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Net benefit of oral anticoagulants in patients with atrial fibrillation and active cancer: a nationwide cohort study

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Aims

To estimate the net cerebrovascular benefit of prophylactic treatment with oral anticoagulants (OACs) in patients with atrial fibrillation (AF) and active cancer.

Methods and results

We included all Swedish patients who had been diagnosed with AF in a hospital or in a hospital-associated outpatient unit between 1 July 2005 and 1 October 2017. Patients with active cancer ($n = 22\,596$) and without cancer ($n = 440\,848$) were propensity score matched for the likelihood of receiving OACs at baseline. At baseline, 38.3% of cancer patients with AF and high stroke risk according to CHA₂DS₂-VASc score received OACs. There was a net benefit of OACs, assessed by the composite outcome of ischaemic stroke, extracranial arterial thromboembolism, all major bleedings, and death, both among patients with active cancer [hazard ratio (HR): 0.81, confidence interval (CI): 0.78–0.85] and among patients without cancer (HR: 0.81, CI: 0.80–0.82). When limiting follow-up to 1 year to minimize the effects of possible treatment cross-over and additionally accounting for death as a competing risk in cancer patients, a net cerebrovascular benefit regarding ischaemic stroke or intracranial bleeding was observed for OACs [subhazard ratio (sHR): 0.67, CI: 0.55–0.83]. A net cerebrovascular benefit was also seen for non-vitamin K antagonist OACs over warfarin after competing risk analyses in cancer patients (sHR: 0.65, CI: 0.48–0.88).

Conclusion

Patients with AF and active cancer benefit from OAC treatment.

Keywords

Atrial fibrillation • Anticoagulation • Cancer • Stroke • Bleeding • CHA₂DS₂-VASc

Introduction

Cancer patients appear to have increased risk of both atrial fibrillation (AF) and ischaemic stroke, and their prognosis after a stroke is worse than that in non-cancer patients.^{1,2} It has been suggested that cancer patients with AF have a higher risk of ischaemic stroke, but most studies on this relationship have used imprecise definitions of active cancer and have been restricted to relatively small populations.³

In the current European Society of Cardiology (ESC) guidelines on AF management,⁴ there are no specific recommendations for patients with concurrent cancer. Clinical decisions are challenged by higher risk of bleeding, which has been observed in cancer patients with venous thromboembolism and in cancer patients with AF.¹

Our hypothesis was that cancer patients with AF benefit from treatment with oral anticoagulants (OACs). The aim of this study was to estimate the net cerebrovascular benefit, defined as reduced

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What's new?

- Patients with atrial fibrillation (AF) and active cancer have lower risk of ischaemic stroke and lower mortality when treated with oral anticoagulants (OACs).
- There is a net cerebrovascular benefit of prophylactic treatment with OACs during the year following a cancer diagnosis in patients with AF.
- Non-vitamin K antagonist OACs seem superior to warfarin regarding net cerebrovascular benefit in patients with AF and active cancer.

risk of any cerebrovascular event, of OAC treatment in patients with AF and active cancer.

Methods

Study design and data source

This is a retrospective cohort study, cross-linking Swedish health registers. All adult individuals with a diagnosis of AF or flutter between 1 July 2005 and 1 October 2017 were identified from the National Swedish Patient Register, which covers all hospital contacts and visits in hospital-associated outpatient units. Exclusions were made for patients aged >100 years, with an absolute indication for OAC due to diagnosis of mitral stenosis or mechanical heart valve, or who died before the start of follow-up.

Registers

Codes for AF and stroke in the National Swedish Patient Register have positive predictive values of 97% and 88.1%, respectively.^{5,6} According to validation studies, codes for other diagnoses generally have positive predictive values in the range 85–95%.⁷ The prospective Cancer Register contains detailed information, including cancer stage, and its completeness is high.⁸ Information about drugs was taken from the Drug Register, which contains information on all dispensed prescription drugs in Sweden since 1 July 2005.

