Safety and Effectiveness of Oral Anticoagulants in Patients with Atrial Fibrillation and Cancer

by

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Abstract

Background: The use of oral anticoagulants (OACs) in patients with atrial fibrillation (AFib) and cancer remains suboptimal due to insufficient evidence in clinical guidelines. In this dissertation, our goals are to (1) screen for clinically relevant drug-drug interactions (DDIs) between direct oral anticoagulants (DOACs) and antineoplastic agents (Aim 1); (2) examine benefits and risks of OAC initiation strategies according to stroke risk and compare the effectiveness and safety between DOACs and warfarin (Aim 2); and (3) develop and validate machine learning (ML) algorithms to predict 1-year risk of stroke and bleeding among patients with AFib and cancer (Aim 3).

Methods: In Aim 1, we conducted a retrospective cross-sectional analysis of adverse events (AE) reports from the 2004-2021 US Food and Drug Adverse Events Reporting System (FAERS) database. Disproportionality analysis, logistic regression, and multi-item Gamma-Poisson shrinker were used to calculate the safety signals in bleeding or stroke of DOAC-antineoplastic agents combination. For Aims 2 and 3, population-based retrospective cohort studies including patients with newly diagnosed AFib and a record of breast, lung, or prostate cancer were conducted using the 2011-2019 Surveillance, Epidemiology, and End Results (SEER)-Medicare database. In Aim 2, we emulated target trials to compare risk of stroke and bleeding among patients who initiated OACs at CHA_2DS_2-VASc score ≥ 1, ≥ 2, ≥ 4, ≥ 6, and never initiated (Aim 2.1) and between DOAC and warfarin initiators (Aim 2.2). Pooled logistic regressions with inverse probability weighting were used to estimate the treatment effect, adjusting for baseline and time-varying covariates. In Aim 3, we fitted elastic net, Random Forest (RF), extreme Gradient Boosting (XGBoost), Support Vector Machine (SVM), and Neural Network on the training dataset and validated ML algorithms

on the testing dataset. Area under the curve (AUC), sensitivity, specificity, F2 score, and Brier score were compared across the models.

Results: No significant risk signal of DDIs between DOACs and antineoplastic agents on therapeutic class level was detected. For individual antineoplastic drugs, only the concomitant DOAC-neratinib exhibited a risk signal [EBGM (EB05-EB95) = 2.71 (2.03-3.54)]. Next, we found that OAC initiation at higher level of CHA_2DS_2-VASc score (≥6) reduced risk of stroke compared to non-initiators, while all OAC initiation strategies at different level of CHA_2DS_2-VASc score reduced risk of bleeding. However, OAC initiation at low CHA_2DS_2-VASc scores were not beneficial or even harmful among patients with lung cancer or advanced cancer stages. Further, DOACs had a similar risk of stroke and major bleeding compared with warfarin in patients with AFib and cancer. Lastly, in prediction of ischemic stroke, RF outperformed other ML models [AUC 0.916, sensitivity 0.868, specificity 0.801, F2 score 0.375, Brier score=0.035]. However, the performance of ML algorithms in prediction of major bleeding was poor.

Conclusions: Most *in vitro* DDIs between DOACs and antineoplastic agents may not be clinically relevant. In addition, among cancer patients with new AFib diagnosis, OAC initiation at higher risk of stroke (CHA_2DS_2-VASc score ≥6) may be more beneficial in preventing ischemic stroke and bleeding. Patients with advanced cancer status or low life-expectancy should be given OACs when CHA_2DS_2-VASc score≥6. Regarding treatment choice, DOACs are safe and effective alternatives to warfarin in patients with AFib and cancer. For risk assessment, we demonstrated a promising application of ML in prediction of stroke among patients with AFib and cancer. This tool may be leveraged in assisting clinicians to identify patients at high risk of stroke and optimize treatment decisions.

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Chapter 1: Introduction

1.1. Overview of oral anticoagulant therapy in patients with atrial fibrillation and cancer

Atrial fibrillation (AFib) is the most common type of cardiac arrhythmia.[1] In the United States (US), AFib has affected 2.7-6.1 million Americans and is expected to reach 12 million by 2030.[2-4] AFib is associated with more than 454000 hospitalizations and 158000 deaths annually.[2-4] Risk factors of AFib include non-modifiable (i.e., age, sex, race/ethnicity, geographical region, and family history) and modifiable lifestyle-related risk factors (i.e., smoking, alcoholism, body mass index, chronic comorbidities, and concomitant treatment such as surgery or medications).[4,5] Patients with AFib are at substantial risk of ischemic stroke and venous thromboembolism (VTE).[6,7] In addition, AFib is associated with substantial economic burden including medication, medical procedure, and consultation costs.[8] Total net incremental direct medical cost for AFib was $8705 per year on individual level and $6.0 to $26.0 billion per year on population level in the US (2008 US $).[9]

Compared with individuals without cancer, patients with cancer had a 47% higher risk of developing AFib.[10] The development of AFib in cancer patients may be triggered by pro-inflammatory status of the immune system, inflammatory responses, surgical interventions, radiation, chemotherapeutic agents and other medications.[11] In the US, the incidence of AFib in cancer patients increased from 8.28% in 2003 to 10.06% in 2014.[12] Compared to patients without cancer, patients with AFib and cancer have 4- to 7-fold higher risk of VTE and 2-fold higher risk of bleeding.[13,14]

Oral anticoagulants (OACs) such as warfarin and direct oral anticoagulants (DOACs) are approved for the prevention of stroke and VTE in AFib patients.[15] The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) and European Society

of Cardiology (ESC) recommend DOACs over warfarin in non-valvular AFib patients due to their superiority in reducing stroke, VTE, bleeding, and mortality.[15,16] However, in patients with AFib and cancer, their effectiveness and safety have not been established. Although studies have shown the benefits of OACs in patients with AFib and cancer, only half of the patients initiated OACs.[17-19] Patients with AFib and cancer were less likely to receive anticoagulants than those without cancer.[20] Such underutilization may be due to limited evidence in safety and effectiveness of OACs in patients with AFib and cancer in current guidelines.[16,21-23]

There have been four main evidence gaps in the management of patients with AFib and cancer. First, although DOACs have been preferred over warfarin in AFib patients, their use in patients with AFib and cancer may be hampered by the concern about *drug-drug interactions* (DDIs) with antineoplastic drugs, proposed by *vitro* studies.[11,22,24]. Second, *optimal OAC initiation strategy* in patients with AFib and cancer is unknown. In general AFib patients, OACs are recommended when CHA_2DS_2-VASc score ≥ 2,[15,16] but such threshold has not been established among patients with cancer. Third, treatment selection between warfarin and DOACs is inconclusive in current clinical guidelines.[16,21-23] Although existing studies have showed DOACs were non-inferior to warfarin in lowering risk of stroke, VTE and bleeding compared with warfarin in patients with AFib and cancer, such findings were generated from either small subgroups of RCTs or from observational studies where important confounders such cancer stage and tumor grade were not missing.[25-27] Fourth, current *risk assessment tools*, such as CHA_2DS_2-VASc (risk of stroke) and HAS-BLED (risk of bleeding) scores, are not highly predictive in patients with AFib and cancer.[28-30] Refining these tools is critical to help clinicians identify patients at high risk of stroke and bleeding and tailor treatment selection.

1.2. Overall objectives of the doctoral dissertation project

The overall goals of this dissertation project are to (1) detect clinically relevant DDIs between DOACs and antineoplastic agents, (2) determine the optimal OAC initiation strategy, (3) compare the safety and effectiveness between DOACs and warfarin in patients with AFib and cancer, and (4) develop new risk assessment tools to identify patients at high risk of stroke and bleeding in patients with AFib and cancer.

1.3. Specific Aims

In this doctoral dissertation project, we proposed a comprehensive, multimethod approach to evaluate safety and effectiveness of OACs in patients with AFib and cancer.

Aim 1: **To generate hypotheses on the association between reported bleeding or stroke events and the combination of DOACs and antineoplastic agents.**

In this aim, our goal is to detect clinically relevant DDIs using pharmacovigilance and data mining approach. We leveraged spontaneous adverse event reporting system (i.e., The FDA Adverse Event Reporting System – FAERS) to identify signals of DDIs between DOACs and antineoplastic agents. FAERS database is a publicly available spontaneous adverse event (AE) reporting system by the US Food and Drug Administration (FDA) containing patient demographic, administrative information, drug information, AEs, and patient outcomes for drug and biologic products. We compared the reporting rates of bleeding and stroke of DOACs and antineoplastic agents using disproportionality analysis, logistic regression, and Multi-item Gamma-Poisson Shrinker.

Aim 2: To compare the risk of stroke and bleeding among different OAC initiation strategies (Aim 2.1) and between DOAC and warfarin (Aim 2.2).

In Aim 2, we used target trial framework to conduct retrospective, population-based cohort studies using Surveillance, Epidemiology, and End Results Program (SEER) registry linked to Medicare database. SEER registry collects and releases data on patient demographics, cancer characteristics and treatment, with a linkage to Medicare database to additionally capture medical events and prescriptions. In Aim 2.1, we compared the risks of stroke and bleeding among patients with AFib and cancer who initiated OACs at different levels of CHA_2DS_2-VASc score (CHA_2DS_2-VASc score ≥1, CHA_2DS_2-VASc score ≥2, CHA_2DS_2-VASc score ≥4, CHA_2DS_2-VASc score ≥6 versus no initiation). In Aim 2.2, we compared risk of stroke and bleeding between DOAC and warfarin users among patients with AFib and cancer. Weighted pooled logistic regression was used to estimate the causal effect of treatment strategies on the outcomes, adjusted for baseline and time-varying confounders.

Aim 3: To develop and validate novel ML algorithms to predict 1-year risk of stroke and bleeding in patients with AFib and cancer.

In Aim 3, we aimed to predict 1-year risk of ischemic stroke and bleeding in patients with AFib and cancer. First, we created a cohort of patients newly diagnosed with AFib and history of cancer using SEER-Medicare data. We then identified potential features by literature review. We trained and validated the performances of the following ML models: elastic net logistic regression, Random Forest, eXtreme Gradient Boosting (XGBoost), support vector machine, and neural network.

1.4. Importance of the project

Findings from this dissertation project are expected to contribute largely to the current practice in patients with AFib and cancer. First, the potential DDIs between DOACs and antineoplastic drugs remain a concern for clinicians to prescribe DOACs. Thus, it is necessary to know whether *in vitro*

DDIs between DOACs and anticancer drugs are clinically important. The pharmacovigilance approach is the initial step to establish safety profile of such DDIs in the absence of RCTs and population-based epidemiological studies. Higher reporting rates of events of interest for a drug-drug combinations compared with the referent drug combinations may warrant a further investigation with rigorous study design (i.e., retrospective cohort study) to explore the causal effects of such DDIs. Our findings on clinically relevant DDIs are expected to help clinicians refine their current DDI 'watch list', alleviate their concern about DDIs, and increase the uptake of OACs in patients with AFib and cancer.

Second, the hesitancy in OAC prescribing by many physicians due to the insufficient evidence on OAC therapy, such as optimal OAC initiation strategy and treatment selection between DOACs and warfarin. In particular, when a cancer patient is newly diagnosed with AFib at low risk of ischemic stroke (i.e., CHA_2DS_2-VASc score <2), whether this patient should start the treatment immediately or wait until they reach a higher risk of stroke (i.e., CHA_2DS_2-VASc ≥2 or ≥4). The benefits of stroke reduction and risk of bleeding should be carefully weighed in AFib patients with cancer to decide whether OACs should be initiated. However, the threshold CHA_2DS_2-VASc score ≥2 has not been validated in patients with cancer. We developed a protocol for a target trial and emulation procedure to compare the outcomes under different treatment strategies. The findings revealed the most favorable outcomes and corresponding optimal treatment strategy. Next, when the decision to initiate OACs is made, clinicians may consider between DOACs and warfarin. Prior observational studies assessing effectiveness and safety of DOACs versus warfarin did not incorporate important confounders such as cancer stage and tumor grade. We leveraged SEER registry linkage to conduct a cohort study by implementing the target trial framework and

analyzing the data like RCTs. We expect the proposed approach to generate solid evidence of the safety and effectiveness of DOACs versus warfarin in patients with AFib and cancer.

Current risk assessment tools for stroke (i.e., $CHADS_2$, CHA_2DS_2-VASc, and ATRIA) and bleeding (i.e., HAS-BLED, ORBIT) have been globally accepted for assessment of AFib patients. However, these tools have not performed well in patients with AFib and cancer. In this project, we used ML technique to develop new risk assessment tools. Compared with traditional risk scores, ML algorithms have more flexibility and capability to handle non-linear outcome-predictor relationship and high-dimensional data. The new tools may help patients at high risk of stroke and consider their risk of bleeding to initiate OACs.

This doctoral dissertation study is innovative in several aspects: (1) using multiple approaches to explore safety and effectiveness of OACs in patients with AFib and cancer, (2) combining individual-level outcome prediction and population-level effect estimation to improve health outcomes (3) implementing a target trial framework on cancer registry-linked claims data improve the quality of observational data, and (4) using ML technique to develop new risk assessment tools in patients with AFib and cancer.

Chapter 2: Literature review

2.1. The association between atrial fibrillation and cancer

2.1.1. Overview of atrial fibrillation

AFib is the most common type of cardiac arrhythmia.[1] AFib is currently a global health issue. In 2017, the prevalence of AFib was 37.574 million cases, which marked a 33% increase during the last 20 years.[31-34] The global incidence rate of AFib was approximately 5 million new cases per year.[4,34] according to the American Heart Association (AHA) and Center for Prevention and Disease Control (CDC), AFib has affected 2.7-6.1 million Americans and is associated with more than 454000 hospitalizations and 158000 deaths annually in the US. [2-4] The number of individuals diagnosed with AFib is projected to reach 12 million in the US. by 2030 and 17.9 million in Europe by 2060.[35,36]

Non-modifiable factors associated with AFib include age, sex, race/ethnicity, geographical region, and family history.[37] About 70% of patients with AFib were diagnosed in individuals aged 65 or more, which represents a prevalence of 10-18% in older adults.[38,39] Overall, men were more likely to develop AFib than women (6.0% vs. 5.1%, respectively).[38] Regarding racial disparities, AFib was less common in non-Whites than Whites. [40-43] North America is the region with the highest burden of AFib (700-775 per 100000) compared to other regions in the world.[33] Additionally, family history such as first-degree relatives is an independent risk factor of AFib.[44]

According to the AHA, modifiable lifestyle-related risk factors of AFib are physical inactivity, alcohol intake, smoking, and body mass index (BMI).[4] Individuals with chronic comorbidities are also at higher risk of developing AFib, including cardiovascular diseases, VTE, obstructive sleep apnea, diabetes, metabolic syndrome, chronic kidney diseases, and hyperthyroidism.[4,5] Additionally, AFib can be triggered by surgical interventions, particularly cardiac surgery.[45-47]

Some medications are associated with increased risk of AFib, such as bisphosphonates,[48-50] antiarrhythmic drugs,[51] non-steroidal anti-inflammatory drugs (NSAIDs),[52] and ivabradine.[53]

Stroke and VTE are the two major complications among patients with AFib. AFib is among the strongest predictors of stroke and has caused at least 20% of ischemic stroke cases each year.[6,7] Patients with AFib had nearly a 5-fold higher risk of stroke compared with individuals without AFib.[54] AFib is also associated with substantial risk of VTE (i.e., deep vein thrombosis and pulmonary embolism), and mortality.[55-59]

AFib has put a substantial financial burden on patients and the US healthcare system. On individual level, total net incremental direct medical cost in presence of AFib was $8705 per patient per year in the US ($20670 versus $11965).[9] On population level, AFib was associated with a higher medical expenditure, mainly on hospitalization (75% of direct and indirect medical costs) compared with non-AFib patients.[9] Estimated national incremental cost for AFib ranged from $6.0 to $26.0 billion per year (2008 US $).[9] In the last 10 years, healthcare cost associated with AFib is expected to increase due to the evolution in AFib management by the emergence of novel anticoagulants, new antiarrhythmic medications, and invasive treatment options.[8]

2.1.2. Atrial fibrillation in patients with cancer

Overall, the prevalence of AFib in patients with cancer is higher than the general population, ranging from 2% to 20%.[12,27,60-66] Cancer patients had a 47% higher risk of AFib compared with individuals without cancer (4.9 to 17.4 cases per 1000 person-years).[10,67-70] The risk of developing AFib was highest during the first three months after cancer diagnosis and decreased after six months.[68] Patients with lung cancer, multiple myeloma, non-Hodgkin and Hodgkin's lymphoma, prostate cancer, leukemia had the highest AFib incidence.[61]

Although the pathophysiological mechanisms by which AFib was developed in patients with cancer were not completely unveiled, the higher risk of AFib in cancer patients can be explained by the pro-inflammatory status of the immune system and inflammatory responses in cancer patients **(Figure 1)**.[71] The potential factors attributable to AFib in cancer patients are surgical interventions, radiation, chemotherapeutic agents, and medications used in palliative care **(Table 1)**.[11] In addition, shared risk factors of cancer and AFib may contribute to the development of AFib in cancer patients such as comorbidities, malnutrition, smoking status, alcohol intake, BMI, socioeconomic status (SES), and family history.[11] The coexistence of AFib and cancer may also be the consequence of new-onset cancer among patients with existing AFib.[65,72]

Table 1. Factors associated with the risk of atrial fibrilation[11]

Cancer-related factors	Description
surgery	lung cancer resections, abdominal surgery, colorectal surgery, neck surgery, thyroidectomy
radiation	ionizing radiation
chemotherapeutic agents	alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), anthracyclines (doxorubicin, idarubicin, epirubicin, mitoxanthone, liposomal anthracyclines), antimetabolites (capecitabine, 5-FU, gemcitabine), tyrosine kinase inhibitors (ponatinib, sorafenib, sunitinib, ibrutinib, bevacizumab), topoisomerase II inhibitors (amsacrine, etoposide), taxanes (docetaxel, paclitaxel), Vinca alkaloids (Vinblastine, Vincristine), and monoclonal antibodies (trastuzumab, etaricizumab)
palliative care medications	NSAIDs, opioids

AFib atrial fibrillation, NSAID non-steroidal anti-inflammatory drugs

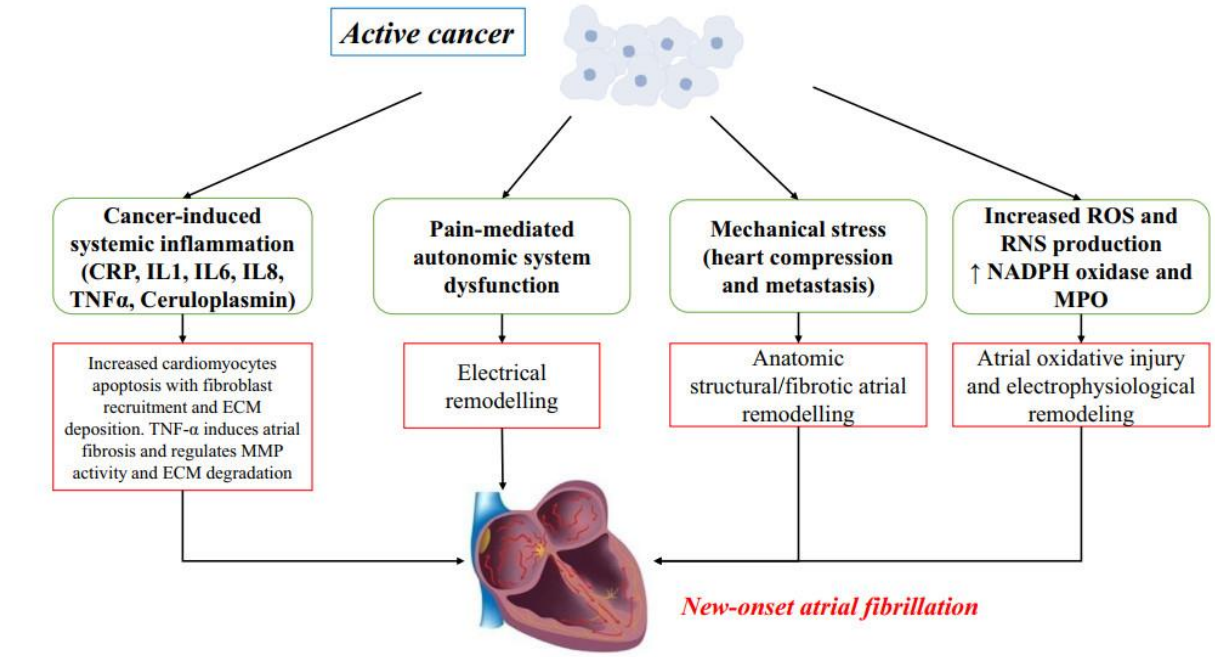


Figure 1. Potential mechanisms for the development of atrial fibrillation in patients with cancer[11]

2.2. Trends and burdens of concomitant atrial fibrillation and cancer

The incidence and prevalence of AFib among cancer patients increased constantly over time.[66,72], Han (2021) found that the rate of AFib in metastatic cancer patients rose from 8.28% to 10.06% in 2003-2014 in the US.[66] Compared with AFib in the general population, AFib with malignancy was associated with higher burden of mortality and mortality. Because both cancer and AFib are independent risk factors of ischemic stroke and VTE, these patients may have a higher risk of developing these events than non-cancer patients.[26,73-79] In addition, the presence of cancer complicates risk of bleeding in patients with AFib due to dysregulated hemodynamics, tumor biology, inflammatory responses, and anticancer treatments.[80] This may potentially exacerbate the risk of bleeding if OACs were given to patients with two conditions.[80] No difference in major bleeding and intracranial hemorrhage was observed in patients with cancer compared with those without cancer in ROCKET-AF (HR 1.17, 95% CI 0.88–1.54) and ARISTOTLE (HR 1.10, 95%

CI 0.99–1.22).[26,75,76] Nonetheless, ENGAGE AF-TIMI 48 and ORBIT-AF found an elevated risk of major bleeding in cancer patients (HR 2.45, 95% CI 2.07–2.89 and HR 1.21, 95% CI 1.04–1.40, respectively).[64,77]

2.3. Management of patients with atrial fibrillation

2.3.1. Overview of treatment strategies for patients with atrial fibrillation

According to the 2019 ACC/AHA/HRS and 2020 ESC guidelines, the goals of treatment for AFib are to reset the heart rhythm, control heart rate, and prevent systemic stroke and VTE.[15,16] Non-pharmacological lifestyle interventions such as weight loss, alcohol abstinence, and physical activity are recommended to reduce the burden of AFib and other underlying conditions related to AFib.[16] Antiarrhythmic medications, percutaneous catheter ablation, and/or a surgical procedure, or electrical cardioversion are recommended in AFib patients who require ventricular rate control.[15,16] For atrioventricular node control, beta blockers, non-dihydropyridine calcium channel blockers, or digoxin can be added.[15,16] OACs are recommended for stroke prevention by ESC and ACC/AHA. Other antithrombotic treatment such as aspirin and/or clopidogrel are not recommended because they are ineffective and potentially harmful in prevention of stroke in AFib patients, except for those with concomitant acute coronary syndrome.[15,16] If OACs are contraindicated, left atrial appendage occlusion and exclusion devices may be used.[15,16] Unfractionated heparin and low-molecular-weight heparin (LMWH) are recommended for OAC interruption and bridging therapy in AFib patients requiring undergoing procedures or surgeries.[15]

2.3.2. Oral anticoagulants for the management of atrial fibrillation

Vitamin K antagonists (VKA) and DOACs are approved for stroke prevention in general non-valvular AFib (NVAF) population. Warfarin has been used for the treatment of AFib since 1950s while DOACs (e.g., dabigatran, rivaroxaban, apixaban, and edoxaban) were approved by the FDA

to prevent stroke and VTE in AFib patients in 2010. Compared with warfarin, DOACs have some major advantages: rapid onset/offset action, more predictable pharmacokinetics, less laboratory monitoring, fewer drug-food and drug-drug interactions (DDIs).[81,82] However, DOACs have higher cost, contraindications in patients with severe chronic kidney diseases, and limited antidotes in case of major bleeding.[81,82] **Table S1, Supplemental Tables** summarizes indications, contraindications, and pharmacokinetics, and other advantages/disadvantages of warfarin and DOACs.

2.3.3. Effectiveness and safety of warfarin and direct oral anticoagulants in atrial fibrillation

Overall, DOACs were non-inferior or superior to warfarin in preventing stroke, VTE, bleeding, and mortality for patients with AFib [83-87]. The evidence is consistent in subgroups of older adults,[88,89] Asian,[90] obesity,[91-93] valvular AFib,[94] renal diseases,[95-97] or cancer.[26] Findings from these studies are summarized in **Table S2, Supplemental Tables**. The latest guidelines of ESC and ACC/AHA/HRS recommend DOACs over warfarin in the prevention of stroke and VTE in non-valvular AFib patients.[15,16]

2.4. Current practice and utilization patterns of anticoagulant treatment in patients with atrial fibrillation cancer

The current management of patients with AFib and cancer with OACs remains suboptimal due to insufficient evidence. The presence of cancer may increase the risk of stroke and VTE and amplify the risk of bleeding compared with general population.[23] Although studies have demonstrated the benefit of OACs in preventing stroke and VTE in patients with AFib and cancer, only half of patients with AFib and cancer initiated OACs.[17-19] These patients were less likely to receive OACs compared those without cancer.[20] Such underutilization may be due to the fact the evidence on safety and effectiveness of OACs in patients with AFib and cancer is scarce and unconvincing for

clinicians to prescribe these medications. ESC, AHA, ASCO, and ISTH currently do not recommend one particular OAC over another.[16,21-23] Instead, risk-benefit assessment should be rigorously considered by a multidisciplinary decision balancing risk of stroke and bleeding in which cancer characteristics (i.e., cancer type, stage, sites), antineoplastic agents, and DDIs are important factors **(Figure 2)**.[16,21,22,50]

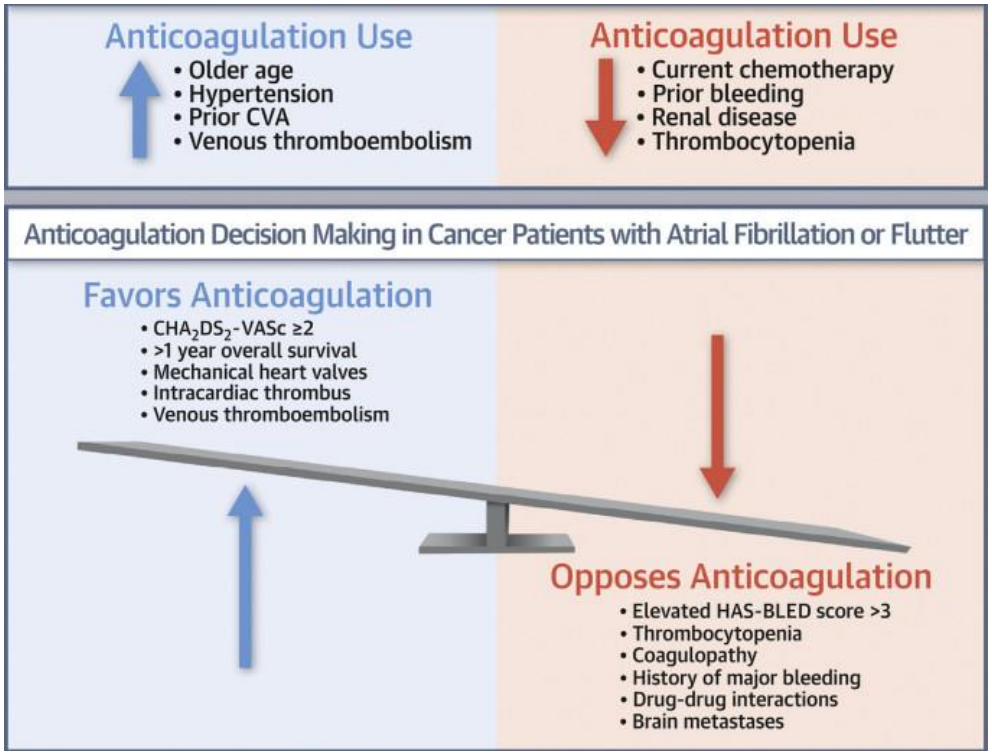


Figure 2. Anticoagulation Decision Making in Cancer Patients With Atrial Fibrillation[17]

Although DOACs were available since 2010 and have some major advantages over warfarin (i.e., dosing, treatment monitoring, DDIs), their uptake was not high because data supporting their use is limited and there is a concern about DDIs with antineoplastic agents.[23] RCTs generally excluded cancer patients due to low life expectancy (e.g., ENGAGE, ROCKET-AF, and ARISTOLE) and DDIs between OACs with chemotherapy.[75-77] A post-hoc analysis of RCTs pooling patients developed cancer after randomization found DOACs were superior to warfarin in reducing stroke

and bleeding.[26] However, the interpretation of the findings may be limited by sample size, clinical and methodological heterogeneity among included studies.[26]

LMWH were also prescribed for the prevention of stroke and VTE in AFib patients with cancer.[19,98,99] However, due to the paucity of data, LMWH is currently not recommended for prevention of thromboembolic events in patients with cancer.[23] ISTH highlighted that LMWH should be used only in patients who cannot tolerate oral anticoagulants (i.e., nausea and vomiting).[22]

2.5. Risk assessment tools in patients with atrial fibrillation cancer

Studies revealed that only half of AFib patients with cancer initiated OACs.[17-19] This may be due to the limited evidence of effectiveness and safety of OACs, lack of validated risk assessment tools, and concern about DDIs when OACs are initiated.[17-19] AFib patients with cancer were at higher risk of stroke, VTE, and bleeding compared with those without cancer. However, there is no validated tool to evaluate risk of stroke and bleeding in patients with AFib and cancer.

2.5.1. Risk of stroke assessment in patients with atrial fibrillation and cancer

In AFib patients, CHA_2DS_2-VASc score has been used to assess risk of stroke.[15,100] CHA_2DS_2-VASc is a composite score of congestive heart failure (1 point), hypertension (1), age ≥75 (2), diabetes mellitus (1), prior stroke, TIA, or thromboembolism (2), vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque) (1), age 65-74 years, and sex category (1).[15,100] The latest ESC guideline recommends OACs for men with CHA_2DS_2-VASc score ≥1 and for women with CHA_2DS_2-VASc scores ≥ 2, while the current ACC/AHA/HRS guidelines recommend OACs for those with CHA_2DS_2-VASc scores ≥2.[15,16] However, CHA_2DS_2-VASc score was not highly predictive of stroke in patients with cancer.[28,29] Other risk scores such as

$CHADS_2$ and Khorana score did not perform well in patients with cancer.[29,101] There is no adapted risk score exclusively developed for cancer patients.

2.5.2. Risk of bleeding assessment in patients with atrial fibrillation and cancer

HAS-BLED score has been widely used to assess risk of stroke in patients with AFib. [102] HAS-BLED is a linear combination of hypertension (1 point), abnormal renal/liver function (1+1), stroke (1), bleeding tendency or predisposition (1), labile INR for patients taking warfarin (1), age ≥65, drugs (concomitant aspirin or NSAIDs) or excess alcohol use (1+1).[102] A score of ≥3 indicates "high risk" and caution and regular monitoring after treatment.[16] However, cancer was an independent risk factor of bleeding, therefore, HAS-BLED may not perform well in patients with AFib and cancer.[103] Pastori found that HAS-BLED outperformed ATRIA and ORBIT scores for intracranial hemorrhage, but not for major and gastrointestinal bleeding.[30]

In conclusion, the traditional assessment scores were not highly predictive of stroke and bleeding in AFib patients with cancer. There is an urgent need to develop new assessment tools in patients with AFib and cancer. In the absence of highly predictive scores in clinical assessment, physicians may over- or under-estimate the risk of life-threatening events for patients, which may result in a wrong decision to initiate or not to initiate OACs.

2.6. Optimal oral anticoagulation initiation strategy in patients with atrial fibrillation and cancer

Prior studies have shown the net benefit of initiating OACs in patients with AFib and cancer. OAC initiation was associated with a slightly reduced risk of composite endpoint of ischemic stroke and intracranial bleeding compared with non-users (HR 0.90 95% CI 0.80-1.00).[18] The incidence of the composite endpoint was lower among OAC users compared with non-users, especially in those with moderate (HR 0.82 95% CI 0.70-0.96) or high (HR 0.82, 95% CI 0.79-0.86) baseline

CHA_2DS_2-VASc score.[18] In another study, O'Neal found that AFib patients with cancer who sought for cardiologist shortly after AFib diagnosis were more likely to receive OACs and had a lower risk of stroke and non-inferior risk of bleeding compared with non-users.[20] While current guidelines recommend OACs for those with CHA_2DS_2-VASc scores ≥2, such threshold has not been established in patients with AFib and cancer. For example, when a cancer patient is newly diagnosed with AFib with low risk of ischemic stroke (i.e., CHA_2DS_2-VASc score <2), should this patient start the treatment immediately or wait until they reach a higher risk of ischemic stroke (i.e., CHA_2DS_2-VASc score ≥2 or CHA_2DS_2-VASc score ≥4)? Future research is warranted to identify the optimal OAC treatment strategy.

2.7. Effectiveness and safety of direct oral anticoagulants versus warfarin in patients with atrial fibrillation and cancer

Currently, there is no high-quality recommendation on treatment selection between DOACs and warfarin in clinical guidelines. A summary of evidence on effectiveness and safety of DOACs in patients with AFib and cancer can be found in **Table S3, Supplemental Tables**. Three RCTs included cancer patients as a small subgroup of study samples, or cancer was diagnosed during follow-up.[75-77] Observational studies have been conducted to compare the safety and effectiveness between DOACs and warfarin: two from the US (Veteran Affairs data, Medicare, and commercial claims data), [25,104], one from Japan (single-center),[105] one from Korean (population-based),[106] two from Denmark (population-based), [107,108] two from Taiwan (population-based),[109,110] and two from Sweden (population-based).[111] The most common cancer types included in these study populations are gastrointestinal, prostate, lung, and breast cancer. Overall, the DOACs were superior or equivalent to warfarin in prevention of stroke or VTE. For safety profile, DOACs were non-inferior to warfarin in reducing rates of bleeding.

In addition, the treatment effect was not generally reported across cancer characteristics (i.e., cancer type, cancer stage). Importantly, these observational studies did not incorporate cancer stage and tumor grade. Cancer characteristics may confound the relationship between OAC selection and treatment outcomes. On one hand, clinicians may consider cancer type, stage, and tumor grade to decide whether warfarin or DOACs should be initiated in AFib patients with cancer. On the other hand, these factors also affect the risk of stroke or bleeding. For example, stroke or bleeding are more likely to occur if the patient is critically severe or in the advanced cancer stage.[112,113] Hence, the absence of such important variables may lead to bias. In addition, concomitant antineoplastic agents may affect OAC selection due to potential DDIs.[11] Therefore, future studies should adjust for these important confounders in the analysis.

2.8. Drug-drug interactions between direct oral anticoagulants and antineoplastic agents

Concomitant use of OACs and antineoplastic agents is unavoidable when managing patients with AFib and cancer. Although DOACs have fewer DDIs than warfarin, concern about DDIs between DOACs and antineoplastic agents have prevented the uptake of DOACs in cancer patients.[11,23]

2.8.1. In vitro drug-drug interactions between oral anticoagulants and antineoplastic agents

Pharmacokinetic (PK) studies have suggested that effect of DOACs might be amplified or mitigated by a co-administration of another drug metabolized by Cytochrome P450 enzymes (CYP) in the liver or P-glycoprotein (P-gp) transporter.[114] Rivaroxaban and apixaban are metabolized mainly by CYP3A4 and all four DOACs are the substrates of P-gp.[115] Therefore, DDIs between DOACs and antineoplastic agents or supportive cancer care medications which are inhibitors or inducers of CYP3A4/P-gp may lead to over-/underexposure of DOACs and give rise to bleeding or stroke. The *in vitro* DDIs of DOACs and anticancer agents can be found in **Table 2**. Oral targeted anticancer therapy (i.e., tyrosine kinase inhibitors and other kinase inhibitors)

makes up a large proportion of *in vitro* DDIs due to the inducive/inhibitory activities on CYP3A4 or P-gp.[24] PK studies also suggested some hormonal therapy (i.e., tamoxifen, anastrozole, abiraterone, bicalutamide, and enzalutamide) may alter the concentrations of DOACs in prostate and breast cancer patients.[116] In addition, chemotherapeutic agents (i.e., anthracyclines, alkylating agents, and Vinca alkaloid) may increase the risk of DDIs for those who are already on DOACs.[116] The 2018 European Heart Rhythm Association Practical Guide recommended against the concomitant use of DOACs and hormonal agents, tyrosine kinase inhibitors, and some chemotherapeutic agents.[117]

Table 2. Proposed pharmacokinetic drug-drug interactions between novel oral anticoagulants and anticancer treatment[24,116,117]

Antineoplastic therapeutic class	**CYP3A4**	**P-glycoprotein**
Kinase inhibitors (tyrosine kinase inhibitors, protein kinase inhibitors)	*Inhibitors*: imatinib, dasatinib, nilotinib, lapatinib, erlotinib, crizotinib, tivozanib, pazopanib, axitinib, brigatinib, ceritinib, lorlatinib, binimetinib, trametinib, palbociclib, ribociclib, entrectinib, larotrectinib, idelalisib *Inducers*: vemurafenib, dabrafenib, encorafenib	*Inhibitors*: imatinib, nilotinib, lapatinib, sunitinib, crizotinib, vandetanib, osimertinib, neratinib, gefitinib, erlotinib, afatinib, sorafenib, regorafenib, ponatinib, alectinib, lorlatinib, vemurafenib, cobimetinib, abemaciclib, pimegatinib, entrectinib, cabozatinib, capmatinib, idelasinib *Inducers*: dabrafenib, encorafenib
Hormone	*Inhibitors*: letrozole, anastrozole, abiraterone, bicalutamide, tamoxifen *Inducers*: enzalutamide	*Inhibitors*: tamoxifen, abiraterone, enzalutamide
Chemotherapy	*Inhibitors*: vinblastine, vincristine, vinorelbine, docetaxel, doxorubicin, idarubicin, cyclophosphamide, ifosfamide, lomustine, irinotecan, etoposide *Inducers:* paclitaxel	*Inhibitors*: vinblastine, doxorubicin, methotrexate
Immune-modulating agents	*Inhibitors*: cyclosporine, sirolimus, temsirolimus, tacrolimus *Inducers*: dexamethasone, prednisolone	*Inhibitors:* cyclosporine, sirolimus, tacrolimus, dexamethasone *Inducers*: dexamethasone

CYP3A4 Cytochrome 3A4

2.8.2. Clinical impact of drug-drug interactions between direct oral anticoagulants and antineoplastic agents

Although the DDIs between DOACs and antineoplastic agents were proposed by *in vitro* studies, the clinical impact of these DDIs is unknown. Pre-clinical studies examine DDIs in a simple context, ignoring the presence of patient-level factors such as patient demographics, clinical characteristics, genetic factors, comorbidities, and other concurrent medications. Therefore, findings from *in vitro* studies may not translate into clinical impact of such DDIs.

Findings from epidemiological studies on DDIs between DOACs and antineoplastic agents may inform decision-making in AFib patients with cancer. However, few studies have been conducted to explore the clinical impact of DDIs between DOACs and antineoplastic agents. Wang (2021) compared the incidence of bleeding among AFib patients who were concurrently exposed to DOACs plus anticancer medications with CYP3A4 and/or P-gp inhibitory activity versus those exposed to DOACs alone.[118] The authors found that concomitant use of DOACs and CYP3A4/P-gp-inhibiting anticancer medications did not result in elevated risk of bleeding compared with DOACs alone. However, this study has several limitations. First, the results may not be generalizable to the scenarios where clinicians consider initiating warfarin or DOACs given they are already on antineoplastic agents. Second, confounding by indication may persist because the patients initiated antineoplastic drugs may not be comparable to those who did not receive the drugs. In addition, potential confounders such as cancer stage and tumor grade were not adjusted in the analysis.

In fact, assessing the clinical impact of DDIs among patients with AFib and cancer using epidemiological studies is challenging. The major challenge is the balance between rigorous design and the availability of the data. Such studies should include patients with AFib and cancer, on the

same chemotherapeutic agents, initiating OACs for the same indication with comparable exposure time to OACs and antineoplastic agents, and the availability of cancer characteristics.[119] Pharmacovigilance studies using spontaneous reporting systems such as FAERS database and European VigiBase can be used to detect signal of DDIs between DOACs and anticancer drugs. This is the initial step to screen for potentially clinically relevant DDIs for further investigation. Several studies have showed the safety signals of DDIs between DOACs and several anticancer drugs (i.e., enzalutamide, lenalidomide, ibrutinib, pomalidomide, sorafenib, and sunitinib) using big data from VigiBase.[120,121] It is also noticed that causality cannot be claimed, but findings have played a critical role in early detection of adverse drug events, especially in oncology,[122] when such events are not reported during RCTs and traditional epidemiological studies are not feasible due to delayed data availability.

In summary, currently, there is limited evidence in the clinical impact of DDIs between DOACs and antineoplastic agents. In the absence and challenges of pharmacoepidemiological studies, pharmacovigilance may play an important role in safety signals detection of such DDIs.

2.9. Baseline risk assessment in patients with atrial fibrillation and the potentials of machine learning in clinical decision-making

Identifying who are at high risk of stroke or bleeding is a critical step in management of patients with AFib and cancer. However, current risk assessment tools of stroke such as $CHADS_2$,[123] CHA_2DS_2-VASc,[100] ATRIA[124] were not highly predictive or not tested in in AFib patients with cancer.[28,29] For risk of bleeding, HAS-BLED, ORBIT and ATRIA scores are widely used in patients with AFib but they do not perform well in patients with cancer.[30] Currently, no risk assessment tool was developed for assessment of risk of stroke and bleeding in patients with AFib and cancer.

CHA_2DS_2-VASc and HAS-BLED are simple and easy for implementation among clinicians because they are linear combinations of patients' diseases and conditions.[100] However, when the relationships between patients' characteristics and outcomes become complicated, these tools may not perform well. Recently, machine learning (ML) algorithms have been increasingly used to support clinical decision-making.[125-127] Compared with conventional regression-based methods, ML models can 'smooth' over the data when the association between dependent and independent variables is not linear (i.e., random forest, boosting, bagging).[128] ML models overperformed parametric regressions in handling high-dimensional data and interactions between variables in a complex data structure.[129-133] ML techniques have been utilized to develop algorithms for AFib management (i.e. screening and diagnosis, risk prediction, personalized treatment decision, and medication management).[134,135] Several ML algorithms have been developed to predict risk of stroke and bleeding in patients with AFib. The area under the curves (AUC) of these algorithms range from 0.71 to 0.93 in stroke prediction and 0.93 in major bleeding in patients with AFib.[136-138] To our knowledge, no ML algorithms to predict risk of stroke and bleeding events in AFib patients with cancer receiving are available. There is an urgent need to develop new algorithms supporting clinical decision-making in AFib patients with cancer.

2.10. Summary of evidence and gaps in the management of atrial fibrillation among cancer patients

Patients with AFib and cancer is a vulnerable population and should receive more public attention. Indeed, they have a higher risk of adverse outcomes (i.e., stroke, VTE, bleeding, mortality) compared to those without cancer. Although DOACs are preferred over warfarin due to their superiority in reducing these adverse outcomes in general AFib, current management including baseline risk assessment, treatment initiation, and treatment selection between remains lack of

evidence. In addition, the potential DDIs between DOACs and antineoplastic drugs is concern for clinicians although the clinical impact of these *in vitro* DDIs is unknown.

There are currently significant gaps to be addressed in the management of AFib in cancer patients. First, it is necessary to know whether DDIs between DOACs and anticancer drugs suggested by PK studies are clinically important. Pharmacovigilance studies should be used to detect clinically relevant DDIs. Second, future research should compare the benefits and risks between different OAC initiation strategies to identify the optimal OAC treatment. Third, the comparative effectiveness and safety between warfarin and DOACs should be further elucidated, considering cancer characteristics and treatment. Finally, there is an urgent need to develop a new risk score or ML-based risk assessment tool to evaluate risk of stroke and bleeding in patients with AFib and cancer.

In this dissertation project, we proposed and completed 3 different aims according to the evidence gaps using an innovative, mixed approach in study design and data sources. First, we used spontaneous reporting system to screen for clinically relevant DDIs between DOACs and antineoplastic agents (*Aim 1*). Next, the linkage between SEER registry and Medicare claims database provides additional information on cancer characteristics such as cancer stage, tumor grade. We conducted high-quality observational studies using target trial framework with SEER-Medicare data to determine the benefit and risk of different OAC initiation strategies according to their CHA_2DS_2-VASc (*Aim 2.1*) and between DOACs and warfarin (*Aim 2.2*) among patients with AFib and cancer. Last, we leveraged ML technique to develop new tools to predict risk of stroke and bleeding. Findings from this project are expected to largely contribute to the current guidelines in management of patients with AFib and cancer. Our results may assist clinicians in baseline assessment of stroke and bleeding in patients with AFib and cancer before starting OACs (1),

considering clinically relevant DDIs between OACs and antineoplastic agents (2) and inform decision-making in selecting optimal OAC treatment strategy (3).

Chapter 3: Methods

3.1. Description of the study

This multi-method approach retrospective study consists of 3 aims. First, we used spontaneous reporting system database (FAERS) to screen for clinically relevant DDIs between DOACs and antineoplastic agents using pharmacovigilance approach (*Aim 1*). In *Aim 2*, we compared the risk and benefit of different OAC initiation strategies at different thresholds of CHA_2DS_2-VASc (*Aim 2.1*) and between DOACs and warfarin (*Aim 2.2*) in AFib patients with cancer. We conducted population-based cohort studies on target trial framework using the SEER-Medicare database. In *Aim 3*, We developed and validated ML algorithms to predict one-year risk of stroke and bleeding in patients diagnosed with AFib and cancer using SEER-Medicare data.

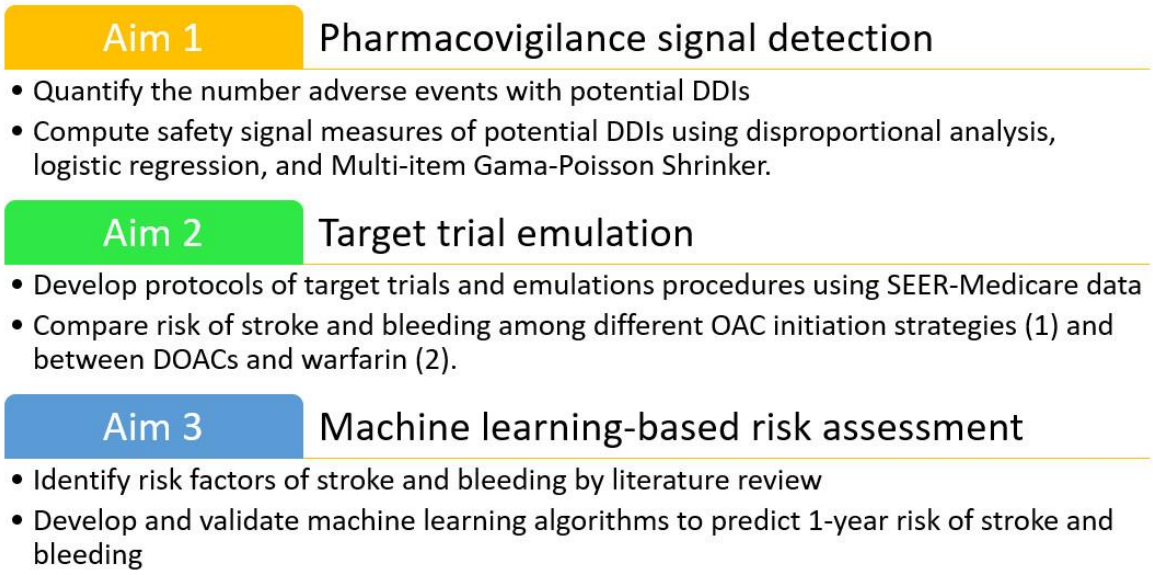


Figure 3. Summary of approach
DDIs drug-drug interactions, SEER The Surveillance, Epidemiology, and End Results (SEER), OAC oral anticoagulant, DOAC direct oral anticoagulant

3.2. Aim 1

3.2.1. Research question and hypothesis

Research question: Is there any signal of DDIs between combination of DOACs- antineoplastic agents and risk of bleeding or stroke in spontaneous reporting system?

Our goal is to generate hypotheses on the association between reported bleeding or stroke and the combination of DOACs and antineoplastic agents.

3.2.2. Study design

We conducted retrospective analyses of AE reports through data mining of the FAERS database containing DOACs-antineoplastic agents. We compared the reported bleeding AEs in FAERS between DOACs-anticancer medications with other combinations.

3.2.3. Data sources

The FAERS database is a publicly available spontaneous AE reporting system developed and maintained by the FDA for the post-marketing safety surveillance program for drug and therapeutic biologic products via MedWatch.[139] FAERS data are collected by submissions of AE reports from customers, healthcare providers, and pharmaceutical companies.[139] As of December 2021, FAERS database contained more than 23 million of AE reports from both US and non-US regions.[140] The FDA released FAERS data files each quarter , which contain the 7 separate tables in .txt format: patient demographic and administrative information, drug information, Medical Dictionary for Regulatory Activities (MedDRA®) terminology for AEs, patient outcomes and seriousness, reporting sources, drug therapy start date and end date, and MedDRA® terminology coded for the indications of reported drugs.[141] FAERS is a useful tool for post-marketing safety surveillance. Safety signal detection is the first step to generate a hypothesis on the association between drugs/biologic products and AEs.[139]

3.2.4. Drug exposure identification

We retrieved AE reports from January 1, 2004 to December 31, 2021 containing either DOACs (including dabigatran, rivaroxaban, apixaban, edoxaban) or warfarin in combination with antineoplastic agents with CYP3A4/P-gp inhibitory activity suggested by PK studies (**Table 2**). Drug names were identified from DRUGyyQq.TXT files by text string search using Nation Drug Code Directory, Purple Book Database, RED BOOK, and IBM Micromedex.[142-145] We anticipated potential abbreviations and misspellings by truncating corresponding search strings of generic and brand names. **Table S1, Appendix** describes the full list of generic and brand names of drug of interest.

We removed duplicates from the analyses by retaining the most recent case number for the same report. Combinations of interest were coded as binary exposure: 1 if an AE report contains the drugs of interest and 0 otherwise (**Table 3**). We included all AE reports regardless of their role coded as Primary Suspect Drug, Secondary Suspect Drug, or Interacting Drug.

3.2.5. Outcomes – Adverse Drug Reactions Definition

Bleeding and stroke events were identified from REACyyQq.TXT files by MedDRA® version 25.0.[146] ADRs are coded using Preferred Terms (PTs) in MedDRA® dictionary in FAERS database. We used Standardized MedDRA Queries (SMQs) to define the outcome of interest: PTs under high level term were selected if the outcomes of interest fall into a broader level term of the high level term.

3.2.6. Covariates

Characteristics of AE reports were extracted from DEMOyyQq.TXT files, including patient's age (continuous), sex (male, female, unknown/unspecified), reporting year, and reporting region (US, non-US).

3.2.7. Statistical analysis

We calculated the total number of reports containing DOACs and pre-specified antineoplastic agents and the number of reports related to bleeding or stroke by therapeutic class and individual drugs. We also stratified the number of AE reports by individual DOACs. The total number of reports was plotted to visualize the patterns of concurrent reporting over the years. We obtained demographics of AE reports with DOACs-anticancer medications (i.e., age, sex, reporting year, reporting source, and reporting region). We used disproportionality analyses (DPA), regression model (LR), and Multi-item Gamma-Poisson Shrinker (MGPS or empirical Bayes data-mining) algorithm to detect safety signals of potential DDIs (5 combinations by therapeutic class of antineoplastic agents and 63 combinations by individual antineoplastic drugs). The unit of analysis is unique AE report ('primaryid') in FAERS data. For DPA, we calculated reporting odds ratios (ROR) and 95% confidence intervals (95% CI) from the 2 × 2 exposure-outcome contingency tables (**Table 3**).[147-149] If the lower limit of 95% CI of ROR is greater 2.00, a significant association is confirmed.[150] LR model computes ROR in a similar way as in case-control studies (**Technical point 1**).[149,151] Signals of DDIs is confirmed if the lower limit of 95% CI of ROR exceeds 1.00.[149,151] MGPS model is currently used by the FDA for DDIs signal detection in FAERS data.[152] Detecting the signals of DDIs using MGPS model is based on Empirical Bayes Geometric Means (EBGM) and corresponding 2-sided 90% confidence intervals (90% CIs, EB05-EB95) were computed to identify reporting rates of DOACs-antineoplastic drugs-bleeding or DOACs-antineoplastic drugs-stroke triplets (**Technical point 2**).[149,153] A threshold of EB05>2 is considered a significant DDIs for MGPS, given the bleeding event is rare.[154] Among these three approaches, MGPS was used as the main analysis since it outperformed DPA and LR in previous studies.[155] SAS (version 9.4, SAS Institute, Inc., Cary, NC, USA) was used for data processing, and analysis

with DPA and LR methods. MGPS was implemented in RStudio (version 3.6.2; Boston, MA, USA) (packages 'openEBGM', 'PhViD').

Table 3. 2 x 2 contingency table for the evaluation of DOACs-antineoplastic drugs DDIs and bleeding events in FAERS data using disproportionality approach

	Bleeding AE reports	**Non-bleeding AE reports**
AE reports with DOACs and antineoplastic drugs combination	a	c
Other reports	b	d

Abbreviation: AE: Adverse Events, DOACs: Novel Oral Anticoagulants, DDI: Drug-Drug Interactions

Table 4. 4 x 2 contingency table for the evaluation of DOACs-antineoplastic drugs DDIs and bleeding events in FAERS data using logistic regression approach

	bleeding	**non-bleeding**	**Total**
drug D_1 and drug D_2	n_{111}	n_{110}	n_{11+}
Only drug D_1	n_{101}	n_{100}	n_{10+}
Only drug D2	n_{011}	n_{010}	n_{01+}
Neither D_1 nor D_2	n_{001}	n_{000}	n_{00+}
Total	n_{++1}	n_{++0}	n_{+++}

Abbreviation: AE: Adverse Events, DOACs: Novel Oral Anticoagulants, DDI: Drug-Drug Interactions

Table 5. 2 x 2 contingency table for the evaluation of DOACs-antineoplastic drugs DDIs and bleeding events in FAERS data

	Drug D_2	**Not drug D_2**
Drug D_1	$p_{11}=n_{111}/n_{11+}$	$p_{10}=n_{101}/n_{10+}$
Not drug D_1	$p_{01}=n_{011}/n_{01+}$	$p_{00}=n_{001}/n_{00+}$

Abbreviation: AE: Adverse Events, DOACs: Novel Oral Anticoagulants, DDI: Drug-Drug Interactions

Technical point 1. Logistic regression for signal detection of DDIs

In LR methods, we categorized AE reports by the following categories: reports containing both DOACs and antineoplastic drugs (yes/no), DOACs only (yes/no), antineoplastic drugs only (yes/no). We used the same coding scheme for the DDIs between warfarin and antineoplastic drugs compared with other drugs. However, to detect the signals of DDIs between DOACs plus

antineoplastics versus warfarin plus antineoplastic drugs, we restricted our sample to AE reports containing DOACs or warfarin only (Sensitivity analysis). **Tables 4** and **5** demonstrate the approach to detect a DDI signal for DOACs (D_1) and anticancer (D_2) by LR algorithm. We then calculated RORs and 95% CIs from LR models. Let p denote the proportion of AE reports (p_{11}=proportion of AE reports with the presence of both D_1 and D_2, p_{10}=proportion of AE reports with the presence of D_1 and absence of D_2, p_{01}=proportion of AE reports with the absence of D_1 and presence of D_2, p_{00}=proportion of AE reports without D_1 and D_2). We assume the DDIs follow multiplicative model, the null statistical hypothesis with no DDIs between D_1 and D_2 is:

$$\frac{p_{11}(1-p_{11})}{p_{00}(1-p_{00})} = \frac{p_{10}(1-p_{10})}{p_{00}\,(1-p_{00})} \text{ x } \frac{p_{01}(1-p_{01})}{p_{00}(1-p_{00})}$$

In LR modeling terminology, the following model can be applied

$$\text{logit}(risk\ of\ event) = \beta_0 + \beta_1 D_1 + \beta_2 D_2 + \beta_{12} D_1 D_2 + \beta_3 L + \varepsilon$$

where risk of event is the proportion of bleeding AE reports out of the total of AE reports, β is the coefficient and D_1, D_2 are dummy variables describing the presence/absence of the drug of interest in a specific AE reports. L denotes other covariates in our analysis (i.e., age, sex, and reporting region), and ε denote random error. $e^{\beta_{12}}$ is the adjusted ROR.

Technical point 2. Multi-item Gamma-Poisson Shrinker model estimation[154,156,157]

For the arbitrary itemset, let λ denote the expectation. Then $\lambda = E\left[\frac{N}{E}\right]$ where $E[]$ is the expectation of N/E, N is the observed number of AE reports, E is the predicted number of AE reports from an assumption that AE reports are independent, or baseline count. For DDIs between DOACs and antineoplastic agents, we consider a set of 3 items *i*, *j*, and *k* (*i* denotes DOACs, *j* denotes antineoplastic drugs, and *k* denotes bleeding event). For example, the observed frequency of AE

reports containing item *i*, *j*, *k* are $N_{i,}$, $N_{j,}$, N_k and the corresponding expected frequency of AE reports are $E_{i,}$ E_j, and E_k, respectively. Under within-stratum independence assumption, the probability of finding items *i*, *j*, and *k* in the same report is P_{ijk} = P_i x P_jx P_k. For a three-dimensional unstratified run, the expected count is computed as E_{ijk} = N_{total} x P_{ijk} = N_{total} x P_i x P_jx P_k. If all AE reports are assigned to the strata denoted by c = 1, 2…, C, the proportion of reports in stratum *c* that contain the item *i* is expressed by P_i^c, and the total number of reports in stratum c is expressed by N_c. In the stratified independence model, it is assumed the above equations are held for each stratum. So, for a given stratum c, P_{ijk}^c = P_i^c x P_j^c x P_k^c and the expected baseline count is $E0_{ijk}$= $\sum E_{ijk}^c$= $\sum N_c$ x P_{ijk}^c = $\sum N_c$ x P_i^c x P_j^c x P_k^c

For an itemset of size 3 or more, an "all-2-factor" loglinear model can be defined as the frequencies *E2* for the itemset that match all the estimated pairwise two-way marginal frequencies but contain no higher order dependencies. For triples, E*2ijk* agrees with the estimates for the three pairs $\lambda_{ij}E0_{ij}, \lambda_{ik}E0_{ik}, , \lambda_{jk}E0_{jk}$. Then we compare the estimated frequency to the all-2-factor prediction by simple subtraction. For example, in case of triples $Excess2_{ijk}$ = $\lambda_{ijk}E0_{ijk}$ - $E2_{ijk}$

The parameters λ above are estimated by the geometric means, denoted by EBGM, of their empirical Bayes posterior distributions. For simplicity, the formula below uses just two subscripts, for itemsets of size 2, such as the occurrence of drug i and event j in an AE report. Estimates for itemsets of size 3 for DDIs are computed analogously. Let N_{ij} = the observed counts, N_{ij} = the expected count RR_{ij} = N_{ij}/E_{ij} = ratio of observed to baseline. We estimate λ_{ij} = μ_{ij}/E_{ij}, where N_{ij}~ Poisson(μ_{ij}). Assume a superpopulation model for λ_{ij} (prior distribution) based on a mixture of two gamma distributions (a convenient 5-parameter family of distributions that can fit almost any empirical distribution):

$$\pi(\lambda;\ \alpha_1, \beta_1, \alpha_2, \beta_2\ , P)\ =\ P\ g(\lambda;\ \alpha_1, \beta_1)\ +\ (1\ -\ P)\ g(\lambda;\ \alpha_2, \beta_2)$$

$$g(\lambda;\ \alpha, \beta)\ =\ \beta^{\alpha}\ \lambda^{\alpha-1}\ \frac{e^{-\beta\lambda}}{\Gamma(\alpha)}$$

First, we estimate the prior distribution from all the (N_{ij}, E_{ij}) pairs. Then we estimate the 5 hyperparameters θ = ($\alpha_1, \beta_1, \alpha_2, \beta_2\ P$) by maximizing the likelihood function $L(\theta)$ in 5 dimensions:

$$L(\theta) = \prod([\mathrm{P\ f}(N_{ij};\ \alpha_1, \beta_1, E_{ij}) +\ (1 - \mathrm{P})\mathrm{f}(N_{ij};\ \alpha_2, \beta_2, E_{ij})]_{\ ij}$$

where $f(n;\ \alpha, \beta, E)$ = $(1 + \beta/E)^{-n}\ (1 + E/\beta)^{-\alpha}\ \Gamma(\alpha\ +\ n)$ / Γ(α) n!

If a threshold (minimum count) for the observed counts is used, these formulas are modified to condition on $N_{ij} \geq$ n* (where n* = the threshold count). Given θ, the posterior distributions of each λ_{ij} are also a mixture of gamma distributions used to create "shrinkage" estimates. Assuming that θ and E are known, then the distribution of N is

$$P(N\ =\ n)\ =\ Pf(n;\ \alpha_1, \beta_1, E)\ +\ (1 - P)f(n;\ \alpha_2, \beta_2, E)$$

Let Q_n be the posterior probability that λ came from the first component of the mixture, given N = n. From Bayes rule, the formula for Q_n is

$$Q_n = \frac{\mathrm{Pf}(n;\ \alpha_1, \beta_1, E)}{\mathrm{Pf}(n;\ \alpha_1, \beta_1, E) + (1 - \mathrm{P})\mathrm{f}(n;\ \alpha_2, \beta_2, E)}$$

Then, the posterior distribution of λ, after observing N = n can be represented as

$$\lambda|\mathrm{N} = n \sim \pi(\lambda;\ \alpha_1\ +\ n, \beta_1 +\ E, \alpha_2\ +\ n, \beta_2 +\ E, Q_n)$$

where (as above) $\pi(\lambda;\ \alpha_1, \beta_1, \alpha_2, \beta_2, P) = P\ g(\lambda;\ \alpha_1, \beta_1) + (1 - P) g(\lambda;\ \alpha_2, \beta_2)$ We use the expectation value E[log(λ_{ij}) | N_{ij}, θ] as a means of estimating the "true" value of λ_{ij}.To obtain a quantity on the same scale as RR, we define the Empirical Bayes Geometric Mean:

$$EGBM_{ij} = E[log(\lambda_{ij})|\ N_{ij}, \theta]$$

where $E[\lambda \mid N = n, \theta] = Q_n\ (\alpha_1 + n)/(\beta_1 + E)] + (1–Q_n)\ (\alpha_2 + n)/(\beta_2 + E)$

$E[log(\lambda) \mid N = n, \theta] = Q_n\ [\psi(\alpha_1 + n) - log(\beta_1 + E)] + (1–Q_n)\ [\psi(\alpha_2 + n) - log(\beta_2 + E)]$

where $\psi(x) = d(log\ \Gamma(x))/dx$. The above expectations follow from known properties of gamma distributions. In the same way, the cumulative gamma distribution function can be used to obtain percentiles of the posterior distribution of λ. The 5th percentile of λ is denoted $EB05_{ij} = P(\lambda < EB05 \mid N_{ij}, \theta)$ = 0.05 and is interpreted as a lower 1-sided 95% confidence limit.

3.2.8. Sensitivity analyses

Three sets of sensitivity analyses were conducted to confirm the robustness of the main findings. First, we restricted the analyses to AE reports from October 19, 2010 (approval date of dabigatran – first DOAC approved by FDA) to December 31, 2021 to rule out the possibility of Weber's effect [158]. Second, since there is no validated algorithm for outcome definition in FAERS database, we used clinicians' assessment to define the outcomes of interest. Specifically, a clinician specializing in cardiovascular diseases and anticoagulation therapy screened and selected any bleeding/stroke PT from MedDRA related to anticoagulation therapy. Third, we conducted the DPA and LR analyses using the combination of warfarin and antineoplastic agents as the referent group because warfarin was considered an alternative to DOACs in patients with AFib.

3.2.9. Interpretation of expected results

For DPA, the lower limit of 95% CI of ROR greater than 2.00 indicates a significant signal.[150] For LR, signals of DDIs can be detected if the lower limit of 95% CI of ROR exceeds 1.00.[149] A threshold of EB05>2 is considered a significant DDIs for MGPS, given that the bleeding event is rare.[154]

3.2.10. Potential challenges and alternative approaches

First, National Drug Code is not frequently reported and there is a large heterogeneity in drug names submitted to the FAERS. To reduce misclassification of AE reports, we retrieved all possible drug names from drug databases such as Micromedex and anticipated potential misspellings. In addition, covariates such as age and sex may contain missing data. If the missing values accounted for more than 10% of total reports, we removed that variable from logistic regression models to ensure meaningful interpretation. Next, the RORs and 95% CIs from DPA and LR are unstable if the number of AE reports in the 2x2 contingency table is small).[149,159] We implemented MGPS to obtain EBGM and 90% CIs (EB05, EB95) because MGPS can generate a stable signal when the number of AE report is small.[160] Finally, due to under/over reporting[161] and unavailability of other risk factors in the FAERS, signals detected for DDIs should not be interpreted as causation and should be further evaluated using more rigorous epidemiological approach.

Table 6. Summary of study design, measurements, and statistical methods for Aim 1

Study design and data sources	Measurements	Statistical analysis
▪ Retrospective analysis	▪ Outcome: bleeding or stroke	▪ Unit of analysis: unique AE reports ▪ Descriptive statistics

▪ FAERS data 2004-2021	▪ Exposure: concomitant use of DOACs/warfarin with pre-specified antineoplastic agents ▪ Covariates: patient's age (continuous), sex (male, female, unknown/unspecified), reporting year, and reporting region (US, non-US).	▪ Main analysis: association between reported bleeding events and concomitant use of OACs and antineoplastic drugs o Disproportionality analysis o Logistic regression o Bayesian analysis

3.3. Aim 2

Our goal is to estimate and compare the risk of stroke and bleeding among five OAC initiation strategies at different levels of CHA_2DS_2-VASc (*Aim 2.1*) and between DOACs and warfarin (*Aim 2.2*). We used target trial framework to conduct retrospective cohort studies using SEER registry linked to Medicare database from 2011-2019.

3.3.1. Data sources

SEER is the most comprehensive data source for cancer research covering 48 percent of US population.[162] SEER collects and releases data on patient demographics, primary tumor site, tumor characteristics, , first course of treatment, and follow-up.[162] Medicare data includes US population aged 65 and older, covering inpatient and hospice care (i.e., Part A), physician, outpatient, skilled nursing facilities and home health bills (Part B), and medications (part D).[163] In addition, the Medicare linkage adds to SEER data important information such as Medicare beneficiaries' health care service utilization (i.e., medical claims and prescriptions).[163]

3.3.2. Research question and hypothesis

Research question

Aim 2.1: Is there any difference in risk of stroke and bleeding among patients with AFib and cancer who initiated OACs at different levels of CHA_2DS_2-VASc score?

Aim 2.2: Is there any difference in risk of stroke and bleeding between DOACs and warfarin in patients with AFib and cancer?

Hypothesis

Aim 2.1: There is a difference in risk of stroke and bleeding among patients with AFib and cancer who initiated OACs at different levels of CHA_2DS_2-VASc score (CHA_2DS_2-VASc score ≥1; ≥2; ≥4; ≥6 and never initiation).

Aim 2.2: There is a difference in risk of stroke and bleeding between DOAC and warfarin among patients with AFib and cancer.

Causal framework[164]

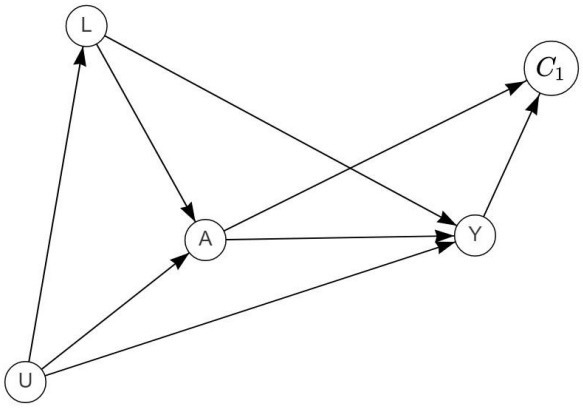


Figure 4. Directed Acyclic Graph (DAG) for the effect of fixed-time intervention on outcome.

Figure 4 illustrates the causal framework of the research questions in *Aim 2* in the fixed-time context. Let A denote the intervention (i.e., DOACs vs. warfarin), Y denote the outcome of interest (i.e., ischemic stroke and major bleeding), L denote measured confounders, U denote unmeasured confounders, C_1 denote censoring due to loss to follow-up or competing events. Administrative

data alone cannot capture some of the important confounders (cancer stage, tumor grade) – then such confounders are unmeasured and contained in U. However, the linkage to SEER registry adds to Medicare important cancer characteristics. Therefore, these confounders are now contained in L. The direct arrow from A to Y denotes the causal effect of A on Y and other indirect paths between A and Y (i.e., A-U-Y, A-L-Y) imply association between A and Y. In the causal context, three important assumptions are required to be hold: exchangeability (no unmeasured confounding U), positivity (all individuals have a non-zero probability of receiving the intervention A), and consistency (well-defined intervention). In the observational context, due to the presence of confounders (L and U) and selection bias due to censoring (C_1), the association between A and Y is not causation. Not conditioning on L opens the back-door path between A and Y. Conditioning on colliders such as C_1 (i.e., restricting the cohort to individuals who are alive during follow-up or have continuous enrollment record) opens the back-door path between A and Y. Thus, our strategy to obtain the unbiased estimate of causal effect of A on Y in study design and analysis include: (1) to identify and measure all potential confounders, (2) to clearly define the treatment strategy, and (3) to adjust for baseline confounders and censoring due to lost to follow-up or competing events.

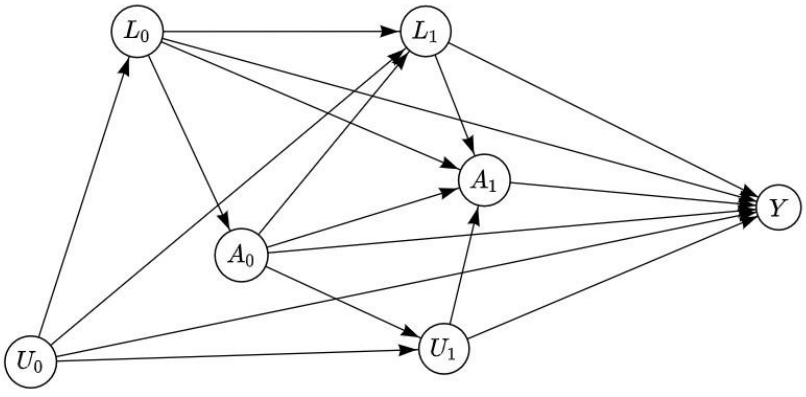


Figure 5. Directed Acyclic Graph (DAG) for the effect of time-varying intervention on outcome.

Figure 5 illustrates the time-varying context of the research questions, with 2 time points (T_0 and T_1) and without censoring for simple reasoning. Treatment effect is now the average treatment effect of intervention A at every time point (A_0 and A_1). The assumptions for causal effects expand to sequential exchangeability, positivity at each time point, and consistency. Adjustments for baseline confounders, time-varying confounders, prior treatment history, and censoring are needed.

3.3.3. Methods for Aim 2.1

3.3.3.1. Study design

We conducted a retrospective cohort study using SEER-Medicare database 2011-2019. We compared risk of stroke and bleeding among different OAC initiation strategies. We developed a protocol of a target trial and emulation procedure using the SEER-Medicare database. [165,166] The target trial emulation is the application of design principles from RCTs to the analysis of observational data to improve the quality of observational epidemiology when a comparator trial is not yet available or feasible.[167] Because no RCT is available to address our research question, we developed the protocol for the hypothetical target trial and adopted the components from existing RCTs comparing the efficacy and safety of DOACs versus warfarin in patients with AFib (RE-LY and ROCKET-AF).[168,169] **Table 7** outlines the protocol for a target trial and emulation procedure in SEER-Medicare.

