibrillation (NVAF) receive warfarin for stroke prevention, the safety and efficacy of which is affected by the time-in-therapeutic range (TTR). This has optimum effectiveness where the mean TTR is ≥70%, whilst no survival benefit is conferred if TTR is <40%.
Objective: To assess the TTR of patients aged 80 and over with NVAF on warfarin.
Methods: A retrospective analysis was performed on patients that had utilised an intermediate care service at a London hospital over one year. Patients were on warfarin for NVAF, aged ≥80 with a minimum of six continuous months of results. The therapeutic range was defined as an international normalised ratio of ≥2 and ≤3 and the TTR was calculated for each patient.
Results: 118 patients were identified with a mean age of 86.1 (80–107). 9 (7.6%) patients were within the therapeutic range for ≥70% of the time and 31 (26.3%) patients were within the therapeutic range for <40% of the time. The mean TTR was 47.5% (standard deviation 14.4%, range 12.5–81.8%). Those with a hospital admission had a significantly lower mean TTR versus those without an admission (*p*-value = 0.013).
Conclusion: The TTR is extremely low in this cohort of patients aged 80 years and older who are on warfarin for NVAF. This exposes patients to significant risks of both bleeding and ischaemic stroke. Assessment of INR control should be carried out and consideration should be given as to whether novel oral anticoagulants should be more widely used in this population.

1. Introduction

Atrial fibrillation (AF) is the commonest arrhythmia in the older population. It causes significant morbidity and mortality and increases the risk of cardioembolic stroke five-fold compared to those in sinus rhythm [1]. Both the 2012 European Society of Cardiology and the 2014 American Heart Association/American College of Cardiology guidelines recommend patients with non-valvular AF (NVAF) are risk-stratified for stroke using the CHA_2DS_2-VASc scoring system. Those with a previous stroke, transient ischaemic attack or a CHA_2DS_2-VASc score ≥1 (or for the American guidelines ≥2) are recommended to receive stroke prevention therapy, traditionally with warfarin [2,3]. Although effective at reducing stroke risk, warfarin use can be problematic due to its complex dose-response relationship, narrow therapeutic index and multiple interactions, thus necessitating regular monitoring [4]. Additionally, the risk of stroke needs to be balanced against the haemorrhagic risk, which can be estimated using the HAS-BLED score, a major bleeding risk assessment tool validated for use in patients anticoagulated for NVAF [5]. Studies have found that in the older population the risk of major haemorrhage whilst taking warfarin is significantly increased [6].

Novel oral anticoagulant agents (NOACs) are also licensed for stroke prevention in NVAF with a comparable bleeding risk profile to warfarin, though their more predictable pharmacodynamics negate the need for regular monitoring [7].

The safety and efficacy of warfarin for stroke prevention is reflected by the time-in-therapeutic range (TTR) [8]. For NVAF, an international normalised ratio (INR) range of 2–3 is accepted as therapeutic with an increased risk of either ischaemic events if <2 or bleeding if >3 [9]. A systematic review and meta-analysis of 21 studies of patients taking warfarin for NVAF demonstrated an

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INR < 2, compared with an INR ≥ 2, was associated with an odds ratio for ischaemic events of 5.07. An INR > 3, compared with an INR ≤ 3, was associated with an odds ratio for bleeding events of 3.215 [10].

Current evidence suggests that stroke prevention with warfarin has optimum effectiveness where mean TTR is ≥70% [3,7]. This is supported by evidence that patients with a TTR ≥ 70% have a significantly reduced risk of stroke, and that those with a TTR < 40% show no survival benefit over patients with NVAF who are not treated with warfarin [11]. Having a TTR < 60% has been shown to be associated with higher rates of mortality (4.2%) and major bleeding rates (3.85%) compared to those with both a TTR of 60–75% (1.84% and 1.96% respectively) and TTR > 75% (1.69% and 1.58%, $p < 0.01$) [8]. Furthermore, a 2006 multi-centre study found no difference in relative risk for vascular events between those taking warfarin and those taking aspirin plus clopidogrel if the mean TTR was <65% [12]. For patients with TTR > 65%, warfarin reduced the risk of vascular events by more than two-fold.

The National Institute for Health and Care Excellence (England) advises that a TTR < 65% constitutes poor anticoagulation control and the HAS-BLED score defines a labile INR as a TTR < 60% [5,13].

