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RESEARCH PAPER

Oral anti-coagulant treatment patterns in atrial fibrillation patients diagnosed with cancer: A Danish nationwide cohort study

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Abstract

Data on the use of oral anti-coagulants (OAC) for stroke prevention in cancer patients with atrial fibrillation (AF) are sparse. Nationwide cohort study of patients with AF (2012–2018) and an indication for OAC who were diagnosed with cancer at least one year later ($N = 12\,756$). We identified treatment with OAC at cancer diagnosis and the following year and described the incidence of discontinuing or switching between warfarin and direct oral anti-coagulants (DOACs). We also described baseline characteristics associated with OAC non-persistence. One third of the cancer patients received no OAC therapy, whereas 42% received warfarin and 24% received DOAC treatment. Switching incidence between OACs was higher for those receiving warfarin treatment (8.6%) than DOAC treatment (1.7%) within one year. Treatment discontinuation was 61% for warfarin and 26% for DOAC. Females were less likely to discontinue DOAC than males (ratio 0.77, 95% confidence interval: 0.66, 0.90). Increasing cancer stage was associated with discontinuation of DOAC, but not warfarin. OAC for stroke prevention in AF was used by two thirds of patients with newly diagnosed cancer. Switching between OACs and discontinuation was more common for warfarin than DOAC, and females had higher persistence with DOACs.

KEYWORDS
Atrial fibrillation, neoplasms, anti-coagulation, medication adherence, factor Xa inhibitors

INTRODUCTION

The burden of non-valvular atrial fibrillation (AF) continues to increase with nearly 40 million cases nationwide in 2017 and major health care costs.[1,2] AF increases the risk of adverse outcomes, such as stroke, heart failure and early death. Long-term oral anti-coagulant (OAC) therapy is recommended for patients at moderate or high stroke risk, as part of an integrated management approach to AF patient care.[3] Such an approach has been associated with improved clinical outcomes.[4,5] There has been a rapid uptake of the direct oral anti-coagulants (DOACs) apixaban, dabigatran, rivaroxaban and edoxaban at the expense of vitamin K antagonists (VKA) for stroke prevention[6] and randomized controlled trials and cohort studies have demonstrated non-inferiority of DOACs for prevention of ischaemic stroke and superior safety with lower bleeding risk compared with VKA.[7,8] Adherence and persistence with OAC therapy in patients with AF in general may be suboptimal in at least one in five patients initiating VKA,[9] and it was recently demonstrated that one in four patients do not persist with recommended therapy over four years after initial DOAC prescription.[10]

Thrombosis and bleeding are common complications in malignancy interfering with OAC management in AF.[11] A cancer diagnosis often requires invasive and systemic treatment and may pose a particular challenge for adherence and persistence with OACs. Indeed, concurrent cancer has been linked with underutilization of OACs in AF patients.[12–15] On the other hand, patients with more than one chronic condition may have a higher degree of persistence than those without multiple chronic disease.[10,16] Importantly, none of these studies have examined whether an incident cancer diagnosis influences persistence with OAC therapy.

We conducted a nationwide registry-based cohort study to describe OAC treatment patterns in AF patients diagnosed with cancer. Specifically, we assessed OAC treatment regimens at cancer diagnosis and changes in treatment following cancer diagnosis.

METHODS

Setting and data sources

We used nationwide medical registries with prospectively collected information covering the entire nation of approximately 5.8 million people. All residents have access to tax-supported universal primary and secondary health care and partial reimbursement for prescribed medications.[17] Vital status, diagnoses and procedures are tracked by nationwide registries for the entire population. Data linkage is facilitated across registries using the unique personal identification number assigned to all Danish residents at birth or upon immigration. Migration, sex and vital status are tracked by the Civil Registration System.[18] The Danish National Patient Registry covering all Danish hospitals has recorded all clinical inpatient discharge diagnoses since 1977 and diagnoses made at outpatient clinic visits since 1995.[19] Diagnoses used for this study were coded according to the Tenth Revision of the International Classification of Diseases (ICD-10) since 1994.[19] The Danish National Prescription Database has recorded information on prescription claims from outpatient pharmacies since 1995 using the Anatomical Therapeutic Chemical (ATC) Classification System.[20] The Danish Cancer Registry records mandatory information on all incident cancer cases in Denmark since 1987, including information on stage at diagnosis.[21]

