

Assumptions, evidence, and calculations in support of the Anticoagulation Choice Conversation Aid

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Risk of Ischemic Stroke

The scoring system used to predict risk of ischemic stroke is the CHA₂DS₂-VASc (table 1) (1-3). This scoring system has been validated in several independent cohorts (1, 4-8), including a large real world cohort of patients with atrial fibrillation in Sweden done by Friberg et al. (9). Additionally, the CHA₂DS₂-VASc score is the recommended means to predict risk of stroke in current guidelines(10-12).

Table 1: clinical risk factors included in the CHA₂DS₂-VASc score

Letter	Risk Factor	Points
C	Congestive heart failure / LVEF ≤ 40%	1
H	Hypertension	1
A ₂	Age ≥ 75	2
D	Diabetes mellitus	1
S ₂	Previous history of Stroke, TIA or TE	2
V	Vascular disease, which includes prior myocardial infarction, peripheral artery disease or aortic plaque	1
A	Age 65 – 74	1
Sc	Sex category = female	1

LVEF = left ventricular ejection fraction. TIA = transient ischemic attack. TE = thromboembolism.

To determine the theoretical baseline risk of ischemic stroke without any treatment, we used the data from the ischemic stroke event rate adjusted for antiplatelet use in the Swedish cohort (9) (Table 2)

Table 2. Annual Risk of Ischemic Stroke by CHA₂DS₂-VASc Score without Anticoagulation

CHA ₂ DS ₂ -VASc Score	
0	0.2
1	0.6
2	2.5
3	3.7
4	5.5
5	8.4
6	11.4
7	13.1
8	12.6
9	14.4

Warfarin vs. Direct anticoagulants (NOACs):

The Non-Vitamin K Oral Anticoagulants (NOACs) represent an alternative to warfarin for stroke prevention in atrial fibrillation. The effectiveness of these drugs has been supported by randomized clinical trials and they generally demonstrate at least equivalent efficacy and improved safety (particularly for risk of intracranial bleeding) in comparison to warfarin(13-16). However, all four NOACs were compared against warfarin and there are no large-scale, head-to-head, randomized trials comparing NOACs. As such, the available comparative effectiveness estimates are derived from observational analyses, or indirect comparisons derived from trial data and are less certain. Based on this limitation, we opted not to offer individualized risk reduction estimates with each NOAC and each dose, but rather to consider all four agents together and provide the estimates of effectiveness and safety under the heading of “Direct Anticoagulants”

The purpose of the decision tool is to help clinicians and patients arrive at a common and explicit understanding of the stroke risk situation of the patient. Having arrived at this understanding, patients and clinicians then move on to determine what action this situation warrants, including the possibilities of using anticoagulation (regardless of how it is achieved) to reduce this risk and if so which one would be best given the patient’s situation. This is achieved by conveying a tailored estimate of stroke risk, risk reduction with anticoagulation, and to outline potentially issues patients may encounter with anticoagulant therapy. The design of the tool supports in this way the conversation, moving to the background as the participants engage. The tool is not designed to support the selection of an individual agent (one NOAC over another) based on agent-level efficacy or safety data or to promote one agent over another. As high quality comparative effectiveness data emerges, we may reassess the practicality of offering individualized risk assessments by drug, dose, and more detailed patient characteristics (baseline renal function, drug interactions, baseline risk) and the extent to which this is necessary to support what patients and clinicians must do in practice to advance the patient situation.

Annual Risk of Ischemic Stroke with anticoagulation therapy by CHA₂DS₂-VASc Score

To determine a patient’s annual absolute risk of stroke with anticoagulation therapy, we used the average of the product of a patient’s baseline risk of stroke- determined by the CHA₂DS₂-VASc score-, and the relative risk (RR) of stroke for each antithrombotic treatment option.