Table 7. Protocol for a target trial and emulation procedure using the SEER-Medicare database to estimate risk of stroke and bleeding among patients initiating OACs at different levels of CHA_2DS_2-VASc score compared with those who never initiated

Protocol component	Hypothetical target trial	Emulation in SEER-Medicare data
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 January 1, 2012 and December 31, 2019.	Same as target trial

	▪ Beneficiaries 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	
Treatment strategies	Eligible individuals are randomly assigned to one of the following treatment strategies (1) initiate OAC when CHA_2DS_2-VASc score ≥1 (2) initiate OAC when CHA_2DS_2-VASc score ≥2 (3) initiate OAC when CHA_2DS_2-VASc score ≥4 (4) initiate OAC when CHA_2DS_2-VASc score ≥6 (5) no initiation of OACs (reference group)	We mimicked randomization at baseline by cloning-censoring-weighting approach
Follow-up	The follow-up started at first AFib diagnosis and ended at 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
Causal contrast	Intention-to-treat effect, per-protocol effect	Observational analog of per-protocol effect

3.3.3.2. Study sample and eligibility criteria

Study sample: We selected individuals aged ≥66 with new onset non-valvular atrial fibrillation (NVAF) between January 1, 2012 and December 31, 2019, with history or active breast, lung, prostate cancer continuously from SEER registry, enrolled in Medicare part A, B, D, and without Medicare Advantage or Health Maintenance Organization (HMO) for 12 months before new NVAF diagnosis. We did not require eligible individuals to have a 12-month post-baseline period to avoid conditioning on post-baseline information and collider bias.[170,171]

Atrial fibrillation: NVAF was defined as any International Classification of Disease-9th Revision-Clinical Modification (ICD-9-CM) codes 427.31 or 427.32 or any International Classification of Disease-10th Revision-Clinical Modification (ICD-10-CM) codes I48.xx in any position on one Medicare inpatient claim or on 2 outpatient claims at least 7 days but <1 year apart.[172] This algorithm has been validated in previous studies with a sensitivity of 80% and positive predicted value (PPV) of 90%.

Cancer: NVAF patients with any record cancer from SEER files, including breast codes (ICD-O-3 codes C50.0-C50.9), lung (ICD-O-3 codes C34.0, C34.1, C34.2, C34.3, C34.8, C34.9, C33.9), and prostate cancer (ICD-O-3 codes C61.9) – the most concomitant cancer in patients with NVAF [25,27] - at any time before the initial AFib diagnosis were included. Active cancer was defined by validated algorithm described in previous studies.[25,27]

Exclusion criteria: We adapted exclusion criteria based on RE-LY and ROCKET-AF trials.[168,169] In addition, we removed individuals with indications for warfarin or DOACs other than NVAF or absolute contra-indications of warfarin or DOACs to assure positivity assumption in causal inference.[173] In brief, patients with the presence of the following diseases or condition were excluded: (1) any OAC use during the 12 months baseline period, (2) presence of mitral valve disease, heart valve repair or replacement, deep vein thrombosis, pulmonary embolism, or joint replacement during the 12 months baseline period, (3) any stroke within 14 days before first NVAF diagnosis, (4) major surgery (i.e., hip fracture, cardiac surgery), intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding, gastrointestinal hemorrhage within 30 days before first NVAF diagnosis, (5) renal impairment stage 5 or end-stage renal diseases.

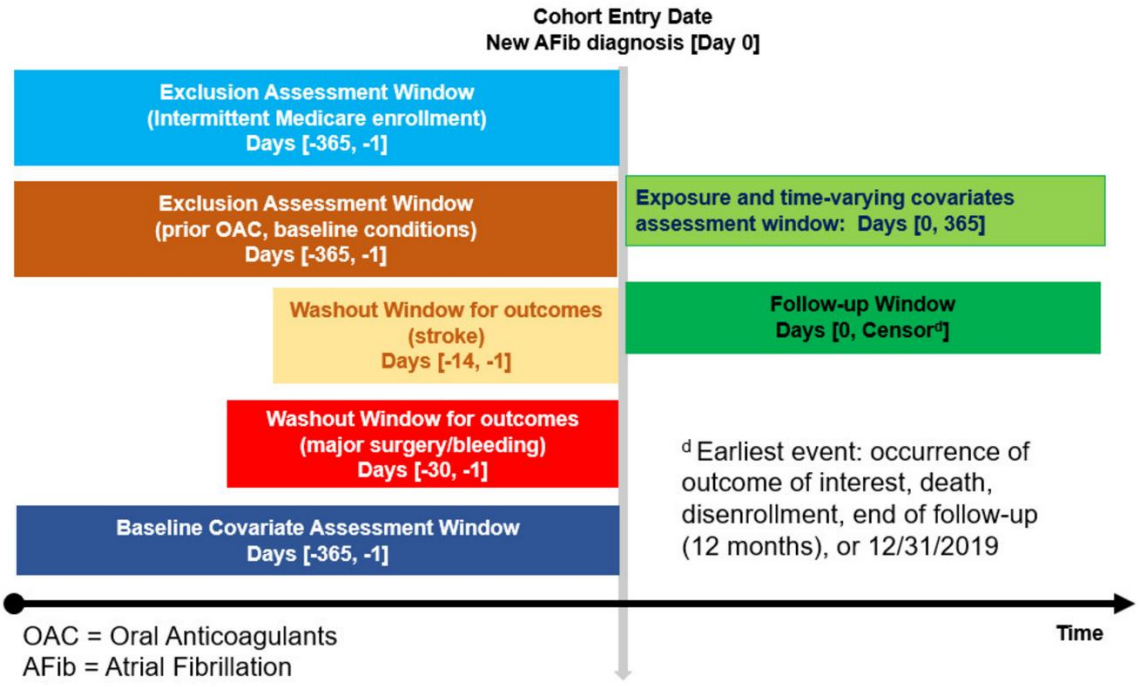


Figure 6. Visualization of study design for Aim 2.[174]

3.3.3.3. Treatment strategies and assignment

In the hypothetical target trial, eligible individuals are randomly assigned to one of the following treatment strategies: (1) initiate OAC when CHA_2DS_2-VASc score ≥1, (2) initiate OAC when CHA_2DS_2-VASc score ≥2, (3) initiate OAC when CHA_2DS_2-VASc score ≥4, (4) initiate OAC when CHA_2DS_2-VASc score ≥6 and (5) no OAC initiation during follow-up (reference group). In the emulation of target trial, we used cloning, censoring, and weighting approach to mimic the randomization.[175] OAC prescriptions (including warfarin and dabigatran, apixaban, rivaroxaban, edoxaban) were identified from Medicare Part D Drug Event (PDE) files using NDC, regardless of OAC dosage.[176] CHA_2DS_2-VASc scores were calculated from Medicare claims at baseline (new NVAF diagnosis) and monthly during follow-up, based on a combination of medical conditions including congestive heart failure (1 point), hypertension (1), age ≥75 (2 point), diabetes mellitus (1 point), prior stroke, TIA, or VTE (2 point), vascular disease (e.g. peripheral artery disease,

myocardial infarction, aortic plaque) (1 point), age 65-74 years (1 point), and sex category (1 point).[100]

3.3.3.4. Follow-up

The follow-up started at first NVAF diagnosis and ended at the occurrence of a specific study outcome, the end of administrative censoring (12 months after baseline), death (all-cause deaths from SEER and Medicare files via the variables of "Date of Death Flag"), loss to follow-up (the earliest of 30 days after the end of continuous Medicare Part A, B, or D enrollment or enrollment in an HMO), or December 31, 2019, whichever came first. In the primary analysis, we did not censor individuals who switched between OACs (warfarin to DOACs and vice versa, or between DOACs), since we assumed the risk of stroke and bleeding between who received DOACs compared with warfarin was much smaller than the risk of outcomes between OAC users versus non-users in the first 3 months after AFib diagnosis.

3.3.3.5. Outcomes

The primary effectiveness and safety outcomes were ischemic stroke and major bleeding, respectively. We defined major bleeding based on the bleeding site (i.e. intraarticular, intracranial, intramuscular, intraocular, intraspinal, pericardial, and retroperitoneal) (PPV 86-96%), identified by ICD-9-CM and ICD-10-CM codes in the primary diagnosis from Medicare medical claims files.[25,177,178] Other clinical outcomes included VTE, intracranial bleeding, and gastrointestinal bleeding, and other bleeding (i.e., genitourinary bleeding, hemopericardium, hemoperitoneum, hemarthrosis, epistaxis, hemoptysis, hemorrhage from throat, and unspecified hemorrhage).[177-179]

3.3.3.6. Covariates

We selected covariates based on published RCTs and observational studies.[25,27,168] Baseline covariates included: *demographics* (index age, sex, race/ethnicity, calendar year, geographical

region, urbanicity), *socioeconomic factors* (household median income, percentage of household with education level below high school, and Medicaid eligibility), *comorbidity risk scores* (CHA_2DS_2-VASc, HAS-BLED, and Comorbidity Scores SEER-Medicare version 2021 by NCI),[180] *individual comorbidities* (asthma/chronic obstructive pulmonary disease, hematological disorders, dementia, depression, thrombocytopenia, acute kidney disease (AKD), peptic ulcer disease), *cancer characteristics* (time from cancer diagnosis to the onset of AFib, cancer type, cancer stage, tumor grade, active cancer status [25,27]), *cancer treatment* (radiation, and cancer-directed surgery, and potentially interacting antineoplastic agents), and *medication history* (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium channel blockers, beta blockers, antiarrhythmic medications, diuretics, statin, pump proton inhibitors, and serotonin reuptake inhibitors). If patients had more than one type of cancer before AFib diagnosis, we retained the most recent cancer diagnosis. Cancer treatment was obtained from diagnosis codes or procedures codes within 30 days before AFib diagnosis.[181] Due to high proportion of missing values, other cancer characteristics such as number of regional nodes examined, tumor size, TMN classification, and other cancer-type specific characteristics (hormone receptor status (HR), and human epidermal growth factor receptor 2 (HER2) for breast cancer or histologic type for lung cancer) were used for descriptive purpose but not adjusted in the models.[182] The following time-varying covariates were extracted monthly after AFib onset, including CHA_2DS_2-VASc score, HAS-BLED score, thrombocytopenia, AKD, radiation, cancer-directed surgery, and use of interacting treatment. We used multiple imputation algorithm (fully conditional specification with logistic regression for categorical variables and predictive mean matching for continuous variables) to impute missing values.[183]

3.3.3.7. Causal contrast

Observational analog of both *intention-to-treat* (ITT) and *per-protocol* (PP) effects can be estimated in target trial emulation. *ITT effect* refers to effect of being assigned to the strategies at baseline, regardless of whether individuals adhere to initial strategies during follow-up.[184,185] PP effect is defined as an 'on treatment' effect – only includes individuals who complied to their assigned treatment.[185] However, if cloning, censoring, and weighting procedure is used, the *ITT effect* cannot be obtained when clones have been assigned to each treatment arm.[186] Therefore, only *PP effect* was estimated.

3.3.3.8. Statistical analysis

Descriptive statistics such as mean and standard deviation (SD) for continuous variables, frequency count and percentage for categorical variables were used to describe the study sample. We quantified the incidence rates of ischemic stroke and major bleeding for each treatment strategy. In the main analysis, cloning, censoring, and weighting procedure was used to estimate the treatment effect of 5 treatment strategies.[175,186] Briefly, we created 5 copies for each individual's person-time data, then assigned each copy to 5 treatment strategies. *At baseline*, replicates with baseline CHA_2DS_2-VASc score that did not comply with their assigned strategy were removed from the dataset. Next, replicates whose data were no longer consistent with their assigned strategy *during follow-up* were censored. To adjust for potential confounding at each time point, unstabilized time-varying censoring weights were used. Cumulative weights at month 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 (See **Technical point 3**). Total weights were truncated at 99^{th} percentile to avoid extreme weights. To estimate the treatment effects for 5 strategies, we fitted a weighted pooled logistic regression

estimated by generalized estimating equations (GEEs) with robust variance estimators. We obtained summary hazard ratios (HRs) with 95% confidence interval (95% CIs) and created weighted survival curves comparing four active treatment strategies with the reference strategy. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

Technical point 3. Cloning, censoring, and weighting procedure to estimate the effect of treatment duration on survival outcomes[164,175,186-189]

Step 1 – cloning: First, we organized each persons' data in discrete-time (person-month) format (month 1 to 12). We then duplicated each individual's data 5 times and assigned them to 5 different treatment strategies. The stacked data set is 5 times as large as the original sample. At this point, there was no difference in baseline covariates between 5 treatment groups as replicates are identical and no confounder exists. At baseline, some of the replicates already passed the cut-off values of CHA_2DS_2-VASc score to start OACs without starting OAC were removed from the dataset and vice versa. These patients were removed from the analysis. For example, a replicate of a patient with baseline CHA_2D_2VASc score of 4 with treatment strategy of "initiate OACs when CHA_2DS_2-VASc score ≥1" without OAC prescription in the first month were deleted.

Step 2 – Censoring: In this step, replicates whose data no longer consistent with their assigned strategy during follow-up were censored. We identified whether replicates in each month adhered to their assigned strategy and censored them if they did not adhere. In particular, there might be individuals with CHA_2DS_2VASc score of 2 at baseline who were assigned to treatment strategies "initiate OACs when CHA_2DS_2-VASc score ≥4". These individuals were censored if they received the treatment when their CHA_2D_2VASc score remained or rose to 3 at a specific month during follow-up. However, these patients were not censored if they remain untreated at CHA_2D_2VASc score is 2 or 3 or start OACs when their CHA_2D_2VASc score increases to 4.

Step 3 – Weighting: Because artificial censoring is informative and this informative censoring introduces selection bias, we weighed those who were artificially censored by IP weighting to reduce selection bias. That is, uncensored replicates have an equal weight as the inverse probability of remaining uncensored, given their own covariate history. The purpose is to upweight the uncensored replicates so that in the pseudo-population, censoring does not depend on baseline fixed-time and time-varying covariates and censoring is no longer informative. To calculate the weights due to protocol violation, we calculated the probability of being censored, which is a product of the probability of starting OACs and by the probability of not being censored due to loss to follow-up.

Specifically, the censoring weight of each replicate at time t is proportional to the probability of being uncensored through time t conditioning on not having the outcome before time t ($Y_{t-1} = 0$), fixed-time covariates (L_0) and time-varying covariates ($\bar{L}_t$), treatment history ($\bar{A}_{t-1}$), where A_t= 1 indicates that an individual has received OACs and A_t= 1 denotes an untreated status by week t.[188] Since the censoring status of individuals depends on OAC initiation, we estimate the probability of remaining uncensored by the probability of initiating OACs for each individual at each month.[186,188-190] In the original dataset, we fitted a logistic regression as follow:

$$logit(\Pr[A_k = 1 | A_{k-1} = 0, \bar{L}_k, \bar{Y}_{t-1} = 0, L_0, L_k]) = \theta_0 + \theta_1^T L_0 + \theta_2^T L_k$$

where the overline (i.e., $\bar{L}_k$) represents the history of covariate from the start of follow-up, the superscript T indicates a transpose of a vector of coefficients, θ_0 is a time-specific intercept (estimated via linear and quadratic terms for t), L_0 is the vector of baseline covariates, and L_k is the vector of time-varying covariates through time k, a is an indicator each treatment regimen,

and i indicates the number of emulated trials. The unstabilized time-varying inverse-probability weight is computed by:

$$W_{i,t}^{a} = \prod_{k=0}^{t} \frac{1}{f(A_k|\bar{A}_{k-1}, \bar{Y}_{k-1}=0, \bar{C}_{k-1}=0, \bar{L}_k, L_0)}$$

We also addressed selection bias due to lost to follow-up and death. Separate logistic regression models for each treatment strategy were constructed to estimate the probability of being lost to follow-up or death, given baseline and time-varying covariates. In the unexpanded dataset, the unstabilized natural censoring weights for loss-to-follow-up (W^{LFU}) for each individual at time t were calculated by

$$W_{i,t}^{n,LFU} = \prod_{k=0}^{t} \frac{1}{f(C_k|\bar{C}_{k-1}=0, \bar{Y}_{k-1}=0, \bar{A}_{k-1}=0, \bar{L}_k, L_0\ )}$$

where C_k is an indicator of natural censoring.[189,190] The final weights are the products of the probability of starting OACs and by the probability of not being censored due to loss to follow-up for each person-month. We truncated weights at 99th percentile to avoid extreme weights.

$$W_{total} = W_{i,t}^{a} \text{ x } SW_{i,t}^{n,LFU}$$

Under the assumption that (i) our measured baseline and time-varying confounders are sufficient to ensure exchangeability, (ii) positivity – that is the probability of each individual is greater than 0 within levels of covariates dynamic treatment effect, and (iii) weighted models are correctly specified, the treatment effect of each treatment regimen can be estimated using a marginal structural model (MSM).

$$logit(\Pr[Y_{t+1}^{a} = 1|\ L_0, Y_t^{a} = 0]) = \gamma_0 + \gamma_1^{T} L_0 + \gamma_2 a$$

where Y_t^{a} is the counterfactual outcome at month t under the strategy a=A.

To estimate the treatment effect, a weighted pooled logistic regression model was used to estimate the per-protocol effect of 4 "active" treatment strategies compared to the reference strategy. The regressors include f(t) – a function of time and time squared (time and time squared), treatment strategy, interactions between time and treatment, and all baseline covariates, weighted for censoring (W_{total})

$$logit(\Pr[Y_{k+1} = 1|A, L_0, \bar{Y}_k = 0]) = \beta_0 + \beta_1^T L_0 + \beta_2 A + \text{f(t)}$$

The pooled logistic regression is equivalent to discrete-time hazard model, with the assumption that the risk of developing a specific outcome of interest within levels of covariates is rare in each time interval (risk <0.1).[191,192] The odds ratio of developing the event is equivalent to the PP HR, estimated by exponentiated coefficient of treatment indicator (e^{β_2}).[191,192]

To estimate the weighted survival curves and standardize the curves to baseline distribution of covariates, we fitted a similar model with an interaction term between treatment regimen A and f(t) – a function of time and time squared to allow for non-proportional hazards. The model was then used to predict outcomes of interest under each treatment strategy $A = a$. The details for creating standardized survival curves can be found in published studies.[193]

3.3.3.9. Subgroup analyses and sensitivity analyses

We conducted the analyses for following subgroups: cancer type (breast, lung, prostate), cancer status at baseline (active, history), cancer stage (in situ, local, regional, and distant), and tumor grade (I, II, and III). A series of sensitivity analyses were conducted. First, we extended follow-up time to 36 months to explore long-term outcomes for each treatment strategy. Second, since metastatic cancer patients were removed from randomized control trials due to their short life expectancy, we excluded them from this analysis.[168,169] Third, we removed individuals

thrombocytopenia at baseline, since these patients are at elevated risk of bleeding and may not eligible for OAC initiation.[194,195] Fourth, we further truncated weights at 95th percentile to test the robustness of the treatment effects to the presence of extreme weights.

3.3.4. Methods for Aim 2.2

3.3.4.1. Study design

We conducted a retrospective cohort study using target trial framework on SEER-Medicare database 2011-2019. We compared the risk of stroke and bleeding among patients with AFib and cancer who initiated DOACs versus warfarin. The protocol for a target trial and emulation procedure in SEER-Medicare is described in **Table 8**.

Table 8. Protocol for a target trial and emulation procedure using the SEER-Medicare data base to estimate the risks of stroke and bleeding between DOAC initiators and warfarin initiators

Protocol component	**Hypothetical target trial**	**Emulation in SEER-Medicare data**
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 January 1, 2012 and December 31, 2019. ▪ Beneficiaries continuously enrolled in Medicare part A, B, D, and without Medicare Advantage for 12 months before the diagnosis. ▪ Baseline CHA_2DS_2-VASc score ≥2 ▪ 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 warfarin or DOACs within a grace period of 3 months	We assume that study participants are randomly assigned conditioning on baseline covariates

Follow-up	The follow-up of target trials started at treatment initiation during a grace period and ended at 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	Primary outcomes: ischemic stroke, major bleeding Secondary outcomes: VTE, intracranial bleeding, gastrointestinal bleeding, non-critical site bleeding	Same as target trial
Causal contrast	Intention-to-treat effect, per-protocol effect	Observational analog of intention-to-treat and per-protocol effect

3.3.4.2. Study sample and eligibility criteria

Same as *Aim 2.1*, but we further restricted the study sample to those with CHA_2DS_2-VASc score ≥2.[168,169] We used the same algorithms to define NVAF, cancer, and exclusion criteria as in **Aim 2.1 Section 3.2.2.2.**

3.3.4.3. Treatment strategies and assignments

In the hypothetical target trial, eligible individuals are randomly assigned to either (1) warfarin (2) DOACs and continue the assigned treatment during follow-up. In the emulation of target trial, we assume randomization based on baseline covariates.[175] OAC prescriptions (including warfarin and dabigatran, apixaban, rivaroxaban, edoxaban) are identified from Medicare Part D Drug Event (PDE) files using NDC, regardless of OAC dosage.[176] We used a grace period of 3 months to determine the observed treatment status of eligible individuals since a 3-month grace period has been specified in previous RCTs and the risk of stroke in AFib patients is highest in the first 3 months after new AFib diagnosis.[196,197] OAC discontinuation is defined as a gap in OAC prescription for ≥ 30 days from the last day of days' supply in PDE file.

3.3.4.4. Follow-up

The follow-up started when the patients received the treatment within a grace period and ended at the occurrence of a specific study outcome, the end of administrative censoring (12 months after

baseline), death (all-cause deaths from SEER and Medicare files via the variables of "Date of Death Flag"), loss to follow-up (the earliest of 30 days after the end of continuous Medicare Part A, B, or D enrollment or enrollment in an HMO), or December 31, 2019, whichever came first. For *per-protocol* analyses, follow-up also ended when the observed treatment was inconsistent with the initial treatment strategy. Specifically, eligible individuals who discontinued the initial treatment or switched their assigned treatment during follow-up (i.e., switch from warfarin to DOACs or vice versa) were censored.

3.3.4.5. Outcomes

Refer to **Aim 2.1, Section 3.3.3.5**.

3.3.4.6. Covariates

Refer to **Aim 2.1, Section 3.3.3.6**.

3.3.4.7. Causal contrast

We computed the observational analog of both *intention-to-treat* (ITT) and *per-protocol* (PP) effects.

3.3.4.8. Statistical analysis

Descriptive statistics with mean and standard deviation (SD) for continuous variables, frequency count and percentage for categorical variables were used to describe the study sample. In the main analysis, we obtained the ITT effect (the effect of initiating DOACs compared with warfarin) and PP effect (the effect of sustaining DOACs compared with warfarin). First, we adjusted for potential confounders between treatment groups at each month using weighting approach. The total weights as a product of stabilized inverse probability treatment weights (IPTWs) and stabilized inverse probability censoring weights (IPCWs) due to loss to follow-up. Next, we fitted a weighted pooled logistic regression estimated by generalized estimating equations (GEEs) with robust variance

estimators, adjusted for baseline and time-varying confounders. Incidence rate (case per person-year), absolute risk difference (RD, 95% CIs), and summary hazard ratios with 95% confidence intervals (HR, 95% CIs), and weighted survival curves were obtained. All weights were truncated at 99th percentile. The technical details of the adjustment were described in **Technical point 4**. Statistical analysis was conducted using SAS (version 9.4, SAS Institute, Inc., Cary, NC, USA).

Technical point 4[164,175,186,187,189,198]

1. ITT analysis

The treatment is estimated effect via a 12-month risk of developing a specific outcome among those who initially started DOACs compared with warfarin.

First, we computed the probability of initiating DOACs or warfarin, conditioning on baseline covariates (A=1 for DOACs, A=0 for warfarin)

$$logit(\Pr[A = 1|L]) = \alpha_0 + \alpha_1^T L_0$$

The stabilized weights (SW) of being assigned to either treatment were estimated by $SW^A = \frac{f[A]}{f[A|L]}$. Therefore, the stabilized weight for treatment A=1: $SW^A = \frac{\widehat{Pr}[A=1]}{\widehat{Pr}[A=1|L]}$ and for A=0: $SW^A = \frac{1-\widehat{Pr}[A=1]}{1-\widehat{Pr}[A=1|L]}$.

We also apply inverse-probability weights to this model to adjust for potential selection bias:

$$logit(\Pr[C = 0|A, L]) = \pi_0 + \tau_1^T L_0 + \pi_1 A \text{ (numerator)}$$

$$logit(\Pr[C = 0|A, L]) = \tau_0 + \tau_1^T L_0 + \tau_2 A \text{ (denominator)}$$

The stabilized weights for censoring due to loss to follow-up is: $SW^{LFU} = \frac{\widehat{Pr}[LFU=0|A]}{\widehat{Pr}[LFU=0|L,A]}$.

Under the assumptions of no unmeasured confounding given the included covariates and a low monthly risk of the outcome within levels of those covariates, the hazards ratios (HR) for developing the outcomes if all eligible individuals had been treated with DOACs (a=1) versus all eligible individuals had been treated with warfarin (a=0) can be estimated by the marginal structural model[164] below:

$$logit(\Pr[Y_{t+1}^{a} = 1 |\, Y_t^a = 0]) = \gamma_0 + \gamma_2 a + \gamma_3 at + \gamma_4 at^2$$

Next, we organized each persons' data in discrete-time (person-month) format (month 1 to 12) and fitted a weighted pooled logistic regression containing the outcome Y, and treatment A, and a function of time (time and its quadratic terms), weighted for SW calculated in the previous step. SWs were truncated at 99th percentile to remove extreme weights.

$$\text{logit } (\Pr[Y_{t+1} = 1|A_0, L_0, \bar{Y}_t = 0]) = \alpha_{0,t} + \alpha_1 A_0 + \alpha_2{}^T L_0$$

The exponentiated coefficient of treatment indicator (e^{β_2}) is the unbiased estimate of ITT HR.

2. PP analysis

We arranged the data in person-month format and calculate subject-specific time-varying non-stabilized inverse-probability weights.[199,200] The denominator of this weight at time *t* is the probability that an individual received his/her observed treatment history given covariate history by *t*. The application of these weights creates a pseudo-population in which treatment is independent of the measured confounders at all time points. To estimate the denominator, we fit two separate models to allow the probabilities to differ according to prior treatment status. The

first model is fit to person-months who received treatment A=0 in the previous month (*i.e.*, $A_{k-1} = 0$)

$$\text{logit}\left(\Pr\left[A_k = 1 \,|A_{k-1} = 0, \bar{L}_k, \overline{Y}_{k-1} = 0\right]\right) = \eta_{0,t} + \eta_1^T L_0 + \eta_2^T L_k$$

Then, we fit the second model for person-months who received treatment A=1 in the previous month (*i.e.*, $A_{k-1} = 1$):

$$\text{logit}\left(\Pr\left[A_k = 1 \,|A_{k-1} = 1, \bar{L}_k, \overline{Y}_{k-1} = 0\right]\right) = \theta_{0,t} + \theta_1^T L_0 + \theta_2^T L_k$$

where covariate history $\bar{L}_k$ were summarized by baseline L_0 and the most recent measurement of L_k. Then, the weights for censoring due to switching treatment is computed by

$$W_t^A = \prod_{k=0}^{t} \frac{1}{f(A_k|\bar{A}_{k-1}, \bar{L}_k, \overline{Y}_{k-1} = 0)}$$

The total weights are the product of time-varying non-stabilized inverse-probability weights for censoring due to treatment switching, time-varying weights censoring due to lost to follow-up

To obtain the treatment effect, we fitted a pooled logistic regression to the censored data, weighted for total weights to adjust for time-varying confounding. We truncated weights at their 99th percentile to prevent extreme weights. Under the same assumptions described in the previous section, the exponentiated coefficient of the treatment indicator (*i.e.*, $exp(\beta_2)$) validly estimates the per-protocol HR.

$$\text{logit}\left(\Pr[Y_{t+1} = 1|A_0, L_0, \bar{Y}_t = 0, \bar{C}_{t+1} = 0]\right) = \beta_0 + \beta_1^T L_0 + \beta_2 A$$

To estimate the weighted survival curves and standardize the curves to baseline distribution of covariates, we fitted a similar model with an interaction term between treatment regimen A and

f(t) – a function of time and time squared to allow for non-proportional hazards. The model was then used to predict outcomes of interest under each treatment strategy $A = a$. The details for creating standardized survival curves can be found in published studies.[193]

3.3.4.9. Subgroup analyses and sensitivity analyses

The treatment effects were estimated under the following subgroups: cancer type (breast, lung, prostate), cancer status at baseline (active, history), cancer stage (local, regional, and distant), and tumor grade (I, II, and III). A series of sensitivity analyses were conducted to confirm the robustness of the findings. First, we extended a grace period to 6 months from AFib diagnosis to warfarin/DOAC initiation to reflect the uncertainty in clinical practice when patients are allowed time to complete clinical tests before treatment initiation or get access to initial treatment. Second, we included individuals with all levels of baseline CHA_2DS_2-VASc score because patients with cancer are at higher risk of stroke and may be eligible to initiate to start OACs. Third, we the long-term treatment effects by extending follow-up time to 36 months. Fourth, we removed individuals with metastatic cancer at baseline, who may have a low life expectancy based on previous RCTs.[168,169] Fifth, we excluded individuals with thrombocytopenia at baseline, since these patients are at elevated risk of bleeding.[194,195] Six, we further truncated stabilized weights at 95th percentile to test the robustness of the treatment effects to the presence of extreme weights.

3.3.5. Interpretation of expected results

HR with 95% CIs and weighted survival curves reflected the incidence of outcomes at each time point and at the end of follow-up under each treatment strategy **(***Aim 2.1***)** and between DOACs and warfarin *(Aim 2.2)*.

3.3.6. Potential challenges and alternative approach

First, the use of retrospective registry & administrative claims data is susceptible to measurement bias.[201] In *Aim 2.2*, we allowed a grace period of 3 months from the time when all eligibility criteria are met to warfarin/DOACs initiation to remove immortal time bias. A grace period of 3 months was selected to mimic the time from baseline to treatment assignment in RCTs and the risk of stroke in general AFib patients was peak in the first 3 months after AFib diagnosis.[168,196,197] Next, sample size may be reduced due to the strict eligibility criteria used in the target trial. However, a recent study found nearly 8,000 patients with AFib and cancer who initiated OACs in the SEER-Medicare.[202] We utilized the discrete time (person-month) data structure[175] to ensure adequate statistical power for the analyses. In addition, unmeasured confounders may persist (i.e., patients' and prescribers' preference, frailty) because such information could not be captured by SEER-Medicare data. It is also noticed that several components of our target trial may not be perfectly emulated due to difference in definitions of diseases/conditions in inclusion/exclusion criteria (i.e., ICD codes in emulation vs. clinician's assessment in real trials) and outcome monitoring (lack of lab values in SEER-Medicare data). Last but not least, results could not be generalized to all types of cancer given that we only focus on patients with breast, lung, and prostate cancer in this study.

Table 9. Summary of study design, measurements, and statistical methods for Aim 2

Study design and data sources	Measurements	Statistical analysis

▪ Retrospective cohort study ▪ Target trial framework ▪ SEER-Medicare 2011-2019 ▪ Population: patients with AFib and cancer	▪ Outcome (primary): ischemic stroke and major bleeding ▪ Treatment strategies o Aim 2.1: five OAC initiation strategies o Aim 2.2: DOACs vs warfarin ▪ Covariates: baseline and time-varying confounders	▪ Unit of analysis: patient-level ▪ Measures: RD, HR, and 95% CI ▪ Main analysis: weighted pooled logistic regression with IP weighting for time-varying treatment and time-varying confounders

3.4. Aim 3

3.4.1. Research question and hypothesis

Instead of hypothesis-testing, our goal is to develop and validate novel ML algorithms to predict 1-year risk of stroke and bleeding in patients with AFib and cancer who initiate OACs. We compared the performance of several ML approaches including random forest, support vector machine, elastic net logistic regression, eXtreme Gradient Boosting (XGBoost), and neural network.

3.4.2. Data sources

We conducted a retrospective cohort study using SEER registry linked to Medicare database 2011-2019. The SEER-Medicare is a cancer registry linked to Medicare claims data managed by Centers for Medicare & Medicaid Services (CMS). SEER registry contains demographics, cancer characteristics, treatment, and follow-up of cancer patients across the US, [162] while Medicare data capture health care services utilization (medical claims, procedures, and prescriptions) of beneficiaries.[163] The study design and study timeline were illustrated by **Figure 7**.

3.4.3. Study sample

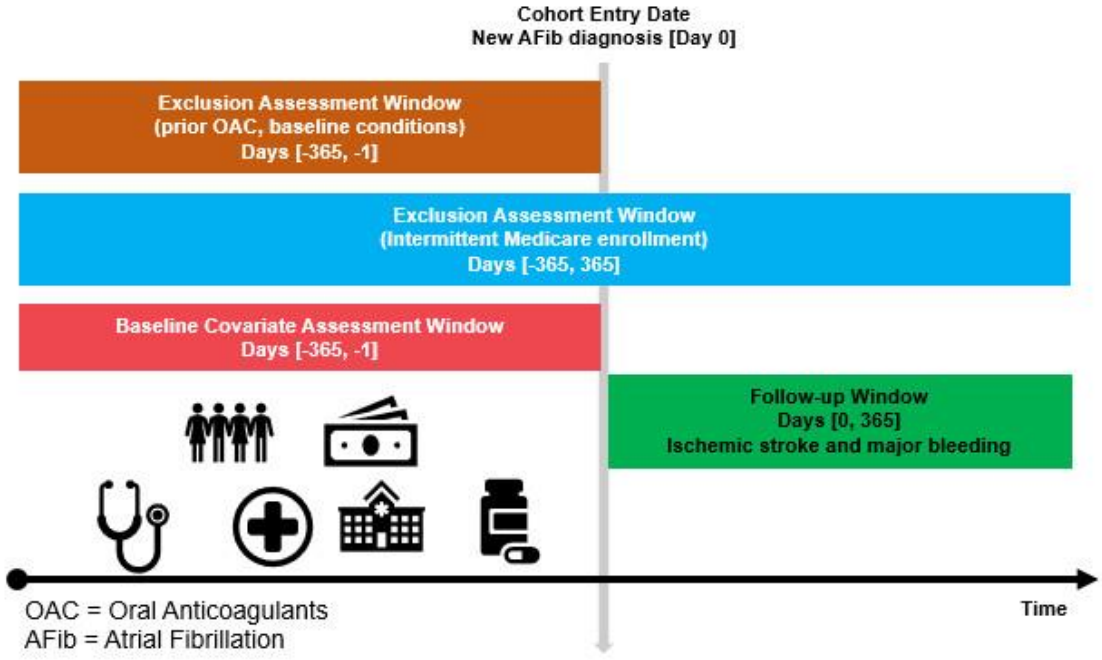
We included individuals aged ≥66, newly diagnosed non-valvular atrial fibrillation (NVAF) from 1/1/2012 to 12/31/2018. AFib was defined as any International Classification of Disease-9th Revision-Clinical Modification (ICD-9-CM) codes 427.31 or 427.32 or any International Classification of Disease-10th Revision-Clinical Modification (ICD-10-CM) codes I48.xx in any position on one Medicare inpatient claim or on 2 outpatient claims at least 7 days but <1 year apart.[172] We removed patients with valvular diseases, repair or replacement, venous thromboembolism, or joint replacement during the 12 months baseline period because OACs were also indicated for these conditions and their clinical management are different from AFib.[203,204] Eligible records were then linked to SEER files to identify patients with breast, lung, or prostate cancer - the most common cancer types with AFib - from at any time before the initial AFib diagnosis (ICD-O-3 codes C50.0-C50.9 for breast; C34.0, C34.1, C34.2, C34.3, C34.8, C34.9, C33.9 for lung; C61.9 for prostate cancer). Patients were required to continuously enroll in Medicare part A, B, D, and without Medicare Advantage or Health Maintenance Organization (HMO) for at least 12 months before and 12 months after NVAF diagnosis. Since OAC initiation

during follow-up may modify the risk of stroke and bleeding, we excluded patients who initiated warfarin or direct anticoagulants (DOACs) within 12 months before or after NVAF diagnosis.

Figure 7. Study design for the machine learning prediction models in Aim 3

3.4.4. Developing machine learning models

We developed separate ML algorithms for ischemic stroke prediction (1) and bleeding predictions (2) in patients with AFib and cancer taking OACs. A stepwise approach for developing the algorithms can be found in **Figure 8.**



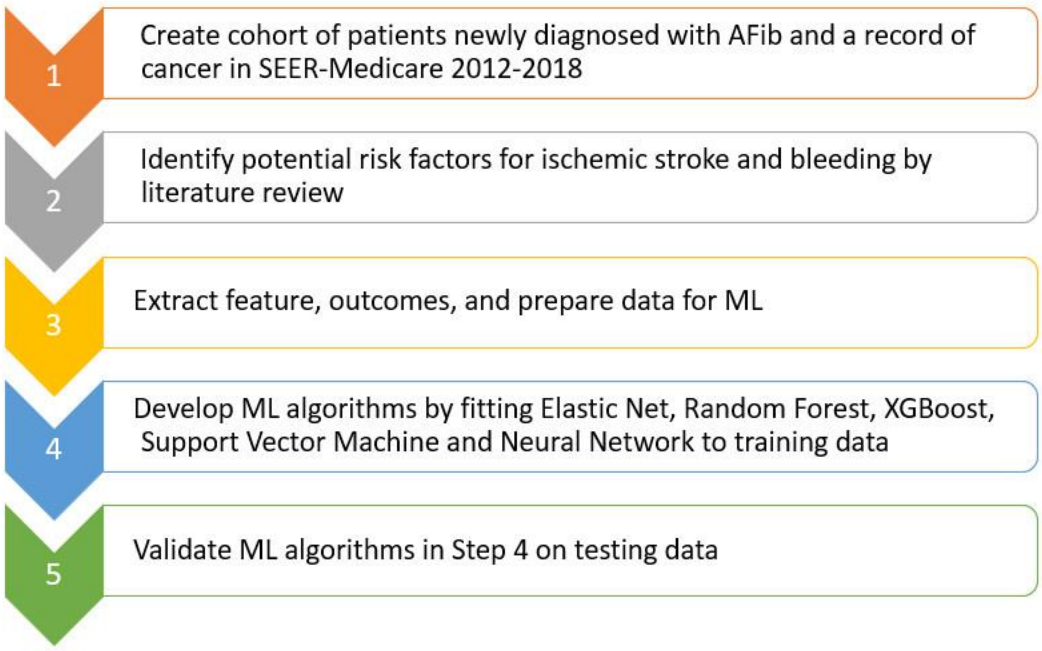


Figure 8. Stepwise approach for developing machine learning algorithms to predict 1-year risk of stroke and bleeding in patients with AFib and cancer

3.4.4.1. Feature selection

We selected potential predictors by literature review and availability in SEER-Medicare data.[25,27,168] The following predictors were included: *demographics* (index age, sex, race/ethnicity, calendar year, geographical region, urbanicity), *socioeconomic factors* (household median income, percentage of household with education level below high school, and Medicaid eligibility), *comorbidities* (hypertension, congestive heart failure, diabetes, prior stroke, vascular diseases, prior bleeding, renal diseases, liver diseases, alcohol use disorders, asthma/chronic obstructive pulmonary disease, hematological disorders, dementia, depression, thrombocytopenia, acute kidney disease, peptic ulcer disease), *cancer characteristics* (time from cancer diagnosis to the onset of AFib, cancer type, cancer stage, tumor grade, active cancer status [25,27]), *cancer treatment* (radiation, and cancer-directed surgery, and potentially interacting antineoplastic agents), and *medication history* (antiplatelet/non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium channel blockers, beta blockers,

antiarrhythmic medications, diuretics, statin, pump proton inhibitors, and serotonin reuptake inhibitors). Cancer characteristics were extracted from the most recent cancer record in SEER files. Other features were obtained from Medicare claims during 12 months before the index date.

3.4.4.2. Algorithms, model training and validation

Descriptive statistics were used to compare the characteristics of the cohort and explore the presence of missing data. MissForest was used to impute missing values for predictors.[205,206] The original dataset was then be randomly split into two datasets: the training dataset (70%) and the testing dataset (30%),[207,208] with the similar distribution of the outcomes in both datasets. In the algorithm training process, ML models (including elastic net logistic regression, random forest, support vector machine, XGBoost, and neural network) were fitted with ten-fold cross-validation (CV).[209]

Specifically, we randomly divided the training dataset into 10 groups (folds) of approximately equal size. The first fold was treated as the testing set, and the other folds were treated as training sets. We performed 10 iterations of this procedure in which a different group was treated as a testing set. The 10-fold CV estimate is the average of Mean Square Error (MSE) for 10 iterations. $CV_{10} = \frac{1}{10}\sum_{i=1}^{10} MSE_i$. The procedure is illustrated in **Figure 9**. The fitted models were then tested on the rest of the data. Since stroke and bleeding occurred in less than 10% within one year among AFib patients [25,210] and our goal is to predict the minority class (stroke and bleeding) our classification is severely imbalanced.[211] Therefore, we shifted the decision threshold to the true event probability rather than using the default threshold of 0.50.[211,212]

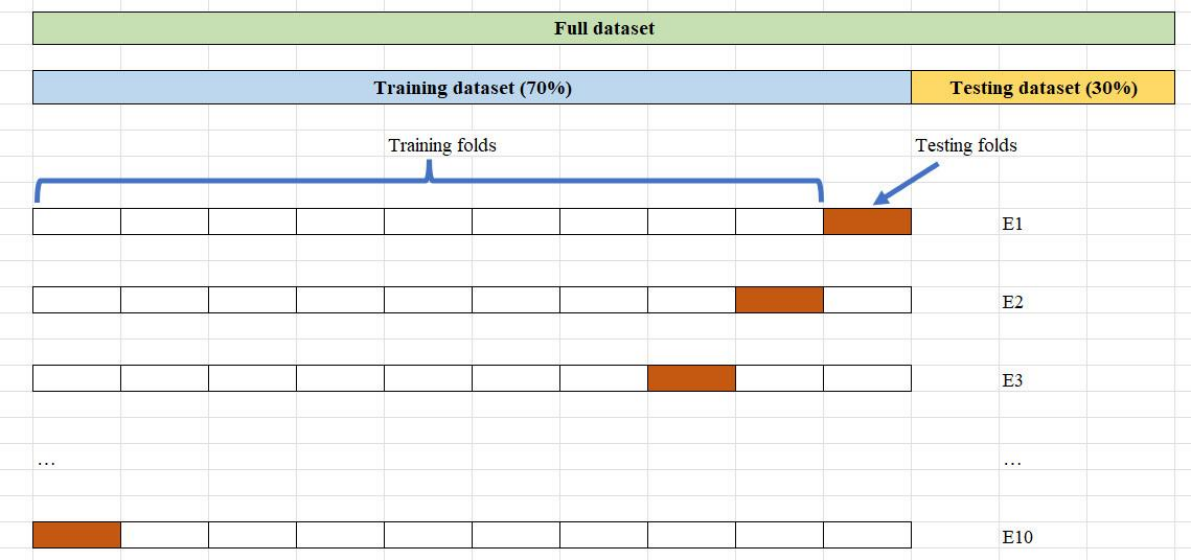


Figure 9. 10-fold cross-validation procedure in development machine learning algorithms for stroke and bleeding prediction in patients with AFib and cancer

Technical point 5

Elastic net logistic regression is the ML algorithm that combines multivariable logistic regression with LASSO and ridge regression penalty terms. For example, consider a ridge regression model

$$\sum_{i=1}^{n}(y_i - \beta_0 - \sum_{j=1}^{p}\beta_i x_{ij})^2 + A = RSS + A$$

where A= $\lambda \sum_{j=1}^{p} \beta_j^2$ is a shrinkage penalty for ridge regression and A= $\lambda \sum_{j=1}^{p} |\beta_j|$ for LASSO. These penalty terms shrink the model coefficients to towards zero to reduce overfitting.[128] Thus, the models have variable selection property and achieve a higher performance.

Random forests and XGBoost are aggregated decision tree models with substantially improved predictive performance.[128] XGBoost improves the accuracy of individual decision trees by building many trees sequentially and weighs the difficult-to-predict cases in a tree to a greater

degree. XGBoost also increases the speed of the algorithm and includes penalty terms to avoid model overfitting. On the other hand, random forests builds each tree separately based on a random sample of the training data. For each split, a random number of predictor variables are available, which results in trees that are different from each other. Therefore, the final model contains thousands of individual decision trees, with each of them combining to make predictions on new patients. When fitting the XGBoost and random forest models, we specified the number of trees, depth of trees, learning rate, and the number of predictor variables available at each split using 10-fold cross-validation in the training data.

Support vector machines (SVMs): SVMs puts the data into hyperplane and creates linear or non-linear decision boundary that maximize the margin between the classes of the outcomes using kernels.[128] The optimal value of the cost penalty (misclassification) was determined using 10-fold cross-validation in the training data.

Neural networks (NNs): NNs mimic how neurons works by combining of individual neuron-like units that take the predictor variables as inputs (input layer), combine them in hidden layers, process them through activation functions, and then output predictions (output layers).[128] In this study, we used a feed-forward multi-layer perceptron NN. We specified the number of hidden layers, size of each hidden layer, learning rate, and decay using ten-fold cross-validation in the training data.

3.4.4.3. Model performance, calibration, and evaluation

To assess algorithm discrimination, we calculated the area under the receiver operating characteristic curve (AUC) as the main metrics and compared the AUC across algorithms using DeLong's test.[213] Other performance metrics were also extracted, including sensitivity, specificity, F2 score. Since predicting patients having stroke/bleeding is more important and false negative

cases (patients at high risk of the event were not identified) are more costly, we focused on sensitivity and F2 score.[212] We generated feature importance plots to identify the contribution of each variable in predicting the outcomes.[214] Model calibration was performed to compare the true probability of the outcome versus a model's prediction with Brier score.[215] ML algorithms were developed using RStudio (version 3.6.2; Boston, MA, USA) and data analysis was conducted using SAS (version 9.4, SAS Institute, Inc., Cary, NC, USA).

3.4.5. Sensitivity analyses

Since our classification problem is severely imbalanced, Synthetic Minority Oversampling Technique (SMOTE) to account for imbalance distribution of the outcome variables.[216] Model fitting and validation were conducted on the resampling dataset. A recent study found a worsened model performance by imbalance correction resampling methods.[217]

3.4.6. Interpretation of expected results

We expect our ML algorithms with high prediction metrics and clinical utility for the risks of stroke and bleeding in patients with AFib and cancer. The ML models may help physicians optimize OACs treatment decision-making by identifying patients at high risk and considering treatment initiation for high-risk patients.

3.4.7. Potential challenges and alternative approaches

First, the performance of ML algorithms may be impacted by the complex mechanism and interactions between a wide range of risk factors of stroke and bleeding. We are unable to capture some important variables in the ML models (i.e., BMI, genetic factors, frailty, and health behaviors – not available in SEER-Medicare). In addition, the inclusion of baseline variables (before the index date) might not reflect the impact of some post-baseline predictors (i.e., treatment dosage, adherence, recent CHA_2DS_2-VASc and HAS-BLED scores, recent use of NSAIDs, and other time-

varying variables). Specifically, time-varying baseline features can be assessed monthly or every 3 months after the index date until the occurrence of the outcome or a censored event (discontinuation of medications, or death).[136,218] In addition, due to the nature of administrative claims data, measurement bias may exist and affect the performance and fairness of ML models. Selection bias may also persist in the development of ML algorithms because we restricted the cohort to patients with continuous Medicare enrollment. Future work may test our ML models developed in this proposed project in other patient populations.

Table 10. Summary of study design, measurements, and statistical methods for Aim 3

Study design and data sources	Measurements	Model development
▪ Cohort study ▪ SEER-Medicare 2011-2019 ▪ Population: patients with AFib and cancer	▪ Outcome: ischemic stroke and major bleeding ▪ Features: potential features were selected from prior literature	▪ Unit of analysis: patient-level ▪ ML algorithm development: o Feature selection o Data processing o Model training Elastic net, RF, XGBoost, SVM, and NN with cross-validation o Model validation and calibration

Chapter 4: Results (Presented with All Four Full manuscripts from Three Study Aims)

Aim 1 Manuscript

Title: Screening for clinically relevant drug-drug interactions between direct oral anticoagulants and antineoplastic agents: a pharmacovigilance approach

Abstract

Background: Use of direct oral anticoagulants (DOACs) in patients with cancer remains suboptimal due to the concern regarding potential drug-drug interactions (DDIs) with antineoplastic treatments. However, the clinical relevance of these DDIs is unknown.

Methods: We conducted a pharmacovigilance study of adverse event (AE) reports from the US Food and Drug Administration Adverse Event Reporting System from 1/1/2004 to 12/31/2021. AE reports containing DOACs and antineoplastic agents with CYP3A4/P-gp inhibitory or inducing activity suggested by published pharmacokinetic studies were included (n=36,066). The outcomes of interest were bleeding or stroke, identified by MedDRA dictionary version 25.0. We used disproportionality analyses (DPA), logistic regression models (LR), and Multi-item Gamma-Poisson Shrinker (MGPS) (Empirical Bayes Geometric Means (EBGM) and 90% credible intervals (90% credible intervals - CIs)) algorithms to identify the safety signal of DDIs.

Results: The highest bleeding reporting rates for each drug class were the combination of DOACs with neratinib (39.08%, n=34), tamoxifen (21.22%, n=104), irinotecan (20.54%, n=83), and cyclosporine (19.17%, n=227). The highest rate of stroke was found for prednisolone (2.43%, n=113). In the primary analysis, no signal of DDIs by the antineoplastic therapeutic class was detected by MGPS, DPA, and LR approaches. By individual antineoplastic drug, DOACs-neratinib was the only signal detected [EBGM (EB05-EB95)=2.71 (2.03-3.54)].

Conclusion: No signal of DDIs between DOACs and antineoplastic agents was detected, except for DOAC-neratinib. Most DDIs between DOACs and antineoplastic agents may not be clinically relevant. The DDIs between DOACs and neratinib should be further examined in future research.

1. Introduction

Compared to patients without cancer, patients both with AFib and cancer have a 4- to 7-fold higher risk of venous thromboembolism (VTE) and a 2-fold higher risk of bleeding.[13,14] Although the benefit of taking oral anticoagulants (OACs) in patients with AFib and cancer has been recognized [18], only half of these patients are initiated OACs.[17,20] In recent years, direct oral anticoagulants (DOACs) have been preferred over warfarin due to their superiority in reducing the risk of stroke in AFib patients.[15,16] However, the use of DOACs in patients with concomitant AFib and cancer may be hampered by the concern about potential drug-drug interactions (DDIs) with antineoplastic drugs[11,22,24] Patients with cancer are also at higher risk of VTE than the general population.[219,220] Although DOACs have been recommended as alternatives to low molecular weight heparins (LMWHs) in the management of patients with cancer and VTE,[221] DDIs between DOACs and cancer therapies have also raised uncertainty in DOACs prescription in this population.[222,223]

Current evidence of DDIs with DOACs has come from pharmacokinetic (PK) studies where the anticoagulating effects are amplified or mitigated by the presence of another drug mainly through their metabolism of Cytochrome P450 enzymes (CYP) in the liver or P-glycoprotein (P-gp) transporters.[11,24] Rivaroxaban and apixaban are mainly metabolized by CYP3A4, and all DOACs are the substrates of P-gp.[115] Therefore, DDIs between DOACs and antineoplastic agents or supportive cancer care treatments with CYP3A4/P-gp inhibitory activity could potentially result in overexposure of DOACs and increase the risk of bleeding. In contrast, concurrent administrations of DOACs and antineoplastic CYP3A4/P-gp inducers may increase the risk of

stroke. Because of this concern, the 2018 European Heart Rhythm Association (ERHA) Practical Guide recommended against the concomitant use of DOACs and hormonal agents, tyrosine kinase inhibitors (TKIs), or some chemotherapeutic agents.[117]

Although the DDIs between DOACs and antineoplastic agents have been predicted by *in vitro* studies, the clinical relevance of these DDIs is not well-established. Pre-clinical studies consider DDIs in a simple context, not accounting for the presence of patient-level factors such as patient demographics, clinical characteristics, genetic factors, comorbidities, and other concurrent medications. However, the evidence in DDIs between DOACs and antineoplastic agents generated from randomized controlled trials (RCTs) and epidemiological studies is limited. In a population-based cohort study, Wang et al. (2021) compared the incidence of bleeding among patients with AFib who were concomitantly exposed to DOACs and anticancer medications with CYP3A4 and/or P-gp inhibitory activity with those exposed to DOACs alone.[118] This study found that concomitant DOACs and CYP3A4/P-gp-inhibiting anticancer medications were not associated with an elevated risk of bleeding compared with DOACs alone. However, the findings may only be generalizable to patients initiating a CYP3A4/P-gp-inhibiting anticancer medication, given that they were already on DOACs. Pharmacovigilance studies using spontaneous reporting systems (SRSs) may help detect the signal of DDIs between DOACs and antineoplastic agents. The major advantage of SRSs is their availability in early detection of adverse drug events, especially in oncology,[122] when such events are not reported from RCTs and traditional epidemiological studies are not feasible due to delayed data availability from administrative databases.

In this study, we aimed to detect clinically relevant DDIs between DOACs and antineoplastic agents to generate hypotheses on the association between reported bleeding events or stroke and the co-existence of DOACs and antineoplastic agents. Our findings may help clinicians narrow

their current DDI ‘watch list’ when treating patients with AFib and cancer or patients with cancer-associated VTE.

2. Materials and methods

2.1. Study design and data sources

We conducted a retrospective analysis of adverse event (AE) reports from the US Food and Drug Administration Adverse Event Reporting System (FAERS) database from January 1, 2004 to December 31, 2021. The FAERS database is a publicly available SRS developed and maintained by the FDA for the post-marketing safety surveillance program for drug and therapeutic biologic products via MedWatch.[139] FAERS data are collected by submission of AE reports from customers, healthcare providers, and pharmaceutical companies.[139] As of December 31, 2021, the FAERS database contained more than 23 million AE reports from US and non-US regions.[140] The FDA releases FAERS data files each quarter, which contain seven separate tables in .txt format: patient demographic and administrative information, drug information, Medical Dictionary for Regulatory Activities (MedDRA®) terminology for AEs, patient outcomes and seriousness, reporting sources, drug therapy start date and end date, and MedDRA® terminology coded for the indications of reported drugs.[141] FAERS is a valuable tool for generating a hypothesis on the association between drugs/biologic products and DDIs or AEs. If a safety signal is identified, further evaluation using other available databases, such as the FDA Sentinel System, is warranted.[139]

2.2. Drug exposure identification

We retrieved AE reports containing DOACs (including dabigatran, rivaroxaban, apixaban, edoxaban) in combination with antineoplastic agents [kinase inhibitors (KIs), chemotherapy, hormone therapy, immunomodulating agents (IMAs)] with CYP3A4/P-gp inhibitory or inducing

activity suggested by PK studies (**Table 1**).[11,24,117,224] Drugs of interest were identified from DRUGyyQq.TXT files by text string search using Nation Drug Code Directory, Purple Book Database, and RED BOOK.[142-144] For non-US products, trade names from IBM Micromedex (Greenwood Village, CO) were extracted.[145] We anticipated potential abbreviations and misspellings by truncating corresponding search strings of generic and brand names (**Table S1, Appendix).** We combined the data files across the years and de-duplicate reports by retaining the most recent case number for the same report as suggested by the FDA.[225] All reports were included regardless of their role coded in FAERS (Primary Suspect, Secondary Suspect, Concomitant, or Interacting).

2.3. Outcomes – Adverse Drug Reactions (ADR) Definition

We identified the bleeding or stroke events in REACyyQq.TXT files by MedDRA® version 25.0.[146] ADRs are coded using Preferred Terms (PTs) in MedDRA® dictionary in the FAERS database. We used Standardized MedDRA Queries (SMQs) to define the outcome of interest: PTs under high-level term were used if the outcomes of interest fell into a broader level term of the high-level term. All PTs used to define bleeding and stroke events were presented in **Tables S2 and S3, Appendix**.

2.4. Covariates

Demographics of AE reports were extracted from DEMOyyQq.TXT files, including patient's age (<18, 18-64, ≥65), sex (male, female), reporting year, and reporting region (US, non-US). Missing data for covariates were categorized into a 'missing/unknown' subgroup.

2.5. Statistical analysis

We calculated the total number of reports containing DOACs and pre-specified antineoplastic agents and the number of reports related to bleeding or stroke by therapeutic class and individual

drugs. We also stratified the number of AE reports by individual DOACs. The total number of reports was plotted to visualize the patterns of concurrent reporting over the years. We obtained demographics of AE reports with DOACs-anticancer medications (i.e., age, sex, reporting year, reporting source, and reporting region). In the primary analysis, we used disproportionality analyses (DPA), logistic regression model (LR), and Multi-item Gamma-Poisson Shrinker (MGPS) to identify disproportionate reporting of potential DDIs between DOACs and antineoplastic agents by therapeutic class and by individual drugs. The unit of analysis was AE report with 'primaryid' as the unique identifier of AE reports in FAERS database. For DPA, we calculated the reporting odds ratios (ROR) and 95% confidence intervals (95% CI) from the 2×2 exposure-outcome contingency tables to measure the disproportionality of bleeding/stroke between AE reports of DOAC-antineoplastic agent combination versus DOAC alone.[147-149] In LR models, we computed the ROR with the interaction term in the models, adjusted for other covariates.[149,151] The FDA currently uses the MGPS model for DDIs signal detection in FAERS data.[152] Therefore, we detected the signals of DDIs using the MGPS model based on Empirical Bayes Geometric Means (EBGM) and corresponding 2-sided 90% credible intervals (90% CIs, EB05 and EB95) to identify disproportionate reporting of DOACs-antineoplastic drugs-bleeding or DOACs-antineoplastic drugs-stroke triplets.[149,153] A safety signal was detected if the lower limit of 95% CI of ROR was >2.00 for DPA,[150] the lower limit of 95% CI of ROR >1.00 for LR[149,151] or EB05>2 for MGPS, given that the bleeding event is rare.[154] Disproportionality measures for DPA and LR were computed when there were three or more AE reports for a triplet drug-drug-event. The details of these methods were described in the **Technical notes (Appendix)**. We used EBGM as the main measure and compared the signals with other methods.[155] SAS (version 9.4,

SAS Institute, Inc., Cary, NC, USA) was used for data processing, DPA, and LR methods. RStudio (version 3.6.2; Boston, MA, USA) was used for the MGPS model (package 'openEBGM').

2.6. Sensitivity analyses

Three sets of sensitivity analyses were conducted to confirm the robustness of the main findings. First, we restricted the analyses to AE reports from October 19, 2010 (approval date of dabigatran – first DOAC approved by FDA) to December 31, 2021 to rule out the possibility of Weber's effect.[158] Second, since there is no validated algorithm for outcome definition in FAERS database, we used clinicians' assessment to define the outcomes of interest. Specifically, a clinician specializing in cardiovascular diseases and anticoagulation therapy screened and selected any bleeding/stroke PT from MedDRA related to anticoagulation therapy. Third, we conducted the DPA and LR analyses using the combination of warfarin and antineoplastic agents as the referent group because warfarin was considered an alternative to DOACs in patients with AFib or VTE (**Tables S4 and S5, Appendix**).

3. Results

3.1. Reporting patterns of DOAC-antineoplastic agent combinations in FAERS (2010-2021)

There were a total of 36066 AE reports with both DOAC and antineoplastic agents in the FAERS in 2010-2021. Overall, there was an increase in trends in AE reports with PK-suggested DDIs by drug class in the FAERS database since the DOACs were launched into the US market in 2010 (**Figure 1**). Reporting patterns by antineoplastic drug class were shown in **Figures S1-S5**. Similar reporting patterns were observed when individual antineoplastic drugs stratified the combinations in each therapeutic class, such as IMAs and chemotherapeutic agents (except for methotrexate) (**Figures S1 and S2**). For other antineoplastic therapeutic classes, such as kinase inhibitors and

hormonal therapy, there was a sharp increase in the reports of the individual drugs in combination with DOACs from 2010, but a slight decline after 2018 was observed (**Figures S3 and S4**).

3.2. Demographics of AE reports with DOAC-antineoplastic agent combinations in FAERS (2010-2021)

Table 2 describes the demographics of AE reports with DOAC-antineoplastic agent combinations by antineoplastic drug class from FAERS. The DOAC-IMA combination was the most frequently reported combination (15475 reports, 42.91%), followed by DOAC-chemotherapy (8236 reports, 22.84%), and DOAC-KI (7006 reports, 19.43%). The majority of these AE reports were from patients aged >65 and female (except for the DOAC-IMA pair). The main reporter source was consumers for DOAC-KIs and DOAC-hormone pairs (41.45% and 41.98%, respectively), and physicians for DOAC-chemotherapy and DOAC-CYP3A4/P-gp inducers (34.27% and 40.83%, respectively). Most of the reports were submitted to FAERS in 2016-2021 (>88% for all combinations). For DOAC-KIs, DOAC-hormone, and DOAC-hormone combinations, most reports were from the US (64.62%, 61.82%, and 72.11%, respectively). In contrast, DOAC-IMAs and DOAC-CYP3A4/P-gp inducers combinations were primarily reported outside the US (64.05% and 81.01%, respectively).

3.3. Main analysis

Tables 3 and 4 demonstrate the total number of AE reports and the number of reports with the event of interest (bleeding or stroke) for each combination by therapeutic class and by individual drug. Palbociclib (n=1333), letrozole (n=1433), methotrexate (n=5173), dexamethasone (n=12973), and prednisolone (n=4642) were the most frequently reported in combination with DOACs in each drug class (KIs, hormone, chemotherapy, IMAs, and inducers, respectively). By individual DOACs, apixaban and rivaroxaban were the more frequently reported in combination

with antineoplastic agents (**Tables S6 and S7**). The highest bleeding reporting rates for each drug class were the combination of DOACs with neratinib (39.08%, n=34), tamoxifen (21.22%, n=104), irinotecan (20.54%, n=83), and cyclosporine (19.17%, n=227). The highest rate of stroke was found for the DOAC-prednisolone combination (2.43%, n=113).

In the main analysis, no signal of DDIs by antineoplastic therapeutic class was detected by MGPS method [EBGM (EB05-EB95) = 1.02 (0.97-1.08) for DOACs-KIs, 1.22 (1.15-1.30) for DOACs-hormone, 1.22 (1.16-1.27) for DOACs-chemotherapy, 0.66 (0.63-0.69) for DOACs-IMAs, and 1.05 (0.90-1.21) for DOACs-inducers] (**Table 5**). The findings from DPA and LR approaches were consistent with MGPS. Regarding individual antineoplastic drugs, DOACs-neratinib was the only signal detected [EBGM (EB05-EB95) = 2.71 (2.03-3.54)], while no elevated EBGM was found for other pairs.

3.4. Sensitivity analyses

Findings from sensitivity analyses were in accordance with the main analysis (**Tables S8, S9, and S10**). DOACs-neratinib remained as the only signal (EBGM (EB05-EB95) = 2.75 (2.07-3.60) in sensitivity analysis 1 and EBGM (EB05-EB95) = 3.36 (2.52-4.39) in sensitivity analysis 2. No other signal was detected for different combinations of DOACs with individual antineoplastic drug or therapeutic class. In the sensitivity analysis 3, the findings remained unchanged when using the combination of warfarin and antineoplastic agents as the reference group.

4. Discussion

Antineoplastic medications have been suggested to inhibit or induce the effect of DOACs through PK mechanisms from *in vitro* studies. However, few studies have explored the clinical impact of these DDIs. To our knowledge, this study is among the first to explore the clinical significance of such DDIs, using a pharmacovigilance approach to detect a safety signal from the FAERS

database. We found an increase in trends in AE reports with DOAC-antineoplastic agent combination by drug class in the FAERS database since the DOACs were introduced in 2010. At the therapeutic class level of antineoplastic drugs, no signal of DDIs with DOACs was detected. However, at the individual antineoplastic drug level, the combination of DOACs and neratinib was associated with increased bleeding reporting rates. These findings demonstrate that the DDIs between DOACs and antineoplastic agents might not be of clinical relevance despite concerns raised in PK studies. However, the combination of DOACs and neratinib should be further investigated with rigorously designed, longitudinal epidemiological studies. Our results may relieve clinicians' concern regarding DDIs between DOACs and antineoplastic agents while prescribing anticoagulants in patients undergoing cancer treatment (i.e., KIs, chemotherapy, hormone therapy, IMAs, or CYP3A4/P-gp inducers).

In the last decade, the trends in the use of OACs have shifted towards DOACs [226-229] due to their favorable efficacy profile and lower risk of overall bleeding in patients with non-valvular AFib and VTE.[15,230] Although there is no guidance on anticoagulant selection in patients with AFib and cancer, DOACs are generally preferred over warfarin in patients this subpopulation.[231] Latest guidelines recommend DOACs and LMWHs as initial treatments among patients with cancer-associated VTE.[221] These recommendations were strongly supported by findings from recent RCTs, where apixaban, rivaroxaban, and edoxaban were non-inferior to LMWHs in management of patients with VTE and cancer.[232-234] These patterns in clinical practice may explain the increased number of AE reports with the DOAC-antineoplastic agent combination observed in our study. In addition, ease of monitoring, administration, and lack of dietary limitations are the major advantages of DOACs over warfarin or LMWH, which may be attributable to the increase in AE reports containing DOACs.[235] However, for several antineoplastic agents, such as KIs and

hormones, we observed a slight decline in AE reports with DOACs after 2018. This change in pattern may reflect the 2018 European Heart Rhythm Association Practical Guide,[117] which recommends against the concomitant use of DOACs and hormonal agents, KIs, chemotherapeutic agents, and IMAs.[227] As a result, clinicians may be cautious and try to avoid concomitantly prescribing DOACs and these antineoplastic medications, which, in turn, may have led to the lower reporting in FAERS database. It is also noticed that our findings may not properly capture the number of patients who had bleeding events while receiving DOACs and antineoplastic agents concurrently due to reporting bias. Under-reporting bias may exist in FAERS since healthcare professionals or individuals who take the drug may not submit the AE to the FDA.

There have been several guidelines/consensuses published on the concomitant use of DOACs and antineoplastic medications. The 2018 EHRA guidelines recommend a contraindication for co-prescription of DOACs and antineoplastic agents with strong CYP3A4/P-gp inhibitory activity (i.e., imatinib, crizotinib, abiraterone, enzalutamide, paclitaxel, vinblastine, doxorubicin, and cyclosporin, tacrolimus) or with CYP3A4/P-gp inducers (i.e., dexamethasone, vandetanib, sunitinib, doxorubicin, vinblastine). In addition, the European Respiratory Society (ERS) advised against the concurrent use of several small-molecule inhibitors (SMIs) with DOACs for non-small cell lung cancer, such as afatinib, alectinib, brigatinib, capmatinib, ceritinib, crizotinib, entrectinib, gefitinib, larotrectinib, lorlatinib, and osimertinib.[236] The American Society of Clinical Oncology (ASCO) recommends a caution or dose reduction when combining DOACs and enzalutamide.[237-239] According to the Consensus workshop on the management of concomitant medication in breast cancer, ribociclib and palbociclib should be avoided or used with caution in combination with DOACs.[240] However, these recommendations were made based on the extrapolations of *in vitro* studies without considering the clinical impact of such DDIs due to a lack of real-world evidence.

In addition, DDIs between DOACs and alectinib, [241] cabozantinib, [242] or cobimetinib [242] were also reported. In our study, none of these suggested DDIs were found. We found no signal of DDIs between DOACs and KIs, DOACs and hormonal therapy, DOACs and chemotherapy, DOACs and IMAs, or DOACs and CYP3A4/P-gp inducers at the therapeutic class level. Using population data from Taiwan, Wang (2020) also found that antineoplastic agents with inhibitory or competitive effects on CYP3A4/P-gp activity were not associated with a higher incidence of major bleeding when they were co-prescribed with DOACs.[118] In a nested case-control study, Kravchenko (2022) found no association between DOAC-dexamethasone versus DOAC alone with risk of thromboembolic events in patients with SARS-CoV-2 infection.[243] These findings were consistent with our study, although some limitations to be acknowledged, such as confounding by indication, unmeasured confounding, and limited sample size. It is also noted that among individual DOACs, apixaban and rivaroxaban were more frequently reported than other DOACs in combination with antineoplastic agent in our studies. Although we did not conduct subgroup analyses for individual DOACs due computational time and intensity, there is a low chance that a signal of DDIs was detected for individual DOACs (except for DOAC-neratinib combinations) given low signal metrics (i.e., ROR and EBGMs) for all DOACs. However, future studies should further investigate the clinical relevance of DDIs between DOACs and antineoplastic agents for individual DOACs. In addition, although marketed earlier than rivaroxaban and apixaban, AE reports of dabigatran were lower than the later medications. This may reflect the overall trend in the use of DOACs over the last decade. In fact, dabigatran prescriptions decreased while prescriptions for apixaban and rivaroxaban increased significantly among Medicare beneficiaries.[226,244] Dabigatran may be less preferred over apixaban and

rivaroxaban due to their dosing (twice daily) and caution for dose reduction in patients with renal impairment.[115]

There were several reasons for which we may not have detected any clinically relevant DDIs in our study. First, clinicians may avoid concomitant use or reduce the dose of DOACs, with antineoplastic agents based on the guidelines. Thus, bleeding events may not occur and not be reported. Second, limitations of FAERS data, such as under-reporting, may hamper the detection of a DDI signal. In addition, *in vitro* studies considered static scenarios of DDIs between DOACs and antineoplastic agents through CYP/P-gp system without considering other factors. Indeed, in human body, multiple factors including patients' condition, medication use, the route of administration, the timing of administration of two or several drugs, and the expression of enzyme activities (i.e., CYP3A4) may all have impact on the development of adverse clinical outcomes. In addition, these factors may vary considerably between patients and it is therefore uncertain to translate in vitro DDIs into clinically meaningful DDIs.[245] It is also acknowledged that clinical scenarios, drug indications, and other clinical information were not available or rarely reported in FAERS data and this may result in bias when generating signals of DDIs in our study.[139]

The interaction between DOACs and neratinib has not been well documented in the literature. Neratinib is a weak P-gp inhibitor and DOACs (i.e., rivaroxaban, dabigatran) are substrates of P-gp.[224,246] Thus, the concomitant use of these agents may increase the plasma levels of DOACs and increase the risk of bleeding.[224,246] The package information for neratinib (NERLYNX) recommends monitoring adverse reactions of narrow therapeutic agents that are P-gp substrates when used concomitantly with neratinib.[246] In our study, 87 AE reports with the DOAC-neratinib combination were reported, and 34 (39.08%) reports were related to bleeding events, representing the combination with the highest bleeding reporting rates in our study. Particularly, the

combination was reported more for rivaroxaban than other DOACs (73 reports, 83.91%). This combination should be further investigated in other interacting mechanisms and using population-based studies with rigorous design.

There are several limitations to acknowledge in our study. First, SRSs such as FAERS may be subject to reporting bias (over- or under-reporting), lack of clinical scenarios, lack of drug indications, misspellings, and missing information.[139] We proactively anticipated potential misspellings using different search strings to avoid misclassification of the exposures and outcomes. We categorized missing values for each covariate into a different level. However, reporting bias or lack of clinical scenarios or drug indications may not be resolved. For example, chemotherapeutic agents such as methotrexate, dexamethasone, or prednisolone have indications other than cancer. The low bleeding/stroke reporting rates also suggested a low likelihood of DDIs for these drugs. Second, for the MGPS approach, we did not adjust for polypharmacy issues in the reports and other covariates.[149] This can be resolved by using the Regression-adjusted gamma-Poisson shrinkage (RGPS) method.[149] However, as the package is not available in R or SAS and due to coding complexity, we did not implement RGPS. In addition, the DDI signal on an antineoplastic therapeutic class in our study may not reflect the signal for the entire drug class because we focused on specific combinations proposed by PK studies. Moreover, we used review articles and the University of Liverpool Cancer DDI checker to identify potential DDIs.[11,24,224] Therefore, several combinations were not included. For example, the DDIs between ibrutinib and OACs were discussed in a recent study but not assessed in our study.[247] In addition, several pharmacodynamic interactions between DOACs and IMAs (i.e., bevacizumab, caplacizumab, ipilimumab, and ramucirumab) were documented in prior literature but not included in our analysis. Caution when using these IMAs in the presence of DOACs is needed.[248]

Apart from these limitations, our study has several strengths. First, this study explored a wide range of combinations between DOACs and cancer treatments among real-world patients that have not been studied before. Second, FAERS data provide rapid availability of DDIs data, whereas other data sources may not gather adequate sample size for evaluating the DOAC-antineoplastic combinations. Third, the implementation of multiple methods for DDI detection increased the rigorousness of our approach and the robustness of the findings. In the paucity of *in vivo* studies, our study brings valuable information to help clinicians optimize treatment decisions to continue DOACs in patients with cancer.

5. Conclusions

In conclusion, no signal of DDIs between DOACs and antineoplastic agents, as suggested by *in vitro* studies, was detected except for neratinib. Our findings may help clinicians narrow the "watch list" of DDIs between DOACs and antineoplastic agents in managing AFib/VTE and concomitant cancer. The DDIs between DOACs and neratinib should be further examined and confirmed in future research.