Study population

From the source population of all persons residing in Denmark during 2012 and 2018, we identified all patients with an incident cancer diagnosis (except non-melanoma skin cancer) recorded in the Danish Cancer Registry between 2012 and 2018 (N = 216 473). We excluded patients aged less than 18 years (N = 1041) as well as patients without an inpatient or outpatient AF diagnosis recorded in the Danish National Patient Registry (N = 196 648). To allow for similar potential exposure time (up to one year) before and after cancer diagnosis, we also excluded patients with <1 year between AF and cancer diagnosis (N = 4021). Finally, we excluded patients without a strong indication for stroke prevention (CHA_2DS_2–VASc score ≤1 for men and ≤2 for women; N = 2007).[3] The final study population included 12 756 cancer patients with a diagnosis of non-valvular AF more than one year before their cancer diagnosis.

Oral anti-coagulant treatment periods

We estimated warfarin and DOAC treatment periods based on prescriptions recorded in the year before and after cancer diagnosis. Treatment periods were estimated from information on drug package size, prescription frequency and the defined daily dose. Warfarin is only available as tablets with a dose of 2.5 mg in Denmark. Exposure to warfarin was defined as an individual variable dose based on the frequency and packet size of each claim. All individuals were assumed to initially receive one tablet (2.5 mg) per day, and this number was updated accordingly after each prescription claim. DOAC was included with the following dosages: dabigatran 110 mg and 150 mg bid, apixaban 2.5 mg and 5 mg bid, edoxaban 30 mg and 60 mg od, rivaroxaban 15 mg and 20 mg od.

The end of a treatment period was defined as the last prescription date plus the number of dosages available since the last purchase. If the end of a period exceeded the start of the next period, these periods were joined into one treatment period. Up to 30 days grace period between filled prescriptions was allowed when defining joined treatment periods.[22]

Patients with no treatment were defined as those having no treatment period overlapping the day of cancer diagnosis. A switch from warfarin to DOAC was defined as the start of a DOAC prescription within a warfarin treatment period, with switch from DOAC to warfarin defined analogously. Discontinuation of warfarin or DOAC therapy was defined as the estimated end of a treatment period with no new treatment period within the next 30 days.

Patient characteristics and follow-up

The Danish National Registry of Patients and the Danish National Prescription Database were used to obtain the medical history of all patients prior to their cancer diagnosis date including comorbid diagnoses using the Charlson comorbidity index, CHA_2DS_2–VASc score and HAS-BLED score.[23,24] Primary diagnoses of intracranial bleeding, major bleeding and stroke after cancer diagnosis were collected from the Danish National Registry of Patients. Cancer treatment recorded in the Danish National Patient Registry within four months after cancer diagnosis included surgery, chemotherapy, radiotherapy, immune-based therapies and endocrine therapies. Using the Danish Cancer Registry, we identified specific cancer sites and grouped them as haematologic, urologic,

gastrointestinal, breast, gynaecological, lung and other solid cancer, and collected information on cancer stage for solid tumours (localized, regional, distant, missing/unknown). The Civil Registration System was used to follow patients for vital status and emigration.[18] We followed all AF patients from cancer diagnosis for up to 12 months until emigration, death, or 31 December 2019, whichever came first.

Statistical analysis

We described frequencies and proportions of patient demographic characteristics and comorbidities overall and according to OAC treatment at cancer diagnosis (warfarin or DOAC or no treatment) and for patients surviving to 12 months after cancer diagnosis.

