Challenges with Warfarin Therapy in the Elderly Population

Sebastian Ferreira, Untitled
Artwork from the National Art Exhibitions of the Mentally Ill, Inc. (NAEMI)
Managing Warfarin Therapy

Warfarin has been the oral anticoagulant of choice for nearly 60 years, and its widespread use has been documented and recommended in treatment guidelines. Warfarin has served as the standard of care for many years in:

- The prophylaxis and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)
- The prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation (AF) and/or cardiac valve replacement

Dose-adjusted warfarin is effective in preventing stroke and other thromboembolic events. However, it often is associated with challenges, including narrow therapeutic range, variable patient response, numerous drug and food interactions, and the need for routine coagulation monitoring. Precise dosing of warfarin is integral to helping to protect against thromboembolic events. Management of patients taking warfarin can be challenging, as many factors can affect time in therapeutic range, including drug-drug interactions, drug-food interactions, and nonadherence. A meta-analysis of 8 studies in AF found that patients spend only an average of 55% of time in therapeutic international normalized ratio (INR) range.

Managing Challenges

Anticoagulation Treatment in the Elderly Population

Advanced age and some of the comorbidities people develop as they age are risk factors for developing AF and other prothrombotic conditions. Older people ≥65 years of age are at an increased risk for more venous thromboembolisms (VTEs), with more DVT alone than DVT/PE, compared to younger people. As the population ages, healthcare providers may evaluate more patients to decide whether anticoagulation is appropriate. Despite VTE occurrence, the elderly are often not adequately treated for VTEs or for their prevention. Inadequate prophylaxis was also identified in a study of nursing home residents with AF, which found that in two different LTC databases, only 36% and 45% of AF patients at a high risk of stroke received an oral anticoagulant (warfarin).

Approximately 80% to 90% of AF patients in long-term care settings may be at high risk of stroke (2 or more moderate or 1 or more high-risk factors).

Rates of VTE increase around age 65 with the highest increase in prevalence observed in people >85 years of age.
Important considerations when choosing anticoagulant therapy for elderly patients include comorbid conditions and concomitant medications. Treatment decisions for these patients may be more complex and challenging.\(^7\)

**TREATMENT BENEFIT > FALL RISK**

The risk of falls may be commonly overestimated when weighing the benefits of anticoagulant treatment (patients would have to fall 5.7 times a week for risk of falls to outweigh treatment benefit) [see Man-Son-Hing study design]\(^3\).

**CERTAIN VTE RISK FACTORS, SUCH AS IMMOBILITY AND COMORBID CONDITIONS [see Samama study design]\(^{14}\) MAY BE HARD FOR THE ELDERLY TO AVOID [see Piazza study design]\(^{10}\).**

<50% of patients with AF and only 73% of patients with VTE in a long-term care (LTC) facility were treated [see Reardon (AF) study design; see Reardon (VTE) study design]\(^{11,15}\).
Study Designs

**Kimmel study design:** A prospective cohort (IN-RANGE) study at 3 anticoagulation clinics in Pennsylvania (n=136 patients) to determine the effect of adherence on anticoagulation control. Warfarin-treated patients with target international normalized ratio between 2.0 and 3.0 were monitored via electronic Medication Event Monitoring System (MEMS) medication bottle caps. Information on other factors that may alter warfarin response was also collected.

**Limitations:** MEMS cap monitoring does not directly measure adherence, as you cannot tell for sure if patients who opened the bottle took the correct dose. Adherence misclassification may underestimate the effect of poor adherence on anticoagulation control. Due to limited size of the study population, the effects of adherence on bleeding or thromboembolic risk could not be examined. Generalizability of study findings to other populations is unknown. Lastly, given the frequency of poor anticoagulation, the study odds ratios were an overestimation of the relative risk.