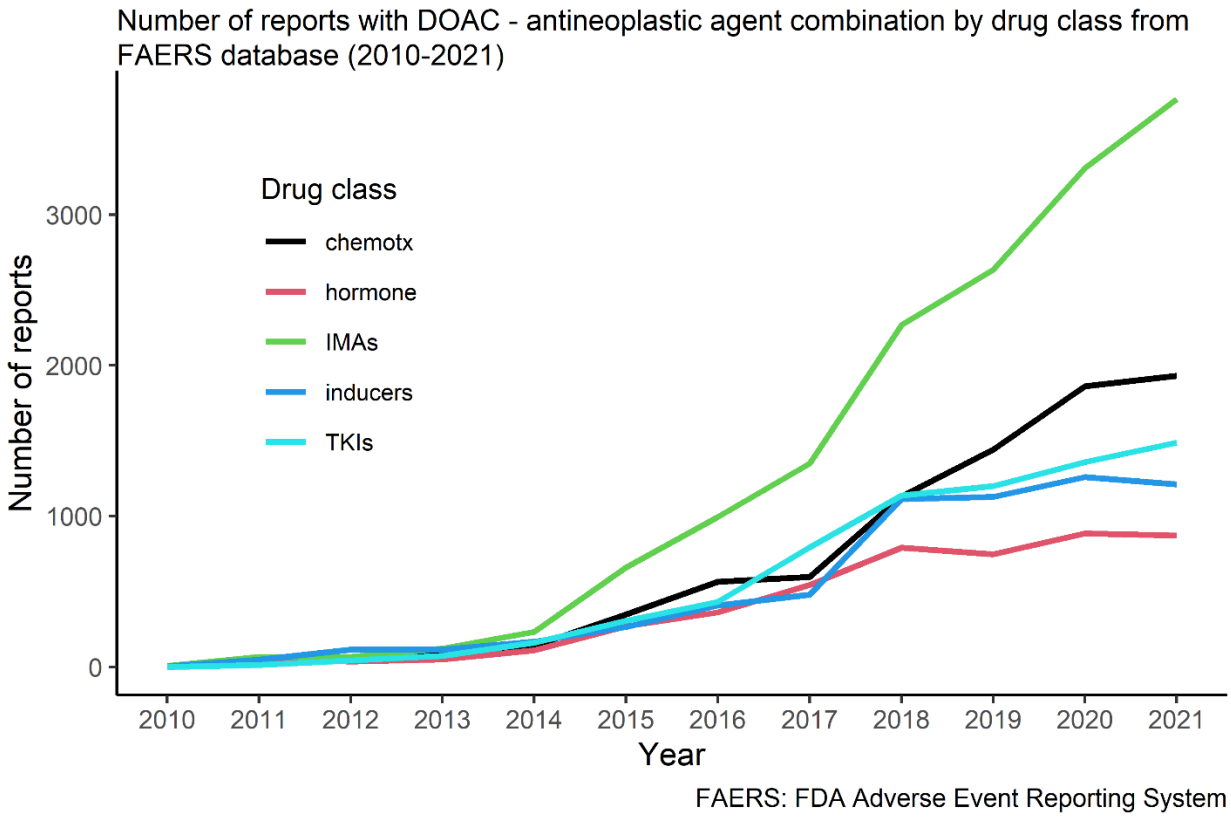


Figure 1. Number of reports with DOAC-antineoplastic agent combination by therapeutic class from FAERS (2010-2021). chemotx: chemotherapeutic agents. IMAs: immune-modulating agents. KIs: kinase inhibitors.

Table 1. Proposed pharmacokinetic drug-drug interactions between novel oral anticoagulants and anticancer treatment[24,116,117]

Antineoplastic therapeutic class	CYP3A4	P-glycoprotein
Kinase inhibitors (tyrosine kinase inhibitors, protein kinase inhibitors)	*Inhibitors*: imatinib, dasatinib, nilotinib, lapatinib, erlotinib, crizotinib, tivozanib, pazopanib, axitinib, brigatinib, ceritinib, lorlatinib, binimetinib, trametinib, palbociclib, ribociclib, entrectinib, larotrectinib, idelalisib *Inducers*: vemurafenib, dabrafenib, encorafenib	*Inhibitors*: imatinib, nilotinib, lapatinib, sunitinib, crizotinib, vandetanib, osimertinib, neratinib, gefitinib, erlotinib, afatinib, sorafenib, regorafenib, ponatinib, alectinib, lorlatinib, vemurafenib, cobimetinib, abemaciclib, pimegatinib, entrectinib, cabozatinib, capmatinib, idelasinib *Inducers*: dabrafenib, encorafenib
Hormone	*Inhibitors*: letrozole, anastrozole, abiraterone, bicalutamide, tamoxifen *Inducers*: enzalutamide	*Inhibitors*: tamoxifen, abiraterone, enzalutamide
Chemotherapy	*Inhibitors*: vinblastine, vincristine, vinorelbine, docetaxel, doxorubicin, idarubicin, cyclophosphamide, ifosfamide, lomustine, irinotecan, etoposide *Inducers:* paclitaxel	*Inhibitors*: vinblastine, doxorubicin, methotrexate
Immune-modulating agents	*Inhibitors*: cyclosporine, sirolimus, temsirolimus, tacrolimus *Inducers*: dexamethasone, prednisolone	*Inhibitors:* cyclosporine, sirolimus, tacrolimus, dexamethasone *Inducers*: dexamethasone

CYP3A4: Cytochrome P450 type 3A4

Table 2. Characteristics of AE reports with DOAC-antineoplastic agent combination from FAERS database (2010-2021)

	Kinase inhibitors (n=7006)	Hormone (n=4728)	Chemotherapeutic agents (n=8236)	Immune-modulating agents (n=15475)	CYP3A4/P-gp inducers (n=6311)
Age					
<18	9 (0.13)	9 (0.19)	79 (0.96)	51 (0.33)	32 (0.51)
18-65	1552 (22.15)	591 (12.50)	2125 (25.81)	2741 (17.71)	1195 (18.94)
>65	3435 (49.03)	2963 (62.67)	4020 (48.82)	6845 (44.24)	3765 (59.68)
Missing	2010 (28.69)	1165 (24.64)	2010 (24.41)	5836 (37.72)	1317 (20.87)
Gender					
Male	2947 (42.06)	2126 (44.97)	3121 (37.90)	7910 (51.12)	2604 (41.27)
Female	3689 (52.65)	2338 (49.45)	4445 (53.98)	6694 (43.26)	3072 (48.69)
Unknown/missing	370 (5.28)	264 (5.58)	668 (8.11)	869 (5.62)	633 (10.03)
Reporter type					
Consumer	2904 (41.45)	1985 (41.98)	2147 (26.07)	2331 (15.06)	1087 (17.23)
Physician	1724 (24.61)	1044 (22.08)	2822 (34.27)	3965 (25.63)	2576 (40.83)
Pharmacist	424 (6.05)	459 (9.71)	584 (7.09)	4418 (28.55)	596 (9.45)
Other HCPs	812 (11.59)	515 (10.89)	933 (11.33)	2536 (16.39)	962 (15.25)
Lawyer	1 (0.01)	35 (0.74)	112 (1.36)	47 (0.30)	12 (0.19)
Missing	1141 (16.29)	690 (14.59)	1636 (19.87)	2176 (14.06)	1076 (17.06)
Reporting year					
2010-2015	596 (8.51)	528 (11.17)	707 (8.59)	1154 (7.46)	710 (11.25)
2016-2021	6410 (91.49)	4200 (88.83)	7527 (91.41)	14319 (92.54)	5599 (88.75)
Reporting region					
US	4527 (64.62)	2923 (61.82)	2960 (35.95)	11157 (72.11)	1198 (18.99)
Non-US	2479 (35.38)	1805 (38.18)	5274 (64.05)	4316 (27.89)	5111 (81.01)

DOAC, Direct Oral Anticoagulant. FAERS, the US Food and Drug Administration Adverse Event Reporting System CYP3A4: Cytochrome P450 type 3A4. Cytochrome P450 enzymes. P-gp, P-glycoprotein. HCP, Healthcare Professional.

Table 3. Number of AE reports with combination DOAC-antineoplastic agents with CYP3A4/P-gp inhibitory activity by therapeutic class and by individual drugs from the FAERS database in 2004-2021

Combination	**Number of reports**	**Number of reports with bleeding events (%)**
DOACs-KIs	7006	944 (13.36)
DOACs-imatinib	327	83 (25.38)
DOACs-dasatinib	276	48 (17.39)
DOACs-nilotinib	225	34 (15.11)
DOACs-lapatinib	102	16 (15.68)
DOACs-erlotinib	422	59 (13.98)
DOACs-crizotinib	243	30 (12.35)
DOACs-tivozanib	60	2 (3.33)
DOACs-pazopanib	335	40 (11.94)
DOACs-axitinib	284	41 (14.44)
DOACs-brigatinib	61	4 (6.56)
DOACs-ceritinib	42	11 (26.19)
DOACs-lorlatinib	77	5 (6.49)
DOACs-binimetinib	170	13 (7.65)
DOACs-trametinib	272	41 (15.07)
DOACs-palbociclib	1333	126 (9.45)
DOACs-ribociclib	221	26 (11.76)
DOACs-entrectinib	19	3 (15.79)
DOACs-larotrectinib	5	0 (0.00)
DOACs-idelalisib	194	9 (4.64)
DOACs-sunitinib	393	108 (27.48)
DOACs-vandetanib	8	2 (0.25)
DOACs-osimertinib	305	34 (11.15)
DOACs-alectinib	143	10 (6.99)
DOACs-neratinib	87	34 (39.08)
DOACs-cabozantinib	830	73 (8.80)
DOACs-capmatinib	16	0 (0.00)
DOACs-sorafenib	121	30 (24.79)
DOACs-regorafenib	179	23 (12.85)
DOACs-ponatinib	198	32 (16.16)
DOACs-vemurafenib	138	20 (14.49)

DOACs-cobimetinib	144	23 (15.97)
DOACs-abemaciclib	100	3 (3.00)
DOACs-pemigatinib	3	0 (0.00)
DOACs-gefitinib	61	9 (14.75)
DOACs-afatinib	114	31 (27.19)
DOACs-hormone	4728	763 (16.14)
DOACs-letrozole	1433	211 (14.72)
DOACs-anastrozole	836	173 (20.69)
DOACs-abiraterone	628	94 (14.97)
DOACs-bicalutamide	605	127 (20.99)
DOACs-tamoxifen	490	104 (21.22)
DOACs-enzalutamide	1137	123 ((10.82)
DOACs-chemotherapy	8236	1322 (16.05)
DOACs-vinblastine	28	0 (0.00)
DOACs-doxorubicin	739	76 (10.28)
DOACs-methotrexate	5173	921 (17.80)
DOACs-vincristine	563	65 (11.55)
DOACs-vinorelbine	120	10 (8.33)
DOACs-docetaxel	745	126 (16.91)
DOACs-idarubicin	12	0 (0.00)
DOACs-cyclophosphamide	1651	157 (9.51)
DOAC-ifosfamide	43	4 (9.30)
DOACs-lomustine	33	3 (9.09)
DOACs-irinotecan	404	83 (20.54)
DOACs-etoposide	305	23 (7.54)
DOACs-IMAs	15475	1351 (8.73)
DOACs-cyclosporine	1184	227 (19.17)
DOACs-sirolimus	233	41 (17.60)
DOACs-temsirolimus	13	0 (0.00)
DOACs-tacrolimus	1299	200 (15.40)
DOACs-dexamethasone	12973	897 (6.91)

DOACs, Direct Oral Anticoagulants. KIs, kinase inhibitors. IMAs, immunomodulating agents.

Table 4. Number of AE reports with combination DOAC-antineoplastic agents with CYP3A4/P-gp inducing activity by therapeutic class and by individual drugs in FAERS database from 2004-2021

Combination	Number of reports	Number of reports with stroke events (%)
DOACs-inducers	6311	152 (2.41)
DOACs-dabrafenib	238	9 (3.78)
DOACs-encorafenib	184	1 (0.54)
DOACs-paclitaxel	1314	29 (2.21)
DOACs-prednisolone	4642	113 (2.43)

DOACs: Direct Oral Anticoagulants

Table 5. Main analysis of signal detection for drug-drug interactions between DOACs and antineoplastic agents in FAERS database

Combination	DPA ROR (95% CI) [a]	Logistic regression ROR (95% CI) [b]	MGPS EGBM (EB05, EB95)
DOACs-KIs	0.30 (0.28-0.32)	0.24 (0.23-0.26)	1.02 (0.97-1.08)
DOACs-imatinib	0.66 (0.51-0.84)	0.46 (0.35-0.59)	1.89 (1.58-2.25)
DOACs-dasatinib	0.41 (0.30-0.55)	0.36 (0.26-0.50)	1.30 (1.02-1.63)
DOACs-nilotinib	0.34 (0.24-0.49)	0.25 (0.24-0.26)	1.13 (0.85-1.48)
DOACs-lapatinib	0.36 (0.21-0.61)	0.48 (0.28-0.82)	1.15 (0.76-1.68)
DOACs-erlotinib	0.31 (0.24-0.41)	0.28 (0.21-0.36)	1.05 (0.85-1.30)
DOACs-crizotinib	0.27 (0.19-0.40)	0.48 (0.32-0.71)	0.93 (0.69-1.24)
DOACs-tivozanib	--	--	0.35 (0.13-0.78)
DOACs-pazopanib	0.26 (0.19-0.36)	0.20 (0.14-0.28)	0.90 (0.69-1.15)
DOACs-axitinib	0.32 (0.23-0.45)	0.31 (0.22-0.44)	1.08 (0.84-1.38)
DOACs-brigatinib	0.14 (0.05-0.37)	0.17 (0.06-0.48)	0.55 (0.26-1.06)
DOACs-ceritinib	0.68 (0.34-1.36)	0.88 (0.42-1.84)	1.73 (1.06-2.70)
DOACs-lorlatinib	0.13 (0.05-0.33)	0.27 (0.10-0.69)	0.54 (0.27-0.99)
DOACs-binimetinib	0.16 (0.09-0.28)	0.16 (0.09-0.29)	0.60 (0.38-0.90)
DOACs-trametinib	0.34 (0.25-0.48)	0.29 (0.20-0.41)	1.12 (0.87-1.44)
DOACs-palbociclib	0.20 (0.17-0.24)	0.23 (0.19-0.27)	0.72 (0.62-0.83)
DOACs-ribociclib	0.26 (0.17-0.39)	0.25 (0.16-0.38)	0.89 (0.64-1.21)
DOACs-entrectinib	0.36 (0.11-1.24)	1.45 (0.33-6.37)	1.05 (0.45-2.17)
DOACs-larotrectinib	-	-	-
DOACs-idelalisib	0.09 (0.05-0.18)	0.11 (0.06-0.22)	0.38 (0.22-0.62)
DOACs-sunitinib	0.73 (0.59-0.91)	0.34 (0.27-0.43)	2.05 (1.75-2.39)
DOACs-vandetanib	--	--	1.14 (0.43-2.56)
DOACs-osimertinib	0.24 (0.17-0.35)	0.35 (0.24-0.51)	0.84 (0.63-1.10)
DOACs-alectinib	0.14 (0.07-0.28)	0.22 (0.11-0.43)	0.55 (0.33-0.88)
DOACs-neratinib	1.24 (0.80-1.90)	1.06 (0.65-1.72)	**2.71 (2.03-3.54)**
DOACs-cabozantinib	0.19 (0.15-0.24)	0.20 (0.16-0.26)	0.67 (0.55-0.81)
DOACs-capmatinib	-	-	-
DOACs-sorafenib	0.63 (0.42-0.96)	0.30 (0.20-0.46)	1.79 (1.32-2.37)
DOACs-regorafenib	0.28 (0.18-0.44)	0.17 (0.11-0.27)	0.97 (0.68-1.33)
DOACs-ponatinib	0.37 (0.25-0.54)	0.29 (0.19-0.43)	1.20 (0.90-1.59)
DOACs-vemurafenib	0.33 (0.20-0.52)	0.31 (0.19-0.51)	1.08 (0.75-1.52)

DOACs-cobimetinib	0.37 (0.23-0.57)	0.25 (0.16-0.40)	1.18 (0.84-1.63)
DOACs-abemaciclib	0.06 (0.02-0.19)	0.12 (0.04-0.39)	0.29 (0.13-0.60)
DOACs-pemigatinib	-	-	-
DOACs-gefitinib	0.33 (0.16-0.68)	0.22 (0.11-0.45)	1.07 (0.62-1.74)
DOACs-afatinib	0.72 (0.48-1.09)	0.51 (0.33-0.78)	1.94 (1.44-2.58)
DOACs-hormone	0.37 (0.34-0.40)	0.30 (0.27-0.32)	1.22 (1.15-1.30)
DOACs-letrozole	0.33 (0.29-0.38)	0.21 (0.18-0.25)	1.12 (1.00-1.25)
DOACs-anastrozole	0.50 (0.43-0.59)	0.38 (0.32-0.45)	1.56 (1.37-1.77)
DOACs-abiraterone	0.34 (0.27-0.42)	0.39 (0.31-0.49)	1.13 (0.95-1.33)
DOACs-bicalutamide	0.51 (0.42-0.62)	0.29 (0.24-0.36)	1.58 (1.36-1.82)
DOACs-tamoxifen	0.52 (0.42-0.64)	0.26 (0.21-0.33)	1.59 (1.35-1.86)
DOACs-enzalutamide	0.23 (0.19-0.28)	0.29 (0.24-0.36)	0.82 (0.70-0.95)
DOACs-chemotherapy	0.36 (0.34-0.39)	0.27 (0.25-0.28)	1.22 (1.16-1.27)
DOACs-vinblastine	-	-	-
DOACs-doxorubicin	0.22 (0.17-0.28)	0.18 (0.14-0.23)	0.78 (0.65-0.93)
DOACs-methotrexate	0.41 (0.39-0.45)	0.30 (0.28-0.33)	1.34 (1.27-1.41)
DOACs-vincristine	0.25 (0.19-0.33)	0.18 (0.14-0.23)	0.88 (0.71-1.07)
DOACs-vinorelbine	0.18 (0.09-0.33)	0.12 (0.06-0.23)	0.65 (0.39-1.03)
DOACs-docetaxel	0.39 (0.32-0.47)	0.36 (0.29-0.44)	1.28 (1.11-1.47)
DOACs-idarubicin	-	-	-
DOACs-cyclophosphamide	0.20 (0.17-0.24)	0.15 (0.13-0.18)	0.72 (0.63-0.82)
DOAC-ifosfamide	0.20 (0.07-0.55)	0.15 (0.05-0.41)	0.73 (0.34-1.41)
DOACs-lomustine	0.20 (0.06-0.63)	0.23 (0.07-0.78)	0.72 (0.31-1.49)
DOACs-irinotecan	0.50 (0.39-0.63)	0.28 (0.22-0.36)	1.54 (1.28-1.83)
DOACs-etoposide	0.16 (0.10-0.24)	0.10 (0.07-0.16)	0.58 (0.41-0.80)
DOACs-IMAs	0.18 (0.17-0.19)	0.14 (0.13-0.15)	0.66 (0.63-0.69)
DOACs-cyclosporine	0.46 (0.40-0.53)	0.31 (0.27-0.36)	1.45 (1.30-1.61)
DOACs-sirolimus	0.41 (0.29-0.58)	0.35 (0.25-0.49)	1.31 (1.01-1.68)
DOACs-temsirolimus	-	-	-
DOACs-tacrolimus	0.35 (0.30-0.41)	0.25 (0.21-0.29)	1.17 (1.04-1.31)
DOACs-dexamethasone	0.14 (0.13-0.15)	0.12 (0.11-0.13)	0.52 (0.50-0.56)
DOACs-inducers	0.36 (0.31-0.43)	0.68 (0.57-0.80)	1.05 (0.90-1.21)
DOACs-dabrafenib	0.58 (0.30-1.14)	0.82 (0.41-1.63)	1.54 (0.87-2.55)
DOACs-encorafenib	-	-	-
DOACs-paclitaxel	0.33 (0.23-0.48)	0.77 (0.53-1.12)	1.00 (0.72-1.37)

DOACs-prednisolone	0.37 (0.31-0.44)	0.64 (0.53-0.78)	1.04 (0.87-1.23)

DPA Disproportionality analysis. ROR, Reporting odds ratio. CI, Confidence Interval. MGPS, Multi-item Gamma Poisson Shrinker. EBGM, Empirical Bayes geometric mean. EB05, the lower bound of the 90% credible interval for the EBGM. EB95, the upper bound of the 90% credible interval for the EBGM. DOACs, Direct Oral Anticoagulants. KIs, kinase inhibitors. IMAs, immunomodulating agents.

[a]: ROR computed from a 2x2 table comparing the reporting rates of the event between the reports containing drug combination and reports with DOACs only

[b]: adjusted for age, sex, reporting country, and reporting year

--: ROR not computed (number of events <3)

-: ROR and EGBM not available (number of events = 0)

Aim 2.1 Manuscript

Title: Benefit and risk of oral anticoagulant initiation strategies in patients with atrial fibrillation and cancer: a target trial emulation using the SEER-Medicare database

Abstract

Background: Oral anticoagulants (OACs) are generally recommended for patients with atrial fibrillation (AFib) having CHA_2DS_2-VASc score ≥2. However, the benefit for OAC initiation in patients with AFib and cancer who are at different risk of stroke is unknown.

Methods: We conducted a retrospective cohort study using the target trial framework. We included patients with newly diagnosed AFib and a record of cancer (breast, prostate, or lung) from the 2012-2019 Surveillance, Epidemiology, and End Results (SEER)-Medicare database (n=39915). Risks of stroke and bleeding were compared between 5 different treatment strategies: (*1*) initiated OAC when CHA_2DS_2-VASc ≥1 (n=6008), (*2*) initiated OAC when CHA_2DS_2-VASc ≥2 (n=8694), (*3*) initiated OAC when CHA_2DS_2-VASc ≥4 (n=20286), (*4*) initiated OAC when CHA_2DS_2-VASc ≥6 (n=30944), and (*5*) never initiated OAC (reference group, n=33907). Confounders were adjusted using time-varying inverse probability weighting. Weighted pooled logistic regressions were used to estimate treatment effect with hazard ratios (HRs) and 95% confidence interval (95% CIs).

Results: After weighting, only patients with OAC initiation at CHA_2DS_2-VASc ≥6 had lower risk of stroke compared to those without OAC initiation (HR=0.64, 95% CI 0.54-0.75). However, patients who underwent all four active treatment strategies had reduced risk of bleeding compared to non-initiators, with OAC initiation at CHA_2DS_2-VASc ≥6 being the most beneficial strategy (HR=0.49, 95% CI 0.44-0.55). In subgroups of patients with lung cancer or 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 initiators at CHA_2DS_2-VASc ≥6).

Conclusion: Among cancer patients newly diagnosed with AFib, OAC initiation at higher risk of stroke (CHA_2DS_2-VASc score ≥6) may be more beneficial in preventing ischemic stroke and bleeding. Patients with advanced cancer status or low life-expectancy may initiate OACs when CHA_2DS_2-VASc score≥6.

1. Introduction

In the United States (US), 2.7-6.1 million people were affected by atrial fibrillation (AFib) annually and it is projected to reach 12 million by 2050.[35] AFib is associated with more than 454,000 hospitalizations and 158,000 deaths each year.[2-4] Among patients with cancer, AFib was also associated with higher burden of adverse outcomes, such as ischemic stroke, venous thromboembolism (VTE), bleeding, and death compared with AFib patients without cancer.[13,14,64,77]

Although the benefit of oral anticoagulants (OACs) in patients with AFib has been well established,[15] the current management of patients with AFib and cancer regarding OAC treatments remains suboptimal due to insufficient evidence.[23] Among patients with AFib and cancer, OAC initiation was associated with a slightly reduced risk of adverse event (ischemic stroke and intracranial bleeding) compared with non-users.[18] However, recent studies found only half of patients with AFib and cancer initiated OAC, much less than those without cancer.[17-20] One of the major challenges is to determine the appropriate time when patients with AFib and cancer should start OACs to maximize the benefit of stroke prevention while minimize the risk of bleeding. In general, OAC initiation is recommended for AFib patients with a CHA_2DS_2-VASc score ≥2, a

composite stroke risk score of congestive heart failure, hypertension, age, diabetes mellitus, prior stroke, transient ischemic attack, thromboembolism, vascular disease and sex category.[100] However, such threshold has not been explored in patients with AFib and cancer. For example, when a cancer patient is newly diagnosed with AFib with low risk of ischemic stroke (i.e., CHA_2DS_2-VASc <2), whether this patient should start the treatment immediately or wait until they reach a higher risk of ischemic stroke (i.e., CHA_2DS_2-VASc ≥4 or CHA_2DS_2-VASc ≥6). In some patient groups, anticoagulation is withheld because of a perceived unfavorable risk-benefit ratio.[249] Since patients with AFib and cancer are at higher risk of stroke and bleeding,[13,14] initiating OAC at low risk may be beneficial in stroke prevention, but may result in increased risk of bleeding. On the other hand, late initiation may prevent risk of bleeding, but increase risk of stroke in these patients. Although recent studies found that patients with AFib and cancer who had CHA_2DS_2-VASc ≥4 were more likely to receive OACs compared to patients with lower risk of stroke,[231] the benefit of this treatment strategy has never been explore. Determining the benefit of initiating OACs at different levels of risk of stroke is critically important to optimize the management of patients with AFib and cancer.

In this study, we assessed and compared benefits of multiple OAC initiation treatment strategies at different thresholds of risk of stroke among newly diagnosed AFib patients with cancer using the target trial framework. The target trial framework is the application of design principles from RCTs to the analysis of observational data to improve the quality of observational epidemiology when a comparator trial is not yet available or feasible.[167] Because no RCT is available to address our research question, we developed the protocol for the hypothetical target trial and adopted the components from existing RCTs comparing the efficacy and safety of DOACs versus warfarin in patients with AFib (RE-LY and ROCKET-AF).[168,169]

2. Materials and methods

2.1. Study design and data source

We used the target trial framework and STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist to conduct a retrospective cohort study using SEER registry linked to Medicare database (cancer sites: breast, prostate, and lung) from 2011-2019.[165,166] The SEER registry contains patient demographics, primary tumor site, tumor characteristics, and cancer stage at diagnosis, treatment, and follow-up of cancer patients across the US.[162] The Medicare data adds to SEER data health care services utilization (medical claims, procedures, and prescriptions).[163] **Table 1** summarizes the protocol for target trial and emulation procedure. The study design and study timeline were illustrated by **Figure S1**. This study was approved by the Institutional Review Board (IRB) at Auburn University.

2.2. Study sample and eligibility criteria

Study sample: We included individuals aged ≥66, newly diagnosed non-valvular atrial fibrillation (NVAF) between January 1, 2012 and December 31, 2019, defined as any International Classification of Disease-9th Revision-Clinical Modification (ICD-9-CM) codes 427.31 or 427.32 or any International Classification of Disease-10th Revision-Clinical Modification (ICD-10-CM) codes I48.xx in any position on one Medicare inpatient claim or on 2 outpatient claims at least 7 days but <1 year apart.[172] We retained patients with breast, lung, or prostate cancer - the most common cancer types with AFib - from SEER files at any time before the initial AFib diagnosis (ICD-O-3 codes C50.0-C50.9 for breast; C34.0, C34.1, C34.2, C34.3, C34.8, C34.9, C33.9 for lung; C61.9 for prostate cancer). Patients were required to continuously enroll in Medicare part A, B, D, and without Medicare Advantage or Health Maintenance Organization (HMO) for at least 12 months before initial NVAF diagnosis.

Exclusion criteria: We adapted exclusion criteria from clinical trials.[168,169] In addition, patients were excluded if they had any other indication than NVAF, contraindication to OACs or had the event of interest shortly before cohort entry: (1) any OAC use during the 12 months baseline period, (2) presence of valvular diseases, repair or replacement, venous thromboembolism, or joint replacement during the 12 months baseline period, (3) any stroke within 14 days before first NVAF diagnosis, (4) major surgery (i.e., hip fracture, cardiac surgery) or critical bleeding within 30 days before first NVAF diagnosis, (5) renal impairment stage 5 or end-stage renal diseases, during the 12 months baseline period. All ICD codes to identify these conditions can be found in **Table S1, Supplementary materials.**

2.3 Treatment strategies and assignments

In the hypothetical target trial, eligible individuals were randomly assigned to one of the following 5 treatment strategies: (*Regimen 1*) initiated OAC when CHA_2DS_2-VASc ≥1, (*Regimen 2*) initiated OAC when CHA_2DS_2-VASc ≥2, (*Regimen 3*) initiated OAC when CHA_2DS_2-VASc ≥4, (*Regimen 4*) initiated OAC when CHA_2DS_2-VASc ≥6, and (*Regimen 5*) never initiated OAC (reference group). In the emulation of target trial, cloning, censoring, and weighting approach were used to mimic the randomization.[175] OAC prescriptions (including warfarin and dabigatran, apixaban, rivaroxaban, edoxaban) were identified from Medicare Part D Prescription Drug Event (PDE) files using national drug code (NDC)).[176] CHA_2DS_2-VASc scores were computed from Medicare claims during12 months before AFib diagnosis and monthly during follow-up, based on a composite of conditions including congestive heart failure (1 point), hypertension (1), age ≥75 (2 point), diabetes mellitus (1 point), prior stroke, TIA, or thromboembolism (2 point), vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque) (1 point), age 65-74 years (1 point), and sex category (1 point).[100]

2.4. Follow-up

The follow-up started at the initial NVAF diagnosis (index date) and ended at the occurrence of a study outcome, the end of administrative censoring (12 months after baseline), death (all-cause deaths from SEER and Medicare files via the variables of "Date of Death Flag"), loss to follow-up (the earliest of 30 days after the end of continuous Medicare Part A, B, or D enrollment or enrollment in an HMO), or December 31, 2019, whichever came first.

2.5. Outcomes

The outcomes of interest were ischemic stroke and major bleeding. We defined major bleeding and ischemic stroke using validated algorithms defined by ICD-9-CM and ICD-10-CM codes in the primary diagnosis from Medicare medical claims files.[25,177,178]

2.6. Covariates

Covariates selected from prior literature were adjusted in the analysis.[25,27,168] Time-fixed baseline covariates were extracted within 12-month period prior to first AFib diagnosis, including: *demographics* (index age, sex, race/ethnicity, calendar year, geographical region, urbanicity), *socioeconomic factors* (household median income, percentage of household with education level below high school, and Medicaid eligibility), *comorbidity risk scores* (CHA_2DS_2-VASc, HAS-BLED, and Comorbidity Scores SEER-Medicare version 2021 by NCI),[180] *individual comorbidities* (asthma/chronic obstructive pulmonary disease, hematological disorders, dementia, depression, thrombocytopenia, acute kidney disease (AKD), peptic ulcer disease), *cancer characteristics* (time from cancer diagnosis to the onset of AFib, cancer type, cancer stage, tumor grade, active cancer status [25,27]), *cancer treatment* (radiation, and cancer-directed surgery, and potentially interacting antineoplastic agents), and *medication history* (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium channel blockers, beta blockers,

antiarrhythmic medications, diuretics, statin, pump proton inhibitors, and serotonin reuptake inhibitors). Socioeconomic factors such as household income and education level are available at the aggregate area level. If patients had more than one type of cancer before AFib diagnosis, we retained the most recent cancer diagnosis. Cancer treatments were obtained from diagnosis codes or procedures codes within 30 days before AFib diagnosis.[181] Due to high proportion of missing values, other cancer characteristics such as number of regional nodes examined, tumor size, TMN classification, and other cancer-type specific characteristics (hormone receptor status (HR), and human epidermal growth factor receptor 2 (HER2) for breast cancer or histologic type for lung cancer) were used for descriptive purpose but not adjusted in the models.[182] The following time-varying covariates were extracted monthly after AFib onset, including CHA_2DS_2-VASc score, HAS-BLED score, thrombocytopenia, AKD, radiation, cancer-directed surgery, and use of interacting treatment. These variables may change over time and has an impact on outcomes and the OAC prescription in each month.[250,251] All diagnosis codes and procedure codes for covariate ascertainment were described in **Table S1, Supplementary materials**. We used multiple imputation algorithm (fully conditional specification with logistic regression for categorical variables and predictive mean matching for continuous variables) to impute missing values.[183]

2.7. Causal contrast

We computed the observational analog of *per-protocol* (PP) effects because censoring-cloning-weighting approach was used.[186] Those who were not compliant to their assigned treatment regimens were censored during follow-up.

2.8. Statistical analysis

Descriptive statistics such as mean and standard deviation (SD) for continuous variables, frequency count and percentage for categorical variables were used to describe the study sample.

We quantified the incidence rates (per 1,000 person-years) of ischemic stroke and major bleeding for each treatment strategy. In the main analysis, cloning, censoring, and weighting procedure was used to estimate the treatment effect of 5 treatment strategies.[175,186] Briefly, we created 5 copies for each individual's person-time data, then assigned each copy to 5 treatment strategies. *At baseline*, replicates with baseline CHA_2DS_2-VASc score that did not comply with their assigned strategy were removed from the dataset. Next, replicates whose data were no longer consistent with their assigned strategy *during follow-up* were censored. To adjust for potential confounding during follow-up, unstabilized time-varying censoring weights were used. Cumulative weights at each time point 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 (See **Technical Appendix**). Total weights were truncated at 99^{th} percentile to avoid extreme weights. To estimate the treatment effects for 5 strategies, we fitted a weighted pooled logistic regression estimated by generalized estimating equations (GEEs) with robust variance estimators. We obtained summary hazard ratios (HRs) with 95% confidence interval (95% CIs) and created weighted survival curves comparing four active treatment strategies with the reference strategy. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

2.9. Subgroup analyses and sensitivity analyses

We conducted the following subgroup analyses: cancer type (breast, lung, prostate), cancer status at baseline (active, history), cancer stage (in situ, local, regional, and distant), and tumor grade (I, II, and III). In addition, a series of sensitivity analyses were conducted. First, we extended follow-up time to 36 months to explore long-term outcomes for each treatment strategy. Second, since metastatic cancer patients were removed from randomized control trials due to their short life expectancy, we excluded them in this sensitivity analysis.[168,169] Third, we removed individuals

with thrombocytopenia at baseline, since these patients are at elevated risk of bleeding and may not eligible for OAC initiation.[194,195] Fourth, we further truncated weights at 95th percentile to test the robustness of the treatment effects to the presence of extreme weights.[252,253]

3. Results

3.1. Study sample and characteristics

Among 70035 patients with newly diagnosis of AFib and concomitant cancer in SEER-Medicare 2012-2019, the final sample included 39915 individuals after applying exclusion criteria. (**Figure 1**). Patient's characteristics were described in **Table S2**. Briefly, study cohort had the mean age of 77.16 (±7.31) with 46.33% female and the majority were White (85.11%). Regarding cancer characteristics, the majority of the patients had lung cancer (42.85%), with local (47.80%) cancer stage. On average, patients were diagnosed with cancer about 15 months before their AFib onset and 29.06% of them had active cancer. At baseline, the distributions of CHA_2DS_2-VASc score at baseline were 3222 patients (8.07%) with the score of 1, 6715 patients (16.82%) with the score of 2, 9759 patients (24.45%) with the score of 3, 10111 patients (25.33%) with the score of 4, 6103 patients (15.29%) with the score of 5, and 4005 patients (10.03%) with the score of 6 and above. Majority of the cohort had a HAS-BLED of 3 or below (83.76%). Only 9898 patients (24.81%) initiated OACs within 12-month follow-up after their initial NVAF diagnosis (**Figure 1**).

3.2. Main analysis

The cloning, censoring, and weighting approach and number of events in each treatment arm are described in **Figure 2**. The incidence rates of ischemic stroke and major bleeding (event per 1,000 person years) for each treatment strategies were 37.75 and 7.87 (*Regimen 1*), 35.03 and 7.90 (*Regimen 2*), 13.88 and 5.81 (*Regimen 3*), 12.18 and 7.64 (*Regimen 4*), and 35.01 and 17.13 (*Regimen 5*). Before weighting, all four OAC initiation strategies (*Regimens 1-4*) reduced risk of

bleeding compared with no initiation, while OAC initiation at CHA_2DS_2-VASc score ≥4 or ≥6 (*Regimen 3 and 4*) reduced more ischemic stroke events compared with no initiation. After weighting, only OAC initiation at CHA_2DS_2-VASc ≥6 (*Regimen 4*) lowered the risk of stroke compared with no initiation (HR=0.64, 95% CI 0.54-0.75). Other OAC initiation strategies were not beneficial for stroke reduction (*Regimen 1*: HR =1.30, 95% CI 1.11-1.54; *Regimen 2*: HR=1.32, 95% CI 1.12-1.56; *Regimen 3:* HR=1.13, 95% CI 0.95-1.33). All four active treatment regimens reduced the risk of major bleeding, with OAC initiation at CHA_2DS_2-VASc ≥6 being the most beneficial strategy (HR=0.49, 95% CI 0.44-0.55) (**Table 2).** The weighted survival curves for each treatment strategy on outcomes of interest are illustrated in **Figures 3 and 4**. The distributions of weights are described in **Table S3, Figures S2 and S3.**

3.2. Subgroup and sensitivity analyses

The main findings were consistent across subgroups of patients with active/inactive cancer status. In addition, initiation of OACs at CHA_2DS_2-VASc ≥6 remained as the most beneficial regimens across all subgroups. However, there was some heterogeneity of treatment effect in other subgroups. 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 CHA_2DS_2-VASc ≥6). For instance, effects of OAC initiation at CHA_2DS_2-VASc ≥1 (Regimen 1) were 2.10 (95% CI 1.55-2.86) on ischemic stroke and 0.83 (95% CI 0.43-1.64) on major bleeding among lung cancer patients. In metastatic cancer patients, the corresponding HRs were 2.09 (95% CI 1.33-3.28) and 1.17 (95% CI 0.48-2.90), respectively. In other subgroups (breast cancer, prostate cancer, in situ/local stage, grade I/II/III), OAC initiation at any level did not increase risk of stroke while reduced risk of bleeding compared with no initiation (**Table S4**). In sensitivity analyses, the main findings remained robust when

extending follow-up to 36 months, removing high-risk patients, and in the absence of extreme weights (**Table S5**).

4. Discussion

Our study is the among the first to assess the benefit and risk of OAC initiation in patients with AFib and cancer at different levels of risk for stroke. First, we found that initiating OACs at higher level of CHA_2DS_2-VASc score (i.e., ≥6) is more beneficial in reducing risk of stroke among patients with AFib and cancer. OAC initiation at a lower level of CHA_2DS_2-VASc score might be harmful or has no effect on risk of stroke. Second, initiating OACs at any level of CHA_2DS_2-VASc score reduced the risk of major bleeding, with OAC initiation at higher level of CHA_2DS_2-VASc score being the most effective strategy. Thus, among cancer patients with new AFib diagnosis, OAC initiation may be considered for patients at high risk of stroke (CHA_2DS_2-VASc score at least ≥4) when a marginal harm on risk of stroke and a benefit on risk on bleeding are observed. In addition, among patients with advanced cancer status or low life-expectancy (i.e., lung cancer or regional/metastatic cancer), OAC should be given only to patients with CHA_2DS_2-VASc score ≥6.

OAC has shown to be underutilized in the management of patients with AFib and cancer in previous studies.[17,231] In fact, we found that only one in four patients initiated OACs within the first year after AFib diagnosis in this study. While current guidelines recommend a CHA_2DS_2-VASc score ≥2 for OAC initiation in general AFib patients, this threshold may not be applicable for patients with cancer because they are at higher risk of stroke and bleeding.[13,14,64,77] In this study, we found that OAC initiation at higher CHA_2DS_2-VASc score (6 or above) was the most beneficial treatment strategy. Starting OACs at lower CHA_2DS_2-VASc score may not be beneficial for stroke

reduction within one year after AFib diagnosis. The treatment effects sustained after 3 years of follow-up in the sensitivity analysis. In addition, starting OAC at any CHA_2DS_2-VASc level was associated with reduced risk of bleeding compared with no initiation.

Similar to our findings, Atterman (2020) found that OAC initiation was associated with a slightly reduced risk of ischemic stroke and intracranial bleeding compared with non-users (HR=0.90 95% CI 0.80-1.00), especially in those with moderate (HR=0.82, 95% CI 0.70-0.96) or high (HR=0.82, 95% CI 0.79-0.86) baseline CHA_2DS_2-VASc score.[18] The authors obtained CHA_2DS_2-VASc score before AFib diagnosis (index date) and stratified the risk of stroke based on baseline CHA_2DS_2-VASc score (0: low, 1: intermediate, ≥2: high).[18] Likewise, O'Neal (2018) found AFib patients with cancer who sought for cardiologists shortly after AFib diagnosis were more likely to receive OACs and had a reduced risk of stroke and non-inferior risk of bleeding compared with those who did not.[20] Indeed, these studies compared the incidence of stroke and bleeding between OAC users and non-users and stratified the comparison by baseline CHA_2DS_2-VASc score, but these previous studies did not directly compare risk of outcomes between different OAC initiation strategies based on their CHA_2DS_2-VASc score as time-varying confounder during follow-up.[18,20] In addition, such design is subjected to immortal time bias since patients would have been stroke-free or bleeding-free long enough to receive OACs.[254] Our study clearly formulated a decision point where cancer patients newly diagnosed with AFib should start treatment at lower risk of stroke or wait until they reach a higher risk level. We used cloning-censoring-weighting approach to assign each patient into different treatment strategies and followed patients after their AFib diagnosis, which minimized immortal time bias by accounting for patient's exposure to OACs and the compliance with their assigned treatment during follow-up.[175,255]

We found that the effects of OAC initiation at different risk levels based on CHA_2DS_2-VASc score were heterogeneous in several subgroups of cancer. OAC initiation may not be beneficial or even harmful in patients with a lower risk of stroke, but beneficial only in patients with high risk of stroke. In subgroups of cancer such as breast cancer or prostate cancer, in situ/local cancer or grade I/II/III, OAC initiation at lower CHA_2DS_2-VASc score did not increase risk of stroke but decreased risk of bleeding, while OAC initiation at higher CHA_2DS_2-VASc score decreased risk of stroke and bleeding compared with no initiation. This heterogeneity can be explained by the differential risk of stroke and bleeding in patients at different stages of cancer. Indeed, patients with advanced cancer (i.e., metastatic cancer or lung cancer) are at higher risk of stroke and bleeding compared with early stage.[113,256] In the sensitivity analyses, we found that starting OAC at any CHA_2DS_2-VASc score was associated with a non-inferior risk of stroke and lower risk of bleeding after excluding patients with metastatic cancer at baseline. These findings may help clinicians tailorize OAC treatment strategy in AFib patients based on their cancer characteristics.

CHA_2DS_2-VASc score has been used for more than a decade for risk of stroke stratification and OAC initiation in patients diagnosed with AFib. In this study, we used CHA_2DS_2-VASc as an indicator for OAC initiation although the tool was found not highly predictive in stroke prediction in patients with AFib and cancer.[257,258] CHA_2DS_2-VASc thresholds for each treatment strategy in our study were selected based on the distribution of baseline CHA_2DS_2-VASc scores of the study sample and in prior study.[231] In fact, all patients enrolled in this study had CHA_2DS_2-VASc $\geq$1. In general AFib patients, OACs are recommended for those with CHA_2DS_2-VASc $\geq$2.[15,259] In addition, recent studies have shown patients with CHA_2DS_2-VASc $\geq$4 or $\geq$6 were more likely to initiate OACs.[231] Therefore, our choice of CHA_2DS_2-VASc thresholds for each treatment strategy reflects multiple scenarios for OAC initiation in patients with AFib and cancer: prescribe OACs

for all patients regardless their risk of stroke; prescribe OACs based on general AFib recommendations; and real-world pattern of OAC use in clinical practice. The major limitation of using CHA_2DS_2-VASc score is that it is not able to capture an independent risk of stroke caused by cancer, especially in patients with advanced cancer.[257,260] However, CHA_2DS_2-VASc score has been widely accepted among clinicians and recommended in clinical guidelines for OAC initiation decision-making.[259,261] There is an urgent need to develop new tools for risk of stroke assessment in patients with AFib and cancer.

Our study is subject to some limitations. First, unmeasured confounding such as patients' frailty, body mass index could not be captured by SEER-Medicare data. In addition, cancer characteristics used in the analysis such as cancer stage and tumor grade were captured at the time of cancer diagnosis rather than at the time of AFib diagnosis since SEER registry is lack of measurements of progression of cancer characteristics (cancer stage, tumor grade) over time. We also could not control for some cancer-specific characteristics such as receptor status (ER, HER2) for breast cancer, histological type, or tumor size in our analysis since they contained large proportions of missing values. In addition, we assumed 12-month baseline period prior to AFib diagnosis was sufficient to capture patients' baseline characteristics, therefore, measurement bias may persist. Measurement bias was also present when we measured patients' behavioral risk factors (i.e., alcohol use disorders in HAS-BLED score) using ICD codes.[262] Also, socioeconomic factors from Census tract were not available on an individual level. Third, residual bias could not be completely eliminated even though we used validated algorithms to define eligibility criteria and outcomes. Fourth, we did not stratify OAC initiation by type of OACs (i.e., warfarin, dabigatran, rivaroxaban) given their safety and effectiveness profile may be different. However, a recent study found warfarin and DOACs are equivalently safe and effective in prevention stroke and bleeding,[263]

which suggests the stratified treatment effects may not be different than the marginal effects of all OACs. Fourth, since we cloned each individual to 5 copies, the 95% CI estimated from GEEs might be conservative due to correlation between clones. In our analysis, we could not perform non-parametric bootstrapping to obtain 95% CIs due to computational time. Fifth, our estimates may be prone to bias in the presence of extreme weights although we truncated the initial weights at 99th percentile.[264] Using stabilized variance may reduce the variance and avoid extreme weights, but the stabilization procedures might not valid for cloning-censoring-weighting approach like our study.[188] However, the results remain robust in the sensitivity analysis after we truncated the weights to 95th percentile. Sixth, our findings may not be generalizable beyond the target population in this study (i.e., patients with newly diagnosed cancer on existing AFib, other cancer types, or non-Medicare populations). Future studies are warranted to investigate the benefits and risks of OACs among patients with other advanced cancer such as hematological cancers due to higher risk of stroke and bleeding in this population.[265,266]

Although our study emulated a hypothetical target trial and adopted components (i.e., inclusion/exclusion criteria, outcomes, and follow-up) from prior RCTs,[168,169] several components were not perfectly mimicked. Specifically, RCTs removed patients platelet count <90,000/μL, systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg, or creatinine clearance less than 30 mL/min at the screening visit.[168,169] However, these lab values were not available in SEER-Medicare. We therefore replaced these conditions with the presence of thrombocytopenia or severe renal impairments. In addition, several components were defined by clinicians' assessment in RCTs, such as AFib definition by an electrocardiogram (ECG) document or congestive heart left failure with ventricular ejection fraction ≤35%.[168,169] Moreover, therapeutic responses and adverse events were monitored with international normalized ratio (INR) and liver-

function tests, which are not available in our emulation.[168,169] Although non-randomization component has been criticized as the main source of bias in observational studies, it was not proven as the primary cause of inconsistency between observational and RCTs. Successful emulation without randomization has been conducted to benchmark the estimates from observational studies to RCTs and vice versa, especially during the COVID pandemic when the need of RCTs could not be met due to time constraint.[267-269] In this study, randomization was assumed using a cloning-censoring-weighting approach and the adjustment of measured time-varying confounding during follow-up.[175] It is also necessary to highlight that misspecification of time zero has been found as the major source of failure in obtaining valid causal effects in observational studies.[165,166] In our study, we specified time zero by aligning the time when all inclusion and exclusion criteria met, start of treatment strategies, and follow-up. Such practice removed immortal time bias and prevalent user bias from our analysis.[165,166]

Our study has many strengths. Using the target trial emulation framework to design the study and the cloning-censoring-weighting approach, we explicitly designed a trial to answer a causal question. We included patients with newly AFib diagnosis and followed them after AFib diagnosis to remove survival bias. In addition, we further adjusted for important confounders such as cancer characteristics by the linkage between Medicare administrative claims data and SEER registry. We pre-specified a wide range of subgroup analyses and sensitivity analyses to confirm the robustness of the main analysis. Our findings are expected to help clinicians' decision making in optimizing OAC initiation and individualizing their decisions based on patient's cancer characteristics.

5. Conclusion

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

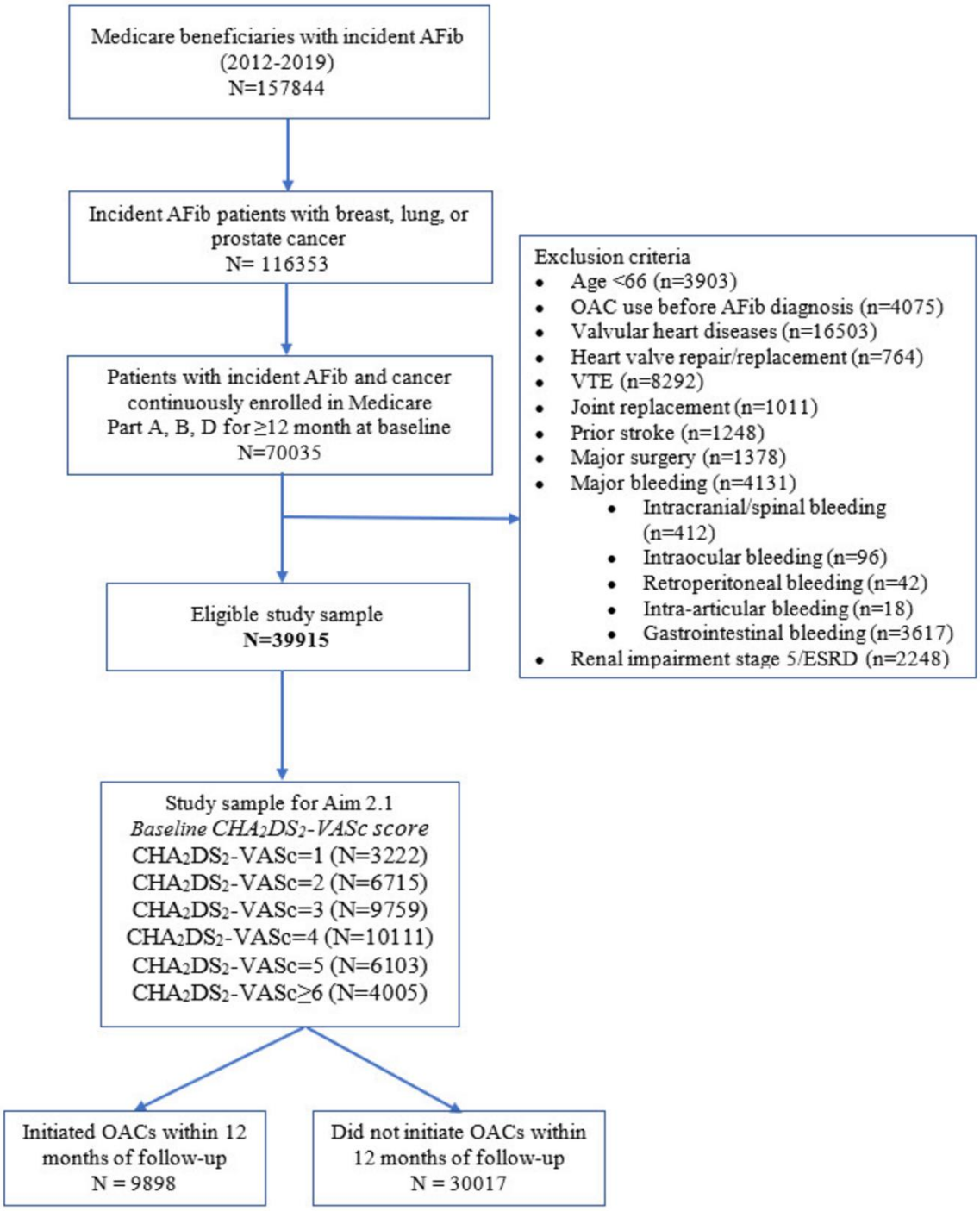


Figure 1. Flowchart diagram for study sample. *VTE Venous thromboembolism, AFib Atrial Fibrillation, OAC Oral Anticoagulant, ESRD End-Stage Renal Diseases*

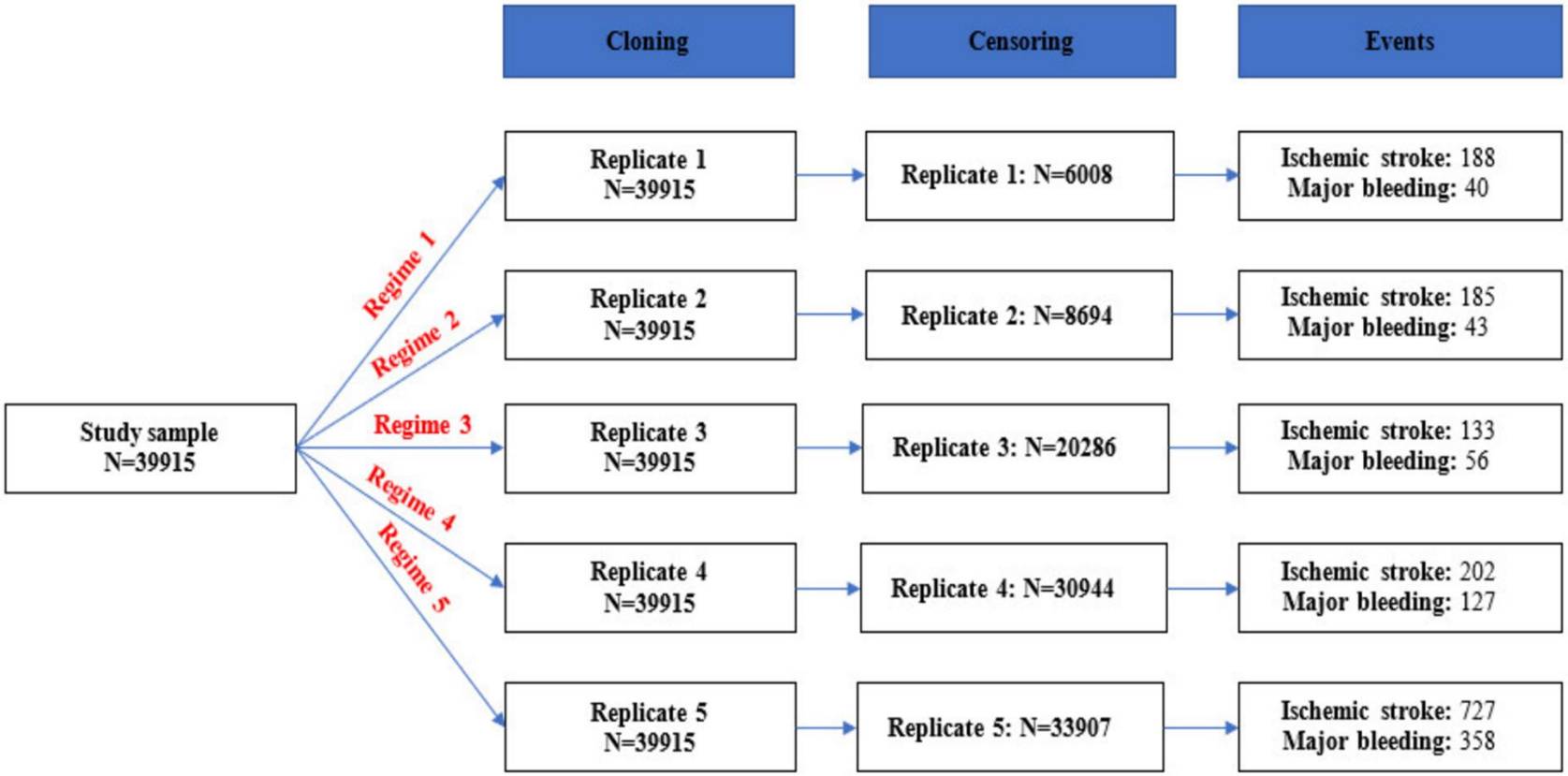


Figure 2. Sample flowchart summarizing cloning and censoring steps

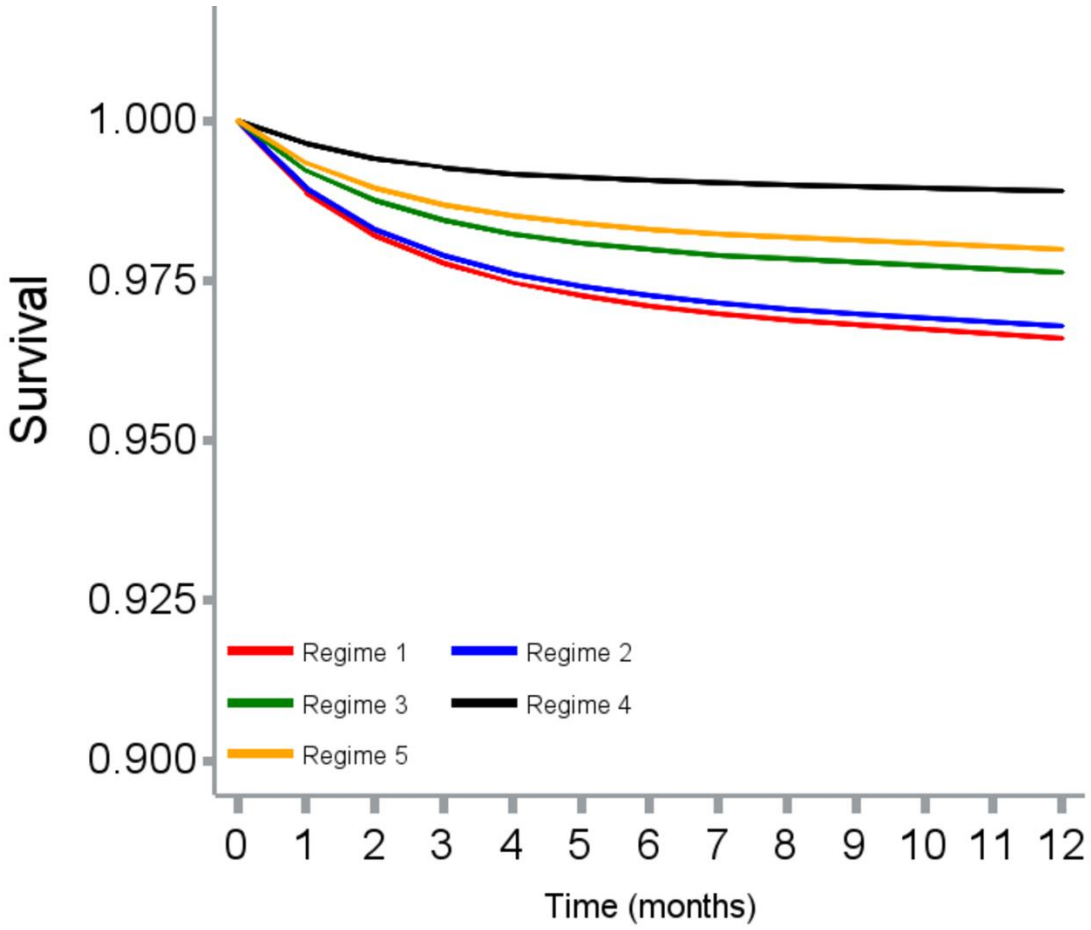


Figure 3. Weighted survival curves for risk of ischemic stroke among 5 treatment regimens.

Regimen 1: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥1.
Regimen 2: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥2.
Regimen 3: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥4.
Regimen 4: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥6.
Regimen 5: Never initiate oral anticoagulants

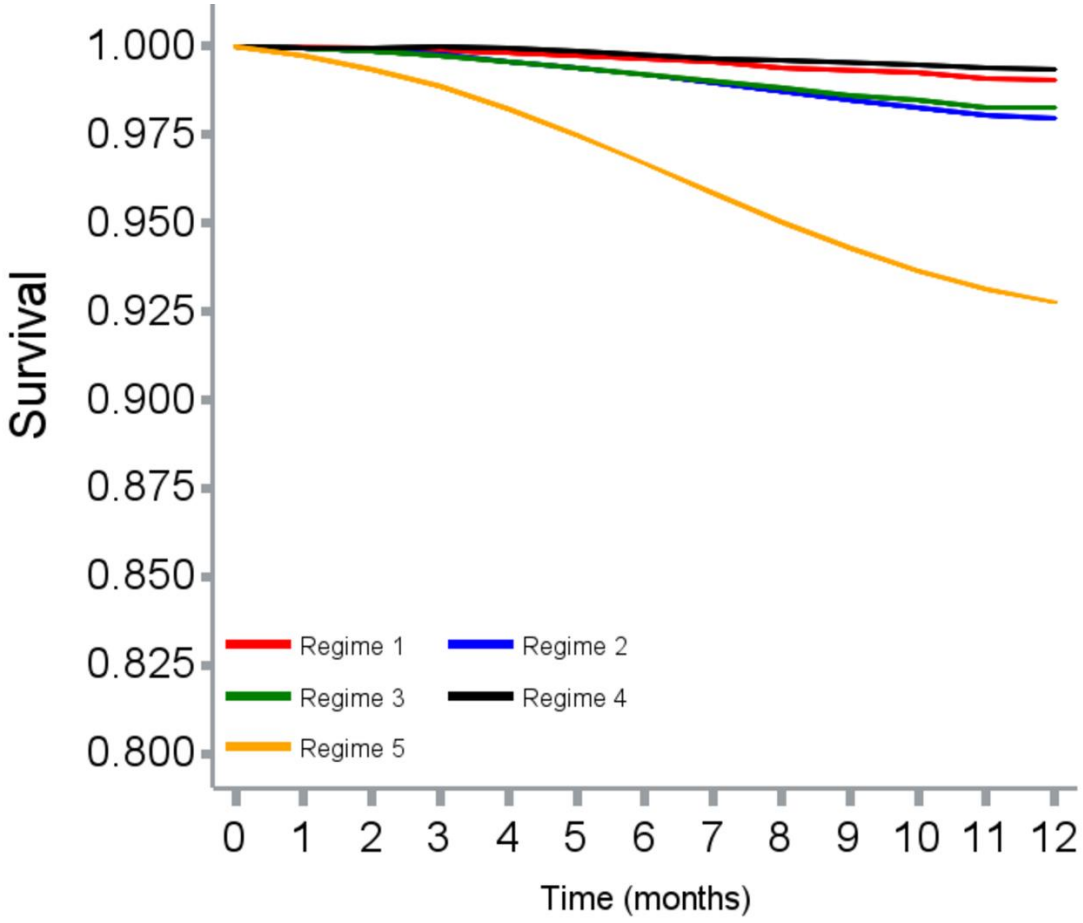


Figure 3. Weighted survival curves for risk of major bleeding among 5 treatment regimens.
Regimen 1: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥1.
Regimen 2: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥2.
Regimen 3: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥4.
Regimen 4: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥6.
Regimen 5: Never initiate oral anticoagulants

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

Protocol component	Hypothetical target trial	Emulation in SEER-Medicare data
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 January 1, 2012 and December 31, 2019. ▪ Beneficiaries 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 4 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) no initiation of OACs (reference group)	We used cloning, censoring, and 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
Causal contrast	Intention-to-treat effect, per-protocol effect	Observational analog of per-protocol effect

OAC Oral Anticoagulants, CHA_2DS_2-VASc A composite score for risk of stroke, SEER Surveillance, Epidemiology, and End Results Program

Table 2. Main analysis comparing 5 treatment regimens of oral anticoagulation initiation in patients with atrial fibrillation and cancer

	Regimen 1	**Regimen 2**	**Regimen 3**	**Regimen 4**	**Regimen 5**
Ischemic stroke					
Event	188	185	133	202	727
Person-years	4980	5282	9480	16589	200767
Incidence rate per 1,000 person-year	37.75	35.03	13.88	12.18	35.01
Unadjusted HR (95% CI)	1.15 (0.99-1.34)	1.02 (0.88-1.18)	**0.45 (0.39-0.51)**	**0.41 (0.38-0.45)**	Reference
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					
Event	40	43	56	127	358
Person-years	5084	5382	9644	16629	20898
Incidence rate per 1,000 person-year	7.87	7.90	5.81	7.64	17.13
Unadjusted HR (95% CI)	**0.45 (0.35-0.60)**	**0.45 (0.34-0.58)**	**0.39 (0.33-0.46)**	**0.53 (0.48-0.58)**	Reference
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

HR Hazard ratio, CI Confidence Interval

The final models incorporated inverse probability of treatment weights (IPTWs, adjusted for baseline, time-varying covariates, and treatment history) and inverse probability of censoring weights (IPCWs, adjusted for baseline, time-varying covariates, and treatment history)

Regimen 1: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥1

Regimen 2: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥2

Regimen 3: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥4

Regimen 4: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥6

Regimen 5: Never initiate oral anticoagulants

Aim 2.2 Manuscript

Title: Effectiveness and safety of direct oral anticoagulant versus warfarin in patients with atrial fibrillation and cancer: a target trial emulation from SEER-Medicare database

Abstract

Background: Direct oral anticoagulants (DOACs) are preferred over warfarin in patients with atrial fibrillation (AFib). However, their safety and effectiveness in patients with AFib and cancer are inconclusive.

Methods: We conducted a retrospective cohort study by emulating a target trial. Patients with a record of cancer (breast, prostate, or lung), newly diagnosed with AFib, and initiated DOACs or warfarin within 3 months after AFib diagnosis from the 2012-2019 Surveillance, Epidemiology, and End Results (SEER)-Medicare database were included. We compared the risk of ischemic stroke, major bleeding, and secondary outcomes (venous thromboembolism, intracranial bleeding, gastrointestinal bleeding, and non-critical site bleeding) between patients who initiated DOACs and those initiated warfarin. Inverse probability treatment weights and inverse probability censoring weights were used to adjust imbalanced patient and disease characteristics and loss to follow-up between the two groups. Weighted pooled logistic regression were used to estimate treatment effect with hazard ratios (HRs) with 95% confidence interval (95% CIs).

Results: The incidence rates of stroke and major bleeding between DOAC and warfarin initiators were 9.97 vs. 9.91 and 7.74 vs 9.24 cases per 1000 person-years, respectively. In adjusted intention-to-treat analysis, patients initiated DOACs had similar risks for ischemic stroke (HR=0.87, 95% CI 0.52-1.44) and major bleeding (HR=1.14, 95% CI 0.77-1.68) compared to those initiated warfarin. In adjusted per-protocol analysis, patients initiated DOACs had similar risk for ischemic stroke (HR=1.81, 95% CI 0.75-4.36) and lower risk for major bleeding

(HR=0.35, 95% CI 0.12-0.99) compared to those initiated warfarin. The treatment effects of secondary outcomes were in favor of DOACs. The findings remained consistent across subgroups and sensitivity analyses.

Conclusion: DOACs are safety and effective alternatives to warfarin in the management of patients with AFib and cancer.

1. Introduction

Atrial fibrillation (AFib) is the most common type of cardiac arrhythmia.[1] In the United States (US), AFib affects 2.7-6.1 million Americans and is associated with more than 454,000 hospitalizations and 158,000 deaths each year.[2-4]

Oral anticoagulants (OACs) including warfarin and direct oral anticoagulants (DOACs) are approved for the management of AFib patients.[15] In the general AFib population, DOACs are associated with lower risk of ischemic stroke and bleeding compared with warfarin.[83] However, in the context of malignancy, AFib is associated with higher burden of mortality and mortality since both cancer and AFib are independent risk factors of ischemic stroke and venous thromboembolism (VTE).[13,14] Specifically, compared to patients with AFib, those with concomitant AFib and cancer have a 4- to 7-fold higher risk of VTE and a 2-fold higher risk of bleeding[13,14]. However, the effectiveness and safety profiles of DOACs and warfarin have not been well established among patients with AFib and cancer. Therefore, current guidelines from American Heart Association (AHA), European Society of Cardiology (ESC), American Society of Clinical Oncology (ASCO), and the International Society on Thrombosis and Haemostasis (ISTH) do not recommend any OAC over another.[16,21-23] As a result, less than half of AFib or atrial flutter patients with cancer initiated OACs.[17-19]

Early randomized controlled trials (RCTs) comparing DOACs and warfarin in AFib patients excluded cancer patients due to potential drug-drug interactions with chemotherapy and low life expectancy (e.g., ENGAGE, ROCKET-AF, and ARISTOLE).[75-77] A meta-analysis of these RCTs was conducted in subgroups of patients who developed cancer after randomization revealed that DOACs were associated with non-inferior rates of thromboembolic and bleeding events and reduced risk of VTE.[26] However, interpretation of the meta-analysis may be limited by heterogeneity in study design, cancer type, and treatment among included studies.[26] Recent observational studies comparing DOACs and warfarin among patients AFib and cancer have shown consistent findings compared with RCTs in favor of DOACs.[25,104,105,107-111,263] However, these observational studies were prone to limitations such as unmeasured confounding (cancer characteristics such as cancer stage, tumor grade, and cancer treatment). In addition, safety and effectiveness were rarely reported across cancer characteristics although they are important for tailoring the treatment selection in patients with cancer.[25,104,110,195]

In this study, we implemented a target trial framework to compare the effectiveness and safety profiles of DOACs and warfarin among newly diagnosed AFib patients with cancer using the Surveillance, Epidemiology, and End Results (SEER) registry linked to Medicare data to further capture cancer characteristics. The target trial emulation framework articulates the causal questions similar to an RCT protocol and explicitly emulating the components of that protocol using the observational data, which improves the quality of observational studies.[167,270] Because no RCT is available to address our research question, we developed the protocol for the hypothetical target trial and adopted the components from existing RCTs comparing the efficacy and safety of DOACs versus warfarin in patients with AFib (RE-LY and ROCKET-AF).[168,169]

2. Materials and methods

2.1. Study design and data source

We followed the Strengthening The Reporting of Observational studies in Epidemiology (STROBE) to report the components of our study.[271] We conducted a retrospective, population-based cohort study on the target trial framework[165,166] using SEER registry linked to Medicare database from 2011-2019. SEER covers 48 percent of US population, which collects and releases data on cancer patients such as demographics, cancer characteristics, of treatment, and follow-up.[162] The linkage to Medicare data adds to SEER health care services utilization of beneficiaries.[163] The protocol for a target trial and emulation procedure is described in **Table 1**. The study design and timeline are illustrated in **Figure S1**. This study was approved by the Institutional Review Board (IRB) at Auburn University.

2.2. Study sample and eligibility criteria

Study sample: The study sample included individuals aged ≥66 with new onset non-valvular atrial fibrillation (NVAF) between January 1, 2012 and December 31, 2019, defined as any International Classification of Disease-9th Revision-Clinical Modification (ICD-9-CM) codes 427.31 or 427.32 or any International Classification of Disease-10th Revision-Clinical Modification (ICD-10-CM) codes I48.xx in any position on one Medicare inpatient claim or on 2 outpatient claims at least 7 days but <1 year apart (**Table S1, Supplemental materials**).[172] We retained new NVAF patients with any record of breast (ICD-O-3 codes C50.0-C50.9), lung ((ICD-O-3 codes C34.0, C34.1, C34.2, C34.3, C34.8, C34.9, C33.9), prostate cancer (ICD-O-3 codes C61.9) - 3 most commonly concomitant cancer in AFib)[25,27,231] in SEER files at any time before the initial AFib diagnosis. We required patients to continuously enroll in Medicare part A, B, D, and without Medicare Advantage or Health Maintenance Organization (HMO) for 12 months before AFib diagnosis. We

furthered restrict the study sample to those with a moderate risk of stroke, defined as CHA_2DS_2-VASc score ≥2.[168,169]

Exclusion criteria: We adapted exclusion criteria based on RE-LY and ROCKET-AF trials.[168,169] In brief, we removed participants with indications for warfarin or DOACs other than NVAF or absolute contra-indications of warfarin or DOACs such as (1) any OAC use during the 12 months baseline period, (2) presence of mitral valve disease, heart valve repair or replacement, deep vein thrombosis, pulmonary embolism, or joint replacement during the 12 months baseline period, (3) any stroke within 14 days before first NVAF diagnosis, (4) major surgery (i.e., hip fracture, cardiac surgery), intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding, gastrointestinal hemorrhage within 30 days before AFib diagnosis, (5) renal impairment stage 5 or end-stage renal diseases, during the 12 months baseline period. Individuals with any outcome of interest occurred before OAC initiation were also excluded from the analysis. All ICD codes to identify these conditions can be found in **Table S1, Supplemental material.**

2.3 Treatment strategies and assignments

In the hypothetical target trial, eligible individuals were randomly assigned to either (1) warfarin (2) DOACs and continued the assigned treatment during follow-up. In the emulation of target trial, we assumed randomization was attained given baseline covariates.[175] OAC prescriptions (including warfarin and dabigatran, apixaban, rivaroxaban, edoxaban) were identified from Medicare Part D Prescription Drug Event (PDE) files using NDC, regardless of OAC dosage.[176] We used a grace period of 3 months to determine the treatment group of eligible individuals since a 3-month grace period has been specified in previous RCTs and the risk of stroke in general AFib patients is highest in the first 3 months after new AFib diagnosis.[196,197] OAC discontinuation was defined as a gap in OAC prescription for ≥ 30 days from the last day of days' supply in PDE file.