Definitions

Index date was defined by the first occurrence of a code for AF between 1 July 2005 and 1 October 2017. Time at risk was calculated from baseline, defined as index date and an additional blanking period of 90 days, which was applied for two reasons: (i) to avoid overestimating event rates by double-counting stroke events when patients receive the same code again in conjunction with transfer to another clinic, e.g. stroke rehabilitation, and (ii) to be able to capture initiation of OAC therapy in patients with AF, which was discovered at the index contact. Information about previous and concomitant diseases was obtained from the Patient Register using information since 1997 when the International Classification of Diseases-10th Revision was implemented in Sweden, and up to 90 days after index date, coinciding with the start of follow-up. Patients with cancer were restricted to those with active cancer defined as a cancer diagnosis within 1 year before the start of follow-up in the Patient Register or in the Cancer Register. The control population without cancer was defined as patients without any cancer diagnosis within 5 years before the start of follow-up. Basaloma was not included in the cancer definition due to its very rarely aggressive nature.

To estimate alcohol-related diseases, a composite of diagnostic codes referred to as 'alcohol index' and used by the Swedish Board of Health and Welfare for estimating alcohol-related deaths, was used.⁹

Anticoagulation therapy was categorized as oral or parenteral, sub-grouping oral into non-vitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists (VKA), which is almost exclusively warfarin in Sweden. Non-vitamin K antagonist oral anticoagulants have been available for stroke prevention in AF in Sweden since December 2011. Parenteral anticoagulants (low-molecular-weight heparins and synthetic pentasaccharides) were not specified in the main analyses since there was no way of distinguishing between therapeutic and bridging use. In analogy with an intention-to-treat approach, a dispensed prescription of a certain drug at baseline (4 months before and up to 90 days after index date) defined the treatment groups during follow-up.

Comorbidities, including CHA₂DS₂-VASc stroke risk stratification, were recorded at baseline.¹⁰ Not taking female sex into account, the stroke risk of a CHA₂DS₂-VASc score of 0 was regarded as low, of 1 point as intermediate, and of 2 or more points as high.

Follow-up lasted until outcome event, emigration, death, or end of follow-up (31 December 2017). Outcome analyses were performed in cancer and non-cancer patients separately. An event was defined as the first registered inpatient diagnosis code of the event during follow-up in the Swedish Patient Register and/or Cause of Death Register. For bleeding events, any diagnosis code position was considered based on a recent validation¹¹; for other events, only the primary or secondary position was considered (Supplementary material online, Table S1).

