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CLINICAL STUDY

Traditional thromboprophylaxis in elderlies with atrial fibrillation: What we can achieve in real life

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ABSTRACT
OBJECTIVES: To investigate real-world data on warfarinisation rates and results in the elderly patients with atrial fibrillation (AF).
BACKGROUND: AF is the most frequent arrhythmia in the elderlies with considerable risk of devastating stroke-related consequences. Guidelines prefer non-vitamin K antagonist oral anticoagulants (NOAC) to warfarin for thromboprophylaxis. Nevertheless, warfarin is still widely used, even if it is challenging, especially in polymorbid elderlies, to achieve the therapeutic international normalised ratio (INR). There are only scarce real-world data on INR in warfarinised elderly AF patients.
METHODS: The study was based on multicentric observational Slovak audit of atrial fibrillation in seniors (SAFIS) performed on 4,252 hospitalised AF patients aged over 64 years (mean age 80.9 yrs.). INR data from warfarinised patients were analysed (955 at admission and 870 at discharge).
RESULTS: At hospital admission and discharge, the warfarin medication rates were 22.6 % and 23.5 %, respectively, INR lower than 2 was present in 41.8 % and 30.6 % of patients, respectively, and INR higher than 3 was in 27.0 % and 7.7 %, respectively and altogether, 68.8 % and 38.3 % of warfarinised patients, respectively, were out of therapeutic range.
CONCLUSION: Warfarin is still frequently used in the elderlies with AF, but the success rates are unsatisfactory in a huge number of patients. It is urgent to improve seniors' access to NOAC *(Fig. 2, Ref. 34)*. Text in PDF *www.elis.sk.*
KEYWORDS: atrial fibrillation, geriatrics, thromboprophylaxis, warfarin, NOAC.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia among the elderly people (1) and is associated with the risk of many unfavourable consequences. Among them, the cardio-embolic stroke is the main adverse outcome. There are well-defined possibilities as to how to mitigate this risk, while pharmacological thromboprophylaxis is its cornerstone. Nowadays, it can be pursued mainly by warfarin (dominant representative of vitamin K antagonists [VKA] in most Western countries) and non-vitamin K antagonist oral anticoagulants (NOAC). Current guidelines prefer NOAC to warfarin (2). There are many good reasons for that, mainly because NOACs are safer than warfarin, and in general they have a favourable efficacy/safety profile, i.e. also in the elderly population (3). Warfarin, on the other hand, is not efficient in achieving the effective long-term anticoagulation (time in therapeutic range [TTR] of at least 65 %), mainly because it interacts with many drugs and foods and patients poorly adhere to therapy. Hence, NOACs provide the convenience of eliminating the necessity of never-ending laboratory testing.

On the other hand, due to a long tradition, there is a lot of experience with warfarin treatment (4, 5) and there are still some clinical conditions under which warfarin is the thromboprophylactic drug of choice (typically moderate-to-severe mitral stenosis or mechanical heart valves). The positive effect of warfarin is attenuated, but still present even if we account for competing death events (6). According to the nationwide Danish registry, the initial treatment with warfarin in AF patients increased steadily by nearly three-fold (from 14 % up to 40 %) between 1996 and 2004, and thereafter stayed stable in the range of 35–40 % (7). VKA were by far the most frequently prescribed anticoagulants in Europe even in the years 2012–2013 (8). During subsequent 3-year follow up, a change from VKA to NOAC occurred only in 5.4 % of patient visits, while the reverse change (from NOAC to VKA), surprisingly, occurred in 8.6 % (9). Unfortunately, as NOACs are substantially more expensive than warfarin, the main reason why warfarin is still so frequently used are administrative barriers limiting the access to NOAC with the aim of attenuating the abrupt cost increase. It is accepted that warfarin therapy re-

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duces the risk of ischaemic stroke with an accepted benefit / risk ratio only if international normalised ratio (INR) values are in the therapeutic interval of 2–3. Anticoagulation effectiveness is estimated in acute settings with a single INR measurement or, over a longer time period, by calculating the TTR. The real-world data on INR in warfarinised elderly patients with AF are scarce. In the Slovak audit of atrial fibrillation in seniors (SAFIS), we analysed, among other parameters examined at admission and discharge, the rate of warfarinisation and INR in patients over 64 years of age and suffering from AF.

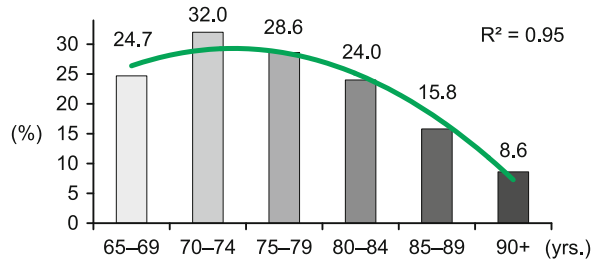

Fig. 1. Warfarin medication at admission (%) and age. Differences 65–69 / 70–74 yrs: p = 0.03; 65–84 / 85+ yrs: < 0.001.