2.4. Follow-up

The follow-up started when the patients received the treatment within a grace period and ended at the occurrence of a specific study outcome, administrative censoring (12 months after baseline), death (all-cause deaths from SEER and Medicare files via the variables of "Date of Death Flag"), loss to follow-up (the earliest of 30 days after the end of continuous Medicare Part A, B, or D enrollment or enrollment in an HMO), or December 31, 2019, whichever came first. For *per-protocol* analyses, follow-up also ends when the observed treatment deviated from initial treatment. Specifically, eligible individuals who discontinued the assigned treatment or switched their assigned treatment during follow-up (i.e., switching from warfarin to DOACs or vice versa) were censored.

2.5. Outcomes

The primary effectiveness and safety outcomes were ischemic stroke and major bleeding, respectively. We defined major bleeding based on the bleeding site, according to the algorithm by previously developed algorithms (i.e. intraarticular, intracranial, intramuscular, intraocular, intraspinal, pericardial, and retroperitoneal), identified by ICD-9-CM and ICD-10-CM codes in the primary diagnosis from Medicare medical claims files.[25,177,178] Secondary outcomes such as VTE, intracranial bleeding, gastrointestinal (GI) bleeding, and other non-critical site bleeding were defined by ICD-9-CM and ICD-10-CM codes from Medicare inpatient claims using validated algorithms.[177-179]

2.6. Covariates

We carefully selected covariates based on published RCTs and observational studies.[25,27,168] Baseline covariates include patient *demographics* (index age, sex, race/ethnicity, calendar year, geographical region, urbanicity), *socioeconomic factors* (household median income, percentage of

household below poverty level, education level, Medicaid eligibility), *risk score* (CHA_2DS_2-VASc, HAS-BLED, and Comorbidity Scores SEER-Medicare version 2021 (NCI)[180]), *individual comorbidities* (asthma/chronic obstructive pulmonary disease, hematological disorders, dementia, depression, thrombocytopenia, acute kidney disease (AKD), peptic ulcer disease (PUD)), *cancer characteristics* (time from cancer diagnosis to the onset of AFib, cancer stage, tumor grade, cancer type, active cancer status[25,27]), *cancer treatment* (radiation, and cancer-directed surgery, and potentially interacting antineoplastic agents), and *medication history* (angiotensin-converting enzyme inhibitors (ACEIs)/ Angiotensin II receptor blockers (ARBs), calcium channel blockers (CCB), beta blockers, antiarrhythmic medications, diuretics, statin, pump proton inhibitors, and serotonin reuptake inhibitors).

If patients had more than one type of cancer, we retained the most recent cancer diagnosis. Cancer treatment was obtained from diagnosis codes or procedures codes within 30 days before NVAF diagnosis. Other cancer characteristics such as number of regional nodes examined, tumor size, TMN classification, and other cancer-type specific characteristics such as hormone receptor status (HR), and human epidermal growth factor receptor 2 (HER2) for breast cancer or histologic type for lung cancer were used for descriptive purpose but not adjusted in the analysis due to high proportion of missing values.[182]

For *per-protocol* analysis, the following time-varying covariates were extracted at a monthly basis after OAC initiations, including CHA_2DS_2-VASc score, HAS-BLED score, thrombocytopenia, AKD, radiation, cancer-directed surgery, and use of interacting treatment. All diagnosis codes and procedure codes for covariate ascertainment are described in **Table S1, Supplementary materials**. We used multiple imputation algorithm (fully conditional specification with logistic

regression for categorical variables and predictive mean matching for continuous variables) to impute missing values.[183]

2.7. Causal contrast

We computed the observational analog of both *intention-to-treat* (ITT) and *per-protocol* (PP) effects. ITT effect refers to effect of being assigned to warfarin or DOACs, regardless of whether individuals adhere to initial strategies during follow-up.[184,185] For PP effect, those who were assigned to warfarin group were censored if they discontinued warfarin or switched from warfarin to DOACs and vice versa.

2.8. Statistical analysis

Descriptive statistics with mean and standard deviation (SD) for continuous variables, frequency count and percentage for categorical variables were used to describe the study sample. In the main analysis, we obtained the ITT effect (the effect of initiating DOACs compared with warfarin) and PP effect (the effect of sustaining DOACs compared with warfarin). First, we adjusted for potential confounders between treatment groups at each month using weighting approach. The total weights were a product of stabilized inverse probability treatment weights (IPTWs) and stabilized inverse probability censoring weights (IPCWs) due to loss to follow-up. Next, we fitted a weighted pooled logistic regression estimated by generalized estimating equations (GEEs) with robust variance estimators, adjusted for baseline and time-varying confounders. Incidence rate (case per person-year), absolute risk difference (RD, 95% CIs), and summary hazard ratios with 95% confidence intervals (HR, 95% CIs), and weighted survival curves were obtained. All weights were truncated at 99th percentile. The technical details of the adjustment are described in **Technical Appendix**. Statistical analysis was conducted using SAS (version 9.4, SAS Institute, Inc., Cary, NC, USA).

2.9. Subgroup analyses and sensitivity analyses

Treatment effects were estimated under the following subgroups: cancer type (breast, lung, prostate), cancer status at baseline (active, history), cancer stage (local, regional, and distant), and tumor grade (I, II, and III). A series of sensitivity analyses were conducted to confirm the robustness of main findings. First, we extended a grace period to 6 months from AFib diagnosis to warfarin/DOAC initiation to reflect the uncertainty in clinical practice when patients are allowed time to complete clinical tests before treatment initiation or get access to initial treatment. Second, we included individuals with all levels of baseline CHA_2DS_2-VASc score because patients with cancer are at higher risk of stroke and may be eligible to initiate OACs. Third, we estimated the long-term treatment effects by extending follow-up time to 36 months. Fourth, we removed individuals with metastatic cancer at baseline, who may have a low life expectancy based on previous RCTs.[168,169] Fifth, we excluded individuals with thrombocytopenia at baseline, since these patients are at elevated risk of bleeding.[194,195] Six, we further truncated stabilized weights at 95^{th} percentile to test the robustness of the treatment effects to the presence of extreme weights.

3. Results

3.1. Study sample and characteristics

Among 70035 patients with newly diagnosis of AFib and concomitant cancer in SEER-Medicare 2012-2019, 5371 DOAC initiators (3264 apixaban, 314 dabigatran, 1786 rivaroxaban, 7 edoxaban) and 1788 warfarin initiators were included in the final sample (**Figure 1**).

Study sample characteristics are fully described in **Table S2**. Patients who initiated DOACs had a higher socio-economic status (higher household median income and education level) and lower comorbidity burden (CHA_2DS_2-VASc, HAS-BLED, and NCI scores) compared to those initiated warfarin. Regarding cancer characteristics, patients with breast or prostate cancer were more likely

to receive DOACs while more patients with lung cancer were on warfarin. Warfarin was more commonly prescribed in patients with active cancer and patients in the advanced stage of cancer (regional and distant) (**Table S2**).

3.2. Main analysis

The incidence rates of stroke and major bleeding between DOAC and warfarin initiators were 9.97 vs. 9.91 and 7.74 vs 9.24 cases per 1000 person-years, respectively. In adjusted *ITT analysis*, DOAC initiators had similar risks of ischemic stroke (HR=1.14, 95% CI 0.77-1.68) and major bleeding (HR=0.87, 95% CI 0.52-1.44) as warfarin initiators. DOAC initiators also had similar risk of VTE (HR=0.73, 95% CI 0.47-1.15), and intracranial bleeding (HR=0.78, 95% CI 0.45-1.35), but lower risk of GI bleeding (HR=0.77, 95% CI 0.59-0.99) and non-critical site bleeding (HR=0.63, 95% CI 0.50-0.77) compared to warfarin initiators (**Figure 2** and **Table 2**). The findings were mostly consistent in adjusted *PP analysis* [ischemic stroke (HR=1.81, 95% CI 0.75-4.36), VTE (HR=0.50, 95% CI 0.20-1.09), intracranial bleeding (HR=0.38, 95% CI 0.13-1.12), GI bleeding (HR=0.91, 95% CI 0.61-1.35), and non-critical site bleeding (HR=0.69, 95% CI 0.48-0.98) (**Figure 3** and **Table 3**). However, DOAC initiators had lower risk of major bleeding (HR=0.35, 95% CI 0.12-0.99) than warfarin initiators in adjusted *PP analysis*. The distributions of total weights and truncated weights are described in **Table S2**.

3.3. Subgroup and sensitivity analyses

The main findings were consistent with minor heterogeneity across subgroups of cancer type, active/inactive cancer status, cancer stage and tumor grade. Due to small sample size and few events, subgroup analyses were not conducted for some outcomes in prostate cancer, regional or metastatic cancer, or tumor grade I. Statistically significant benefits of DOACs over warfarin were detected for VTE in breast cancer; GI bleeding and non-critical site bleeding in prostate cancer

and local cancer stage; VTE and non-critical site bleeding in inactive cancer and tumor grade II; major bleeding and intracranial bleeding in patients with regional cancer stage and tumor grade III (**Table S3**). Finding remained robust under different assumption of grace period, additional inclusion and inclusion criteria, extended follow-up, and extreme weights (**Table S4**).

4. Discussion

By explicitly emulating the target trial comparing effectiveness and safety between DOACs and warfarin, we found that although DOAC initiators had slightly increased risk of ischemic stroke and decreased risk of major bleeding compared with warfarin, the absolute risk differences were small and not statistically significant. In both adjusted ITT and PP analyses, DOACs initiators had similar risk for ischemic stroke as those initiated warfarin. However, DOAC initiators had a lower risk of major bleeding than warfarin initiators in adjusted PP analysis. DOACs initiators also had reduced risk of secondary outcomes including GI bleeding and non-critical site bleeding than warfarin initiators. Findings remain consistent across subgroups and robust in sensitivity analyses.

The management of patients with AFib and cancer are more complicated than general AFib patients because the presence of cancer increases the risk of stroke and bleeding in these patients.[13,77] Although clinical guidelines are inconclusive, DOACs were increasingly preferred for the management of AFib in the presence of cancer.[25,231,263] The growing body of evidence in the literature showed inconsistent findings in comparative effectiveness and safety between DOACs and warfarin in patients with AFib and cancer. In RCTs such as ENGAGE, ROCKET-AF, and ARISTOLE, patients with existing cancer were generally excluded due to their low life expectancy.[75-77] A meta-analysis of these RCTs found that DOACs were associated with non-inferior rates of thromboembolic and bleeding events compared with warfarin.[26] A potential limitation of the meta-analysis is clinical heterogeneity (i.e., patient characteristics, treatment,

follow-up) and methodological heterogeneity (i.e., study design and analysis) among included studies.[26] Using administrative claims data, Shah (2018) and Deitelzweig (2021) found similar risk of stroke and bleeding between DOACs and warfarin, except for apixaban (lower risk of stroke and bleeding).[25,27] Shah also found a lower risk of stroke among DOAC user compared with warfarin. An important limitation of these studies is unmeasured confounding, such as cancer stage and tumor grade (not available in claims data), which may result in a differential risk of stroke and bleeding between DOACs and warfarin. Recently, Mehta (2022) used the SEER-Medicare data and conducted a new-user cohort study comparing risk of stroke and bleeding between DOACs and warfarin to further capture cancer characteristics from SEER registry.[263] The authors found an increased risk of stroke (HR=1.41, 95% CI 0.92–2.14) but decreased risk of bleeding (HR=0.90, 95% CI 0.70–1.17) among DOACs users compared to warfarin users.[163] Since Mehta included patients with existing AFib and prior stroke or recent bleeding before OAC initiation, some patients may take DOACs or warfarin for secondary prevention of stroke. As a result, the observed incidence rates of ischemic stroke and bleeding are higher than our study because prior stroke or bleeding are strong risk factors for subsequent events.[100,272-274]

In the current study, we emulated a target trial to explicitly answer a causal question: among patients with existing cancer who were newly diagnosed with AFib, what is the effect of initiating and/or sustaining DOACs compared with warfarin? We required patients to be outcome-free shortly before AFib diagnosis and during the grace period before they actually received OACs. This approach ascertains unbiased estimates for effectiveness and safety of OACs for primary prevention purposes and better interpretability in our study. Other strengths of our study included the adjustment for selection bias due to loss to follow-up,[275] and adjustment for time-varying covariates,[276] and estimand of interest specification (ITT or PP).[277] Our findings contribute to the

growing evidence and are expected to help clinicians optimize anticoagulation therapy in patients with AFib and cancer.

Although our study emulated a hypothetical target trial and adopted components (i.e., inclusion/exclusion criteria, outcomes, and follow-up) from prior RCTs,[168,169] several components were not perfectly mimicked. Specifically, RCTs removed patients platelet count <90,000/μL, systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg, or creatinine clearance less than 30 mL/min at the screening visit.[168,169] However, these lab values were not available in SEER-Medicare. We therefore replaced these conditions with the presence of thrombocytopenia or severe renal impairments. In addition, several components were defined by clinicians' assessment in RCTs, such as AFib definition by an electrocardiogram (ECG) document or congestive heart left failure with ventricular ejection fraction ≤35%.[168,169] Also, therapeutic responses and adverse events were monitored with international normalized ratio (INR) and liver-function tests, which are not available in our emulation.[168,169] Although non-randomization component has been criticized as the main source of bias in observational studies, it was not proven as the primary cause of inconsistency between observational and RCTs. Successful emulation without randomization has been conducted to benchmark the estimates from observational studies to RCTs and vice versa, especially during the COVID pandemic when the need of RCTs could not be met due to time constraint.[267-269] In this study, randomization was assumed using a cloning-censoring-weighting approach and the adjustment of measured time-varying confounding during follow-up.[175] It is also necessary to highlight that misspecification of time zero has been found as the major source of failure in obtaining valid causal effects in observational studies.[165,166] In our study, we specified time zero by aligning the time when all inclusion and exclusion criteria met,

start of treatment strategies, and follow-up. Such practice removed immortal time bias and prevalent user bias from our analysis.[165,166]

This study has several limitations. First, unmeasured confounding such as patient frailty, body mass index, or physician's preference were not adjusted in the analysis. Frailty was found to be a predictor of OAC selection and adverse outcomes in previous studies.[278] However, these variables are not available in SEER-Medicare data and we did not quantify the magnitudes of these unmeasured confounding in our analysis. Second, although we used validated algorithms to define exposure, outcomes, and covariates, measurement bias may still persist in claims data. Third, the presence of extreme weights may increase the variability of the treatment effects, although we found consistent findings after truncating weights to 95th percentile.[279] Fourth, some analyses, especially subgroup analyses may be underpowered or could not be performed due to small sample size, leading to unstable treatment effects and wide 95% CIs. Likewise, we could not conduct the analysis stratified by individual DOACs due to limited sample size. Prior studies suggested apixaban stood out among DOACs in reducing risk of stroke and bleeding.[25,27] Fifth, our findings may not be generalizable to non-Medicare populations or those who developed cancer after AFib diagnosis.

5. Conclusions

In this target trial emulation using linked cancer registry and administrative claims data, we found that DOACs are safety and effective alternatives to warfarin in the management of patients with AFib and cancer.

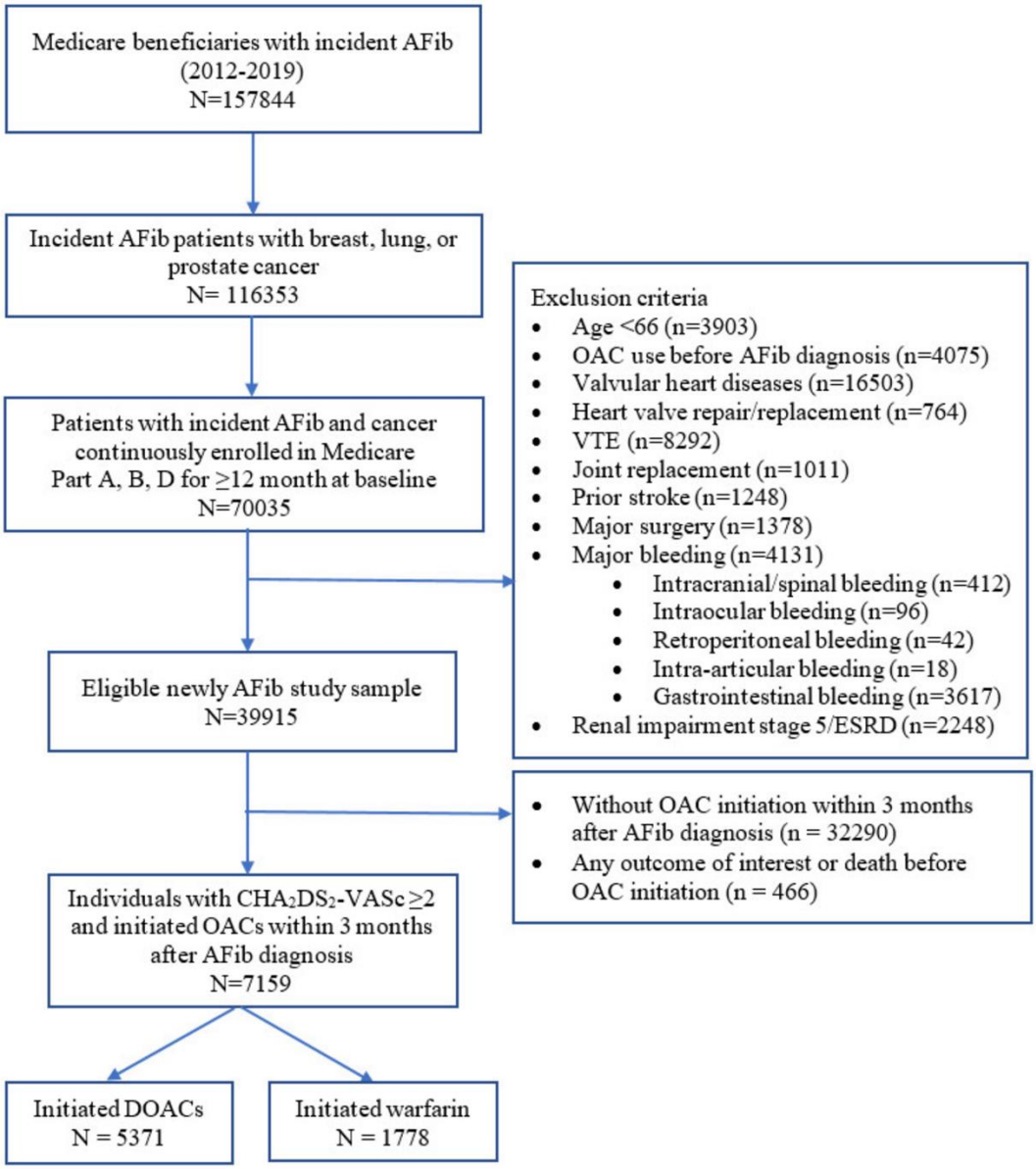


Figure 1. Flowchart diagram for study sample

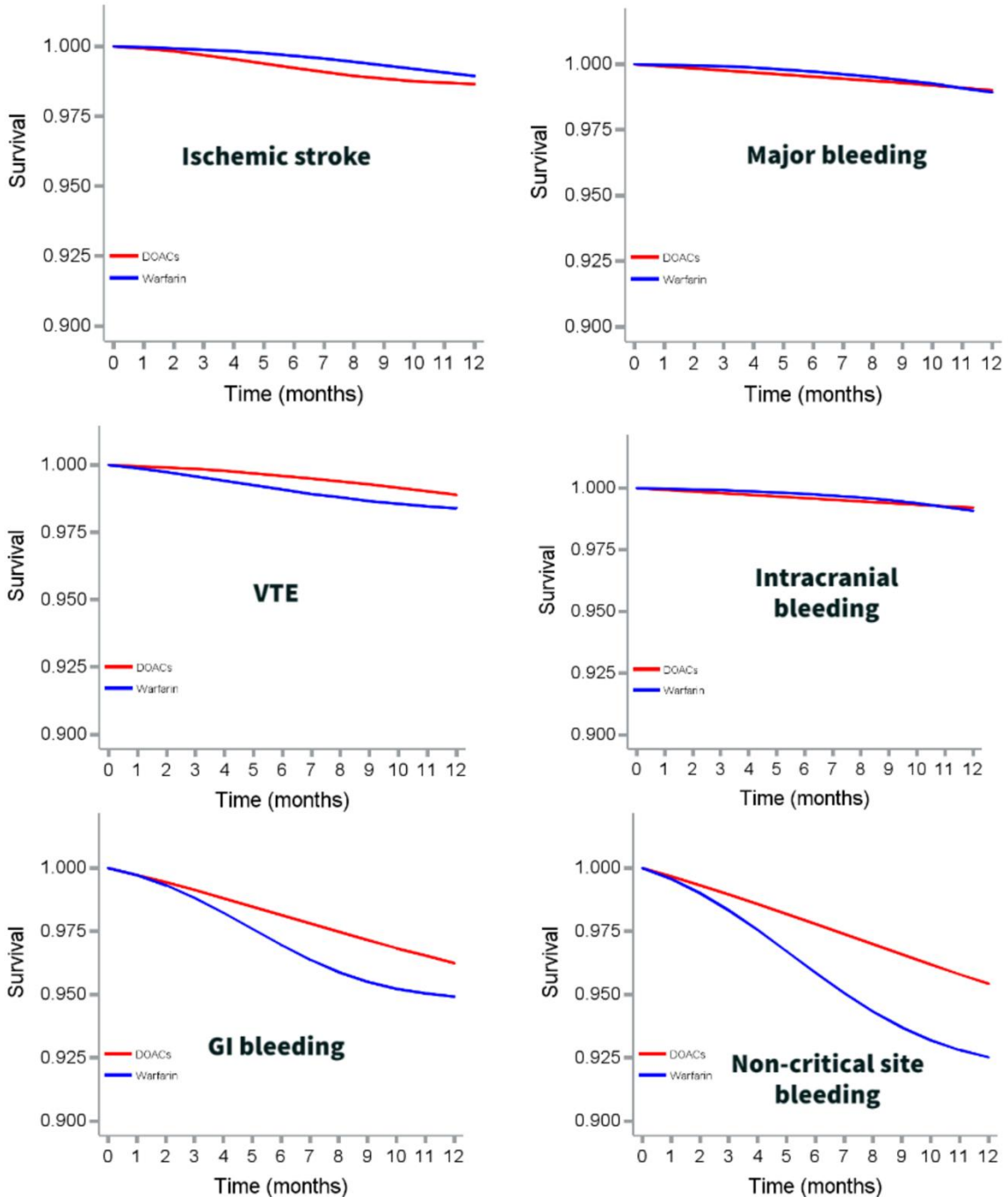


Figure 2. Weighted survival curves for intention-to-treat analysis comparing safety and effectiveness between direct oral anticoagulants and warfarin in patients with atrial fibrillation and cancer

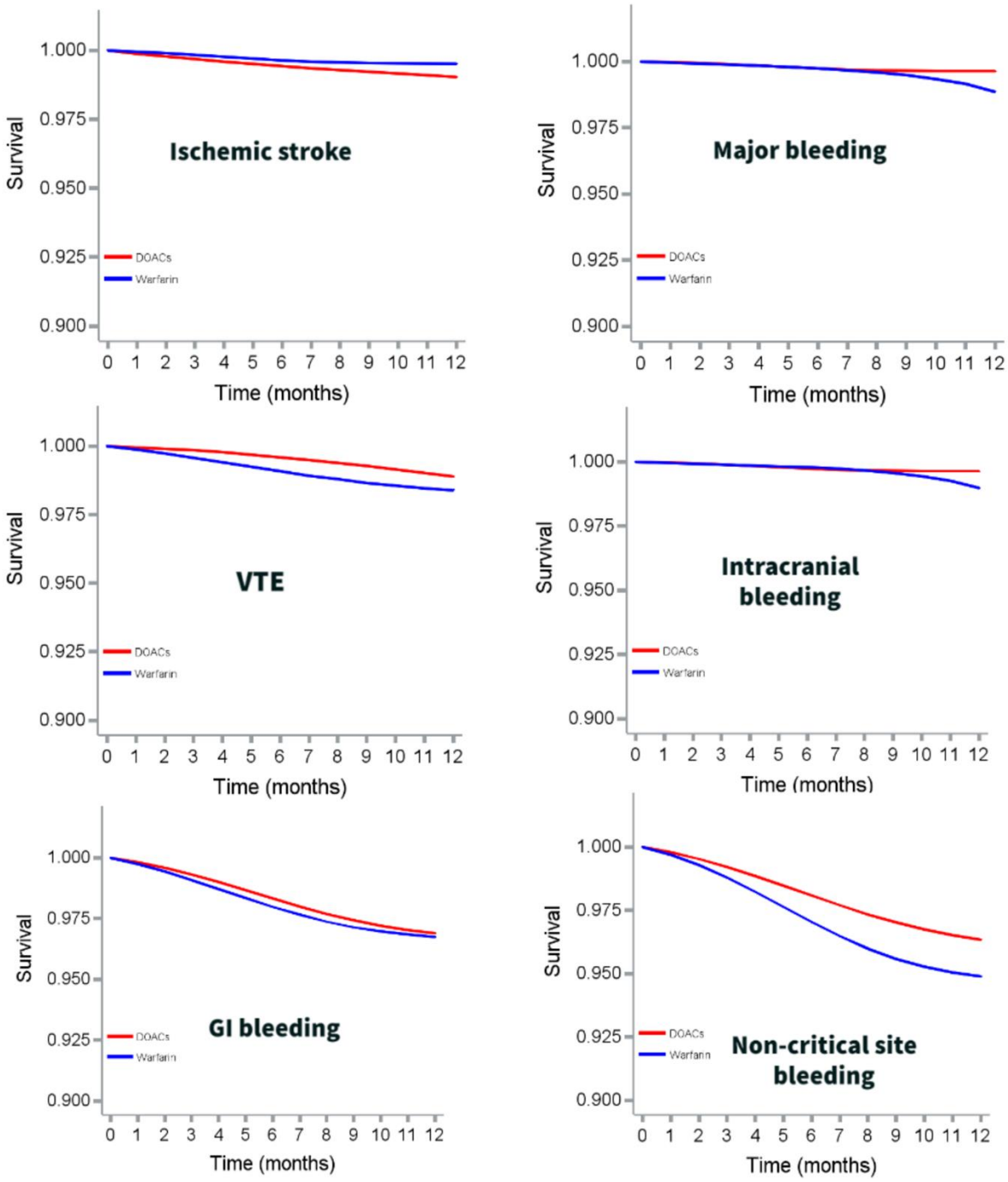


Figure 3. Weighted survival curves for per-protocol analysis comparing safety and effectiveness between direct oral anticoagulants and warfarin in patients with atrial fibrillation and cancer

Table 1. Protocol for a target trial and emulation procedure using the SEER-Medicare data base to estimate the risks of stroke and bleeding between warfarin users and DOAC users

Protocol component	Hypothetical target trial	Emulation in SEER-Medicare data
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 January 1, 2012 and December 31, 2019. ▪ Beneficiaries continuously enrolled in Medicare part A, B, D, and without Medicare Advantage for 12 months before the diagnosis. ▪ Baseline CHA_2DS_2-VASc score ≥2 ▪ 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 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 warfarin or DOACs within a grace period of 3 months.	We assume that study participants are randomly assigned conditioning on baseline covariates
Follow-up	The follow-up of target trials starts at the earliest time when treatment could be initiated, that is when the patients actually started their treatment within a grace period. 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	Primary outcomes: ischemic stroke and major bleeding Secondary outcomes: VTE, intracranial bleeding, gastrointestinal bleeding, and non-critical site bleeding	Same as target trial
Causal contrast	Intention-to-treat effect, per-protocol effect	Observational analog of intention-to-treat and per-protocol effect

AFib atrial fibrillation, OAC oral anticoagulant, SEER The Surveillance, Epidemiology, and End Results, DOAC direct oral anticoagulant, VTE venous thromboembolism, CHA_2DS_2-VASc A composite score for risk of stroke

Table 2. Intention-to-treat analysis for comparative effectiveness and safety between DOACs and warfarin in patients with AFib and cancer

	DOACs (N=5371)		**Warfarin (N=1788)**	
Primary outcomes	**Event (%)**	**Incidence rate***	**Event (%)**	**Incidence rate ***
Stroke	45 (0.84)	9.97	15 (0.84)	9.91
Unadjusted RD (95% CI)	0.00% (-0.49%, 0.49%)		Reference	
Unadjusted HR (95% CI)	1.00 (0.56, 1.80)		Reference	
Adjusted RD (95% CI)	0.02% (-0.05%, 0.09%)		Reference	
Adjusted HR (95% CI)	1.14 (0.77-1.68)		Reference	
Major bleeding	35 (0.65)	7.74	14 (0.78)	9.24
Unadjusted RD (95% CI)	-0.13% (-0.59%, 0.33%)		Reference	
Unadjusted HR (95% CI)	0.84 (0.45, 1.55)		Reference	
Adjusted RD (95% CI)	-0.02% (-0.08%, 0.07%)		Reference	
Adjusted HR (95% CI)	0.87 (0.52-1.44)		Reference	
Secondary outcomes				
Venous thromboembolism	32 (0.60)	7.07	20 (1.2)	13.25
Unadjusted RD (95% CI)	-0.52% (-1.05%, 0.01%)		Reference	
Unadjusted HR (95% CI)	**0.53 (0.31, 0.93)**		Reference	
Adjusted RD (95% CI)	-0.04% (-0.13%, 0.05%)		Reference	
Adjusted HR (95% CI)	0.73 (0.47, 1.15)		Reference	
Intracranial bleeding	28 (0.52)	6.19	12 (0.67)	7.92
Unadjusted RD (95% CI)	-0.15% (-0.57%, 0.27%)		Reference	
Unadjusted HR (95% CI)	0.78 (0.40, 1.53)		Reference	
Adjusted RD (95% CI)	-0.01% (-0.06%, 0.04%)		Reference	
Adjusted HR (95% CI)	0.78 (0.45, 1.35)		Reference	
Gastrointestinal bleeding	153 (2.85)	34.24	62 (3.47)	41.71
Unadjusted RD (95% CI)	-0.62% (-1.58%, 0.34%)		Reference	
Unadjusted HR (95% CI)	0.82 (0.61, 1.10)		Reference	
Adjusted RD (95% CI)	**-1.03% (-2.25%, -0.05%)**		Reference	
Adjusted HR (95% CI)	**0.77 (0.59, 0.99)**		Reference	
Non-critical site bleeding	185 (3.44)	41.53	88 (4.92)	59.64
Unadjusted RD (95% CI)	**-1.48% (-2.59%, -0.36%)**		Reference	
Unadjusted HR (95% CI)	**0.69 (0.54, 0.90)**		Reference	
Adjusted RD (95% CI)	**-1.78% (-2.45%, -1.11%)**		Reference	
Adjusted HR (95% CI)	**0.63 (0.50, 0.77)**		Reference	

*: number of events per 1000 person-years. DOACs Direct Oral Anticoagulants, RD Risk Difference, HR Hazard Ratio, CI Confidence Interval

Table 3. Per-protocol analysis for comparative effectiveness and safety between DOACs and warfarin in patients with AFib and cancer

	DOACs (N=5317)		**Warfarin (N=1788)**	
Primary outcomes	**Event (%)**	**Incidence rate***	**Event (%)**	**Incidence rate***
Stroke	35 (0.65)	11.1	6 (0.34)	6.13
Unadjusted RD (95% CI)	0.32% (-0.03, 0.66)		Reference	
Unadjusted HR (95% CI)	1.69 (0.75, 4.03)		Reference	
Adjusted RD (95% CI)	0.04% (-0.01%,0.09%)		Reference	
Adjusted HR (95% CI)	1.81 (0.75-4.36)		Reference	
Major bleeding	23 (0.43)	7.29	9 (0.50)	9.18
Unadjusted RD (95% CI)	-0.08% (-0.05%, 0.30%)		Reference	
Unadjusted HR (95% CI)	0.48 (0.21, 1.12)		Reference	
Adjusted RD (95% CI)	-0.06% (-0.14%, 0.02%)		Reference	
Adjusted HR (95% CI)	**0.35 (0.12, 0.99)**		Reference	
Secondary outcomes				
Venous thromboembolism	18 (0.34)	5.70	15 (0.84)	15.34
Unadjusted RD (95% CI)	**-0.50% (-0.95%, -0.05%)**		Reference	
Unadjusted HR (95% CI)	0.46 (0.22, 1.00)		Reference	
Adjusted RD (95% CI)	-0.04% (-0.10%, 0.01%)		Reference	
Adjusted HR (95% CI)	0.50 (0.20, 1.09)		Reference	
Intracranial bleeding	18 (0.34)	5.70	8 (0.45)	8.16
Unadjusted RD (95% CI)	-0.11% (-0.46%, 0.23%)		Reference	
Unadjusted HR (95% CI)	0.51 (0.21, 1.23)		Reference	
Adjusted RD (95% CI)	-0.05% (-0.13%, 0.03%)		Reference	
Adjusted HR (95% CI)	0.38 (0.13, 1.12)		Reference	
Gastrointestinal bleeding	120 (2.23)	38.20	44 (2.46)	45.29
Unadjusted RD (95% CI)	-0.23% (-1.05%, 0.59%)		Reference	
Unadjusted HR (95% CI)	0.83 (0.57, 1.21)		Reference	
Adjusted RD (95% CI)	-0.03% (-0.14%, 0.08%)		Reference	
Adjusted HR (95% CI)	0.91 (0.61-1.35)		Reference	
Non-critical site bleeding	144 (2.68)	45.87	65 (3.64)	67.10
Unadjusted RD (95% CI)	-0.95% (-1.92%, 0.01%)		Reference	
Unadjusted HR (95% CI)	**0.69 (0.50, 0.95)**		Reference	
Adjusted RD (95% CI)	**-0.94% (-1.26%, -0.62%)**		Reference	
Adjusted HR (95% CI)	**0.69 (0.48, 0.98)**		Reference	

*: number of events per 1000 person-years. DOACs Direct Oral Anticoagulants, RD Risk Difference, HR Hazard Ratio, CI Confidence Interval

Aim 3 Manuscript

Title: Development and validation of machine learning algorithms to predict 1-year ischemic stroke and bleeding events in patients with atrial fibrillation and cancer

Abstract

Background: Traditional risk assessment tools such as CHA_2DS_2-VASc for stroke and HAS-BLEED for bleeding have a poor predictability in patients with atrial fibrillation (AFib) and cancer. In this study, we leveraged machine learning approach to develop and validate new assessment tools for stroke and bleeding among this patient population.

Methods: We conducted a retrospective cohort study including patients who were newly diagnosed with AFib and had a record of cancer from the 2012-2018 Surveillance, Epidemiology, and End Results (SEER)-Medicare database. Potential features were identified through literature review of risk factors of stroke and bleeding and obtained in the data. The ML algorithms were developed and validated separately for each outcome by fitting elastic net, random forest (RF), extreme gradient boosting (XGBoost), support vector machine (SVM), and neural network models with 10-fold cross-validation (train:test=7:3). We obtained area under the curve (AUC), sensitivity, specificity, and F2 score as performance metrics. Model calibration was assessed using Brier score. In sensitivity analysis, we resampled data using Synthetic Minority Oversampling Technique (SMOTE).

Results: Among 18388 patients with AFib and cancer, 523 (2.84%) had ischemic stroke and 221 (1.20%) had major bleeding within one year after AFib diagnosis. In prediction of ischemic stroke, RF significantly outperformed other ML models [AUC (0.916, 95% CI 0.887-0.945), sensitivity 0.868, specificity 0.801, F2 score 0.375, Brier score=0.035]. However, the performance of ML algorithms in prediction of major bleeding was poor with highest AUC achieved by RF (0.623,

95% CI 0.554-0.692). Feature importance plots identified history of stroke and time from cancer diagnosis to AFib onset as top factors in all models for stroke prediction. SMOTE did not improve the performance of the ML algorithms.

Conclusion: Our study demonstrated a promising application of ML in stroke prediction among patients with AFib and cancer. This tool may be leveraged in assisting clinicians to identify patients at high risk of stroke and optimize treatment decisions.

1. Introduction

In the United States (US), atrial fibrillation (AFib) is projected to affect 12 million people by 2030.[35] AFib has been recorded as the primary diagnosis for more than 454,000 hospitalizations and contributed to more than 158,000 deaths annually.[2-4] The coexistence of cancer among patients with AFib increases incidence of adverse events such as ischemic stroke, venous thromboembolism (VTE), bleeding, and death compared with AFib patients without cancer.[13,14,64,77] Current management of patients with AFib and cancer with oral anticoagulants (OACs) remains suboptimal due to insufficient evidence regarding risk assessment and treatment optimization from clinical practice guidelines.[23]

CHA_2DS_2-VASc score, a composite score of congestive heart failure (1 point), hypertension (1), age ≥75 (2), diabetes mellitus (1), prior stroke, TIA, or thromboembolism (2), vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque) (1), age 65-74 years, and sex category (1), has been used to evaluate of risk of stroke in patients with AFib.[15,100] The clinical guidelines recommend OACs for patients with CHA_2DS_2-VASc scores ≥2.[15,16] However, CHA_2DS_2-VASc score is not highly predictive in patients with AFib and cancer.[28,29] HAS-BLED score has been widely used for risk of bleeding stratification. The HAS-BLED is calculated by the

presence of hypertension (1), abnormal renal/liver function (1+1), stroke (1), bleeding tendency or predisposition (1), labile INR for patients taking warfarin (1), age ≥65, drugs (concomitant aspirin or NSAIDs) or excess alcohol use (1+1)).[102] The 2020 European Society of Cardiology (ESC) guideline suggests a score of ≥3 indicates "high risk".[16] However, it is not recommend against the use of anticoagulants, but caution and regular monitoring after treatment initiation are needed.[16] Nonetheless, the usefulness of HAS-BLED in cancer patients are inconclusive because cancer is an independent risk factor of bleeding among patients with AFib.[103] Pastori et al. compared the performances of multiple bleeding risk scores among cancer patients and found that HAS-BLED was not highly predictive of major and gastrointestinal bleeding.[30]

Therefore, there is an urgent need to develop new risk assessment tools for stroke and bleeding in patients with AFib and cancer. Traditional risk assessment tools such as CHA_2DS_2-VASc and HAS-BLED are simple and easy for implementation among clinicians because they are linear combinations of patients' diseases and conditions. However, when the relationships between patients' characteristics and outcomes become more complicated, these tools may not perform well in patients with AFib and cancer. Recently, machine learning (ML) algorithms have been increasingly used to support clinical decision-making such as or identifying patients with dementia in primary care, anticoagulation monitoring, and measuring pretreatment quality of care before treatment in patients with hepatitis C.[131,133,136] Compared with conventional regression-based methods, ML models are able to learn from the data when the association between predictors and outcome variables is not linear. ML models have overperformed parametric regressions in handling high-dimensional data and interactions between variables in a complex data structure.[129,132,133]

In this study, we developed and validated ML algorithms to predict risk of stroke and bleeding events among patients with AFib and cancer, using US cancer registry and administrative claims linked datasets.

2. Materials and methods

2.1. Study design and data source

We followed the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guideline to develop and validate ML algorithms to separately predict risk of stroke and risk of bleeding in patients with AFib and cancer.[280] We conducted a retrospective cohort study using the 2011-2019 Surveillance, Epidemiology, and End Results (SEER) registry linked to Medicare database. The SEER-Medicare is a cancer registry linked to Medicare administrative claims data managed by Centers for Medicare & Medicaid Services (CMS). SEER registry contains demographics, cancer characteristics, treatment, and follow-up of cancer patients across the US, [162] while Medicare data capture health care services utilization (medical claims, procedures, and prescriptions) of beneficiaries.[163] The study design and approach are illustrated in **Figures S1-S2.** This study was approved by the Institutional Review Board (IRB) at Auburn University.

2.2. Participants

We included individuals aged ≥66, newly diagnosed non-valvular atrial fibrillation (NVAF) from 1/1/2012 to 12/31/2018. AFib was defined as any International Classification of Disease-9th Revision-Clinical Modification (ICD-9-CM) codes 427.31 or 427.32 or any International Classification of Disease-10th Revision-Clinical Modification (ICD-10-CM) codes I48.xx in any position on one Medicare inpatient claim or on two outpatient claims at least 7 days but <1 year apart.[172] We removed patients with valvular diseases, repair or replacement, venous

thromboembolism, or joint replacement during the 12 months baseline period because OACs are also indicated for these conditions and their clinical management are different from AFib.[203,204] Eligible records were then linked to SEER files to identify patients with breast, lung, or prostate cancer - the most common cancer types with AFib - from at any time before the initial AFib diagnosis (ICD-O-3 codes C50.0-C50.9 for breast; C34.0, C34.1, C34.2, C34.3, C34.8, C34.9, C33.9 for lung; C61.9 for prostate cancer). Patients were required to continuously enroll in Medicare part A, B, D, and without Medicare Advantage or Health Maintenance Organization (HMO) for at least 12 months before and 12 months after NVAF diagnosis. Since OAC initiation during follow-up may modify the risk of stroke and bleeding, we excluded patients who initiated warfarin or direct anticoagulants (DOACs) within 12 months before or after NVAF diagnosis.

2.3. Outcomes

The outcomes of interest were ischemic stroke and major bleeding events identified within 12 months after AFib diagnosis. We defined major bleeding and ischemic stroke using validated algorithms defined by ICD-9-CM and ICD-10-CM codes in the primary diagnosis from Medicare medical claims files.[25,177,178]

2.4. Predictors

We selected potential predictors from literature review and based on availability in SEER-Medicare data.[25,27,168] The following predictors were included: *demographics* (index age, sex, race/ethnicity, calendar year, geographical region, urbanicity), *socioeconomic factors* (household median income, percentage of household with education level below high school, and Medicaid eligibility), *comorbidities* (hypertension, congestive heart failure, diabetes, prior stroke, vascular diseases, prior bleeding, renal diseases, liver diseases, alcohol use disorders, asthma/chronic obstructive pulmonary disease, hematological disorders, dementia, depression, thrombocytopenia,

acute kidney disease, peptic ulcer disease), *cancer characteristics* (time from cancer diagnosis to the onset of AFib, cancer type, cancer stage, tumor grade, active cancer status[25,27]), *cancer treatment* (radiation, and cancer-directed surgery, and potentially interacting antineoplastic agents), and *medication history* (antiplatelet/non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), calcium channel blockers, beta blockers, antiarrhythmic medications, diuretics, statin, pump proton inhibitors, and serotonin reuptake inhibitors). Cancer characteristics were extracted from the most recent cancer record in SEER files. Socioeconomic factors such as household income and education level are available at the aggregate area level. Other features were obtained from Medicare claims during 12 months before the index date. All diagnosis codes and procedure codes for covariate ascertainment are described in **Table S1, Supplementary materials**.

2.5. Algorithms, model training and validation

Descriptive statistics was used to compare the characteristics of the full cohort and between patients with and without the outcomes. MissForest was used to impute missing values for predictors.[205,206] The original dataset was then randomly split into two datasets: the training (70%) and testing datasets (30%),[207,208] with similar distribution of the outcomes in both datasets. In the algorithm training process, ML models (including elastic net logistic regression, random forest (RF), support vector machine (SVM), extreme gradient boosting (XGBoost), and neural network) were fitted with ten-fold cross-validation (CV).[209] The fitted models were then tested on the rest of the data. Since stroke and bleeding occurred in less than 10% within one year among AFib patients,[25,210] our classification is severely imbalanced due to the prediction of minority class (stroke and bleeding).[211] Therefore, we shifted the decision threshold to the true event probability

rather than using the default threshold of 0.50.[211,212] The description of the models can be found in **Technical Appendix**.

2.6. Model performance, calibration, and evaluation

To assess algorithm discrimination, we calculated the area under the receiver operating characteristic curve (AUC) as the main metrics and compared the AUC across algorithms using DeLong's test.[213] Other performance metrics were also extracted, including sensitivity, specificity, and F2 score. Since true positive (patients actually having stroke/bleeding) is more important and false negative cases (patients at high risk of the event were not identified) are more costly, we selected F2 score over F1 score.[212,281] In addition, we generated feature importance plots to identify the contribution of each variable in predicting the outcomes.[214] Since feature importance using Gini index in tree-based algorithms (i.e., RF and XGBoost) are subject to bias,[282] we computed out-of-bag impurity reduction feature importance as an alternative.[283] Model calibration was performed to compare the true probability of the outcome versus a model's prediction with Brier score.[215] ML algorithms were developed using RStudio (version 3.6.2; Boston, MA, USA) and data analysis was conducted using SAS (version 9.4, SAS Institute, Inc., Cary, NC, USA).

2.7. Sensitivity analyses

Since our classification problem was severely imbalanced, we used Synthetic Minority Oversampling Technique (SMOTE) to account for imbalance distribution of the outcome variables.[216] Model development and validation were conducted on the resampling dataset.

3. Results

3.1. Study sample and characteristics

The final cohort consisted of 18388 patients, of whom 523 (2.84%) had ischemic stroke and 221 (1.20%) had major bleeding within one year after AFib diagnosis (**Figure 1**). The characteristics

of study sample are described in **Table 1**. Overall, the mean (standard deviation) age was 76.59 (7.13), 8483 (46.13%) were women, and the majority were White (85.11%) and residing in the Northeast (39.13%), or West (34.40%) region. The median (interquartile range) duration from cancer diagnosis to AFib onset was 17 (2-40) months. Compared with non-stroke patients, patients who had stroke were more likely to have breast cancer [(227 (43.40%) vs. 5416 (30.32%)], use potential interaction agents [139 (26.58%) vs. 825 (21.41%)], diabetes [188 (35.95%) vs. 5433 (30.41)], history of stroke [96 (18.36) vs. 1446 (8.09)], and vascular diseases [136 (26.00) vs. 4249 (23.78)] but less likely to have lung cancer [106 (20.27%) vs 6059 (33.92%)]. Compared with non-bleeding patients, patients who had bleeding were more likely to have breast cancer [84 (38.01%) vs. 5559 (30.60%)], history stroke [53 (23.98%) vs. 1489 (8.20%)], vascular diseases [63 (28.51%) vs. 4322 (23.79%)], and history of bleeding [72 (32.58%) vs. 3771 (20.76%)] (**Table S1**).

3.2. Algorithm performance and comparison

3.2.1. Ischemic stroke prediction

The performances of ML models in the original sample are described in **Table 2**. The AUCs of elastic net, RF, XGBoost, SVM, and neural network were 0.684 (95% CI 0.641-0.727), 0.916 (95% CI 0.887-0.945), 0.737 (95% CI 0.698-0.777), 0.545 (95% CI 0.502-0.588), and 0.625 (95% CI 0.579-0.672), respectively. RF outperformed other ML models in AUC (0.916, 95% CI 0.887-0.945), sensitivity (0.868), specificity (0.801), and F2 score (0.375). The best calibration was achieved in RF algorithm (Brier score=0.035) (**Table 2**). Top 5 important features of RF algorithm were socioeconomic factors (proportion of household with no high school education level and median household median income), time from cancer diagnosis to AFib onset, history of stroke, and concomitant use of ACE inhibitors or ARBs. History of stroke and time from cancer diagnosis to AFib onset were the most important features in all ML models (**Figures 2, S3-S6**).

3.2.2. Major bleeding prediction

For bleeding prediction, performances of ML models were poor (all AUCs < 0.7 in original sample) (**Table 3**). The AUCs of elastic net, RF, XGBoost, SVM, and neural network were 0.575 (95% CI 0.503-0.649), 0.623 (95% CI 0.554-0.692), 0.578 (95% CI 0.510-0.646), 0.546 (95% CI 0.472-0.619), 0.504 (95% CI 0.432-0.575), respectively. RF outperformed other models in AUC (0.623 (95% CI 0.554-0.692). However, sensitivity was highest for SVM algorithm (0.652), and best specificity was achieved in elastic net algorithm (0.689). There was no difference in calibration of five algorithms. Proportion of household with no high school education level, median household median income, time from cancer diagnosis to AFib onset, history of stroke, history of bleeding were top five important features of RF algorithm. History of bleeding was among top 5 important features in elastic net, RF, XGBoost, and neural network algorithms (**Figures 3, S7-S10**).

3.3. Sensitivity analysis

There was no major improvement in the performance metrics using SMOTE resampling for ischemic stroke and major bleeding prediction across five ML algorithms. SMOTE resampling worsened the calibration of the algorithms with larger Brier score compared with original sample (**Tables 2 and 3**). Feature importance of ML algorithms in SMOTE samples are described in **Figures S11-S15** (ischemic stroke) and **Figures S16-20** (major bleeding).

4. Discussion

Our study is among the first studies that developed and validated ML algorithms to predict adverse outcomes exclusively for patients with AFib and cancer. In this cohort study, we demonstrated that incorporating ML algorithms into SEER-Medicare data can be a promising tool to predict short-

term (one year) risk of stroke among patients with AFib and cancer. Among older adults with cancer who were newly diagnosed with AFib, clinicians can collect patients' demographics, socioeconomic status, medical history, and medication history from routine medical records and/or patient survey, then leverage this tool to predict patients' risk of stroke. Our ML algorithms help clinicians identify high-risk patients and facilitate treatment decisions (i.e., medication or non-pharmacological intervention) among older adults with AFib and cancer across the US.

First, RF outperformed other ML models in all metrics (AUC, sensitivity, specificity, and F2 score) for ischemic stroke. Although widely accepted as a risk assessment tool for stroke among patients with AFib, CHA_2DS_2-VASc score failed to achieve high performance in patients with AFib and cancer, especially in new onset AFib.[23,29,257] The major limitation of CHA_2DS_2-VASc is the absence of cancer indicator, which has been suggested as an independent risk factor of stroke.[284,285] A recently published studies suggested the incorporation of cancer to CHA_2DS_2-VASc score to improve predictability of the original score.[286] Indeed, CHA_2DS_2-VASc score is the linear combination of conditions in prediction of stroke.[100] In the presence of cancer, the relationship between patient characteristics and ischemic stroke may become more complicated (i.e., non-linear), it is not surprising that CHA_2DS_2-VASc score failed to achieve high performance. In our study, linear models such as elastic net and SVM had lower performance metrics compared with non-linear models such as RF and XGBoost. Similar to CHA_2DS_2-VASc, we found prior stroke was among the most important features in all ML algorithms. However, our approach incorporated a comprehensive set of patients' characteristics. For example, patients' socioeconomic status (household median income and education level) and cancer characteristics (cancer type, active cancer status) were ranked among top features in RF and XGBoost. The importance of these features highlighted contributions of health disparities and cancer characteristics in stroke

prediction. The inclusion of these variables may be useful in identifying high-risk patients.[287] However, it is also noticed that tree-based models may inflate the impact of continuous features in their prediction.[282] Although we reduced the impact of these features, this should be interpreted with caution. Clinicians may consider initiating OACs for those who are at high risk of stroke identified by our RF algorithm.

Traditional tools such as HAS-BLED or HEMORR$_2$HAGES showed poor predictability in patients with cancer.[30,103,288] Our ML algorithms also failed to obtain high performance metrics in prediction of major bleeding. Such poor performance suggested complex interactions between patients' characteristics and outcomes in the presence of cancer. First, although we obtained additional cancer characteristics compared with traditional risk scores, the performance was not improved.[289] This may suggest that our models failed to capture important features in prediction of major bleeding. In fact, genetic factors and disease severity were not available in SEER-Medicare data and dynamic features (i.e., cancer progression, new diagnosis of diseases) were not included in the models due to complexities. Similar to previous risk scores, we found that bleeding history was an important factor in prediction of subsequent major bleeding.[30,289] Second, the relationship between risk factors and major bleeding may be more complicated (i.e., dynamic relationship or non-linear interactions) in which simple ML models could not handle. Third, we excluded patients who have already initiated OACs before AFib diagnosis and those who initiated AFib during follow-up because OACs may increase risk of bleeding. As a result, only 1.2% patients in our cohort experienced bleeding events during follow-up and this created a severe imbalance classification problem for our ML algorithms and may lead to poor predictability.[290] Future studies may expand the outcomes to other types of bleeding (i.e., intracranial bleeding,

gastrointestinal bleeding, or other non-critical site bleeding) to improve the performance and the clinical utility of the algorithms.

In our study, SMOTE resampling approach did not improve the performance of the model. In the training set, SMOTE created new synthetic 'stroke' individuals from interpolations of the original, real 'stroke' cases.[216] Thus, the resampled training set has a 1:1 ratio between stroke and non-stroke cases. Studies have shown that SMOTE-like methods could improve the performance of weak classifiers such as SVM, decision tree.[291] In fact, SMOTE improved AUCs in SVM only. Another limitation of SMOTE is that it resulted in poorly calibrated models where the probability of the minority class (stroke) was strongly inflated demonstrated by Brier score. In this study, we shifted the probability threshold to the true event probability and the performance metrics were higher than SMOTE in most of the cases.[291,292]

Our study is subject to several limitations. We were unable to capture some important variables in the ML models (i.e., BMI, genetic factors, frailty, and health behaviors – not available in SEER-Medicare). Socioeconomic factors such as household income and education level are available on the aggregate area level (Census tract) but not individual level. In addition, our algorithms did not incorporate the impact of some post-baseline predictors (i.e., treatment dosage, adherence, recent CHA_2DS_2-VASc and HAS-BLED scores, recent use of NSAIDs, and other time-varying variables). Specifically, time-varying features can be assessed every 3 months after the index date until the occurrence of the outcome or a censored event (discontinuation of medications, or death) and the algorithms may be updated based on real-time features.[136,218] In addition, due to the nature of administrative claims data, measurement bias may exist and affect the performance and fairness of ML models. Selection bias may also persist in the development of ML algorithms because we restricted the cohort to patients with continuous Medicare enrollment during follow-up. In fact,

inverse-probability censoring weighted ML technique can be used to adjusted for censoring due to loss to follow-up or competing events.[293] Last, the generalizability of our ML algorithms to other populations may be limited (i.e., commercial insurance, anticoagulated patients, or patients with other cancer types). Future studies are warranted to externally validate our algorithms to non-Medicare populations (i.e., younger adults, patients with private insurance), patients who had other critical cancer types (i.e., blood cancer, bladder cancer), or those who developed cancer after AFib diagnosis. An ML-based monitoring tool to predict adverse outcomes among patients with AFib and cancer who were already on anticoagulants is also needed to optimize the standard of care for this population.

5. Conclusion

Our study demonstrated a promising application of ML in stroke prediction among older adults with cancer who are newly diagnosed with AFib in the US. This tool may be leveraged in assisting clinicians in identification of patients at high risk of stroke and improving treatment decisions.

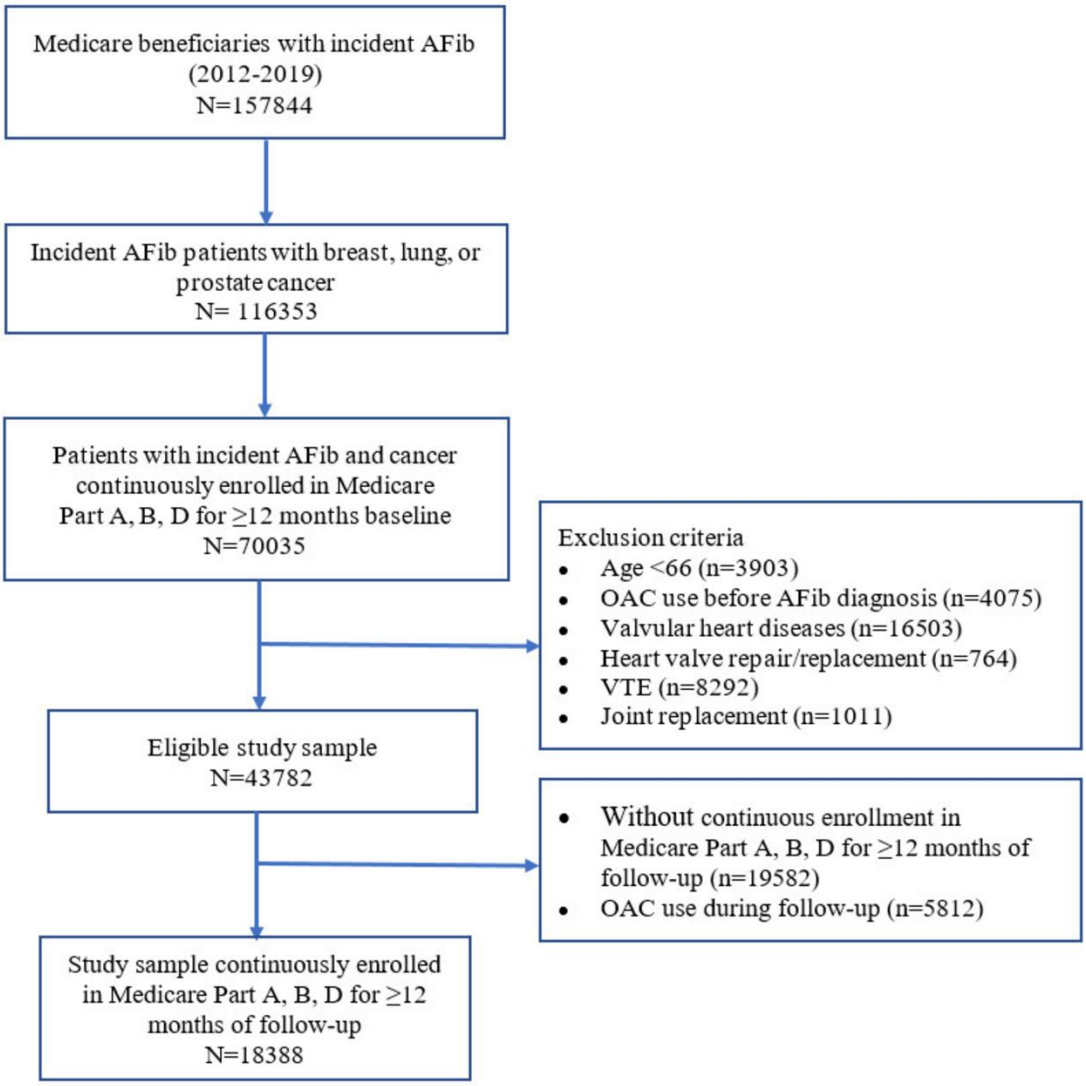


Figure 1. Flowchart diagram for study sample. *VTE Venous thromboembolism, AFib Atrial Fibrillation, OAC Oral Anticoagulant,*

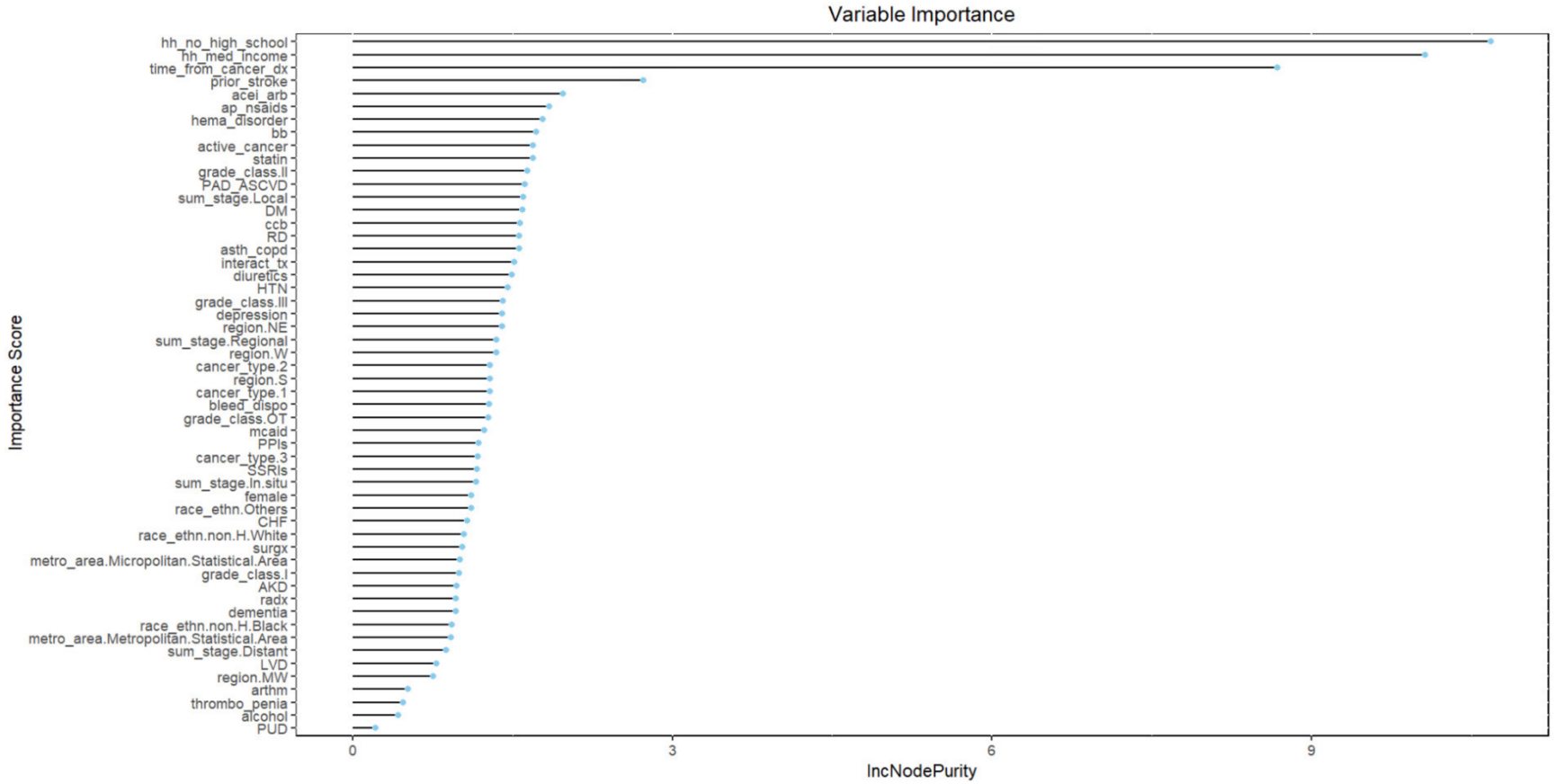


Figure 2. Feature importance plot of random forest algorithm for ischemic stroke prediction (original data)

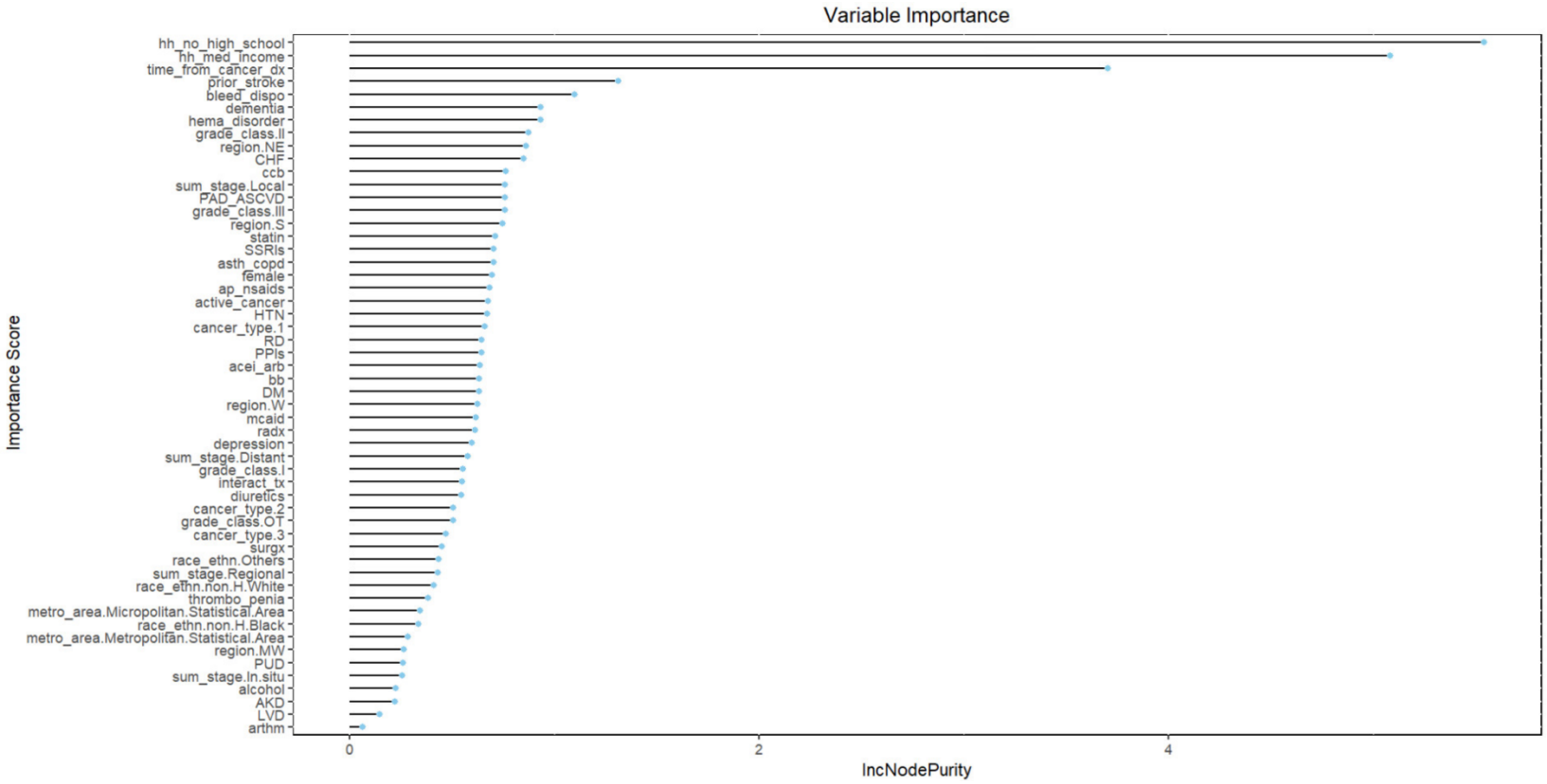


Figure 3. Feature importance plot of random forest algorithm for major bleeding prediction (original data)

Table 1. Characteristics of patients with new onset AFib and history of cancer in SEER-Medicare registry from 2012 to 2018

	Overall (N=18388)	**Stroke (N=523)**	**Non-stroke (N=17865)**
Demographics			
Index age (Mean, SD)	76.59 (7.13)	78.55 (7.72)	76.53 (7.11)
Female	8483 (46.13)	270 (51.63)	8213 (45.97)
Race/ethnicity			
Non-Hispanic White	15650 (85.11)	432 (82.60)	15218 (85.18)
Non-Hispanic Black	1134 (6.17)	38 (7.27)	1096 (6.13)
Others	1604 (8.72)	53 (10.13)	1551 (8.68)
Region			
Midwest	1604 (8.72)	34 (6.50)	1570 (8.79)
Northeast	7195 (39.13)	216 (41.30)	6979 (39.07)
South	3263 (17.75)	93 (17.78)	3170 (17.74)
West	6326 (34.40)	180 (34.42)	6146 (34.40)
Medicaid eligible	2007 (10.91)	63 (12.05)	1944 (10.88)
Urbanicity			
Metropolitan	15895 (86.44)	459 (91.98)	15436 (91.48)
Micropolitan	1478 (8.04)	40 (8.02)	1438 (8.52)
Unknown	1015 (5.52)		
Socioeconomic status (Census Tract)			
Household median income (Median, IQR) (N=18086)	62122 (45499-84935)	63092 (47253-85846)	62096 (45482-84914)
Percentage of non-high school graduates (Median, IQR) (N=18090)	9.53 (5.20-16.56)	9.28 (5.07-15.45)	9.54 (5.20-16.58)
Cancer characteristics			
Time from cancer diagnosis to the onset of AFib (month, Median, IQR)	17 (2-40)	28 (9-51)	16 (2-40)
Cancer type			
Breast	5643 (30.69)	227 (43.40)	5416 (30.32)
Lung	6165 (33.53)	106 (20.27)	6059 (33.92)
Prostate	6580 (35.78)	190 (36.33)	6390 (35.77)
Active cancer	4629 (25.17)	128 (24.47)	4501 (25.19)
Cancer grade			

I	2583 (14.05)	83 (15.87)	2500 (13.99)
II	6583 (35.80)	198 (37.86)	6385 (35.74)
III	5955 (32.39)	160 (30.59)	5795 (32.44)
Others	3267 (17.77)	82 (15.68)	3185 (17.83)
Cancer stage			
In situ	883 (4.80)	839 (4.97)	44 (8.87)
Local	10782 (58.64)	311 (62.70)	10471 (61.99)
Regional	3941 (21.43)	100 (20.16)	3841 (22.74)
Distant	1781 (9.69)	41 (8.27)	1740 (10.30)
Unknown/missing	1001 (5.44)		
Cancer treatment			
Potential interacting antineoplastic agents	3964 (21.56)	139 (26.58)	3825 (21.41)
Radiation	2419 (13.16)	51 (9.75)	2368 (13.25)
Surgery	1692 (9.20)	54 (10.33)	1638 (9.17)
Individual comorbidities			
HTN	13259 (72.11)	384 (73.42)	12875 (72.07)
CHF	2343 (12.74)	54 (10.33)	2289 (12.81)
Diabetes	5621 (30.57)	188 (35.95)	5433 (30.41)
Prior stroke	1542 (8.39)	96 (18.36)	1446 (8.09)
Prior vascular diseases	4385 (23.85)	136 (26.00)	4249 (23.78)
Prior major bleeding	3843 (20.90)	86 (16.44)	3757 (21.03)
Renal diseases	3631 (19.75)	104 (19.89)	3527 (19.74)
Liver diseases	1635 (8.89)	38 (7.27)	1597 (8.94)
Alcohol use disorders	526 (2.86)	13 (2.49)	513 (2.87_
Asthma/COPD	6323 (34.39)	119 (22.75)	6204 (34.73)
Hematological disorders	5664 (30.80)	139 (26.58)	5525 (30.93)
Dementia	1044 (5.68)	33 (6.31)	1011 (5.66)
Depression	2650 (14.41)	76 (14.53)	2574 (14.41)
Acute kidney diseases	1183 (6.43)	31 (5.93)	1152 (6.45)
Thrombocytopenia	1120 (6.09)	22 (4.21)	1098 (6.15)
Peptic ulcer diseases	279 (1.52)	--	274 (1.53)
Medications			
Antiplatelet/NSAIDs	2957 (16.08)	93 (17.78)	2864 (16.03)

ACE inhibitors/ARBs	4691 (25.51)	172 (32.89)	4519 (25.30)
CCB	2952 (16.05)	115 (21.99)	2837 (15.88)
Beta blockers	4135 (22.49)	155 (29.64)	3980 (22.28)
Antiarrhythmic medications	915 (4.98)	15 (2.87)	900 (5.04)
Diuretics	3235 (17.59)	104 (19.89)	3131 (17.53)
Statin	4856 (26.41)	152 (29.06)	4704 (26.33)
PPIs	2844 ((15.47)	80 (15.30)	2764 (15.47)
SSRIs/SNRIs	1979 (10.76)	63 (12.05)	1916 (10.72)
Outcome			
Ischemic stroke	523 (2.84)		
Major bleeding	221 (1.20)		

AFib Atrial Fibrillation. SD Standard Deviation. IQR Interquartile Range. HTN hypertension. CHF congestive heart failure. COPD Chronic obstructive pulmonary disease. ACE Angiotensin-converting enzyme. ARB Angiotensin receptor blockers. CCB Calcium Channel Blockers. PPI Pump Proton Inhibitors. SSRI Selective serotonin reuptake inhibitors. SNRI Serotonin and norepinephrine reuptake inhibitors. NSAIDs non-steroidal anti-inflammatory drugs.

