SUPPLEMETNAL MATERIAL

Appendix to Variation in Published Stroke Rates Results in Wide Variation in the Net Clinical Benefit of Anticoagulation for Atrial Fibrillation

Section 1: Model Structure

Overview

The Markov model contains 29 states of health. **Appendix Figure 1** shows the 7 strategies compared – no antithrombotic therapy, aspirin, warfarin (target INR 2-3), dabigatran, apixaban, rivaroxaban, and edoxaban – at the solid black, square decision node. In this analysis, we present results of the no antithrombotic therapy, warfarin (target INR 2-3), and apixaban strategies. The bracket after the 7 treatment strategies indicates that the sub-trees are attached to each strategy. A simplified list of the Markov states is shown next at the Markov node. The actual model contains 29 states. Many of the states not shown in this figure are additional combination states for several events, such as short-term symptoms after intracerebral hemorrhage and long-term symptoms after embolism, or temporary states that last a single cycle, such as the first month after an intracerebral hemorrhage or ischemic stroke. In addition, there are separate states for each level of functional outcome after intracerebral hemorrhage (that is, Glasgow Outcome Scale score of 3, 4, or 5). At the beginning of the Markov, patients start in the state appropriate to the treatment strategy (e.g., those receiving warfarin start in the state, "Well on Warfarin," while those not receiving therapy start in the state, "Well off Warfarin.")

Appendix Figure 2 illustrates the chance events that may occur during each monthly cycle. We denote choice events with solid black and chance nodes with circles. Patients face the same chance events during each monthly cycle of the simulation. Patient-specific decision analyses are performed by setting parameter values for these chance events based upon a given patient's risk profile for ischemic stroke due to AF, major extracranial hemorrhage, and intracerebral hemorrhage, as well as the choice of treatment. Chance events include thromboembolism and major bleeding events (intracerebral hemorrhage, subdural hematoma, or non-central nervous system bleeding). After both types of events, patients face death, permanent symptoms (severe or mild), or resolution of symptoms. Finally, patients may die from non-explicitly modeled causes (for example, demographic characteristics; age, gender; or

excess risk for death following a stroke or intracerebral hemorrhage; or excess mortality risk due to major comorbid diseases such as type II diabetes, congestive heart failure, or hypertension). At the end of each monthly cycle, there is a new distribution across the health states shown at the Markov node that reflects the effect of the initial intervention and outcomes of subsequent chance events.

Scoring Details for CHA_2DS_2-VASc

Predicted ischemic stroke risk in patients with nonvalvular atrial fibrillation can be quantified by the CHA_2DS_2-VASc scoring algorithm. CHA_2DS_2-VASc assigns 1 point for each of the following risk factors: Congestive heart failure, Hypertension, Age 65 - 74, Diabetes, Vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque), and female sex category. Two points are assigned for a history of stroke or transient ischemic attack, and Age ≥ 75 years. We present the corresponding ischemic stroke risk in the main manuscript, Table 1.

Scoring details for ATRIA stroke score

While the CHA2DS2-VASc score is used in clinical guidelines, it does not perform as well as the ATRIA stroke score.(1,2) The ATRIA stroke score accounts for the following risk factors: age, prior stroke, sex, diabetes, congestive heart failure, hypertension, proteinuria, and end-stage renal disease or estimated glomerular filtration rate of less than 45 mL/min/1.73m^2. The scoring system assigns different points to age based on whether the patient has had a prior stroke or not. The table below displays the scoring system.