We calculated the frequency of first-time switchers and first-time discontinuers in the year after cancer diagnosis. We applied the complement of the Kaplan–Meier method to calculate the mortality risk in the year after cancer, and the Aalen–Johansen method to compute incidences of stroke, intracranial bleeding and major bleeding. Among those who used OAC therapy at the time of cancer diagnosis (OAC experienced), the cumulative incidence for switching between warfarin and DOAC, and for discontinuation in the year after cancer diagnosis, was calculated based on the Aalen–Johansen estimator with death considered as the competing event. These analyses were stratified by sex, age group, cancer type, cancer stage, Charlson comorbidity index, CHA_2DS_2–VASc score and HAS-BLED score. To examine the associations between these baseline characteristics and incidence of switching or discontinuation of warfarin or DOAC therapy, we constructed Fine and Gray regression models for the competing risk of death, with adjustment for sex and age group. Because OAC therapy may be paused or stopped rapidly due to competing treatments and health issues, we conducted a sensitivity analysis defining the grace period as 14 days.

RESULTS

Table 1 displays the characteristics of 12 756 cancer patients (36% female, median age 78 years) with a diagnosis of AF one year (or earlier) before the incident cancer diagnosis. Median time from AF to cancer diagnosis was seven years for warfarin-treated patients and four years for patients with DOAC treatment and more patients in the DOAC group had a history of stroke (25.4% vs. 23.1%) (Table 1). Those without OAC treatment at cancer diagnosis had a lower CHA_2DS_2–VASc score and a higher HAS-BLED score than patients who received OAC therapy.

All-cause mortality was 36.5% at one year. Incidences of stroke, intracranial bleeding and major bleeding after accounting for the competing risk of death were 1.8%, 0.4% and 3.7% respectively (data not shown). Among the 8115 patients alive at one year after cancer diagnosis, the sex and age distributions were nearly similar compared with the initial cohort (Table S2).

Oral anti-coagulant use after cancer diagnosis

For the entire cancer population, including non-survivors, the cumulative incidence for either switching of discontinuing OAC treatment in the year after cancer diagnosis is shown in Figure 1 and separately in Table 2 for warfarin and Table 3 for DOAC. The cumulative incidence of switching was 8.6% for switching from warfarin to DOAC (Table 2) and 1.7% were switching from DOAC to warfarin (Table 3), whereas the cumulative incidence of discontinuing OAC therapy was 60.7% for warfarin and 26.2% for DOAC. In all subgroups of cancer types, cancer stages, CHA_2DS_2–VASc score and HAS-BLED score, the incidence of switching or discontinuing treatment was higher from warfarin to DOAC than vice versa.

Non-persistence with warfarin and DOAC

When examining baseline characteristics according to switching, the point estimates mostly demonstrated lower switching incidences from DOAC to warfarin by higher age group and higher stage (though imprecisely estimated because of few events) (Table 2), whereas switching from warfarin to DOAC was less consistent and in the opposite direction (Table 3). In addition, female sex was associated with a lower incidence of discontinuing DOAC compared with males [subdistribution hazard ratio 0.77 (95% confidence interval: 0.66, 0.90)].

Using a grace period of 14 days instead of 30 days had limited impact on most cumulative incidence estimates and subdistribution hazard ratios (Tables S3 and S4). The incidence of switching OAC in the year after cancer diagnosis was lower and more patients discontinued their OAC therapy in this sensitivity analysis.

DISCUSSION

In this nationwide cohort of patients with AF and incident cancer, we found that a substantial proportion of patients with indication for stroke prophylaxis did not receive OAC therapy at the time of the subsequent cancer diagnosis. Second, among those who were treated with OAC, switching or discontinuation of warfarin therapy was more frequent than with DOAC after cancer diagnosis. Third, men and patients with metastatic cancer were more likely to be non-persistent with DOAC.

Adherence and persistence with OAC is vital for achieving a clinical benefit of stroke prophylaxis.[10,25,26] Monitoring warfarin therapy allows for some treatment control related to continuous dose adjustments, but suboptimal adherence has been reported in one third of all AF

TABLE 1 Descriptive characteristics of patients with atrial fibrillation at subsequent cancer diagnosis