Table 2. Model performance of machine learning models for ischemic stroke prediction

	Sensitivity	Specificity	AUROC	p-value*	F2 score	Brier score
Original data						
Elastic net	0.698	0.574	0.684 (0.641-0.727)	Reference	0.183	0.055
RF	0.868	0.801	0.916 (0.887-0.945)	<0.001	0.375	0.035
XGBoost	0.723	0.608	0.737 (0.698-0.777)	0.005	0.202	0.054
SVM	0.434	0.589	0.545 (0.502-0.588)	<0.001	0.121	0.055
NN	0.692	0.511	0.625 (0.579-0.672)	0.023	0.161	0.056
SMOTE resampling						
Elastic net	0.577	0.620	0.648 (0.603-0.693)	Reference	0.164	0.446
RF	0.801	0.334	0.633 (0.587-0.675)	0.0352	0.213	0.442
XGBoost	0.667	0.529	0.633 (0.588-0.678)	0.0408	0.160	0.440
SVM	0.560	0.633	0.650 (0.604-0.695)	0.1027	0.172	0.446
NN	0.372	0.752	0.580 (0.534-0.626)	<0.001	0.152	0.309

AUROC area under receiver operating characteristic curve

*DeLong’s test

Table 3. Model performance of machine learning models for major bleeding prediction

	Sensitivity	Specificity	AUC	p-value*	F2	Brier score
Original data						
Elastic net	0.424	0.689	0.575 (0.503-0.649)	Reference	0.070	0.023
RF	0.515	0.671	0.623 (0.554-0.692)	0.0003	0.081	0.024
XGBoost	0.439	0.641	0.578 (0.510-0.646)	0.7210	0.064	0.024
SVM	0.652	0.357	0.546 (0.472-0.619)	0.0726	0.056	0.024
NN	0.470	0.497	0.504 (0.432-0.575)	0.0122	0.051	0.024
SMOTE resampling						
Elastic net	0.348	0.722	0.564 (0.492-0.635)	Reference	0.064	0.378
RF	0.863	0.182	0.551 (0.478-0.625)	0.2752	0.057	0.048
XGBoost	0.515	0.517	0.553 (0.477-0.630)	0.2813	0.057	0.050
SVM	0.348	0.714	0.562 (0.490-0.634)	0.4052	0.062	0.375
NN	0.136	0.849	0.520 (0.449-0.590)	0.2752	0.041	0.200

AUROC area under receiver operating characteristic curve
*DeLong's test

Chapter 5: Discussion and conclusions

Findings from this project provide new evidence in effectiveness and safety of OACs, which could help clinicians optimize treatments in patients with AFib and cancer. In this chapter, we summarize the overall findings, discuss the implications of these findings, and provide potential directions for future research.

In this dissertation project, we used a multimethod approach to examine the effectiveness and safety of OACs and optimize treatment decisions among patients with AFib and cancer. In *Aim 1*, we explored the clinical impact of in vitro DDIs between DOACs and antineoplastic agents using a pharmacovigilance approach. We found an increase in reporting trends of DOAC-antineoplastic agent combinations by therapeutic class in the FAERS. The highest bleeding rates in each drug class were the combination of DOACs with neratinib among kinase inhibitors, tamoxifen among hormonal agents, irinotecan among chemotherapeutic agents, and cyclosporine among immunomodulating agents. The highest rate of stroke was found for prednisolone among CYP3A4/P-gp inducers. In the primary analysis, we implemented 3 different methods DPA, LR, and MGPS with MGPS as the main metrics to detect DDIs signals of 5 combinations by therapeutic class and 63 combinations by individual drugs. We found no risk signal of DDIs between DOACs and antineoplastic agents by therapeutic class (kinase inhibitors, hormonal therapy, chemotherapeutic agents, immunomodulating agents, and antineoplastic CYP3A4/P-gp inducers). However, at individual antineoplastic drug level, DOACs-neratinib was the only risk signal detected. The clinical impact of *in vitro* DDIs in this study may contribute to the growing evidence in clinical guidelines and DDIs database. First, our findings may help clinicians refine the DDI "watch list" of DOACs and antineoplastic agents in managing patients with AFib and concomitant cancer. Among patients with AFib and cancer who are already on DOACs, antineoplastic agents

without elevated risk signal in this study can be considered if indicated and vice versa. Second, the combination of DOACs and neratinib should be further investigated in future studies with rigorous study design and high-quality data sources.

The overall goal of Aim 2 is to examine the safety and effectiveness of OACs among patients with AFib and cancer. In *Aim 2.1,* we explored the risk and benefit of multiple OAC initiation strategies at different levels of CHA_2DS_2-VASc score. We conducted a retrospective cohort study by emulating a hypothetical target trial using SEER-Medicare database. We compared risk of ischemic stroke and bleeding among cancer patients newly diagnosed with AFib who initiated OACs at CHA_2DS_2-VASc ≥1; CHA_2DS_2-VASc ≥2, CHA_2DS_2-VASc ≥4, CHA_2DS_2-VASc ≥6, and never initiated OACs. We found that initiating OACs at higher level of CHA_2DS_2-VASc score (i.e., ≥6) is more beneficial in reducing risk of stroke among patients with AFib and cancer. OAC initiation at a lower level of CHA_2DS_2-VASc score might be harmful or has no effect on risk of stroke. Second, initiating OACs at any level of CHA_2DS_2-VASc score reduced the risk of major bleeding, with OAC initiation at higher level of CHA_2DS_2-VASc score (i.e., CHA_2DS_2-VASc score ≥6) being the most effective strategy. In addition, among patients with advanced cancer such as lung cancer or regional/metastatic cancer, OAC initiation at a lower risk of stroke may not be beneficial or even harmful. Among these patients, OAC initiation reduced risk of stroke and bleeding only in patients with CHA_2DS_2-VASc score ≥6. In *Aim 2.2,* we compared the effectiveness and safety of DOACs and warfarin among patients with AFib and cancer. A retrospective cohort study was conducted using SEER-Medicare data on a target trial framework. Overall, DOACs are safe and effective alternatives to warfarin in the management of patients with AFib and cancer. Specifically, compared with warfarin, DOACs increased risk of ischemic stroke and decreased risk of major bleeding in both ITT and PP analysis; however, the absolute risk

difference was small and not statistically significant. Additionally, DOACs initiators also had reduced risk of secondary outcomes including GI bleeding and non-critical site bleeding than warfarin initiators. Little heterogeneity was observed across subgroups and findings remained robust in sensitivity analyses. Our findings in *Aim 2* may significantly improve the availability and quality of evidence to the clinical guidelines in managing patients with AFib and cancer. First, we suggest a revised CHA_2DS_2-VASc score threshold of ≥6 for OAC initiation with AFib and cancer. OACs should be initiated among patients with high risk of stroke based on CHA_2DS_2-VASc score. In addition, we expect our findings to help clinicians individualize treatment decisions based on patients' cancer characteristics. Among patients with advanced cancer or short life expectancy such as lung cancer, starting OACs at low risk of stroke may even increase risk of stroke and have no effect on risk of bleeding. Regarding treatment choice, DOACs are as safe and effective as warfarin in prevention of stroke and major bleeding and have more benefit than warfarin in reducing GI bleeding and non-critical site bleeding. Other factors should be further considered for treatment selection between DOACs and warfarin, such as medication cost and regular monitoring requirement. A shared decision-making should be made between patients and clinicians on treatment choice. Since our study focuses on patients with breast, lung, and prostate cancer, future research should further explore the benefits and risks of OACs in patients with other cancer types, especially in cancer types with a short life expectancy or in high risk of bleeding. In addition, risk and benefit of individual DOACs (i.e., dabigatran, rivaroxaban, apixaban, and edoxaban) should be examined to further tailor treatment choices in patients with AFib and cancer.

In *Aim 3*, we developed and validated ML algorithms to predict 1-year risk of ischemic stroke and major bleeding in patients with AFib and cancer in SEER-Medicare database. In prediction of ischemic stroke, RF significantly outperformed other ML models. Feature importance plots

identified history of stroke and time from cancer diagnosis to AFib onset as top factors in all models for stroke prediction. However, the performance of ML algorithms in prediction of major bleeding was low. Feature importance plots identified history of stroke and time from cancer diagnosis to AFib onset as top factors for stroke prediction in all ML models. We demonstrated a promising application of ML in stroke prediction among patients with AFib and cancer. This tool may be leveraged in assisting clinicians to identify patients at high risk of stroke and optimize treatment decisions. Future research should expand the ML algorithms to predict risk of stroke and bleeding in patients with other types of cancer, health insurance coverages, and in patients who are already on OACs. Advanced algorithms for further stratification of risk of stroke and bleeding among patients with AFib and cancer are needed to guide clinicians' decision making.

In summary, in this dissertation project, we implemented a comprehensive approach to optimize OAC treatment among patients with AFib and cancer from DDI assessment, treatment evaluation, and risk stratification. We believe our findings will make an important contribution to the growing body of evidence and improve health outcomes in this patient population.

Appendix for Aim 1 Manuscript

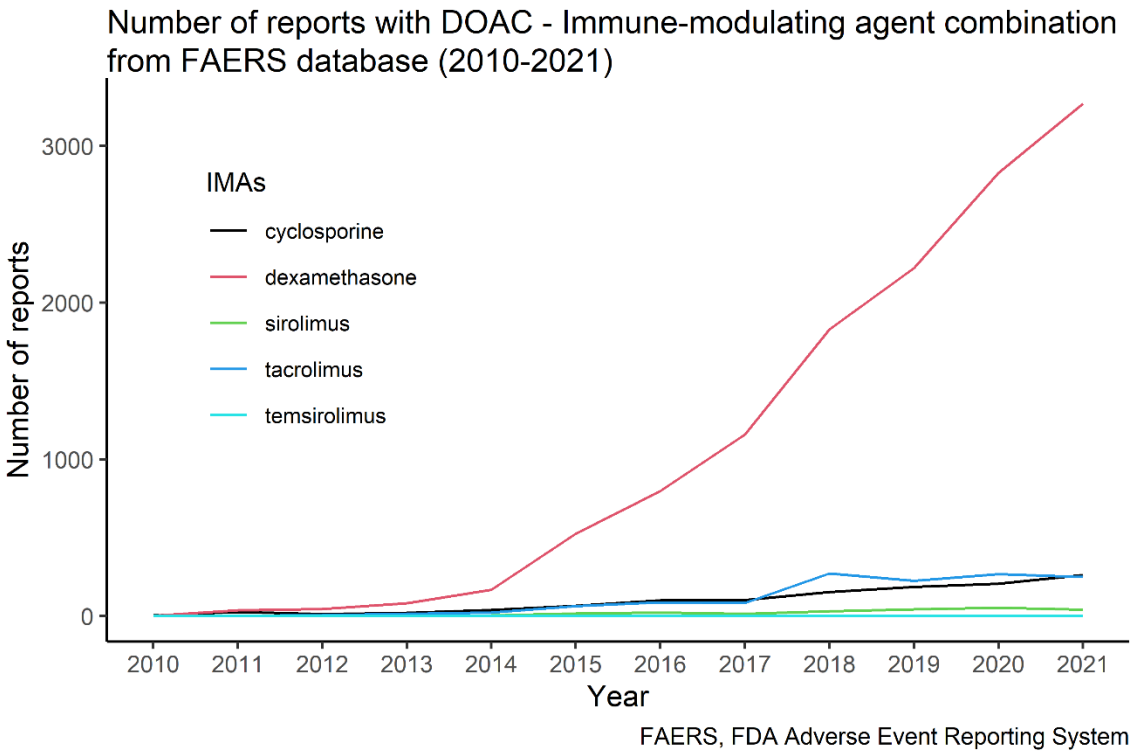


Figure S1. Number of reports with DOAC-immunomodulating agent combination from FAERS (2010-2021).

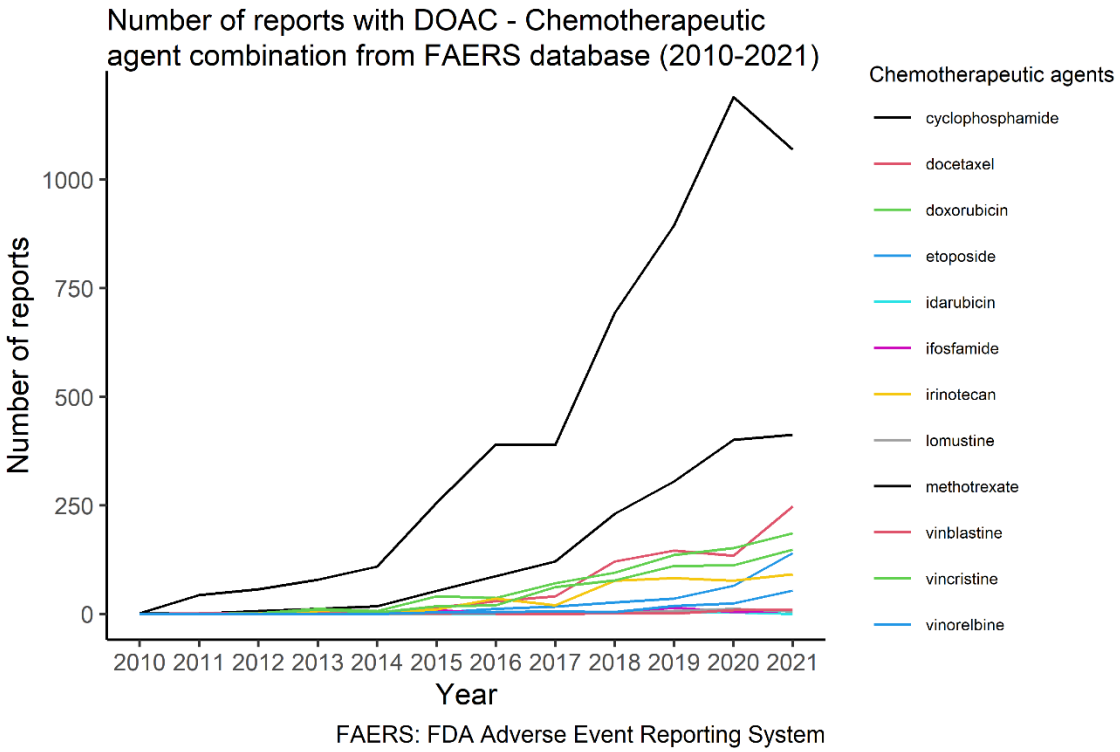


Figure S2. Number of reports with DOAC-chemotherapeutic agent combination from FAERS (2010-2021).

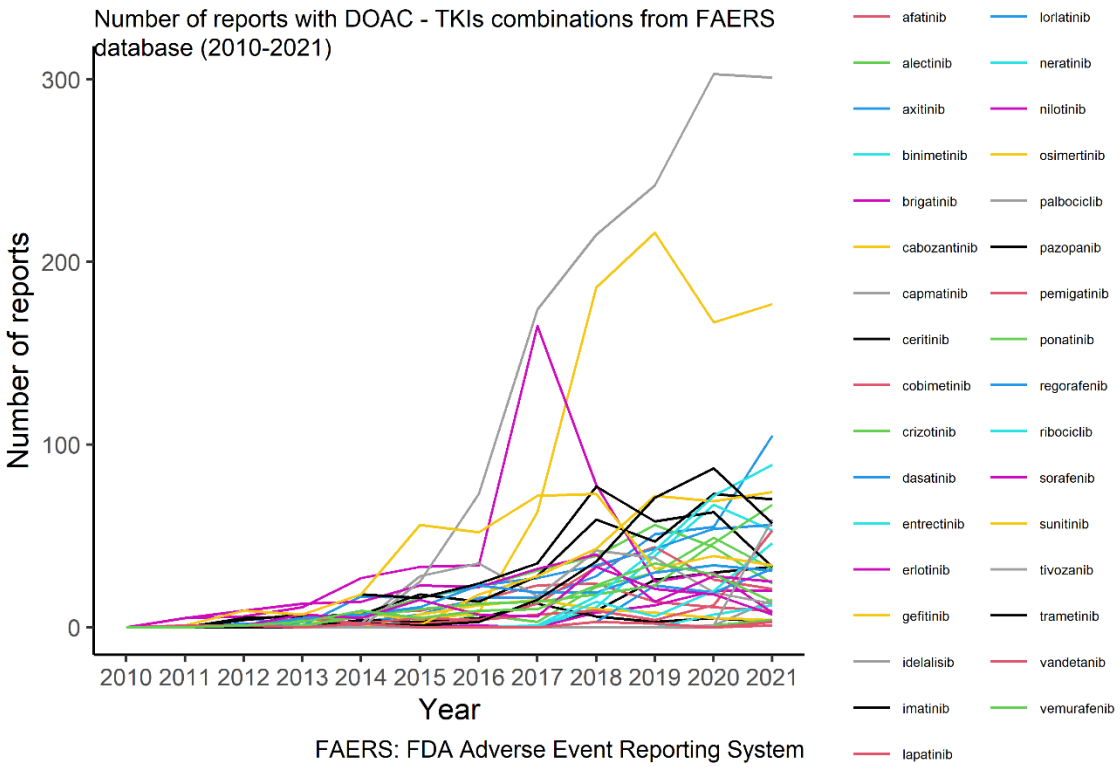


Figure S3. Number of reports with DOAC-KI combination from FAERS (2010-2021).

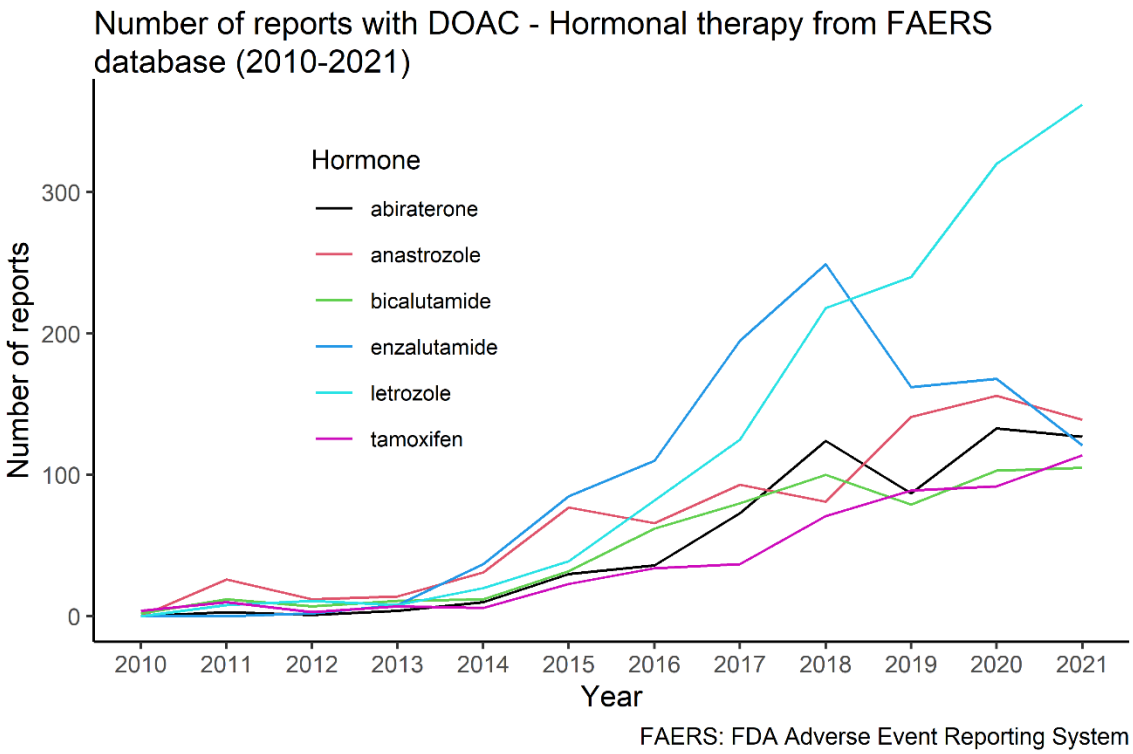


Figure S4. Number of reports with DOAC-hormonal therapy combination from FAERS (2010-2021).

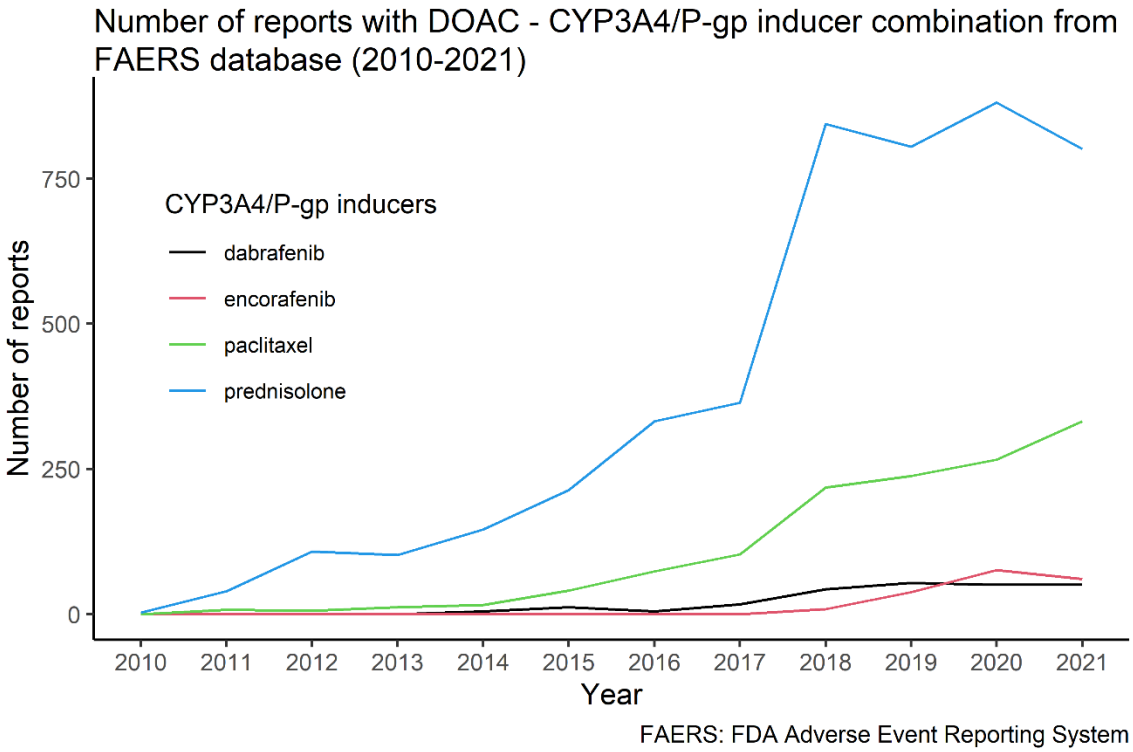


Figure S5. Number of reports with DOAC-CYP3A4/P-gp inducer combination from FAERS (2010-2021).

Table S1. Drug name for identification of exposure in FAERS database

Drug class	Generic name	Brand name
DOACs	dabigatran	pradaxa
	rivaroxaban	xarelto rivadia runaplax
	apixaban	eliquis, tevix
	edoxaban	savaysa, lixiana
VKA	warfarin	coumadin, jantoven, aldocumar, anasmol, apo-warfarin, befarin, cogulax, cumar fargem, gen-warfarin, lin warfarin, maforan, marevan, marfarin, morfarin, notistil, orfarin, panwarfin, romesa, simarc-2, sofarin, Taro-Warfarin, Tedicumar, Tufam, Varfine, Waran, Waran, Warfarin Sodium, Warfilone, Warfin, Warik, Warnerin, Warx, Zydarin, Zyfarin
Kinase inhibitors	imatinib	Imatinib Mesylate, Gleevec
	dasatinib	Sprycel
	nilotinib	Tasigna
	lapatinib	Tykerb, Lapatinib
	erlotinib	Alvoceva, Erlonat, Erlotinib, Ertinob, Tarceva, Varlota
	crizotinib	Xalkori
	tivozanib	Fotivda
	pazopanib	Vorifas, Votrient
	axitinib	Inlyta
	brigatinib	Alunbrig
	ceritinib	Zykadia
	lorlatinib	Lorbrena, Lorviqua
	binimetinib	Mektovi
	trametinib	Mekinist
	palbociclib	Ibrance, Reampla
	ribociclib	Kisqali, Kryxana
	entrectinib	Rozlytrek
	larotrectinib	Vitrakvi
	idelalisib	Zydelig
	sunitinib	SUNItinib malate, Sutent
	vandetanib	Caprelsa
	osimertinib	Tagrisso
	alectinib	Alecensa
	neratinib	Nerlynx
	cabozatinib	Cabometyx, Cometriq
	capmatinib	Tabrecta
	idelasinib	Zydelig
	sorafenib,	NexAVAR
	regorafenib	Stivar, Stivarga
	ponatinib	Iclusig

	vemurafenib	Zelboraf
	cobimetinib	Cotellic
	abemaciclib	Verzenio
	pemigatinib	Pemazyre
	gefitinib	Gefimira, Gefitad, Geritsa, Iressa, Veiasu
	afatinib	Gilotrif
Hormone	letrozole	Femara, Aletro, Apo-Letro, Arogen, Aromara, Aromed, Aromek, Attozette, Brenea, Britagal, Britapons, Calantha, Cetezol, Clarzole, Devazol, Dracenax, Eirfem, Etruzil, Famos, Femaplex, Femara, Femar, Femozol, Fempro, Femtozette, Femzole, Fera, Florazole, Fu Rui, Galdar, Garion, Gesamaf, Gosuran, Gynotril, Helzette, Hentrozole, Insegar, Kisqali Femara Co-Pack – Femara, Lambda, Lametta, Lebrest, Lentronat, Leoncon, Lerana, Lestara, Letaris, Letero, Letmylan, Letoripe, Letov, Letraccord, Letrafem, Letralan, Letrasan, Letrazan, Letraz, Letregio, Letregio, Letride, Letroarom, Letroblock, Letro-cell, Letrodotril, Letrofam, Letrofem, Letroger, Letrokabi, Letroks, Letrolan, Letrole, Letrol, Letroman, Letromara, Letromataz, Letromedac, Letromedica, Letronat, Letronofi, Letronorm, Letropen, Letroregiozol, Letrostad, Letrostar, Letrovena, Letroveres, Letrovitae, Letrozette , Letroz, Letrozin, Letrozole, Letu, Letvex, Letzo, Levinox, Lexeroll, Lezol, Lezra, Likarda, Linol, Loosyn, Lortanda, Losiral, Lostar, Lotestrol, Loxelza, Loxifan, Loxoprel, Luro, Mamira, Mangrol, Mimor, Mionica, Ninivet, Nucleus, OncoZol, Oralet, Oreta, Picozone, Ratroz, Regioletrozol, Religan, Stefaplex, Symletrol, Tiadis, Trezor, Trodis, Trozara, Trozebax, Trozel, Trozolt, Viobrest, Zolstro
	anastrozole	Acydex, Agerdex, Ai Da, Alozex, Alozex, Amenur, Amidex,Anablock, Anabrest, Anabrest, Anabrez, Anacyne, Anadex, Anamataz, Anamidex, Anaprex, Anaromat, Anarom, Anasolde, Anastar, Anastarrow, Anastelb, Anastelb, Anastrad, Anastralan, Anastro-cell, Anastro, Anastrogen, Anastrolan, AnastroLek, Anastrol, Anastrolibbs, Anastrolkabi, Anastromin, Anastrose, Anastrozole, Anasvitae, Anatero, Anaya, Anazo, Anazole, Anazol, Anebol, Ankarma, Anotrole, Anoxidil, Ansuzole, Ansyn, Anzole, Anzol, Anzonat, Apo-Nastrol, Aremed, Arianna, Arilla, Arimidex, Arinel, Arinib, Aristu, Armida, Armotraz, Aromatt, Asnea, Asoinacor, Astoz, Astrazol, Astrozol, Astzol, Atrocela, Atrocela, Atrozol, Avomin, Axastrol, Axastrol, Azastrole, Barstra, Betasolde, Biostrol, Brestazol, Castra, Curmyl, Deltasolde, Ebezolid, Egistrozol, Enastros, Epsisolde, Eristrol, Everdex,

		Extroplex, Femistra, Femizet, Gadozol, Gammasolde, Genstra, Kirana, Londer, Madelen, Mammozole, Mamostrol, Mastoren, Mastrol, Mimastran, Nastrin, Nobrec, OncoFem, Orminib, Oxeda, Probitor, Raoloz, Regost, Remidex, Renazole, Renazole, Rolin, Rui Si Yi, Rui Ting, Sananas, Santra, Strakir, Strazal, Symanastrol, Trasolette, Trozolet, Valmidex, Veridex, Vexal-A, Viastrol, Xtrodex, Xtrozol, Zelotrin, Zenbrest, Zenstra, Zolastrol, Zolitrat, Zolkir, Zolzyn, Zynzol
	abiraterone	Abiraterone Acetate, Abiratex, Abitiga, Yonsa, Zytiga
	bicalutamide	Advanpro, Alidex, Anandroca, Androbloc, Androcal, Apex, Areclok, Atembin, Baculamyl, Balutar, Bicadex, Bicalaccord, Bicalem, Bicalex, Bicalide, Bicalinn, Bicalox, BicaluPel, Bicaluplex, Bicalustad, Bicalutagen, Bicalutamide, Bicalutanorm, Bicalutatam, Bicalut, Bicalutin, Bicamal, Bicamed, Bicamid, Bicamylan, Bicaprol, Bicapros, Bicarbex, Bicasil, Bicastad, Bicatero, Bicatin, Bicatlon, Bicavan, Bicotexida, Bictamid, Bicusan, Bidanil, Bikalard, Bikalen, Bikalex, Bikauk, Bikulid, Biludex, Bilumide, Biluron, Biluta, Bilutamid, Binabic, Binabic, Binarex, Biobica, Biolev,Bjorgeina, Bypro, Calubloc, Calumide, Calumid, Calumin, Calutex, Calutide, Calutol, Calutol, Calux, Capro, Casdrogen, Casodex, Casomide, Casomid, Cosamide, Cosudex, Diproca, Encalor, Gepeprostin, Glanuta, Grommar, Kandex, Lanbica, Lanbicamid, Lutamidal, Lutamidal, Lutamid, Lutrak, Medimide, MPL Bica, Neoprost, Nycolutamid, Omidex, Ormandyl, Pencial, Praxis, Probic, Probicon, Procadex, Procalut, Procure, Prostide, Safedex, Sanotamid, Saveprost, Skylutamide, Venibyk, Verodex, Vistamid, Wibical, Yan Lie Shu, Zarmol
	tamoxifen	Adifen, Alpha-Tamoxifen, Apo-Tamox, Bagotam, Bilem, Bioxifeno, Clonoxifen, Cytrolic, Defarol, De Fu Ling, Dignotamoxi, Doctamoxifene, duratamoxifen, Ebefen, Emblon, Estrocur, Estroxyn, Fenahex, Fentamox, Festone, Genox, Gynatam, Gynatam, Gyraxen, Jenoxifen, Kessar, Ledertam,Lesporene, Mamofen, Mandofen, Mastofen, Medtax, Moxafen, Moxelle, Tamoxil, Neophedan, Nolgen, Noltam, Nolvadex, Nolvadex Forte, Nomafen, Nourytam, Novofen, Novo-Tamoxifen, Noxitem, Oestrifen, Oncotam, Oncotamox, Oxeprax, Puretam, Sinmaren, Soltamox, Tadex, Tamax, Tamaxin, Tamec, Tamexin, Tamifen, Tamimex, Tamizam, Tamobeta, Tamofen, Tamofene, Tamofen, Tamokadin, Tamolem, Tamone, Tamone, Tamooex, Tamopham, Tamophar, Tamoplex, Tamosin, Tamoxan, Tamoxasta, Tamoxene, Tamoxen, Tamox,

		Tamoxifencell, Tamoxifen Citrate, Tamoxi, Tamoxigenat,Tamoximerck, Tamoxin, Tamoxistad, Tamoxit, Tamoxsta, Tasuomin, Taxen, Taxofen, Taxus, Tecnofen, Tecnotax, Terimon, Tuosomin, Virtamox, Xifen, Yacesal, Zemide, Zitazonium, Zymoplex, Novoclair, Nuvya
	enzalutamide	Xtandi
Chemotherapy	vinblastine	Alkaban, Blastivin, Blastovin, Cellblastin, Faulblastina, Lemblastine, Lemblastine, Oncostin, Periblastine, Solblastin, Velban, Velbastine, Velbe, Velsar, Vinatin, Vinblasin, Vinblastine, Weibaoding
	doxorubicin	AD Mycin, Adriacin, Adriamycin, Adriblastina, Adriblastine, Adriblastin, Adricin, Adrimedac, Adrim, Adrimisin, Adrosal, Axibin, Axidoxo, Biorrub, Biorubina, Carcinocin, Cesius, Daxotel, Debdox, Diox, Doxfos. Doxiprol, DOXO-Cell, Doxolem, Doxorubicin, Doxorubin, Doxosan, Doxotec, Doxo-Teva, Doxotil, Doxovid, Doxtie, Doxtu, Ebedoxo, Farmiblastina, Fauldoxo, Ifadox, Myocet, Neoxane, Oncodox, Onkodox, Oxocina, Pallagicin, PremierPro Rx DOXOrubicin, Rastocin, Ribodoxo, Rubexet, Rubex, Rubicin, Rubidox, Sandobicin, Sindroxocin, Xorucin, Zodox, Zytokil, Doxil
	methotrexate	Abitrexate, Alti-Methotrexate Sodium, Bertanel, Biometrox, Brimexate, Ebetrexat, Ebetrex, Emthexate, Farmitrexat, Folex, Hextrate, Imeth, Injexate, Lantarel, Ledertrexate, Leulin, Maxtrex, Medsatrexate, Metex, Methoblastin, Methofill, Methotrexamed, Methotrexate, Methotrexate Sodium, Methrexx, Metoart, Metoject, Metotab, Metrexato, Mexate, MTX, Nordimet, Novaplus, Methotrexate, Otaxem, Quinux, Ratio-Methotrexate, Rheumatrex, Trexall, Trexject, Zexate, Zlatal, Aldesta, Alltrex, Bendatrexat, Ebetrexat, Emthexate, Fauldexato, Fauldmetro, Folex Preservative Free, Hytas, Ifamet, Injexate, Jylamvo, Ledertrexate, Ledertrexate, Ledertrexato, Lexato, Lumexon, Matrex, Maxtrex, Meisusheng, Meksratu, Methaccord, Methacor, Methobax, Methobion, Methoblastin, Methoblastin, Methofill, Methotrexate, Metojectpen, Metolate, Metrex, Metrotex, Mexate, Mexate-Aq, Mextu, Miantrex, Midu, MPL Methoxil, MTX, Namaxir, Neometho, Neotrexat, Nordimet, Novatrex, Onkomet, O-trexat, Otrexup, Pterin, Rasuvo, RediTrex, Reumaflex, Reutrexato, Rheumatrex, Rheu-Trex, Rhodamer, Sactiva, Sanotrexat, Securact, Tecnomet, Tevametho, Texate, Texorate, Tratoben, Traxacord, Tremetex, Trexall, Trexamette, Trexan, Trexate, Trexeron, Trexol, Trixilem, Unitrexate, Xaken, Xatmep, Zexate, Zexate

	vincristine	Alcavixin, Biocrist, Cellcristin, Citomid, Crivosin, Farmistin, Faulcris, Fauldvincri, Nevexitin, Norcristine, Novaplus vinCRIStine Sulfate, Oncocristin, Oncovin, Onkocristin, Pericristine, Rasteo, Tecnocris, VCS, Vinblax, Vincasar, Vincizina, Vincrin, Vincrisin, Vincristex, vinCRIStine Sulfate, Vincrisul, Vinracine, Vinracine, Vinracine, Vinsulgen, Vintec
	vinorelbine	Ai Ke Ning, Bagovir, Bendarelbin, Biovelbin, Carcyt, Eberelbin, Eunades, Gai Nuo, Jie Bin, Kang Neng, LeWei, Min Nuo Bin, Navelbine, Navildez, Navin, Navirel, Neocitec, Nibrevin, Norelbin, Oncobine, Rui Ze, Sui Bin, Tai Bin, Velbimeda, Vieby, Viessia, Vincanorel, Vinelbine, Vinilex, Vinorelbine, Vinorel, Vinorkal, Vinotel, Zaolin
	docetaxel	Ai Su, Ao Ming Run, Aritaxel, Asodoc, Bendadocel, Brexel, Camitotic, Camitotic, Cetadocure, Cetadocure, Daxotel, Demotaxel, Dincilezan, Docefim, Docefim, Docefrez, Docelibbs, Docetactin, DOCEtaxel, Docetax, Docetaxin, Docetere, Doceter, Docetu, Docexel, Docexus, Doci, Docirena, Docirena, Docirena, Dodetax, Dostradixinol, Dotaxel, Doxecal, Doxel, Doxen, Doxestad, Doxetasan, Doxitax, Ducesol, Duo Pa Fei, Ebedoce, Edoxel, Hentaxel, Kamdocon, Lexadoz, Newtaxel-A, Oncodocel, Oncotaxel, Onkotaxel, Qvidadotax, Ribodocel, Ruilibo, Santax, Si Qu Di, Soulaxin, Taceedo, Tadocel, Taxanit, Taxceus, Taxegis, Taxespira, Taxotere, Taxotere, Taxovina, Tevadocel, Tolnexa, Trixotene, Tynen, Vexdo, Xi Cun, Yi You Rui, Kang, Zakotax
	idarubicin	Ai Nuo Ning, Geppi, Idamen, Idamycin, Idaralem, Idarub, IDArubicin HCl, Novaplus, Ondarubin, Zacorist, Zadoss, Zavedos,
	cyclophosphamide	Alkyloxan, Amerinet Choice Cyclophosphamide, Biodoxan, Carloxan, Ciclodrax, Ciclosmida, Cicloxal, Cryofaxol, Cyclan, Cycloblastin, Cycloblastine, Cyclo-cell, Cyclolest, Cyclonex, Cyclophosphamide, Cyclostin, Cyclovid, Cycram, Cyphos, Cytophosphan, Cytoxan, Demacylan, Endoxana, Endoxana, Endoxan, Enduxan, Evociclo, Formitex, Fosfaseron, Fossabra, Genoxal, Genuxal, Hidrofosmin, Ledoxan, Ledoxina, Neosar, NovaPlus Cyclophosphamide, Procytox, Sendoxan, Xyclomed
	ifosfamide	Alquimid, Crifty, Evolox, Famifoda, Fosfa, Fosfidex, Haloxan, Ifadex, Ifex, IFO-cell, Ifolem, Ifosfamide, Ifos, Ifoxan, Iphox, Isoxan, Macdafen, Mitoxana, Mitoxana, Pi Fu Ping, Seromida, Seromida, Tronoxal, Ifex/Mesnex, Ifosfamide And Mesna

	lomustine	Belustine, Ccnu, Cecenu, CeeNU, CiNU, Citostal, Gleostine, Lomeblastin, Lucostine, Lucostin, Prava
	irinotecan	Actatecan, Ai Li, Asinib, Axinotecan, Biotecan, Biotecan, Brofugal, Campteril, Campto, Camptolem, Camptomeda, Camptosar, Canri, Cetomedica, Daritex A, Elinatecan, Faultenocan, Ican, Iraplax, Irenax, Iricam, Irican, Irinkan, Irinocam, Irinocan, Irinoccord, Irinocol, Irino, Irinokabi, Irinolibbs, Irinoliquid, Irinoll, Irinomedac, Irinomed, Irinosin, Irinosor, Irinosyn, Irinotel, Irinotesin, Irinoxin, Iritec, Irkan, Irnocam, Irnocam, Irontu, Iroten, Itoxaril, Jovadolin, Linatecan, Mizantrone, Narimed, Nevotecam, Novaplus Camptosar, Riboirino, Riemid, Romisan, Santacil, Tecan, Tecnotecan, Tekamen, Tekazol, Terican, Topotecin, Vintecan, Xavetta, Zotecan
	etoposide	Abiposid, Bo Rui, Cavep, Cehaposid, Celltop, Cryosid, Dom-Etoposide, Ebeposide, Entaplen, Eposid, Eposin, Epsidox, Etobion, Eto-cell, ETO CS, Eto-Gry, Etomedac, Etomorase, Etonco, Etonolver, Etopex, Etopos, Etopoxan, Etopul, Etosid, Etosin, Eunades, Evoposdo, Exitop, Fytosid, Kenazol, Lastet, , MPL Toposid, Neoposid, Onkoposid, Pesidet, Pms-Etoposide, Posid, Posidon, Posyd, Riboposid, Sedol, Seroposide, Sintopozid, Tevaetopo, Topo, Toposar, Toposin, Topresid, Topside, Tosuben, Vepesid, VP-Tec, Wei Ke, Etopophos, Nexvep
Immune-modulating agents	cyclosporine	Atopica, Gengraf, Cequa, Neoral, Restasis, Sandimmun, SandIMMUNE, Sangcya, Verkazia
	sirolimus	Cypher, P-Hysplan, Rapalimus, Rapamune, Renacept, Rui Pa Ming, Saimosi, Sirotan, Yixinke
	temsirolimus	Torisel
	tacrolimus	Adoport, Adport, Advagraf, Capexion, Carefinast, Cellmune, Cidimus, Conferoport, Crilomus, Cromidin , Dailiport, Dermitopic, Envarsus, Framebin, Gecrol, Graceptor, Imugraft, Insupres, Lecron, Limustin, Lytomi-C , Modigraf, Octralin, Oligma, Pacrolim, Panolimus, Perixis, Pesodon, Proalid, Prograf, Prograft, Prolimus, Protopic, Protopy, Remus, Rocimus, Tacforius, Tacni, Tacpan, Tacrocel, Tacro-cell, Tacrocin, Tacrocor, Tacro, Tacrofort , Tacrograf, Tacrolin, Tacromax, Tacrotec, Tacrotu, Tacroz, Tacrum, Tagraf, Takrozem, , Taliximun, Tarfic, Tarograf, Tartrime, Teinmun, T-Inmun, Topiclin, Traderma, Transgraf, Vingraf, Hecoria
	dexamethasone	
CYP3A4/P-gp inducers	dabrafenib	Tafinlar
	encorafenib	Braftovi

	paclitaxel	Aclipak, Aclixel, Acoexcel, Anzatax, Apealea, Asotax, Ataxil, Axitaxel, Bendatax, Biolyse, Biopaxel, Biotax, Brevitax, BrisTaxol, Britaxol, Cantaxel, Cantaxel, Cedol, celltaxel, Clipax, Clitaxel, Cryoxet, Daburex, Ebetaxel, Ebexel, Egilitax, Eucol, Evotaxel, Formoxol, Genetaxyl, Genexol, Ifaxol, Inoxel, Intaxel, Letpar, Lexatax, Magytax, Medaxol, Medixel, Mitotax, Nanoxel, Napro-Tax, NeoTaxan, Nov-Onxol, Ofoxel, Oncoplaxel, Oncotaxel, Oncotaxen, OncoTax, Ontax, Onxel, Onxol, Ovapac, Pacliavenir, Paclib, Pacliccord, Pacligen, Paclihope, Paclikal, Paclimedac, Paclimeiz, Pacli MPL, Pacline, Pacli-One, Paclired, Paclisan, Paclistad, Paclitaxin, Paclitera, Paclitero, Paclit, Paclitol, Paclixel, Paclizel, Pactal, Paklitaxfil, Palat, Palitax, Pantium, Parexel, Pataxel, Paxel, Paxene, Paxital, Paxoll, Paxomed, Paxus, Placlitaxel, Plaxel, Poltaxel, Praxel, Ribotal, Ribotax, Santotaxel, Sindaxel, Tacli, Taclipaxol, Taclix, Taksen, Tarvexol, Taxilan, Taxobine, Taxocris, Taxodiol, Taxogen, Taxol, Taxomedac, Taxomeda, Taxoprol, Te Su, Tevapacli, Unitaxel, Vexel, Vitax, Xenius, Yewtaxan
	prednisolone	

Table S2. Preferred Terms (PTs) for identification of bleeding/hemorrhage events from MedDRA (main analysis)

PT
ABDOMINAL WALL HAEMORRHAGE
ABNORMAL UTERINE BLEEDING
ABNORMAL WITHDRAWAL BLEEDING
ABORTION COMPLETE COMPLICATED
ABORTION COMPLICATED
ABORTION INCOMPLETE COMPLICATED
ABORTION INDUCED COMPLETE COMPLICATED
ABORTION INDUCED COMPLICATED
ABORTION INDUCED INCOMPLETE COMPLICATED
ABORTION SPONTANEOUS COMPLETE COMPLICATED
ABORTION SPONTANEOUS COMPLICATED
ABORTION SPONTANEOUS INCOMPLETE COMPLICATED
ACUTE HAEMORRHAGIC CONJUNCTIVITIS
ACUTE HAEMORRHAGIC LEUKOENCEPHALITIS
ACUTE HAEMORRHAGIC OEDEMA OF INFANCY
ACUTE HAEMORRHAGIC ULCERATIVE COLITIS
ADENOVIRAL HAEMORRHAGIC CYSTITIS
ADMINISTRATION SITE HAEMORRHAGE
ADRENAL HAEMORRHAGE
AMYLOID RELATED IMAGING ABNORMALITY-MICROHAEMORRHAGES AND HAEMOSIDERIN DEPOSITS
ANAL FISSURE HAEMORRHAGE
ANAL HAEMORRHAGE
ANAL ULCER HAEMORRHAGE
ANASTOMOTIC HAEMORRHAGE
ANASTOMOTIC ULCER
ANASTOMOTIC ULCER HAEMORRHAGE
ANASTOMOTIC ULCER PERFORATION
ANASTOMOTIC ULCER, OBSTRUCTIVE
ANGINA BULLOSA HAEMORRHAGICA
ANORECTAL VARICES HAEMORRHAGE
AORTIC ANEURYSM RUPTURE
APLASTIC ANAEMIA
APPLICATION SITE HAEMORRHAGE
ARENAVIRAL HAEMORRHAGIC FEVER
ARGENTINE HAEMORRHAGIC FEVER
ARTERIAL HAEMORRHAGE
ARTERIOVENOUS FISTULA SITE HAEMORRHAGE
ARTERIOVENOUS GRAFT SITE HAEMORRHAGE
BASAL GANGLIA HAEMORRHAGE

BLEEDING ANOVULATORY
BLEEDING TIME
BLEEDING TIME ABNORMAL
BLEEDING TIME NORMAL
BLEEDING TIME PROLONGED
BLEEDING TIME SHORTENED
BLEEDING VARICOSE VEIN
BLOOD LOSS ANAEMIA
BOLIVIAN HAEMORRHAGIC FEVER
BONE MARROW HAEMORRHAGE
BRAIN STEM HAEMORRHAGE
BRAIN STEM MICROHAEMORRHAGE
BREAST HAEMORRHAGE
BRONCHIAL HAEMORRHAGE
BRONCHIAL VARICES HAEMORRHAGE
BUBONIC PLAGUE
BULLOUS ERYSIPELAS
BULLOUS HAEMORRHAGIC DERMATOSIS
CATHETER SITE HAEMORRHAGE
CENTRAL NERVOUS SYSTEM HAEMORRHAGE
CEREBELLAR HAEMORRHAGE
CEREBELLAR MICROHAEMORRHAGE
CEREBRAL ARTERIOVENOUS MALFORMATION HAEMORRHAGIC
CEREBRAL CYST HAEMORRHAGE
CEREBRAL HAEMORRHAGE
CEREBRAL HAEMORRHAGE FOETAL
CEREBRAL HAEMORRHAGE NEONATAL
CEREBRAL MICROHAEMORRHAGE
CEREBROVASCULAR ARTERIOVENOUS MALFORMATION
CERVICAL FRIABILITY
CERVIX HAEMORRHAGE UTERINE
CHOROIDAL DETACHMENT
CHOROIDAL HAEMORRHAGE
CHRONIC GASTRITIS
CHRONIC GASTROINTESTINAL BLEEDING
CILIARY BODY HAEMORRHAGE
COITAL BLEEDING
CONGO-CRIMEAN HAEMORRHAGIC FEVER
CONJUNCTIVAL HAEMORRHAGE
CORNEAL BLEEDING
CYSTITIS HAEMORRHAGIC
DENGUE HAEMORRHAGIC FEVER
DIARRHOEA HAEMORRHAGIC

DISSEMINATED INTRAVASCULAR COAGULATION
DIVERTICULITIS
DIVERTICULITIS INTESTINAL HAEMORRHAGIC
DIVERTICULUM INTESTINAL
DIVERTICULUM INTESTINAL HAEMORRHAGIC
DUODENAL ULCER
DUODENAL ULCER HAEMORRHAGE
DUODENAL ULCER PERFORATION
DUODENAL ULCER, OBSTRUCTIVE
DUODENITIS
DUODENITIS HAEMORRHAGIC
EAR HAEMORRHAGE
EBOLA DISEASE
ENCEPHALITIS HAEMORRHAGIC
ENTEROCOLITIS HAEMORRHAGIC
EPIDURAL HAEMORRHAGE
EPISTAXIS
ESSENTIAL THROMBOCYTHAEMIA
EXTRA-AXIAL HAEMORRHAGE
EXTRAVASATION BLOOD
EYE HAEMORRHAGE
EYELID BLEEDING
FOETAL-MATERNAL HAEMORRHAGE
GANGRENE
GASTRIC HAEMORRHAGE
GASTRIC MUCOSAL HYPERTROPHY
GASTRIC ULCER
GASTRIC ULCER HAEMORRHAGE
GASTRIC ULCER HAEMORRHAGE, OBSTRUCTIVE
GASTRIC ULCER PERFORATION
GASTRIC ULCER, OBSTRUCTIVE
GASTRIC VARICES HAEMORRHAGE
GASTRITIS
GASTRITIS ALCOHOLIC
GASTRITIS ALCOHOLIC HAEMORRHAGIC
GASTRITIS HAEMORRHAGIC
GASTRODUODENAL HAEMORRHAGE
GASTROENTERITIS ESCHERICHIA COLI
GASTROINTESTINAL ANASTOMOTIC HAEMORRHAGE
GASTROINTESTINAL ANGIODYSPLASIA
GASTROINTESTINAL HAEMORRHAGE
GASTROINTESTINAL POLYP HAEMORRHAGE
GASTROINTESTINAL ULCER HAEMORRHAGE

GASTROINTESTINAL VASCULAR MALFORMATION HAEMORRHAGIC
GASTROOESOPHAGEAL VARICEAL HAEMORRHAGE PROPHYLAXIS
GENITAL HAEMORRHAGE
GINGIVAL BLEEDING
GRAFT HAEMORRHAGE
HAEMARTHROSIS
HAEMATOSALPINX
HAEMATOTYMPANUM
HAEMATURIA
HAEMOBILIA
HAEMOPERITONEUM
HAEMORRHAGE
HAEMORRHAGE CORONARY ARTERY
HAEMORRHAGE FOETAL
HAEMORRHAGE IN PREGNANCY
HAEMORRHAGE INTRACRANIAL
HAEMORRHAGE NEONATAL
HAEMORRHAGE PROPHYLAXIS
HAEMORRHAGE SUBCUTANEOUS
HAEMORRHAGE SUBEPIDERMAL
HAEMORRHAGE URINARY TRACT
HAEMORRHAGIC ADRENAL INFARCTION
HAEMORRHAGIC ARTERIOVENOUS MALFORMATION
HAEMORRHAGIC ASCITES
HAEMORRHAGIC BREAST CYST
HAEMORRHAGIC CEREBELLAR INFARCTION
HAEMORRHAGIC CEREBRAL INFARCTION
HAEMORRHAGIC CHOLECYSTITIS
HAEMORRHAGIC CYST
HAEMORRHAGIC DIATHESIS
HAEMORRHAGIC DISEASE OF NEWBORN
HAEMORRHAGIC DISORDER
HAEMORRHAGIC EROSIVE GASTRITIS
HAEMORRHAGIC FEVER
HAEMORRHAGIC FEVER WITH RENAL SYNDROME
HAEMORRHAGIC GASTROENTERITIS
HAEMORRHAGIC HEPATIC CYST
HAEMORRHAGIC INFARCTION
HAEMORRHAGIC NECROTIC PANCREATITIS
HAEMORRHAGIC OCCLUSIVE RETINAL VASCULITIS
HAEMORRHAGIC OVARIAN CYST
HAEMORRHAGIC PNEUMONIA
HAEMORRHAGIC STROKE

HAEMORRHAGIC THYROID CYST
HAEMORRHAGIC TRANSFORMATION STROKE
HAEMORRHAGIC TUMOUR NECROSIS
HAEMORRHAGIC URTICARIA
HAEMORRHAGIC VARICELLA SYNDROME
HAEMORRHAGIC VASCULITIS
HAEMORRHOIDAL HAEMORRHAGE
HAEMOSTASIS
HAEMOTHORAX
HEAVY MENSTRUAL BLEEDING
HEPATIC ARTERY HAEMORRHAGE
HEPATIC HAEMORRHAGE
HEREDITARY HAEMORRHAGIC TELANGIECTASIA
HYPHAEMA
HYPOMENORRHOEA
IMPLANT SITE HAEMORRHAGE
INCISION SITE HAEMORRHAGE
INDUCED ABORTION FAILED
INDUCED ABORTION HAEMORRHAGE
INFUSION SITE HAEMORRHAGE
INJECTION SITE HAEMORRHAGE
INSTILLATION SITE HAEMORRHAGE
INTERMENSTRUAL BLEEDING
INTERNAL HAEMORRHAGE
INTESTINAL HAEMORRHAGE
INTESTINAL VARICES HAEMORRHAGE
INTRA-ABDOMINAL HAEMORRHAGE
INTRACRANIAL HAEMORRHAGE NEONATAL
INTRACRANIAL TUMOUR HAEMORRHAGE
INTRAPARTUM HAEMORRHAGE
INTRAVENTRICULAR HAEMORRHAGE
INTRAVENTRICULAR HAEMORRHAGE NEONATAL
IRIS HAEMORRHAGE
ISCHAEMIC STROKE
JOINT MICROHAEMORRHAGE
JUGULAR VEIN HAEMORRHAGE
KAPOSI'S SARCOMA
KAPOSI'S SARCOMA AIDS RELATED
KAPOSI'S SARCOMA CLASSICAL TYPE
LACRIMAL HAEMORRHAGE
LARGE INTESTINAL HAEMORRHAGE
LARGE INTESTINAL ULCER HAEMORRHAGE
LARYNGEAL HAEMORRHAGE

LIP HAEMORRHAGE
LOWER GASTROINTESTINAL HAEMORRHAGE
LUJO HAEMORRHAGIC FEVER
LYMPH NODE HAEMORRHAGE
MALLORY-WEISS SYNDROME
MARBURG DISEASE
MEDIASTINAL HAEMORRHAGE
MEDICAL DEVICE SITE HAEMORRHAGE
MENINGORRHAGIA
MENOMETRORRHAGIA
MENSTRUAL DISORDER
MESENTERIC HAEMORRHAGE
MOUTH HAEMORRHAGE
MUCOCUTANEOUS HAEMORRHAGE
MUCOSAL HAEMORRHAGE
MUSCLE HAEMORRHAGE
MYOCARDIAL HAEMORRHAGE
NAEVUS HAEMORRHAGE
NAIL BED BLEEDING
NEONATAL GASTROINTESTINAL HAEMORRHAGE
NEPHRITIS HAEMORRHAGIC
OCCULT BLOOD POSITIVE
OCULAR RETROBULBAR HAEMORRHAGE
OESOPHAGEAL HAEMORRHAGE
OESOPHAGEAL ULCER HAEMORRHAGE
OESOPHAGEAL VARICES HAEMORRHAGE
OESOPHAGITIS HAEMORRHAGIC
OMENTAL HAEMORRHAGE
OMSK HAEMORRHAGIC FEVER
OPTIC DISC HAEMORRHAGE
OPTIC NERVE SHEATH HAEMORRHAGE
ORBITAL HAEMORRHAGE
OSTEORRHAGIA
OVARIAN HAEMORRHAGE
PANCREATIC HAEMORRHAGE
PANCREATIC PSEUDOCYST HAEMORRHAGE
PANCREATITIS HAEMORRHAGIC
PAPILLARY MUSCLE HAEMORRHAGE
PARANASAL SINUS HAEMORRHAGE
PARATHYROID HAEMORRHAGE
PAROTID GLAND HAEMORRHAGE
PELVIC HAEMORRHAGE
PENILE HAEMORRHAGE

PEPTIC ULCER
PEPTIC ULCER HAEMORRHAGE
PEPTIC ULCER PERFORATION
PEPTIC ULCER, OBSTRUCTIVE
PERICARDIAL HAEMORRHAGE
PERIORBITAL HAEMORRHAGE
PERIPARTUM HAEMORRHAGE
PERIPHERAL EXUDATIVE HAEMORRHAGIC CHORIORETINOPATHY
PERIVENTRICULAR HAEMORRHAGE NEONATAL
PETECHIAE
PHARYNGEAL HAEMORRHAGE
PITUITARY HAEMORRHAGE
PLACENTA PRAEVIA
PLACENTA PRAEVIA HAEMORRHAGE
POLYMYOSITIS
POST ABORTION HAEMORRHAGE
POST PROCEDURAL HAEMORRHAGE
POSTHAEMORRHAGIC HYDROCEPHALUS
POSTMENOPAUSAL HAEMORRHAGE
POSTPARTUM HAEMORRHAGE
POST-TRAUMATIC PUNCTATE INTRAEPIDERMAL HAEMORRHAGE
PROCEDURAL HAEMORRHAGE
PROCTITIS HAEMORRHAGIC
PROSTATIC HAEMORRHAGE
PULMONARY ALVEOLAR HAEMORRHAGE
PULMONARY HAEMORRHAGE
PULMONARY HAEMORRHAGE NEONATAL
PUNCTURE SITE HAEMORRHAGE
PURPURA
PUTAMEN HAEMORRHAGE
RADIATION ASSOCIATED HAEMORRHAGE
RECTAL HAEMORRHAGE
RECTAL ULCER HAEMORRHAGE
RENAL CYST HAEMORRHAGE
RENAL HAEMORRHAGE
RESPIRATORY TRACT HAEMORRHAGE
RESPIRATORY TRACT HAEMORRHAGE NEONATAL
RETAINED PLACENTA OR MEMBRANES
RETINAL HAEMORRHAGE
RETINOPATHY HAEMORRHAGIC
RETROPERITONEAL HAEMORRHAGE
RUPTURED CEREBRAL ANEURYSM
SCLERAL HAEMORRHAGE

SCROTAL HAEMORRHAGE
SHOCK HAEMORRHAGIC
SKIN HAEMORRHAGE
SKIN NEOPLASM BLEEDING
SKIN ULCER HAEMORRHAGE
SKULL FRACTURE
SKULL FRACTURED BASE
SMALL INTESTINAL HAEMORRHAGE
SMALL INTESTINAL ULCER HAEMORRHAGE
SOFT TISSUE HAEMORRHAGE
SPERMATIC CORD HAEMORRHAGE
SPINAL CORD HAEMORRHAGE
SPINAL EPIDURAL HAEMORRHAGE
SPINAL SUBARACHNOID HAEMORRHAGE
SPINAL SUBDURAL HAEMORRHAGE
SPLENIC HAEMORRHAGE
SPLENIC VARICES HAEMORRHAGE
SPLINTER HAEMORRHAGES
SPONTANEOUS HAEMORRHAGE
STOMA SITE HAEMORRHAGE
STOMATITIS HAEMORRHAGIC
STRESS ULCER HAEMORRHAGE
SUBARACHNOID HAEMORRHAGE
SUBARACHNOID HAEMORRHAGE NEONATAL
SUBCHORIONIC HAEMORRHAGE
SUBDURAL HAEMORRHAGE
SUBDURAL HAEMORRHAGE NEONATAL
SUBENDOCARDIAL HAEMORRHAGE
SUBGALEAL HAEMORRHAGE
TESTICULAR HAEMORRHAGE
THALAMUS HAEMORRHAGE
THIRD STAGE POSTPARTUM HAEMORRHAGE
THORACIC HAEMORRHAGE
THYROID HAEMORRHAGE
THYROID INFARCTION
TONGUE HAEMORRHAGE
TONSILLAR HAEMORRHAGE
TOOTH PULP HAEMORRHAGE
TOOTH SOCKET HAEMORRHAGE
TRACHEAL HAEMORRHAGE
TRAUMATIC HAEMORRHAGE
TRAUMATIC INTRACRANIAL HAEMORRHAGE
TUMOUR HAEMORRHAGE

ULCER HAEMORRHAGE
UMBILICAL CORD HAEMORRHAGE
UMBILICAL HAEMORRHAGE
UPPER GASTROINTESTINAL HAEMORRHAGE
URETERIC HAEMORRHAGE
URETHRAL HAEMORRHAGE
URINARY BLADDER HAEMORRHAGE
UROGENITAL HAEMORRHAGE
UTERINE HAEMORRHAGE
VACCINATION SITE HAEMORRHAGE
VAGINAL HAEMORRHAGE
VARICELLA ZOSTER PNEUMONIA
VARICES OESOPHAGEAL
VASCULAR ACCESS SITE HAEMORRHAGE
VASCULAR ANASTOMOTIC HAEMORRHAGE
VASCULAR GRAFT HAEMORRHAGE
VASCULAR PSEUDOANEURYSM RUPTURED
VENOUS HAEMORRHAGE
VESSEL PUNCTURE SITE HAEMORRHAGE
VIRAL HAEMORRHAGIC CYSTITIS
VITREOUS HAEMORRHAGE
VULVAL HAEMORRHAGE
WEIL'S DISEASE
WITHDRAWAL BLEED
WOUND HAEMORRHAGE

Table S3. Preferred Terms (PTs) for identification of stroke/cerebrovascular events from MedDRA (main analysis)

PT
CEREBROVASCULAR ACCIDENT
BASAL GANGLIA STROKE
BRAIN STEM STROKE
EMBOLIC STROKE
CENTRAL PAIN SYNDROME
CEREBELLAR STROKE
CHA2DS2-VASC ANNUAL STROKE RISK HIGH
CHA2DS2-VASC ANNUAL STROKE RISK LOW
CHA2DS2-VASC ANNUAL STROKE RISK MODERATE
HAEMORRHAGIC TRANSFORMATION STROKE
HAEMORRHAGIC STROKE
HEAT STROKE
ISCHAEMIC STROKE
LACUNAR STROKE
METABOLIC STROKE
TRANSIENT ISCHAEMIC ATTACK
MELAS SYNDROME
NIH STROKE SCALE
NIH STROKE SCALE ABNORMAL
NIH STROKE SCALE SCORE DECREASED
NIH STROKE SCALE SCORE INCREASED
STROKE VOLUME NORMAL
PERINATAL STROKE
POST PROCEDURAL STROKE
POST STROKE DEPRESSION
POST STROKE EPILEPSY
POST STROKE SEIZURE
PRECEREBRAL ARTERY OCCLUSION
PSEUDOSTROKE
SCANDINAVIAN STROKE SCALE
SPINAL STROKE
STROKE IN EVOLUTION
STROKE VOLUME
STROKE VOLUME DECREASED
STROKE VOLUME INCREASED
STROKECTOMY
STROKE-LIKE MIGRAINE ATTACKS AFTER RADIATION THERAPY
THROMBOTIC STROKE

VERTEBROBASILAR STROKE
CEREBROVASCULAR ACCIDENT PROPHYLAXIS

Table S4. Preferred Terms (PTs) for identification of bleeding/hemorrhage events from MedDRA screened by clinician (sensitivity analysis 2)

PT
ABDOMINAL WALL HAEMORRHAGE
ANAL HAEMORRHAGE
ARTERIAL HAEMORRHAGE
BASAL GANGLIA HAEMORRHAGE
BLOOD LOSS ANAEMIA
BRAIN STEM HAEMORRHAGE
BRAIN STEM MICROHAEMORRHAGE
BRONCHIAL HAEMORRHAGE
BULLOUS HAEMORRHAGIC DERMATOSIS
CENTRAL NERVOUS SYSTEM HAEMORRHAGE
CEREBELLAR HAEMORRHAGE
CEREBELLAR MICROHAEMORRHAGE
CEREBRAL HAEMORRHAGE
CEREBRAL MICROHAEMORRHAGE
CONJUNCTIVAL HAEMORRHAGE
CORNEAL BLEEDING
DUODENAL ULCER HAEMORRHAGE
EAR HAEMORRHAGE
EPISTAXIS
EXTRA-AXIAL HAEMORRHAGE
EYE HAEMORRHAGE
GASTRIC HAEMORRHAGE
GASTRIC ULCER HAEMORRHAGE
GASTRITIS HAEMORRHAGIC
GASTRODUODENAL HAEMORRHAGE
GASTROINTESTINAL HAEMORRHAGE
GASTROINTESTINAL ULCER HAEMORRHAGE
GINGIVAL BLEEDING
HAEMARTHROSIS
HAEMATURIA
HAEMOPERITONEUM
HAEMORRHAGE
HAEMORRHAGE INTRACRANIAL
HAEMORRHAGE SUBEPIDERMAL
HAEMORRHAGE URINARY TRACT
HAEMORRHAGIC CEREBELLAR INFARCTION
HAEMORRHAGIC CEREBRAL INFARCTION
HAEMORRHAGIC STROKE
HAEMORRHAGIC URTICARIA

HAEMORRHOIDAL HAEMORRHAGE
HAEMOTHORAX
HEAVY MENSTRUAL BLEEDING
HYPHAEMA
INTERNAL HAEMORRHAGE
INTESTINAL HAEMORRHAGE
INTRA-ABDOMINAL HAEMORRHAGE
IRIS HAEMORRHAGE
JOINT MICROHAEMORRHAGE
LARGE INTESTINAL HAEMORRHAGE
LARGE INTESTINAL ULCER HAEMORRHAGE
LOWER GASTROINTESTINAL HAEMORRHAGE
MEDIASTINAL HAEMORRHAGE
MENINGORRHAGIA
MUCOCUTANEOUS HAEMORRHAGE
MUCOSAL HAEMORRHAGE
OCCULT BLOOD POSITIVE
OCULAR RETROBULBAR HAEMORRHAGE
ORBITAL HAEMORRHAGE
OSTEORRHAGIA
PEPTIC ULCER HAEMORRHAGE
PERIORBITAL HAEMORRHAGE
PETECHIAE
PULMONARY ALVEOLAR HAEMORRHAGE
PULMONARY HAEMORRHAGE
PURPURA
RECTAL HAEMORRHAGE
RECTAL ULCER HAEMORRHAGE
RENAL HAEMORRHAGE
RESPIRATORY TRACT HAEMORRHAGE
RETINAL HAEMORRHAGE
RETROPERITONEAL HAEMORRHAGE
SCLERAL HAEMORRHAGE
SKIN HAEMORRHAGE
SMALL INTESTINAL HAEMORRHAGE
SMALL INTESTINAL ULCER HAEMORRHAGE
SOFT TISSUE HAEMORRHAGE
SPINAL CORD HAEMORRHAGE
SPINAL SUBARACHNOID HAEMORRHAGE
SPINAL SUBDURAL HAEMORRHAGE
SPLENIC HAEMORRHAGE
SPONTANEOUS HAEMORRHAGE
SUBARACHNOID HAEMORRHAGE

SUBDURAL HAEMORRHAGE
THORACIC HAEMORRHAGE
UPPER GASTROINTESTINAL HAEMORRHAGE
URETHRAL HAEMORRHAGE
URINARY BLADDER HAEMORRHAGE
UROGENITAL HAEMORRHAGE
VENOUS HAEMORRHAGE
VITREOUS HAEMORRHAGE

Table S5. Preferred Terms (PTs) for identification of stroke/cerebrovascular events from MedDRA screened by clinician (sensitivity analysis 2)

PT
CEREBROVASCULAR ACCIDENT
BRAIN STEM STROKE
EMBOLIC STROKE
CEREBELLAR STROKE
HAEMORRHAGIC TRANSFORMATION STROKE
ISCHAEMIC STROKE
TRANSIENT ISCHAEMIC ATTACK
THROMBOTIC STROKE

Table S6. Number of reports with combination DOAC-antineoplastic agents with CYP3A4/P-gp inhibitory activity by therapeutic class and by individual drugs (antineoplastic drugs and DOAC) in FDA Adverse Event Reporting System (FAERS) database from 2004-2021

Combination	**DOACs**	**dabigatran**	**apixaban**	**rivaroxaban**	**edoxaban**
TKIs	7006	443	3351	2925	344
imatinib	327	46	136	132	21
dasatinib	276	19	143	102	12
nilotinib	225	37	74	117	5
lapatinib	102	5	13	41	43
erlotinib	422	43	148	227	9
crizotinib	243	11	98	118	17
tivozanib	60	0	44	16	0
pazopanib	335	37	140	155	4
axitinib	284	6	193	84	3
brigatinib	61	0	30	27	4
ceritinib	42	1	12	29	0
lorlatinib	77	3	40	25	9
binimetinib	170	2	94	55	19
trametinib	272	21	114	114	23
palbociclib	1333	36	717	576	19
ribociclib	221	4	119	73	27
entrectinib	19	1	11	7	0
larotrectinib	5	0	2	3	0
idelalisib	194	18	83	83	12
sunitinib	393	41	167	176	11
vandetanib	8	2	2	7	0
osimertinib	305	8	150	106	45
alectinib	143	0	93	43	7
neratinib	87	0	14	73	0
cabozantinib	830	33	459	310	30
capmatinib	16	0	13	3	0
sorafenib	121	11	45	64	2
regorafenib	179	11	79	83	6
ponatinib	198	9	111	68	16
vemurafenib	138	30	55	53	2

cobimetinib	144	26	64	50	6
abemaciclib	100	0	65	22	13
pemigatinib	3	0	2	1	0
gefitinib	61	11	25	20	7
afatinib	114	6	55	49	4
hormone	4728	537	2146	1929	165
letrozole	1433	86	627	682	53
anastrozole	836	131	341	352	21
abiraterone	628	54	320	243	13
bicalutamide	605	86	261	230	36
tamoxifen	490	46	156	280	13
enzalutamide	1137	162	570	385	34
chemotherapy	8236	693	3498	3744	419
vinblastine	28	2	12	14	0
doxorubicin	739	43	267	394	41
methotrexate	5173	538	2273	2328	123
vincristine	563	21	225	281	41
vinorelbine	120	9	24	18	69
docetaxel	745	56	247	401	50
idarubicin	12	0	9	1	2
cyclophosphamide	1651	81	721	797	72
ifosfamide	43	3	16	27	0
lomustine	33	0	19	14	0
irinotecan	404	3	162	188	56
etoposide	305	8	140	97	64
IMAs	15475	923	7846	6465	458
cyclosporine	1184	183	551	461	17
sirolimus	233	12	161	61	3
temsirolimus	13	3	0	10	0
tacrolimus	1299	101	612	536	66
dexamethasone	12973	639	6671	5473	372

DOACs, Direct Oral Anticoagulants. KIs, kinase inhibitors. IMAs, immunomodulating agents.

Table S7. Number of reports with combination DOAC-antineoplastic agents with CYP3A4/P-gp inducing activity by therapeutic class and by individual drugs (antineoplastic drugs and DOAC) in FDA Adverse Event Reporting System (FAERS) database from 2004-2021

Combination	DOACs	dabigatran	apixaban	rivaroxaban	edoxaban
inducers	6311	665	2522	2587	635
dabrafenib	238	28	70	120	23
encorafenib	184	2	104	58	20
paclitaxel	1314	97	509	605	113
prednisolone	4642	539	1864	1823	501

DOACs, Direct Oral Anticoagulants

Table S8. Sensitivity analysis 1 of signal detection of drug-drug interactions between direct oral anticoagulants and antineoplastic agents in FDA Adverse Event Reporting System (FAERS) database from 2010-2021.

