

CLINICAL AND POPULATION SCIENCES

Effectiveness and Safety of Anticoagulation Therapy in Frail Patients With Atrial Fibrillation

Daehoon Kim^{ID}, MD*; Pil-Sung Yang^{ID}, MD*; Jung-Hoon Sung, MD; Eunsun Jang^{ID}, MS; Hee Tae Yu^{ID}, MD; Tae-Hoon Kim^{ID}, MD; Jae-Sun Uhm^{ID}, MD; Jong-Youn Kim^{ID}, MD; Hui-Nam Pak^{ID}, MD; Moon-Hyoung Lee^{ID}, MD; Gregory Y.H. Lip^{ID}, MD†; Boyoung Joung^{ID}, MD†

BACKGROUND: Frail patients with atrial fibrillation (AF) are less likely to receive anticoagulation than nonfrail patients with AF despite frailty being associated with poorer clinical outcomes including stroke. Using a population-based cohort, we sought to assess the effectiveness and safety of oral anticoagulants (OACs) in frail patients with AF.

METHODS: This retrospective cohort study analyzed 83635 patients aged at least 65 years with AF and frailty (≥ 5 Hospital Frailty Risk Score) between January 1, 2013 and December 31, 2016 from the Korean National Health Insurance Service database. To account for the differences between patients receiving OAC or not and across different OAC regimens, propensity score-weighting was used. Net adverse clinical event, defined as the first event of ischemic stroke, major bleeding, or cardiovascular death, was compared. In addition, each individual outcome was examined separately.

RESULTS: In the study population (57.1% women; mean age, 78.5 ± 7.2 years), a total of 14968 net adverse clinical event, 3718 ischemic stroke, 5536 major bleeding, and 6188 cardiovascular death occurred. In comparison with no OAC use, OAC use was associated with lower risks of net adverse clinical event (hazard ratio, 0.78 [95% CI, 0.75–0.82]), ischemic stroke (hazard ratio, 0.91 [95% CI, 0.86–0.97]), and cardiovascular death (hazard ratio, 0.52 [95% CI, 0.49–0.55]), but no difference was observed for major bleeding (hazard ratio, 1.02 [95% CI, 0.95–1.10]). Compared with warfarin, all four individual direct OAC were associated with decreased risks of net adverse clinical event, ischemic stroke, major bleeding, and cardiovascular death. The associations for OAC use (compared to no OAC use) or direct OAC use (compared to warfarin) with favorable outcomes were more prominent in individuals with a higher CHA₂DS₂-VAsC score of at least 3.

CONCLUSIONS: Among frail patients with AF, OAC treatment was associated with a positive net clinical outcome. Direct OACs provided lower incidences of stroke, bleeding, and mortality, compared with warfarin.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: Editorials ■ anticoagulant ■ atrial fibrillation ■ frailty ■ ischemic stroke ■ mortality

Frailty is described as a biologic syndrome appearing as a decreased ability to recover from stressors due to cumulative declines in multiple physiological systems, in homeostatic reserve, and in resiliency, and has been shown to be ultimately associated with more

adverse clinical outcomes.^{1,2} Atrial fibrillation (AF) poses enormous socioeconomic implications given the risk of mortality and morbidity resulting from stroke, congestive heart failure, and impaired quality of life.³ AF may be a marker of frailty in older adults and may be related to

Correspondence to: Boyoung Joung, MD, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, Republic of Korea 03722, Email cby6908@yuhs.ac or Gregory Y.H. Lip, MD, Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool, England, United Kingdom, Email gregory.lip@liverpool.ac.uk

*D. Kim and P.-S. Yang contributed equally.

†G.Y.H. Lip and B. Joung are joint senior authors.

This manuscript was sent to Jean-Claude Baron, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.121.036757>.

For Sources of Funding and Disclosures, see page 1882.

© 2022 The Authors. *Stroke* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the [Creative Commons Attribution Non-Commercial License](#), which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited and is not used for commercial purposes.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
DOAC	direct oral anticoagulant
NACE	net adverse clinical end point
NHIS	National Health Insurance Service
OAC	oral anticoagulant

a loss of independence in performing activities of daily living.^{4,5} Also, AF could worsen a state of frailty, with a 4-fold increased odds of being classified as frail, compared with patients without AF.⁶

The most feared consequence of AF is a thromboembolic event, notably ischemic stroke, and stroke prevention with oral anticoagulation is the cornerstone for the management of AF.⁷ Despite an elevated stroke risk, the rate of adequate oral anticoagulation is lower in frail patients with AF than in nonfrail patients with AF.^{8,9} Concerns for complications, mainly bleeding, could lead physicians to withhold oral anticoagulants (OACs) for frail patients who are more susceptible thereto, due to multimorbidity, interacting polypharmacy, cognitive impairment, and/or lowered elimination capacities of the liver and kidneys.^{10,11} In recent years, direct OAC (DOACs) have been shown to be much safer than warfarin in regards to the risk of intracranial hemorrhage and at least as effective.¹² However, there is a paucity of published data on DOACs against warfarin in frail patients with AF, who are generally under-represented in trial cohorts.^{12,13}

Altogether, there is currently clinical uncertainty on whether or not to use OAC and on which OAC to use in frail patients with AF.^{14,15} Our aim was to assess the effectiveness and safety of OAC treatment in comparison with non-OAC treatment among frail patients with AF. Also, we compared clinical outcomes between frail OAC users taking DOACs and warfarin.

METHODS

This study is a retrospective analysis based on the national health claims database established by the National Health Insurance Service (NHIS) of Korea. Further details are presented in the [Supplemental Methods](#). This study was approved by the Institutional Review Board of the Yonsei University Health System (4-2016-0179). The requirement for informed consent was waived because personal identification information was removed after cohort generation, in accordance with strict confidentiality guidelines. All data and materials of the NHIS are accessible to the public on the National Health Insurance Data Sharing Service homepage of the NHIS (<http://nhiss.nhis.or.kr>). Applications to use the NHIS data are reviewed by the inquiry committee of research support and once approved, raw data is provided, on payment of a fee, to the authorized researcher at several permitted sites.

