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Use of oral anticoagulants after ischaemic stroke in patients with atrial fibrillation and cancer

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Abstract. Atterman A, Asplund K, Friberg L, Engdahl J (Danderyd University Hospital, Stockholm; Umeå University, Umeå, Sweden). Use of oral anticoagulants after ischaemic stroke in patients with atrial fibrillation and cancer (Original Article). *J Intern Med* 2020; **288**: 457–468.

Background and objectives. The use of oral anticoagulants (OACs) amongst patients with atrial fibrillation (AF) has increased in the last decade. We aimed to describe temporal trends in the utilization of OACs for secondary prevention after ischaemic stroke amongst patients with AF and active cancer.

Methods. This is a cross-sectional and cohort study of patients with active cancer (n = 1518) and without cancer (n = 50 953) in the Swedish national register Riksstroke, including all patients with ischaemic stroke between 1 July 2005 and 30 December 2017, discharged with AF. Prescription and dispensation before and after the introduction of nonvitamin K OACs (NOACs) in late 2011 were compared. We used logistic and Cox regression to analyse associations with OAC use, adjusting for hospital clustering and the competing risk of death.

Results. The proportion of cancer patients with AF prescribed OACs at discharge after ischaemic stroke increased by 40.2% after 2011, compared with 69.3% in noncancer patients during the same period. Stroke and bleeding risk scores remained similar between patients with and without cancer. OAC dispensation during the following year did not increase as much in cancer patients (43.8% to 64.5%) as that in noncancer patients (46.0% to 74.9%), and the median time to OAC dispensation or censoring was significantly longer in cancer patients (94 vs. 30 days).

Conclusion. OAC treatment in poststroke patients with AF and active cancer has increased after the introduction of NOACs. However, the growing treatment gap in these patients compared to that in noncancer patients raises the possibility of underutilization.

Keywords: atrial fibrillation, anticoagulation, cancer, ischaemic stroke, NOAC, secondary prevention.

Introduction

Oral anticoagulants (OACs) reduce the risk of ischaemic stroke in patients with atrial fibrillation (AF) [1]. Warfarin was the only registered OAC in Sweden until nonvitamin K oral anticoagulants (NOACs) were introduced in December 2011 as subsidized stroke prevention treatments for patients with AF, starting with dabigatran and later followed by rivaroxaban, apixaban and edoxaban. Compared to vitamin K antagonists (VKA) treatment with high mean time in therapeutic range, NOACs have been shown to be at least as effective and reduce the risk of intracranial bleeding, although they have a higher risk of gastrointestinal bleeding [2,3,4,5]. The current European AF guidelines recommend NOACs over VKA in eligible patients with AF; however, the issue of NOAC use in cancer patients is not addressed [6].

Patients with cancer have increased risk for both ischaemic stroke and bleeding, including haemorrhagic stroke [7,8], which may be clinically challenging when prescribing OACs. Recent register-based studies have explored the temporal correlation between the introduction of NOACs and total OAC use in patients with AF, however not specifically of OAC as secondary prevention after ischaemic stroke in patients with concomitant cancer [9,10,11].

Our aim was to study OAC use amongst AF patients after ischaemic stroke before and after

the introduction of NOACs in the presence of active cancer.

Materials and methods

Study design and data source

This study used both descriptive cross-sectional and cohort study designs. All adult patients discharged alive after the first registered event of ischaemic stroke between 1 July 2005 and 30 December 2017 were identified from the Swedish national stroke register Riksstroke. These patients were cross-matched on civic registration numbers with the hospital-based Patient Register. Individuals without a diagnosis of AF before or at the time of discharge, patients aged > 100 years and patients with absolute indications for OACs owing to mitral stenosis or mechanical heart valves were excluded.

Registers

The prospective stroke register Riksstroke was established in 1994 to monitor, support and improve the quality of stroke care in Sweden by providing information on comorbidity, procedures and treatment during and adjacent to registered stroke events [12]. During the study period, the register has been estimated to cover, on average, 89% of all patients with stroke treated in all the 72 hospitals admitting patients with acute stroke [13]. Hospitals were categorized into three types: community, specialized nonuniversity or university hospitals.

The positive predictive values for AF and stroke in the Patient Register are 97% and 88%, respectively [14,15]. Validation studies have shown predictive values in the range of 85–95% for other diagnoses [16]. Additional information was obtained by cross-matching the Cancer Register [17], as well as the Drug Register which holds information on all prescription drugs dispensed in Sweden from 1 July 2005.

Definitions

The year of the stroke event (index year) was used as an ordinal variable (2005–2008, 2009–2011, 2012–2014, and 2015–2017), including a break between 2011 and 2012 to identify possible differences following the introduction of NOACs in December 2011.

Comorbidity at discharge was obtained from the Patient Register using information from 1997 onwards, when the International Classification of Diseases-10th Revision was implemented in Sweden, and up to the day of discharge (Table S1). In addition, information about hypertension, diabetes, home assistance, alertness at index stroke, smoking, hospital and discharge destination was provided by Riksstroke. A first AF diagnosis within one month before the index was considered recent. Patients with cancer were restricted to those with active cancer, which was defined as a new cancer diagnosis other than that of basalioma recorded within one year prior to the index stroke event in either the Patient or the Cancer Registers, preceded by no cancer diagnoses up to 5 years prior to the index year. Noncancer patients were defined as patients without any cancer diagnosis in the previous 5 years. A composite of codes used by the Swedish Board of Health and Welfare for estimating alcohol-related deaths was used to determine the presence of alcohol-related diseases [18].