Combination	DPA ROR (95% CI) [a]	Logistic regression ROR (95% CI) [b]	MGPS EGBM (EB05, EB95)
DOACs-TKIs	0.30 (0.28-0.32)	0.25 (0.24-0.28)	1.02 (0.97-1.08)
DOACs-imatinib	0.66 (0.51-0.84)	0.51 (0.39-0.65)	1.89 (1.58-2.26)
DOACs-dasatinib	0.41 (0.30-0.55)	0.38 (0.28-0.52)	1.28 (1.01-1.62)
DOACs-nilotinib	0.34 (0.24-0.49)	0.25 (0.17-0.36)	1.11 (0.84-1.46)
DOACs-lapatinib	0.36 (0.21-0.61)	0.47 (0.27-0.81)	1.13 (0.76-1.65)
DOACs-erlotinib	0.31 (0.24-0.41)	0.31 (0.23-0.41)	1.05 (0.85-1.29)
DOACs-crizotinib	0.27 (0.19-0.40)	0.48 (0.32-0.71)	0.93 (0.69-1.22)
DOACs-tivozanib	--	--	0.35 (0.13-0.78)
DOACs-pazopanib	0.26 (0.19-0.36)	0.20 (0.15-0.29)	0.90 (0.70-1.15)
DOACs-axitinib	0.32 (0.23-0.45)	0.31 (0.22-0.44)	1.07 (0.83-1.37)
DOACs-brigatinib	0.14 (0.05-0.37)	0.17 (0.06-0.48)	0.59 (0.28-1.07)
DOACs-ceritinib	0.68 (0.34-1.36)	0.88 (0.42-1.83)	1.71 (1.02-2.74)
DOACs-lorlatinib	0.13 (0.05-0.33)	0.27 (0.10-0.70)	0.59 (0.29-1.00)
DOACs-binimetinib	0.16 (0.09-0.28)	0.16 (0.09-0.29)	0.62 (0.40-0.91)
DOACs-trametinib	0.34 (0.25-0.48)	0.29 (0.20-0.41)	1.12 (0.87-1.43)
DOACs-palbociclib	0.20 (0.17-0.24)	0.23 (0.19-0.27)	0.72 (0.62-0.83)
DOACs-ribociclib	0.26 (0.17-0.39)	0.25 (0.16-0.38)	0.89 (0.65-1.19)
DOACs-entrectinib	0.36 (0.11-1.24)	1.44 (0.33-6.35)	1.04 (0.49-2.15)
DOACs-larotrectinib	-	-	-
DOACs-idelalisib	0.09 (0.05-0.18)	0.11 (0.06-0.22)	0.40 (0.23-0.65)
DOACs-sunitinib	0.73 (0.59-0.91)	0.35 (0.28-0.44)	2.06 (1.75-2.24)
DOACs-vandetanib	--	--	1.13 (0.47-2.62)
DOACs-osimertinib	0.24 (0.17-0.35)	0.35 (0.24-0.51)	0.85 (0.65-1.10)
DOACs-alectinib	0.14 (0.07-0.28)	0.22 (0.11-0.43)	0.58 (0.35-0.89)
DOACs-neratinib	1.24 (0.80-1.90)	1.06 (0.65-1.72)	**2.75 (2.07-3.60)**
DOACs-cabozantinib	0.19 (0.15-0.24)	0.20 (0.16-0.26)	0.68 (0.56-0.81)
DOACs-capmatinib	-	-	-
DOACs-sorafenib	0.63 (0.42-0.96)	0.28 (0.18-0.42)	1.79 (1.30-2.39)
DOACs-regorafenib	0.28 (0.18-0.44)	0.17 (0.11-0.27)	0.96 (0.69-1.31)
DOACs-ponatinib	0.37 (0.25-0.54)	0.29 (0.20-0.43)	1.18 (0.88-1.57)

DOACs-vemurafenib	0.33 (0.20-0.52)	0.31 (0.19-0.51)	1.06 (0.74-1.49)
DOACs-cobimetinib	0.37 (0.23-0.57)	0.25 (0.16-0.40)	1.16 (0.82-1.60)
DOACs-abemaciclib	0.06 (0.02-0.19)	0.12 (0.04-0.39)	0.31 (0.13-0.65)
DOACs-pemigatinib	-	-	-
DOACs-gefitinib	0.33 (0.16-0.68)	0.27 (0.13-0.55)	1.05 (0.63-1.69)
DOACs-afatinib	0.72 (0.48-1.09)	0.51 (0.33-0.78)	1.96 (1.46-2.61)
DOACs-hormone	0.37 (0.34-0.40)	0.31 (0.29-0.34)	1.23 (1.15-1.30)
DOACs-letrozole	0.33 (0.29-0.38)	0.22 (0.19-0.25)	1.11 (0.99-1.25)
DOACs-anastrozole	0.50 (0.43-0.59)	0.38 (0.31-0.44)	1.56 (1.37-1.77)
DOACs-abiraterone	0.34 (0.27-0.42)	0.39 (0.31-0.49)	1.12 (0.95-1.32)
DOACs-bicalutamide	0.51 (0.42-0.62)	0.28 (0.23-0.35)	1.58 (1.36-1.82)
DOACs-tamoxifen	0.52 (0.42-0.64)	0.26 (0.21-0.33)	1.60 (1.35-1.87)
DOACs-enzalutamide	0.23 (0.19-0.28)	0.29 (0.24-0.36)	0.82 (0.71-0.95)
DOACs-chemotherapy	0.36 (0.34-0.39)	0.27 (0.25-0.28)	1.22 (1.16-1.27)
DOACs-vinblastine	-	-	-
DOACs-doxorubicin	0.22 (0.17-0.28)	0.18 (0.14-0.23)	0.79 (0.65-0.94)
DOACs-methotrexate	0.41 (0.39-0.45)	0.30 (0.28-0.33)	1.35 (1.28-1.41)
DOACs-vincristine	0.25 (0.19-0.33)	0.18 (0.14-0.23)	0.88 (0.72-1.06)
DOACs-vinorelbine	0.18 (0.09-0.33)	0.12 (0.06-0.23)	0.67 (0.41-1.03)
DOACs-docetaxel	0.39 (0.32-0.47)	0.36 (0.29-0.44)	1.25 (1.08-1.45)
DOACs-idarubicin	-	-	-
DOACs-cyclophosphamide	0.20 (0.17-0.24)	0.15 (0.13-0.18)	0.73 (0.63-0.82)
DOAC-ifosfamide	0.20 (0.07-0.55)	0.15 (0.05-0.41)	0.76 (0.38-1.38)
DOACs-lomustine	0.20 (0.06-0.63)	0.23 (0.07-0.78)	0.76 (0.35-1.46)
DOACs-irinotecan	0.50 (0.39-0.63)	0.28 (0.22-0.36)	1.53 (1.27-1.83)
DOACs-etoposide	0.16 (0.10-0.24)	0.10 (0.07-0.16)	0.60 (0.42-0.82)
DOACs-IMAs	0.18 (0.17-0.19)	0.14 (0.13-0.15)	0.66 (0.63-0.69)
DOACs-cyclosporine	0.46 (0.40-0.53)	0.31 (0.27-0.36)	1.43 (1.28-1.60)
DOACs-sirolimus	0.41 (0.29-0.58)	0.35 (0.25-0.49)	1.291 (1.00-1.66)
DOACs-temsirolimus	-	-	-
DOACs-tacrolimus	0.35 (0.30-0.41)	0.25 (0.21-0.29)	1.16 (1.03-1.31)
DOACs-dexamethasone	0.14 (0.13-0.15)	0.12 (0.11-0.13)	0.52 (0.50-0.56)
DOACs-inducers	0.36 (0.31-0.43)	0.68 (0.57-0.80)	1.05 (0.90-1.21)
DOACs-dabrafenib	0.58 (0.30-1.14)	0.82 (0.41-1.63)	1.50 (0.84-2.58)
DOACs-encorafenib	-	-	-

DOACs-paclitaxel	0.33 (0.23-0.48)	0.77 (0.53-1.12)	0.99 (0.72-1.34)
DOACs-prednisolone	0.37 (0.31-0.44)	0.64 (0.53-0.78)	1.04 (0.87-1.22)

In this analysis, we restricted the AE reports from October 19, 2010 (approval date of dabigatran – first DOAC).

DPA Disproportionality analysis. ROR, Reporting odds ratio. CI, Confidence Interval. MGPS, Multi-item Gamma Poisson Shrinker. EBGM, Empirical Bayes geometric mean. EB05, the lower bound of the 90% credible interval for the EBGM. EB95, the upper bound of the 90% credible interval for the EBGM. DOACs, Direct Oral Anticoagulants. TKIs, tyrosine kinase inhibitors. IMAs, immunomodulating agents.

[a]: ROR computed from a 2x2 table comparing the reporting rates of the event between the reports containing drug combination and reports with DOACs only

[b]: adjusted for age, sex, reporting country, and reporting year

--: ROR not computed (number of events <3)

-: ROR and EGBM not available (number of events = 0)

Table S9. Sensitivity analysis 2 of signal detection of drug-drug interactions between direct oral anticoagulants and antineoplastic agents in FDA Adverse Event Reporting System (FAERS) database from 2004-2021.

Combination	DPA ROR (95% CI) [a]	Logistic regression ROR (95% CI) [b]	MGPS EGBM (EB05, EB95)
DOACs-TKIs	0.28 (0.26-0.31)	0.20 (0.18-0.21)	1.04 (0.98-1.10)
DOACs-imatinib	0.77 (0.61-1.00)	0.46 (0.36-0.60)	2.31 (1.91-2.76)
DOACs-dasatinib	0.41 (0.29-0.57)	0.28 (0.20-0.39)	1.38 (1.06-1.77)
DOACs-nilotinib	0.27 (0.18-0.42)	0.18 (0.12-0.28)	0.98 (0.69-1.35)
DOACs-lapatinib	0.38 (0.22-0.67)	0.24 (0.18-0.33)	1.27 (0.82-1.89)
DOACs-erlotinib	0.33 (0.25-0.44)	0.28 (0.21-0.36)	1.16 (0.92-1.45)
DOACs-crizotinib	0.26 (0.17-0.40)	0.43 (0.28-0.67)	0.95 (0.68-1.31)
DOACs-tivozanib	--	--	0.42 (0.16-0.96)
DOACs-pazopanib	0.29 (0.20-0.41)	0.18 (0.13-0.26)	1.03 (0.78-1.34)
DOACs-axitinib	0.31 (0.21-0.44)	0.26 (0.18-0.38)	1.08 (0.81-1.43)
DOACs-brigatinib	0.17 (0.06-0.47)	0.17 (0.06-0.50)	0.67 (0.31-1.30)
DOACs-ceritinib	0.48 (0.21-1.08)	0.55 (0.23-1.31)	1.41 (0.77-2.40)
DOACs-lorlatinib	--	--	0.54 (0.31-0.87)
DOACs-binimetinib	0.13 (0.07-0.26)	0.13 (0.06-0.25)	0.60 (0.38-0.90)
DOACs-trametinib	0.28 (0.19-0.41)	0.19 (0.13-0.29)	0.99 (0.72-1.33)
DOACs-palbociclib	0.21 (0.16-0.25)	0.18 (0.14-0.22)	0.77 (0.65-0.90)
DOACs-ribociclib	0.25 (0.16-0.39)	0.21 (0.13-0.34)	0.92 (0.64-1.28)
DOACs-entrectinib	0.45 (0.13-1.55)	1.59 (0.32-7.83)	1.22 (0.52-2.51)
DOACs-larotrectinib	-	-	-
DOACs-idelalisib	0.06 (0.03-0.15)	0.07 (0.03-0.18)	0.29 (0.14-0.53)
DOACs-sunitinib	0.67 (0.53-0.86)	0.26 (0.20-0.33)	2.08 (1.74-2.47)
DOACs-vandetanib	--	--	1.26 (0.47-2.87)
DOACs-osimertinib	0.20 (0.13-0.30)	0.24 (0.16-0.38)	0.74 (0.52-1.01)
DOACs-alectinib	0.13 (0.06-0.26)	0.19 (0.09-0.42)	0.51 (0.28-0.87)
DOACs-neratinib	**1.54 (1.00-2.37)**	1.49 (0.89-2.51)	**3.36 (2.52-4.39)**
DOACs-cabozantinib	0.20 (0.15-0.26)	0.20 (0.16-0.26)	0.74 (0.60-0.90)
DOACs-capmatinib	-	-	-
DOACs-sorafenib	0.53 (0.34-0.84)	0.25 (0.16-0.40)	1.01 (0.69-1.44)
DOACs-regorafenib	0.29 (0.18-0.46)	0.15 (0.09-0.24)	0.97 (0.68-1.33)
DOACs-ponatinib	0.18 (0.11-0.32)	0.16 (0.09-0.27)	0.70 (0.45-1.04)

DOACs-vemurafenib	0.13 (0.06-0.27)	0.10 (0.05-0.22)	0.52 (0.29-0.90)
DOACs-cobimetinib	0.13 (0.06-0.26)	0.07 (0.03-0.14)	0.5 (0.28-0.86)
DOACs-abemaciclib	--	--	0.28 (0.10-0.62)
DOACs-pemigatinib	-	-	-
DOACs-gefitinib	0.21 (0.09-0.54)	0.14 (0.06-0.35)	0.80 (0.40-1.47)
DOACs-afatinib	0.58 (0.36-0.92)	0.31 (0.19-0.51)	1.75 (1.23-2.43)
DOACs-hormone	0.37 (0.34-0.40)	0.27 (0.24-0.29)	1.22 (1.07-1.37)
DOACs-letrozole	0.34 (0.29-0.40)	0.19 (0.16-0.23)	1.12 (1.00-1.25)
DOACs-anastrozole	0.56 (0.47-0.66)	0.42 (0.35-0.50)	1.81 (1.58-2.06)
DOACs-abiraterone	0.31 (0.24-0.39)	0.28 (0.21-0.36)	1.09 (0.90-1.32)
DOACs-bicalutamide	0.50 (0.40-0.62)	0.25 (0.20-0.31)	1.65 (1.40-1.93)
DOACs-tamoxifen	0.56 (0.43-0.71)	0.29 (0.23-0.37)	1.81 (1.53-2.14)
DOACs-enzalutamide	0.21 (0.17-0.26)	0.20 (0.16-0.25)	0.78 (0.65-0.92)
DOACs-chemotherapy	0.31 (0.30-0.34)	0.26 (0.24-0.28)	1.14 (1.08-1.21)
DOACs-vinblastine	-	-	-
DOACs-doxorubicin	0.08 (0.06-0.13)	0.07 (0.04-0.10)	0.34 (0.25-0.46)
DOACs-methotrexate	0.37 (0.34-0.40)	0.34 (0.31-0.37)	1.29 (1.21-1.37)
DOACs-vincristine	0.06 (0.03-0.10)	0.04 (0.02-0.07)	0.24 (0.15-0.37)
DOACs-vinorelbine	0.22 (0.11-0.42)	0.14 (0.07-0.28)	0.81 (0.48-1.29)
DOACs-docetaxel	0.36 (0.29-0.45)	0.32 (0.25-0.39)	1.26 (1.06-1.48)
DOACs-idarubicin	-	-	-
DOACs-cyclophosphamide	0.13 (0.11-0.17)	0.10 (0.08-0.12)	0.51 (0.43-0.61)
DOAC-ifosfamide	-	-	-
DOACs-lomustine	--	--	0.66 (0.25-1.50)
DOACs-irinotecan	0.53 (0.41-0.68)	0.27 (0.21-0.35)	1.72 (1.42-2.08)
DOACs-etoposide	0.06 (0.03-0.13)	0.04 (0.02-0.08)	0.28 (0.16-0.47)
DOACs-IMAs	0.16 (0.15-0.17)	0.12 (0.11-0.13)	0.64 (0.60-0.67)
DOACs-cyclosporine	0.45 (0.39-0.53)	0.31 (0.27-0.36)	1.53 (1.36-1.72)
DOACs-sirolimus	0.44 (0.31-0.63)	0.38 (0.26-0.54)	1.46 (1.10-1.90)
DOACs-temsirolimus	-	-	-
DOACs-tacrolimus	0.28 (0.23-0.34)	0.22 (0.19-0.27)	1.02 (0.88-1.16)
DOACs-dexamethasone	0.13 (0.12-0.14)	0.09 (0.08-0.10)	0.50 (0.47-0.53)
DOACs-inducers	0.39 (0.33-0.46)	0.74 (0.63-0.88)	1.05 (0.91-1.19)
DOACs-dabrafenib	0.66 (0.34-1.29)	1.01 (0.59-2.02)	1.52 (0.89-2.47)
DOACs-encorafenib	--	--	0.41 (0.13-1.06)

DOACs-paclitaxel	0.38 (0.26-0.55)	0.88 (0.60-1.28)	1.00 (0.73-1.34)
DOACs-prednisolone	0.39 (0.32-0.47)	0.69 (0.53-0.85)	1.04 (0.89-1.22)

In this analysis, we defined the outcomes of interest by clinicians' assessment.

DPA Disproportionality analysis. ROR, Reporting odds ratio. CI, Confidence Interval. MGPS, Multi-item Gamma Poisson Shrinker. EBGM, Empirical Bayes geometric mean. EB05, the lower bound of the 90% credible interval for the EBGM. EB95, the upper bound of the 90% credible interval for the EBGM. DOACs, Direct Oral Anticoagulants. TKIs, tyrosine kinase inhibitors. IMAs, immunomodulating agents.

[a]: ROR computed from a 2x2 table comparing the reporting rates of the event between the reports containing drug combination and reports with DOACs only

[b]: adjusted for age, sex, reporting country, and reporting year

--: ROR not computed (number of events <3)

-: ROR and EGBM not available (number of events = 0)

Table S10. Sensitivity analysis 3 of signal detection of drug-drug interactions between direct oral anticoagulants and antineoplastic agents in FDA Adverse Event Reporting System (FAERS) database from 2004-2021.

Combination	Reference	Number of AE reports with outcomes (Total number of AE reports)	DPA ROR (95% CI) [a]	Logistic regression ROR (95% CI) [b]
DOACs-TKIs	***warfarin-TKIs***	1031 (6095)	0.76 (0.70-0.50)	0.35 (0.32-0.39)
DOACs-imatinib	warfarin-imatinib	81 (551)	1.97 (1.40-2.78)	0.91 (0.64-1.29)
DOACs-dasatinib	warfarin-dasatinib	36 (217)	1.06 (0.66-1.71)	0.47 (0.29-0.76)
DOACs-nilotinib	warfarin-nilotinib	53 (337)	0.95 (0.60-1.52)	0.38 (0.24-0.62)
DOACs-lapatinib	warfarin-lapatinib	54 (305)	0.86 (0.47-1.59)	0.67 (0.35-1.27)
DOACs-erlotinib	warfarin-erlotinib	167 (965)	0.77 (0.56-1.07)	0.33 (0.24-0.46)
DOACs-crizotinib	warfarin-crizotinib	11 (175)	2.10 (1.02-4.32)	0.82 (0.40-1.70)
DOACs-tivozanib	warfarin-tivozanib	0 (7)	--	--
DOACs-pazopanib	warfarin-pazopanib	41 (340)	0.99 (0.62-1.57)	0.49 (0.31-0.79)
DOACs-axitinib	warfarin-axitinib	27 (167)	0.87 (0.51-1.48)	0.49 (0.29-0.84)
DOACs-brigatinib	warfarin-brigatinib	0 (17)	-	-
DOACs-ceritinib	warfarin-ceritinib	0 (17)	-	-
DOACs-lorlatinib	warfarin-lorlatinib	0 (6)	-	-
DOACs-binimetinib	warfarin-binimetinib	2 (23)	--	--
DOACs-trametinib	warfarin-trametinib	4 (32)	1.24 (0.41-3.73)	0.60 (0.20-1.83)
DOACs-palbociclib	warfarin-palbociclib	41 (524)	1.23 (0.85-1.78)	0.59 (0.41-0.86)
DOACs-ribociclib	warfarin-ribociclib	6 (25)	0.42 (0.15-1.15)	0.23 (0.08-0.65)
DOACs-entrectinib	warfarin-entrectinib	0 (0)	-	-
DOACs-larotrectinib	warfarin-larotrectinib	0 (1)	-	-
DOACs-idelalisib	warfarin-idelalisib	16 (99)	0.25 (0.11-0.59)	0.12 (0.05-0.27)
DOACs-sunitinib	warfarin-sunitinib	240 (898)	1.04 (0.80-1.36)	0.37 (0.28-0.49)
DOACs-vandetanib	warfarin-vandetanib	3 (13)	--	--
DOACs-osimertinib	warfarin-osimertinib	7 (54)	0.84 (0.35-2.01)	0.37 (0.15-0.89)
DOACs-alectinib	warfarin-alectinib	1 (25)	--	--
DOACs-neratinib	warfarin-neratinib	6 (18)	1.28 (0.44-3.74)	1.22 (0.41-3.63)
DOACs-cabozantinib	warfarin-cabozantinib	37 (333)	0.77 (0.51-1.17)	0.32 (0.21-0.50)
DOACs-capmatinib	warfarin-capmatinib	0 (3)	-	-
DOACs-sorafenib	warfarin-sorafenib	163 (595)	0.87 (0.56-1.37)	0.37 (0.23-0.58)
DOACs-regorafenib	warfarin-regorafenib	17 (87)	0.60 (0.31-1.21)	0.27 (0.14-0.55)

DOACs-ponatinib	warfarin-ponatinib	10 (77)	1.29 (0.60-2.77)	0.71 (0.38-1.54)
DOACs-vemurafenib	warfarin-vemurafenib	9 (64)	1.21 (0.52-2.80)	0.55 (0.23-1.29)
DOACs-cobimetinib	warfarin-cobimetinib	2 (12)	--	--
DOACs-abemaciclib	warfarin-abemaciclib	1 (22)	--	--
DOACs-pemigatinib	warfarin-pemigatinib	0 (0)	-	-
DOACs-gefitinib	warfarin-gefitinib	39 (241)	0.89 (0.41-1.97)	0.43 (0.19-0.95)
DOACs-afatinib	warfarin-afatinib	19 (74)	1.08 (0.55-2.10)	0.43 (0.22-0.85)
DOACs-hormone	***warfarin-hormone***	1095 (4998)	0.69 (0.62-0.76)	0.28 (0.26-0.32)
DOACs-letrozole	warfarin-letrozole	387 (1222)	0.37 (0.31-0.45)	0.16 (0.13-0.29)
DOACs-anastrozole	warfarin-anastrozole	255 (1032)	0.80 (0.64-0.99)	0.33 (0.26-0.41)
DOACs-abiraterone	warfarin-abiraterone	47 (469)	1.58 (1.09-2.29)	0.67 (0.45-0.98)
DOACs-bicalutamide	warfarin-bicalutamide	209 (862)	0.83 (0.65-1.07)	0.36 (0.28-0.47)
DOACs-tamoxifen	warfarin-tamoxifen	348 (835)	0.38 (0.29-0.49)	0.17 (0.13-0.23)
DOACs-enzalutamide	warfarin-enzalutamide	132 (1252)	1.03 (0.79-1.33)	0.42 (0.32-0.54)
DOACs-chemotherapy	***warfarin-chemotherapy***	1776 (9975)	0.88 (0.82-0.95)	0.41 (0.38-0.45)
DOACs-vinblastine	warfarin-vinblastine	18 (39)	-	-
DOACs-doxorubicin	warfarin-doxorubicin	509 (1585)	0.24 (0.19-0.31)	0.13 (0.10-0.17)
DOACs-methotrexate	warfarin-methotrexate	667 (5163)	1.46 (1.31-1.62)	0.63 (0.56-0.70)
DOACs-vincristine	warfarin-vincristine	276 (679)	0.19 (0.14-0.26)	0.11 (0.08-0.15)
DOACs-vinorelbine	warfarin-vinorelbine	179 (354)	0.09 (0.05-0.18)	0.06 (0.03-0.13)
DOACs-docetaxel	warfarin-docetaxel	479 (1651)	0.50 (0.40-0.62)	0.28 (0.22-0.35)
DOACs-idarubicin	warfarin-idarubicin	0 (10)	-	-
DOACs-cyclophosphamide	warfarin-cyclophosphamide	405 (2048)	0.43 (0.35-0.52)	0.31 (0.17-0.26)
DOAC-ifosfamide	warfarin -ifosfamide	7 (53)	0.67 (0.18-2.47)	0.15 (0.05-0.41)
DOACs-lomustine	warfarin-lomustine	0 (5)	-	-
DOACs-irinotecan	warfarin-irinotecan	104 (624)	1.29 (0.94-1.78)	0.28 (0.22-0.36)
DOACs-etoposide	warfarin-etoposide	36 (291)	0.58 (0.33-1.00)	0.37 (0.21-0.65)
DOACs-IMAs	***warfarin-IMAs***	2325 (15360)	0.54 (0.50-0.58)	0.24 (0.23-0.26)
DOACs-cyclosporine	warfarin-cyclosporine	250 (1740)	1.41 (1.16-1.72)	0.58 (0.48-0.72)
DOACs-sirolimus	warfarin-sirolimus	52 (473)	1.72 (1.11-2.69)	0.69 (0.44-1.08)
DOACs-temsirolimus	warfarin-temsirolimus	35 (162)	-	-
DOACs-tacrolimus	warfarin-tacrolimus	275 (2340)	1.37 (1.12-1.66)	0.55 (0.45-0.67)
DOACs-dexamethasone	warfarin-dexamethasone	1805 (11147)	0.38 (0.35-0.42)	0.18 (0.17-0.20)
DOACs-inducers	***warfarin-inducers***	94 (5776)	1.49 (1.15-1.93)	0.72 (0.55-0.93)
DOACs-dabrafenib	warfarin-dabrafenib	0 (44)	-	-

DOACs-encorafenib	warfarin-encorafenib	0 (22)	-	-
DOACs-paclitaxel	warfarin-paclitaxel	34 (1373)	0.89 (0.54-1.47)	0.44 (0.26-0.72)
DOACs-prednisolone	warfarin-prednisolone	60 (4344)	1.78 (1.30-2.44)	0.85 (0.62-1.17)

The combination of warfarin and corresponding antineoplastic agents were used as the referent groups.

DPA Disproportionality analysis. ROR, Reporting odds ratio. CI, Confidence Interval. MGPS, Multi-item Gamma Poisson Shrinker. EBGM, Empirical Bayes geometric mean. EB05, the lower bound of the 90% credible interval for the EBGM. EB95, the upper bound of the 90% credible interval for the EBGM. DOACs, Direct Oral Anticoagulants. TKIs, tyrosine kinase inhibitors. IMAs, immunomodulating agents.

[a]: ROR computed from a 2x2 table comparing the reporting rates of the event between the reports containing drug combination and reports with DOACs only

[b]: adjusted for age, sex, reporting country, and reporting year

--: ROR not computed (number of events <3)

-: ROR and EGBM not available (number of events = 0)

Technical notes for statistical analysis

1. Disproportionality analysis (DPA)

We calculate reporting odds ratios (ROR) and 95% confidence intervals (95% CI) from the 2 × 2 exposure-outcome contingency tables to measure disproportionality of bleeding rates between reports with DOAC-antineoplastic agent combination versus reports with DOAC alone (**Table 1**).[147-149] If the lower limit of 95% CI of ROR is greater than 2.00, a significant association is interpreted.[150]

Table 1. 2 x 2 contingency table for the evaluation of DOACs-antineoplastic drugs DDIs and bleeding events in FAERS data using disproportionality approach

	Bleeding AE reports	**Non-bleeding AE reports**
AE reports with DOACs and antineoplastic drugs combination	a	c
AE reports with DOACs alone	b	d

Abbreviation: AE: Adverse Events, DOACs: Novel Oral Anticoagulants, DDI: Drug-Drug Interactions

2. Logistic regression

LR model computes ROR in a similar way as in case-control studies.[149,151] Signals of DDIs can be detected if the lower limit of 95% CI of ROR exceeds 1.00.[149,151]

We categorize AE reports by the following categories: reports containing both DOACs and antineoplastic drugs (yes/no), DOACs only (yes/no), antineoplastic drugs only (yes/no). We use the same coding scheme for the DDIs between warfarin and antineoplastic drugs compared with other drugs. We then calculate RORs and 95% CIs from LR models. Let p denote the proportion of AE reports (p_{11}=proportion of AE reports with the presence of both D_1 and D_2, p_{10}=proportion of AE reports with the presence of D_1 and absence of D_2, p_{01}=proportion of AE reports with the absence of D_1 and presence of D_2, p_{00}=proportion of AE reports without D_1 and D_2). We assume

the DDIs follow multiplicative model, the null statistical hypothesis with no DDIs between D_1 and D_2 is:

$$\frac{p_{11}(1-p_{11})}{p_{00}(1-p_{00})} = \frac{p_{10}(1-p_{10})}{p_{00}\,(1-p_{00})} \text{ x } \frac{p_{01}(1-p_{01})}{p_{00}(1-p_{00})}$$

In LR modeling terminology, the following model can be applied

$$\text{logit}(risk\ of\ event) = \beta_0 + \beta_1 D_1 + \beta_2 D_2 + \beta_{12} D_1 D_2 + \beta_3 L + \varepsilon$$

where risk of event is the proportion of bleeding AE reports out of the total of AE reports, β is the coefficient and D_1, D_2 are dummy variables describing the presence/absence of the drug of interest in a specific AE reports. L denotes other covariates in our analysis (i.e., age, sex, and reporting region), and ε denote random error. $e^{\beta_{12}}$ is the adjusted ROR of the LR approach.

3. Multi-item Gamma-Poisson Shrinker[154,156,157]

MGPS model is currently used by the FDA for DDIs signal detection in FAERS data.[152] Detecting the signals of DDIs using MGPS model is based on Empirical Bayes Geometric Means (EBGM) and corresponding 2-sided 90% confidence intervals (90% CIs, EB05 and EB95) are computed to identify disproportionate reporting of DOACs-antineoplastic drugs-bleeding and warfarin-antineoplastic drugs-bleeding triplets.[149,153] A threshold of EB05>2 is considered a significant DDIs for MGPS, given the bleeding event is rare.[154] Among these three approaches, we used MGPS as the main analysis since it has been suggested to outperform DPA and LR in previous studies.[155]

For the arbitrary itemset, let λ denote the expectation. Then $\lambda = E\left[\frac{N}{E}\right]$ where $E[]$ is the expectation of N/E, N is the observed number of AE reports, E is the predicted number of AE reports from an assumption that AE reports are independent, or baseline count. For DDIs between DOACs and

antineoplastic agents, we consider a set of 3 items *i*, *j*, and *k* (*i* denotes DOACs, *j* denotes antineoplastic drugs, and *k* denotes bleeding event). For example, the observed frequency of AE reports containing item *i*, *j*, *k* are $N_{i,}$, $N_{j,}$, N_k and the corresponding expected frequency of AE reports are $E_{i,}$ E_j, and E_k, respectively. Under within-stratum independence assumption, the probability of finding items *i*, *j*, and *k* in the same report is $P_{ijk} = P_i$ x P_jx P_k. For a three-dimensional unstratified run, the expected count is computed as $E_{ijk} = N_{total}$ x $P_{ijk} = N_{total}$ x P_i x P_jx P_k. If all AE reports are assigned to the strata denoted by c = 1, 2…,C, the proportion of reports in stratum *c* that contain the item *i* is expressed by P_i^c, and the total number of reports in stratum c is expressed by N_c. In the stratified independence model, it is assumed the above equations are held for each stratum. So, for a given stratum c, $P_{ijk}^c = P_i^c$ x P_j^c x P_k^c and the expected baseline count is $E0_{ijk} = \sum E_{ijk}^c = \sum N_c$ x $P_{ijk}^c = \sum N_c$ x P_i^c x P_j^c x P_k^c

For an itemset of size 3 or more, an "all-2-factor" loglinear model can be defined as the frequencies *E2* for the itemset that match all the estimated pairwise two-way marginal frequencies but contain no higher order dependencies. For triples, E*2ijk* agrees with the estimates for the three pairs $\lambda_{ij}E0_{ij}, \lambda_{ik}E0_{ik}, , \lambda_{jk}E0_{jk}$. Then we compare the estimated frequency to the all-2-factor prediction by simple subtraction. For example, in case of triples $Excess2_{ijk} = \lambda_{ijk}E0_{ijk}$ - $E2_{ijk}$

The parameters λ above are estimated by the geometric means, denoted by EBGM, of their empirical Bayes posterior distributions. For simplicity, the formula below use just two subscripts, for itemsets of size 2, such as the occurrence of drug i and event j in an AE report. Estimates for itemsets of size 3 for DDIs are computed analogously. Let N_{ij} = the observed counts, N_{ij} = the expected count $RR_{ij} = N_{ij}/E_{ij}$ = ratio of observed to baseline. We estimate $\lambda_{ij} = \mu_{ij}/E_{ij}$, where N_{ij}~ Poisson(μ_{ij}). Assume a superpopulation model for λ_{ij} (prior distribution) based on a mixture

of two gamma distributions (a convenient 5-parameter family of distributions that can fit almost any empirical distribution):

$$\pi(\lambda;\ \alpha_1, \beta_1, \alpha_2, \beta_2\ , P)\ =\ P\ g(\lambda;\ \alpha_1, \beta_1)\ +\ (1\ -\ P)\ g(\lambda;\ \alpha_2, \beta_2)$$

$$g(\lambda;\ \alpha, \beta)\ =\ \beta^{\alpha}\ \lambda^{\alpha-1}\ \frac{e^{-\beta\lambda}}{\Gamma(\alpha)}$$

First, we estimate the prior distribution from all the (N_{ij}, E_{ij}) pairs. Then we estimate the 5 hyperparameters θ = ($\alpha_1, \beta_1, \alpha_2, \beta_2\ P$) by maximizing the likelihood function $L(\theta)$ in 5 dimensions:

$$L(\theta) = \prod([\mathrm{P\ f}(N_{ij};\ \alpha_1, \beta_1, E_{ij}) +\ (1 - \mathrm{P})\mathrm{f}(N_{ij};\ \alpha_2, \beta_2, E_{ij})]_{\ ij}$$

where $f(n;\ \alpha, \beta, E)$ = $(1 + \beta/E)^{-n}\ (1 + E/\beta)^{-\alpha}\ \Gamma(\alpha\ +\ n)$ / $\Gamma(\alpha)$ n!

If a threshold (minimum count) for the observed counts is used, these formula are modified to condition on $N_{ij} \geq$ n* (where n* = the threshold count). Given θ, the posterior distributions of each λ_{ij} are also a mixture of gamma distributions used to create "shrinkage" estimates. Assuming that θ and E are known, then the distribution of N is

$$P(N\ =\ n)\ =\ Pf(n;\ \alpha_1, \beta_1, E)\ +\ (1 - P)f(n;\ \alpha_2, \beta_2, E)$$

Let Q_n be the posterior probability that λ came from the first component of the mixture, given N = n. From Bayes rule, the formula for Q_n is

$$Q_n = \frac{\mathrm{Pf}(n;\ \alpha_1, \beta_1, E)}{\mathrm{Pf}(n;\ \alpha_1, \beta_1, E) + (1-\mathrm{P})\mathrm{f}(n;\ \alpha_2, \beta_2, E)}$$

Then, the posterior distribution of λ, after observing N = n can be represented as

$$\lambda|\mathrm{N} = n \sim \pi(\lambda;\ \alpha_1\ +\ n, \beta_1 +\ E, \alpha_2\ +\ n, \beta_2 +\ E, Q_n)$$

where (as above) $\pi(\lambda;\ \alpha_1, \beta_1, \alpha_2, \beta_2, P) = P\ g(\lambda;\ \alpha_1, \beta_1) + (1 - P) g(\lambda;\ \alpha_2, \beta_2)$ We used the expectation value E[log(λ_{ij}) | N_{ij}, θ] as a means of estimating the "true" value of λ_{ij}.To obtain a quantity on the same scale as RR, we define the Empirical Bayes Geometric Mean:

$$EGBM_{ij} = E[log(\lambda_{ij})|\ N_{ij}, \theta]$$

where $E[\lambda \mid N = n, \theta] = Q_n\ (\alpha_1 + n)/(\beta_1 + E)] + (1–Q_n)\ (\alpha_2 + n)/(\beta_2 + E)$

$E[log(\lambda) \mid N = n, \theta] = Q_n\ [\psi(\alpha_1 + n) - log(\beta_1 + E)] + (1–Q_n)\ [\psi(\alpha_2 + n) - log(\beta_2 + E)]$

where $\psi(x) = d(log\ \Gamma(x))/dx$. The above expectations follow from known properties of gamma distributions. In the same way, the cumulative gamma distribution function can be used to obtain percentiles of the posterior distribution of λ. The 5th percentile of λ is denoted $EB05_{ij} = P(\lambda < EB05 \mid N_{ij}, \theta)$ = 0.05 and is interpreted as a lower 1-sided 95% confidence limit.

Technical discussion

In our study, we used different methods to reduce the chance of detecting false negative signals. We compared the reported bleeding/stroke rates for DPA between DOAC-antineoplastic agent combinations and DOAC alone. Most of the combinations showed ROR point estimates of less than 1, suggesting the reported bleeding rates for the combinations were lower than DOACs alone. Thus, the DDIs were insignificant when previous studies used the ROR threshold of 2 for a significant signal.[150] However, this approach has a limitation since it does not compare the reported bleeding/stroke rates between DOAC-antineoplastic agents and antineoplastic agents alone. To overcome this limitation, we conducted a LR analysis by assessing the reported bleeding/stroke considering four scenarios (1) with both DOACs and antineoplastic agents, (2)

DOACs alone, (3) antineoplastic agents alone, and (4) without either drug, adjusted for other covariates. Again, most RORs did not exceed 1, except for entrectinib (ROR 1.45, 95% CI 0.33-6.37) and neratinib (ROR 1.06, 95% CI 0.65-1.72). However, the signal for DOAC-entrectinib and DOAC-neratinib interactions was not stable due to the small number of AE reports reported for these combinations in FAERS. The only significant DDI signal between DOACs and neratinib was confirmed by the MGPS method (EGBM 2.71, EB05- EB95 2.03-3.54). The MGPS was superior to the frequentist and machine learning approach to detect drug-adverse event associations and was routinely implemented by several FDA centers.[152,155] In sensitivity analysis 1, we tested the assumption that the signal may not be affected by the calendar time and Weber's effect. In sensitivity analysis 2, we hypothesized that the outcome definition may not impact the findings. We included all PTs related to bleeding/stroke in the MedDRA dictionary in the main analysis. However, some of these PTs may not be relevant to the event induced by OACs. Therefore, a clinician in our team screened the relevant PTs. In sensitivity analysis 3, we assumed that physician may prescribe warfarin as an alternative to DOACs if they suspect a DDI between DOACs and antineoplastic agents. However, no risk signal was detected. The findings from these sensitivity analyses confirmed the robustness of the findings in the main analysis.

Appendix for Aim 2.1 Manuscript

Table S1. Algorithms to identify study components from SEER-Medicare data

Component	Code type	Codes
Eligibility criteria		
AFib	ICD-9-CM	427.31 or 427.32
	ICD-10-CM	I48.xx
Breast cancer	ICD-O-3	C50.0-C50.9
Lung cancer	ICD-O-3	C34.0, C34.1, C34.2, C34.3, C34.8, C34.9, C33.9
Prostate cancer	ICD-O-3	C61.9
Valvular heart diseases	ICD-9-CM	0932, 394, 395, 396, 3970, 3971, 240, 4241, 242, 4243, 7460, 7461, 7462, 7463, 7464, 7465, 7466, 99602, 99671, V422
	ICD-10-CM	I05, I06, I07, I08, I34, I35, I36, I37, I39, Q22, Q23, T820, T8201, T8202, T8203, T8209, T8222, T826, Z952, Z953, Z954
	ICD-9-CM PX	351, 352, 3533, 3595, 3599
	ICD-10-PCS	02RF, 02RG, 02RH, 02RJ, 02QF, 02QG, 02QH, 02QJ
Heart valve repair or replacement	ICD-9-CM	V433
Venous thromboembolism	ICD-9-CM	4151 ,453, V1251, V1255
	ICD-10-CM	I26, I80, I81, I82, Z8671
Joint replacement	ICD-9-CM PX	8151, 8152, 8154
	ICD-10-PCS	0SR9019, 0SR901A, 0SR901Z, 0SR9029, 0SR902A, 0SR902Z, 0SR9039, 0SR903A, 0SR903Z, 0SR9049, 0SR904A, 0SR904Z, 0SR9069, 0SR906A, 0SR906Z, 0SR907Z, 0SR90EZ, 0SR90J9, 0SR90JA, 0SR90JZ, 0SR90KZ, 0SRA009, 0SRA00A, 0SRA00Z, 0SRA019, 0SRA01A, 0SRA01Z, 0SRA039, 0SRA03A, 0SRA03Z, 0SRA07Z, 0SRA0J9, 0SRA0JA, 0SRA0JZ, 0SRA0KZ, 0SRB019, 0SRB01A, 0SRB01Z, 0SRB029, 0SRB02A, 0SRB02Z, 0SRB039, 0SRB03A, 0SRB03Z, 0SRB049, 0SRB04A, 0SRB04Z, 0SRB069, 0SRB06A, 0SRB06Z, 0SRB07Z, 0SRB0EZ, 0SRB0J9, 0SRB0JZ, 0SRB0KZ, 0SRE009, 0SRE00A, 0SRE00Z, 0SRE019, 0SRE01A, 0SRE039, 0SRE03A, 0SRE03Z, 0SRE07Z, 0SRE0J9, 0SRE0JA,

		0SRE0JZ, 0SRR019, 0SRR01A, 0SRR01Z, 0SRR039, 0SRR03A, 0SRR03Z, 0SRB0JA, 0SRR07Z, 0SRR0J9, 0SRR0JA, 0SRR0JZ, 0SRR0KZ, 0SRS019, 0SRE01Z, 0SRS01A, 0SRS01Z, 0SRS039, 0SRS03A, 0SRS03Z, 0SRS07Z, 0SRE0KZ, 0SRS0J9, 0SRS0JA, 0SRS0JZ, 0SRS0KZ, 0SRC069, 0SRC06A, 0SRC06Z, 0SRC07Z, 0SRC0EZ, 0SRC0J9, 0SRC0JA, 0SRC0JZ, 0SRC0KZ, 0SRC0L9, 0SRC0LA, 0SRC0LZ, 0SRC0M9, 0SRC0MA, 0SRC0MZ, 0SRC0N9, 0SRC0NA, 0SRC0NZ, 0SRD069, 0SRD06A, 0SRD06Z, 0SRD07Z, 0SRD0EZ, 0SRD0J9, 0SRD0JA, 0SRD0JZ, 0SRD0KZ, 0SRD0L9, 0SRD0LA, 0SRD0LZ, 0SRD0M9, 0SRD0MA, 0SRD0MZ, 0SRD0N9, 0SRD0NA, 0SRD0NZ, 0SRT07Z, 0SRT0J9, 0SRT0JA, 0SRT0JZ, 0SRT0KZ, 0SRU07Z, 0SRU0J9, 0SRU0JA, 0SRU0JZ, 0SRU0KZ, 0SRV07Z, 0SRV0J9, 0SRV0JA, 0SRV0JZ, 0SRV0KZ, 0SRW07Z, 0SRW0J9, 0SRW0JA, 0SRW0JZ, 0SRW0KZ
Renal impairment stage 5/ESRD	ICD-9-CM	40301, 40311, 40391, 5855, 5856, V451, V56
	ICD-10-CM	I120, I1311, I132, N185, Y841, Z49, Z9115, Z992
	ICD-9-CM PX	3995, 5498
	ICD-10-PCS	3E1M39Z, 5A1D70Z, 5A1D80Z, 5A1D90Z
History of stroke/TIA	ICD-9-CM	36231, 36232, 36233, 36234, 43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, 436, 430, 431, 43391, 435
	ICD-10-CM	H340, H341, H342, I63, I60, I61, I62, I63, G45, I6782, I6789
Major surgery		Not included due to large number of codes
Intracranial/Spinal bleeding	ICD-9-CM	430, 431, 432, 852, 853,
	ICD-10-CM	I60, I61, I62, S064, S065, S066
Intraocular bleeding	ICD-9-CM	36281, 37923, 36361, 36362,
	ICD-10-CM	H356, H3130, H3131, H431
Retroperitoneal bleeding	ICD-9-CM	56881
	ICD-10-CM	K661
Atraumatic intra-articular bleeding	ICD-9-CM	7191
	ICD-10-CM	M250
Gastrointestinal bleeding	ICD-9-CM	4560, 45620, 5301, 5307, 53082, 5310, 5311, 5312, 5313, 5314, 5315, 5316, 5317, 5319, 5320, 5321, 5322, 5323, 5324, 5325, 5326, 5327, 5329, 5330, 5331, 5332, 5333, 5334, 5335, 5336, 5337, 5339, 5340, 53400, 53401, 5341, 5342, 5343, 5344, 5345, 5346, 5347, 5349, 53500, 53501, 53510, 53511, 53520, 53521, 53530, 53531, 53540, 53541, 53550, 53551, 53560, 53561,

		53783, 5780, 4551, 4552, 4554, 4555, 4556, 4557, 4558, 4559, 56200, 56201, 56202, 56203, 56210, 56211, 56212, 56213, 5693, 56985, 5781, 5789
	ICD-10-CM	I8501, I8511, K20, K210, K2211, K226, K250, K251, K252, K254, K255, K256, K260, K261, K262, K264, K265, K266, K270, K271, K272, K274, K275, K276, K280, K281, K282, K284, K285, K286, K2901, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K31811, K920, K5521, K5701, K5711, K5721, K5731, K5741, K5751, K5753, K5781, K5791, K5793, K625, K640, K641, K642, K643, K644, K645, K648, K649, K921, K922
Outcomes		
Ischemic stroke (new diagnosis)	ICD-9-CM	36231, 36232, 36233, 36234, 43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, 436, H340, H341, H342, I63
	ICD-10-CM	
Major bleeding	ICD-9-CM	3361, 36361, 36362, 36372, 37632, 37742, 37923, 4230, 430, 431, 432, 56881, 7191, 72992, 852, 853, 86601, 86602, 86611, 86612
	ICD-10-CM	G9519, H0523, H3130, H3131, H3141, H431, H4702, I230, I312, I60, I61, I62, K661, M250, M7981, S064, S065, S066, S260, S3701, S3702, S3703, S3704, S3705, S3706
Covariates		
CHF	ICD-9-CM	39891, 40201, 40211, 40291, 40401, 40403, 40411, 40413, 40491, 40493, 4254, 4259, 428
	ICD-10-CM	I0981, I110, I130, I132, I425, I428, I50
HTN	ICD-9-CM	401, 402, 403, 404, 405
	ICD-10-CM	I10, I11, I12, I13, I14, I15, I16
DM	ICD-9-CM	250, 3572, 3620, 36641,
	ICD-10-CM	E10, E11, E13
Vascular diseases	ICD-9-CM	410, 412, 4400, 4402, 4403, 4409, 4442, 4439, 44481
	ICD-10-CM	I21, I252, I700, I702, I703, I704, I705, I706, I707, I709, I742, I743, I744, I739, I745
Renal diseases	ICD-9-CM	0160, 0954, 1890, 1899, 2230, 23691, 2504, 2714, 2741, 28311, 403, 404, 4401, 4421, 4473, 5724, 580, 581, 582, 583, 584, 585, 586, 587, 588, 591, 6421, 6462, 75312, 75313, 75314, 75315, 75316, 75317, 75319, 7532, 7944, V420, V451, V56
	ICD-10-CM	A1811, A5275, C649, C689, D4100, E1129, E1029, E1121, E1021, E748, M1030, N200, D593, I120, I129, I1310, I130, I1311, I132, I1311, I701, I722, I773, K767, N00, N01, N02, N03, N04, N05, N06, N07, N08, N1330, O10419, O10411, O10412, O10413, O1042, O1043, O26839, O1214, O26831, O26832, O26833, Q613, Q612, Q6119, Q614, Q615, Q6102, Q618, Q6239, Q6211, Q6212, Q6231, Q6210, Q6211, R944, Z940, Z992, Z9115, Z4931, Z4901, Z4902, Z4932

Liver diseases	ICD-9-CM	070, 07271, 09162, 1305, 571, 573, 7948
	ICD-10-CM	A5145, B0081, B15, B16, B17, B18, B19, B251, B2681, B581, B942, K70, K71, K72, K73, K74, K75, K76, K77, R94.5
Bleeding disposition	ICD-9-CM	430, 431, 432, 56881, 5997, 5307, 5310, 5312, 5314, 5316, 5320, 5322, 5324, 5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 5693, 53501, 53511, 53521, 53531, 53541, 53551, 53561, 53571, 53783, 53784, 56202, 56203, 56212, 56213, 56985, 578, 7847, 7863, 6262, 7191, 37272, 459
	ICD-10-CM	I60, I61, I62, K661, R31, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K2901, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K31811, K3182, K5701, K5711, K5713, K5721, K5731, K5733, K5741, K5751, K5753, K5781, K5791, K5793, K5521, K920, K921, K922, R040, R042, N920, M250, M122, H113, R58
Alcohol use disorders	ICD-9-CM	291, 303, 3050, 3575, 4255, 5353, 5710, 5711, 5712, 5713, 7903
	ICD-10-CM	E8600, V113, F10, Z714
Asthma/COPD	ICD-9-CM	491, 492, 496, 49300, 49301, 49302, 49310, 49311, 49312, 49320, 49321, 49322, 49381, 49382, 49390, 49391, 49392
	ICD-10-CM	J41, J42, J43, J44, J4520, J4521, J4522, J4530, J4531, J4532, J4540, J4541, J4542, J4550, J4551, J4552, J45901, J45902, J45909, J45990, J45991, J45998
Hematological disorders	ICD-9-CM	280, 281, 282, 283, 284, 285, 286, 2871, 2873, 2874, 2875
	ICD-10-CM	D46, D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64
Dementia	ICD-9-CM	3310, 3311, 3312, 3317, 290, 2940, 2941, 2948, 797
	ICD-10-CM	G30, G310, G311, G312, G319, F02, F03, F04, R4181
Depression	ICD-9-CM	2962, 2963, 2965, 3004, 309, 311
	ICD-10-CM	F32, F33, F341, F43
Thrombocytopenia	ICD-9-CM	286, 287
	ICD-10-CM	D68, D69
AKD	ICD-9-CM	584
	ICD-10-CM	N17
Peptic ulcer diseases	ICD-9-CM	533, V1271,
	ICD-10-CM	K27, Z8711
Aspirin/NSAIDs	Generic drug name	ASPIRIN, CLOPIDOGREL, CELECOXIB, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLURBUPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN,

		KETOROLAC, MEFENAMIC, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PIROXICAM, SULINDAC, TOLMETIN
ACEI/ARB	Generic drug name	BENAZEPRIL, CAPTOPRIL, ENALAPRIL, FOSINOPRIL, LISINOPRIL, MOEXIPRIL, PERINDOPRIL, QUINAPRIL, RAMIPRIL, TRANDOLAPRIL LOSARTAN, IRBESARTAN, OLMESARTAN, VALSARTAN, TELMISARTAN, CANDESARTAN, AZILSARTAN
CCB	Generic drug name	AMLODIPINE, DILTIAZEM, FELODIPINE, ISRADIPINE, LEVAMLODIPINE, NIFEDIPINE, NISOLDIPINE, VERAPAMIL
BB	Generic drug name	ACEBUTOLOL, ATENOLOL, BETAXOLOL, BISOPROLOL, CARVEDILOL, LABETALOL, METOPROLOL , NADOLOL, NEBIVOLOL, PINDOLOL, PROPRANOLOL, TIMOLOL
Antiarrhythmic drugs	Generic drug name	QUINIDINE, PROCAINAMIDE, DISOPYRAMIDE, LIDOCAINE , MEXILETINE, FLECAINIDE, PROPAFENONE, AMIODARON, EDRONEDARONE, DOFETILIDE, SOTALOL, IBUTILID, DIGOXIN
Diuretics	Generic drug name	HYDROCHLOROTHIAZIDE, CHLOROTHIAZIDE, CHLORTHALIDONE, EPLERENONE, FUROSEMIDE, INDAPAMIDE, SPIRONOLACTONE , TORSEMIDE, METOLAZONE
Statins	Generic drug name	ATORVASTATIN, FLUVASTATIN, LOVASTATIN, PITAVASTATIN, PRAVASTATIN, ROSUVASTATIN, SIMVASTATIN
PPIs	Generic drug name	OMEPRAZOLE, ESOMEPRAZOLE, LANSOPRAZOLE, DEXLANSOPRAZOLE, PANTOPRAZOLE, RABEPRAZOLE
SSRI/SNRI	Generic drug name	CITALOPRAM, ESCITALOPRAM, FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE, VILAZODONE, DULOXETINE, VENLAFAXINE, LEVOMILNACIPRAN DESVENLAFAXINE

Table S2. Characteristics of patients with new onset AFib and concomitant cancer in SEER-Medicare registry from 2012 to 2019

	Overall (N=39915)
Demographics	
Index age (Mean, SD)	77.16 (7.31)
Year of AFib diagnosis	
2012-2015	19805 (49.62)
2016-2019	20110 (50.38)
Female	18494 (46.33)
Race/ethnicity	
Non-Hispanic White	33971 (85.11)
Non-Hispanic Black	2555 (6.40)
Others	3389 (8.49)
Region	
Midwest	2672 (9.20)
Northeast	15669 (39.26)
South	7662 (19.20)
West	12912 (32.35)
Medicaid eligible	5739 (14.38)
Urbanicity	
Metropolitan	34157 (85.57)
Micropolitan	3306 (8.28)
Unknown	2452 (6.14)
Socioeconomic status (Census Tract)	
Household median income (Median, IQR)	60508.00 (44107.00- 82930.00)
Percentage of residents living below poverty (Median, IQR)	9.61 (5.17-17.07)
Percentage of non-high school graduates (Median, IQR)	10.01 (5.53-17.49)
Percentage of high school only (Median, IQR)	27.49 (19.43-35.01)
Percentage of some college education (Median, IQR)	28.54 (23.35-33.97)
Percentage of college education and above (Median, IQR)	27.18 (16.44-43.18)
Cancer characteristics	
Time from cancer diagnosis to the onset of AFib (month, Median, IQR)	15.00 (2.00-41.00)
Cancer type	
Breast	10762 (26.96)

Lung	17502 (42.85)
Prostate	11651 (29.19)
Active cancer	11601 (29.06)
Cancer grade	
I	4557 (11.42)
II	12015 (30.10)
III	12208 (30.58)
Others/unknown	11135 (27.90)
Number of regional nodes examined	
<12	24794 (62.12)
≥12	2366 (5.93)
Unknown/missing	12755 (31.96)
Tumor size	
≤2 cm	7557 (18.93)
2-5 cm	7259 (18.19)
>5 cm	3799 (9.52)
Unknown/missing	21300 (53.36)
TMN classification	
T stage	
TX	2124 (5.32)
T0	1172 (2.94)
T1	10342 (25.91)
T2	8504 (21.31)
T3	3363 (8.43)
T4	2940 (7.37)
Unknown/missing	11470 (28.74)
N stage	
NX	1812 (4.54)
N0	18495 (46.34)
N1	2595 (6.50)
N2	4159 (10.42)
N3	1384 (3.47)
Unknown/missing	11470 (28.74)
M stage	

M0	22573 (56.55)
M1	5842 (14.64)
Unknown/missing	11500 (28.81)
Summary stage	
In situ	1574 (3.94)
Local	19079 (47.80)
Regional	8283 (20.75)
Distant	8908 (22.32)
Unknown/missing	2071 (5.19)
Breast cancer-specific (N=10762)	
ER positive	6407 (59.53)
PR positive	5516 (51.25)
HER2 positive status	639 (5.94)
Lung cancer-specific (N=17502)	
Histologic type	
Adenoma	7232 (41.32)
NOS	3512 (20.07)
Squamous	4867 (27.81)
Others	1891 (10.80)
Cancer treatment	
Use of potentially interacting antineoplastic agents	7692 (19.27)
Radiation	2233 (5.59)
Surgery	350 (0.88)
Disease risk score	
CHA_2DS_2-VASc	
1	3222 (8.07)
2	6715 (16.82)
3	9759 (24.45)
4	10111 (25.33)
5	6103 (15.29)
≥6	4005 (10.03)
HAS-BLED	
1	8094 (20.28)
2	14112 (35.36)

3	11224 (28.12)
4	4910 (12.30)
5	1314 (3.29)
≥6	261 (0.65)
CCI (Mean, SD)	2.02 (2.04)
NCI Comorbidity score (Mean, SD)	0.68 (0.64)
Individual comorbidities	
Asthma/COPD	15538 (38.93)
Hematological disorders	12985 (32.53)
Dementia	2671 (6.69)
Depression	6602 (15.19)
Thrombocytopenia	2650 (6.64)
Acute kidney diseases	2768 (6.93)
Peptic ulcer diseases	485 (1.22)
Medications	
ACE inhibitors/ARBs	12545 (31.43)
CCB	7957 (19.93)
Beta blockers	10694 (26.79)
Antiarrhythmic medications	2122 (5.54)
Diuretics	9198 (23.04)
Statin	12656 (31.71)
PPIs	7264 (18.20)
SSRIs/SNRIs	4971 (12.45)

AFib Atrial Fibrillation. SD Standard Deviation. IQR Interquartile Range. ER estrogen receptor. PR progesterone receptor. HER2 human epidermal growth factor receptor 2. NOS not otherwise specified. CHA_2DS_2-VASc: a composite score for risk of stroke. HAS-BLED a composite score for risk of bleeding. CCI Charlson Comorbidity Index. NCI National Cancer Institute Comorbidity Index. COPD Chronic obstructive pulmonary disease. ACE Angiotensin-converting enzyme. ARB Angiotensin receptor blockers. CCB Calcium Channel Blockers. PPI Pump Proton Inhibitors. SSRI Selective serotonin reuptake inhibitors. SNRI Serotonin and norepinephrine reuptake inhibitors.

Table S3. Distributions of time-varying unstabilized weights and truncated weights

	Mean	Minimum	Maximum	95th Pctl	Std Dev	Median	25th Pctl	75th Pctl
Stroke								
Unstabilized weighted	3.75	1.01	12087.07	11.36	31.02	1.59	1.31	2.94
Unstabilized weights truncated at 99th percentile	3.21	1.01	27.28	11.36	4.20	1.59	1.31	2.94
Major bleeding								
Unstabilized weighted	3.61	1.01	19456.91	10.86	36.34	1.60	1.31	2.84
Unstabilized weights truncated at 99th percentile	3.12	1.01	26.87	10.86	4.09	1.60	3.31	2.84

Pctl percentile, Std Dev: Standard Deviation

Table S4. Subgroup analysis comparing 5 treatment regimens of oral anticoagulation initiation in patients with atrial fibrillation and cancer

	Regimen 1	Regimen 2	Regimen 3	Regimen 4	Regimen 5
Subgroup analysis 1: Active cancer status					
Active cancer (N =11601)					
Ischemic stroke	1.51 (1.09-2.08)	1.53 (1.10-2.11)	1.27 (0.90-1.79)	0.61 (0.44-0.85)	Reference
Major bleeding	0.81 (0.41-1.59)	0.83 (0.42-1.61)	0.59 (0.33-1.07)	0.49 (0.41-0.60)	Reference
Inactive cancer (N =28314)					
Ischemic stroke	1.26 (1.04-1.52)	1.27 (1.05-1.54)	1.09 (0.90-1.31)	0.65 (0.54-0.77)	Reference
Major bleeding	0.49 (0.33-0.73)	0.56 (0.37-0.85)	0.59 (0.39-0.87)	0.49 (0.43-0.56)	Reference
Subgroup analysis 2: Cancer type					
Breast cancer (N =10762)					
Ischemic stroke	0.99 (0.78-1.25)	0.99 (0.78-1.25)	0.86 (0.69-1.08)	0.50 (0.41-0.61)	Reference
Major bleeding	0.38 (0.21-0.67)	0.38 (0.22-0.68)	0.35 (0.21-0.59)	0.41 (0.32-0.51)	Reference
Lung cancer (N=17502)					
Ischemic stroke	2.10 (1.55-2.86)	2.17 (1.59-2.94)	1.94 (1.43-2.63)	0.92 (0.64-1.33)	Reference
Major bleeding	0.83 (0.43-1.64)	0.86 (0.44-1.69)	0.66 (0.33-1.30)	0.47 (0.36-0.60)	Reference
Prostate cancer (N=11651)					
Ischemic stroke	0.86 (0.63-1.18)	0.87 (0.63-1.19)	0.61 (0.43-0.86)	0.58 (0.47-0.70)	Reference
Major bleeding	0.43 (0.24-0.77)	0.54 (0.30-0.96)	0.67 (0.43-1.06)	0.59 (0.53-0.67)	Reference
Subgroup analysis 3: Cancer stage					
In situ (N=1658)					
Ischemic stroke	0.85 (0.46-1.58)	0.85 (0.46-1.57)	0.81 (0.45-1.46)	0.36 (0.26-0.49)	Reference
Major bleeding	1.01 (0.44-2.31)	1.00 (0.44-2.30)	1.06 (0.49-2.32)	0.50 (0.25-1.01)	Reference
Local (N=20125)					
Ischemic stroke	0.94 (0.76-1.16)	0.95 (0.76-1.17)	0.75 (0.60-0.93)	0.48 (0.41-0.56)	Reference
Major bleeding	0.35 (0.22-0.55)	0.41 (0.25-0.65)	0.45 (0.29-0.70)	0.43 (0.37-0.49)	Reference
Regional (N=8703)					
Ischemic stroke	1.53 (1.10-2.14)	1.56 (1.12-2.18)	1.28 (0.94-1.75)	0.98 (0.70-1.39)	Reference
Major bleeding	0.78 (0.35-1.76)	0.81 (0.36-1.81)	0.60 (0.31-1.18)	0.55 (0.44-0.69)	Reference
Distant (N=9411)					
Ischemic stroke	2.09 (1.33-3.28)	2.14 (1.37-3.35)	2.18 (1.37-3.45)	0.95 (0.54-1.67)	Reference
Major bleeding	1.17 (0.48-2.90)	1.20 (0.49-2.98)	0.81 (0.31-2.17)	0.54 (0.40-0.73)	Reference
Subgroup analysis 4: Tumor grade					
Grade I (N=4557)					

Ischemic stroke	0.92 (0.60-1.41)	0.93 (0.61-1.42)	0.67 (0.45-1.02)	0.52 (0.32-0.83)	Reference
Major bleeding	0.59 (0.25-1.40)	0.60 (0.26-1.42)	0.40 (0.21-0.79)	0.29 (0.20-0.41)	Reference
Grade II (N=12015)					
Ischemic stroke	1.07 (0.82-1.39)	1.10 (0.84-1.43)	0.98 (0.75-1.28)	0.60 (0.47-0.76)	Reference
Major bleeding	0.27 (0.14-0.50)	0.28 (0.15-0.53)	0.33 (0.21-0.52)	0.45 (0.38-0.54)	Reference
Grade III (N=12208)					
Ischemic stroke	1.14 (0.81-1.59)	1.13 (0.81-1.59)	1.02 (0.72-1.43)	0.66 (0.48-0.91)	Reference
Major bleeding	0.53 (0.29-0.96)	0.67 (0.34-1.29)	0.75 (0.41-1.38)	0.58 (0.48-0.68)	Reference

***Effect measure was average hazard ratio (HR) and 95% Confidence Interval (95% CI) over 12-month follow-up, adjusted for baseline and time-varying covariates*

Regimen 1: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥1
Regimen 2: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥2
Regimen 3: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥4
Regimen 4: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥6
Regimen 5: Never initiate oral anticoagulants

Table S5. Sensitivity analysis comparing 5 treatment regimens of oral anticoagulation initiation in patients with atrial fibrillation and cancer

	Regime 1	Regime 2	Regime 3	Regime 4	Regime 5
Sensitivity analysis 1 (N=39915)					
Ischemic stroke	1.25 (1.07-1.46)	1.27 (1.09-1.49)	1.18 (1.00-1.39)	0.84 (0.70-1.01)	Reference
Major bleeding	0.76 (0.59-0.98)	0.79 (0.61-1.02)	0.71 (0.56-0.91)	0.47 (0.41-0.54)	Reference
Sensitivity analysis 2 (N=30504)					
Ischemic stroke	1.07 (0.90-1.26)	1.08 (0.91-1.28)	0.88 (0.74-1.04)	0.58 (0.50-0.67)	Reference
Major bleeding	0.48 (0.34-0.68)	0.53 (0.37-0.77)	0.55 (0.39-0.77)	0.47 (0.42-0.52)	Reference
Sensitivity analysis 3 (N=37265)					
Ischemic stroke	1.32 (1.11-1.56)	1.34 (1.13-1.58)	1.10 (1.93-1.32)	0.63 (0.54-0.75)	Reference
Major bleeding	0.58 (0.40-0.83)	0.63 (0.44-0.92)	0.60 (0.42-0.85)	0.49 (0.44-0.56)	Reference
Sensitivity analysis 4 (N=39915)					
Stroke	1.27 (1.09-1.47)	1.27 (1.10-1.48)	0.99 (0.86-1.15)	0.56 (0.50-0.63)	Reference
Major bleeding	0.52 (0.39-0.72)	0.56 (0.41-0.76)	0.53 (0.41-0.68)	0.51 (0.46-0.57)	Reference

***Effect measure was average hazard ratio (HR) and 95% Confidence Interval (95% CI) over 12-month follow-up, adjusted for baseline and time-varying covariates*

Regime 1: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥1
Regime 2: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥2
Regime 3: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥4
Regime 4: Initiate oral anticoagulants when CHA_2DS_2-VASc score ≥6
Regime 5: Never initiate oral anticoagulants

Sensitivity analysis 1. Extending maximum follow-up to 36 months
Sensitivity analysis 2. Excluding patients with metastatic cancer at baseline
Sensitivity analysis 3. Excluding patients with thrombocytopenia at baseline
Sensitivity analysis 4. Truncating stabilized weights at 95^{th} percentile

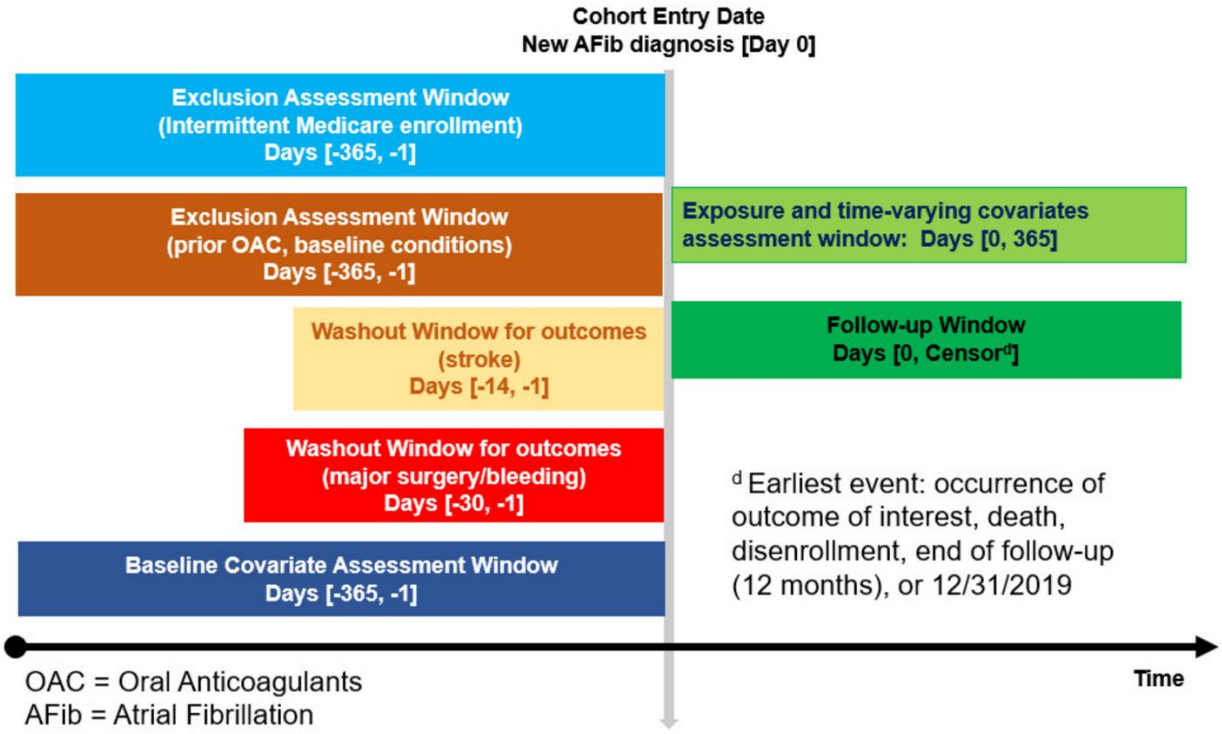


Figure S1. Visualization of study timeline

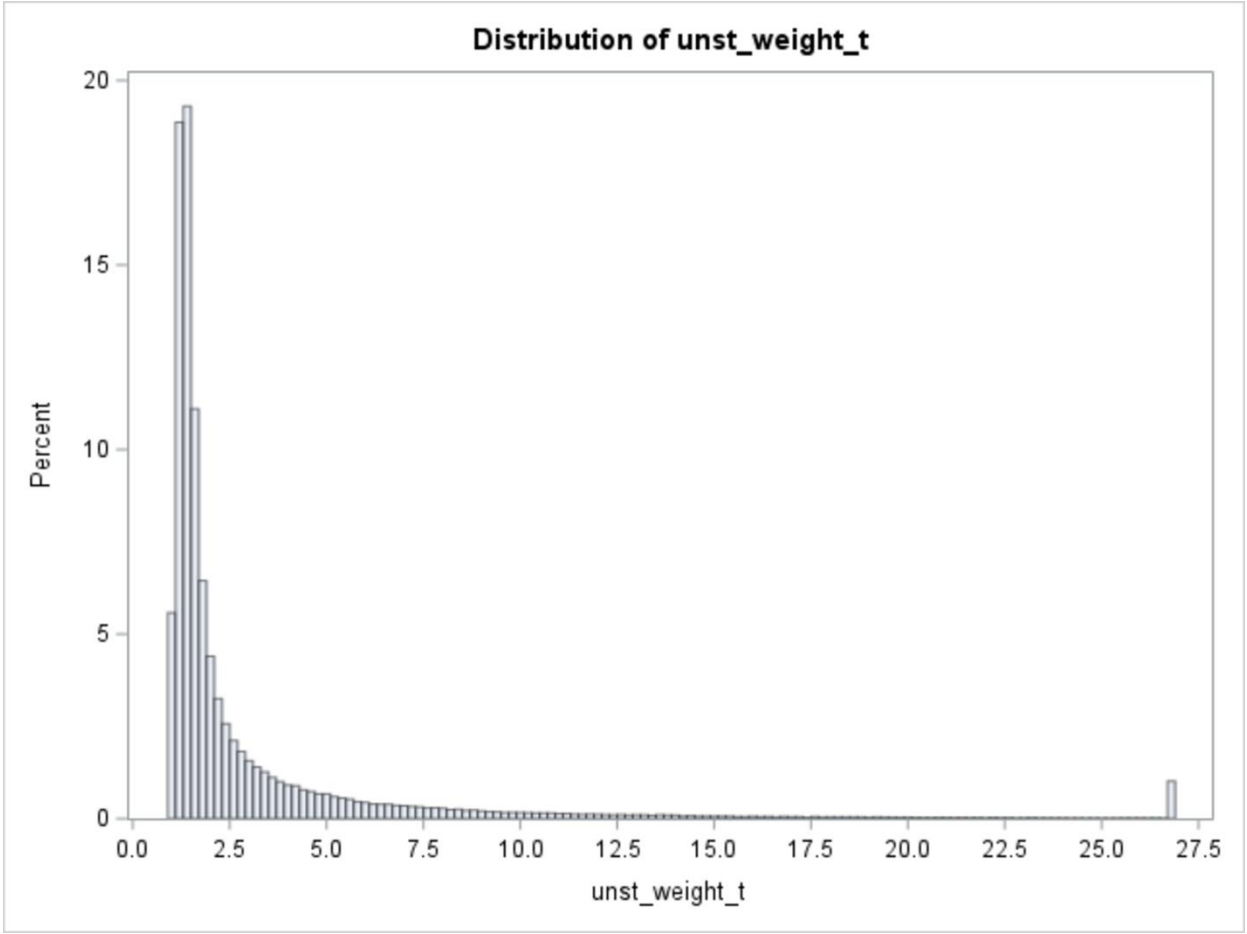


Figure S2. Distribution of unstabilized weights truncated at 99th percentile in the analysis of ischemic stroke

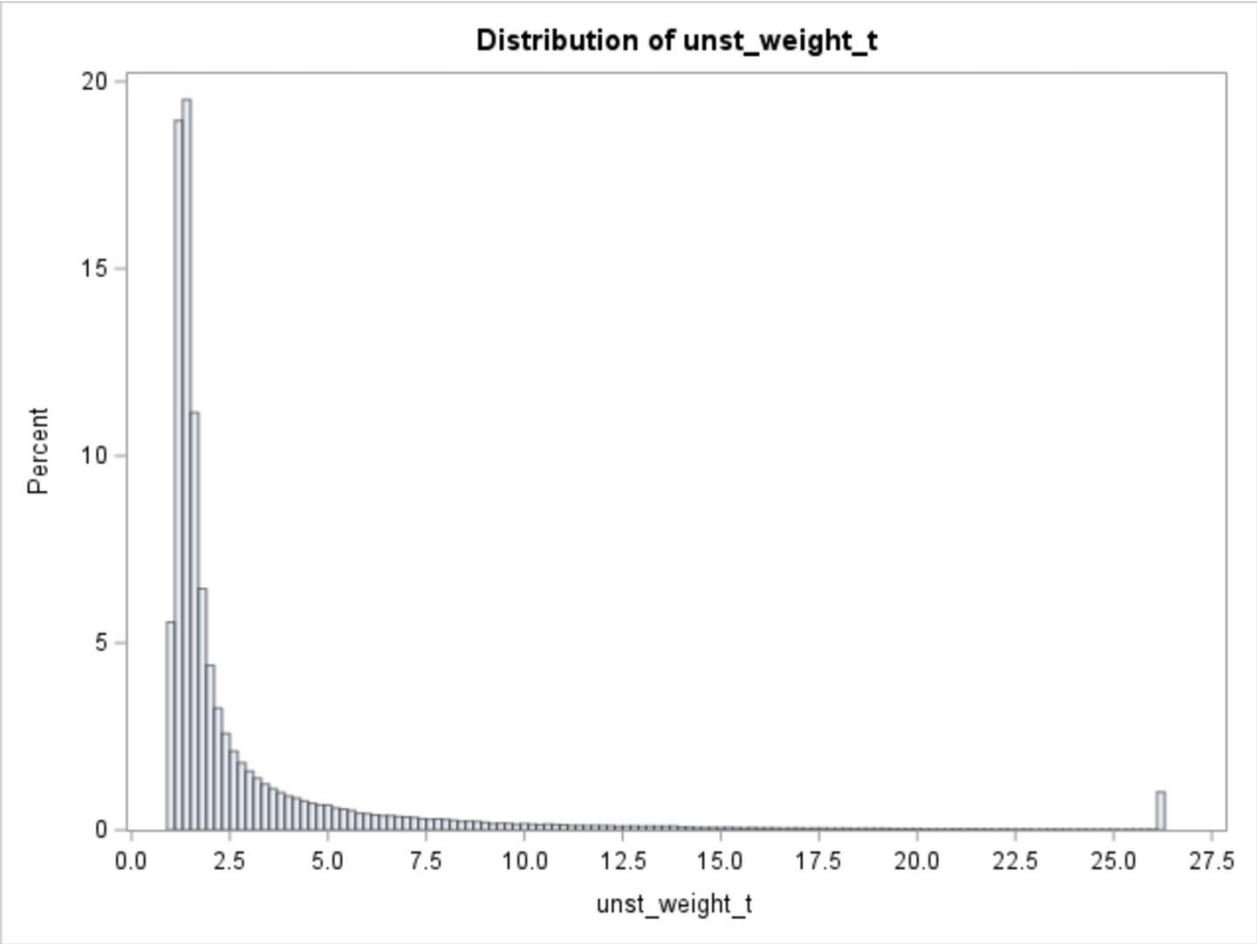


Figure S3. Distribution of unstabilized weights truncated at 99th percentile in the analysis of major bleeding

Technical appendix[164,175,186-189]

Step 1 – cloning: First, we organized each persons' data in discrete-time (person-month) format (month 1 to 12). We then duplicated each individual's data 5 times and assigned them to 5 different treatment strategies. The stacked data set is 5 times as large as the original sample. At this point, there was no difference in baseline covariates between 5 treatment groups as replicates are identical and no confounder exists. At baseline, some of the replicates already passed the cut-off values of CHA_2DS_2-VASc score to start OACs without starting OAC were removed from the dataset and vice versa. These patients were removed from the analysis. For example, a replicate of a patient with baseline CHA_2D_2VASc score of 4 with treatment strategy of "initiate OACs when CHA_2DS_2-VASc score ≥1" without OAC prescription in the first month were deleted.