There is limited data available on INR control in those aged 80 years and over, despite the high burden of AF in this age group. We hypothesised that a large number of patients aged 80 and over do not have adequate INR control and therefore may be at greater risk than benefit from warfarin therapy. Our primary objective was to determine what proportion of 80 year olds and above with NVAF have a TTR which is sufficient to achieve effective stroke prevention whilst minimising the risk of bleeding. Secondary aims were to examine whether gender or number of hospital admissions affected TTR in this population.

2. Methods

2.1. Study design

A retrospective analysis was performed on all patients that had previously utilised an intermediate care service at a London district general hospital in a one year period from 1st March 2014 to 28th February 2015. The intermediate care service aims to avoid hospital admissions by reviewing patients either at home, after referral from their General Practitioners, or in Accident and Emergency to facilitate their safe discharge. All patients that had an INR on the results reporting system, used by the hospital and many of the local GP surgeries, within the time frame were selected. Diagnosis of AF and prescription of warfarin were confirmed by viewing hospital discharge letters or outpatient clinic letters. To meet inclusion criteria patients had to be on warfarin treatment for NVAF within the study period, aged 80 years or older with a minimum of six continuous months of INR results whilst on warfarin. An interval between INRs of up to two months was permitted, to ensure those who required less frequent monitoring due to adequate control were included. Patients with a concurrent diagnosis requiring anticoagulation, such as a deep vein thrombosis or pulmonary embolism, were excluded.

INR results in the 1 year period between 1st March 2014 and 28th February 2015 were recorded. Exceptions to data collection between these dates were: if the patient turned 80 during the study period, if warfarin had been newly commenced or permanently stopped, if the patient had died or if for some other reason the patient's INR results no longer were available e.g. the patient had moved out of area. In all of these cases the time frame of extracted INR results was shifted to accommodate a minimum of 6 months, up to a full 12 months of data collection. Where warfarin had been permanently stopped, the patient had died or continuous INR results were no longer available, then up to 12 months prior to the last INR whilst on warfarin were extracted. To ascertain whether admission to hospital had an effect on INR control, the number and duration of local hospital admissions for each patient was recorded for the 1 year period prior to the date of the patient's last INR result collected for this study.

2.2. Data analysis

INR results for each patient were reviewed. The therapeutic range was defined as an INR of ≥2 and ≤3 [10]. For each patient the percentage of readings that were sub-therapeutic (<2), in therapeutic range (≥2 and ≤3), and out of range (>3) were calculated. Hence TTR was calculated using one of the validated methods recommended by NICE, which is the proportion of INR results in range. Those patients who had sufficiently controlled INR, defined as a TTR ≥ 70%, were identified. The number of patients with a TTR ≥ 65% as well the number with a TTR ≥ 60% were also identified, to allow for the variation in the definition of adequate INR control within different guidelines [14,15]. The number of patients with a TTR < 40% were also identified as there is no survival benefit once the TTR is <40% versus no warfarin [11].

2.3. Statistical analysis

Descriptive statistics were calculated including the mean of the individual TTRs for different subsets. The two-tailed *T*-test was used to test for differences in the mean TTR between genders and also between those that had been admitted to hospital and those that had not. Pearson's product-moment correlation coefficient was used to test for an association between the number of hospital admissions and mean TTR.

Microsoft Excel 14.5.8 (151023) and IBM-SPSS.23 were used to conduct data analysis.

3. Results

3.1. Patient characteristics

535 patients over 80 years of age who had an INR test sent within the 1 year time period were screened. 309 were not taking warfarin for any reason, 61 were excluded for not having minimum of six continuous months of INR results and 47 were excluded as they were taking warfarin for other reasons. This left a cohort of 118 patients of whom 70 (59.3%) were female. Mean age was 86.1 (range 80–107); 86.7 (range 80–107) among females and 85.3 (range 80–92) among males. A total of 3645 INR results were recorded with a mean of 30.9 INRs per patient (11–80). 25 (21.2%) patients had less than 12, but at least 6 continuous months of INR results, with the overall mean duration of results being 11.2 months (range 6–12 months).

3.2. Time in therapeutic range

Only 9 (7.6%) patients were within the therapeutic range for ≥70% of the time and 31 (26.3%) patients were within the therapeutic range for <40% of the time. Table 1 displays the number of patients achieving the different TTRs recommended by the different guidelines.

The mean TTR was 47.5% (standard deviation 14.4%, range 12.5–81.8%). There was no significant difference between males and females for mean TTR (mean difference 5.18%, *p*-value = 0.055).