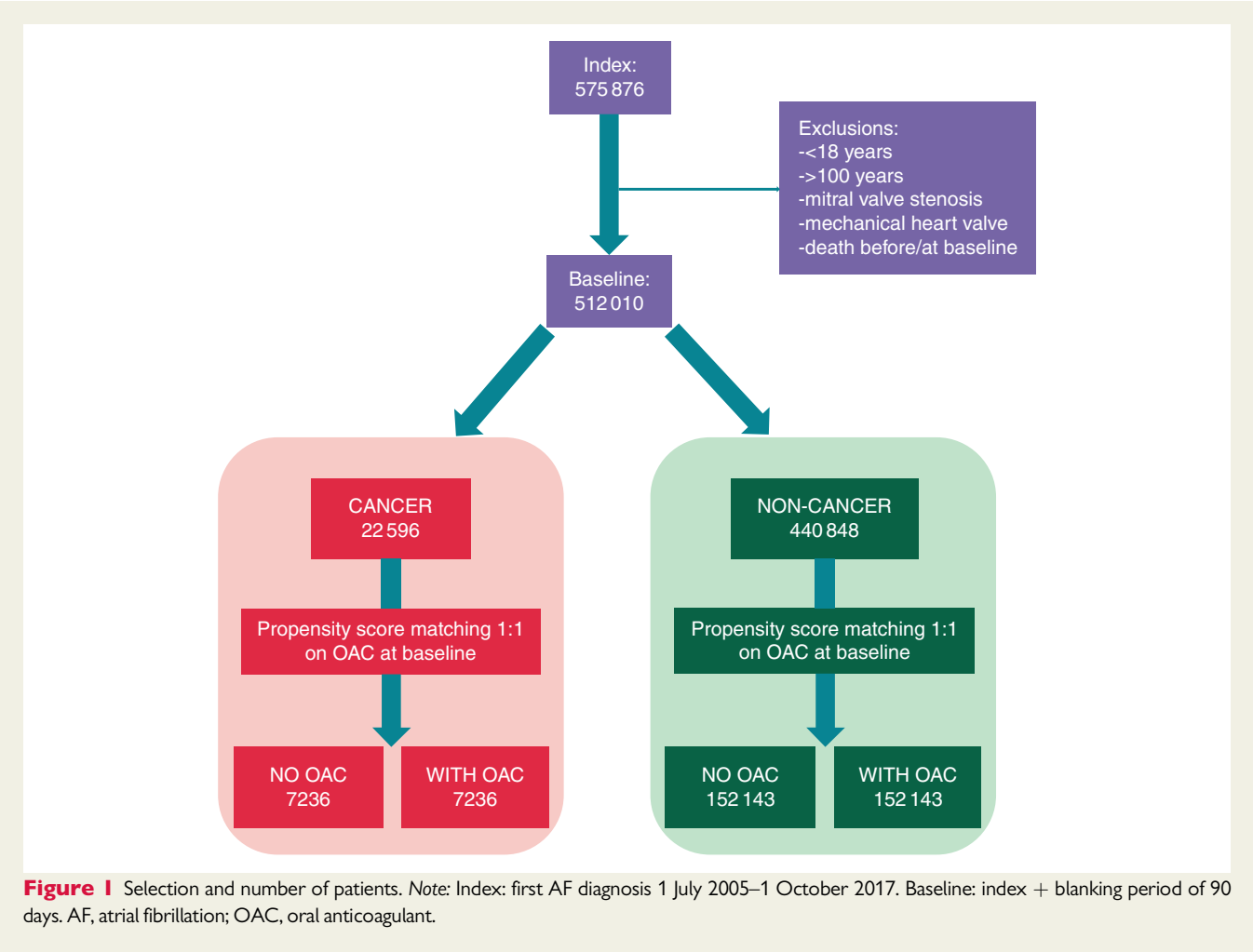
Statistical methods

Descriptive baseline data are presented as means or proportions and standardized differences. Means and proportions were tested using Student's *t*-test and Pearson's χ^2 test, respectively. Incidence rates are presented as events per 100 patient-years.

To reduce indication bias, patients were propensity score matched on OAC treatment at baseline. This was made separately for cancer and non-cancer patients. Propensity scores for the probability of receiving OAC were obtained by logistic regression using age, sex, cardiac failure, hypertension, diabetes, ischaemic stroke, transient ischaemic attack, vascular disease, bleeding, anaemia, venous thromboembolism, chronic obstructive pulmonary disease, dementia, alcohol-related diagnoses, obesity, thyroid disease, liver disease, percutaneous transluminal coronary angioplasty, cardioversion, two or more falls causing a hospital visit, and time since first registered AF diagnosis. Among cancer patients, cancer type and metastasis status were included in the propensity score regression. In case of missing metastasis data, multiple imputation was performed. A greedy nearest neighbour matching 1:1, without replacement and a caliper of 0.001, was made.

All outcome analyses were performed after propensity score matching. Hazard ratios (HRs) were calculated using the Cox proportional hazards model. The primary outcome was a composite of ischaemic stroke or intracranial bleeding. Additional analyses accounting for competing risk, defined as death due to other causes than the studied endpoint, were performed according to Fine and Gray's proportional subhazards model. The secondary outcome adverse events (AE) was a composite of ischaemic stroke, extracranial arterial thromboembolism, all major bleedings, and death. With the objective to study OAC treatment on strict AF indication, additional restricted analyses were performed on patients without a diagnosis of venous thromboembolism for 6 months before baseline.