Step 2 – Censoring: In this step, replicates whose data no longer consistent with their assigned strategy during follow-up were censored. We checked whether replicates in each month adhered to their assigned strategy and censored them if they did not adhere. In particular, suppose that individuals with CHA_2DS_2VASc score of 2 at baseline were assigned to treatment strategies "initiate OACs when CHA_2DS_2-VASc score ≥4". These individuals were censored if they received the treatment when their CHA_2D_2VASc score remained or rose to 3 at a specific month during follow-up. However, these patients were not censored if they remain untreated at CHA_2D_2VASc score is 2 or 3 or start OACs when their CHA_2D_2VASc score increases to 4.

Step 3 – Weighting: Because artificial censoring is informative and this informative censoring introduces selection bias, we weighed those who were artificially censored by IP weighting to reduce selection bias. That is, uncensored replicates have an equal weight as the inverse probability of remaining uncensored, given their own covariate history. The purpose is to upweight the uncensored replicates so that in the pseudo-population, censoring does not depend on baseline

fixed-time and time-varying covariates and censoring is no longer informative. To calculate the weights due to protocol violation, we need to calculate the probability of being censored, which is a product of the probability of starting OACs and by the probability of not being censored due to loss to follow-up.

Specifically, the censoring weight of each replicate at time t is proportional to the probability of being uncensored through time t conditioning on not having the outcome before time t ($Y_{t-1} = 0$), fixed-time covariates (L_0) and time-varying covariates ($\bar{L_t}$), treatment history ($\bar{A}_{t-1}$), where A_t= 1 indicates that an individual has received OACs and A_t= 1 denotes an untreated status by week t.[188] Since the censoring status of individuals depends on OAC initiation, we estimate the probability of remaining uncensored by the probability of initiating OACs for each individual at each month.[186,188-190] In the original dataset, we fitted a logistic regression as follow:

$$logit(\Pr[A_k = 1|A_{k-1} = 0, \bar{L}_k, \bar{Y}_{t-1} = 0, L_0, L_k]) = \theta_0 + \theta_1^T L_0 + \theta_2^T L_k$$

where the overline (i.e., $\bar{L}_k$) represents the history of covariate from the start of follow-up, the superscript T indicates a transpose of a vector of coefficients, θ_0 is a time-specific intercept (estimated via linear and quadratic terms for t), L_0 is the vector of baseline covariates, and L_k is the vector of time-varying covariates through time k, a is an indicator each treatment regimen, and i indicates the number of emulated trials. The unstabilized time-varying inverse-probability weight is computed by:

$$W_{i,t}^a = \prod_{k=0}^{t} \frac{1}{f(A_k|\bar{A}_{k-1}, \bar{Y}_{k-1}=0, \bar{C}_{k-1}=0, \bar{L}_k, L_0)}$$

We also address selection bias due to lost to follow-up and death. Separate logistic regression models for each treatment strategy were constructed to estimate the probability of being lost to

follow-up or death, given baseline and time-varying covariates. In the unexpanded dataset, the unstabilized natural censoring weights for loss-to-follow-up (W^{LFU}) for each individual at time t were calculated by

$$W_{i,t}^{n,LFU} = \prod_{k=0}^{t} \frac{1}{f(C_k|\bar{C}_{k-1}=0, \bar{Y}_{k-1}=0, \bar{A}_{k-1}=0, \bar{L}_k, L_0)}$$

where C_k is an indicator of natural censoring.[189,190] The final weights are the products of the probability of starting OACs and by the probability of not being censored due to loss to follow-up for each person-month. We truncated weights at 99th percentile to avoid extreme weights.

$$W_{total} = W_{i,t}^{a} \text{ x } SW_{i,t}^{n,LFU}$$

Under the assumption that (i) our measured baseline and time-varying confounders are sufficient to ensure exchangeability, (ii) positivity – that is the probability of each individual is greater than 0 within levels of covariates dynamic treatment effect, and (iii) weighted models are correctly specified, the treatment effect of each treatment regimen can be estimated using a marginal structural model (MSM).

$$logit(\Pr[Y_{t+1}^{a} = 1| L_0, Y_t^{a} = 0]) = \gamma_0 + \gamma_1^T L_0 + \gamma_2 a$$

where $Y_t^a$is the counterfactual outcome at month t under the strategy a=A.

To estimate the treatment effect, a weighted pooled logistic regression model was used to estimate the per-protocol effect of 4 "active" treatment strategies compared to the reference strategy. The regressors include f(t) – a function of time and time squared (time and time squared), treatment strategy, interactions between time and treatment, and all baseline covariates, weighted for censoring (W_{total})

$$logit(\Pr[Y_{k+1} = 1|A, L_0, \bar{Y}_k = 0]) = \beta_0 + \beta_1^T L_0 + \beta_2 A + \text{f(t)}$$

The pooled logistic regression is equivalent to discrete-time hazard model, with the assumption that the risk of developing a specific outcome of interest within levels of covariates is rare in each time interval (risk <0.1).[191,192] The odds ratio of developing the event is equivalent to the PP HR, estimated by exponentiated coefficient of treatment indicator (e^{β_2}).[191,192]

To estimate the weighted survival curves and standardize the curves to baseline distribution of covariates, we fitted a similar model with an interaction term between treatment regimen A and f(t) – a function of time and time squared to allow for non-proportional hazards. The model was then used to predict outcomes of interest under each treatment strategy $A = a$. The details for creating standardized survival curves can be found in published studies.[193]

Appendix for Aim 2.2 Manuscript

Table S1. Algorithms to identify study components from SEER-Medicare data

Component	Code type	Codes
Eligibility criteria		
AFib	ICD-9-CM	427.31 or 427.32
	ICD-10-CM	I48.xx
Breast cancer	ICD-O-3	C50.0-C50.9
Lung cancer	ICD-O-3	C34.0, C34.1, C34.2, C34.3, C34.8, C34.9, C33.9
Prostate cancer	ICD-O-3	C61.9
Exclusion criteria		
Valvular heart diseases	ICD-9-CM	0932, 394, 395, 396, 3970, 3971, 240, 4241, 242, 4243, 7460, 7461, 7462, 7463, 7464, 7465, 7466, 99602, 99671, V422
	ICD-10-CM	I05, I06, I07, I08, I34, I35, I36, I37, I39, Q22, Q23, T820, T8201, T8202, T8203, T8209, T8222, T826, Z952, Z953, Z954
	ICD-9-CM PX	351, 352, 3533, 3595, 3599
	ICD-10-PCS	02RF, 02RG, 02RH, 02RJ, 02QF, 02QG, 02QH, 02QJ
Heart valve repair or replacement	ICD-9-CM	V433
VTE	ICD-9-CM	4151 ,453, V1251, V1255
	ICD-10-CM	I26, I80, I81, I82, Z8671
Joint replacement	ICD-9-CM PX	8151, 8152, 8154
	ICD-10-PCS	0SR9019, 0SR901A, 0SR901Z, 0SR9029, 0SR902A, 0SR902Z, 0SR9039, 0SR903A, 0SR903Z, 0SR9049, 0SR904A, 0SR904Z, 0SR9069, 0SR906A, 0SR906Z, 0SR907Z, 0SR90EZ, 0SR90J9, 0SR90JA, 0SR90JZ, 0SR90KZ, 0SRA009, 0SRA00A, 0SRA00Z, 0SRA019, 0SRA01A, 0SRA01Z, 0SRA039, 0SRA03A, 0SRA03Z, 0SRA07Z, 0SRA0J9, 0SRA0JA, 0SRA0JZ, 0SRA0KZ, 0SRB019, 0SRB01A, 0SRB01Z, 0SRB029, 0SRB02A, 0SRB02Z, 0SRB039, 0SRB03A, 0SRB03Z, 0SRB049, 0SRB04A, 0SRB04Z, 0SRB069, 0SRB06A, 0SRB06Z, 0SRB07Z, 0SRB0EZ, 0SRB0J9, 0SRB0JZ, 0SRB0KZ, 0SRE009, 0SRE00A, 0SRE00Z,

		0SRE019, 0SRE01A, 0SRE039, 0SRE03A, 0SRE03Z, 0SRE07Z, 0SRE0J9, 0SRE0JA, 0SRE0JZ, 0SRR019, 0SRR01A, 0SRR01Z, 0SRR039, 0SRR03A, 0SRR03Z, 0SRB0JA, 0SRR07Z, 0SRR0J9, 0SRR0JA, 0SRR0JZ, 0SRR0KZ, 0SRS019, 0SRE01Z, 0SRS01A, 0SRS01Z, 0SRS039, 0SRS03A, 0SRS03Z, 0SRS07Z, 0SRE0KZ, 0SRS0J9, 0SRS0JA, 0SRS0JZ, 0SRS0KZ, 0SRC069, 0SRC06A, 0SRC06Z, 0SRC07Z, 0SRC0EZ, 0SRC0J9, 0SRC0JA, 0SRC0JZ, 0SRC0KZ, 0SRC0L9, 0SRC0LA, 0SRC0LZ, 0SRC0M9, 0SRC0MA, 0SRC0MZ, 0SRC0N9, 0SRC0NA, 0SRC0NZ, 0SRD069, 0SRD06A, 0SRD06Z, 0SRD07Z, 0SRD0EZ, 0SRD0J9, 0SRD0JA, 0SRD0JZ, 0SRD0KZ, 0SRD0L9, 0SRD0LA, 0SRD0LZ, 0SRD0M9, 0SRD0MA, 0SRD0MZ, 0SRD0N9, 0SRD0NA, 0SRD0NZ, 0SRT07Z, 0SRT0J9, 0SRT0JA, 0SRT0JZ, 0SRT0KZ, 0SRU07Z, 0SRU0J9, 0SRU0JA, 0SRU0JZ, 0SRU0KZ, 0SRV07Z, 0SRV0J9, 0SRV0JA, 0SRV0JZ, 0SRV0KZ, 0SRW07Z, 0SRW0J9, 0SRW0JA, 0SRW0JZ, 0SRW0KZ
Renal impairment stage 5/ESRD	ICD-9-CM	40301, 40311, 40391, 5855, 5856, V451, V56
	ICD-10-CM	I120, I1311, I132, N185, Y841, Z49, Z9115, Z992
	ICD-9-CM PX	3995, 5498
	ICD-10-PCS	3E1M39Z, 5A1D70Z, 5A1D80Z, 5A1D90Z
History of stroke/TIA	ICD-9-CM	36231, 36232, 36233, 36234, 43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, 436, 430, 431, 43391, 435
	ICD-10-CM	H340, H341, H342, I63, I60, I61, I62, I63, G45, I6782, I6789
Major surgery		Not included due to large number of codes
Intracranial/Spinal bleeding	ICD-9-CM	430, 431, 432, 852, 853,
	ICD-10-CM	I60, I61, I62, S064, S065, S066
Intraocular bleeding	ICD-9-CM	36281, 37923, 36361, 36362,
	ICD-10-CM	H356, H3130, H3131, H431
Retroperitoneal bleeding	ICD-9-CM	56881
	ICD-10-CM	K661
Atraumatic intra-articular bleeding	ICD-9-CM	7191
	ICD-10-CM	M250
Gastrointestinal bleeding	ICD-9-CM	4560, 45620, 5301, 5307, 53082, 5310, 5311, 5312, 5313, 5314, 5315, 5316, 5317, 5319, 5320, 5321, 5322, 5323, 5324, 5325, 5326, 5327, 5329, 5330, 5331, 5332, 5333, 5334, 5335, 5336, 5337, 5339, 5340, 53400, 53401, 5341, 5342, 5343, 5344, 5345, 5346, 5347, 5349, 53500,

		53501, 53510, 53511, 53520, 53521, 53530, 53531, 53540, 53541, 53550, 53551, 53560, 53561, 53783, 5780, 4551, 4552, 4554, 4555, 4556, 4557, 4558, 4559, 56200, 56201, 56202, 56203, 56210, 56211, 56212, 56213, 5693, 56985, 5781, 5789
	ICD-10-CM	I8501, I8511, K20, K210, K2211, K226, K250, K251, K252, K254, K255, K256, K260, K261, K262, K264, K265, K266, K270, K271, K272, K274, K275, K276, K280, K281, K282, K284, K285, K286, K2901, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K31811, K920, K5521, K5701, K5711, K5721, K5731, K5741, K5751, K5753, K5781, K5791, K5793, K625, K640, K641, K642, K643, K644, K645, K648, K649, K921, K922
Outcomes		
Ischemic stroke (new diagnosis)	ICD-9-CM	36231, 36232, 36233, 36234, 43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, 436
	ICD-10-CM	H340, H341, H342, I63
Major bleeding	ICD-9-CM	3361, 36361, 36362, 36372, 37632, 37742, 37923, 4230, 430, 431, 432, 56881, 7191, 72992, 852, 853, 86601, 86602, 86611, 86612
	ICD-10-CM	G9519, H0523, H3130, H3131, H3141, H431, H4702, I230, I312, I60, I61, I62, K661, M250, M7981, S064, S065, S066, S260, S3701, S3702, S3703, S3704, S3705, S3706
VTE	ICD-9-CM	See eligibility criteria
	ICD-10-CM	
Intracranial bleeding	ICD-9-CM	See eligibility criteria
	ICD-10-CM	
GI bleeding	ICD-9-CM	See eligibility criteria
	ICD-10-CM	
Non-critical site bleeding	ICD-9-CM	2800, 2851, 4551, 4552, 4554, 4555, 4556, 4557, 4558, 4559, 4560, 45620, 4590, 5301, 5307, 5310, 5311, 5312, 5313, 5314, 5315, 5316, 5317, 5319, 5320, 5321, 5322, 5323, 5324, 5325, 5326, 5327, 5329, 5330, 5331, 5332, 5333, 5334, 5335, 5336, 5337, 5339, 5340, 5341, 5342, 5343, 5344, 5345, 5346, 5347, 5349, 53500, 53501, 53510, 53511, 53520, 53521, 53530, 53531, 53540, 53541, 53550, 53551, 53560, 53561, 53783, 56200, 56201, 56202, 56203, 56210, 56211, 56212, 56213, 5693, 56985, 5780, 5781, 5789, 59381, 59970, 59971, 6236, 6238, 6266, 6268, 7847, 7848, 7863, D500, D62, I8501, I8511, K20, K210, K2211, K226, K250
	ICD-10-CM	K251, K252, K254, K255, K256, K260, K261, K262, K264, K265, K266, K270, K271, K272, K274, K275, K276, K280, K281, K282, K284, K285, K286, K2901, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K31811, K5521, K5701, K5711, K5721, K5731, K5741, K5751, K5753, K5781, K5791, K5793, K625, K640, K641, K642, K643, K644, K645, K648, K649, K920, K921, K922, N897, N898, N921, N938, N939, R040, R041, R042, R310, R319, R58

Covariates		
CHF	ICD-9-CM	39891, 40201, 40211, 40291, 40401, 40403, 40411, 40413, 40491, 40493, 4254, 4259, 428
	ICD-10-CM	I0981, I110, I130, I132, I425, I428, I50
HTN	ICD-9-CM	401, 402, 403, 404, 405
	ICD-10-CM	I10, I11, I12, I13, I14, I15, I16
DM	ICD-9-CM	250, 3572, 3620, 36641,
	ICD-10-CM	E10, E11, E13
Vascular diseases	ICD-9-CM	410, 412, 4400, 4402, 4403, 4409, 4442, 4439, 44481
	ICD-10-CM	I21, I252, I700, I702, I703, I704, I705, I706, I707, I709, I742, I743, I744, I739, I745
Renal diseases	ICD-9-CM	0160, 0954, 1890, 1899, 2230, 23691, 2504, 2714, 2741, 28311, 403, 404, 4401, 4421, 4473, 5724, 580, 581, 582, 583, 584, 585, 586, 587, 588, 591, 6421, 6462, 75312, 75313, 75314, 75315, 75316, 75317, 75319, 7532, 7944, V420, V451, V56
	ICD-10-CM	A1811, A5275, C649, C689, D4100, E1129, E1029, E1121, E1021, E748, M1030, N200, D593, I120, I129, I1310, I130, I1311, I132, I1311, I701, I722, I773, K767, N00, N01, N02, N03, N04, N05, N06, N07, N08, N1330, O10419, O10411, O10412, O10413, O1042, O1043, O26839, O1214, O26831, O26832, O26833, Q613, Q612, Q6119, Q614, Q615, Q6102, Q618, Q6239, Q6211, Q6212, Q6231, Q6210, Q6211, R944, Z940, Z992, Z9115, Z4931, Z4901, Z4902, Z4932
Liver diseases	ICD-9-CM	070, 07271, 09162, 1305, 571, 573, 7948
	ICD-10-CM	A5145, B0081, B15, B16, B17, B18, B19, B251, B2681, B581, B942, K70, K71, K72, K73, K74, K75, K76, K77, R94.5
Bleeding disposition	ICD-9-CM	430, 431, 432, 56881, 5997, 5307, 5310, 5312, 5314, 5316, 5320, 5322, 5324, 5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 5693, 53501, 53511, 53521, 53531, 53541, 53551, 53561, 53571, 53783, 53784, 56202, 56203, 56212, 56213, 56985, 578, 7847, 7863, 6262, 7191, 37272, 459
	ICD-10-CM	I60, I61, I62, K661, R31, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K2901, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K31811, K3182, K5701, K5711, K5713, K5721, K5731, K5733, K5741, K5751, K5753, K5781, K5791, K5793, K5521, K920, K921, K922, R040, R042, N920, M250, M122, H113, R58
Alcohol use disorders	ICD-9-CM	291, 303, 3050, 3575, 4255, 5353, 5710, 5711, 5712, 5713, 7903
	ICD-10-CM	E8600, V113, F10, Z714

Asthma/COPD	ICD-9-CM	491, 492, 496, 49300, 49301, 49302, 49310, 49311, 49312, 49320, 49321, 49322, 49381, 49382, 49390, 49391, 49392
	ICD-10-CM	J41, J42, J43, J44, J4520, J4521, J4522, J4530, J4531, J4532, J4540, J4541, J4542, J4550, J4551, J4552, J45901, J45902, J45909, J45990, J45991, J45998
Hematological disorders	ICD-9-CM	280, 281, 282, 283, 284, 285, 286, 2871, 2873, 2874, 2875
	ICD-10-CM	D46, D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64
Dementia	ICD-9-CM	3310, 3311, 3312, 3317, 290, 2940, 2941, 2948, 797
	ICD-10-CM	G30, G310, G311, G312, G319, F02, F03, F04, R4181
Depression	ICD-9-CM	2962, 2963, 2965, 3004, 309, 311
	ICD-10-CM	F32, F33, F341, F43
Thrombocytopenia	ICD-9-CM	286, 287
	ICD-10-CM	D68, D69
AKD	ICD-9-CM	584
	ICD-10-CM	N17
Peptic ulcer diseases	ICD-9-CM	533, V1271,
	ICD-10-CM	K27, Z8711
Aspirin/NSAIDs	Generic drug name	ASPIRIN, CLOPIDOGREL, CELECOXIB, DICLOFENAC, DIFLUNISAL, ETODOLAC, FENOPROFEN, FLURBUPROFEN, IBUPROFEN, INDOMETHACIN, KETOPROFEN, KETOROLAC, MEFENAMIC, MELOXICAM, NABUMETONE, NAPROXEN, OXAPROZIN, PIROXICAM, SULINDAC, TOLMETIN
ACEI/ARB	Generic drug name	BENAZEPRIL, CAPTOPRIL, ENALAPRIL, FOSINOPRIL, LISINOPRIL, MOEXIPRIL, PERINDOPRIL, QUINAPRIL, RAMIPRIL, TRANDOLAPRIL LOSARTAN, IRBESARTAN, OLMESARTAN, VALSARTAN, TELMISARTAN, CANDESARTAN, AZILSARTAN
CCB	Generic drug name	AMLODIPINE, DILTIAZEM, FELODIPINE, ISRADIPINE, LEVAMLODIPINE, NIFEDIPINE, NISOLDIPINE, VERAPAMIL
BB	Generic drug name	ACEBUTOLOL, ATENOLOL, BETAXOLOL, BISOPROLOL, CARVEDILOL, LABETALOL, METOPROLOL , NADOLOL, NEBIVOLOL, PINDOLOL, PROPRANOLOL, TIMOLOL
Antiarrhythmic drugs	Generic drug name	QUINIDINE, PROCAINAMIDE, DISOPYRAMIDE, LIDOCAINE , MEXILETINE, FLECAINIDE, PROPAFENONE, AMIODARON, EDRONEDARONE, DOFETILIDE, SOTALOL, IBUTILID, DIGOXIN
Diuretics	Generic drug name	HYDROCHLOROTHIAZIDE, CHLOROTHIAZIDE, CHLORTHALIDONE, EPLERENONE, FUROSEMIDE, INDAPAMIDE, SPIRONOLACTONE , TORSEMIDE, METOLAZONE

Statins	Generic drug name	ATORVASTATIN, FLUVASTATIN, LOVASTATIN, PITAVASTATIN, PRAVASTATIN, ROSUVASTATIN, SIMVASTATIN
PPIs	Generic drug name	OMEPRAZOLE, ESOMEPRAZOLE, LANSOPRAZOLE, DEXLANSOPRAZOLE, PANTOPRAZOLE, RABEPRAZOLE
SSRI/SNRI	Generic drug name	CITALOPRAM, ESCITALOPRAM, FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE, VILAZODONE, DULOXETINE, VENLAFAXINE, LEVOMILNACIPRAN DESVENLAFAXINE

Table S1. Characteristics of patients with AFib and cancer who initiated oral anticoagulants in SEER-Medicare (2012-2019)

	DOAC initiators (N=5371)	Warfarin initiators (N=1778)	p-value
Demographics			
Index age (Mean, SD)	77.32 (6.73)	77.09 (6.50)	0.2108
Year of AFib diagnosis			<.0001
2012-2015	1478 (27.52)	1175 (65.72)	
2016-2019	3893 (72.48)	613 (34.28)	
Female	2883 (53.68)	911 (50.95)	0.0454
Race/ethnicity			0.6995
Non-Hispanic White	4660 (86.76)	1558 (86.76)	
Non-Hispanic Black	274 (5.10)	95 (5.31)	
Others	437 (8.14)	135 (7.55)	
Region			<.0001
Midwest	484 (9.01)	266 (14.88)	
Northeast	2386 (44.42)	761 (42.56)	
South	977 (18.19)	275 (15.38)	
West	1524 (28.36)	486 (27.18)	
Medicaid eligible	886 (16.50)	321 (17.95)	0.1541
Urbanicity			<.0001
Metropolitan	4676 (87.06)	1449 (81.04)	
Micropolitan	388 (7.22)	191 (10.68)	
Unknown/Missing	307 (5.72)	148 (8.28)	
Socioeconomic status (Census Tract)			
Household median income (Median, IQR)	64894.00 (46275.00-90291.00)	58494.00 (44751.00-80924.00)	<.0001
Percentage of residents living below poverty (Median, IQR)	8.39 (4.56-15.64)	9.51 (5.32-16.59)	<.0001
Percentage of non-high school graduates (Median, IQR)	9.00 (4.91-16.21)	9.59 (5.55-16.31)	0.0054
Percentage of high school only (Median, IQR)	26.20 (17.74-34.56)	28.57 (20.35-36.05)	<.0001
Percentage of some college education (Median, IQR)	27.56 (22.31-33.01)	29.05 (23.78-34.31)	<.0001

Percentage of college education and above (Median, IQR)	30.98 (17.82-47.72)	26.27 (16.51-42.08)	<.0001
Cancer characteristics			
Time from cancer diagnosis to the onset of AFib (month, Median, IQR)	32 (11-56)	14 (2-37)	<.0001
Time from the onset of AFib to treatment initiation (month, Median, IQR)	0.26 (0.07-0.93)	0.30 (0.10-0.89)	0.0036
Cancer type			<.0001
Breast	2182 (40.63)	577 (32.27)	
Lung	1361 (25.34)	705 (39.43)	
Prostate	1828 (34.03)	506 (28.30)	
Active cancer	1399 (26.05)	519 (29.03)	0.0137
Cancer grade			<.0001
I	814 (15.16)	250 (13.98)	
II	1997 (37.18)	586 (32.77)	
III	1614 (30.05)	561 (31.38)	
Others	946 (17.61)	391 (21.87)	
Number of regional nodes examined			0.0026
<12	3378 (62.89)	1046 (58.50)	
≥12	317 (5.90)	112 (6.26)	
Unknown/missing	1676 (31.20)	630 (35.23)	
Tumor size			<.0001
≤2 cm	1361 (25.34)	384 (21.48)	
2-5 cm	834 (15.53)	280 (15.66)	
>5 cm	287 (5.34)	140 (7.83)	
Unknown/missing	2889 (53.79)	984 (55.03)	
TMN classification			
T stage			<.0001
TX	158 (2.94)	70 (3.91)	
T0	276 (5.14)	59 (3.30)	
T1	1761 (32.79)	455 (25.45)	
T2	1096 (20.41)	349 (19.52)	
T3	300 (5.59)	128 (7.16)	
T4	226 (4.21)	92 (5.15)	

Unknown/missing	1554 (28.93)	635 (35.51)	
N stage			<.0001
NX	179 (3.33)	62 (3.47)	
N0	2877 (53.57)	802 (44.85)	
N1	354 (6.59)	104 (5.82)	
N2	303 (5.64)	132 (7.38)	
N3	104 (1.94)	53 (2.96)	
Unknown/missing	1554 (28.93)	635 (35.51)	
M stage			<.0001
M0	3446 (64.53)	964 (53.83)	
M1	349 (6.50)	213 (10.89)	
Unknown/missing	1556 (28.97)	636 (35.57)	
Summary stage			<.0001
In situ	390 (7.26)	91 (5.09)	
Local	3187 (59.34)	954 (53.36)	
Regional	983 (18.30)	361 (20.19)	
Distant	564 (10.50)	287 (16.05)	
Unknown/missing	247 (4.60)	95 (5.31)	
Breast cancer-specific (N=2759)			
ER positive	1350 (61.87)	314 (54.42)	0.0014
PR positive	1167 (53.48)	269 (46.62)	0.0005
HER2 positive	121(5.55)	27 (4.68)	0.0251
Lung cancer-specific (N=2066)			
Histologic type			0.7832
Adenoma	635 (46.66)	324 (45.94)	
NOS	208 (15.28)	110 (15.60)	
Squamous	409 (30.05)	222 (31.49)	
Others	109 (8.01)	49 (6.95)	
Cancer treatment			
Use of potentially interacting antineoplastic agents	1482 (27.59)	427 (23.88)	0.0021
Radiation	219 (4.08)	103 (5.76)	0.0029
Surgery	33 (0.61)	19 (1.06)	0.0532
Disease risk score			

CHA_2DS_2-VASc			0.1393
2	864 (16.44)	294 (16.44)	
3	1505 (28.02)	450 (25.17)	
4	1562 (29.08)	544 (30.43)	
5	962 (17.91)	316 (17.67)	
≥6	478 (8.90)	184 (10.35)	
HAS-BLED			0.0048
1	544 (10.13)	213 (11.91)	
2	2191 (40.79)	651 (36.41)	
3	1709 (31.82)	568 (31.77)	
4	714 (13.29)	282 (15.77)	
5	184 (3.43)	62 (3.47)	
≥6	29 (0.54)	12 (0.67)	
NCI Comorbidity score (Mean, SD)	0.62 (0.57)	0.70 (0.60)	<.0001
Individual comorbidities			
Asthma/COPD	1766 (32.88)	732 (40.94)	<.0001
Hematological disorders	1557 (29.36)	516 (28.86)	0.6856
Dementia	249 (4.64)	55 (3.08)	0.0046
Depression	791 (14.73)	231 (12.92)	0.0584
Thrombocytopenia	285 (5.31)	97 (5.43)	0.8465
Acute kidney diseases	243 (4.52)	96 (5.37)	0.1452
Peptic ulcer diseases	35 (0.65)	18 (1.01)	0.1293
Medications			
ACE inhibitors/ARBs	3065 (57.07)	985 (55.09)	0.1442
CCB	1853 (34.50)	605 (33.84)	0.6088
Beta blockers	2389 (44.48)	807 (45.13)	0.6296
Antiarrhythmic medications	297 (5.53)	124 (6.94)	0.0068
Diuretics	2145 (39.94)	733 (41.00)	0.4290
Statin	2906 (54.11)	938 (52.46)	0.1804
PPIs	1446 (26.92)	450 (25.17)	0.1453
SSRIs/SNRIs	967 (18.00)	280 (15.66)	0.0236

Table S2. Distributions of time-varying weights before and after truncation

Variable	Mean	Minimum	Maximum	99th Pctl	Std Dev	Median	25th Pctl	75th Pctl
ITT analysis								
Stabilized weights	1.43	0.02	4377.91	5.99	21.34	0.99	0.93	1.02
Truncated stabilized weights (99th percentile)	1.08	0.02	5.99	5.99	0.67	0.99	0.93	1.02
PP analysis								
Stabilized weights	1.51	0.02	6130.76	6.06	28.59	0.99	0.93	1.02
Truncated stabilized weights (99th percentile)	1.08	0.02	6.06	6.06	0.68	0.99	0.93	1.02

ITT Intention-to-treat, PP Per-protocol, Pctl percentile

Table S3. Subgroup analyses for comparative effectiveness and safety between DOACs and warfarin in patients with atrial fibrillation and cancer

	Event (n, %)		Adjusted HR (95% CI)
	DOACs	**Warfarin**	
Cancer type			
Breast (N=2759)			
Stroke	17 (0.78)	5 (0.87)	0.95 (0.42-2.19)
Major bleeding	11 (0.50)	4 (0.69)	0.88 (0.28-2.72)
VTE	6 (0.27)	7 (1.21)	**0.17 (0.07-0.44)**
Intracranial bleeding	10 (0.46)	3 (0.52)	1.04 (0.29-3.66)
Gastrointestinal bleeding	48 (2.20)	13 (2.25)	0.91 (0.55-1.51)
Non-critical site bleeding	60 (2.75)	20 (3.47)	0.78 (0.50-1.15)
Lung (N=2066)			
Stroke	17 (1.25)	8 (1.13)	1.07 (0.56-2.02)
Major bleeding	10 (0.73)	8 (1.13)	0.57 (0.27-1.19)
VTE	18 (1.32)	12 (1.70)	1.46 (0.81-2.61)
Intracranial bleeding	7 (0.51)	7 (0.99)	0.49 (0.22-1.09)
Gastrointestinal bleeding	65 (4.78)	25 (3.55)	0.99 (0.67-1.47)
Non-critical site bleeding	72 (5.53)	39 (5.53)	0.73 (0.52-1.02)
Prostate (N =2334)			
Stroke	11 (0.60)	2 (0.40)	-
Major bleeding	14 (0.77)	2 (0.40)	-
VTE	8 (0.44)	1 (0.20)	-
Intracranial bleeding	11 (0.60)	2 (0.40)	2.18 (0.49-9.68)
Gastrointestinal bleeding	39 (2.13)	24 (4.74)	**0.67 (0.42-0.98)**
Non-critical site bleeding	53 (2.90)	29 (5.73)	**0.66 (0.44-0.99)**
Cancer status			
Active cancer (N=1918)			
Stroke	10 (0.71)	3 (0.58)	1.34 (0.41-4.41)
Major bleeding	9 (0.64)	7 (1.35)	1.20 (0.57-2.77)
VTE	12 (0.86)	4 (0.77)	1.12 (0.50-2.50)
Intracranial bleeding	6 (0.43)	6 (1.16)	0.74 (0.28-1.94)
Gastrointestinal bleeding	50 (3.57)	19 (3.66)	0.72 (0.47-1.12)
Non-critical site bleeding	61 (4.36)	29 (5.59)	0.58 (0.58-1.83)
Inactive (N=5241)			

Stroke	35 (0.88)	12 (0.95)	1.12 (0.63-1.98)
Major bleeding	26 (0.65)	7 (0.55)	0.85 (0.44-1.65)
VTE	20 (0.50)	16 (1.26)	**0.58 (0.34-0.99)**
Intracranial bleeding	22 (0.55)	6 (0.47)	0.81 (0.40-1.63)
Gastrointestinal bleeding	103 (2.59)	43 (3.39)	0.76 (0.56-1.05)
Non-critical site bleeding	124 (3.12)	59 (4.65)	**0.62 (0.48-0.81)**
Cancer stage			
Local (N=4333)			
Stroke	22 (0.66)	7 (0.70)	1.53 (0.69-3.42)
Major bleeding	19 (0.57)	5 (0.50)	1.69 (0.65-4.39)
VTE	14 (0.42)	7 (0.70)	0.91 (0.44-2.00)
Intracranial bleeding	16 (0.48)	5 (0.50)	1.19 (0.44-3.18)
Gastrointestinal bleeding	88 (2.64)	36 (3.57)	**0.69 (0.49-0.98)**
Non-critical site bleeding	110 (3.30)	52 (5.16)	**0.58 (0.44-0.78)**
Regional (N=1414)			
Stroke	11 (1.07)	2 (0.52)	-
Major bleeding	6 (0.58)	4 (1.05)	**0.41 (0.17-0.97)**
VTE	9 (0.87)	4 (1.05)	0.88 (0.32-2.42)
Intracranial bleeding	5 (0.48)	4 (1.06)	**0.36 (0.15-0.88)**
Gastrointestinal bleeding	35 (3.39)	12 (3.17)	0.76 (0.44-1.32)
Non-critical site bleeding	43 (4.17)	17 (4.45)	0.77 (0.47-1.24)
Distant (N=899)			
Stroke	8 (1.34)	4 (1.34)	0.92 (0.27-3.12)
Major bleeding	5 (0.84)	4 (1.34)	0.91 (0.24-3.35)
VTE	8 (1.34)	6 (2.01)	0.58 (0.20-1.66)
Intracranial bleeding	4 (0.67)	2 (0.66)	-
Gastrointestinal bleeding	24 (4.03)	11 (3.69)	0.96 (0.47-1.96)
Non-critical site bleeding	26 (4.37)	15 (5.03)	1.19 (0.73-1.95)
Tumor grade			
Grade I (N=1064)			
Stroke	4 (0.49)	0 (0.00)	-
Major bleeding	6 (0.74)	1 (0.40)	-
VTE	4 (0.49)	2 (0.49)	-
Intracranial bleeding	5 (0.61)	1 (0.40)	-
Gastrointestinal bleeding	21 (2.58)	4 (1.60)	0.70 (0.37-1.32)

Non-critical site bleeding	25 (3.07)	8 (3.20)	0.74 (0.39-1.42)
Grade II (N=2583)			
Stroke	20 (1.00)	4 (0.68)	2.24 (0.80-6.29)
Major bleeding	11 (0.55)	4 (0.68)	0.98 (0.32-3.10)
VTE	8 (0.40)	6 (1.02)	**0.42 (0.19-0.98)**
Intracranial bleeding	9 (0.45)	3 (0.51)	1.31 (0.33-3.96)
Gastrointestinal bleeding	49 (2.45)	24 (4.10)	0.72 (0.45-1.14)
Non-critical site bleeding	61 (3.05)	31 (5.29)	**0.61 (0.41-0.90)**
Grade III (N=2175)			
Stroke	9 (0.56)	4 (0.71)	1.12 (0.34-3.69)
Major bleeding	5 (0.50)	6 (1.07)	**0.28 (0.12-0.67)**
VTE	9 (0.56)	7 (1.25)	0.60 (0.24-1.48)
Intracranial bleeding	6 (0.37)	5 (0.89)	**0.22 (0.08-0.60)**
Gastrointestinal bleeding	48 (2.97)	22 (3.92)	0.74 (0.47-1.16)
Non-critical site bleeding	57 (3.53)	27 (4.81)	0.73 (0.48-1.09)

VTE Venous Thromboembolism, DOACs Direct Oral Anticoagulants, HR Hazard Ratio, CI Confidence Interval

Table S4. Sensitivity analysis for comparative effectiveness and safety between DOACs and warfarin in patients with atrial fibrillation and cancer

	Event (n, %)		Adjusted HR (95% CI)
	DOACs	**Warfarin**	
Sensitivity analysis 1 (N=7934)			
Stroke	51 (0.86)	16 (0.80)	1.16 (0.73-1.85)
Major bleeding	36 (0.61)	16 (0.80)	0.82 (0.51-1.34)
VTE	34 (0.57)	22 (1.10)	0.75 (0.49-1.15)
Intracranial bleeding	29 (0.47)	14 (0.70)	0.71 (0.42-1.20)
Gastrointestinal bleeding	169 (2.84)	69 (3.46)	0.79 (0.62-1.00)
Non-critical site bleeding	204 (3.03)	99 (4.97)	**0.63 (0.52-0.78)**
Sensitivity analysis 2 (N=7558)			
Stroke	46 (0.81)	15 (0.79)	1.24 (0.75-2.05)
Major bleeding	35 (0.62)	14 (0.74)	0.91 (0.54-1.52)
VTE	35 (0.62)	22 (1.16)	0.74 (0.48-1.15)
Intracranial bleeding	28 (0.49)	12 (0.63)	0.81 (0.46-1.41)
Gastrointestinal bleeding	155 (2.74)	63 (3.32)	**0.77 (0.60-0.99)**
Non-critical site bleeding	187 (3.30)	92 (4.85)	**0.61 (0.50-0.76)**
Sensitivity analysis 3 (N=7159)			
Stroke	89 (1.65)	31 (1.73)	1.21 (0.98-1.50)
Major bleeding	69 (1.28)	34 (1.89)	0.74 (0.49-1.12)
VTE	54 (1.00)	33 (1.84)	**0.80 (0.66-0.98)**
Intracranial bleeding	60 (1.12)	27 (1.50)	0.81 (0.51-1.28)
Gastrointestinal bleeding	248 (4.61)	97 (5.40)	0.90 (0.71-1.14)
Non-critical site bleeding	301 (5.60)	135 (7.52)	**0.64 (0.56-0.74)**
Sensitivity analysis 4 (N=6266)			
Stroke	37 (0.77)	11 (0.74)	1.68 (0.88-3.24)
Major bleeding	30 (0.63)	10 (0.67)	0.88 (0.49-1.59)
VTE	24 (0.50)	14 (0.94)	0.64 (0.38-1.07)
Intracranial bleeding	24 (0.50)	10 (0.67)	0.67 (0.37-1.24)
Gastrointestinal bleeding	129 (2.70)	51 (3.42)	**0.69 (0.52-0.91)**
Non-critical site bleeding	159 (3.33)	73 (4.90)	**0.59 (0.47-0.76)**
Sensitivity analysis 5 (N=6777)			
Stroke	41 (0.81)	14 (0.83)	1.20 (0.72-2.01)
Major bleeding	33 (0.65)	14 (0.83)	0.84 (0.51-1.41)

VTE	27 (0.53)	20 (1.18)	0.66 (0.42-1.05)
Intracranial bleeding	27 (0.53)	12 (0.71)	0.76 (0.44-1.03)
Gastrointestinal bleeding	145 (2.85)	59 (3.47)	0.77 (0.60-1.01)
Non-critical site bleeding	176 (3.46)	84 (4.97)	**0.63 (0.51-0.79)**
Sensitivity analysis 6 (N=7159)			
Stroke	45 (0.84)	15 (0.84)	1.17 (0.66-2.06)
Major bleeding	35 (0.65)	14 (0.78)	0.84 (0.47-1.50)
VTE	32 (0.60)	20 (1.12)	0.59 (0.35-1.00)
Intracranial bleeding	28 (0.52)	12 (0.67)	0.81 (0.43-1.54)
Gastrointestinal bleeding	153 (2.58)	62 (3.47)	0.80 (0.60-1.06)
Non-critical site bleeding	185 (3.44)	88 (4.92)	**0.67 (0.53-0.86)**

VTE Venous Thromboembolism, DOACs Direct Oral Anticoagulants, HR Hazard Ratio, CI Confidence Interval

Sensitivity analysis 1. Using a grace period of 6 months for OAC initiation
Sensitivity analysis 2. Including individuals with all levels of baseline CHA_2DS_2-VASc score
Sensitivity analysis 3. Extending maximum follow-up to 36 months
Sensitivity analysis 4. Excluding patients with metastatic cancer at baseline
Sensitivity analysis 5. Excluding patients with thrombocytopenia at baseline
Sensitivity analysis 6. Truncating stabilized weights at 95^{th} percentile

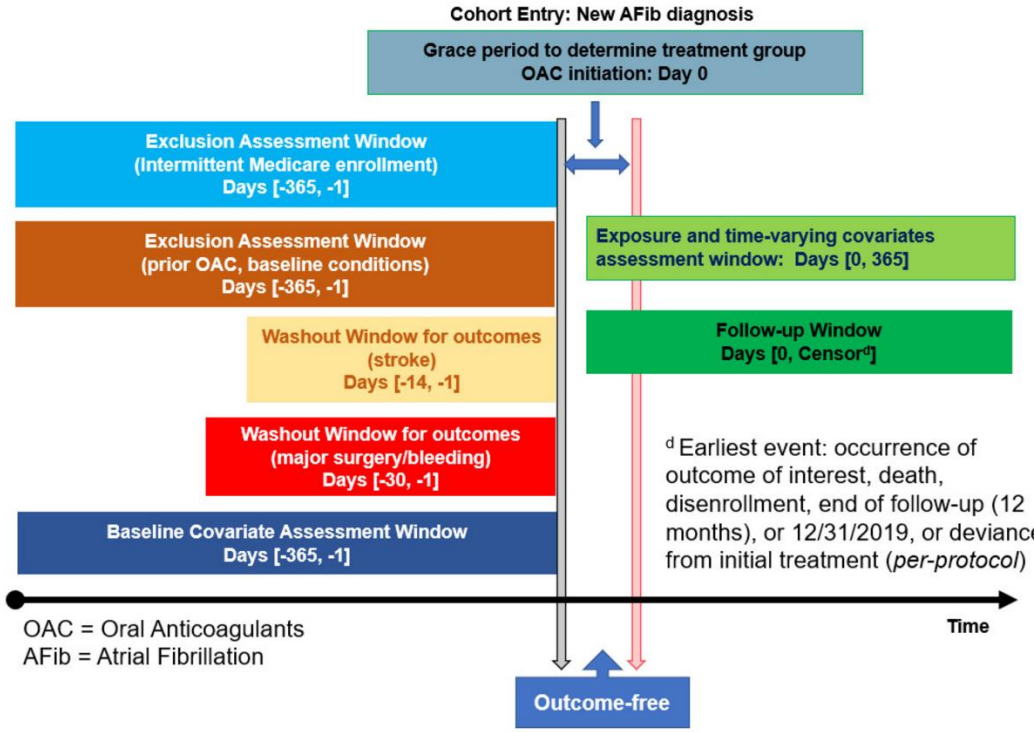


Figure S1. Visualization of study timeline

Technical appendix[164,175,186,187,189,198]

1. ITT analysis

The treatment is estimated effect via a 12-month risk of developing a specific outcome among those who initially started DOACs compared with warfarin.

First, we computed the probability of initiating DOACs or warfarin, conditioning on baseline covariates (A=1 for DOACs, A=0 for warfarin)

$$logit(\Pr[A = 1|L]) = \alpha_0 + \alpha_1^T L_0$$

The stabilized weights (SW) of being assigned to either treatment were estimated by $SW^A = \frac{f[A]}{f[A|L]}$. Therefore, the stabilized weight for treatment A=1: $SW^A = \frac{\widehat{Pr}[A=1]}{\widehat{Pr}[A=1|L]}$ and for A=0: $SW^A = \frac{1-\widehat{Pr}[A=1]}{1-\widehat{Pr}[A=1|L]}$.

We also apply inverse-probability weights to this model to adjust for potential selection bias:

$$logit(\Pr[C = 0|A, L]) = \pi_0 + \tau_1^T L_0 + \pi_1 A \text{ (numerator)}$$

$$logit(\Pr[C = 0|A, L]) = \tau_0 + \tau_1^T L_0 + \tau_2 A \text{ (denominator)}$$

The stabilized weights for censoring due to loss to follow-up is: $SW^{LFU} = \frac{\widehat{Pr}[LFU=0|A]}{\widehat{Pr}[LFU=0|L,A]}$.

Under the assumptions of no unmeasured confounding given the included covariates and a low monthly risk of the outcome within levels of those covariates, the hazards ratios (HR) for developing the outcomes if all eligible individuals had been treated with DOACs (a=1) versus all eligible individuals had been treated with warfarin (a=0) can be estimated by the marginal structural model[164] below:

$$logit(\Pr[Y_{t+1}^{a} = 1 | Y_t^a = 0]) = \gamma_0 + \gamma_2 a + \gamma_3 at + \gamma_4 at^2$$

Next, we organized each persons' data in discrete-time (person-month) format (month 1 to 12) and fitted a weighted pooled logistic regression containing the outcome Y, and treatment A, and a function of time (time and its quadratic terms), weighted for SW calculated in the previous step. SWs were truncated at 99th percentile to remove extreme weights.

$$\text{logit}\,(\Pr[Y_{t+1} = 1 | A_0, L_0, \bar{Y}_t = 0]) = \alpha_{0,t} + \alpha_1 A_0 + \alpha_2{}^T L_0$$

The exponentiated coefficient of treatment indicator (e^{β_2}) is the unbiased estimate of ITT HR.

2. PP analysis

We arranged the data in person-month format and calculate subject-specific time-varying non-stabilized inverse-probability weights.[199,200] The denominator of this weight at time *t* is the probability that an individual received his/her observed treatment history given covariate history by *t*. The application of these weights creates a pseudo-population in which treatment is independent of the measured confounders at all time points. To estimate the denominator, we fit two separate models to allow the probabilities to differ according to prior treatment status. The first model is fit to person-months who received treatment A=0 in the previous month (*i.e.*, $A_{k-1} = 0$)

$$\text{logit}\left(\Pr\left[A_k = 1 \,|A_{k-1} = 0, \bar{L}_k, \overline{Y}_{k-1} = 0\right]\right) = \eta_{0,t} + \eta_1^T L_0 + \eta_2^T L_k$$

Then, we fit the second model for person-months who received treatment A=1 in the previous month (*i.e.*, $A_{k-1} = 1$):

$$\text{logit}\left(\Pr\left[A_k = 1 \,|A_{k-1} = 1, \bar{L}_k, \overline{Y}_{k-1} = 0\right]\right) = \theta_{0,t} + \theta_1^T L_0 + \theta_2^T L_k$$

where covariate history $\bar{L}_k$ was summarized by baseline L_0 and the most recent measurement of L_k. Then, the weights for censoring due to switching treatment is computed by

$$W_t^A = \prod_{k=0}^{t} \frac{1}{f(A_k|\bar{A}_{k-1}, \bar{L}_k, \overline{Y}_{k-1} = 0)}$$

The total weights are the product of time-varying non-stabilized inverse-probability weights for censoring due to treatment switching, time-varying weights censoring due to lost to follow-up

To obtain the treatment effect, we fitted a pooled logistic regression to the censored data, weighted for total weights to adjust for time-varying confounding. We truncated weights at their 99th percentile to prevent extreme weights. Under the same assumptions described in the previous section, the exponentiated coefficient of the treatment indicator (*i.e.*, $exp(\beta_2)$) validly estimates the per-protocol HR.

$$\text{logit } (\Pr[Y_{t+1} = 1|A_0, L_0, \bar{Y}_t = 0, \bar{C}_{t+1} = 0]) = \beta_0 + \beta_1^T L_0 + \beta_2 A$$

To estimate the weighted survival curves and standardize the curves to baseline distribution of covariates, we fitted a similar model with an interaction term between treatment regimen A and f(t) – a function of time and time squared to allow for non-proportional hazards. The model was then used to predict outcomes of interest under each treatment strategy $A = a$. The details for creating standardized survival curves can be found in published studies.[193]

Appendix for Aim 3 Manuscript

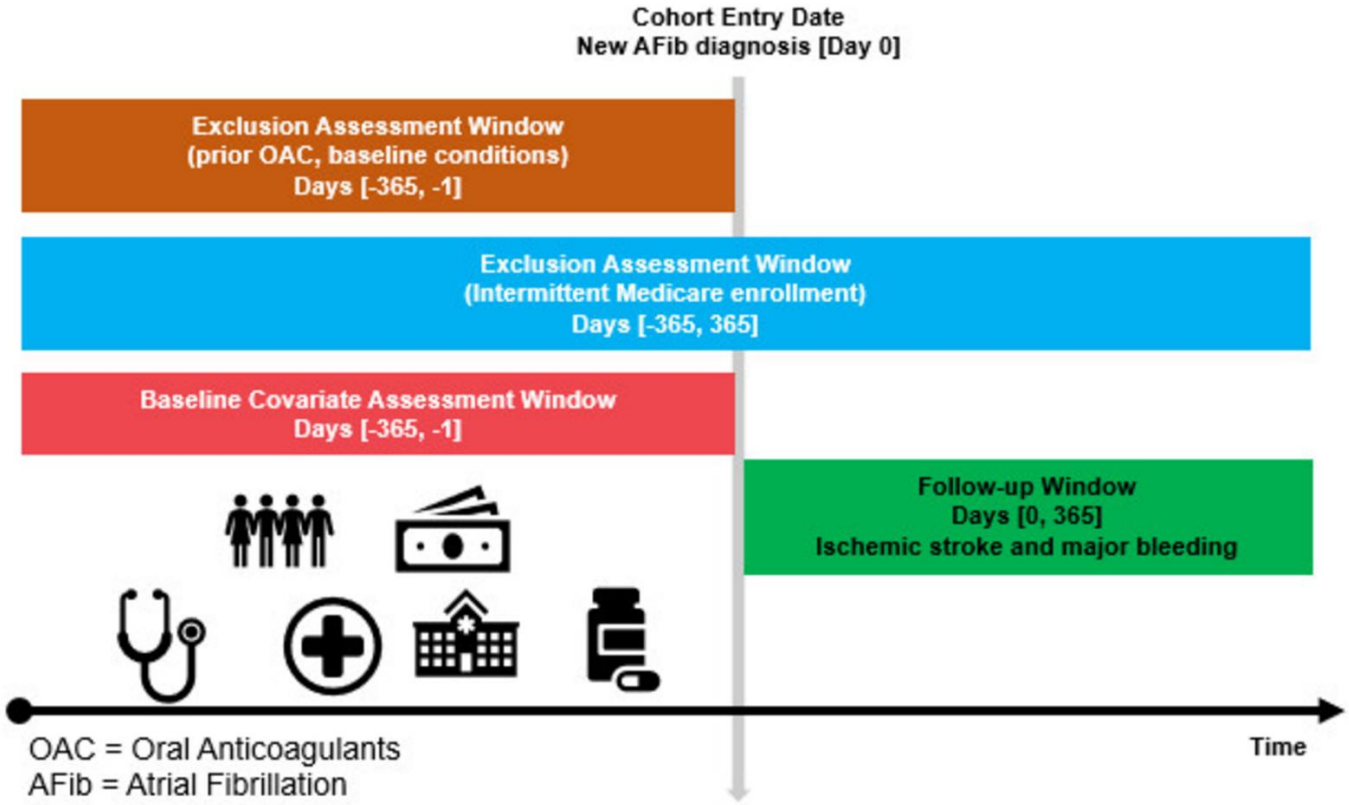


Figure S1. Visualization of study design

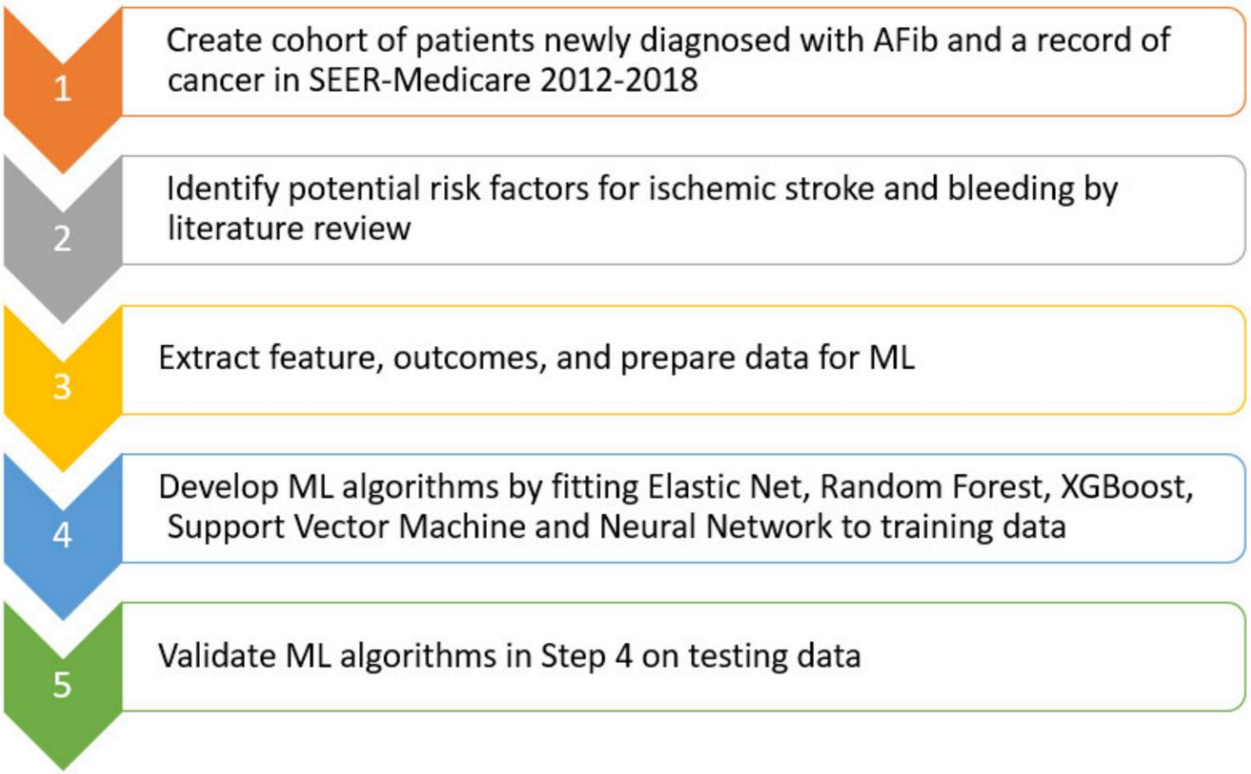


Figure S2. Summary of approach

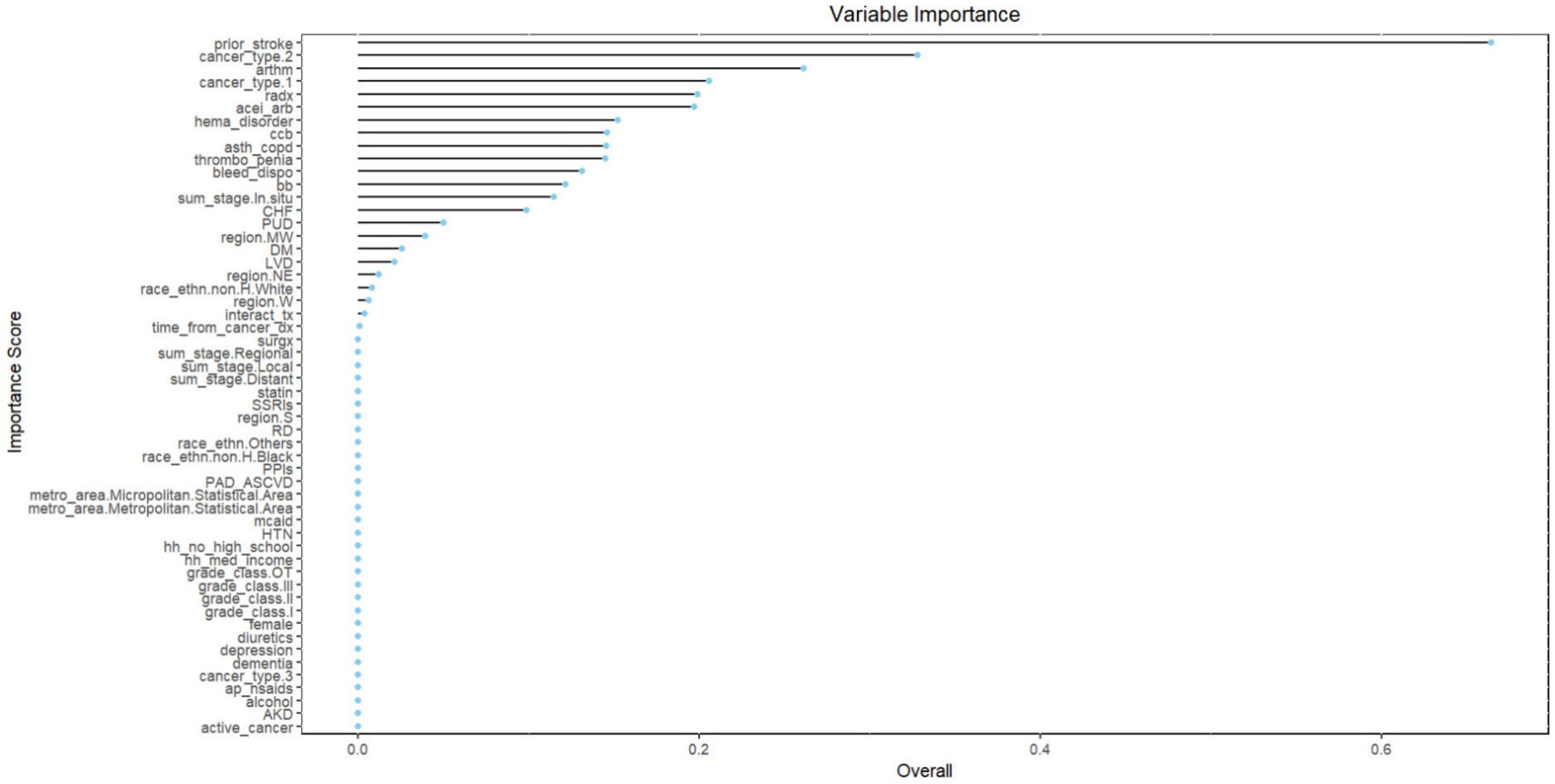


Figure S3. Feature importance plot of elastic net algorithm for ischemic stroke prediction (original data)

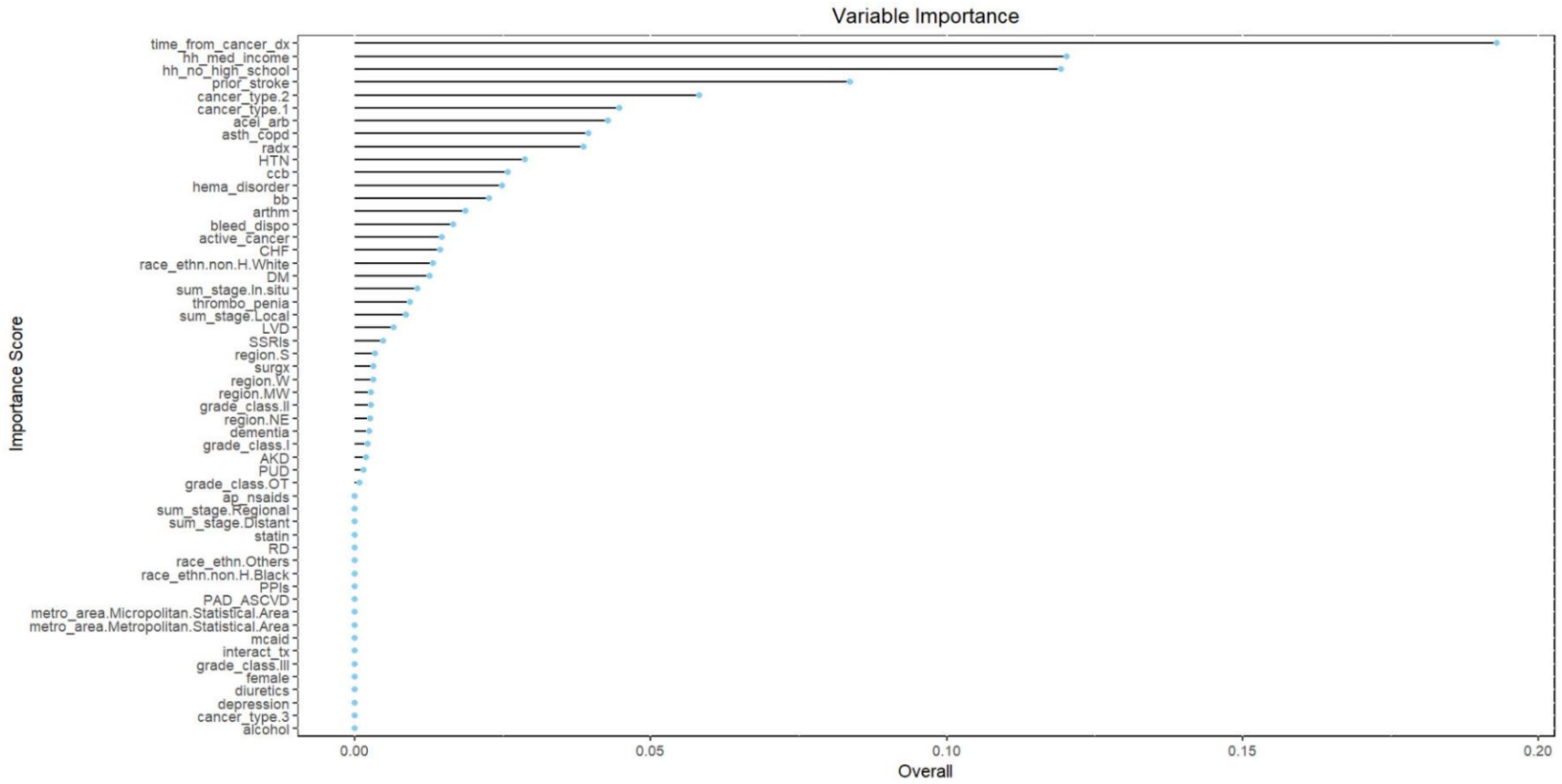


Figure S4. Feature importance plot of XGBoost algorithm for ischemic stroke prediction (original data)

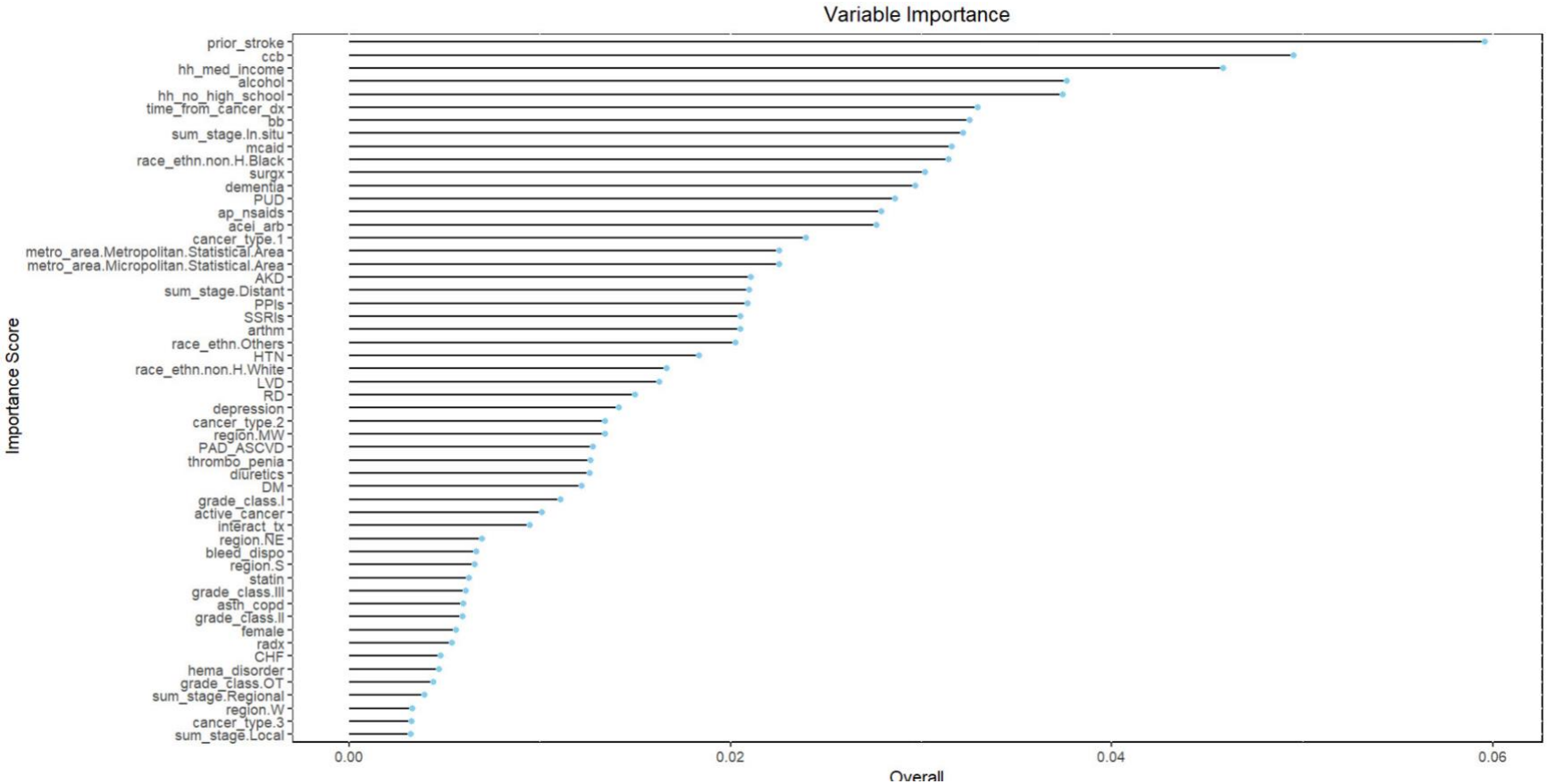


Figure S5. Feature importance plot of support vector machine algorithm for ischemic stroke prediction (original data)

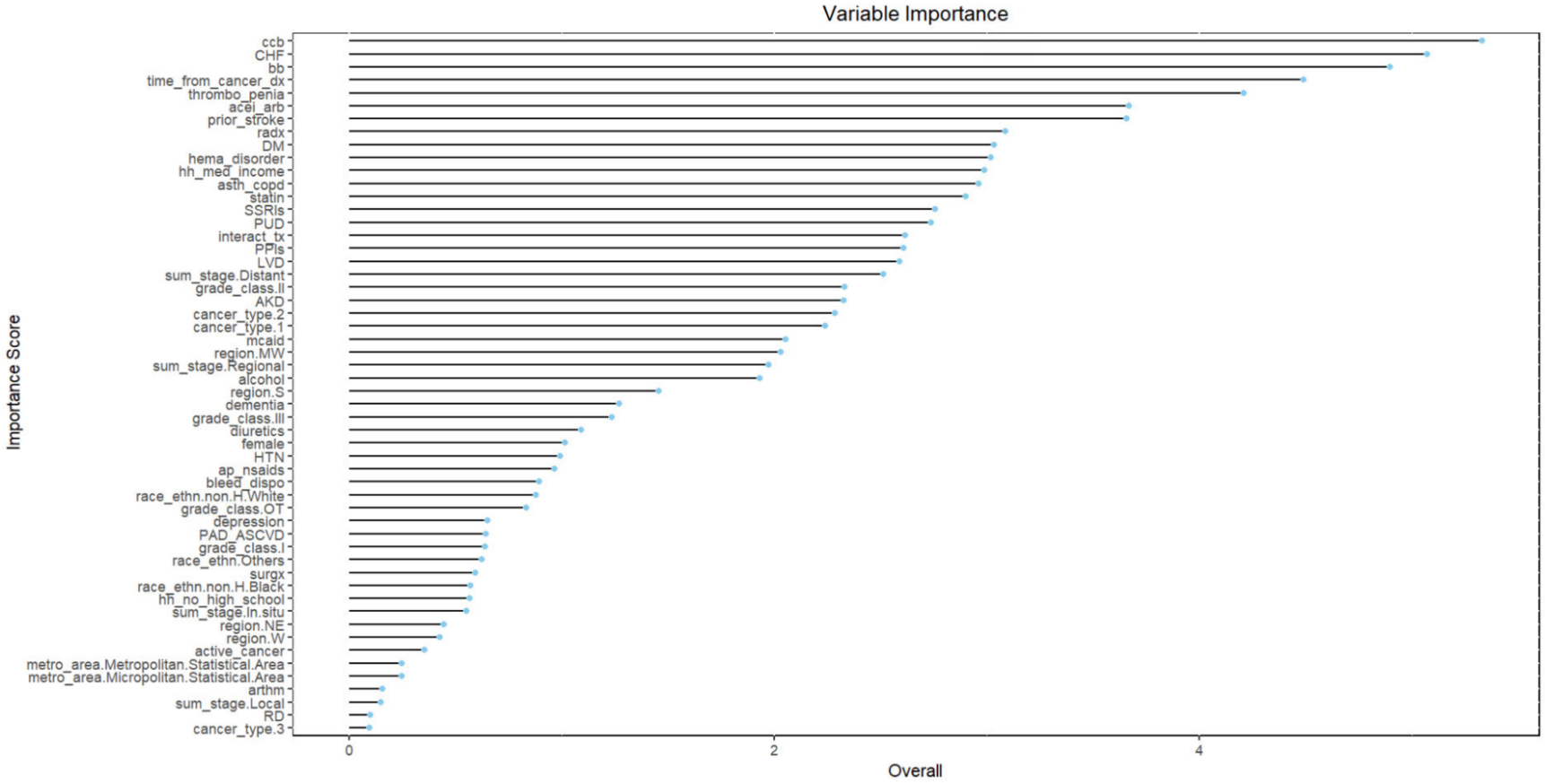


Figure S6. Feature importance plot of neural network algorithm for ischemic stroke prediction (original data)