	At cancer diagnosis		
	No treatment	**Warfarin**	**DOAC**
Participants (*N* = 12 756)	34.1 (4352)	41.9 (5339)	24.0 (3065)
Age, years — median (IQR)	78.0 (72.0, 85.0)	78.0 (73.0, 83.0)	78.0 (72.0, 83.0)
Age group, years			
0–74	33.7 (1465)	32.3 (1722)	35.8 (1096)
75+	66.3 (2887)	67.7 (3617)	64.2 (1969)
Females	39.3 (1711)	31.8 (1698)	38.6 (1182)
Years between AF and cancer diagnosis, median (IQR)	6.7 (3.5, 11.4)	7.2 (3.7, 11.7)	4.4 (2.3, 8.6)
Cancer type			
Haematologic	9.3 (404)	9.3 (497)	8.3 (254)
Urologic	21.1 (919)	24.0 (1283)	20.6 (630)
Gastrointestinal	26.3 (1145)	27.6 (1476)	27.7 (848)
Breast	9.6 (417)	8.7 (463)	10.2 (314)
Gynaecologic	4.3 (188)	3.5 (186)	3.8 (115)
Lung cancer	15.6 (678)	13.7 (731)	14.8 (455)
Other solid	13.8 (601)	13.2 (703)	14.6 (449)
Cancer stage			
Localized	25.7 (1119)	27.1 (1445)	30.1 (922)
Regional	9.1 (396)	9.5 (505)	9.1 (278)
Distant	11.6 (506)	11.8 (629)	11.0 (338)
Missing/unknown	53.6 (2331)	51.7 (2760)	49.8 (1527)
Cancer treatment			
Chemotherapy	16.5 (717)	17.2 (919)	16.2 (495)
Radiotherapy	16.3 (708)	17.4 (928)	15.7 (481)
Endocrine therapy	11.5 (501)	12.5 (670)	11.4 (348)
Immunotherapy	3.2 (138)	3.4 (183)	3.0 (93)
Surgery	49.6 (2158)	53.7 (2868)	53.4 (1637)
Comorbidities			
Heart failure	37.5 (1630)	45.6 (2432)	40.9 (1253)
Diabetes	25.2 (1098)	27.1 (1446)	26.1 (801)
Hypertension	63.0 (2740)	73.6 (3927)	73.5 (2253)
Stroke	22.5 (978)	23.1 (1233)	25.4 (778)
Vascular disease	25.0 (1086)	21.1 (1129)	21.5 (658)
Charlson comorbidity index score			
0	3.0 (131)	3.3 (177)	2.8 (86)
1	3.4 (147)	4.5 (238)	3.5 (106)
2	20.2 (879)	20.2 (1080)	21.7 (666)
3+	73.4 (3195)	72.0 (3844)	72.0 (2207)
CHA_2DS_2–VASc score			
2–4	67.2 (2925)	63.6 (3396)	63.4 (1942)
5+	32.8 (1427)	36.4 (1943)	36.6 (1123)
HAS-BLED score			
0–1	10.1 (441)	12.3 (659)	12.6 (387)
2	28.7 (1250)	41.2 (2197)	42.0 (1288)
3+	61.1 (2661)	46.5 (2483)	45.4 (1390)

Note: Data present the % (number of patients) or the median (interquartile range), as indicated.

