Temporal trends of time in therapeutic range and cardiovascular outcomes in atrial fibrillation patients.

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Abstract

Background

Methods

Results

Conclusions

Keywords
**Introduction**

Atrial fibrillation (AF) 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 strictly dependent on the intensity of anticoagulant treatment and on the quality of VKA-therapy(2) (connolly circulation 2008 18955670). Indeed, an inadequate therapeutic anticoagulation remains a main cause of ischemic stroke in AF patients (jama 2017 28291892)

The time in therapeutic range (TiTR) of International Normalized Ratio (INR) and the percentage of INR in range have been proposed as reliable tools to assess the quality of VKA therapy (10.1016/j.cjca.2015.10.029, wan 20031794). In particular, a TiTR >70% was shown to be associated with the most favourable net clinical benefit for AF patients, as it is associated to the lowest rate of ischemic and bleeding complications(3). Indeed, a TiTR >70% is actually considered as gold-standard for VKA-treatment, and is warranted for all AF patients(4). Nevertheless, previous studies showed that a high proportion of AF patients is unable to achieve a TiTR >70%, remaining with a suboptimal thromboprophylaxis therapy and thus exposed to an increased risk of thromboembolic events (Garfield 27792741 ). Characteristics of AF patients who are likely to have a low TiTR when starting VKAs have been described, and include younger age (<60 years), more than two cardiovascular comorbidities, smoking habit, non-white race, rhythm control strategy and female sex (5). In addition to this, a significant number of AF patients stop anticoagulant therapy over time(6), and cessation of VKA was shown to be a risk factor for CVEs and mortality(7).

Another issue with patients receiving long-term treatment with VKAs anticoagulants is that very few patients remain stable over time, as most of them frequently change drugs, develop comorbidities and experience hospitalisation for several different reasons, such as elective surgery or acute infections. As a consequence, the quality of anticoagulation may also change and patients that are initially stable, may show a worsening of TiTR over time. However, factors associated to changes (i.e. worsening) of TiTR over time have never been reported.
Aims of the study were 1) to estimate proportion of AF patients with worsening TiTR (i.e. from ≥ to <70%) and to investigate their clinical characteristics, and 2) to compare incidence rates of CVEs according to modifications of TiTR in a large cohort of patients starting therapy with VKAs for thromboprophylaxis of non-valvular AF in an anticoagulation clinic.

Methods

Consecutive patients with non-valvular AF who were referred to the outpatient Anticoagulation Clinic 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) were included.

At baseline, a complete work-up of patients included assessment of co-morbidities and concomitant treatments, as previously described (unrefereed). In addition, each patient received a personalized counselling from a medical doctor of the centre about the meaning of being on AF, the importance of anticoagulation and modality of VKA therapy.

During follow-up, 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 healthy conditions.

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 (unrefereed). Only the first CVE was used to estimate relative incidence rate in each group of TiTR.

Time in Therapeutic Range (TiTR)

The TiTR was calculated with the method described by Rosendaal(8), which uses linear interpolation of INR values to assign to each follow-up day a value of INR. Then, the percentage of days that the INR was in the therapeutic range was calculated for each patient.
Each TiTR 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). 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, or those presenting with interruptions >30 days were excluded. The calculation of TiTR was stopped when a CVE occurred.

For the analysis, patients were divided into four according to the modification of TiTR over time. In particular, the first value of TTR was used to define the starting value of TiTR, such as <70% or ≥70%; then the patients were assigned to one of the following groups (figure 1): group 0: patients remaining with a stable TiTR ≥70%; group 1: patients passing from above to below 70% of TTR; group 2: patients passing from below to above 70% of TiTR; group 3: patients remaining with a stable TTR <70% of TTR during follow-up. For patients with long follow-up (i.e. ≥3 annual values of TiTR), an improvement or a worsening of TTR was defined as two consecutive TiTR ≥70% or <70%, respectively.

**Statistical analysis**

Categorical variables were reported as counts (percentage), continuous variables were expressed as mean ± standard deviation (SD). Pearson Chi-Square was used to compare proportions and ANOVA test with post-hoc LSD correction was used to compare means among groups.