OACs were sub-grouped into VKAs and NOACs. Parenteral anticoagulants consisted of low-molecular-weight heparins and synthetic pentasaccharides. A drug was regarded as prescribed at discharge if registered as such in Riksstroke. Information on drug dispensation was collected from the Drug Register.

The stroke risk score CHA_2DS_2-VASc [19], not counting points for female sex, was used to determine stroke risk, and the bleeding risk score HAS-BLED [20], not counting points for labile prothrombin time and international normalized ratio, was used to determine bleeding risk.

Follow-up lasted until the first dispensed OAC prescription according to the Drug Register, emigration, death according to the Cause of Death Register, 1 year since discharge or study end (31 December 2017).

Statistical methods

Descriptive data are presented as means or proportions. Standardized differences were calculated between groups for both continuous and categorical variables.

Age, sex and clinically nonoverlapping covariates with a P-value < 0.10 in the univariate analyses were included in the multivariable analyses. Associations between covariates and OAC prescription

at discharge were analysed using logistic regression and presented as odds ratios (ORs). A Cox proportional hazards model was used for analyses of hazard ratios (HRs) for first drug dispensation during the year following discharge. The inverse Kaplan–Meier estimate yielded the cumulative dispensation at 1 year.

To adjust for possible clustering owing to not-entirely independent observations within the same hospital, generalized estimating equations with an exchangeable correlation structure were used for the logistic regressions. For time-to-event analyses, we used a shared frailty model with a gamma distribution using the hospital term as a random effect.

The competing risk of death was accounted for using the Aalen–Johansen estimator for cumulative dispensation and the Fine and Gray's proportional sub-hazards model for adjusted analyses presented as sub-hazard ratios (sHRs).

All tests were two-sided and used 95% confidence intervals (CIs), and P-values < 0.05 were considered significant. Standardized differences > 10% were considered as showing clinically relevant differences between groups.

All analyses were performed using Stata version 15.1 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845, USA).

Ethics

The study conforms to the Declaration of Helsinki and was approved by the regional ethics committee (EPN 2018/1252-31). Consistent with the approval, an opt-out model for patient consent was used.

Results

Patient characteristics at stroke onset and discharge

During the study period, Riksstroke registered 52 471 patients who fulfilled the inclusion criteria. The study population, of which 53.1% were women, comprised patients with a new cancer diagnosis during the year preceding the index stroke event (n = 1518) and patients without a cancer diagnosis in the last 5 years (n = 50 953). The most common cancer types were urological cancer (31.0%) and gastrointestinal cancer (27.7%, Table 1).

Overall, female participants were older (mean age 82.5 years vs. 77.5 years in males), and the proportion of patients using OACs at stroke onset was 21.4%. No differences were observed between patients with and without cancer regarding OAC use at stroke onset, index years, home assistance or stroke severity by the level of consciousness at hospital admission. Cancer patients used parenteral anticoagulants more often (16.8% vs. 2.1%) than noncancer patients at stroke onset (Table 1).

At discharge after ischaemic stroke, the majority had been treated at specialized nonuniversity hospitals (46.9%), followed by 33.5% at community hospitals and 19.6% at university hospitals, with similar distributions in patients with and without cancer. Cancer and noncancer patients shared the same cardiovascular profile, with both groups showing a mean CHA_2DS_2-VASc score of 5.9 points, and a minimum of 2 points owing to the index stroke. The HAS-BLED score was slightly higher amongst cancer patients (3.5 vs. 3.3 points). Amongst cancer patients, there were fewer women and patients with dementia, and more patients with previously known AF, venous thromboembolism, chronic obstructive pulmonary disease, platelet or coagulation dysfunction, and gastrointestinal bleeding or anaemia. Cancer and noncancer groups did not differ regarding discharge destination or platelet inhibitor prescriptions at discharge (Table 1). A comparison of the time periods before (2005–2011) and after (2012–2017) the introduction of NOACs showed that stroke and bleeding risks remained similar between patients with and without cancer over time (Table 2). Amongst cancer patients, the proportion with gastrointestinal location increased (24.5% to 30.9%), whereas that with urological and breast cancers decreased (34.8% to 27.0% and 10.0% to 7.1%, respectively, Table S2a).

OAC prescription at discharge after ischaemic stroke

During 2005–2011, 32.1% of patients with cancer and 36.5% of patients without cancer were discharged with OAC prescriptions. After the introduction of NOACs, the corresponding figures were 45.0% and 61.8%, respectively, giving an increase of 40.2% in OAC prescriptions amongst cancer patients compared with 69.3% amongst noncancer patients (Table 3a). The observed temporal increase in OACs was more pronounced during the later time period, which coincided with an increasing proportion of patients on NOACs (Fig. 1).