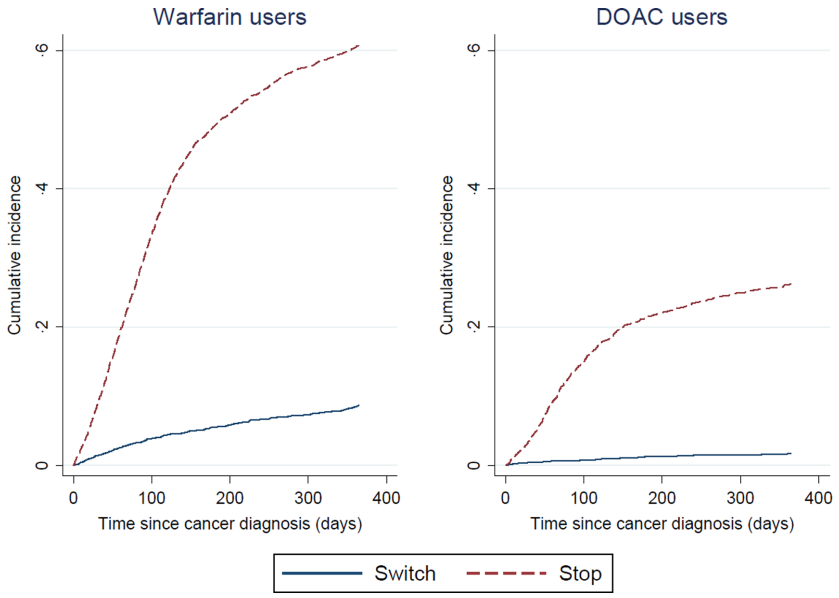

FIGURE 1 Cumulative incidence of switching or discontinuing warfarin (left) and DOAC (right) in the year after cancer diagnosis [Colour figure can be viewed at wileyonlinelibrary.com

patients.[27,28] Although DOAC treatment does not require routine monitoring, some studies dispute that patients treated with DOAC should be prone to non-adherence in daily clinical practice,[16,29] whereas others have found that one in four patients did not persist with recommended DOAC therapy over four years,[10,22] None of these studies focused on OAC treatment patterns in patients with incident cancer, and comparison of persistence across studies are challenged by methodological differences. Our estimated one-year incidence of DOAC discontinuation of 26% is lower than reported in a previous meta-analysis showing persistence at 62%; however, this was not focused on patients with cancer.[30] Data from the United States with experienced users of warfarin found that 16% were switched to DOAC and 15% discontinued treatment over 375 days of follow-up between 2008 and 2016.[31] In our study, incidences of switching were much lower. It should be noted, however, that one third of all cancer patients in our study died during the year of follow-up, and patients could have switched OAC drugs before cancer diagnosis. Similar to our study, some trials and population-based studies have also reported better persistence with OAC among women.[10,32] Our finding of higher DOAC discontinuation with advancing cancer stages is not surprising, since such patients may have a limited life expectancy and a high risk of bleeding. Indeed, it has been shown that the risk of major and clinically relevant non-major bleeding associated with anti-coagulant use in French hospice inpatients (including >90% with cancer) was nearly 10% at three months.[33]

Given that both cancer and AF are common diseases with increasing prevalence and incidence, the need to balance the potentially competing interests of treatments for both diseases is likely to increase in clinical practice. In our study, one in three of all patients did not have a calculated OAC treatment period overlapping cancer diagnosis despite strong indication for stroke prevention OAC therapy. These patients had a higher baseline bleeding risk in terms of the HAS-BLED score, which may be perceived as a contraindication for OAC therapy, despite guidelines' recommendations.[3]

Addressing the information needs for patients with AF[34] may contribute to increased compliance. However, switching and temporary discontinuation of OAC or bridging to low-molecular weight heparin after cancer diagnosis may be necessary in the priority of treating the malignancy, or be related to terminal illness with re-evaluation of medication and advanced palliative care planning, complications of cancer, such as thromboembolism, or other factors. Our results may suggest that prescribers' and patients' preference favoured DOAC for this cohort of AF patients with cancer. Concerns regarding DOAC therapy in cancer patients relate to interactions with anti-cancer drugs and other therapy, while warfarin therapy is difficult to manage in cancer patients due to side effects of anti-cancer treatments, such as nausea and vomiting requiring continuous dose adjustment.[35,36] DOACs are now recommended over VKA therapy for treatment of venous thromboembolism in cancer,[37] whereas no guideline recommendations are available for cancer patients with AF.

Strengths and limitations

The strengths of this study include the nationwide cohort with no loss to follow-up and the linkage across validated databases through a unique identifier. Additionally, information on the AF diagnosis in the Danish National Patient

TABLE 2 Cumulative incidence (%) and subdistribution hazard ratios associating baseline characteristics with first-time switching or discontinuation of warfarin in the year after cancer diagnosis