Study Population

From the entire Korean population in the Korean NHIS database, we initially identified 232948 OAC-naïve patients with AF aged ≥ 65 years between January 1, 2013 and December 31, 2016. Patients with AF were identified using the *International Classification of Disease Tenth Revision* codes I48, only for a discharge diagnosis or when confirmed at least twice in the outpatient department to ensure diagnostic accuracy. AF diagnosis was previously validated in the NHIS database with a positive predictive value of 94.1%.¹⁶ The entire cohort at entry consisted of OAC nonusers. The date of cohort entry was recorded as the date of first AF diagnosis (for incident AF in 2013–2016) or the date of first medical contact with a record of an AF diagnosis in 2013–2016 (for prevalent AF diagnosed before January 1, 2013). For the patients who subsequently started OAC, the date an OAC was first prescribed was defined as the index date. For those who did not start OAC until December 31, 2016, we defined the index date as the date of cohort entry. For each patient, the Hospital Frailty Risk Score was calculated retrospectively using all available *International Classification of Disease Tenth Revision* diagnostic codes that were documented before the index date.¹⁷ The score comprises 109 codes found to be associated with frailty (Table 1). Each of these codes was given a specific value proportional to how strongly it predicted frailty. Frailty was defined as having the aggregate score of at least 5 points.¹⁷

Outcomes and Covariates

The primary outcome was a net adverse clinical end point (NACE), defined as the first occurrence of ischemic stroke, major bleeding, or cardiovascular death. Secondary outcomes included the individual components of the NACE. If ≥ 2 individual outcomes were observed on the same day, they were counted separately as individual outcomes. The definitions of clinical outcomes are presented in [Table S1](#). Patients in the non-OAC group were followed up from their cohort entry until the occurrence of NACE, initiation of OAC treatment, death, or at the end of the study period (December 31, 2016), whichever occurred first. From the date of OAC initiation, patients were followed up as the OAC group until the occurrence of NACE, switching to other OACs, death, or December 31, 2016, whichever came earliest. Details about covariates are presented in the [Supplemental Methods](#) and [Table S1](#).

Statistical Analysis

Characteristics of the study populations were reported as means \pm SD or percentages. In this observational study comparing a population that received different treatments, propensity score analyses were used to reduce bias by accounting for differences between groups and mimicking randomized clinical trials that examine different target populations.¹⁸ In assessing the association between OAC use and outcomes, OAC use was entered into the models as a time-varying exposure. Any patient who subsequently started an OAC was assigned to the OAC group and contributed time to the no OAC group until the first date of OAC prescription. We used a propensity score overlap weighting approach to account for the differences in characteristics between frail patients with AF who underwent OAC treatment or not. During the follow-up, 28547 frail patients underwent OAC treatment with at least 30 days

Table 1. Characteristics of Frail Patients With Atrial Fibrillation According to Oral Anticoagulation Treatment Before and After Propensity Score Weighting

Variables	Before weighting			After weighting		
	OAC (N=28547)	No OAC (N=55088)	ASD	OAC (N=28547)	No OAC (N=55088)	ASD
Sociodemographics						
Age, y	77.4±6.7	79.1±7.4	0.24	77.9±6.7	78.4±7.2	0.07
Female	56.2%	57.6%	0.03	56.9%	56.9%	<0.01
Income, high tertile	41.8%	38.5%	0.07	40.3%	40.3%	<0.01
Risk scores						
CHA ₂ DS ₂ -VASc score*	5.8±1.7	5.4±1.8	0.23	5.6±1.7	5.6±1.8	<0.01
mHAS-BLED score†	4.2±1.2	4.1±1.3	0.12	4.2±1.2	4.2±1.3	<0.01
Charlson Comorbidity Index	7.4±3.4	7.4±3.6	0.01	7.4±3.5	7.4±3.4	<0.01
Hospital Frail Risk Score	13.4±8.1	15.6±9.5	0.25	14.1±8.7	14.1±8.3	<0.01
Comorbidities						
Heart failure	66.6%	54.4%	0.25	62.7%	62.7%	<0.01
Hypertension	89.6%	83.4%	0.18	87.7%	87.7%	<0.01
Diabetes	38.3%	38.9%	0.01	39.0%	39.0%	<0.01
Dyslipidemia	91.6%	80.8%	0.32	88.6%	88.6%	<0.01
Ischemic stroke	57.0%	41.7%	0.31	50.7%	50.7%	<0.01
Transient ischemic attack	18.0%	16.9%	0.03	17.7%	17.7%	<0.01
Intracranial hemorrhage	6.1%	8.1%	0.08	6.8%	6.8%	<0.01
Myocardial infarction	15.5%	16.2%	0.02	15.9%	15.9%	<0.01
Peripheral artery disease	24.9%	22.2%	0.06	24.2%	24.2%	<0.01
Chronic kidney disease	14.1%	15.1%	0.03	14.7%	14.7%	<0.01
Proteinuria	8.5%	6.6%	0.07	7.8%	7.8%	<0.01
Osteoporosis	62.3%	63.0%	0.02	62.7%	62.7%	<0.01
COPD	34.8%	37.0%	0.05	35.9%	35.9%	<0.01
Chronic liver disease	52.8%	51.4%	0.03	52.2%	52.2%	<0.01
Malignant neoplasm	39.8%	43.3%	0.07	41.3%	41.3%	<0.01
Medications						
Statin	48.8%	38.4%	0.21	45.1%	45.1%	<0.01
Beta blocker	57.5%	45.5%	0.24	52.7%	52.7%	<0.01
ACE inhibitor/ARB	65.9%	57.5%	0.17	63.1%	63.1%	<0.01
CCB DHP	58.0%	54.9%	0.06	57.5%	57.5%	<0.01
CCB Non DHP	13.9%	8.9%	0.16	11.6%	11.6%	<0.01
Loop/thiazide diuretics	68.0%	61.4%	0.14	65.9%	65.9%	<0.01
K ⁺ sparing diuretics	19.9%	16.0%	0.10	18.5%	18.5%	<0.01
AAD class Ic	21.1%	13.5%	0.20	17.6%	17.6%	<0.01
AAD class III	6.1%	2.3%	0.19	45.1%	45.1%	<0.01
Digoxin	5.6%	2.6%	0.15	52.7%	52.7%	<0.01
Variables contributing to the Hospital Frail Risk Score (ICD-10 codes)‡						
Dementia in Alzheimer disease (F00)	13.5%	21.4%	0.21	15.9%	15.9%	<0.01
Hemiplegia (G81)	19.5%	12.6%	0.19	16.0%	16.0%	<0.01
Alzheimer disease (G30)	2.0%	2.5%	0.04	2.1%	2.1%	<0.01
Sequelae of cerebrovascular disease (I69)	16.6%	16.2%	0.01	16.6%	16.6%	<0.01
Other symptoms and signs involving the nervous and musculo-skeletal systems (R29)	0.4%	0.3%	0.02	0.4%	0.4%	<0.01
Other disorders of urinary system (N39)	26.4%	31.9%	0.12	28.4%	28.4%	<0.01
Superficial injury of head (S00)	5.7%	6.1%	0.02	5.8%	5.8%	