Table 1. *Patients' characteristics at the time of discharge after ischaemic stroke, cancer vs. noncancer patients. Standardized differences > 0.10 in bold*

Characteristics	Cancer n = 1518 (2.9%)	Noncancer n = 50 953 (97.1%)	Standardized difference
Female sex	44.7%	53.4%	**0.173**
Age (mean)	79.9	80.2	0.027
Age distribution			
<65 years	3.4%	6.8%	**0.232**
65–74 years	20.8%	18.1%	
75–84 years	45.2%	37.8%	
>84 years	30.6%	37.3%	
Index year			
2005–2008	25.0%	28.2%	0.093
2009–2011	25.5%	25.9%	
2012–2014	24.9%	24.8%	
2015–2017	24.6%	21.2%	
Hospital type			
Community	31.5%	33.6%	0.089
Specialized nonuniversity	45.5%	46.9%	
University	23.1%	19.5%	
Index stroke characteristics			
Alert at index	85.7%	84.9%	0.022
No home assistance at index	70.4%	67.8%	0.057
Discharge destination: home	52.2%	51.5%	0.015
Risk scores at discharge			
CHA_2DS_2-VASc score (mean)	5.9	5.9	−0.050
HAS-BLED score (mean)	3.5	3.3	−**0.208**
Comorbidity at discharge			
Prior AF	73.7%	63.4%	**0.224**
Heart failure	35.9%	31.2%	0.100
Hypertension	84.3%	82.9%	0.038
Ischaemic heart disease	37.7%	33.9%	0.078
Prior PCI	7.0%	7.7%	0.025
Diabetes	25.6%	23.7%	0.044
Ischaemic stroke prior to index stroke	22.7%	19.0%	0.090
Prior TIA	10.1%	10.4%	0.012
Prior intracerebral bleeding	1.0%	2.1%	0.087
Impaired kidney function	8.1%	6.1%	0.080
CKD 5/Dialysis	0.7%	0.4%	0.029
Prior anaemia	27.2%	15.5%	**0.289**
Prior major bleeding	14.5%	11.5%	0.088
Prior GI bleeding	12.2%	7.8%	**0.148**
COPD	11.1%	6.8%	**0.149**
Dementia	4.2%	7.1%	**0.127**

Table 1 (*Continued*)

Characteristics	Cancer n = 1518 (2.9%)	Noncancer n = 50 953 (97.1%)	Standardized difference
Frequent falls	7.3%	9.3%	0.073
Alcohol-related disease	3.0%	3.4%	0.019
Obesity	3.4%	2.5%	0.052
Thyroid disease	9.4%	9.1%	0.009
Liver disease	2.5%	1.3%	0.089
Venous thromboembolism < 6 months	2.7%	1.1%	**0.120**
Platelet or coagulation dysfunction	4.5%	2.5%	**0.111**
Smoker at index	7.2%	7.7%	0.041
Antithrombotic medication at index			
OAC	22.9%	21.3%	0.038
VKA	18.2%	17.9%	0.006
NOAC	4.7%	3.5%	0.064
Parenteral anticoagulant	16.8%	2.1%	**0.517**
Platelet inhibitor	39.8%	46.5%	**0.136**
Antithrombotic medication at discharge			
OAC	38.5%	48.2%	**0.196**
VKA	26.4%	33.5%	**0.156**
NOAC	12.1%	14.7%	0.079
Platelet inhibitor	41.0%	44.4%	0.068
Cancer site			
Breast	8.6%		
Gastrointestinal	27.7%		
Gynaecological	5.5%		
Haematological	7.4%		
Intracranial	1.1%		
Lung	8.0%		
Urological	31.0%		
Other	12.9%		
Metastasesa	15.5%		
Previous cancer treatment at index			
Chemotherapy at hospital	2.0%		
Dispensed anti-tumoral drug	15.5%		
Radiotherapy	4.4%		

AF, atrial fibrillation; CKD 5, chronic kidney failure stage 5; TIA, transient ischaemic attack; GI, gastrointestinal; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; VKA, vitamin K antagonists; NOAC, nonvitamin K antagonist oral anticoagulants; OAC, oral anticoagulant.
[a]Missing data on cancer stage 43.9%.

There was an overall inverse relationship between stroke risk as indicated by the CHA_2DS_2-VASc score and OAC prescriptions at discharge in patients with and without cancer alike (Fig. 2a). Bleeding risk assessed by the HAS-BLED score was also inversely associated with OAC prescriptions at discharge, but greater differences between cancer and noncancer patients were observed during the years 2012–2017 after the introduction of NOACs (Fig. 2b).