To assess the presence and magnitude of hidden confounding data that affect decisions about OAC treatment, falsification endpoints were used. These are endpoints without known relation to the use of OAC but



reflect frailty.¹² We used a composite falsification endpoint comprising cholecystitis, acute bronchitis, herpes zoster infection, cholelithiasis, ankle distortion, and lumbago.

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

All analyses were performed by using Stata version 15.1 (StataCorp, 4905 Lakeway Dr, College Station, TX 77856, USA).

Ethics

The study conforms to the Declaration of Helsinki and was approved by the regional ethics committee (EPN 2018/1252-31). Individual patient consent was not required or obtained.

Results

During the observation period of 12 years and 3 months, 512 010 patients satisfied the inclusion and exclusion criteria. The study population comprised 22 596 patients with cancer within the preceding year and 440 848 patients without cancer within 5 years. After propensity score matching for the likelihood of OAC treatment at baseline, the cancer population consisted of 7236 patients with OAC and

an equal number of patients without OAC at baseline. Propensity score matching within the non-cancer population generated two groups, with and without OAC treatment, with 152 143 patients in each (Figure 1).

Baseline characteristics before propensity score matching

Among cancer patients, 36.9% received OAC (out of which approximately one-third used a NOAC) (Supplementary material online, Table S2). Low, intermediate, and high stroke risk patients received treatment in 19.6%, 33.8%, and 38.3% of the cases, respectively. In non-cancer patients, 52.5% had OAC at baseline. Low, intermediate, and high stroke risk patients were treated in 33.0%, 56.4%, and 54.5% of the cases, respectively.

Baseline characteristics after propensity score matching

After propensity score matching, the cohorts were well balanced with respect to known background characteristics (Table 1). The mean follow-up time was 2.4 years (interquartile range: 0.8–5.4 years).

Table 1 Cancer and non-cancer patients at baseline, after propensity score matching

| | Cancer | | | Non-cancer | | |
|--|----------------------|------------------------|----------------------------|-------------------------|---------------------------|----------------------------|
| | No OAC (n = 7236) | With OAC (n = 7236) | Standardized difference | No OAC (n = 152 143) | With OAC (n = 152 143) | Standardized difference |