(Continued)

Table 1. Continued

Variables	Before weighting			After weighting		
	OAC (N=28547)	No OAC (N=55088)	ASD	OAC (N=28547)	No OAC (N=55088)	ASD
Delirium, not induced by alcohol and other psychoactive substances (F05)	5.4%	8.6%	0.13	6.4%	6.4%	<0.01
Unspecified fall (W19)	0.1%	0.1%	0.02	0.1%	0.1%	<0.01
Unspecified hematuria (R31)	9.8%	10.8%	0.04	10.2%	10.2%	<0.01
Other bacterial agents as the cause of diseases classified to other chapters (B96)	1.4%	2.1%	0.05	1.6%	1.6%	<0.01
Other symptoms and signs involving cognitive functions and awareness (R41)	2.5%	2.6%	0.01	2.4%	2.4%	<0.01
Other cerebrovascular diseases (I67)	13.0%	12.8%	0.01	13.0%	13.0%	<0.01
Convulsions, not elsewhere classified (R56)	4.2%	4.3%	0.01	4.2%	4.2%	<0.01
Abnormalities of gait and mobility (R26)	3.7%	4.6%	0.05	3.8%	3.8%	<0.01
Somnolence, stupor and coma (R40)	3.1%	4.9%	0.09	3.7%	3.7%	<0.01
Intracranial injury (S06)	13.0%	14.5%	0.04	13.6%	13.6%	<0.01
Complications of genitourinary prosthetic devices, implants and grafts (T83)	0.1%	0.1%	0.03	0.1%	0.1%	<0.01
Other disorders of fluid, electrolyte and acid base balance (E87)	32.8%	42.4%	0.20	36.5%	36.5%	<0.01
Other joint disorders, not elsewhere classified (M25)	13.4%	13.8%	0.01	13.5%	13.5%	<0.01

Values are presented as mean±SD or %. AAD indicates antiarrhythmic agent; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ASD, absolute standardized difference; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DHP, dihydropyridine; *ICD-10*, *International Classification of Diseases, Tenth Revision*; and OAC, oral anticoagulant.

*CHA₂DS₂-VASc = heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), age 65–74 years (1 point), diabetes (1 point), previous stroke/transient ischemic attack (2 points), vascular disease (prior myocardial infarction or peripheral artery disease, 1 point) and female sex (1 point).

†Modified (m) HAS-BLED = hypertension, 1 point; >65 years old, 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; liable international normalized ratio, not assessed; ethanol or drug abuse, 1 point; drug predisposing to bleeding, 1 point.

‡Variables with the top 20 points, each of which contributes ≥2 points are presented in this table. All variables are presented in Table S5.

of prescription for dabigatran (150 or 110 mg bid), rivaroxaban (20 or 15 mg qd), apixaban (5 or 2.5 mg bid), edoxaban (60 or 30 mg QD), or warfarin (Figure 1). A propensity score, the probability of undergoing OAC treatment, was calculated based on a total of 141 variables measured at the index dates: sex, age, income status, risk scores, comorbidities, medication use (presented in Table 1), and 109 variables contributing to Hospital Frail Risk Score calculation (fully presented in Table S2). The overlap weight was calculated as 1–propensity score for the OAC-treated patients and the propensity score for the patients without OAC treatment (details are presented in the Supplemental Methods).¹⁹

To account for the differences across 5 different OAC regimens (dabigatran, apixaban, rivaroxaban, edoxaban, or warfarin), we used an inverse probability of treatment weighting approach for multiple treatment options. The weights were derived to obtain estimates representing population average treatment effects with optimal balance between the treatment populations by using generalized boosted models based on 10 000 regression trees.²⁰ Propensity scores were derived based on the 141 variables measured at the index dates (defined as the time of OAC initiations in OAC users). The examined treatment regimens should be contrasted on comparable populations and any patient must have positive probability for any treatment (positivity assumption), hence substantial overlap between the propensities for each treatment should be present.

Incidence rates were calculated by dividing the number of events by person-time at risk. We compared the incidences of outcomes using the weighted log-rank test and plotted weighted failure curves. Competing risk regression by Fine

and Gray was used to consider all-cause death as a competing event when estimating the relative hazards of clinical outcomes.²¹ Balance between treatment populations was additionally evaluated by standardized differences of all baseline covariates, using a threshold of 0.1 to indicate imbalance. Cofactors that had not been balanced by weighting were included as covariates in the competing risk regression. The proportional hazards assumption was tested on the basis of Schoenfeld residuals. Negative binomial regression models were developed to compare the total number of adverse clinical events between treatment groups. Cofactors that had not been balanced by weighting and duration of follow-up were included as exposure variables in the models.

There were no missing values in this study because all variables were ascertained by identifying claims in the national health insurance database and laboratory data or health-related risk factors were not included. A 2-sided *P* value of <0.05 was considered significant. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC) and R version 3.5.3 (The R Foundation, www.R-project.org).

Sensitivity Analyses

First, we performed subgroup analyses for the primary outcome stratified by age (<65, 65–74, or ≥75 years), sex, ischemic stroke, intracranial hemorrhage, CHA₂DS₂-VASc score, HAS-BLED score, Hospital Frailty Risk Score, and DOAC dosing by refitting separate propensity score weighted models for each subgroup. Second, one-to-one propensity score matching (without replacement with a caliper of 0.001) was

