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A decisional model to individualize warfarin recommendations: Expected impact on treatment and outcome rates in a real-world population with atrial fibrillation☆

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ABSTRACT

Background: How the adoption of prediction models to decide which patient with atrial fibrillation (AF) to anticoagulate can affect prescription rates and outcomes is unclear.
Methods: We retrospectively analyzed data from Danish registries on patients with a first-time recorded AF from 2005 to 2010. We simulated the adoption of a decisional model based on the individual absolute risk reduction of stroke and absolute risk increase of bleeding with warfarin, as expected from the patient CHA_2DS_2-VASc and HAS-BLED, adjusted for a 0.6 relative value for bleeding versus stroke. We studied 3 different model versions and calculated for each of them the net benefit associated with its adoption, measured as the value-adjusted reduction in stroke and bleeding events at 1 year, compared with i) the actual practice, or ii) recommending warfarin consistently with the European Society of Cardiology (ESC) guidelines, irrespective of HAS-BLED.
Results: We included 41,455 patients; 31.9% actually received warfarin. The expected treatment rate with the model ranged from 21% to 87% according to the version used. The model version resulting into the highest treatment rate (i.e. treating any patient with CHA_2DS_2-VASc ≥1) was associated with the greatest net benefit (0.98; 95% credible interval 0.72–1.23), compared with the actual practice, with a 1/3 reduction in overall mortality, as with the adoption of ESC guidelines.
Conclusions: Preliminarily to a randomized impact study, our analysis suggests that individualizing anticoagulation for AF using a decisional model might have a clinical advantage over actual practice, and no added advantage over following ESC guidelines.

1. Introduction

The underuse or misuse of Vitamin K antagonists (VKAs) in real-world patients with atrial fibrillation (AF) is still a concern [1–3]. Prescribing anticoagulants for stroke prevention requires to assess and balance the risks of stroke and of bleeding complications. Clinical prediction scores for an easy assessment of the patient risk of stroke or bleeding have been available for years and are currently considered in most scientific guidelines [4–6]. However, scientific societies do not indicate how to account for the two risks according to a logical framework, and the practitioner may feel overwhelmed by the task. The availability of new therapeutic options with the direct oral anticoagulants might make the choice even more complex. In this context, the use of decisional models, which mathematize the two types of risk and calculate the expected individualized treatment-related net benefit, has been proposed to assist the physician [7,8].

The gold standard for testing whether the adoption in practice of a decisional model can bring relevant advantages over the usual practices is a randomized controlled impact trial, in which patients, physicians or clinics are randomized to a management strategy based on the decisional model or to a usual management [9]. Performing such a trial is resource demanding and requires to take into account methodological issues, like the unblinded allocation, the risk of contamination, the effect of physicians aptitude and experience with decisional aids [10–13]. A

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study that simulates the application of a decisional model to a real population might represent an easier way to provide useful preliminary information. Using data collected in national registries in Denmark, the aim of our study was to retrospectively evaluate the expected impact on treatment rates and overall outcomes of a decisional strategy which individualizes treatment recommendations based on the predicted individual cardio-embolic and bleeding risks, as compared with: 1) the actual practice; 2) recommendations based only on the individual cardio-embolic risk consistently with the European Society of Cardiology (ESC) guidelines [4].

2. Methods

The analyses were based on three nationwide Danish databases [14,15,16], unequivocally linked through the civil registration number assigned to each Danish resident. According to the Danish laws, no ethical approval is needed for the publication of research data based on routine collection of data. The registries used are approved by the Danish Data Protection Agency (Journal no. 2012-41-0633).

2.1. Study population

The study cohort was composed by patients diagnosed for the first time with nonvalvular AF or flutter at the discharge from Danish hospitals from January 1, 2005 to December 31, 2010. Detailed exclusion criteria are available as Supplementary Material.

From the three databases we extracted demographic and medical data to calculate for each patient the baseline CHA_2DS_2-VASc (congestive heart failure, hypertension, age > 75, diabetes mellitus, and prior stroke or transient ischemic attack, vascular disease, age 65–75, sex category i.e. females) [17] and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (inr), elderly (>65 years), drugs/alcohol concomitantly) [18] risk scores. A reduced version of HAS-BLED was used because the INR trend was unavailable and the alcohol consumption could only be coded as alcohol related-diseases. Patients were then characterized according to their baseline anticoagulation status into patients prescribed and not prescribed a VKA. The active treatment with VKAs at baseline was identified by converting the time series of purchased doses into periods of probable treatment.

The baseline time was set at 30 days from the index diagnosis in order to overcome the limits of administrative databases in defining the temporal relationship between events. This should have reduced the chance to count as outcomes those early events that in fact occurred around the time of the diagnosis of AF and affected the therapeutic choice (and not vice versa).

2.2. Application of a model to individualize treatment recommendations

As strategy to individualize recommendations for anticoagulation we adopted a variable benefit/variable harm model elsewhere described [19]. In this specific clinical scenario, we defined as benefit the expected reduction of the target outcome meant as cerebral or systemic cardio-embolic events, and as harm the expected increase of bleeding. In brief, the decisional model is based on the assumption that, beyond the average beneficial and harmful effects of VKAs as showed at group level in randomized controlled trials, the expected absolute benefit and absolute harm may differ at individual level according to the patient baseline risks of stroke and bleeding, which can be predicted using available risk scores like CHA_2DS_2-VASc and HAS-BLED [19]. Then the model suggests to recommend VKAs to a patient when the predicted individualized benefit numerically exceeds the predicted individualized harm, adjusted for the relative value that a patient may assign to bleeding versus stroke ($RV_{bleed/stroke}$) [19]. In order to test the sensitivity to methodological constraints, we applied the same model principles using three methods that differed for the data sources and the type of calculations they used to predict the individualized benefit and the individualized harm: method 1, all-literature-estimates-based, which adopted estimates from the literature for all the input variables used by the model; [8,20] method 2, actual + literature-estimates-based, which adopted the estimates for the relative treatment (VKAs) effect from the literature [20] and estimated the baseline (off VKAs) cardio-embolic and bleeding risks from the Danish cohort; and method 3, actual-estimates-based, which estimated all the input variables from the Danish cohort. The algebra and the methodological and practical advantages and disadvantages of each method are summarized in the Supplementary Material.