| Time since first AF diagnosis (years), mean | 1.66 | 1.85 | −0.056 | 1.60 | 1.73 | −0.041 |
| Female sex | 37.9% | 38.1% | 0.004 | 46.3% | 46.7% | 0.009 |
| Age, median (IQR) | 77 (71–83) | 77 (71–83) | | 77 (67–84) | 76 (67–83) | |
| Cardiac failure | 27.3% | 28.2% | 0.019 | 27.8% | 28.4% | 0.014 |
| Hypertension | 58.5% | 57.9% | 0.011 | 54.4% | 51.6% | 0.056 |
| Diabetes | 19.4% | 19.5% | 0.002 | 17.4% | 18.2% | 0.022 |
| Previous ischaemic stroke/TIA/systemic arterial emboli | 18.4% | 18.9% | 0.011 | 19.4% | 23.0% | 0.088 |
| Previous vascular disease | 19.9% | 20.7% | 0.019 | 23.7% | 26.6% | 0.068 |
| Impaired kidney function | 5.5% | 5.5% | 0.001 | 5.2% | 5.6% | 0.019 |
| CKD 5 or dialysis | 0.7% | 0.4% | 0.039 | 0.7% | 0.4% | 0.033 |
| CHA ₂ DS ₂ -VASc score (mean) | 3.5 | 3.5 | −0.011 | 3.5 | 3.5 | −0.032 |
| VKA at baseline | 0.0% | 75.5% | 2.485 | 0.0% | 75.5% | 2.485 |
| NOAC at baseline | 0.0% | 25.2% | 0.821 | 0.0% | 25.3% | 0.823 |
| Platelet inhibitor at baseline | 48.2% | 17.9% | 0.682 | 60.2% | 22.3% | 0.833 |
| Parenteral anticoagulants at baseline | 21.3% | 30.2% | 0.206 | 4.8% | 7.7% | 0.121 |
| Anaemia | 19.8% | 21.0% | 0.028 | 12.0% | 12.4% | 0.012 |
| Previous bleeding events | 9.0% | 8.8% | 0.009 | 7.2% | 7.3% | 0.004 |
| Venous thromboembolism <6 months | 4.8% | 5.1% | 0.013 | 1.3% | 1.9% | 0.047 |
| Chronic obstructive pulmonary disease | 9.1% | 9.0% | 0.003 | 7.4% | 8.2% | 0.031 |
| Dementia | 1.8% | 1.8% | 0.003 | 2.7% | 2.6% | 0.005 |
| Alcohol-related disease | 2.0% | 2.1% | 0.013 | 2.8% | 3.0% | 0.015 |
| PTCA | 6.6% | 6.8% | 0.008 | 8.3% | 9.3% | 0.033 |
| Liver disease | 1.5% | 1.6% | 0.010 | 1.2% | 1.4% | 0.016 |
| Frequent falls | 3.9% | 4.2% | 0.018 | 5.5% | 5.5% | 0.000 |
| Gastrointestinal cancer | 23.1% | 23.8% | 0.016 | | | |
| Pancreatic cancer | 2.2% | 2.0% | 0.011 | | | |
| Lung cancer | 7.9% | 8.5% | 0.022 | | | |
| Breast cancer | 8.7% | 8.3% | 0.012 | | | |
| Gynaecological cancer | 4.9% | 5.1% | 0.008 | | | |
| Urological cancer | 33.1% | 31.7% | 0.028 | | | |
| Prostate cancer | 21.4% | 22.4% | 0.024 | | | |
| Intracranial cancer | 1.4% | 1.5% | 0.007 | | | |
| Haematological cancer | 9.2% | 10.3% | 0.038 | | | |
| Other cancers | 13.1% | 13.0% | 0.004 | | | |
| Chemotherapy in hospital at baseline | 3.0% | 3.0% | 0.001 | | | |
| Anti-tumoural medication prescribed at baseline | 15.0% | 15.5% | 0.014 | | | |
| Radiotherapy | 5.1% | 5.7% | 0.026 | | | |