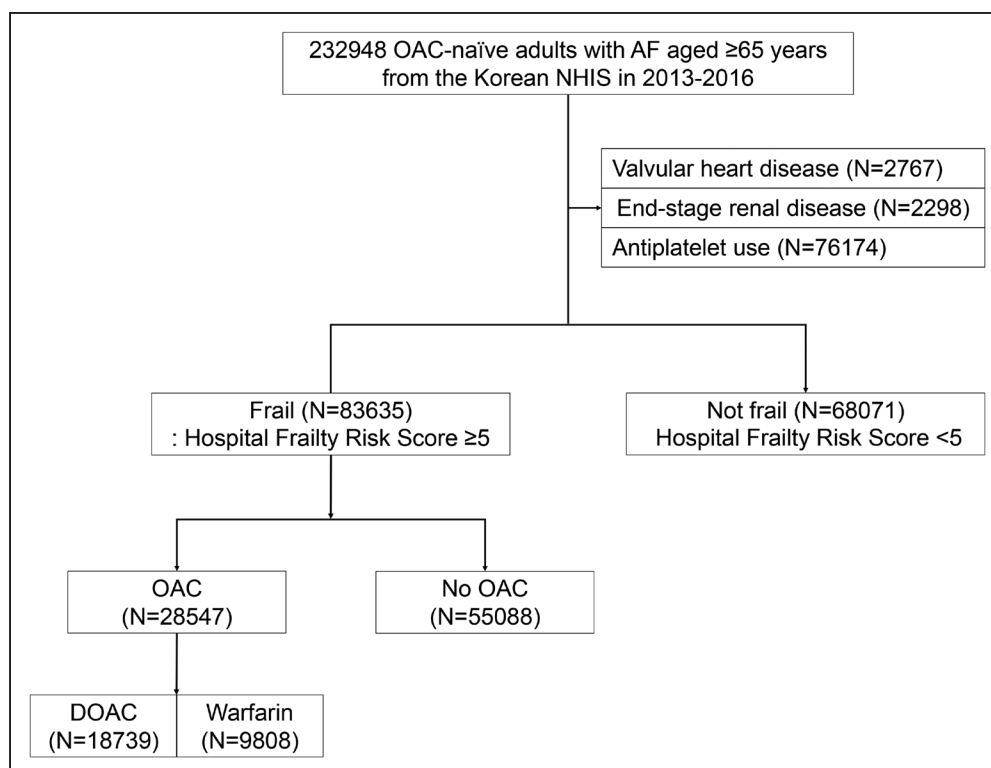


Figure 1. Flowchart of study population enrollment and analysis.

Exclusion criteria are as follows: (1) valvular heart disease (diagnosed as mitral stenosis or prosthetic heart valves or with insurance claims for valve replacement or valvuloplasty); (2) end-stage renal disease; and (3) concomitant antiplatelet use. AF indicates atrial fibrillation; DOAC, direct oral anticoagulant; NHIS, National Health Insurance Service; and OAC, oral anticoagulant.

performed instead of propensity score weighting as an alternative method to create target populations in observational cohort studies. Third, we performed separate propensity weighting analyses in analogy with the on-treatment principle by restricting the analysis to patients with access to OACs covering 80% of the time at risk.

We assessed residual confounding using two methods. First, in our main overlap weighting models, we analyzed three falsification end points that are unlikely to be causally affected by anticoagulant treatment but might be related to unmeasured confounders, including influenza, varicella-zoster (chickenpox and shingles), and fall accident (detailed definitions in Table S3). Second, we used the method of Lin et al²² to assess whether the observed differences in the risk of the primary outcome could be fully explained by an unmeasured confounder.

RESULTS

This study identified 83 635 frail patients with AF (Figure 1). In comparison to patients without frailty ($n=68\,071$), frail patients tended to be older and female, to have lower income, higher CHA₂DS₂-VASc scores, and more comorbidities, and to take more cardiovascular medications (Table S4). Among frail patients, other functional intestinal disorders (64.2%), other disorders of fluid, electrolyte, acid-base balance (39.2%), pneumonia, organism unspecified (38.6%), nausea, and vomiting (37.0%) were the 4 most

frequently diagnosed codes comprising the Hospital Frailty Risk Score (Table S2). Characteristics of the frail patients according to prevalent or incident AF are presented in Table S5.

OAC Versus No OAC

Among frail patients with AF, a total of 20 190 (24.1%) patients experienced NACE: 5253 (6.3%) ischemic stroke, 7424 (8.9%) major bleeding, and 8142 (9.7%) had cardiovascular death (≥ 2 individual outcomes that were observed on the same day were counted separately as individual outcomes). During the study period, a total of 24 146 adverse clinical event occurred; 3327 of these were additional events that occurred after first events during the study, which were not included in the primary analyses for time to first events.

Table 1 summarizes the characteristics of the frail patients according to the use of OAC before and after propensity score overlap weighting. OAC users tended to be younger and male; to have higher income, higher CHA₂DS₂-VASc scores, and lower Hospital Frailty Risk Scores; to take more cardiovascular medications. After overlap weighting, the covariates were well balanced with all the standardized differences less than 0.1 (Table 1 and Table S6). We noted sufficient overlap in propensity scores between the weighted cohorts

(Figure S1). In multivariable logistic regression, the factors independently associated with the likelihood of undergoing OAC treatment in frail patients with AF were younger age, male, high income, and higher CHA₂DS₂-VASc, lower HAS-BLED, and Hospital Frailty Risk Scores (Table S7).

The weighted cumulative hazards of NACE, ischemic stroke, and cardiovascular death were significantly lower in the OAC group than in the no OAC group, whereas no significant difference was observed for major bleeding (log-rank $P=0.066$) (Figure 2). Event numbers, incidence rates, and hazard ratios by OAC treatment are presented in Table 2. During a mean follow-up of 15.1 ± 14.2 months, OAC treatment was associated with a 22% decreased risk of NACE (95% CI, 18%–25%), a 9% decreased risk of ischemic stroke (95% CI, 3%–14%), and a 48% decreased risk of cardiovascular death (95% CI, 45%–51%), compared with no OAC

treatment, whereas there were no significant associations between OAC treatment and bleeding outcomes. Restriction of the follow-up duration to 1 year did not affect the associations between OAC use and outcomes. OAC treatment was associated with a fewer number of total clinical events (incidence rate ratio, 0.72 [95% CI, 0.69–0.75]; $P<0.001$), compared with no treatment.