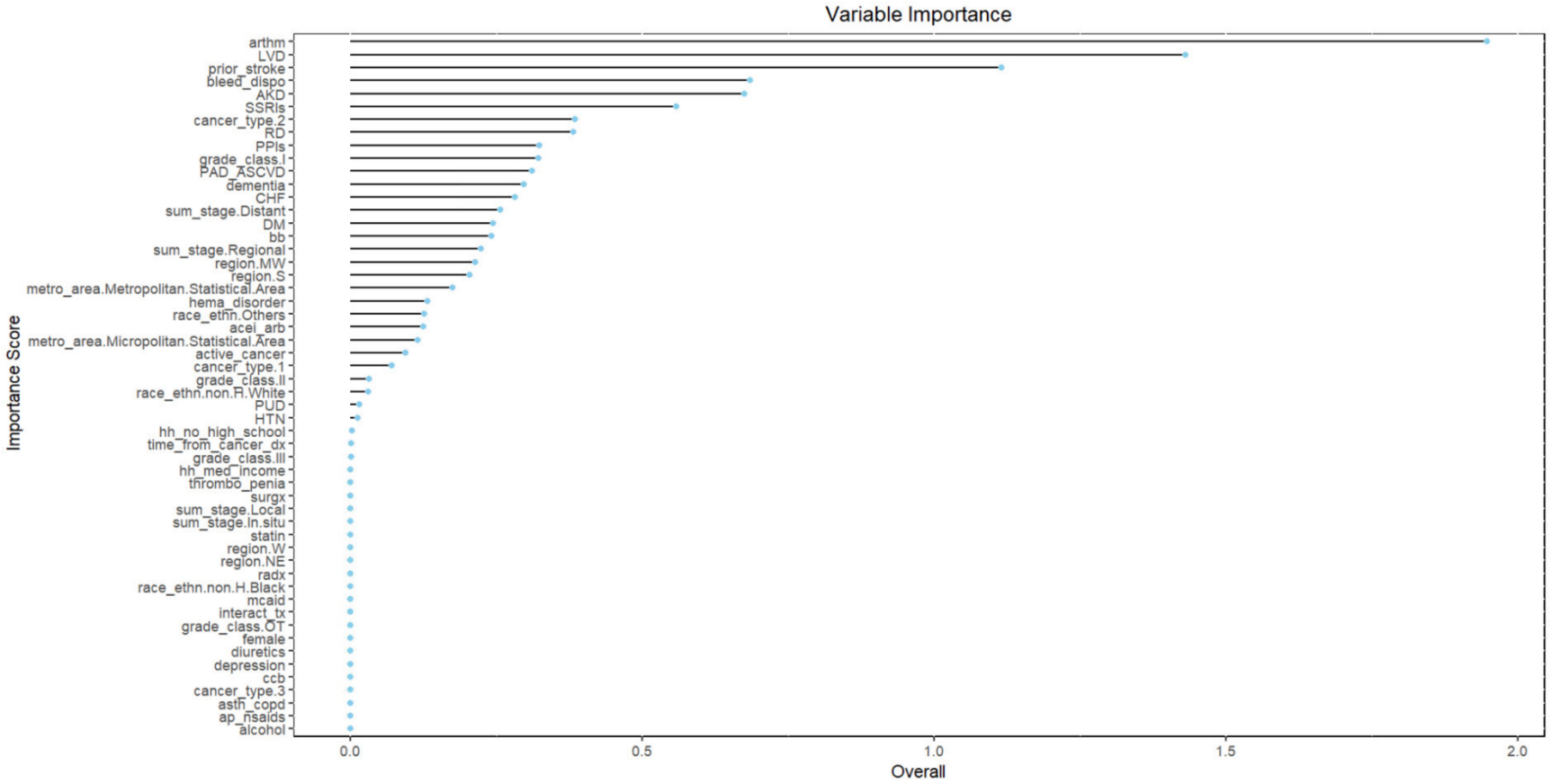


Figure S7. Feature importance plot of elastic net algorithm for major bleeding prediction (original data)

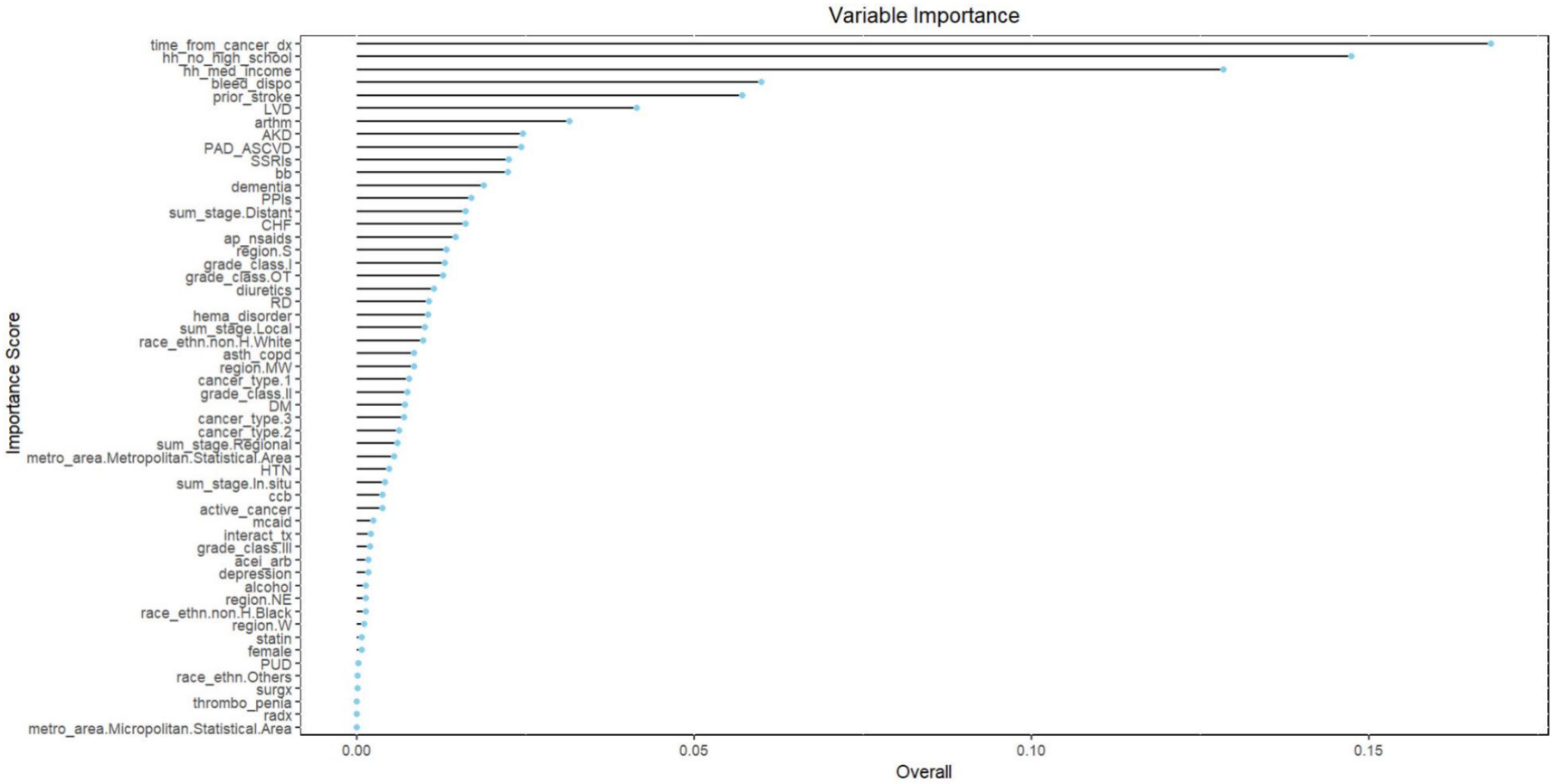


Figure S8. Feature importance plot of XGBoost algorithm for major bleeding prediction (original data)

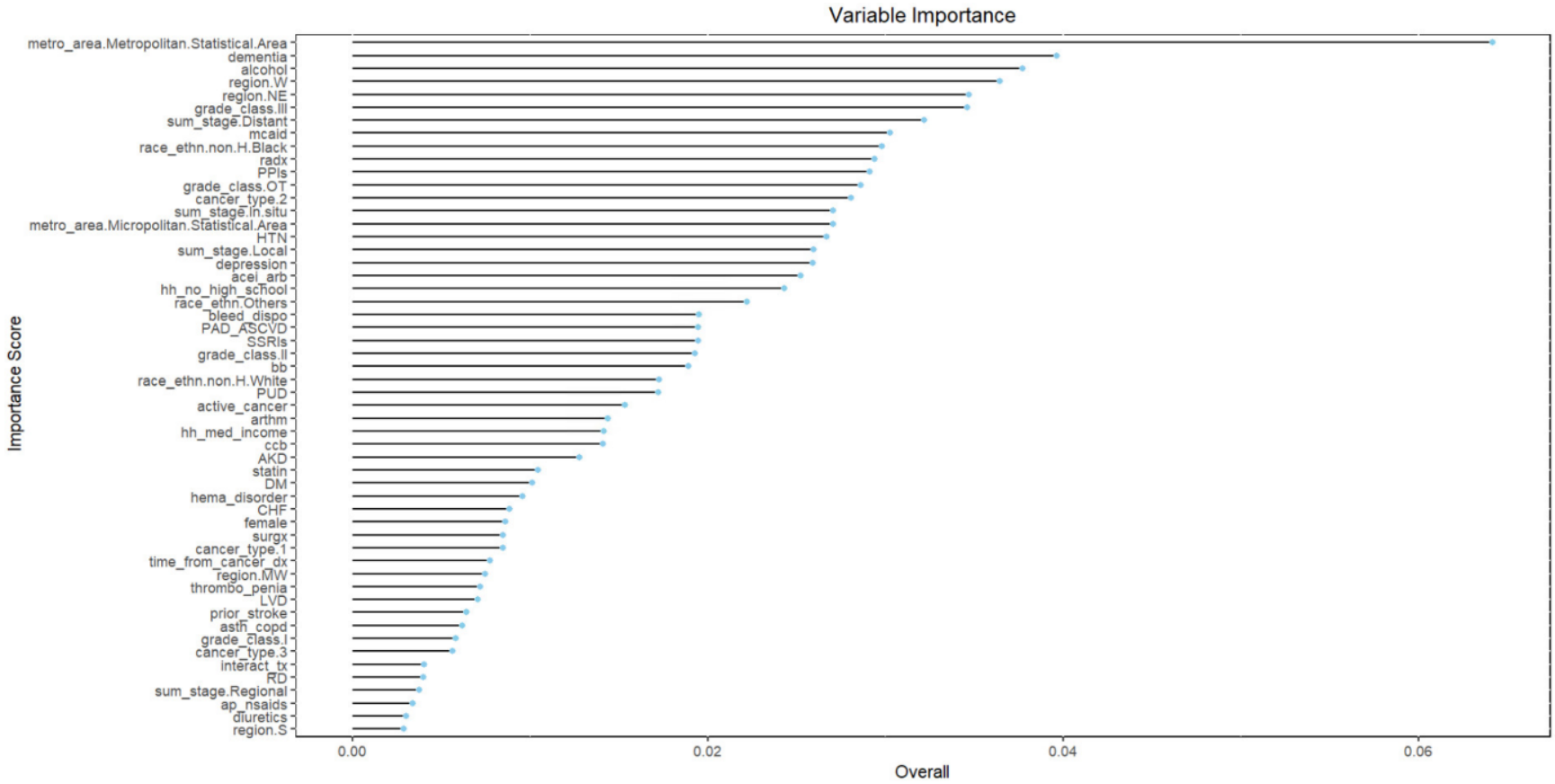


Figure S9. Feature importance plot of support vector machine algorithm for major bleeding prediction (original data)

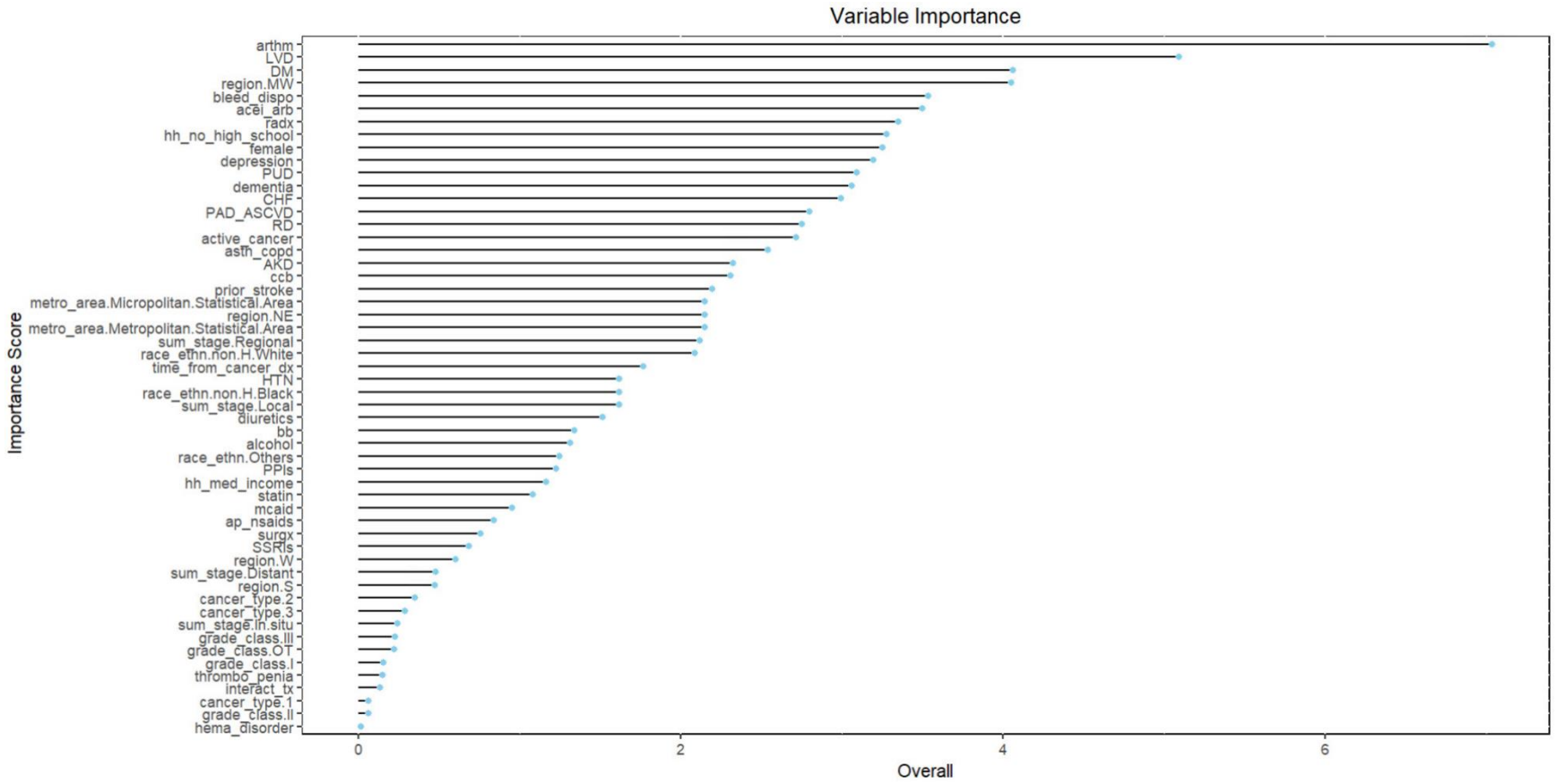


Figure S10. Feature importance plot of neural network algorithm for major bleeding prediction (original data)

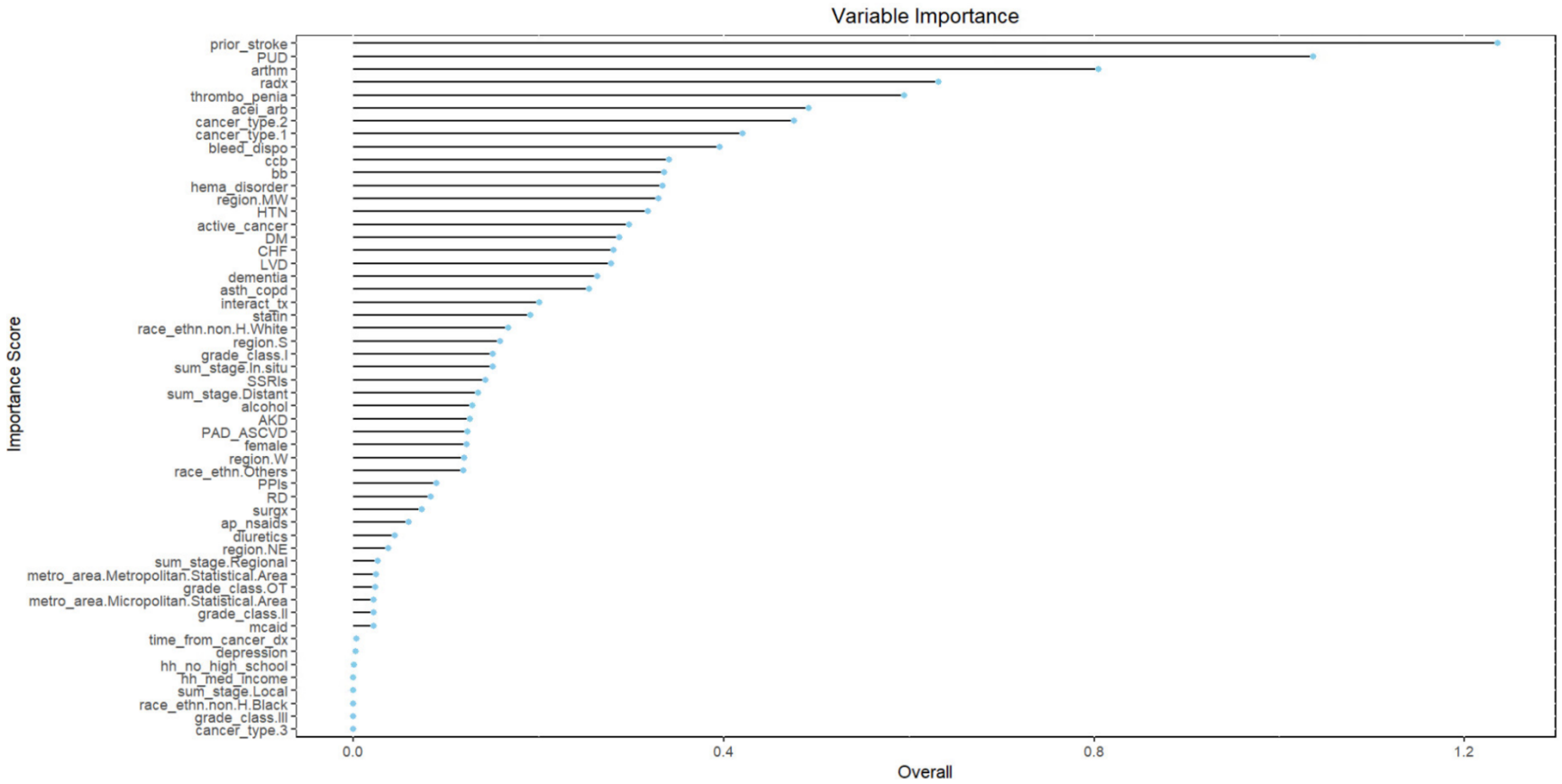


Figure S11. Feature importance plot of elastic net algorithm for ischemic stroke prediction (SMOTE resampled data)

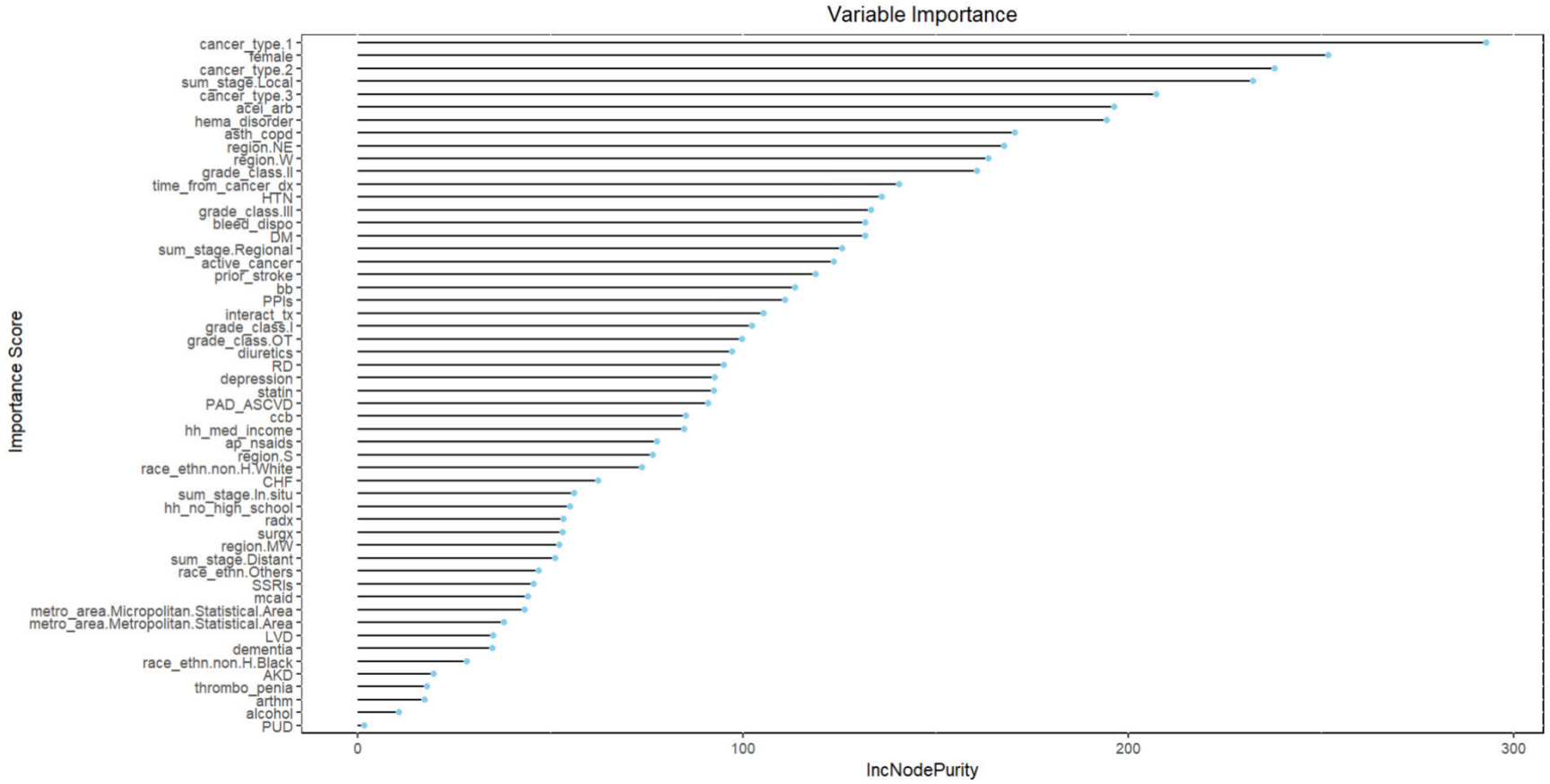


Figure S12. Feature importance plot of elastic net algorithm for ischemic stroke prediction (SMOTE resampled data)

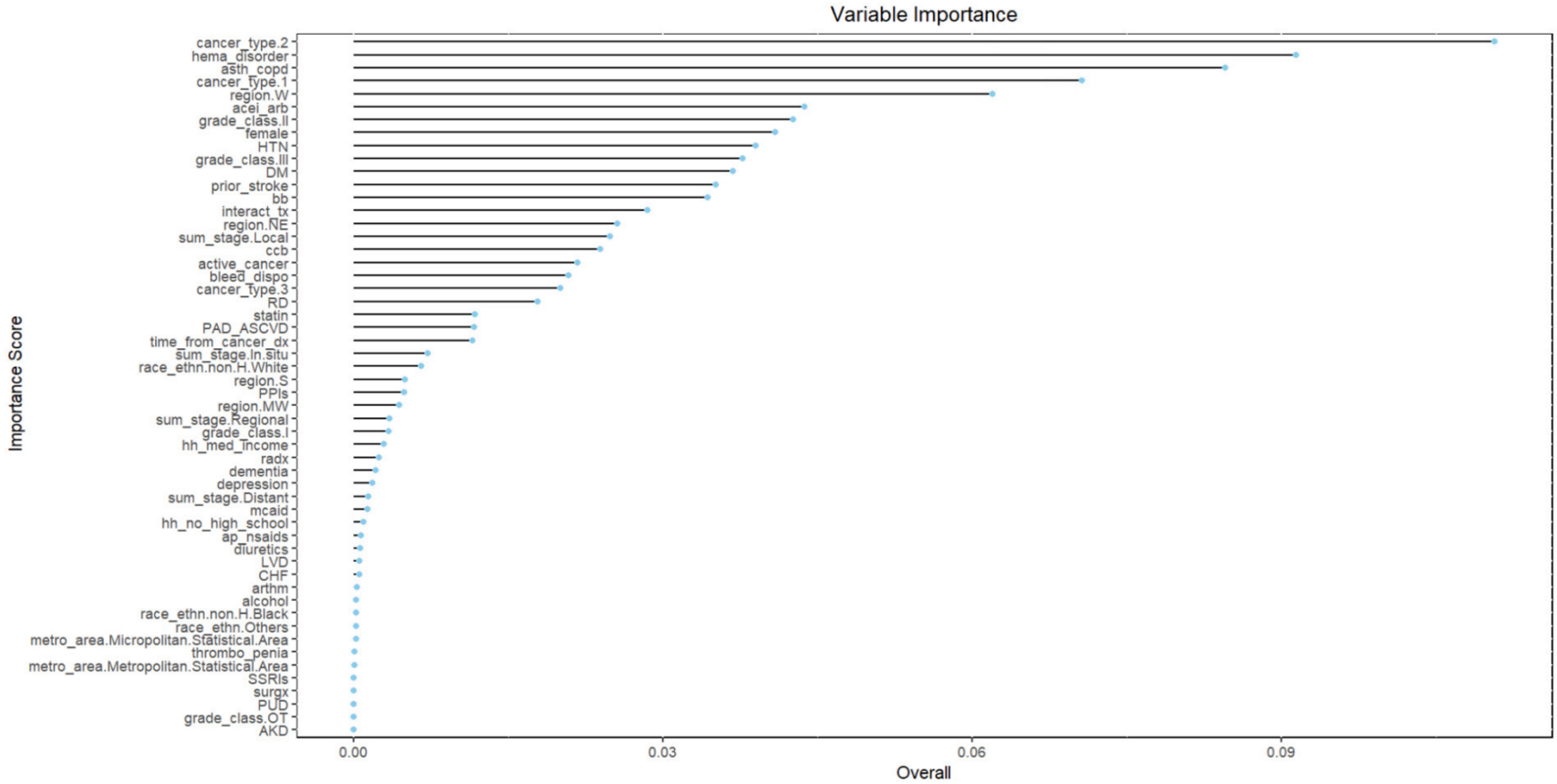


Figure S13. Feature importance plot of XGBoost algorithm for ischemic stroke prediction (SMOTE resampled data)

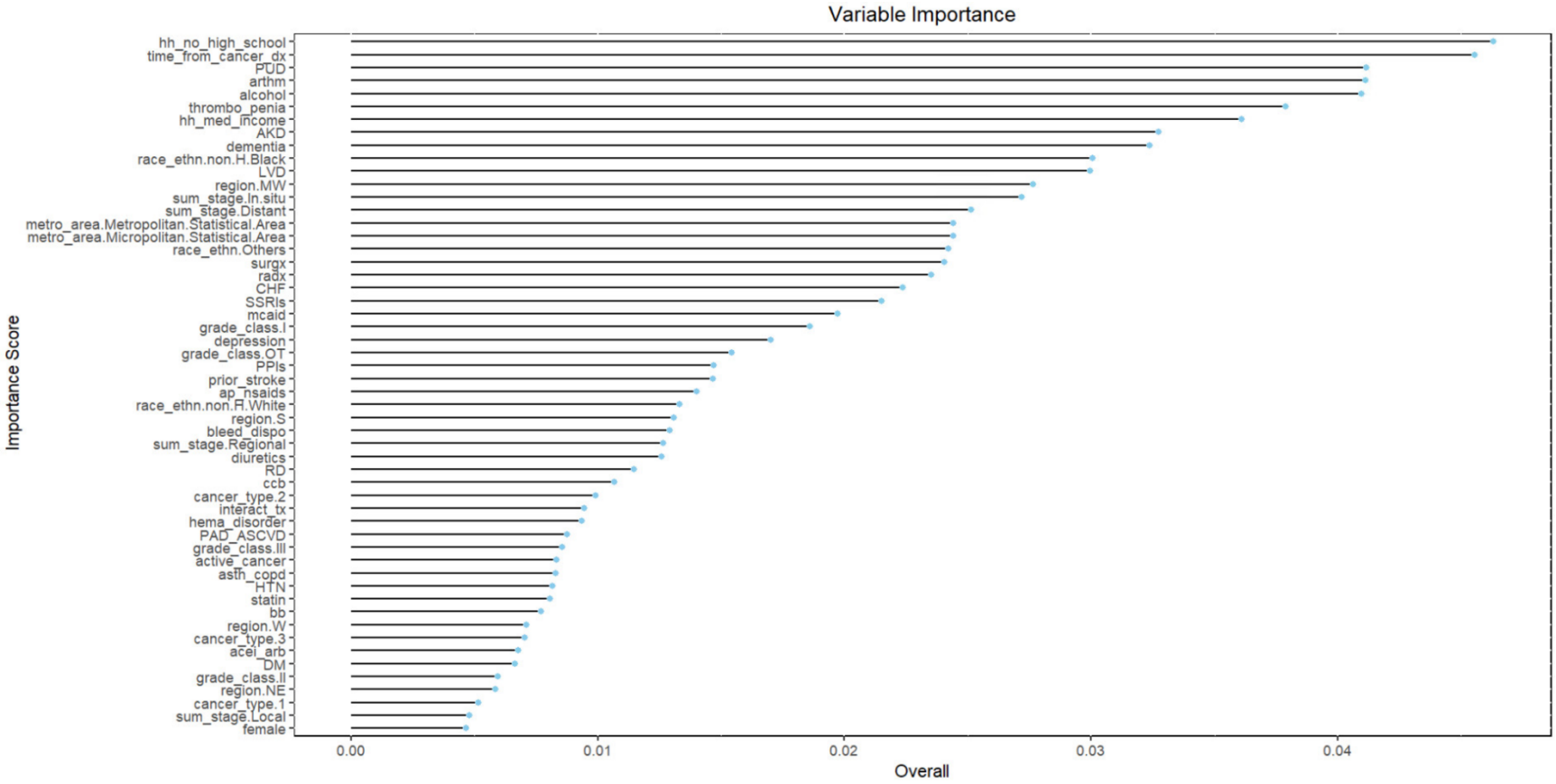


Figure S14. Feature importance plot of support vector machine algorithm for ischemic stroke prediction (SMOTE resampled data)

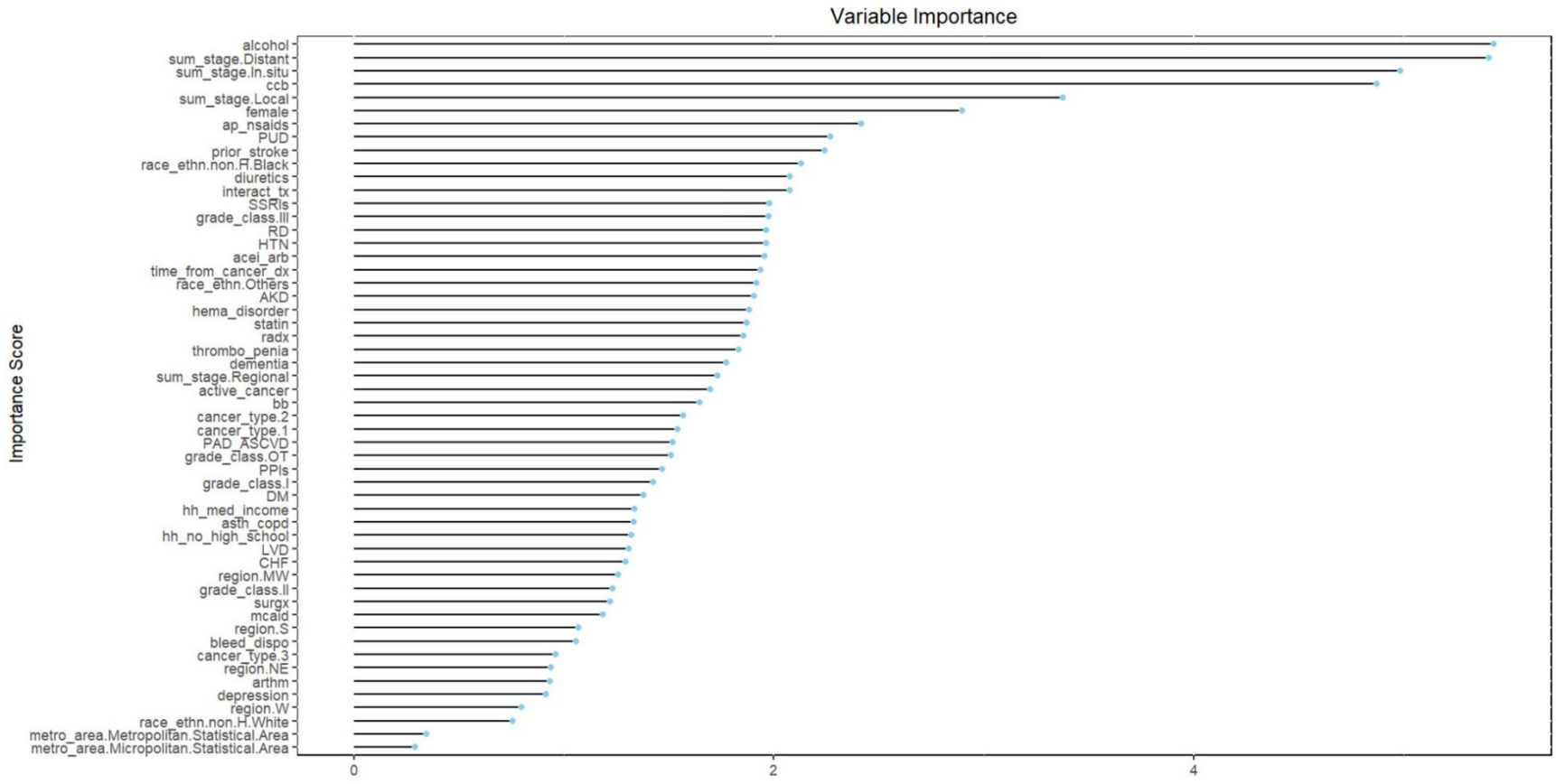


Figure S15. Feature importance plot of neural network algorithm for ischemic stroke prediction (SMOTE resampled data)

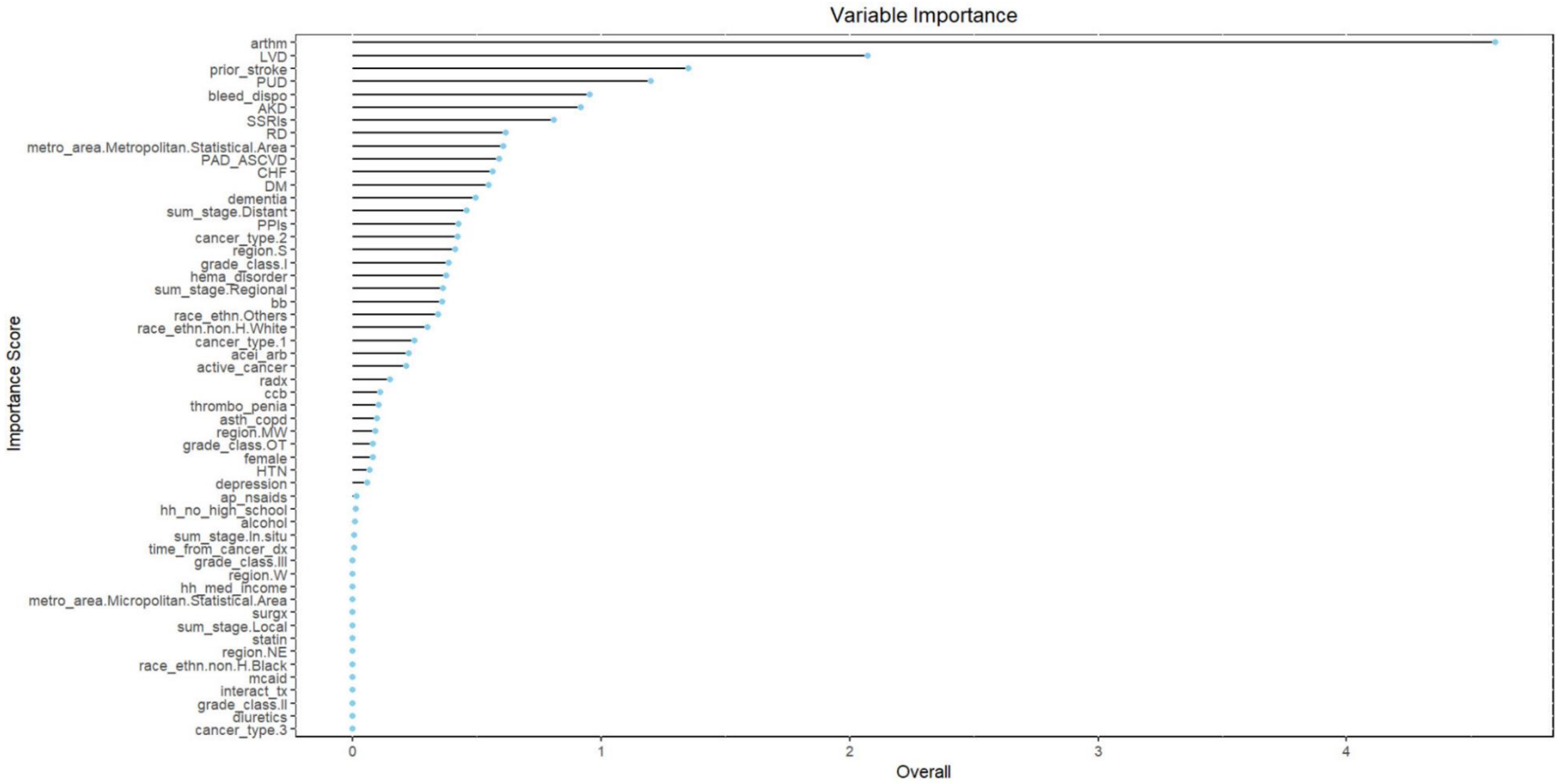


Figure S16. Feature importance plot of elastic net algorithm for major bleeding prediction (SMOTE resampled data)

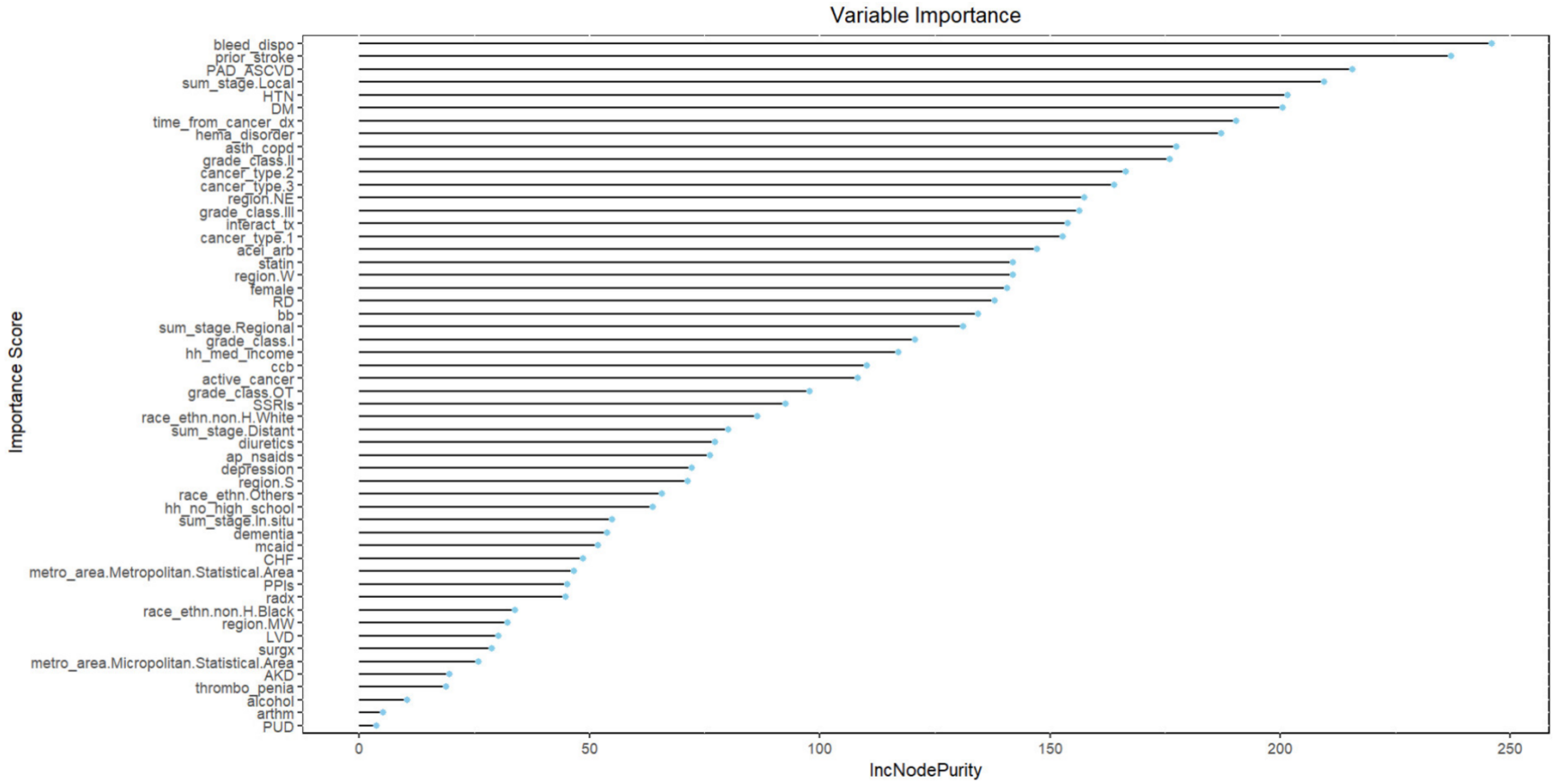


Figure S17. Feature importance plot of elastic net algorithm for major bleeding prediction (SMOTE resampled data)

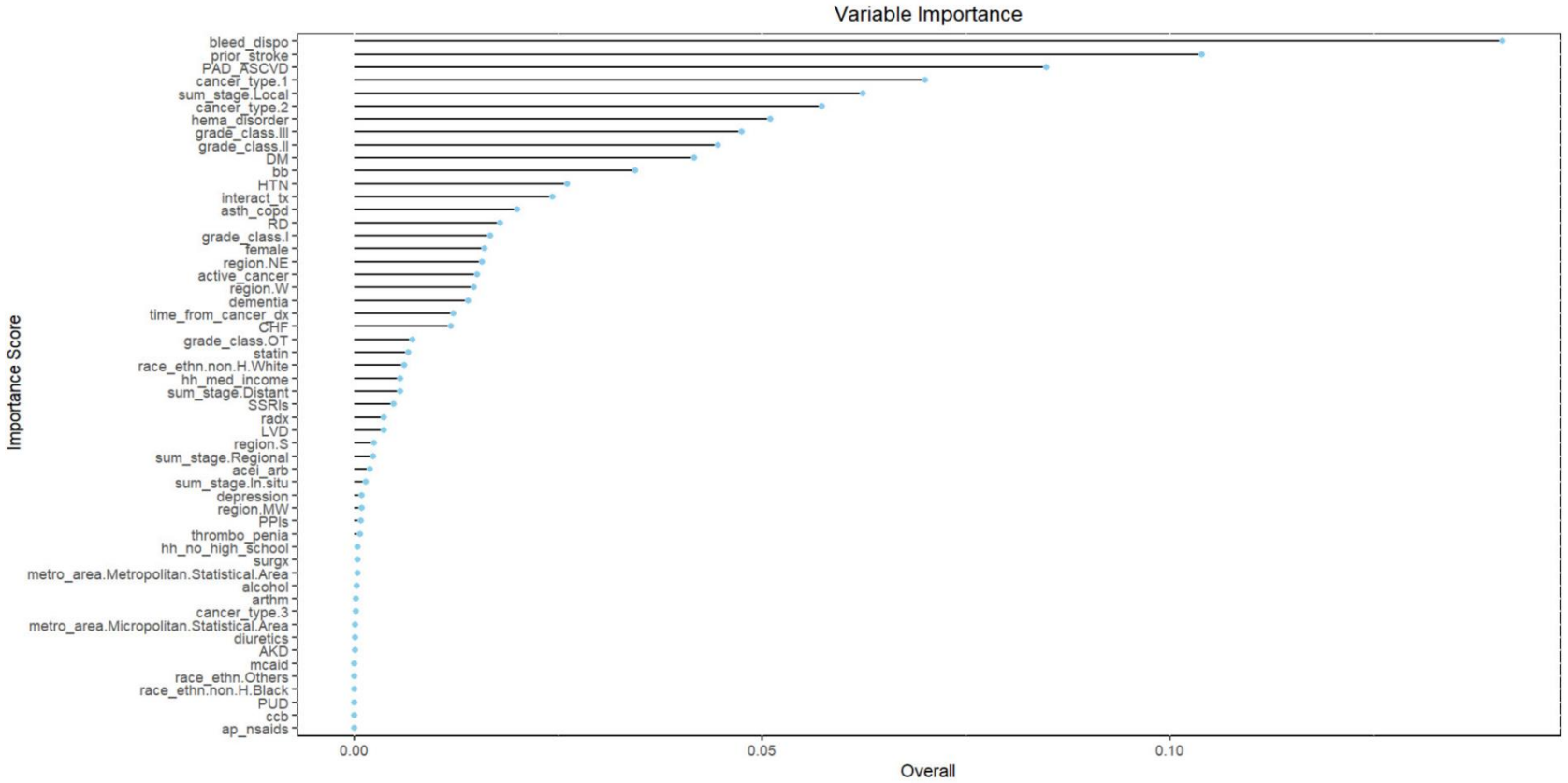


Figure S18. Feature importance plot of XGBoost algorithm for major bleeding prediction (SMOTE resampled data)

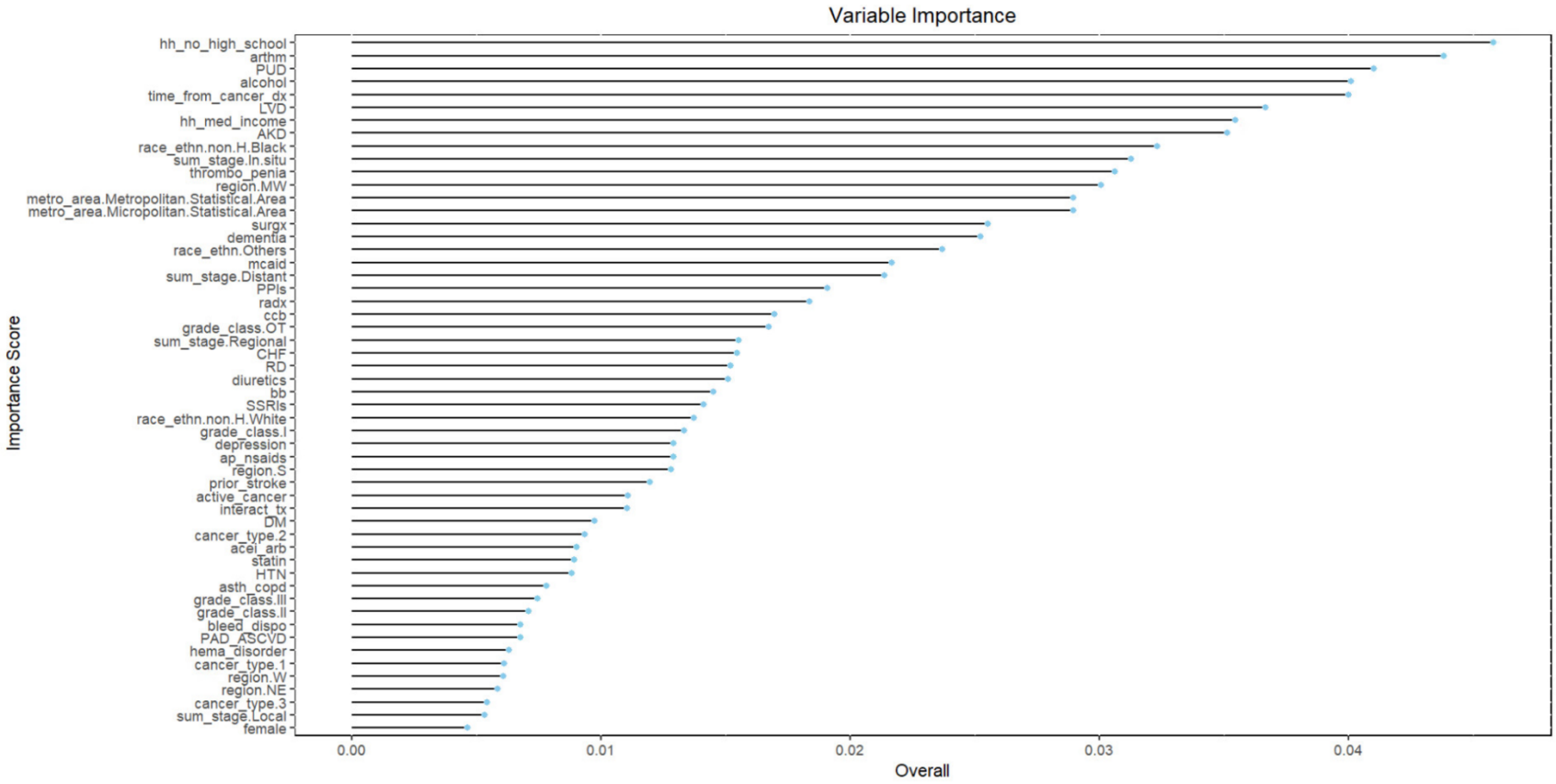


Figure S19. Feature importance plot of support vector machine algorithm for major bleeding prediction (SMOTE resampled data)

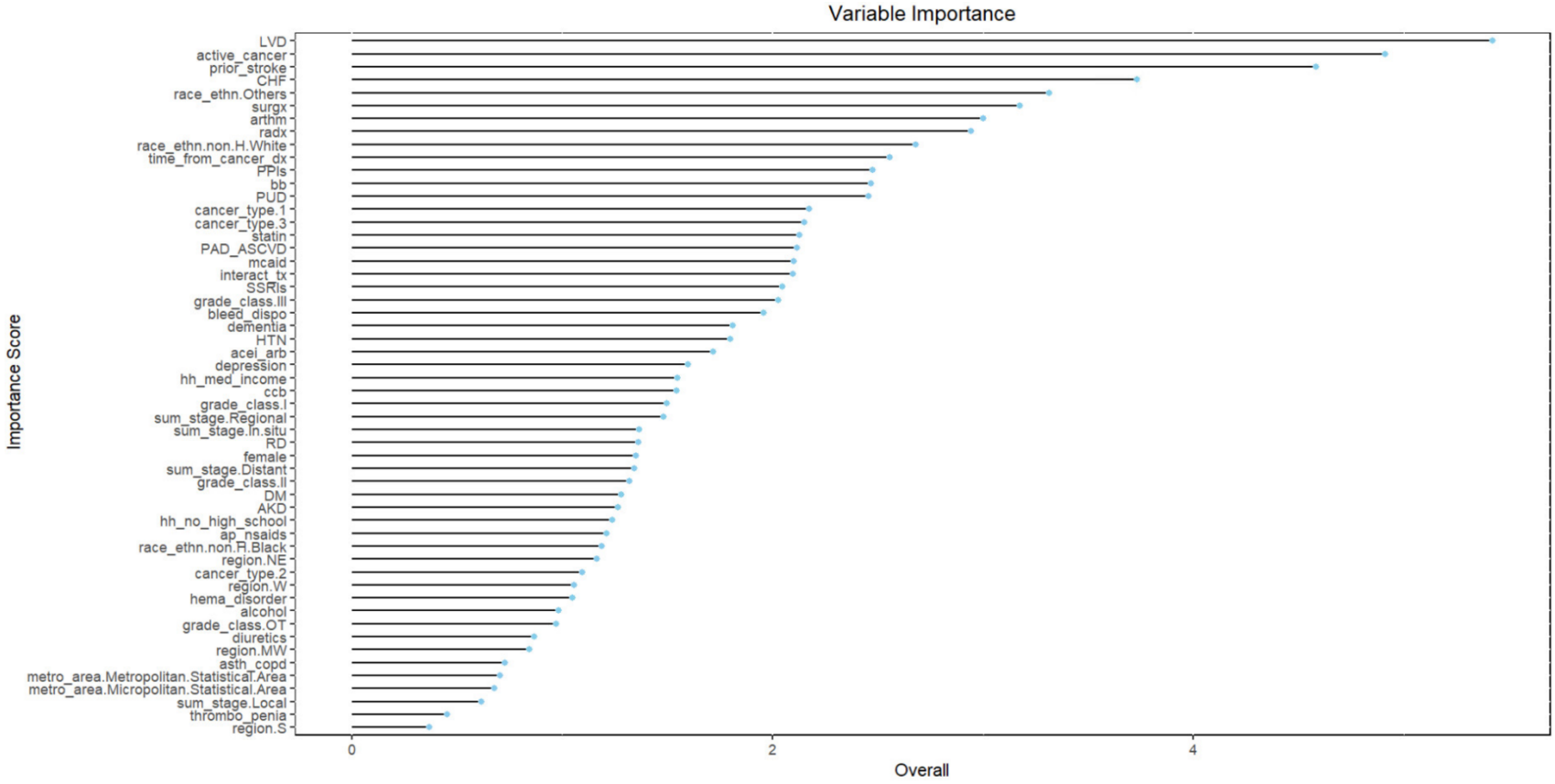


Figure S20. Feature importance plot of neural network algorithm for major bleeding prediction (SMOTE resampled data)

Table S1. Characteristics of patients with new onset AFib and history of cancer in SEER-Medicare registry from 2012 to 2018 (bleeding)

	Overall (N=18838)	**Bleeding (N=221)**	**Non-bleeding (N=17865)**
Demographics			
Index age (Mean, SD)	76.59 (7.13)	78.98 (7.15)	76.56 (7.13)
Female	8483 (46.13)	101 (45.70)	8382 (46.14)
Race/ethnicity			
Non-Hispanic White	15650 (85.11)	182 (82.35)	15468 (85.14)
Non-Hispanic Black	1134 (6.17)	13 (5.88)	1121 (6.17)
Others	1604 (8.72)	26 (11.76)	1578 (8.69)
Region			
Midwest	1604 (8.72)	10 (4.52)	1594 (8.77)
Northeast	7195 (39.13)	94 (42.53)	7101 (39.09)
South	3263 (17.75)	42 (19.00)	3221 (17.73)
West	6326 (34.40)	75 (33.94)	6251 (34.41)
Medicaid eligible	2007 (10.91)	25 (11.31)	1982 (10.91)
Urbanicity			
Metropolitan	15895 (86.44)	204 (94.88)	15691 (91.45)
Micropolitan	1478 (8.04)	11 (5.12)	1467 (8.55)
Unknown	1015 (5.52)		
Socioeconomic status (Census Tract)			
Household median income (Median, IQR)	62122 (45499-84935)	72723 (52492-93610)	62051 (45435-84839)
Percentage of non-high school graduates (Median, IQR) (N=18086)	9.53 (5.20-16.56)	7.65 (4.33-14.73)	9.55 (5.21-16.60)
Cancer characteristics			
Time from cancer diagnosis to the onset of AFib (month, Median, IQR) (N=18090)	17 (2-40)	25 (6-46)	16 (2-40)
Cancer type			
Breast	5643 (30.69)	84 (38.01)	5559 (30.60)
Lung	6165 (33.53)	57 (25.79)	6108 (33.62)
Prostate	6580 (35.78)	80 (36.20)	6500 (35.78)
Active cancer	4629 (25.17)	55 (24.89)	4574 (25.18)

Cancer grade			
I	2583 (14.05)	37 (16.74)	2546 (14.01)
II	6583 (35.80)	67 (30.32)	6516 (35.87)
III	5955 (32.39)	74 (33.48)	5881 (32.37)
Others	3267 (17.77)	43 (19.46)	3224 (17.75)
Cancer stage			
In situ	883 (4.80)	13 (6.22)	870 (5.06)
Local	10782 (58.64)	137 (65.55)	10645 (61.97)
Regional	3941 (21.43)	33 (15.79)	3908 (22.75)
Distant	1781 (9.69)	26 (12.44)	1755 (10.22)
Unknown/missing	1001 (5.44)		
Cancer treatment			
Potential interacting antineoplastic agents	3964 (21.56)	49 (22.17)	3915 (21.55)
Radiation	2419 (13.16)	30 (13.57)	2389 (13.15)
Surgery	1692 (9.20)	20 (9.05)	1672 (9.20)
Individual comorbidities			
HTN	13259 (72.11)	167 (75.57)	13092 (72.06)
CHF	2343 (12.74)	32 (14.48)	2311 (12.72)
Diabetes	5621 (30.57)	66 (29.86)	5555 (30.58)
Prior stroke	1542 (8.39)	53 (23.98)	1489 (8.20)
Prior vascular diseases	4385 (23.85)	63 (28.51)	4322 (23.79)
Prior major bleeding	3843 (20.90)	72 (32.58)	3771 (20.76)
Renal diseases	3631 (19.75)	34 (15.38)	3597 (19.80)
Liver diseases	1635 (8.89)	4 (1.81)	1631 (8.98)
Alcohol use disorders	526 (2.86)	10 (4.52)	516 (2.84)
Asthma/COPD	6323 (34.39)	69 (31.22)	6254 (34.43)
Hematological disorders	5664 (30.80)	82 (37.10)	5582 (30.73)
Dementia	1044 (5.68)	24 (10.86)	1020 (5.61)
Depression	2650 (14.41)	43 (19.46)	2607 (14.35)
Acute kidney diseases	1183 (6.43)	12 (5.43)	1171 (6.45)
Thrombocytopenia	1120 (6.09)	12 (5.43)	1108 (6.10)
Peptic ulcer diseases	279 (1.52)	3 (1.36)	276 (1.52)
Medications			

Antiplatelet/NSAIDs	2957 (16.08)	34 (15.38)	2923 (16.09)
ACE inhibitors/ARBs	4691 (25.51)	53 (23.98)	4638 (25.53)
CCB	2952 (16.05)	34 (15.38)	2918 (16.06)
Beta blockers	4135 (22.49)	46 (20.81)	4089 (22.51)
Antiarrhythmic medications	915 (4.98)	3 (1.36)	912 (5.02)
Diuretics	3235 (17.59)	35 (15.84)	3200 (17.61)
Statin	4856 (26.41)	57 (25.79)	4799 (26.42)
PPIs	2844 ((15.47)	32 (14.48)	2812 (15.48)
SSRIs/SNRIs	1979 (10.76)	35 (15.84)	1944 (10.70)
Outcome			
Ischemic stroke	523 (2.84)		
Major bleeding	221 (1.20)		

AFib Atrial Fibrillation. SD Standard Deviation. IQR Interquartile Range. HTN hypertension. CHF congestive heart failure. COPD Chronic obstructive pulmonary disease. ACE Angiotensin-converting enzyme. ARB Angiotensin receptor blockers. CCB Calcium Channel Blockers. PPI Pump Proton Inhibitors. SSRI Selective serotonin reuptake inhibitors. SNRI Serotonin and norepinephrine reuptake inhibitors. NSAIDs non-steroidal anti-inflammatory drugs.

Overview of machine learning models

Elastic net logistic regression is the ML algorithm that combines multivariable logistic regression with LASSO and ridge regression penalty terms. For example, consider a ridge regression model

$$\sum_{i=1}^{n}(y_i - \beta_0 - \sum_{j=1}^{p}\beta_i x_{ij})^2 + A = RSS + A$$

where A= $\lambda \sum_{j=1}^{p} \beta_j^2$ is a shrinkage penalty for ridge regression and A= $\lambda \sum_{j=1}^{p} |\beta_j|$ for LASSO. These penalty terms shrink the model coefficients to towards zero to reduce overfitting.[128] Thus, the models have variable selection property and achieve a higher performance.

Random forests and XGBoost are aggregated decision tree models with substantially improved predictive performance.[128] XGBoost improves the accuracy of individual decision trees by building many trees sequentially and weighs the difficult-to-predict cases in a tree to a greater degree. XGBoost also increases the speed of the algorithm and includes penalty terms to avoid model overfitting. On the other hand, random forests builds each tree separately based on a random sample of the training data. For each split, a random number of predictor variables are available, which results in trees that are different from each other. Therefore, the final model contains thousands of individual decision trees, with each of them combining to make predictions on new patients. When fitting the XGBoost and random forest models, we specified the number of trees, depth of trees, learning rate, and the number of predictor variables available at each split using 10-fold cross-validation in the training data.

Support vector machines (SVMs): SVMs puts the data into hyperplane and creates linear or non-linear decision boundary that maximize the margin between the classes of the outcomes using

kernels.[128] The optimal value of the cost penalty (misclassification) was determined using 10-fold cross-validation in the training data.

Neural networks (NNs): NNs mimic how neurons works by combining of individual neuron-like units that take the predictor variables as inputs (input layer), combine them in hidden layers, process them through activation functions, and then output predictions (output layers).[128] In this study, we used a feed-forward multi-layer perceptron NN. We specified the number of hidden layers, size of each hidden layer, learning rate, and decay using ten-fold cross-validation in the training data.

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Supplemental Tables

Table S1. Comparisons between warfarin and novel oral anticoagulants[115]

	Warfarin	DOACs			
		Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**
Approval year (US FDA)	1950s	2010	2011	2012	2015
Dosing	Variable, (1.5-12 mg) (PT-INR dependent)	Fixed (110-150 mg)	Fixed (15-20 mg)	Fixed (2.5-5 mg)	Fixed (30-60 mg)
Frequency	Once daily	Twice daily	Once daily	Twice daily	Once daily
Onset of action	Slow	Rapid			
Pharmacokinetics					
Bioavailability	>95%	6.5%	66% without food, ~100% with food	50%	62%
Effect of food on absorption	Variable (Intake with food to be avoided)	Prolongs T_{max} to 2 h (Intake with food discouraged)	Mean AUC increases to ≈40% (Intake with food mandatory)	No effect (Intake with food discouraged)	No effect (Intake with food: no official recommendation)
T_{max} (hours)	72-96	0.5-2.0	2-4	3-4	1-3
Vd (L/kg)	0.08-0.12	70	50	21	107
Plasma protein binding	>99%	35%	92-95%	87%	55%
$T_{1/2}$ (hours)	24-58	12-14	5-9 (young) 11-13 (older adults)	12 (8-15)	10-14
Transport protein	None	P-gp	P-gp, BCRP	P-gp, BCRP	P-gp
Liver metabolism	2C9, 1A2, 3A4, 2C8, 2C19	No	CYP3A4 (~66%)	CYP3A4 (25%)	CYP3A4 (<4%)
Renal excretion (normal renal function)	<1%	85%	66%	27%	35-50%
Routine laboratory monitoring	Yes	No			
Duration of blood-thinning effect	Long	Short			
Availability of reversal agents	Vitamin K	Idarucizumab	Andexanet Alfa	Andexanet Alfa	Andexanet Alfa
Pregnancy use	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Cost	$	$$$			

Drug-food interactions	Yes	No			
Drug-drug interactions	CYP3A4/1A2/2C9 inhibitors and inducers, food	Strong P-gp inhibitors and inducers	Strong P-gp and CYP3A4 inhibitors and inducers	Strong P-gp and CYP3A4 inhibitors and inducers	Strong P-gp inhibitors

Abbreviation: FDA: Food and Drug Administration, DOACs: novel oral anticoagulants, PT-INR: Prothrombin Time-International Normalized Ratio, CYP: cytochrome P450, P-gp: P glycoprotein, BCRP: breast cancer resistance protein, V_d: Volume of distribution, T_{max}: time to reach peak plasma concentration, $T_{1/2}$: half-life, AUC: Area under the curve

Table S2. Safety and effectiveness of DOACs compared with warfarin from published systematic reviews and meta-analyses

Author (year)	Population	Number of studies included	Sample size	DOACs versus warfarin (95% CI)		
				Stroke/VTE	Bleeding	All-cause mortality
Ruff (2014)	AFib (general)	3 RCTs	71,683	RR 0.81 (0.73-0.91)	***Intracranial hemorrhage*** RR 0.48 (0.39-0.59) ***Gastrointestinal bleeding*** RR 1.25 (1.01-1.55)	RR 0.90 (0.85-0.95)
Hicks (2015)	AFib (general)	12 (phase II + III RCTs)	77,011	OR 0.85 (0.75-0.98)	***Intracranial hemorrhage*** OR 0.48 (0.40- 0.57)	OR 0.86 (0.82-0.91)
Kim (2018)	AFib in older adults	5 RCTs	28,137	RR 0.83 (0.69–1.00)	***Intracranial hemorrhage*** RR 0.42 (0.29-0.61) ***Gastrointestinal bleeding*** RR 1.04 (0.56-1.95) ***Major bleeding*** RR 0.87 (0.45-1.70)	RR 0.88 (0.61-1.27)
Deng (2019)	AFib and cancer	3 RCTs and 2 observational studies	21,348	Stroke RR 0.52 (0.28-0.99) VTE RR 0.37 (0.22-0.63)	***Intracranial or gastrointestinal bleeding*** RR 0.65 (0.42–0.98) ***Major bleeding*** RR 0.73 (0.53–1.00)	RR 0.81 (0.49-1.32)
Wang (2019)	non-valvular AFib (general)	35 studies	2,356,201	-	***Major bleeding*** HR 0.78 (0.71-0.85)	-
Bitar (2019)	AFib and valvular heart disease	4 phase III RCTs and 2 phase II RCTs	13,853	RR 0.78 (0.66-0.91)	***Intracranial hemorrhage*** RR 0.51 (0.33-0.79) ***Major bleeding*** RR 0.77 (0.58-1.02)	-
Grymonprez (2020)	AFib in older adults	6 RCTs and 6 observational studies	-	HR 0.83 (0.74–0.94)	***Intracranial hemorrhage*** HR 0.58 (0.50-0.67) ***Major bleeding*** HR 0.93 (0.86-1.01) ***Gastrointestinal bleeding*** HR 1.17 (0.99-1.38)	-
Xue (2020)	AFib in Asians	5 RCTs + 21 observational studies	-	RR 0.73 (0.59-0.90)	***Intracranial hemorrhage*** 0.36 (0.26-0.49) ***Gastrointestinal bleeding*** 0.85 (0.64-1.13) Major bleeding 0.59 (0.48-0.72)	RR 0.83 (0.73-0.95)

Kido (2020)	AFib and obesity	1 RCT and 4 observational studies	-	OR 0.85 (0.60-1.19)	***Major bleeding*** OR 0.63 (0.43-0.94)	-
Jiang (2021)	AFib (general)	38 observational studies	1,332,956	-	***Intracranial hemorrhage*** OR 0.59 (0.53-0.66) ***Gastrointestinal bleeding*** OR 1.06 (0.96-1.17)	-
Waranugraha (2021)	non-valvular AFib (general)	34 observational studies	2,287,288	HR 0.77 (0.69-0.87)	***Intracranial hemorrhage*** HR 0.54 (0.42-0.70) ***Major bleeding*** (HR 0.68 (0.54-0.86)	HR 0.71 (0.63-0.81)
Abdullah (2021)	AFib and ESRD	1 RCT and 7 observational studies	30,806	Apixaban HR 1.09 (0.85-1.39) Rivaroxaban HR 1.39 (0.59-3.29)	***Major bleeding*** Apixaban: HR 0.61 (0.44-0.85) Rivaroxaban: HR 0.95 (0.50-1.81)	-
Chen (2021)	AFib and CKD/Dialysis	6 RCTs and 19 observational studies	NA	HR 0.78 (0.64-0.95)	***Major bleeding*** HR 0.83(0.71–0.97)	-
Su (2021)	AFib and CKD	8 RCTs and 46 observational studies	170,059	HR 0.86 (0.78-0.95)	***Major bleeding*** HR, 0.81 (0.66-0.99)	-
Mhanna (2021)	AFib and obesity	2 RCTs and 8 observational studies	89,494	OR 0.71 (0.62-0.81)	***Major bleeding*** OR 0.60 (0.46-0.78)	-
Thangjui (2021)	AFib and obesity	5 RCTs and 8 observational studies	-	OR 0.85 (0.56-1.29)	***Major bleeding*** OR 0.62 (0.48-0.80)	-

Abbreviation: DOACs Direct Oral Anticoagulants, CI: Confidence Interval, OR: Odds Ratio, RR Relative Risk, HR Hazard Ratio, VTE venous thromboembolism, RCT randomized controlled trials, AFib Atrial fibrillation, NA not reported

Table S3. Safety and effectiveness of DOACs compared with warfarin in patients with AFib and cancer

Author (year) country	Study design	Type of cancer	Antineoplastic agents	Sample size	DOACs versus warfarin (95% CI)	
					Stroke/VTE	Bleeding
Melloni (2017)[64] (international)	post-hoc analysis of RCT	breast (16%), prostate (29%), and colon (11%) cancer	-	1,236	HR 1.09 (0.53-2.26)	***Major bleeding*** 0.78 (0.58-1.04) ***Any bleeding*** 1.10 (0.99-1.22)
Shah (2017)[27] USA	observational study	breast (~20%), lung (~12%), gastrointestinal (~11%), genitourinary (~30%)	chemotherapy, hormonal therapy, radiation	16,096 (6075 DOAC users)	***Stroke*** Dabigatran HR 0.89 (0.56-1.42) Rivaroxaban HR 0.74 (0.40-1.39) ***VTE*** Dabigatran HR 0.28 (0.21-0.38) Apixaban HR 0.14 (0.07-0.32) Rivaroxaban HR 0.51 (0.41-0.63)	***Severe bleeding*** Dabigatran HR 0.96 (0.72-1.27) Apixaban HR 0.37 (0.17-0.79) Rivaroxaban HR 1.09 (0.79-1.50)
Chen (2018)[75] (international)	post-hoc analysis of RCT	prostate (28.6%), colorectal (16.1%), and breast (14.7%) cancer	leuprolide acetate, bicalutamide, anastrozole, tamoxifen	640	HR 0.52 (0.22-1.21)	**Major bleeding** HR 1.09 (0.82–1.44)
Ording (2017)[107] Denmark	observational study	gastrointestinal (12%), breast cancer (12%), urological (15%) cancer	-	10,046 (1,809 DOAC users)	HR 0.80 (0.61-1.1)	***Any bleeding*** HR 1.2 (0.92-1.7)
Fanola (2018)[77] (international)	post-hoc analysis of RCT	gastrointestinal (20.6%), prostate (13.6% overall, 20.0% of cancers in men), lung (11.1%), bladder (7.7%), and breast (6.7% overall, 21.0% of cancers in women)	-	1,153	HR 0.60 (0.31-1.15)	***Major bleeding*** HR 0.98 (0.69-1.40)
Kim (2018)[106] Korea	observational study	-	-	1,651 (572 DOAC users) before	5.9% vs. 1.3%/year. p<0.001	***Any bleeding*** 5.1% vs. 1.2%/year , p<0.001

				matching, 766 after matching		
Yasui (2019)[105] Japan	observational study	gastrointestinal (44.2%), lung (24.1%), genitourinary (11.2%) cancer	-	224 (127 DOAC users)	2.8%/year (0.9-8.3) vs. 5.4%/year (2.0-13.4) (p=0.35)	***Major bleeding*** 4.0%/year (1.5-10.4) vs. 6.5%/year (2.4-16.2) (p=0.50)
Wu (2020)[110] Taiwan	observational study	-	-	933 before matching (672 after matching)	At 6 months HR 0.45 (0.25-0.82) At 1 year HR 0.42 (0.24-0.74)	***Major bleeding*** At 6 months HR 0.21 (0.05-0.96) At 1 year HR 0.26 (0.09-0.76)
Ording (2021)[108] Denmark	observational study	gastrointestinal cancer	-	2128 (1476 DOAC users)	-	***Intracranial hemorrhage*** HR 0.32 (0.12-0.86) ***Any bleeding*** HR 0.95 (0.70-1.29) ***Major bleeding*** 1.11 (0.69-1.79) ***Gastrointestinal bleeding*** HR 0.95 (0.63-1.45)
Deitelzweig (2021)[25] USA	observational study	prostate (29%), female breast (17%), genitourinary (14%), and lung (13%)	chemotherapy, hormone therapy, radiation, surgery	40,271	Apixaban HR 0.59 (0.45-0.78) Dabigatran HR 0.88 (0.54-1.41) Rivaroxaban HR 0.82 (0.62-1.08)	***Major bleeding*** Apixaban HR 0.58 (0.50-0.68) Dabigatran HR 0.76 (0.57-1.01) Rivaroxaban HR 0.95 (0.85-1.06)
Chan (2021)[109] Taiwan	observational study	-	-	7,955 (6,274 DOAC users)	HR 0.37 (0.23-0.61)	Major bleeding 0.73 (0.56–0.94)
Atterman (2021)[111] Sweden	observational study	gastrointestinal (19.1%), urological (35.6%), prostate (27.2%) cancer.	chemotherapy, radiation	8,828	HR 0.78 (0.73-0.83)	Gastrointestinal bleeding HR 0.88 (0.80–0.96) Intracranial bleeding HR 0.62 (0.55–0.70)

Abbreviation: DOACs Direct Oral Anticoagulants, CI: Confidence Interval, OR: Odds Ratio, RR Relative Risk, HR Hazard Ratio, VTE venous thromboembolism, RCT randomized controlled trials, AFib Atrial fibrillation