Table 2. *Stroke and bleeding risk scores in 2005–2011 and 2012–2017 in patients with AF and ischaemic stroke, cancer vs. noncancer patients*

	2005–2011			2012–2017		
Risk scores at discharge	Cancer	Noncancer	Standardized difference	Cancer	Noncancer	Standardized difference
CHA2DS2-VASc score (mean)	5.8	5.8	−0.005	6.0	5.9	−0.093
HAS-BLED score (mean)	3.4	3.2	**−0.231**	3.6	3.4	**−0.175**

AF, atrial fibrillation.
Standardized differences > 0.10 in bold

Table 3. *(a) Proportions of patients with AF discharged with OAC prescription after ischaemic stroke per time period, cancer vs. noncancer. (b) Estimated cumulative dispensed OAC during year following ischaemic stroke amongst patients with AF per time period, cancer vs. noncancer*

OAC prescription at discharge	Cancer	Noncancer	Standardized difference
(a)			
2005–2011	32.1%	36.5%	0.094
2012–2017	45.0%	61.8%	**0.342**

OAC dispensation during follow-up	Cancer	Noncancer	Log rank test for entire follow-up
(b)			
2005–2011	43.8% (40.0–47.9%)	46.0% (45.4–46.7%)	0.073
2012–2017	64.5% (60.2–68.8%)	74.9% (74.3–75.5%)	**<0.001**

AF, atrial fibrillation; OAC, oral anticoagulant.
Standardized differences > 0.10 in bold.
P-values < 0.05 in bold.

Factors independently associated with OAC prescription at discharge amongst cancer patients were later index year, ongoing OAC treatment at stroke onset, no previous need of home assistance and discharge back to own home. Advanced age, dementia, prior ischaemic stroke and major bleeding were negatively associated with OACs. Compared to patients with gastrointestinal cancer, patients with lung cancer were less likely to be prescribed OACs at discharge, whereas patients with gynaecological, urological and other cancers were more likely to receive OACs at discharge (Fig. S1, Tables S3a/b, including information on patients without cancer).

Temporal trends in dispensation of VKA and NOACs after ischaemic stroke

The initiation of OAC treatment in patients with AF may be delayed after stroke. Therefore, we assessed dispensations made during the first year of follow-up, which is influenced by nonadherence to prescription and patients with a previous OAC prescription; the study population contributed 19 110 person-years, and 28 529 patients were dispensed OACs.

A comparison of the time periods before and after NOACs had been introduced showed an increase in OAC dispensation for patients with (HR: 1.52, CI: 1.30–1.79) and without (HR: 2.02, CI: 1.97–2.07) cancer. During the time period 2005–2011, there were no differences in the cumulative OAC dispensation at 1 year of follow-up in patients with or without cancer ($P = 0.073$). In the later period 2012–2017, the cumulative dispensation at 1 year was 64.5% in cancer patients compared to 74.9% in noncancer patients ($P < 0.001$, Table 3b), and the median time to dispensation or censoring was 94 days (CI: 81–140) in cancer patients vs. 30 days (CI: 28–31) in noncancer patients (Fig. 3).

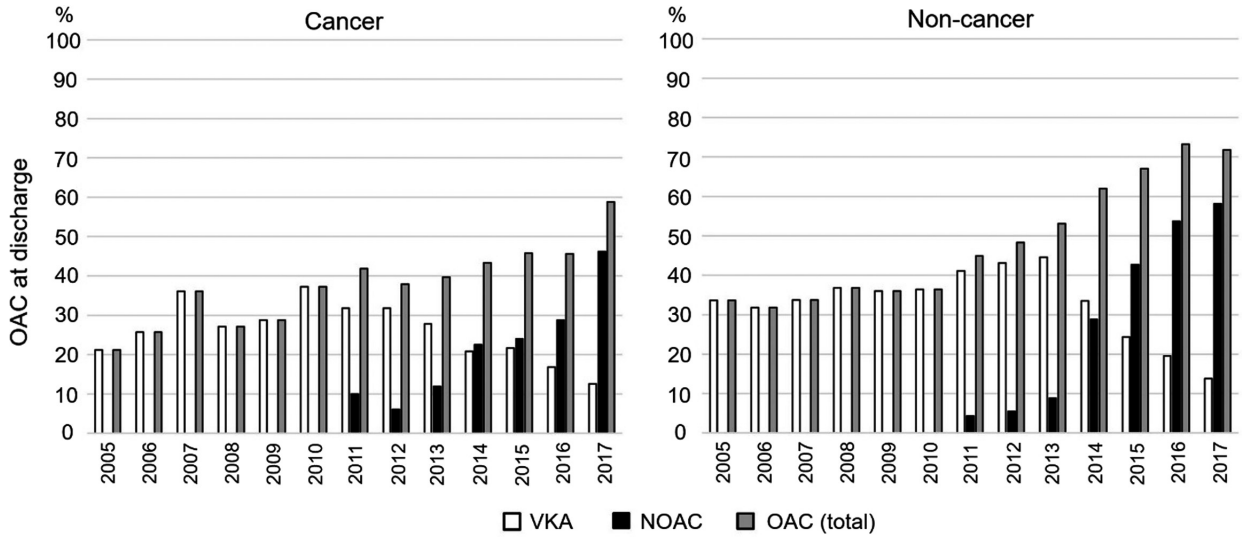

Fig. 1 *Proportion with prescribed OACs at the time of discharge after ischaemic stroke in patients with AF, 2005–2017.* Note*: VKA, vitamin K antagonist; NOAC, nonvitamin K antagonist oral anticoagulant; OAC, oral anticoagulant.*

Most factors independently associated with OAC prescription at discharge were also associated with dispensation during follow-up, including later index year. However, amongst cancer patients, a recent AF diagnosis and being alert at the index stroke were also associated with dispensation (Fig. S2 and Table S4a,b).

