Benefits and Risks of Oral Anticoagulant Initiation Strategies in Patients with Atrial Fibrillation and Cancer: A Target Trial Emulation Using the SEER-Medicare Database

Bang Truong, PhD[1]; Lori Hornsby, PharmD[2], Brent I. Fox, PharmD, PhD[1]; Chiahung Chou, PhD[1]; Jingyi Zheng, PhD[3]; Jingjing Qian, PhD[1].
[1] Department of Health Outcomes Research and Policy, Auburn University Harrison College of Pharmacy, Auburn, AL, USA
[2] Department of Pharmacy Practice, Auburn University Harrison College of Pharmacy, Auburn, AL, USA
[3] Department of Mathematics and Statistics, Auburn University College of Sciences and Mathematics, Auburn, AL, USA

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INTRODUCTION

- Oral anticoagulants (OACs) are recommended for patients with atrial fibrillation (AFib) having CHA_2DS_2-VASc score ≥2. However, the benefits of OAC initiation in patients with AFib and cancer at different levels of CHA_2DS_2-VASc is unknown.
- In this study, our goal is to compare benefits and risks of multiple OAC initiation treatment strategies at different thresholds of risk of stroke among newly diagnosed AFib patients with cancer.

METHODS

- Study design and data source: retrospective, population-based cohort study with target trial framework using the SEER-Medicare database 2011-2019.
- Study components of emulation are described in **Table 1**

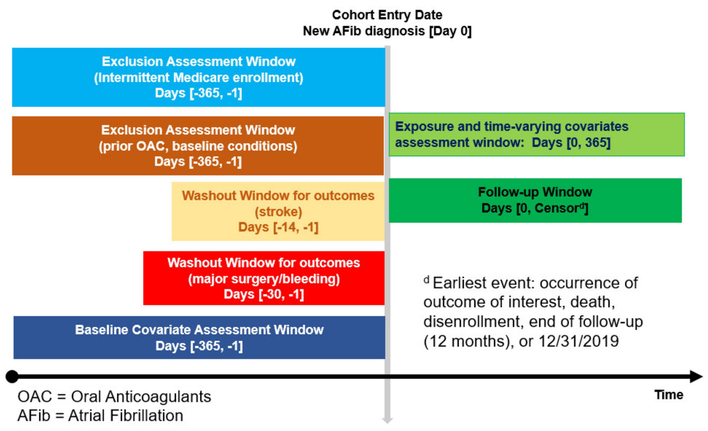

Figure 1. Study design and timeline

- Confounder: a set of 37 time-fixed baseline covariates and 7 time-varying covariates.
- Statistical analysis: cloning-censoring-weighting approach
  - Unstabilized time-varying censoring weights were used. Cumulative weights at each time points due to protocol violation are the product of inverse probability of weights for treatment initiation (IPTWs) and inverse probability of censoring weights (IPCWs) due to loss to follow-up.
  - Weighted pooled logistic regression were used to estimate treatment effects of 4 active treatment strategies compared with referent strategy. Hazard ratios (HRs) and 95% confidence interval (95% CIs) were obtained.
  - Subgroup analyses: cancer type (breast, lung, prostate), cancer status at baseline (active, history), cancer stage (local, regional, and distant), and tumor grade (I, II, and III).
  - Sensitivity analyses: (1) 36-month follow-up, (2) removing patients with metastatic cancer at baseline, (3) removing patients with thrombocytopenia, (4) truncated stabilized weights at 95th percentile.

REFERENCES AND ADDITIONAL INFO

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Table 1. Protocol for a target trial and emulation procedure using the SEER-Medicare database

Protocol component	Hypothetical target trial	Emulation in SEER-Medicare
Eligibility criteria	▪ Patients aged ≥66, newly diagnosed with non-valvular AFib within 12 months before enrollment and history or active breast, lung, prostate cancer between 01/01/2012 and 12/31/2019, continuously enrolled in Medicare part A, B, D, and without Medicare Advantage for 12 months before the diagnosis. ▪ No history of OAC use; no history of mitral valve disease, heart valve repair or replacement, deep vein thrombosis, pulmonary embolism, or joint replacement ▪ Without any diagnosis of stroke within the previous 14 days ▪ Without any conditions associated with an increased risk of bleeding, including major surgery within the previous month, history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding, gastrointestinal hemorrhage within the last 30 days ▪ Without renal impairment stage 5 or end-stage renal diseases within the last 12 months	Same as target trial
Treatment strategies	Eligible individuals are randomly assigned to one of the following 5 treatment strategies (1) initiate OAC when CHA_2DS_2-VASc ≥1, (2) initiate OAC when CHA_2DS_2-VASc ≥2 (3) initiate OAC when CHA_2DS_2-VASc ≥4, (4) initiate OAC when CHA_2DS_2-VASc ≥6, (5) never initiation of OACs (reference group)	Cloning-censoring-weighting approach to mimic randomization.
Follow-up	The follow-up of target trial starts at first diagnosis of AFib. End of follow-up = the occurrence of a specific study outcome, the end of administrative censoring (12 months after baseline), death, loss to follow-up, or December 31, 2019, whichever came first.	Same as target trial
Outcomes	Ischemic stroke and major bleeding	Same as target trial, identified by diagnosis and procedure codes
Causal contrast	Intention-to-treat effect, per-protocol effect	Observational analog of per-protocol effect