Propensity score matching on OAC treatment at baseline was made separately in cancer and non-cancer patients. Standardized difference <0.10 in italics.

AF, atrial fibrillation; CKD 5, chronic kidney failure stage 5; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulant; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischaemic attack; VKA, vitamin K antagonists.

Main outcomes

In cancer patients, the overall incidence of ischaemic stroke/intracranial bleeding was 2.7 per 100 years at risk (CI: 2.5–2.8). The incidence among those who used OAC at baseline was 2.4 per 100 years at risk (2.2–2.6), compared to 2.9 per 100 years at risk (CI: 2.7–3.1) among

those who did not, giving a subhazard ratio (sHR) of 0.90 (CI: 0.80–1.00, $P = 0.056$) after competing risk analyses.

The corresponding incidence rates among patients without cancer was 2.1 per 100 years at risk (CI: 2.1–2.1) with OAC, and 2.8 per 100 years at risk (CI: 2.7–2.8) without OAC, resulting in a sHR of

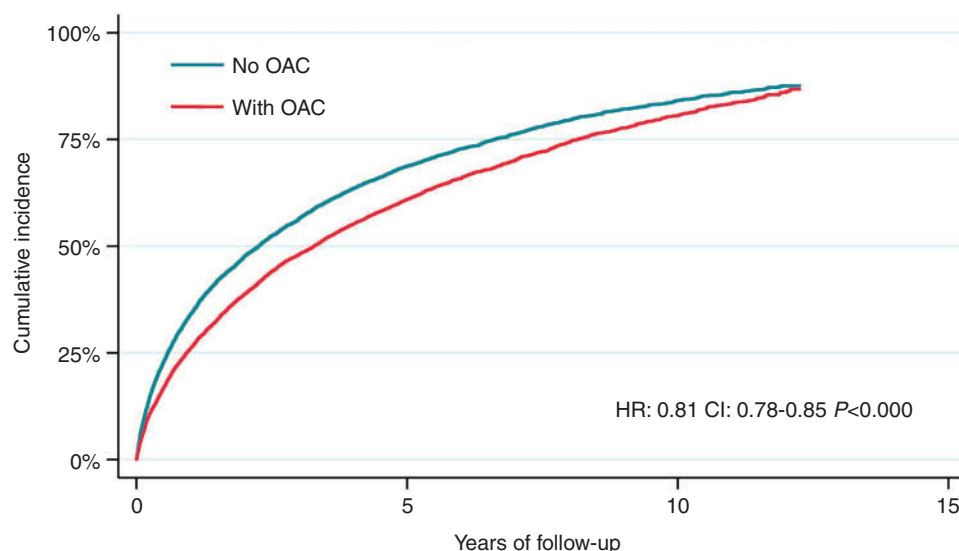


Figure 2 Adverse events in relation to OAC treatment among AF patients with cancer. Patients were propensity score matched on OAC treatment at baseline. Adverse events: composite of ischaemic stroke, extracranial arterial thromboembolism, all major bleedings, and death. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; OAC, oral anticoagulant.

Table 2 Net benefit analyses for different stroke risk levels in treated vs. not treated AF patients

| CHA ₂ DS ₂ -VASc stroke risk level | Cancer Adverse events | | | Non-cancer Adverse events | | |
|--|--------------------------|-----------|---------|------------------------------|-----------|---------|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| Any | | | | | | |
| No OAC | Reference | | | Reference | | |
| With OAC | 0.81 | 0.78–0.85 | 0.000 | 0.81 | 0.80–0.82 | 0.000 |
| Low | | | | | | |
| No OAC | Reference | | | Reference | | |
| With OAC | 1.25 | 0.82–1.91 | 0.307 | 1.13 | 1.05–1.21 | 0.001 |
| Intermediate | | | | | | |
| No OAC | Reference | | | Reference | | |
| With OAC | 0.82 | 0.70–0.96 | 0.014 | 1.00 | 0.96–1.04 | 0.911 |
| High | | | | | | |
| No OAC | Reference | | | Reference | | |
| With OAC | 0.82 | 0.79–0.86 | 0.000 | 0.79 | 0.78–0.80 | 0.000 |

Cancer and non-cancer patients separately propensity score matched on OAC use at baseline. Non-significant P values in italics. Adverse events: composite of ischaemic stroke, extracranial arterial thromboembolism, all major bleedings, and death.

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; OAC, oral anticoagulant.

0.80 (CI: 0.78–0.81) in favour of OAC treatment ([Supplementary material online, Table S3](#)).

Secondary outcomes and sensitivity analyses

OAC treatment was associated with lower risk of the composite AE in cancer patients (HR: 0.81, CI: 0.78–0.85) ([Figure 2](#)), as well as in

non-cancer patients (HR: 0.81, CI: 0.80–0.82). Stratification showed benefit at both intermediate and high stroke risk levels in cancer patients (HR: 0.82, CI: 0.79–0.86 and HR: 0.82, CI: 0.70–0.96, respectively) ([Table 2](#)).

Among patients without OAC treatment, the incidence of all major bleedings leading to hospital admission was higher in cancer patients (7.4 per 100 years at risk, CI: 7.1–7.8) than in non-cancer