DOACs Versus Warfarin

Among 28547 frail patients with AF undergoing OAC treatment, 34.4% received warfarin, 26.3% rivaroxaban, 17.2% apixaban, 16.7% dabigatran, and 5.3% edoxaban. Mean follow-up duration of the population was 12.3 months, with the edoxaban group having the shortest mean follow-up (edoxaban was introduced to Korean market in February 2016). Apixaban users have the highest average age (77.9 years) and Hospital Frailty

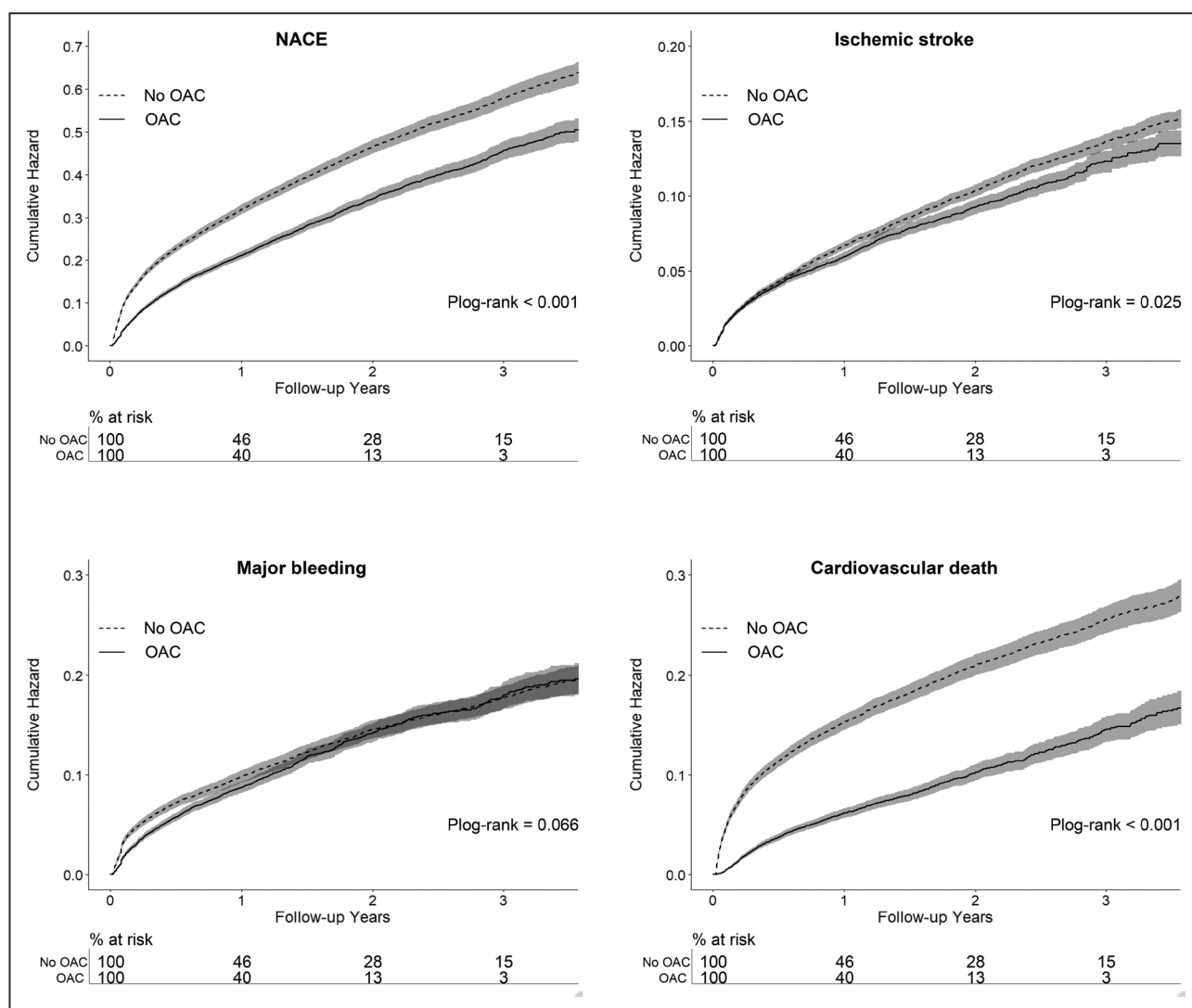


Figure 2. Weighted cumulative hazards of clinical outcomes for frail patients with atrial fibrillation receiving oral anticoagulation (OAC) or not.

NACE indicates net adverse clinical event.

Table 2. Outcomes of OAC Treatment Compared With Propensity Overlap Weighted No OAC Treatment (N=83 635)

	OAC (N=28547)		No OAC (N=55088)		Hazard ratio (95% CI)	P value
	Event number	Event rate per 100 PYs	Event number	Event rate per 100 PYs		
One-year follow-up						
NACE	4695	23.0	10273	37.0	0.70 (0.66–0.74)	<0.001
Ischemic stroke	1931	7.9	1787	8.5	0.91 (0.85–0.97)	0.006
Major bleeding	1740	10.6	3796	11.3	1.05 (0.99–1.11)	0.071
Cardiovascular death	1247	6.4	4941	18.1	0.40 (0.36–0.44)	<0.001
Overall follow-up						
NACE	6003	17.7	14187	22.9	0.78 (0.75–0.82)	<0.001
Ischemic stroke	2397	5.2	2856	5.4	0.91 (0.86–0.97)	0.002
Major bleeding	2223	7.8	5201	7.6	1.02 (0.95–1.10)	0.563
Cardiovascular death	1673	5.2	6469	10.6	0.52 (0.49–0.55)	<0.001

Event rates and hazard ratios were propensity score overlap weighted. NACE indicates net adverse clinical event; OAC, oral anti-coagulant; and PYs, person-years.

Risk Scores (13.5 points), whereas warfarin and edoxaban users frequently had chronic kidney disease with the prevalences of 16.7% and 15.8% (Table S8). After inverse probability of treatment weighting, sufficient overlap in individual propensity score distributions was observed, suggesting application of the inverse probability of treatment weighting approach resulted in a cohort in which the distribution of variables were comparable between treatment groups (Figure S2). Maximum pairwise standardized differences of all covariates were less than 0.1 (Table S9 and Figure S3). The weighted cumulative hazards of clinical outcomes were shown in Figure 3. During the first year of follow-up, the weighted event rates for NACE were similar for 4 DOACs; 24.8 per 100 person-years for edoxaban, 22.6 for rivaroxaban, 21.0 for apixaban, and 19.9 dabigatran, and higher for warfarin with 30.4 per 100 person-years. All 4 DOACs were associated with lower risks of NACE, ischemic stroke, major bleeding, and cardiovascular death, compared with warfarin use (Table 3). During overall follow-up of the population, the protective associations of DOAC use were consistently observed. During the study period, a total of 7511 adverse clinical event occurred in OAC users. All 4 DOAC cases were associated with a fewer number of total events, compared with warfarin (Table S10).