Sensitivity analyses

After accounting for the competing risk of death, negative associations with OAC dispensation were seen in cancer patients with a history of major bleeding (sHR: 0.78, CI: 0.62–0.99).

The proportion of patients using parenteral anticoagulants as the only antithrombotic treatment at stroke onset was higher in cancer patients than in noncancer patients (9.4% vs. 0.8%), but did not change significantly after excluding patients with venous thromboembolism (8.5% vs. 0.7%).

The proportion of gastrointestinal cancer increased significantly over the study time, and together with lung cancer, it was associated with lower OAC use (Tables S2a and S3a/S4a). In sensitivity analyses, OAC use amongst cancer patients was analysed without these two cancer subtypes separately. This did not change the differences in OAC prescription at discharge or in cumulative dispensation during follow-up as compared to patients without cancer, also after accounting for the competing risk of death (data not shown).

Discussion

In this nationwide register study of stroke survivors, our main finding was that patients with active cancer were less likely to receive OAC treatment after ischaemic stroke, despite known AF and cardiovascular risk similar to that of noncancer patients. Since the introduction of NOACs, their use in patients with AF and ischaemic stroke has increased less amongst patients with cancer than in those without, even though stroke and bleeding risk scores remained similar between cancer and noncancer patients over time. There was also a noticeable delay in OAC initiation after ischaemic stroke in patients with cancer compared to that in patients without cancer.

Previous studies have shown lower OAC use in AF patients with a high stroke risk, especially in the presence of cancer [21,22]. In this study, we confirmed this inverse relationship between estimated stroke risk and likelihood of OAC treatment, which probably reflects that a high stroke risk is often conceived to involve a higher risk of bleeding. With increasing bleeding risk (high HAS-BLED score), prescription of OACs as secondary prevention was reduced to a similar extent in patients with and without cancer. In the present study,