Warfarin decreases the risk of stroke by 64% (RR=0.36)(17) and the NOACs reduced stroke events (combined ischemic and hemorrhagic) by 19% compared with warfarin (RR 0.81)(18). However, since these differences are small, and the difference is largely driven by lower hemorrhagic stroke rates with NAOCS, we consider the ischemic stroke rates equivalent for the purpose of the Anticoagulation choice conversation aid.

$$\text{Stroke risk}_{\text{anticoagulation}} = \text{Average} (\text{Stroke risk}_{\text{warfarin}}, \text{Stroke risk}_{\text{NOACs}})$$

$$\text{Stroke risk}_{\text{warfarin}} = \text{baseline risk of stroke} * \text{RR of stroke}_{\text{warfarin}}$$

$$\text{Stroke risk}_{\text{NOACs}} = \text{baseline risk of stroke} * \text{RR of stroke}_{\text{NOACs}}$$

Ischemic Stroke severity

Numerous studies have reported that atrial fibrillation is associated with an increased risk of severe ischemic strokes with subsequent disability and mortality, compared to patients without atrial fibrillation(19-23)

A widely-used scale to assess baseline stroke severity and a strong clinical predictor of outcomes is the National Institute Health Stroke Scale (NIHSS) that has a range from 0 to 42, with a higher score indicating greater stroke severity(24). Severe stroke is associated with an increased risk of death, disability, length of time for recovery and improvement, and hospital stay (24-30)

To determine the proportion of patients presenting with moderate or severe stroke, we used the data from Xian et al., which considered patients with an NIHSS score of 16 or higher as having a moderate or severe stroke (23). According to this study, patients receiving no anticoagulation therapy, were more often presented with moderate or severe stroke (27.1% [95% CI, 26.6%-27.7%]) than those receiving therapeutic warfarin (15.8% [95% CI, 14.8%-16.7%]) or NOACs (17.5% [95% CI, 16.6%-18.4%]) (P < .001). Similarly, patients receiving no anticoagulation therapy presented with higher unadjusted rates of in-hospital mortality (9.3% [95% CI, 8.9%-9.6%]), compared to patients receiving therapeutic warfarin (6.4% [95% CI, 5.8%-7.0%]), and NOACs (6.3% [95% CI, 5.7%-6.8%]) (P < .001). These two values were combined (moderate/severe stroke and in-hospital mortality) to provide an indicator for those that at risk of a stroke (number out of 100), how many of those would fall in one of these categories.

Risk of bleeding

Major bleeding, referred to in the Anticoagulation choice conversation aid as a serious bleed or life threatening and requiring emergency treatment, was defined as hospital admission or death from gastrointestinal bleeding, intracranial bleeding, or bleeding from other sites. Our data relied on a large US administrative claims database that uses codes to define baseline comorbidities and outcomes such as major bleeding (31). Therefore, we were not able to define events based on more precise clinical criteria, such as the International Society of Thrombosis and Haemostasis major bleeding criteria(32). However, the algorithms we used, adapted from Yao et al (31), to define major bleeding are commonly used and have demonstrated good performance in several validation studies (33-35).

To determine and predict major bleeding, we used the HAS-BLED scoring system (table 3)(3, 36). This score was developed by Dr. Gregory Y. H. Lip et al to provide a user-friendly tool for quantifying the risk of major bleeding in patients with atrial fibrillation (36). The HAS-BLED score has been validated in several different cohorts, including large real-world and clinical trial populations (37-40). Overall, HAS-BLED offers better prediction of bleeding compared with many other bleeding risk scores although the predictive accuracy varies, depending on the cohort in which it is validated (39, 41, 42). As HAS-BLED should not be used on its own to exclude patients from anticoagulation therapy, we show bleeding risk by 3 categories: population with average risk (HAS-BLED =2), below average risk (HAS-BLED =0-1) or above average risk (HAS-BLED >=3). The Anticoagulation choice conversation aid begins discussion of bleeding risk for all patients with the average risk of needing emergency treatment for bleeding and invites consideration of if a patient is at higher or lower risk. This conversation should highlight those patients in whom caution with anticoagulation treatment, and regular review, is warranted. It will also help to identify, and potentially modify, risk factors for bleeding in the patient's day-to-day life and to discuss the possibility of correcting factors that are medically modifiable, i.e., by controlling blood pressure, removing concomitant antiplatelet or non-steroidal anti-inflammatory drugs, and counseling the patient about reducing alcohol intake (if excessive).