Sensitivity Analyses

First, in subgroup analysis, compared with no OAC use, OAC treatment was consistently associated with a lower risk of NACE across all subgroups stratified according to age, sex, history of stroke or intracranial hemorrhage, and CHA₂DS₂-VASc, HAS-BLED, Hospital Frailty Risk scores, except for those with CHA₂DS₂-VASc of 1–2 or HAS-BLED <3 (Figure S4). Compared with warfarin

use, all 4 DOACs showed lower risks of NACE across all subgroups, except for those with CHA₂DS₂-VASc of 1–2 (Figure S5). Second, one-to-one propensity matching produced a pair of patients with or without OAC treatment (each of 22 078) and 4 pairs of OAC-treated patients taking one of 4 DOACs or warfarin. The associations of OAC use (compared with no use) and DOAC use (compared with warfarin) were consistently observed (Tables S11 and S12). Third, the results from sensitivity propensity weighting analyses using an on-treatment approach were consistent with the main findings (Table S13 and S14).

There were no significant differences for any of the falsification end points in overlap weighted cohorts of OAC-treated and untreated patients (Table S15). An unmeasured confounder could explain the observed differences in the primary outcome only if the confounder was related to a substantially increased risk of the outcome by ≈2-fold or if there was substantial imbalance in its prevalence (Figures S6 and S7).

DISCUSSION

This nationwide population-based cohort study demonstrated that among frail patients with AF, compared with no treatment, OAC treatment was associated with lower risks of stroke, cardiovascular death, and NACE, whereas bleeding risk was not altered, suggesting a positive net clinical benefit. The use of any of 4 individual DOACs, compared with warfarin, was associated with lower hazards of developing thrombotic, bleeding, and mortality outcomes irrespective of the doses of DOAC.

Definitions of frailty in general populations have included age, nutritional status, mobility, social withdrawal, income, number of prior hospitalizations, and cognitive impairment. Many studies demonstrated that

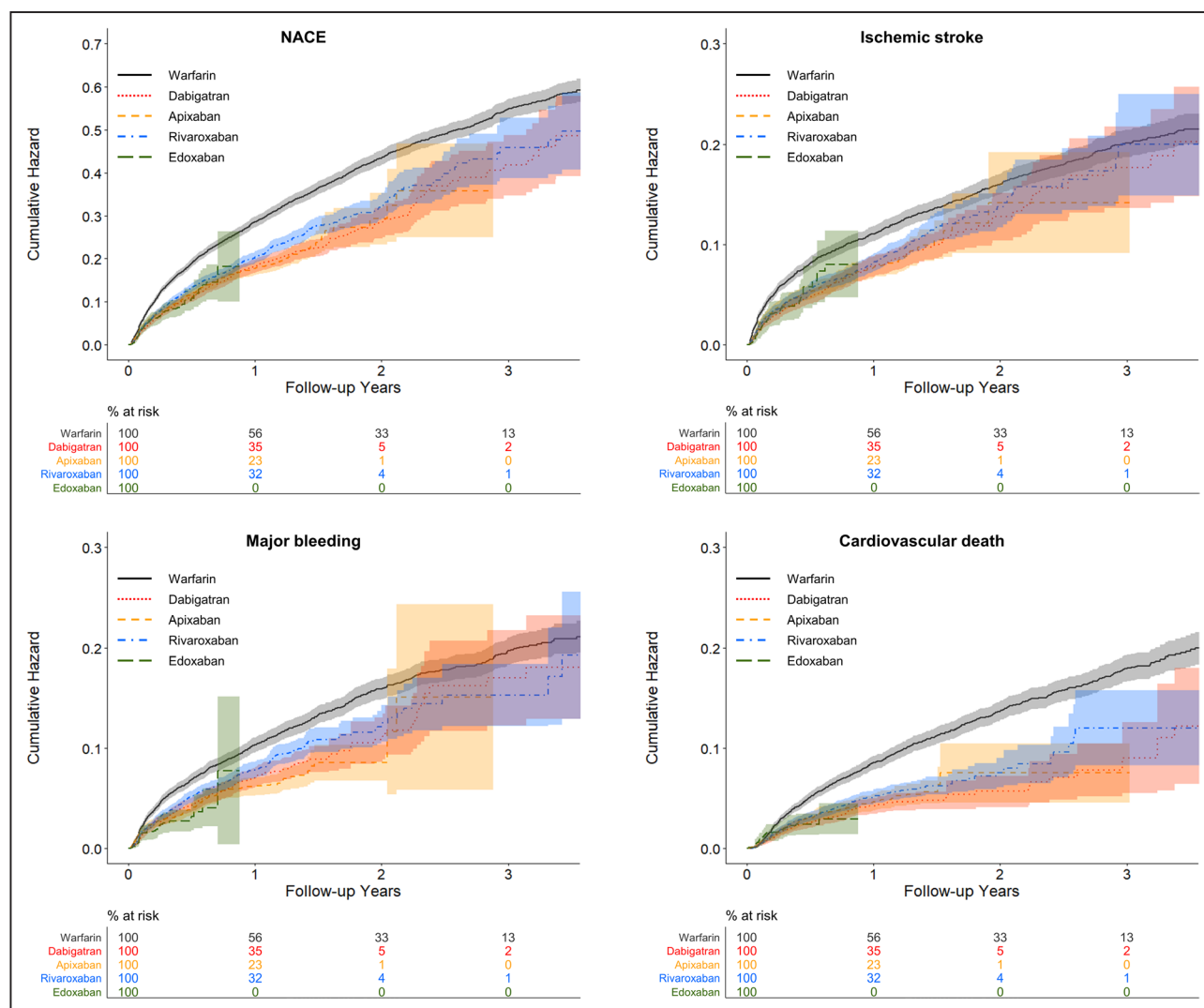


Figure 3. Weighted cumulative hazards of clinical outcomes for frail patients with atrial fibrillation receiving direct oral anticoagulants or warfarin.