Subjects and methods

Data on INR and other parameters were collected in the SAFIS study which is a multicentric observational study in all AF patients older than 64 years and discharged between 1 August 2012 and 30 June 2015. The study was performed in three phases, namely in time periods of 1.8.2012–31.7.2013, 1.8.2013–31.7.2014, and 1.1.2015–30.6.2015. The data were gathered from four different types of health care facilities (university hospital providing acute care, faculty hospital providing mainly acute care and district hospital providing mainly long-term care for seniors) providing care in different regions in Slovakia (4,252 patients; mean age of 80.9 yrs,; 59.9 % of patients were women). We analysed 122 primary parameters, including 36 comorbidities in each patient (a simple quantitative comorbidity index was created by counting the presence of 23 selected diseases). Patients were divided into age groups as follows: 65–69, 70–74, 75–79, 80–84, 85–89, and 90+ years. The mean length of hospital stay was 11.3 days (the first and last day of hospitalisation was counted as two days) and decreased during the study from 11.6 days in phase I to 10.7 days in phase III. The INR value at discharge was defined as the last INR value which was estimated during the hospital stay. The study design is described in detail elsewhere (10). Among those 4,252 patients, the information on warfarin treatment was known in 961 (22.6 %) patients at admission. Out of latter patients, 955 had their INR estimated at admission. Warfarin was recommended to 870 patients at discharge. The data were analysed using routine statistical methods (means, standard deviation (SD), proportion, chi-square test, unpaired T-test, and odds ratio [OR]; p value of ≤ 0.05 was considered statistically significant).

Results

Warfarin / INR at admission

The warfarin medication rate at admission was 22.6 %. There was no significant gender difference. The rate declined during the study (phase I, II, III: 24.4–23.4–18.5 %; significant differences: I vs III – p < 0.001, II vs III – p = 0.005) and with age (Fig. 1). The mean INR at admission was 2.72 (in range of 0.89–22.3; SD 1.28), without important gender or age group differences. Those who were discharged from hospitalisation had a lower mean INR value at admission compared with those who deceased (2.67 vs 3.50; p = 0.04). INR < 2 was present in 399 warfarinised patients (41.8 %; without significant gender difference) at admission. This was the case in 41.2 % and 50.0 % in elderlies living at home and in nursing homes, respectively; p > 0.05. There was an insignificant tendency towards an increase in the percentage of those with INR < 2 with age (from 38.1 % in 65–69 yrs. old up to 46.7 % in 85–89 yrs. old). INR > 3 was present in 258 warfarinised patients (27.0 %; without significant gender difference) at admission (in 25.8 % of survivors and 43.8 % of deceased; p = 0.002; OR 2.24, 95 % confidence interval: 1.33–3.75). Altogether 68.8 % of warfarinised AF patients were out of the therapeutic range (INR outside 2.0–3.0) at admission.

Warfarin / INR at discharge

The warfarin medication rate at discharge was 23.5 %, without a significant gender difference, with a decline during the study (phase I, II, III: 24.7–24.1–19.9 %; significant differences: I vs III – p = 0001, II vs III – p = 0.03) and with age (Fig. 2). Warfarin was recommended for 25.9 % at home-living elderlies and for 8.1 % in nursing home-living seniors (p < 0.001). The mean INR at discharge was 2.24 (in a range of 0.98–5.58; SD 0.63), without important gender difference and differences between age groups. INR < 2 was present in 266 warfarinised patients (30.6 %; without a significant gender difference) at discharge. This was the case in 30.0 % at home-living elderlies and in 41.5 % in nursing home-living seniors (p > 0.05). There was an increase of the INR < 2 share beyond the age of 89 yrs. (65-89 yrs.: 24.4–29.0 % and 90+ yrs.: 58.3 %; p = 0.003) and during the study (phase I vs III = 26.2 and 36.6 %, p = 0.02). INR > 3 was present in 67 warfarinised patients (7.7 %; without a significant gender difference)

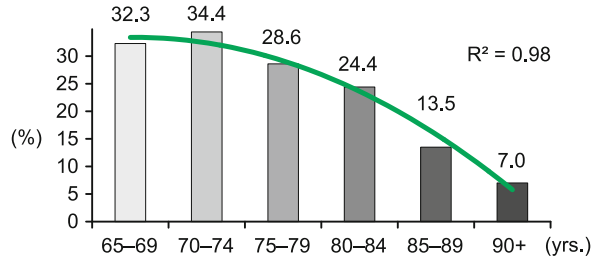

Fig. 2. Warfarin medication at discharge (%) and age. Differences 65–74 (33.7 %) / 75–84 (26.2 %) yrs: p < 0.001; 65–84 (28.4 %) / 85+ (11.5 %).

at discharge. Altogether 38.3 % of warfarinised AF patients were out of the therapeutic range (INR outside 2.0–3.0) at discharge.

