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Original Article

Temporal trends of time in therapeutic range and incidence of cardiovascular events in patients with non-valvular atrial fibrillation

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ABSTRACT

Background: Optimal time in therapeutic range (TTR) of vitamin K antagonists (VKAs) is crucial for cardiovascular events (CVEs) prevention in non-valvular atrial fibrillation (NVAF). The relationship between temporal changes of TTR and the incidence of CVEs has been poorly investigated. We investigated 1) temporal trends of TTR in a long-term follow-up of NVAF patients; 2) the incidence of CVEs according to changes of TTR.

Methods: Prospective observational study including 1341 NVAF outpatients (mean age 73.5 years, 42.5% male) starting VKAs. Patients were divided into 4 groups: Group 0: Optimal TTR, consistently ≥70% (n = 241); Group 1: Temporally worsening TTR, from above to below 70% (n = 263); Group 2: Temporally improving TTR, from below to above 70% (n = 270); Group 3: Suboptimal TTR, consistently < 70% (n = 567).

Results: In a mean follow-up of 37.7 months (4214.2 patient-years), 108 CVEs occurred (2.6%/year). Survival analysis showed a graded increased risk of CVEs in relation to temporal changes in TTR, with the worst outcomes in Groups 1 and 3 (log-rank test p = 0.013). Multivariable Cox proportional hazards regression analysis showed that Group 1 vs. 0 (HR: 2.096; 95%CI 1.061–4.139, p = 0.033), Group 3 vs. 0 (HR: 2.292; 95%CI 1.205–4.361, p = 0.011), CHA_2DS_2VASc score (HR:1.316; 95%CI 1.153–1.501, p < 0.001) and PPIs (HR:0.453; 95%CI 0.285–0.721, p = 0.001) were independently associated with CVEs.

Conclusion: A decrease of TTR < 70% over time is observed in almost 20% of NVAF patients. Patients with worsening TTR temporally (ie. from initially above 70% to below 70%) have similar risk of CVEs of patients with consistently suboptimal anticoagulation.

1. Introduction

Non-valvular atrial fibrillation (NVAF) is associated to an increased risk of thromboembolic and cardiovascular events (CVEs) [1]. Oral anticoagulation with vitamin K antagonists (VKAs) is effective for the prevention of ischemic complications, but its efficacy is highly dependent on the quality of anticoagulation control [2–4]. Of note, an inadequate therapeutic anticoagulation remains a main cause of ischemic stroke and mortality in NVAF patients [5–7].

The time in therapeutic range (TTR) of the International Normalized Ratio (INR) and the percentage of INR in range have been proposed as reliable tools to assess the quality of anticoagulation control with VKA therapy [4,8]. A TTR ≥70% is associated with the most favourable net clinical benefit for NVAF patients, with the lowest rate of ischemic and bleeding complications [9]. Indeed, a TTR ≥70% is considered as the gold-standard for VKA-treatment and is recommended for all NVAF patients [10]. Nevertheless, a high proportion of NVAF patients (up to 50% [7]) is unable to achieve a TTR ≥70%, thus having suboptimal thromboprophylaxis and being exposed to an increased risk of thromboembolism [11]. Various characteristics of NVAF patients who are likely to have a low TTR while on VKAs have been described, and include younger age (< 60 years), cardiovascular comorbidities, smoking habit, non-white race, interacting drugs and female sex [12]. In addition, many NVAF patients stop anticoagulant therapy over time

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[13,14], and treatment cessation is a risk factor for CVEs and mortality [6,15]. Clearly, adherence and persistence with well managed NVAF therapy is crucial [16].

Nevertheless, few patients receiving long-term treatment with VKAs anticoagulants remain in a "static" clinical state over time, as most would change drug therapies, develop comorbidities and experience hospitalisations for several different reasons, such as elective surgery or acute infections. As a consequence, the quality of anticoagulation may also change and patients that were initially stable may show a worsening of TTR over time. However, factors associated to temporal changes (i.e. improvement/worsening) of TTR over time have never been previously reported.

The aims of the present study in a cohort of NVAF patients starting therapy with VKAs were as follows: (i) to report the proportion of NVAF patients with worsening TTR (i.e. from ≥ to < 70%) and to investigate their clinical characteristics, and (ii) to investigate the relationship between temporal changes of TTR and the incidence of CVEs over a long-term follow-up.

2. Methods

We included consecutive NVAF patients who were referred to the outpatient Atherothrombosis Centre of the Department of Internal Medicine and Medical Specialties from January 2009 to January 2015 with at least 2 consecutive years of anticoagulation with VKAs (last follow-up visit completed in January 2017). Before entering the study, each patient provided written informed consent. The study protocol was approved by the local ethical board of Sapienza-University of Rome (n° 1306/2007) and was conducted according to principles of the Declaration of Helsinki.

At baseline, a complete work-up of patients included assessment of co-morbidities and concomitant treatments, as previously described [17]. In addition, each patient received personalized counselling from a medical doctor of the centre about the meaning of being on NVAF, the importance of anticoagulation treatment and adherence to VKA therapy.