NACE indicates net adverse clinical event.

frail patients with AF are less likely to receive anticoagulation than nonfrail patients despite the fact that there is an increasing trend of stroke in frail patients.^{8,9} Therefore, the effectiveness and safety of OAC treatment options for frail patients do need to be clarified, especially since such patients are commonly encountered in everyday clinical practice. Although we did not observe any significant increase in the risk of bleeding outcomes, the protective associations of OAC treatment with lower risks of stroke and mortality were consistently observed in frail patients with AF, in agreement with a recent study by Madhavan et al.⁹ The risk of NACE (ie, the earliest event occurring among stroke, major bleeding, and cardiovascular death) was markedly lower in OAC-treated patients than in those untreated, suggesting a positive net clinical benefit. The results from our subgroup analyses suggested that OAC may be considered for frail patients with a $\text{CHA}_2\text{DS}_2\text{-VASc}$ score ≥ 3 , in whom a stronger association with a lower risk of NACE was observed.

A recent US cohort study reported that rivaroxaban, but not apixaban or dabigatran, was associated with reduced stroke/systemic embolism versus warfarin in frail patients with AF and no significant difference in bleeding versus warfarin.²³ In the present study, we expounded on prior observations by enrolling a substantially larger number of participants and accounting for treatment adherence (by restricting analyses to those covered with OAC $\geq 80\%$ of follow-up time), showing decreased risks of stroke and major bleeding in DOAC users, compared with warfarin users. The protective associations were consistent regardless of DOAC dosing or individual agent and stronger than demonstrated in the nonfrail AF population, suggesting that the relative effectiveness and safety of DOACs, compared with warfarin, might be more pronounced among frail patients in routine clinical practice, which is important given that frail patients are under-represented in clinical trial cohorts.^{12,13} The present study might provide clinicians with added confidence in prescribing DOACs for the frail AF population. In

Table 3. Outcomes of DOAC Treatment Compared With Inverse Probability Treatment Weighted Warfarin Treatment (N=28547)

	Warfarin (N=9808)			Dabigatran (N=4792)			Apixaban (N=4917)			Rivaroxaban (N=7519)			Edoxaban (N=1511)*		
	Event N	Rate/100 PYs	HR (95% CI)	Event N	Rate/100 PYs	HR (95% CI)	Event N	Rate/100 PYs	HR (95% CI)	Event N	Rate/100 PYs	HR (95% CI)	Event N	Rate/100 PYs	HR (95% CI)
One-year follow-up															
NACE	2355	30.4	1 (ref)	600	19.9	0.63 (0.60–0.65)	600	21.0	0.64 (0.62–0.67)	1043	22.6	0.71 (0.68–0.74)	97	24.8	0.62 (0.58–0.65)
Ischemic stroke	945	12.2		268	8.6	0.67 (0.63–0.71)	265	9.4	0.70 (0.65–0.75)	408	9.3	0.72 (0.68–0.77)	45	12.4	0.71 (0.66–0.77)
Major bleed-ing	841	11.0		231	7.4	0.67 (0.63–0.72)	214	7.7	0.62 (0.58–0.67)	419	8.7	0.76 (0.71–0.81)	35	7.9	0.53 (0.49–0.58)
Cardio-vascular death	684	8.7		131	4.5	0.51 (0.47–0.55)	149	5.2	0.57 (0.52–0.62)	260	5.5	0.62 (0.57–0.67)	23	5.8	0.57 (0.51–0.63)
Overall follow-up															
NACE	3374	21.8	1 (ref)	698	17.9	0.64 (0.62–0.66)	643	19.9	0.64 (0.62–0.67)	1191	20.8	0.72 (0.70–0.75)
Ischemic stroke	1280	8.3		315	7.8	0.71 (0.67–0.75)	283	8.9	0.72 (0.68–0.77)	474	8.7	0.77 (0.73–0.81)
Major bleed-ing	1208	7.9		269	7.0	0.69 (0.65–0.73)	230	7.0	0.63 (0.59–0.67)	481	8.1	0.78 (0.73–0.82)
Cardio-vascular death	1056	6.7		148	4.0	0.48 (0.45–0.52)	159	4.9	0.55 (0.51–0.59)	287	5.0	0.59 (0.55–0.63)

Event rates and hazard ratios were inverse probability of treatment weighted. DOAC indicates direct oral anticoagulant; HR, hazard ratio; NACE, net adverse clinical event; and PYs, person-years. *Outcome analyses were performed with restriction of the follow-up period to 1 y because of the short follow-up duration in the edoxaban group.

the present study, taking into account possible biases from previous OAC use, we enrolled only OAC-naïve patients with AF. Thus, safety and efficacy of switching from warfarin to DOAC in frail patients still remain uncertain. Given an analysis using routine clinical practice data tends to be confounded by the reason to switch,²⁴ a randomized clinical trial focusing on the outcomes of OAC switching has been initiated (results are expected in 2022).¹¹

Study Limitations

This study has limitations. First, owing to the observational nature, causal relationships could not be assessed, and residual confounding is likely to persist. We used propensity score–weighting and one-to-one propensity score–matching, resulting in identical groups on 141 variables, and assessed falsification end points to investigate the presence of confounding by indication. Although no evidence of a hidden bias was found, the potential remains for unmeasured confounders to have influenced the findings. Second, such studies using administrative databases may be susceptible to errors arising from coding inaccuracies. To minimize this, we used definitions previously validated for the Korean NHIS cohort.^{3,16–20} Third, we did not have access to information on time in therapeutic range among warfarin users. Instead, we were able to assess treatment adherence among the users of DOAC and warfarin, and the results were consistent in subjects covered with OAC ≥80% of the time at risk. Nevertheless, our comparisons between DOAC and warfarin users should still be interpreted carefully.

Fourth, we estimated frailty based on the Hospital Frailty Risk Score, which was calculated using administrative claim data. Potential weaknesses of this approach are that frailty among older people with few or no past hospital visits might be missed and coding inaccuracy could contribute to measurement error. Conversely, the advantages are that it can be calculated using routine data for all patients in hospital and eliminates the inter-operator variability and the need to apply a manual score.¹⁷ The Hospital Frailty Risk Score has been extensively validated and has shown fair overlap with the two most commonly accepted approaches to define frailty (ie, the Fried Frailty phenotype and the Rockwood Frailty Index).^{17,25,26} Lastly, the study enrolled only Asian patients, so it is unknown whether the results apply to other populations.

Conclusions

In this propensity score–weighted analysis using a large Asian nationwide cohort of frail patients with AF, OAC treatment was associated with reduced risks of ischemic stroke and cardiovascular death without an increased risk of major bleeding, suggesting a positive net clinical benefit, compared with no OAC use. All 4 individual DOACs provided lower incidences of stroke, bleeding, and mortality, compared with warfarin.