	Switch from warfarin to DOAC		Warfarin discontinuation	
	Incidence, %	sHR[a] (95% CI)	Incidence, %	sHR[a] (95% CI)
Overall	8.6		60.7	
Sex				
Male	7.9	Ref	60.3	Ref
Female	10.3	1.24 (0.97, 1.58)	61.6	1.06 (0.98, 1.14)
Age group, year				
18–74	7.5	Ref	65.0	Ref
75+	9.1	1.24 (0.95, 1.61)	58.7	0.85 (0.79, 0.92)
Cancer type				
Haematological	8.8	1.22 (0.76, 1.97)	60.0	1.08 (0.92, 1.25)
Urological	7.3	0.83 (0.55, 1.26)	58.1	0.96 (0.85, 1.08)
Gastrointestinal	9.4	1.21 (0.82, 1.78)	63.2	1.19 (1.06, 1.34)
Breast	8.2	0.74 (0.53, 1.29)	60.0	0.99 (0.84, 1.17)
Gynaecologic	7.0	0.80 (0.38, 1.70)	62.7	1.12 (0.90, 1.40)
Lung	10.0	1.20 (0.76, 1.89)	62.0	1.20 (1.04, 1.38)
Other solid tumour	6.6	Ref	58.4	Ref
Cancer stage				
Localized	7.9	Ref	73.9	Ref
Regional	10.5	1.14 (0.75, 1.75)	61.0	1.44 (1.28, 1.63)
Distant	8.0	1.44 (1.28, 1.63)	55.9	0.98 (0.86, 1.11)
Charlson comorbidity index score				
0	9.4	Ref	57.1	Ref
1	9.5	1.15 (0.54, 2.45)	60.0	1.06 (0.83, 1.35)
2	8.1	0.83 (0.44, 1.58)	58.7	1.05 (0.86, 1.28)
3+	8.5	0.96 (0.53, 1.75)	61.4	1.16 (0.96, 1.41)
CHA_2DS_2–VASc score				
2–4	8.4	Ref	61.6	Ref
5+	8.6	1.07 (0.84, 1.37)	59.2	0.98 (0.91, 1.06)
HAS-BLED score				
0–1	9.2	Ref	60.6	Ref
2	8.2	0.93 (0.65, 1.33)	60.6	0.98 (0.87, 1.09)
3+	8.6	0.92 (0.64, 1.31)	60.8	1.02 (0.91, 1.14)

[a]Subdistribution hazard ratio, adjusted for sex and age group, except for the association with sex (only adjusted for age group) and age group (only adjusted for sex).

Registry has a positive predictive value of more than 90%.[38] The Danish Cancer Registry records mandatory information on all incident cancers diagnoses since 1987, and most tumours are histologically verified.[21]

This study had some limitations. The estimates of switching and discontinuation may not be comparable with those of existing studies,[9] since our cohort included a selected group of patients with AF at least one year before cancer. The use of prescription data from pharmacies is useful for information on intended treatment, but we did not have information on actual treatment discontinuation, and we may have overestimated persistence since we relied on the filled prescription pack size for calculation of the date of discontinuation. Further, warfarin and DOAC treatment should not directly be compared, since the treatment periods are calculated based on standard and variable treatment assumptions, respectively. Some patients may initiate or bridge from OAC to parenteral anti-coagulation during cancer diagnosis and treatment. It is likely that the clinical decision to start or bridge to parenteral anti-coagulation will vary for different OAC classes and thus affect the estimates of discontinuation. Therefore, this study design was not suitable for estimating incidence of stroke and bleeding following switching or discontinuation of OAC therapy.

In conclusion, one in three patients with AF received no OAC therapy at incident cancer diagnosis, and a larger

TABLE 3 Cumulative incidence (%) and subdistribution hazard ratios associating baseline characteristics with first time-switching or discontinuing DOAC in the year after cancer diagnosis