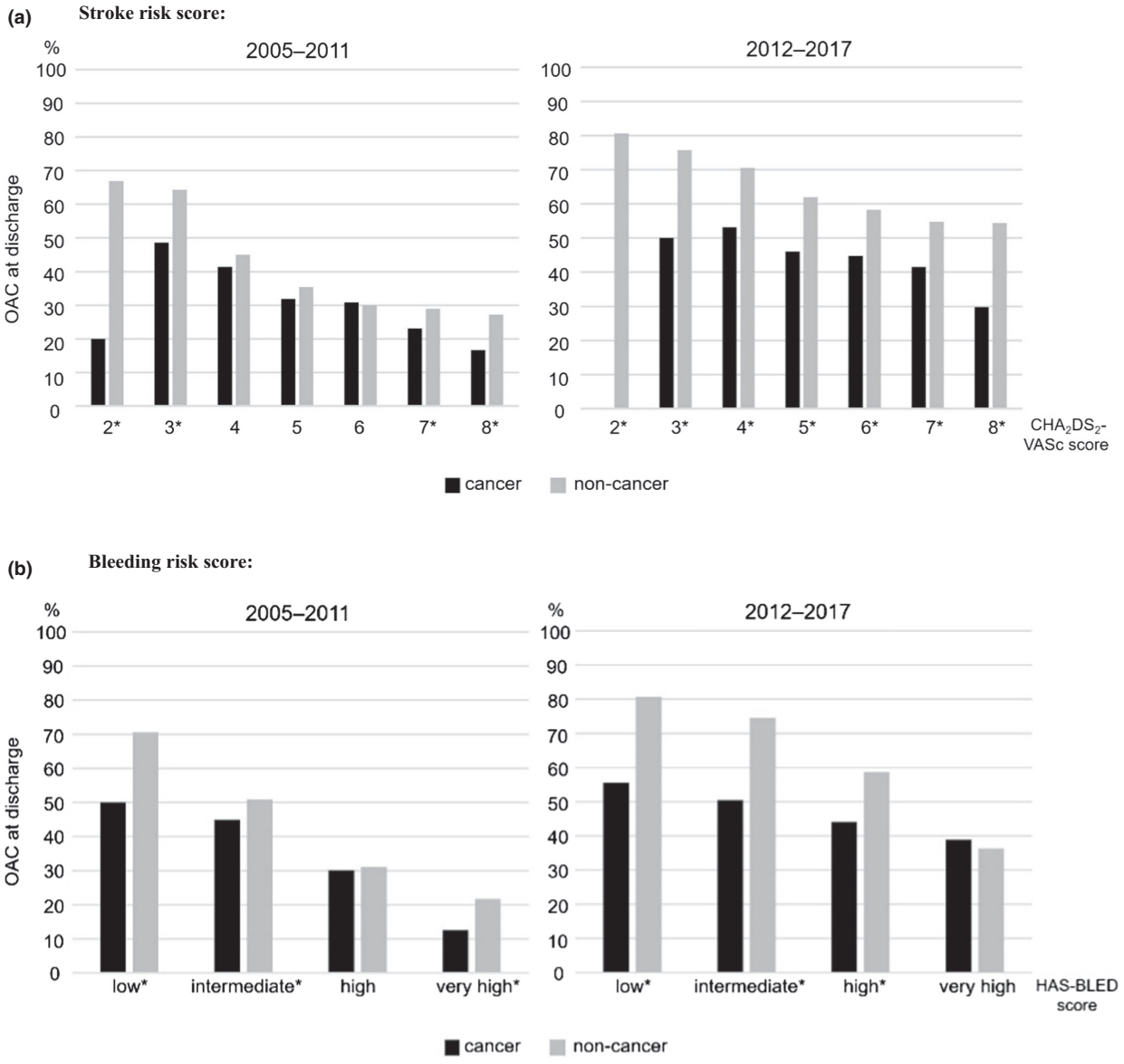

Fig. 2 *Stroke (a) and bleeding (b) risks: proportion with prescribed OACs at the time of discharge after ischaemic stroke in patients with AF.* Note*: CHA_2DS_2-VASc not counting points for female sex (maximum 8 points). HAS-BLED not counting points for labile prothrombin time and international normalized ratio: 0–1 points, low risk; 2 points, intermediate risk; 3–5 points, high risk; and > 5 points, very high risk. *Standardized differences between cancer and noncancer patients > 0.10.*

several negative predictors of OAC treatment were identified. These included factors reflecting frailty at stroke onset, as well as others implicating a worse stroke outcome. We observed that cancer patients were less likely than noncancer patients to be discharged with OACs, irrespective of the estimated stroke risk. This suggests that clinicians exert extra caution in the presence of cancer. Cancer may be associated with issues such as nausea, weight loss and impaired kidney function, making OAC treatment challenging, but also with an increased risk of bleeding. For example, we noticed a negative correlation between OAC and lung cancer. This disease's aggressive clinical

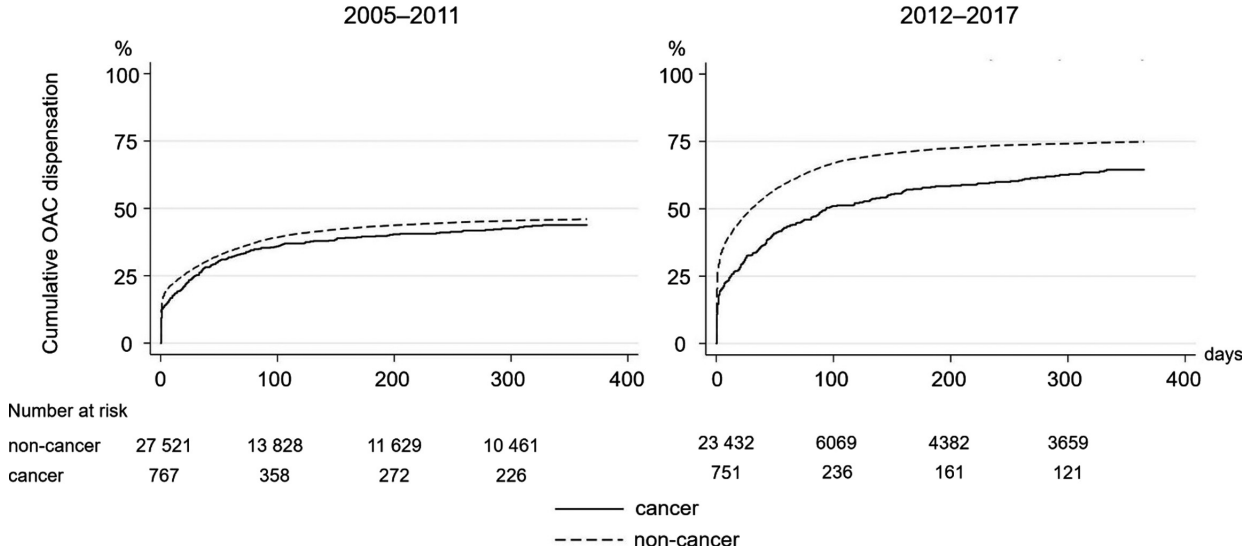

Fig. 3 *Estimated cumulative OAC dispensation during the first year after ischaemic stroke in patients with AF in 2005–2011 and 2012–2017; cancer vs. noncancer.*

characteristics with associated high risk of bleeding, either spontaneously or during diagnostic and therapeutic procedures, may have contributed to this. However, excluding lung cancer from the analyses did not change our results.

For the clinician, balancing risks and benefits of OAC use in patients with AF and cancer is a dilemma. Awaiting results from randomized controlled trials, available scientific guidance comes from observational studies. They indicate reasonable safety of NOACs and net benefits compared to that of VKA in patients with cancer [23,24]. In a recently published nationwide register study, we observed a net cerebrovascular benefit of OACs overall, and also an apparent benefit of NOACs over VKA in patients with AF and active cancer [25]. The guidelines of the European Society of Cardiology for the management of atrial fibrillation emphasize that a high bleeding risk score should generally not result in withholding OAC. Rather, bleeding risk factors should be identified and manageable factors corrected [6]. This is in line with a guidance statement by the International Society on Thrombosis and Haemostasis [26]. There is, however, no specific guidance on OAC use in secondary prevention after ischaemic stroke for patients with AF and cancer.