ARTICLE INFORMATION

Received July 26, 2021; final revision received November 17, 2021; accepted December 9, 2021.

Affiliations

Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea (D.K., E.J., H.T.Y., T.-H.K., J.-S.U., J.-Y.K., H.-N.P., M.-H.L., B.J.). Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea (P.S.Y., J.-H.S.). Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, United Kingdom (G.Y.H.L.).

Sources of Funding

This research was supported by a grant from Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (grant numbers: H19C0481, HC19C013, H115C1200).

Disclosures

Dr Lip has served as a consultant for Bayer/Janssen, Bristol Myers Squibb (BMS)/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseeon, and Daiichi-Sankyo and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. Dr Joung has served as a speaker for Bayer, BMS/Pfizer, Medtronic, and Daiichi-Sankyo and received research funds from Medtronic and Abbott. Neither author has received any fees directly. The other authors report no conflicts.

REFERENCES

- Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381:752–762. doi: 10.1016/S0140-6736(12)62167-9
- Villacampa-Fernández P, Navarro-Pardo E, Tarín JJ, Cano A. Frailty and multimorbidity: two related yet different concepts. *Maturitas*. 2017;95:31–35. doi: 10.1016/j.maturitas.2016.10.008
- Kim D, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, Joung B, et al. 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. *Am Heart J*. 2018;202:20–26. doi: 10.1016/j.ahj.2018.04.017
- Fumagalli S, Tarantini F, Guarducci L, Pozzi C, Pepe G, Boncinelli L, Valoti P, Baldasseroni S, Masotti G, Marchionni N; GIFA Study Research Group. Atrial fibrillation is a possible marker of frailty in hospitalized patients: results of the GIFA Study. *Aging Clin Exp Res*. 2010;22:129–133. doi: 10.1007/BF03324785
- Marzona I, O'Donnell M, Teo K, Gao P, Anderson C, Bosch J, Yusuf S. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *CMAJ*. 2012;184:E329–E336. doi: 10.1503/cmaj.111173
- Polidoro A, Stefanelli F, Ciacciarelli M, Pacelli A, Di Sanzo D, Alessandri C. Frailty in patients affected by atrial fibrillation. *Arch Gerontol Geriatr*. 2013;57:325–327. doi: 10.1016/j.archger.2013.04.014
- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373–498. doi: 10.1093/eurheartj/ehaa612
- Induruwa I, Evans NR, Aziz A, Reddy S, Khadjoor K, Romero-Ortuno R. Clinical frailty is independently associated with non-prescription of anticoagulants in older patients with atrial fibrillation. *Geriatr Gerontol Int*. 2017;17:2178–2183. doi: 10.1111/ggi.13058
- Madhavan M, Holmes DN, Piccini JP, Ansell JE, Fonarow GC, Hylek EM, Kowey PR, Mahaffey KW, Thomas L, Peterson ED, et al; ORBIT AF Investigators. Association of frailty and cognitive impairment with benefits of oral anticoagulation in patients with atrial fibrillation. *Am Heart J*. 2019;211:77–89. doi: 10.1016/j.ahj.2019.01.005
- Torn M, Bollen WL, van der Meer FJ, van der Wall EE, Rosendaal FR. Risks of oral anticoagulant therapy with increasing age. *Arch Intern Med*. 2005;165:1527–1532. doi: 10.1001/archinte.165.13.1527
- Joosten LPT, van Doorn S, Hoes AW, Nierman MC, Wiersma NM, Koek HL, Hemels MEW, Huisman MV, Roes KC, van den Bor RM, et al. Safety of switching from vitamin K antagonist to non-vitamin K antagonist oral anticoagulant in frail elderly with atrial fibrillation: rationale and design of the FRAIL-AF randomised controlled trial. *BMJ Open*. 2019;9:e032488. doi: 10.1136/bmjopen-2019-032488
- Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383:955–962. doi: 10.1016/S0140-6736(13)62343-0
- Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and meta-analysis. *Circulation*. 2015;132:194–204. doi: 10.1161/CIRCULATIONAHA.114.013267
- Diener HC, Aisenberg J, Ansell J, Atar D, Breithardt G, Eikelboom J, Ezekowitz MD, Granger CB, Halperin JL, Hohnloser SH, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. *Eur Heart J*. 2017;38:860–868. doi: 10.1093/eurheartj/ehw069
- Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. Comparing the guidelines and practical decision-making. *Thromb Haemost*. 2017;117:1230–1239. doi: 10.1160/TH16-11-0876
- Lee SS, Ae Kong K, Kim D, Lim YM, Yang PS, Yi JE, Kim M, Kwon K, Bum Pyun W, Joung B, et al. Clinical implication of an impaired fasting glucose and prehypertension related to new onset atrial fibrillation in a healthy Asian population without underlying disease: a nationwide cohort study in Korea. *Eur Heart J*. 2017;38:2599–2607. doi: 10.1093/eurheartj/ehx316
- Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, Arora S, Street A, Parker S, Roberts HC, et al. Development and validation of a Hospital Frailty Risk Score focusing on older people in acute care settings using electronic hospital records: an observational study. *Lancet*. 2018;391:1775–1782. doi: 10.1016/S0140-6736(18)30668-8
- Thomas L, Li F, Pencina M. Using propensity score methods to create target populations in observational clinical research. *JAMA*. 2020;323:466–467. doi: 10.1001/jama.2019.21558
- Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. *Am J Epidemiol*. 2019;188:250–257. doi: 10.1093/aje/kwy201
- McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med*. 2013;32:3388–3414. doi: 10.1002/sim.5753
- Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
- Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics*. 1998;54:948–963.
- Martinez BK, Sood NA, Bunz TJ, Coleman CI. Effectiveness and safety of apixaban, dabigatran, and rivaroxaban versus warfarin in frail patients with nonvalvular atrial fibrillation. *J Am Heart Assoc*. 2018;7:e008643. doi: 10.1161/JAHA.118.008643
- Hellfritsch M, Adelborg K, Damkier P, Paaske Johnsen S, Hallas J, Pottegård A, Grove EL. Effectiveness and safety of direct oral anticoagulants in atrial fibrillation patients switched from vitamin K antagonists: a systematic review and meta-analysis. *Basic Clin Pharmacol Toxicol*. 2020;126:21–31.
- Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156. doi: 10.1093/gerona/56.3.m146
- Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci*. 2007;62:722–727. doi: 10.1093/gerona/62.7.722