Stepwise logistic regression analysis was used to investigate odds ratio (OR) for clinical characteristics of patients from group 1.

The cumulative incidence of CVEs was estimated using a Kaplan–Meier product-limit estimator. Survival curves were formally compared using the log-rank test. Cox proportional hazards 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 Cox regression analysis was adjusted for CHA2DS2-VASc score, persistent/permanent AF (vs. paroxysmal), antiplatelet drugs, and lipid-
lowering agents. 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.

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.

Results

Of the 2006 AF patients referring to the anticoagulation clinic, 512 were excluded as already on VKAs at entry, and 153 patients were also excluded as they presented with unstable TiTR (passing above and below 70% repeatedly) so that a clear temporal trend was not identifiable. Thus, the final cohort was composed by 1341 AF patients followed for a mean of 37.7 (±21.3) months yielding 4212.4 patient-years of observation. Characteristics of study population according to the TiTR groups are listed in table 1. Mean age was 73.5±8.7 years and 42.5% of patients were women.

After the first year of follow-up, 504 patients had a TiTR ≥70% (37.6%), and 837 were <70% (62.4%).

During follow-up (figure 1), 241 patients (18%, group 0) remained consistently ≥70%, 263 patients passed from above to <70% (19.6%, group 1), 270 improved TiTR from below to ≥70% (20.1%, group 2), and 567 remained <70% (42.3%, group 3).

When we investigated clinical characteristics of patients from group 1, we found that arterial hypertension (OR:1.65, 95%CI 1.04-2.62) was associated with a higher risk of worsening TiTR <70%, whilst the use of antiplatelet (OR:0.44, 95%CI 0.23-0.83) and lipid-lowering drugs (OR: 0.65, 95%VI 0.48-0.88) was associated with a lower risk.

Cardiovascular events
During follow-up, 108 CVEs were recorded (2.6%/year): 19 fatal/non-fatal ischemic stroke, 21 cardiac revascularization, 29 cardiovascular death, 27 fatal/non-fatal MI, 3 systemic embolism and 9 TIA. Of these, 12 CVEs occurred in group 0, 28 in group 1, 17 in group 2, and 51 in group 3.

Survival analysis showed an increased risk of CVEs across groups of TiTR (log-rank test p=0.013). In particular, the univariate Cox regression analysis (figure 2) showed that patients with worsening TiTR (group 1) had a significantly higher risk of CVEs as compared to group 0, and that this risk was similar to that of patients belonging to the poor anticoagulation group (group 3).

Multivariable Cox regression analysis showed that Group 1 vs. 0 (HR:2.006, 95%CI 1.016-3.961, p=0.045), Group 3 vs. 0 (HR:2.072, 95%CI 1.095-3.922, p=0.025) and CHA$_2$DS$_2$ VASc Score (HR:1.316, 95%CI 1.158-1.496, p<0.001) were independently associated to CVEs.

Discussion

Then, the clinical characteristics of patients with worsening quality of VKA therapy were investigated. We found that……

Patients with worsening TTR should be considered for non-vitamin K oral anticoagulants, as they experience a similar rate of CVEs than patients with stable poor anticoagulation (i.e. TiTR <70%).
2 lavori su statine ed ezetimibe e ttr e overcoagulation (21880698) e sul beneficio delle statine per la prevenzione dello stroke (che potrebbe dipendere dall’effetto sul TTR stroke 28596457)

We also found that the use of antiplatelet drugs at entry was associated with a lower risk of worsening TiTR. Data regarding the effect of concomitant antiplatelet use on anticoagulation stability are few and controversial.

Aspirina e TTR apparentemente in contrasto con precedente lavoro spagnolo (25814183) e con post-hoc analysis from SPORTIF trials (27428440)

Effetto neutro invece in questo lavoro (27319745)

However, despite our results suggest a positive effect of antiplatelet on temporal changes of TiTR, the use of antiplatelet in addition to oral anticoagulation in AF patients is not associated with a significant benefit in terms of reduction of ischemic outcomes, whilst it is associated with an increased risk of bleeding (25923742).

References

5. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control amongst atrial fibrillation patients on warfarin: The SAMe-TT2R2
(Sex female, Age less than 60, Medical history, Treatment strategy [rhythm control], Tobacco use [doubled], Race [doubled] score. Chest 2013.