RESULTS

- The final sample included 39915 individuals.
- Baseline characteristics: 77.16 ±7.31 years old, 46.33% female, 85.11% White, 42.85% with lung cancer (42.85%), 47.8% with local cancer stage.
- At baseline:
  - CHA_2DS_2-VASc = 1: N = 3222 (8.07%)
  - CHA_2DS_2-VASc = 2: N = 6715 (16.82%)
  - CHA_2DS_2-VASc = 3: N = 9759 (24.45%)
  - CHA_2DS_2-VASc = 4: N = 10111 (25.33%)
  - CHA_2DS_2-VASc = 5: N = 6103 (15.29%)
  - CHA_2DS_2-VASc ≥ 6: N = 4005 (10.03%)
- Only 9898 patients (24.81%) initiated OACs within 12-month follow-up after their initial NVAF diagnosis

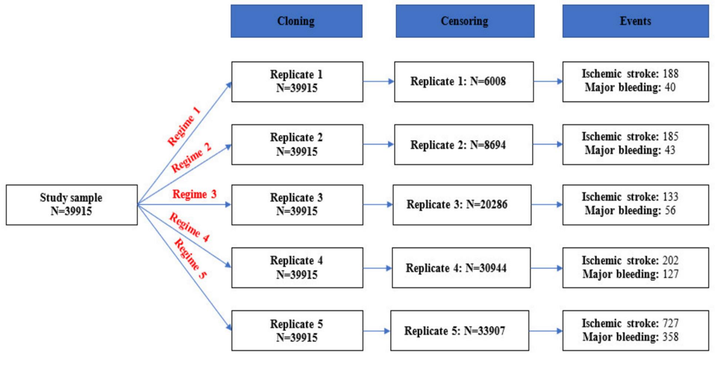

Figure 2. Summary of cloning and censoring steps

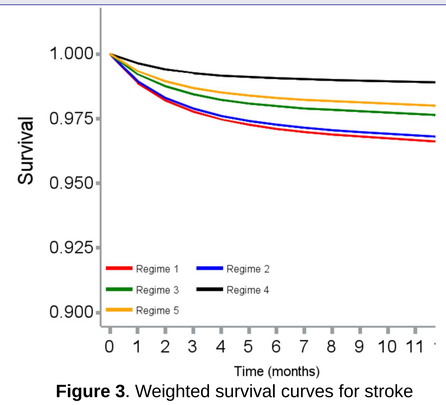

Figure 3. Weighted survival curves for stroke

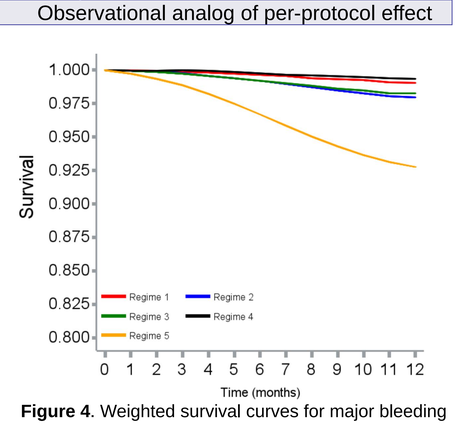

Figure 4. Weighted survival curves for major bleeding

Table 2. Incidence rates and HR (95% CI) of 5 treatment strategies of OAC initiation

	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Regimen 5
Ischemic stroke					
Incidence rate*	37.75	35.03	13.88	12.18	35.01
Adjusted HR (95% CI)	1.30 (1.11-1.54)	1.32 (1.12-1.56)	1.13 (0.95-1.33)	0.64 (0.54-0.75)	Reference
Major bleeding					
Incidence rate*	7.87	7.90	5.81	7.64	17.13
Adjusted HR (95% CI)	0.55 (0.38-0.78)	0.61 (0.42-0.87)	0.58 (0.41-0.81)	0.49 (0.44-0.55)	Reference

per 1000 person-years

- In patients with short life expectancy or advanced cancer such as lung cancer and regional/metastatic cancer, OAC initiation at any CHA_2DS_2-VASc level increased risk of stroke and did not reduce risk of bleeding (except for starting at CHA_2DS_2-VASc ≥6).
- The main findings remained robust in sensitivity analyses.

CONCLUSION

Among cancer patients with new AFib diagnosis, OAC initiation at higher risk of stroke is more beneficial in preventing ischemic stroke and bleeding. Patients with advanced cancer or low life-expectancy may initiate OACs when CHA_2DS_2-VASc score≥6.