Our findings corroborate those of other large Scandinavian register-based studies that have shown increased OAC treatment amongst elderly and frail patients since NOACs were introduced [27,28]. We noticed that the introduction of NOACs coincided with a larger proportion of patients with OACs, both at discharge and during follow-up. The share of NOAC prescriptions at discharge increased in both patients with and without cancer. Despite unchanged differences in stroke and bleeding risk scores over time, the proportion of patients with cancer discharged with any OAC increased only by 40.2%, compared to 69.3% in patients without cancer. This difference may reflect not only a general reluctance in treating cancer patients with OACs, but it may also indicate a delay in implementation because AF guidelines lack specific information on NOAC treatment in patients with cancer.

Overall, the proportion of patients that were dispensed OACs during the year following ischaemic stroke was higher than the proportion who were discharged with an OAC prescription. Part of this could reflect postponed treatment decisions after recovery from the ischaemic stroke event, including those with haemorrhagic components. Despite the increase owing to late initiation of OAC treatment during follow-up amongst cancer patients, rates of dispensation were consistently higher in patients without cancer. This difference was more pronounced after the introduction of NOACs. Amongst cancer patients, a recently diagnosed AF showed no significant association with OAC

prescriptions at discharge but became a positive predictor for dispensation during follow-up. This suggests that cancer patients, whose prognosis or therapeutic procedures might be uncertain at first, have not been given the benefits from the fast treatment decisions that NOACs allow in patients without cancer.

Our study shares the limitations of other register-based studies. First, owing to the lack of clinical information beyond codes, and the inability to incorporate metastases as a variable because of a high proportion of missing data, it is possible that misclassification and residual confounding were introduced. Second, the Drug Register does not provide information on indication, which prevents the analyses of possible use of parenteral anticoagulants as secondary stroke prevention beyond bridging use. Moreover, drug use amongst cancer patients could be influenced by nonadherence, which we could not monitor. Third, the unexpectedly low proportions of patients with previous antitumoral treatment may suffer from irregular and nonvalidated reporting of these treatments to the Patient Register, increasing the risk of underestimating the issue of drug interaction. Fourth, the relatively low proportion of patients with active cancer, which was probably a result of studying an elderly population of stroke survivors, could introduce type II errors. Finally, it should be noted that HAS-BLED performs only modestly well as a bleeding risk score [29]. The strength of our observational study is that the data comprised all patients in Sweden with active cancer during the study period. Therefore, our study results have generated clinically relevant real-world information.

Conclusion

Although OAC use in cancer patients with AF and a recent ischaemic stroke has increased since the introduction of NOACs, the treatment gap between patients with and without cancer has increased. Present knowledge suggests that treatment with OACs, and with NOACs in particular, confers net benefits for AF patients with cancer. Our observations raise the possibility that NOACs are underutilized as secondary prevention after ischaemic stroke in cancer patients with AF.

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Author contribution

Adriano Atterman: Conceptualization (equal); Formal analysis (lead); Funding acquisition (equal); Methodology (equal); Visualization (lead); Writing-original draft (lead); Writing-review & editing (equal). **Kjell Asplund:** Conceptualization (equal); Methodology (equal); Resources (supporting); Supervision (equal); Writing-review & editing (equal). **Leif Friberg:** Conceptualization (equal); Formal analysis (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal). **Johan Engdahl:** Conceptualization (equal); Funding acquisition (lead); Methodology (lead); Project administration (lead); Resources (lead); Supervision (lead); Writing-review & editing (equal).

Conflict of interest statement

A.A. and K.A. report no conflicts of interest. L.F. has received consultant fees from Bayer, Boehringer Ingelheim, BMS/Pfizer and Sanofi. J.E. reports speaker or consultant fees from Pfizer, Bristol Myers Squibb, Merck Sharp & Dome, and Medtronic.

References

1 Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Inter Med* 2007; **146:** 857–67.
2 Ruff CT, Giugliano RP, Braunwald E *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:** 955–62.
3 Wallentin L, Yusuf S, Ezekowitz MD *et al.* Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010; **376:** 975–83.
4 Bjorck F, Renlund H, Lip GY, Wester P, Svensson PJ, Sjalander A. Outcomes in a warfarin-treated population with atrial fibrillation. *JAMA Cardiol* 2016; **1:** 172–80.
5 Piccini JP, Hellkamp AS, Lokhnygina Y *et al.* Relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin: results from the ROCKET AF trial. *J Am Heart Assoc* 2014; **3:** e000521.
6 Kirchhof P, Benussi S, Kotecha D *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016; **18:** 1609–78.
7 Mosarla RC, Vaduganathan M, Qamar A, Moslehi J, Piazza G, Giugliano RP. Anticoagulation strategies in patients with