Discussion

With current guidelines (2) in mind, our study has proved warfarin medication rates to be inappropriately high, both at admission and at discharge (22.6 % and 23.5 %, respectively). One reason for these rates is that at the beginning of the SAFIS study (year 2012), the marketing of NOAC just started to mount in Slovakia. This is mirrored by an impressive decline of warfarinisation rates during the three years of the study. Another reason is that AF patients with some comorbidities should be treated with warfarin, rather than with NOAC (e.g. mitral stenosis was present in 3.1 % of SAFIS patients). It could be questioned why the warfarin recommendation rate did not decrease more during the hospital stay. Beside the two above-mentioned factors, we have also to think about the power of tradition in medicine and the reimbursement barriers set up for NOAC by public health insurance. To our knowledge, the study most comparable to SAFIS was that carried out in Italy on 980 patients aged over 65 years (mean age of 83 years) hospitalised at an acute geriatric department with AF in 2010–2013). In this study, 38 % of patients were warfarinised (11). A little later, these authors (12) found the warfarinisation rate to be 45 % at discharge among 452 AF patients at mean age of 82 years (hospitalised at acute medical and geriatric departments in 2013–2014), while warfarin was the leading oral anticoagulant (prescribed in 85 % of patients on oral anticoagulation). In Israel, warfarin was recommended in 17.4 % and NOAC in 25.0 % of 11,760 patients first diagnosed with AF at age over 74 in years 2013–2015 (13). In Canada (14), warfarin was the most commonly used anticoagulant (58 % of anticoagulated outpatients with median age of 78 years) in 2013. In Denmark, only 11.5 % out of 7,276 AF patients on VKA (mean age of 76 years.) switched to NOAC over 16 months in years 2011/2012 (15) and only 29.6 % of 62,065 patients did so over a longer period of 52 months between 2011–2015 while subjects who were shifted from a VKA to NOAC were more likely to be younger (16). Even in the years 2011–2016, VKAs were the choice in 38.5 % of AF patients in whom oral anticoagulant therapy was initiated (17).

As a rule, AF in seniors is accompanied by many other serious chronic diseases (18, 19, 20). However, none of them have a specific association with AF (21). Polymorbidity, which is characteristic for advanced age, independently worsens the quality of warfarinisation (22). In geriatrics, there is always an important disparity between those living at home and in nursing homes—with worse state of health in the latter (23). We have seen the tendency to a more expressed warfarin undertreatment (INR < 2) in incoming AF seniors who lived in nursing homes (50.0 %) compared with those living at home (41.2 %). This can signalise the physician´s concern about bleeding in frail and more polymorbid seniors and explain greater vigilance over warfarin dosage. Our comorbidity index in seniors living at home and in nursing homes was 5.40 and 6.08, respectively ($p < 0.001$). The same concern is probably in the background of an important difference in the frequency with which warfarin was recommended to those living at home and in nursing homes (25.9 vs 8.1 %) at discharge. Such a concern in the course of AF management in the elderly patients can be quite complex (24). It is known that insufficient anticoagulation is not thromboprotective enough but still bears the risk of major bleeding also in elderlies (25). In Japanese warfarinised AF outpatients, INR lower than 2 was present in 63.5 % of those aged 70–84 yrs. and in 67.7 % of those aged over 84 yrs. (26). During warfarin treatment, the INR of very old people was even lower (mean INR of 1.76) while TTR in VKA-treated nonagenarians was 29.5 % (27). In our patients, the overtreatment at admission (INR > 3) was frequent as well (27 %). In Japan, the proportion of warfarinised AF patients with INR over 3 was much lower, namely 2.6 % of those aged 70–84 yrs. and 3.8 % of those older than 84 yrs. (26).