Table 1. Clinical characteristics of patients according to changes of TiTR.

<table>
<thead>
<tr>
<th></th>
<th>Whole cohort (n=1341)</th>
<th>Group 0 (n=241)</th>
<th>Group 1 (n=263)</th>
<th>Group 2 (n=270)</th>
<th>Group 3 (n=567)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.5±8.7</td>
<td>73.4±8.6</td>
<td>73.8±7.4</td>
<td>72.5±8.8</td>
<td>73.8±9.2</td>
<td>0.215**</td>
</tr>
<tr>
<td>Women (%)</td>
<td>42.5</td>
<td>38.2</td>
<td>44.1</td>
<td>39.6</td>
<td>45.0</td>
<td>0.217**</td>
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<tr>
<td>Persistent/permanent AF (%)</td>
<td>65.8</td>
<td>68.0</td>
<td>66.9</td>
<td>60.7</td>
<td>66.7</td>
<td>0.267**</td>
</tr>
<tr>
<td>Arterial Hypertension (%)</td>
<td>87.1</td>
<td>87.6</td>
<td>89.4</td>
<td>87.8</td>
<td>85.5</td>
<td>0.462**</td>
</tr>
<tr>
<td>Previous cardiovascular events (%)</td>
<td>17.5</td>
<td>12.4</td>
<td>15.6</td>
<td>14.5</td>
<td>21.9</td>
<td>0.003**</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>21.4</td>
<td>14.5</td>
<td>20.5</td>
<td>21.1</td>
<td>24.9</td>
<td>0.012**</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>11.7</td>
<td>8.3</td>
<td>13.7</td>
<td>7.1</td>
<td>14.5</td>
<td>0.004**</td>
</tr>
<tr>
<td>Previous cerebrovascular events (%)</td>
<td>13.9</td>
<td>8.7</td>
<td>12.5</td>
<td>13.3</td>
<td>16.9</td>
<td>0.016**</td>
</tr>
<tr>
<td>Antiplatelet drugs (%)</td>
<td>9.8</td>
<td>10.4</td>
<td>4.9</td>
<td>6.3</td>
<td>13.4</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>37.7</td>
<td>35.7</td>
<td>31.2</td>
<td>40.7</td>
<td>40.2</td>
<td>0.051**</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score</td>
<td>3.1±1.4</td>
<td>2.8±1.2</td>
<td>3.1±1.3</td>
<td>2.9±1.4</td>
<td>3.3±1.5</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

χ² test; ANOVA test; *group 1 vs. group 0; **group 3 vs. group 0
Table 2. Multivariable Cox regression analysis of factors associated to cardiovascular events

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>Hazard ratio</th>
<th>95.0% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Group 1 vs. 0</td>
<td>0.045</td>
<td>2.006</td>
<td>1.016</td>
</tr>
<tr>
<td>Group 2 vs. 0</td>
<td>0.539</td>
<td>1.264</td>
<td>0.599</td>
</tr>
<tr>
<td>Group 3 vs. 0</td>
<td>0.025</td>
<td>2.072</td>
<td>1.095</td>
</tr>
<tr>
<td>CHA₂DS₂ VASc Score</td>
<td>&lt;0.001</td>
<td>1.316</td>
<td>1.158</td>
</tr>
<tr>
<td>Persistent/Permanent AF (vs. paroxysmal)</td>
<td>0.627</td>
<td>0.908</td>
<td>0.614</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>0.639</td>
<td>1.160</td>
<td>0.624</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>0.702</td>
<td>1.083</td>
<td>0.721</td>
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</table>
Figure 1. Groups of TiTR according to temporal trends of therapeutic range.
Figure 2. Relative Hazard Ratios of cardiovascular events of each group of TiTR as compared to Group 0.

- Group 1: 2.27 (1.15-4.47), p=0.018*
- Group 2: 1.42 (0.68-2.98), p=0.352*
- Group 3: 2.45 (1.30-4.61), p=0.005*

*Group 0 as reference group
Figure 3. Kaplan-Meier curves estimate of survival free from cardiovascular events according to groups of TiTR.