**Baker study design:** A meta-analysis of 8 studies published between 2000 and 2008 with a total of 14 unique groups involving 22,237 warfarin-treated AF patients in the United States to evaluate the effect of specialty clinic versus usual care by community physicians on anticoagulation control, measured as the proportion of time spent in therapeutic international normalized ratio (INR) range. Proportion of time spent within therapeutic INR range for each study group was expressed as an incidence density using a person-time approach (in years). All studies were pooled using a random effects model and weighted by the inverse of the variance of proportion of time spent in the therapeutic range. Both subgroup and meta-regression analyses were conducted.

**Limitations:** Publication bias was a potential concern. INR control in randomized controlled trials could not be evaluated, since none were identified in the systematic literature search. Differing interpolation methods were used to report time in therapeutic range among the included studies.

**Björck study design:** A population-based study with data extracted from hospitals, specialized outpatient, primary healthcare and drug registries in the Västra Götaland Swedish region to update the knowledge regarding atrial fibrillation, associated stroke risk and anticoagulation benefits. Individuals who had an AF diagnosis during the past 5 years (N=38,446 still alive in 2010); all stroke events in 2010 (N=5426); and AF patients ≥50 years of age who received warfarin in 2009 (N=17,023) were identified. Binary logistic regression was used to calculate the risk contribution of different stroke factors in AF patients and the general population. Odds ratios for stroke in the presence or absence of co-factors were calculated within 10-year age strata ≥50 years.

**Limitations:** Study could not account for all clinical variables or for changes in therapy over time, and were reliant on the accuracy of diagnostic records. As this was a registry study, patients might have had more risk factors than study authors were aware of and therefore could not adjust for all risk factors. Confounding by indication was also possible, as patients were not randomized to receive warfarin therapy and may differ from patients who did not receive warfarin.

**Naess study design:** Study estimated the incidence and mortality of a first VTE event in a general population >20 years of age, from residents of Nord-Trondelag county in Norway. Cases with an objectively verified VTE that occurred between January 1995 and December 2001 (n=740) were identified through hospital discharge registries in the HUNT2 database (generated from a large-scale general health study). Thrombosis events were classified as first or recurrent and secondary non-cancer, secondary cancer, or idiopathic. The study population was followed from the date of entry until the event, emigration, death or end of follow-up, whichever occurred first.

**Limitations:** The study may have underestimated incidence rates due to the following reasons: migration from the Nord-Trondelag county to other counties was not available; presence of patients in the study with unknown previous thrombosis; cases diagnosed postmortem were not included in the study. Also, 182 cases identified that were otherwise eligible among 258 possible VTE events (no objective diagnostic procedure performed or indeterminate results) were not included in the incidence estimate.

**Piazza study design:** Study described the clinical characteristics, prophylaxis, and initial treatment of 1932 elderly patients compared to 2554 nonelderly patients enrolled in the 183-center US DVT registry of patients with ultrasound-confirmed DVT from October 2001 to March 2002. The registry included both inpatients and outpatients with proximal lower extremity DVT, distal lower extremity DVT, or upper extremity DVT. Data were extracted from medical records at each study site and recorded on case report forms.

**Limitations:** Selection bias and unrecognized confounding may have been present despite extensive evaluation of patient characteristics. Pulmonary embolism (PE) frequency was likely underestimated, given that this registry did not require evaluation for PE. The registry lacked data on patient outcomes and survival.
Reardon (AF) study design: A retrospective cross-sectional analysis of LTC residents with AF to evaluate the usage rates of warfarin in stroke prophylaxis and the association with assessed stages of stroke and bleeding risk. Residents included in this study were identified from the 2004 National Nursing Home Survey (n=1454) and the AnalytiCare LTC database (study period of January 2007 to June 2009, n=3757). Consensus guideline algorithms were used to classify residents by stroke risk categories and residents were also classified by number of risk factors for bleeding. A logistic regression model predicted odds of warfarin use associated with the stroke and bleeding risk categories.