Due to the impossibility to elicit individual values, we adopted for every patient a typical group-level $RV_{bleed/stroke}$ of 0.6 generated from a lost utility analysis [21], which means to value a bleeding event as a 60% of a stroke event. The following analyses were then performed for each model method separately.

2.3. Outcomes and follow-up

For the purpose of this study, patients were followed up until 1 year from the baseline time, or until death or emigration from Denmark, whichever came first. Among cardio-embolic events, the composite of ischemic stroke, transient ischemic attacks (TIA) and systemic embolism was included. Among major bleeding events, the composite of any intracranial and extracranial bleeding leading to hospitalization was included. Death for any cause was additionally analyzed even if not directly included in the decisional model and in its evaluation.

Baseline and outcome diseases were identified using the corresponding ICD codes (Supplementary Material).

2.4. Evaluation of the individualizing strategy

Patients were classified into those that would be and those that would not be recommended VKAs according to the model. Then we calculated the expected outcome rates at 1 year that would have been observed if the cohort had been managed according to the model. For this purpose, we generated a sub-population composed by congruent groups, i.e. by those patients that the model would have recommended a VKA and that were actually receiving a VKA, plus those that the model would have recommended no antithrombotic therapy that actually were off treatment. The overall stroke and bleeding event rates of this sub-population were then calculated. The treatment rate (which percentage of patients would receive a VKA) and the outcome rates that would be theoretically associated with the individualizing strategy were then compared with the actual treatment and outcome rates in the whole Danish cohort. The comparison between outcome rates was synthesized as

$$\text{Net benefit} = \text{Diff}_{\text{stroke}} + (\text{RV}_{\text{bleed/stroke}} \times \text{Diff}_{\text{bleed}})$$

where $\text{Diff}_{\text{stroke}}$ and $\text{Diff}_{\text{bleed}}$ were the difference in, respectively, stroke and bleeding rates between the actual practice and the individualizing strategy. Both a $RV_{bleed/stroke}$ of 0.6 and a $RV_{bleed/stroke}$ of 1 were tested. A net benefit greater than 0 was expression of an advantage of the individualizing strategy over the actual practice.

A similar evaluating approach was then performed for the comparison between the variable benefit/variable harm model and recommendations based only on the patient cardio-embolic risk consistently with ESC guidelines [4]. Two variants of the guidelines were evaluated: i) to recommend oral anticoagulation for males with CHA_2DS_2-VASc 1, and any patient with CHA_2DS_2-VASc ≥2 (ESC-A); ii) to recommend oral anticoagulation for any patient with CHA_2DS_2-VASc ≥2 (ESC-B).

2.5. Statistical Analyses

Baseline characteristics of patients prescribed or not a VKA were compared using t test and Fisher's exact test. Time-to-event analyses were performed to calculate annual rates over 1 year of follow-up. As main analysis, an "Intention-To-Treat" (ITT)-like approach was adopted, in which each patient's anticoagulation status was defined once at the baseline. Any cardio-embolic or bleeding event was assigned to an "on VKA" status even if the therapy was later withdrawn, and vice versa. A sensitivity analysis was then performed using a "continuous-treatment" approach in which patients changing their anticoagulation status (from "on" to "off", and vice versa) during the follow-up were censored at the time of the change.

In order to obtain a measure of confidence around the strategy-related net benefit accounting for the uncertainty around the outcome rate estimates, a probabilistic Bayesian approach was used based on Markov Chain Monte Carlo simulations. A point estimate and a 95% credible interval for each net benefit calculation were provided.

STATA (version 12.0) and WinBUGS (version 1.4) were used to perform the statistical analyses.

3. Results

We included in the current analyses 41,455 patients with an incident AF or flutter; of them, 13,228 patients (31.9%) were prescribed a VKA. Table 1 shows the baseline characteristics of the study population and according to the anticoagulation status. Both the CHA_2DS_2-VASc and HAS-BLED score were on average slightly higher in patients prescribed VKAs.

Over 1 year of follow-up, 1.7%/year of patients (95% confidence interval: 1.6, 1.9) experienced a stroke; 2.0%/year (1.8, 2.1) a major bleeding; and 14.7%/year (14.3, 15.0) died for any cause. The stroke and bleeding outcome rates in patients prescribed or not VKAs, for each CHA_2DS_2VASc and HAS-BLED score, are reported in Tables 2 and 3, respectively.

Table 4 shows what the model would have recommended according to the combination of the individual cardio-embolic and bleeding risk scores, using the three methods of model application. The detailed math that brought to those recommendations is provided as Supplementary Material. When theoretically applied to the Danish cohort, only the all-literature-estimates-based approach (method 1) would have recommended VKAs to a lower percentage of patients than the 31.9% actually treated, with the discordance mostly represented by patients that actually received VKAs but that would have not been