cancer: JACC review topic of the week. *J Am Coll Cardiol* 2019; **73:** 1336–49.
8 Andersen KK, Olsen TS. Risk of ischemic and hemorrhagic strokes in occult and manifest cancers. *Stroke* 2018; **49:** 1585–92.
9 Gadsboll K, Staerk L, Fosbol EL *et al.* Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. *Eur Heart J* 2017; **38:** 899–906.
10 Morgan A, Joshy G, Schaffer A *et al.* Rapid and substantial increases in anticoagulant use and expenditure in Australia following the introduction of new types of oral anticoagulants. *PLoS ONE* 2018; **13:** e0208824.
11 Maura G, Billionnet C, Drouin J, Weill A, Neumann A, Pariente A. Oral anticoagulation therapy use in patients with atrial fibrillation after the introduction of non-vitamin K antagonist oral anticoagulants: findings from the French healthcare databases, 2011–2016. *BMJ Open* 2019; **9:** e026645.
12 Asplund K, Hulter Asberg K *et al.* The Riks-Stroke story: building a sustainable national register for quality assessment of stroke care. *Int J Stroke* 2011; **6:** 99–108.
13 Riks-stroke. Årsrapporter [Annual Reports]. http://www.riksstroke.org/sve/forskning-statistik-och-verksamhet sutveckling/rapporter/arsrapporter/?archived=1. Accessed 10 February 2020.
14 Smith JG, Platonov PG, Hedblad B, Engstrom G, Melander O. Atrial fibrillation in the Malmo Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity. *Eur J Epidemiol* 2010; **25:** 95–102.
15 Koster M, Asplund K, Johansson A, Stegmayr B. Refinement of Swedish administrative registers to monitor stroke events on the national level. *Neuroepidemiology* 2013; **40:** 240–6.
16 Ludvigsson JF, Andersson E, Ekbom A *et al.* External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011; **11:** 450.
17 Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol* 2009; **48:** 27–33.
18 National Board of Health and Welfare. Statistik om dödsorsaker 2018. [Statistics on Causes of Death 2018]. http://www.socialstyrelsen.se/statistik-och-data/statistik/. Accessed 10 February 2020.
19 Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; **137:** 263–72.
20 Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; **138:** 1093–100.
21 Friberg L, Rosenqvist M, Lindgren A, Terent A, Norrving B, Asplund K. High prevalence of atrial fibrillation among patients with ischemic stroke. *Stroke* 2014; **45:** 2599–605.
22 Malavasi VL, Fantecchi E, Gianolio L *et al.* Atrial fibrillation in patients with active malignancy and use of anticoagulants: Under-prescription but no adverse impact on all-cause mortality. *Eur J Intern Med* 2019; **59:** 27–33.
23 Cavallari I, Verolino G, Romano S, Patti G. Efficacy and safety of nonvitamin K oral anticoagulants in patients with atrial fibrillation and cancer: a study-level meta-analysis. *Thromb Haemost* 2020; **120:** 314–21.
24 Russo V, Bottino R, Rago A *et al.* Atrial fibrillation and malignancy: the clinical performance of non-vitamin K oral anticoagulants-A systematic review. *Semin Thromb Hemost* 2019; **45:** 205–14.
25 Atterman A, Friberg L, Asplund K, Engdahl J. Net benefit of oral anticoagulants in patients with atrial fibrillation and active cancer: a nationwide cohort study. *Europace* 2020; **22:** 58–65.
26 Delluc A, Wang TF, Yap ES *et al.* Anticoagulation of cancer patients with non-valvular atrial fibrillation receiving chemotherapy: Guidance from the SSC of the ISTH. *J Thromb Haemost* 2019; **17:** 1247–52.
27 Staerk L, Fosbol EL, Gadsboll K *et al.* Non-vitamin K antagonist oral anticoagulation usage according to age among patients with atrial fibrillation: Temporal trends 2011–2015 in Denmark. *Sci Rep* 2016; **6:** 31477.
28 Urbaniak AM, Strom BO, Krontveit R, Svanqvist KH. Prescription patterns of Non-Vitamin K oral anticoagulants across indications and factors associated with their increased prescribing in atrial fibrillation between 2012–2015: a study from the norwegian prescription database. *Drugs Aging* 2017; **34:** 635–45.
29 Proietti M, Hijazi Z, Andersson U *et al.* Comparison of bleeding risk scores in patients with atrial fibrillation: insights from the RE-LY trial. *J Intern Med* 2018; **283:** 282–92.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Variable definitions.

Table S2. (a) Cancer patients' characteristics at the time of discharge after ischaemic stroke, 2005–2011 vs. 2012–2017. (b) Non-cancer patients' characteristics at the time of discharge after ischaemic stroke, 2005–2011 vs. 2012–2017.

Table S3. (a) Cancer patients with AF: Factors associated with OACs at the time of discharge after ischaemic stroke. (b) Non-cancer patients with AF: Factors associated with OAC at the time of discharge after ischaemic stroke.

Table S4. (a) Cancer patients with AF: Factors associated with OAC dispensation during the first year after ischaemic stroke. (b) Non-cancer patients with AF: Factors associated with OAC dispensation during the first year after ischaemic stroke.

Figure S1. Variable definitions Cancer patients with AF: Factors associated with prescribed OACs at the time of discharge after ischaemic stroke.

Figure S2. Cancer patients with AF: Factors associated with OAC dispensation during the first year after ischaemic stroke.