We excluded patients with mechanical heart prosthetic valve, severe mitral stenosis and patients with a life expectancy < 2 years (i.e. those with active cancer or liver cirrhosis).

After inclusion, all patients were followed for the occurrence of CVEs. All patients were asked to provide the discharge summary after a hospitalisation or results from instrumental examinations or blood tests when performed. Patients missing more than one INR check were contacted directly or through relatives or general practitioner to assess their clinical condition.

Cardiovascular events (CVEs) including ischemic fatal/non-fatal ischemic stroke and myocardial infarction (MI), cardiac revascularization (stent placement or coronary artery bypass), and cardiovascular death were recorded prospectively [17]. Only the first CVE was used to estimate relative incidence rate in each group of TTR.

2.1. Time in therapeutic range (TTR)

The TTR was calculated using the method described by Rosendaal [18], which uses linear interpolation of INR values to assign to each follow-up day a value of INR. Thus, the percentage of days that the INR was in the therapeutic range was calculated for each patient.

Each TTR was calculated over a period of 1 year (i.e. 1st January 2009 to 31st December 2009) with a computerized clinical decision support system (PARMA program, Instrumentation Laboratory SpA, Milan). All years with at least 6 months of continuous VKA therapy were considered for the analysis. Only patients with at least ≥2 consecutive years of uninterrupted therapy with VKA were included for the analysis. Patients who received therapy with VKA for ≤1 year, those already on VKA at entry, or presenting with interruptions > 30 days were excluded. The calculation of TTR stopped when a CVE occurred.

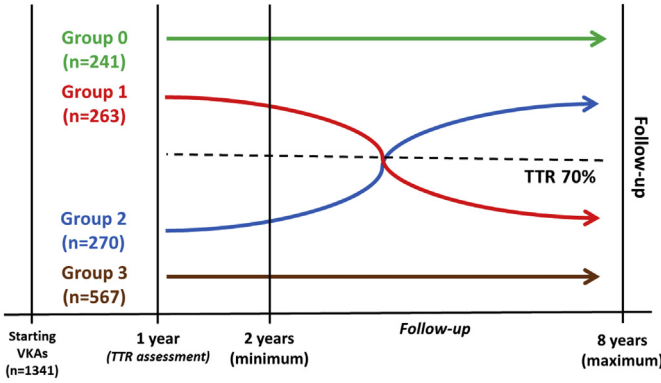

Fig. 1. Study design. After the first year of anticoagulation, the Time in Therapeutic Range (TTR) was calculated. Then patients were divided into four groups according to temporal trends of TTR.

The first value of TTR (computed on the first year of treatment, Fig. 1) was used to define the starting value of TTR, such as < 70% or ≥ 70%. The choice of grouping patients after the first year of treatment was made to avoid possible confounding due to the inception period, which was shown to be associated to a lower TTR [19].

Thereafter, patients were assigned to one of the following groups according to changes of TTR from year to year (Fig. 1): Group 0: Optimal TTR, consistently ≥70% (n = 241); Group 1: Temporally worsening TTR, from above to below 70% (n = 263); Group 2: Temporally improving TTR, from below to above 70% (n = 270); and Group 3: Suboptimal, TTR consistently < 70% (n = 567).

For patients with longer follow-up (i.e. ≥3 annual values of TTR), an improvement or a worsening of TTR was defined as TTR ≥70% or < 70%, respectively in two consecutive years. Patients presenting with *unstable* TTR, i.e. passing above and below 70% repeatedly so that a clear temporal trend was not identifiable, were excluded from the study (n = 153).

2.2. Statistical analysis

Categorical variables were reported as counts (percentage), continuous variables were expressed as mean ± standard deviation or median and interquartile range depending on their distribution. Pearson Chi-Square was used to compare proportions and ANOVA test with post-hoc LSD correction was used to compare means among groups. Medians were compared by using Mann-Whitney and Kruskal-Wallis tests.

Stepwise logistic regression analysis was used to investigate odds ratio (OR) for clinical characteristics compared to patients from Group 1. The cumulative incidence of CVEs was estimated using a Kaplan–Meier product-limit estimator, and survival curves were formally compared using the log-rank test. Cox's proportional hazards regression analysis was used to calculate the adjusted relative hazard ratios (HR) of CVEs by each clinical variable (Group 0 was used as reference group). Multivariate model was adjusted for CHA_2DS_2-VASc score, persistent/permanent NVAF (vs. paroxysmal), antiplatelet drugs, proton-pump inhibitors (PPIs), lipid-lowering agents, smoking, verapamil, amiodarone, angiotensin-converting-enzyme (ACE) inhibitors/sartans and beta-blockers. All tests were two-tailed and analyses were performed using computer software packages (SPSS-18.0, SPSS Inc.). Only p values < 0.05 were considered as statistically significant.

3. Results

Of the 2006 NVAF patients referring to the anticoagulation clinic, we excluded 512 patients as being already on VKAs at entry, and 153 for unstable TTR. Thus, the final cohort was composed of 1341 NVAF