Table 3. Clinical Risk Factors in the HAS-BLED Scoring System

Letter	Risk Factor	Points
H	Hypertension: uncontrolled (systolic > 160 mm Hg)	1
A	Abnormal renal ^a and liver function ^b (1 point each)	1 or 2
S	Stroke: previous history of strokes, particularly lacunar strokes	1
B	Bleeding history or predisposition (anemia)	1
L	Labile INRs: less than 60% time in therapeutic range	1
E	Elderly: age over 65 years	1
D	Drugs or alcohol: antiplatelet agents ^c or NSAIDs, or alcohol excess ^d (1 point each)	1 or 2

^a Abnormal kidney function indicated by need for chronic dialysis, renal transplantation or serum creatinine \geq 200 μ mol/L.

^b Abnormal liver function indicated by chronic hepatic disease, such as cirrhosis, or biochemical evidence of impairment, such as bilirubin > 2x upper limit normal in association with aspartate aminotransferase/alanine amino-transferase/alkaline phosphatase > 3x upper limit normal.

^c Aspirin or clopidogrel.

^d Alcohol excess > 8 units per week

Annual Risk of Major bleeding by HAS- BLED score

We did not find data consistency on HAS BLED score in the available cohorts and they did not show sensitivity to anticoagulation therapy (Studies show the same HASBLED risk for patients without anticoagulation and with anticoagulation). We used data on bleeding event rates by HAS-BLED score in NOAC-treated patients from a large US administrative claims database (OPTUM) (43) to determine the baseline risk of major bleeding in the Anticoagulation choice conversation aid and the risk of bleeding with anticoagulation based on the HAS BLED score (table 4). According to Ruff's meta-analysis (18), NOACs decrease the risk of bleeding by 14% (RR=0.86) vs. warfarin. Warfarin increases the risk of bleeding by 130%-200% (RR=2.3-3) vs. no anticoagulation therapy (44, 45). So, to determine a patient's baseline annual risk of major bleeding (based on the 3 categories of HAS-BLED) we used the following formula:

$$\text{Annual baseline risk of bleeding} = \frac{\text{Annual risk of bleeding with NOACs}}{\text{RR of bleeding with warfarin} * \text{RR of bleeding with NOACs}}$$

Table 4. Annual Risk of major bleeding by HAS-BLED Score

HAS BLED	Baseline risk (no therapy)	Warfarin	NOACs
0-1	0.5	1.5	1.2
2	1	3	2.4
>=3	2.7	8.1	6.5

Conversion of risk to 5 year rates

To convert the 1 year risk to a 5-year risk of stroke and risk of bleed the following formula was used (46, 47):

Probability = $1 - \exp(-r * t)$, where r is the rate and t is the number of years. This formula assumes that the rate is consistent over time, while this is a reasonable assumption we do not have data to confirm it.

Cost

As we were not able to determine the cost of each medication for each individual patient, we used references of out of pocket costs from <https://www.goodrx.com/>. The table 5 shows the lowest prices we found on February 3rd 2017 for each medication.

The cost of INR monitoring test could vary between studies and for each particular case, depending on the clinical setting, monitoring modality, patient's insurance, etc. However, for the purpose of the Anticoagulation choice conversation aid, we have estimated the average between the lowest and the highest price of INR monitoring test according to Chambers's systematic review(48).

Table 5. Annual out of pocket cost

NOACs-Yearly cost	Apixaban 5mg twice daily	Dabigatran 150mg twice daily	Edoxaban 60mg once daily	Rivaroxaban 20mg once daily	Average cost
	\$4,876.00	\$4,575.00	\$4,090.00	\$4,460.00	\$4,500.25*

Warfarin-Yearly cost	Generic 5mg once daily	INR monitoring lowest price	INR monitoring highest price	INR monitoring average cost	Generic warfarin + INR average cost
Based on 8 tests per year	\$40.00	\$73.28	\$710.08	\$391.68	\$431.68 *

*Rounded to nearest \$50 in the ANTICOAGULATION CHOICE conversation aid

Future issues

Although the non-inferior efficacy and safety profile of all NOACs compared to warfarin have been demonstrated in larger randomized trials, an increased risk of bleeding and other safety signals are known possible complications as their use extends over time and volume. We will remain attuned to include this data as it emerges, as well as data on efficacy of reversing agents.

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