Limitations: A primary datasource in both the NNHS and AnalytiCare databases was the Minimum Data Set (MDS) 2.0, and though validity and reliability of the MDS can vary by a given indicator, it has been reported to have moderate, or moderate to high, validity and reliability. In both study databases, current medication use was evaluated by temporal proximity to the AFib diagnosis, with the AnalytiCare database having under-reporting of aspirin use. Other non-AFib indications for warfarin use, such as post-myocardial infarction secondary prevention, were possible. Specific stroke and bleeding risk factors identified in consensus guidelines have not been validated against stroke and bleeding outcomes in the LTC setting. Several factors are counted as both stroke and bleeding risks, and this remains a limitation since the degree of overlap limits the ability of models to discriminate among summary stroke and bleeding categories when they are considered together.

Silverstein study design: A retrospective population-based study of DVT and PE patient medical records to estimate the incidence of first-time episodes of DVT and PE and to describe trends in incidence among 2218 patients who resided in Olmsted County, Minnesota. Medical records were identified during the 25-year period from January 1966 through December 1990. Episodes of DVT and PE were categorized by 3 levels of diagnostic certainty: definite, probable, and possible.

Limitations: VTE incidence among minority populations was not addressed due to the demographic structure of the Olmsted County population. Study authors could not exclude the possibility that the decreasing incidence trend in PE by calendar year was confounded due to decreasing autopsy rates.

Man-Son-Hing study design: A Markov decision analytic model was used to determine the preferred treatment strategy for older AF patients by analyzing the rate and consequence of falls and the associated chance of subdural hematoma (SDH). Input data were obtained via MEDLINE systematic review (1966 to August 1996) and outcomes were expressed as quality-adjusted life years.

Limitations: The possibility of inaccuracy of the input variables derived from the literature cannot be excluded. Also, the combination of warfarin therapy and falls may have led to adverse outcomes besides SDH, which were not accounted for in the study. Clinically important factors that may increase the chances of warfarin-related serious bleeding were not captured. Stroke rates and subsequent outcomes used in the model were derived from randomized controlled trials, where subjects are more closely monitored than in usual practice. Therefore, compared to usual clinical practice, it is possible that the benefits and complications of antithrombotic therapy were overestimated and underestimated, respectively.
Samama study design: An epidemiologic case-control study on deep vein thrombosis (DVT) risk factors among 1272 outpatients seen in 624 general practitioner centers between October 1990 and December 1991. 636 patients with DVT (cases) were paired, according to sex and age, with 636 control patients presenting with influenza or rhinopharyngeal syndrome. DVT had to be documented by at least 1 objective test. Risk factors were classified into “intrinsic” (ie. permanent) and “triggering” (ie. transient) factors and were evaluated using univariate analysis.

Limitations: The control population was chosen to represent the least severe conditions requiring ambulatory health care, however, they may have significantly differed from the general population on risk factors that could affect risk of developing DVT. Assessment of etiologic importance of some risk factors (ie. violent effort or muscular trauma, general condition deterioration, regular smoker, infectious diseases, and long-distance travel) was difficult given that these factors were determined by the investigator. Multivariable regression analysis could not be performed due to large number of significant interaction tests.14

Reardon (VTE) study design: Analysis of anticoagulant use and patient characteristics in nursing home residents with VTE (n=489) using data extracted from the AnalytiCare LTC database from January 2007 through June 2009 (VTE index events occurred during the data uptake period of April 2007 to December 2008). Logistic regression models were used to evaluate the association of resident characteristics with warfarin use. Resident demographics possibly associated with warfarin use included age, sex, race/ethnicity, history of falling, AF, previous stroke, and other comorbidities. Cox regression models were used to evaluate persistence with warfarin therapy.

Limitations: The study did not assess the appropriateness of warfarin or other anticoagulants for treating VTE in study residents. The validity and reliability of MDS measures can vary differentially by a given indicator. The MDS did not encompass the full resident medical chart and may not have captured all current VTE and comorbid conditions. Survival analysis was used to analyze persistence, which did not account for any later therapy restarts once a subject was identified as having a discontinuation event.15

References