A two-sided evaluation of benefit and harm from antithrombotic treatment in atrial fibrillation: Balancing clinical application and statistical methodology

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The choice of treating atrial fibrillation (AF) patients for stroke prevention with an oral anticoagulant (OAC) is not a unilateral decision. OACs can refer to vitamin K antagonists (VKAs) with good anticoagulation control, as reflected by a high time in therapeutic range (TTR) (1) or one of the non-VKA OACs (NOACs) which have shown efficacy, safety and convenience in trials (2, 3) and in real-world clinical practice (4–6).

Primarily, the prescribing physician has to estimate the risk of ischemic stroke in case of not providing sufficient therapy, and balance this against the risk of serious bleeding in case of initiating treatment. This has to be also considered in relation to patient values and preferences (7).

Various risk assessment tools have been developed and evaluated to guide the physician, but need to be used appropriately and correctly (8, 9). To assess the risk of stroke, contemporary guidelines suggest use of CHA₂DS₂-VASc score (Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke/systemic embolism/transient ischemic attack, Vascular disease, Age 65–74 years, and female sex category) for stroke risk stratification. Similarly, the risk of bleeding can be assessed by the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly age >65, drugs/alcohol concomitantly) score.

It is evident that it is a complex problem to draw a conclusion on whether to initiate treatment based on such risk scores. A number of studies on observational data have investigated what may be the optimal decision for various patient groups. Even then, important additional considerations on whom, how, and when to initiate OAC include ethnic or geographical differences (10), associated comorbidities (e.g. valvular heart disease (11)), renal impairment or recent stroke (12); adherence and persistence with therapy are additional issues (13).

A general approach has been to balance the risk of thromboembolic events (i.e. ischaemic stroke or systemic embolism) against serious bleeding based on weighing the cost of the included events. The attempt is to answer the question of “what is the cost of not treating?”, that may be translated into “what is the hypothetical cost of one thromboembolic event against the potential harm from treatment?” Historically, the weight of 1 for ischaemic stroke was offset by a weight of 1.5 for intracranial haemorrhage (14). A more sophisticated approach was later proposed by Connolly et al. including weights for other potential important outcomes in AF patients, i.e. myocardial infarction and major (extracranial) bleeding, with weights directly related to the expected fatality of the included events (15). In a Danish nationwide observational study, these two methods were investigated and the method by Connolly et al. was evaluated based on weights derived from the Danish nationwide cohort (16). Albeit specific weights for each potential outcome are utilised, interpretation of a single number as a “Net Clinical Benefit” (NCB) measure inherently suffers of loss of potential clinically valuable information.

In this issue of Thrombosis and Haemostasis, Kittelson et al. provide a novel approach based on a bivariate evaluation of benefit against harm from treatment (17). The novelty of the method is in particular related to maintaining the distinct evaluation of benefit and harm, and not confining NCB into a single entity. This approach will unambiguously also maintain potential clinically important information in the evaluation. The evaluated efficacy (benefit) and safety (harm) endpoints are investigated using a chart with effect on efficacy as x-axis and effect on safety as y-axis spanning a two-dimensional plane separated into two regions representing situations, where treatment is judged as clinically beneficial or not being clinically beneficial. Specifically, the authors applied their method using published data from four pivotal trials in stroke prevention from AF comparing the NOACs versus warfarin.

The two-dimensional plane was defined according to risk differences based on treatment arm for both efficacy (x-axis, e.g. thromboembolism) and safety (y-axis, e.g. major bleeding). The null-hypothesis of no clinical benefit can be represented by a line/curve depending on how benefit and harm are weighted.

The most simple approach introduced by Singer et al. corresponds to a straight line passing through origin with the slope being equal to the applied weight (-1.5 for intracranial haemorrhage) and all situations under the line indicate treatment benefit. Arguing that the importance of bleeding outcomes and thromboembolic outcomes may be different, the authors...
wisely propose a non-linear function to separate the plane rather than a linear discrimination. By changing the evaluation of risk differences to the multiplicative scale the authors suggest representing the null-hypothesis of no clinical benefit by a curve with features from a rectangular hyperbola. The parameters of this curve may be directly related to clinical meaningful reflections upon acceptable trade-off between benefit and harm from treatment. By answering four questions the user will thus actively select sound clinical boundaries. This is an essential –but often overlooked– part in interpretation of research results (4). Joint evaluation of benefit and harm for a particular patient profile or trial is afterwards done by representing the expected benefit and harm including 95% confidence intervals by a rectangle in the diagram. The position of the rectangle relative to the curve will indicate the how beneficial the decision of treatment may be. Some may tend to merely look at confidence intervals as being an indirect significance test (similar to p-value < 0.05) by gauging whether or not the 95% confidence interval contains unity, when contrasting two treatments. However, this simplification of results perhaps emphasises focus on statistical testing but de-emphasises interpretation of clinical importance.

How will the bivariate evaluation aid prescribing physicians in clinical practice? Ultimately, the output of this method will still be subject to individual interpretation and is based on the selected criteria and magnitude of benefit and harm (from answering the four aforementioned questions). Clearly, the framework should be made easily accessible (e.g. in an app or similar device), since the produced chart—including curvature boundary and box of expected NCB— may be used as a communication platform for the physician and patient. Perhaps the easiest way to explain and communicate the output from the chart, is to describe the area of the ‘NCB box’ within the benefit region opposed to the harmful area (if any) on the other side of the curve.

For the hectic clinician in a busy outpatient clinic or ward, practicality and ease of use may ultimately outweigh statistical methodology. The CHA2DS2-VASC score consistently identifies low risk patients (score 0 in males, 1 in females) who do not need any antithrombotic therapy. Even a single stroke risk factor confers a high risk of stroke or death, and OAC results in a positive NCB for treatment compared to no therapy or aspirin (18, 19). Hence, the first step is to identify the low risk patients where OAC offers no advantage; the subsequent step is to offer effective stroke prevention to those with 1 or more additional stroke risk factors. Thus, the decision process for initiating OAC is made, irrespective of CHA2DS2-VASc score (2, 3 or more) or adding in multiple biomarkers or imaging modalities. Simplicity is really best, cheaper and more convenient.

Conflicts of interest

P. B. N. has served as a speaker for Boehringer Ingelheim. F. S. declares no conflicts of interest.

References


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