Title of Research
Falling for Direct Oral Anticoagulants in the Elderly: Can Improved Safety Profiles Overcome Anticoagulation Underutilization in Older Adults with Atrial Fibrillation at High Risk for Falls?

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Summary of Research
Atrial fibrillation (AF) is the most common cardiac arrhythmia, increasing in incidence with age. Nearly 25% of elderly patients 80 years or older are diagnosed with AF. The attributable risk of stroke increases from 1.5% for those with AF aged 50-59 to 23.5% for those aged 80-89. Oral anti-thrombotic therapy decreases the risk of ischemic stroke in patients with AF, with meta-analyses revealing a relative risk reduction of approximately 60% with warfarin vs. placebo. There is evidence that direct oral anticoagulants (DOACs) are non-inferior or superior to warfarin in preventing stroke. The most recent (2014) American College of Cardiology/ American Heart Association/Heart Rhythm Society (AHA/ACC/HRS) Atrial Fibrillation Guideline gives a class I recommendation to anticoagulate patients with a CHADS2VASc score ≥2 with warfarin INR 2-3 (level of evidence (LOE) A), dabigatran (LOE B), rivaroxaban (LOE B), or apixaban (LOE B).

Nonetheless, underutilization of anticoagulation remains a problem, with only 50-73% of guideline-eligible patients receiving appropriate therapy. AF accounts for 36% of all ischemic strokes, for which only 15% of patients are adequately anticoagulated. Underutilization is even more common in older adults than the general AF population due to perceived risks of fall, frailty, or hemorrhagic stroke inappropriately contraindicating therapy. Fall risk is among the most frequently cited reasons for not prescribing anticoagulation to elderly patients. Some 32-50% of elderly persons in the community fall at least once per year, with fall risk increasing linearly with the accrued number of predisposing factors. There have been multiple studies on choosing antithrombotic therapy for elderly patients with AF who are at risk for falls. Man-Son-Hing et al[1] suggested that a history of and/or the presence of risk factors of falls should not be considered important factors in deciding whether to offer anti-thrombotic therapy to elderly patients with AF. They calculated that an individual taking warfarin would need to fall about 295 times in one year before the fall-associated bleeding risks outweighed stroke reduction benefits. However, the decision to anti-coagulate an elderly person with AF who is at high risk for stroke and also at risk for falls remains a problem facing many physicians.

DOACs have a favorable risk-benefit profile, with significant reductions in stroke, intracranial hemorrhage and mortality with similar major bleeding as for warfarin. There also is evidence that DOACs reduce the risk of intracranial hemorrhage by about half compared to warfarin.

This study will investigate the competing risks and benefits of elderly patients at risk for falls taking DOACs for atrial fibrillation. All available strategies for oral anticoagulants will be evaluated in patients at risk for stroke from atrial fibrillation. It is expected that the risks associated with major bleeding will be far lower than the risk for stroke. Such results would further increase physician comfort with anticoagulation in this population.

Study Design
The study hypothesis is that elderly patients with fall risk on DOACs for AF will have a decreased likelihood of intracranial hemorrhage compared to elderly patients with fall risk on warfarin. This analysis will apply a Markov decision analytic model, which was used in a previous study[1] to investigate the risk of bleeding compared to the risk from falls warfarin vs. aspirin. Markov modeling strategies allow for the use of historical data from multiple data sets on risk for falls and stroke from various patient populations and clinical trials. A comprehensive analysis will be performed, including DOACs, warfarin, and aspirin, to determine risk for various outcomes such as stroke, intracranial hemorrhage, and subdural hematoma in an elderly population at risk for falls. Probability of chance events and fall data from the previous study[1] will be used. Input variables regarding rates of chance events will also be extracted from multiple studies (ARISTOTLE, ROCKET-AF, and RE-LY). The Markov cycle length will be fixed at three months, with all relevant probabilities and utilities adjusted to reflect this cycle length. The starting point for all the patients is the well state. Results will be reported for a one-year period.

Study Population
The study population will comprise patients with atrial fibrillation who are 65 years of age and older, have CHADsVASC of 1 or greater, are at risk of falling and have no other contraindications to antithrombotic therapy.

Funding Source of Research
This project is funded by Yale New Haven Hospital: Scholarship and Innovation Fund in Primary Care.

Requested Study
CV185-030 (NCT00412984): Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE).

Statistical Analysis Plan
The study will consist of running a Markov decision model using a tailored model programmed in VBA (Microsoft Excel) or TreeAge software. Because of the stochastic nature of the study and the availability of secondary data, no sample size justification is needed upfront and no primary endpoint should be reported. The sample will consist of applying the study population inclusion criteria to the ARISTOTLE, RE-LY and ROCKET-AF datasets.

The main outcome from the model will be quality adjusted life years (QALY) with DOAC therapy (apixaban, dabigatran and rivaroxaban), warfarin therapy vs. no therapy. A sensitivity analysis will then be performed to determine the relative risk of stroke, subdural hematoma (SDH) intracranial bleed, major non-CNS bleed, and transient ischemic attack (TIA) for DOAC therapy vs. warfarin. The QALY data and the risk of SDH with each DOAC will be used to calculate how many falls in one year a patient must have for the risks of SDH to outweigh the benefits of

stroke prophylaxis. The model will be validated based on Man-Song Hing et al 1999.[1] The results for each therapy will be summarized in a table to facilitate the interpretation and analysis.

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[1] Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med. 1999;159(7):677-85. https://www.ncbi.nlm.nih.gov/pubmed/10218746