Altogether two-thirds (68.8 %) of warfarinised patients were out of the therapeutic range at admission. There can be two main reasons for this unsatisfactory finding. The first one is the well-known multifactorial difficulty with chronic warfarin dose adjustment which is especially expressed in seniors. The second one may be attributed to the acute medical condition which leads to hospital admission and can worsen the anticoagulation control. Our findings match those reported by Turkish research (28) where the effective INR was achieved in 38 % of cardiology out-patients (n = 233; age ≥ 75 yrs.; mean age of 80 yrs.). In the RE-LY registry (29) which maintains 15,400 AF patients (mean age 65.9 yrs.) reported by visiting emergency departments in 46 countries in years 2008–2011the proportion of INR values between 2 and 3 was 59 % while in the Eastern Europe, (2,542 patients; mean age 69.3 yrs.) the mean TTR is 56.0 %, and overall mean TTR is 48.6 %. The share of warfarinised Japanese AF outpatients (26) with INR in range of 2–3 was 33.9 % in 70–84 year-old subjects and 28.5 % in those older than 84 yrs. An analysis of a large general practitioners' database revealed that TTR over 70 % in selected AF patients on VKA with sufficient INR data (mean age of 71.7–74.4 yrs.), namely from France, Germany, Italy and the United Kingdom was found in 47.8 %, 44.2 %, 46.1 % and 65.4 %, respectively (30). In a large Israeli study (13), the value of TTR ≥ 60 % was observed only in 20.0 % of 75–84 year-old patients and in 15.5 % of patients over 84 years. Out of 4,772 AF patients maintained in the Danish registry, 65.6 % had the value of TTR below 70 % while among patients with prior value of TTR ≥ 70 %, there was only a proportion of 55.7 % who yielded the same value during the following year (31). Even in anticoagulation clinics (5,707 patients on VKA; mean age of 73 yrs.) with an intensive follow-up (i.e. time between two INR measurements was 19 days in average), the median value of TTR was 66 % (21 % and 9 % of time was spent below and above the 2.0–3.0 INR range, respectively). These TTR results were not better when they were compared with a similar study conducted 20 years earlier, but they were achieved in comparable settings in patients older by 9.4 years, which corresponds with the ageing of the population (32).

Our results also suggest that higher INR values at admission could be a marker of the unfavourable *quoad vitam* prognosis in hospitalised elderly AF patients (OR 2.24 for INR > 3). We assume that this is not due to an increased rate of haemorrhagic compli-

cations, but rather brought about by a more complicated state of general health, which is reflected in worse INR control (this idea is not supported directly by our complex quantitative comorbidity index which did not differ significantly in warfarinised patients with INR ≤ 3 and > 3 at admission, but these patients differ in their rate of immobility, which was 8.6 % vs 14.0 %; p = 0.01).

Our study showed that during their hospital stay, the warfarinised patients had a decrease in the frequency of inappropriate INR rates lower than 2 and higher than 3, namely from 41.8 % to 30.6 % and from 27.0 % to 7.7 %, respectively. Nevertheless, these data can be also interpreted as a finding that despite the achieved decline there was a large share of warfarinised AF patients who were discharged with INR out of the therapeutic range (38.3 %). One can explain this with the relatively short duration of the hospital stay, but the management of seniors outside the hospital is even more complicated due to many reasons such as that immobility and dementia at admission was present in 10.1 % and 12.7 % of warfarinised patients, respectively, especially if more INR controls and subsequent warfarin therapy adjustments are necessary.

Therefore, we must see to a lot of chances for further improvements in anticoagulation adjustment in warfarinised AF elderly patients. One possibility is to reduce the warfarin use to those patients for whom there is a clear evidence-based medical (EBM) indication for its use. The best EBM experience is included in current international guidelines. Unfortunately, real-world prescribing regulations add some other conditions which are not listed in the guidelines. We understand that this discrepancy between EBM and real life is due to the decisions of various authorities with the aim of controlling the abrupt direct pharmacy cost increase, but the trend to cope more closely with EBM must be seen. It is useful to underline that total health care costs in AF patients are lower in the NOAC group compared with patients on warfarin (as was proved also in a large recent study with 21,493 AF patients at mean age of 74 yrs: median costs were lower by 12 % and annually by $ 4,122 (33)).

We firmly believe that the age beyond 65 yrs is not a homogenous period of life. Therefore, we are offering data on warfarin medication rates in hospitalised elderly AF patients per five-year age intervals. To out best knowledge, such detailed data from larger cohorts have not been published so far. We found an important and continuous decline in warfarin usage after the age of 74 yrs, which can reflect a more intensive concern about the increasing risk of complications with advancing age. Nevertheless, in our warfarinised patients, age itself did not influence INR values either at admission or at discharge. Comparable age dynamics were described from the registry of British general practitioners (34): there were 57 % of warfarinised AF patients aged 60–69 yrs, and 55 % aged 70–79 yrs, but only in 32 % in over 80 years old. The markedly higher proportion of warfarinisation, when compared with our study, can be explained with the timing of the British study: NOACs were not a real warfarin alternative in the study years 2000–2009 because dabigatran was freshly introduced into clinical practice as the first NOAC in 2008.

We conclude that AF is predominantly a disease of the elderly patients and can lead to devastating consequences. The still frequently used traditional warfarin thromboprophylaxis is ineffective in a huge number of patients. Therefore, the financially based restriction of the access to a more effective (NOAC) treatment could be seen as another example of ageism which should be unacceptable in modern societies.

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