	Switch from DOAC to warfarin		DOAC discontinuation	
	Incidence, %	sHR[a] (95% CI)	Incidence, %	sHR[a] (95% CI)
Overall	1.7		26.2	
Sex				
Male	1.7	Ref	28.3	Ref
Female	1.4	0.94 (0.50, 1.78)	22.5	0.77 (0.66, 0.90)
Age group, years				
18–74 years	2.5	Ref	30.2	Ref
75+ years	1.1	0.44 (0.24, 0.81)	23.9	0.83 (0.72, 0.97)
Cancer type				
Haematological	2.1	2.03 (0.59, 6.98)	34.0	2.18 (1.59, 2.99)
Urological	1.5	1.17 (0.39, 3.51)	22.3	1.22 (0.91, 1.64)
Gastrointestinal	1.1	1.20 (0.41, 3.51)	32.1	2.08 (1.60, 2.71)
Breast	2.0	2.09 (0.58, 7.51)	14.8	0.97 0.65, 1.44)
Gynaecologic	1.0	1.03 (0.11, 9.36)	24.9	1.80 (1.14, 2.82)
Lung	1.6	1.54 (0.49, 4.87)	30.8	1.93 (1.45, 2.57)
Other solid tumour	1.0	Ref	17.1	Ref
Cancer stage				
Localized	1.8	Ref	23.2	Ref
Regional	1.8	0.93 (0.31, 2.79)	36.6	1.75 (1.36, 2.24)
Distant	0.6	0.61 (0.18, 2.05)	29.1	1.32 (1.02, 1.70)
Charlson comorbidity index score				
0	0.0	Ref	28.5	Ref
1	0.0	1.04 (0.66, 1.63)	24.5	0.85 (0.48, 1.50)
2	1.6	NA	24.4	0.80 (0.52, 1.25)
3+	1.6	NA	26.5	0.89 (0.59, 1.34)
CHA_2DS_2–VASc score				
2–4	1.7	Ref	27.8	Ref
5+	1.2	1.11 (0.54, 2.25)	23.4	0.95 (0.80, 1.12)
HAS-BLED score				
0–1	0.8	Ref	24.3	Ref
2	1.1	0.57 (0.21, 1.53)	25.7	0.97 (0.76, 1.23)
3+	1.8	1.01 (0.41, 2.50)	26.8	1.02 (0.80, 1.29)

[a]Subdistribution hazard ratio, adjusted for sex and age group, except for the association with sex (only adjusted for age group) and age group (only adjusted for sex).

proportion of AF patients switched from warfarin to DOAC than from DOAC to warfarin. Those treated with warfarin had a higher incidence of treatment discontinuation than those treated with DOAC. These results suggest that patients' and providers' preferences have favoured DOAC. Studies examining factors related to potential suboptimal OAC treatment and the clinical consequences in patients with AF and cancer are warranted.

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CONFLICT OF INTEREST

All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest. Mette Søgaard and Flemming Skjøth reports personal fees from Bayer, outside the submitted work. Erik Lerkevang Grove has received speaker honoraria or consultancy fees from Organon, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, MSD, MundiPharma, Portola Pharmaceuticals, Lundbeck Pharma and Roche. He is an investigator in ongoing studies sponsored by AstraZeneca and has received unrestricted research grants from Boehringer Ingelheim. Gregory Y. H. Lip reports consultancy and speaker fees from BMS/Pfizer, Boehringer

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AUTHOR CONTRIBUTIONS

Anne Gulbech Ording: conceptualization, methodology, investigation, formal analysis, writing the original draft preparation, reviewing and editing the manuscript, and project administration. Mette Søgaard: conceptualization, investigation, reviewing and editing the manuscript. Peter Brønnum Nielsen: conceptualization, investigation, formal analysis, reviewing and editing the manuscript. Gregory Y. H. Lip: conceptualization, investigation, resources, reviewing and editing the manuscript. Torben Bjerregaard Larsen: conceptualization, investigation, resources, reviewing and editing the manuscript. Erik Lerkevang Grove: conceptualization, investigation, resources, reviewing and editing the manuscript. Flemming Skjøth: conceptualization, methodology, investigation, data curation, resources, formal analysis, software, validation, visualization, reviewing and editing the manuscript.

DATA AVAILABILITY STATEMENT

Our approvals for using the data sources for the current study did not allow us to distribute or make patient data directly available to other parties. Interested researchers may apply for data access through the Research Service at the Danish Health Data Authority (e-mail: forskerservice@sundhedsdata.dk; phone: +45 3268 5116). Up-to-date information on data access is available online (http://sundhedsdatastyrelsen.dk/da/forskerservice). Access to data from the Danish Health Data Authority requires approval from the Danish Data Protection Agency (https://www.datatilsynet.dk/english/the-danish-data-protection-agency/introduction-to-the-danish-data-protection-agency/).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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