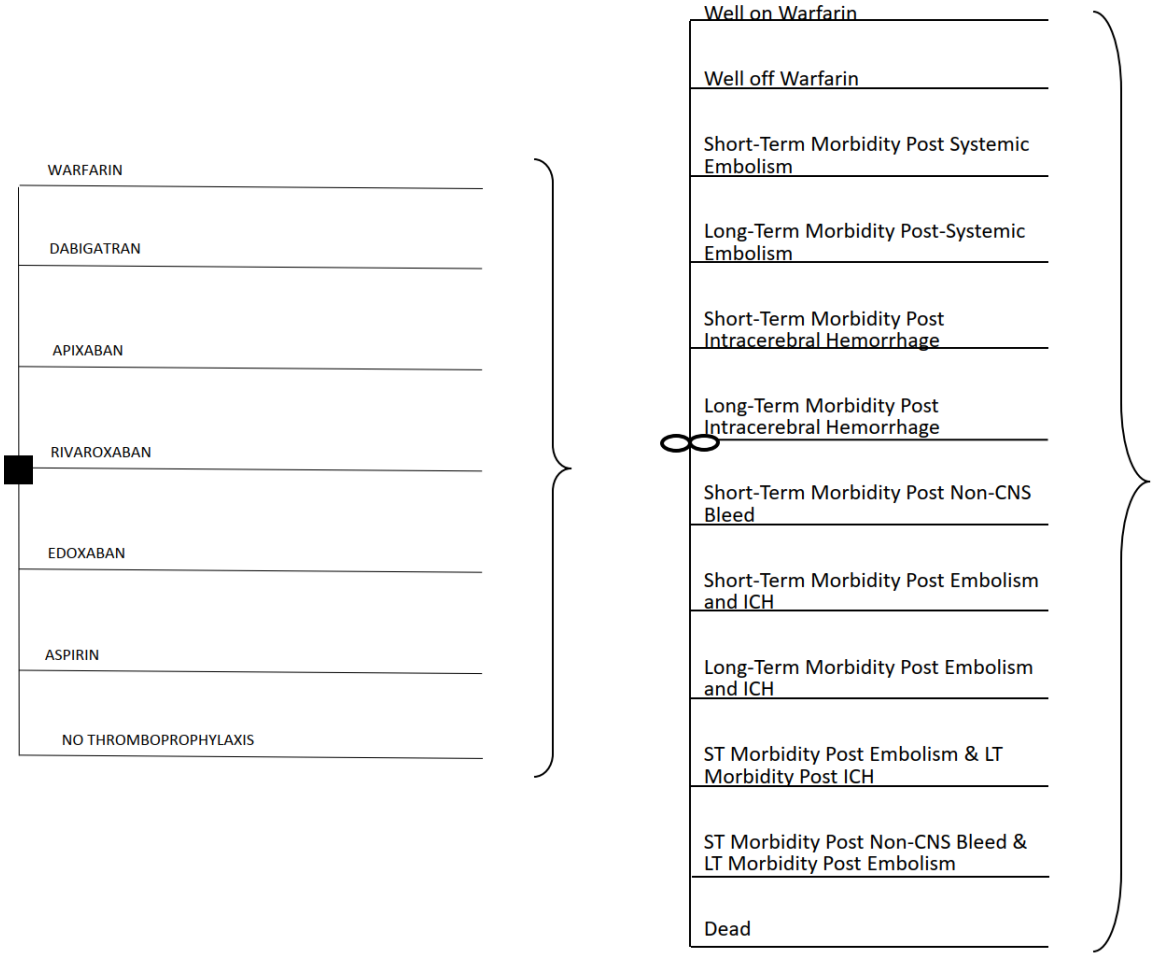
Risk factor	Points without prior stroke	Points with prior stroke
Age		
85+	6	9
75 to 84	5	7
65 to 74	3	7
< 65	0	8
Female	1	1
Diabetes	1	1
Congestive heart failure	1	1

Hypertension	1	1
Proteinuria	1	1
eGFR < 45 or ESRD	1	1

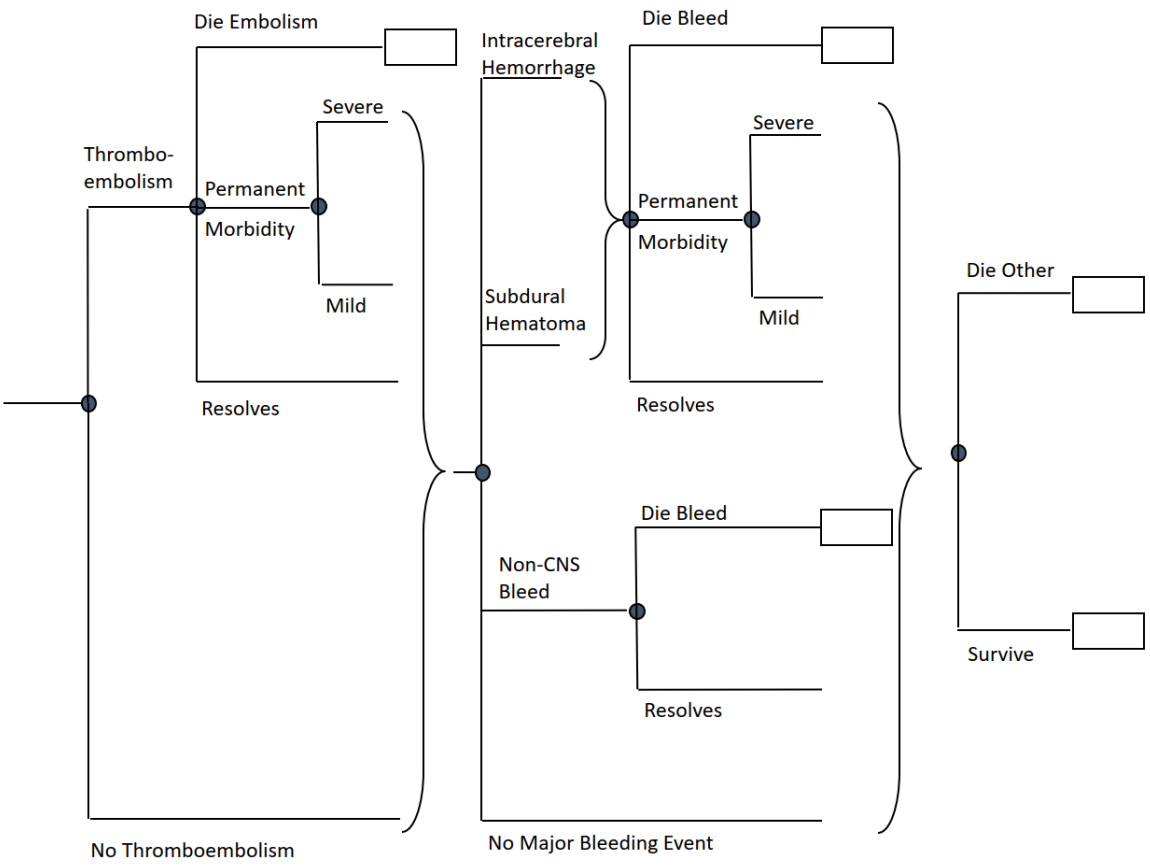
Scoring Details for HAS-BLED

Predicted risk of major bleeding in patients with nonvalvular atrial fibrillation receiving treatment with warfarin can be quantified by the HAS-BLED scoring algorithm. HAS-BLED assigns 1 point for each of the following risk factors: poorly controlled Hypertension (systolic blood pressure ≥ 160 mmHg), Abnormal renal or liver function (one point each – renal transplantation or dialysis, or serum creatinine ≥ 2.26 mg/dl or 200 umol/L; chronic hepatitis or biochemical evidence of significant hepatic derangement – bilirubin > 2 x upper limit of normal in conjunction with AST/ALT > 3 x upper limit of normal), Stroke history, Bleeding history (history of previous bleed or predisposition to bleeding, Labile INR (time in therapeutic range < 60%), Elderly (age ≥ 65), Drugs or alcohol (one point each – alcohol abuse, or concomitant use of antiplatelet or non-steroidal anti-inflammatory drugs). Because this analysis focuses on patients with incident AF, we do not include information on labile INR. In addition, reliable information on drug (specifically over-the-counter NSAIDs) and alcohol use are not available for the ATRIA-CVRN cohort. We present the corresponding hemorrhage risk in the main manuscript Table 1.

Appendix Figure 1: Markov with Health States



Appendix Figure 2: Markov Decision Tree



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