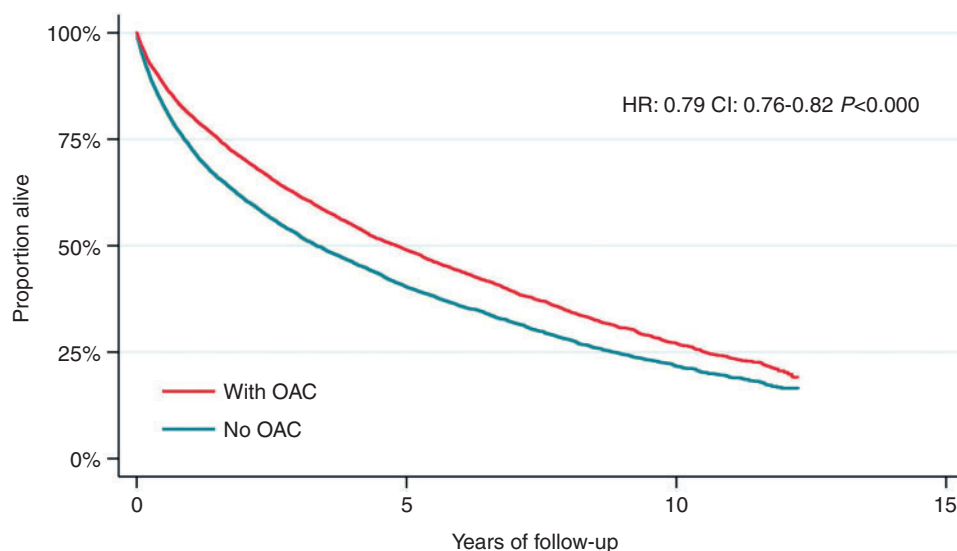


Figure 3 Survival in relation to OAC treatment among AF patients with cancer. Patients were propensity score matched on OAC treatment at baseline. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; OAC, oral anticoagulant.

patients (4.0 per 100 years at risk, CI: 4.0–4.0). Oral anticoagulant treatment remained associated with an increase in major bleedings in cancer patients after competing risk analyses (sHR: 1.09, CI: 1.02–1.17).

The incidence of all-cause death among cancer patients was 16.7 per 100 years at risk (CI: 16.3–17.1). Oral anticoagulant use at baseline was associated with a lower mortality during follow-up (HR: 0.79, CI: 0.76–0.82) (Figure 3). This was driven by a lower risk of all-cause death at intermediate and high stroke risk (HR: 0.77, CI: 0.64–0.93 and HR: 0.79, CI: 0.75–0.82, respectively).

When limiting the follow-up to one year to minimize the effects of treatment cross-over and furthermore accounting for competing risk in cancer patients, benefit was seen for OACs with regard to ischaemic stroke/intracranial bleeding (sHR: 0.67, CI: 0.55–0.83), and ischaemic stroke alone (sHR: 0.54, CI: 0.43–0.69), as well as for death (HR: 0.68, CI: 0.64–0.73). The risk of intracranial bleeding did not seem to increase (sHR: 1.03, CI: 0.72–1.46) neither did the composite endpoint all major bleedings (sHR: 0.93, CI: 0.84–1.03).

Subanalyses within each studied cancer type showed significant associations only between OAC treatment and lower risk of AE or all-cause death, except for in pancreatic, lung, and prostate cancer, where no statistical significance was reached.

A sensitivity analysis, excluding metastasis status, did not alter results.

Excluding cancer patients who had redeemed at least one prescription of parenteral anticoagulants before propensity score matching ($n = 5538$) did not alter outcome analyses for ischaemic stroke (sHR: 0.75, CI: 0.65–0.87), intracranial bleeding (sHR: 1.46, CI: 1.16–1.84), or death (HR: 0.80, CI: 0.76–0.84). Patients with venous thromboembolism, who had only parenteral anticoagulation, constituted 1.9% of the cancer patients after propensity score matching. In another sensitivity analysis, cancer patients with venous thromboembolism within 6 months before baseline were excluded before

propensity score matching, but this did not cause a significant difference in AE risk reduction (HR: 0.82, CI: 0.79–0.86).

No difference was seen among cancer patients treated with NOACs and VKA regarding intracranial bleeding (sHR: 0.96, CI: 0.64–1.45), all major bleedings (sHR: 1.03, CI: 0.88–1.21), the composite AE (HR: 0.98, CI: 0.88–1.09), or all-cause death (HR: 0.92, CI: 0.81–1.04); however, there was a decrease in ischaemic stroke events (sHR: 0.45, CI: 0.30–0.69), and in the composite ischaemic stroke/intracranial bleeding (sHR: 0.65, CI: 0.48–0.88) for NOACs vs. VKA treatment.

No significant association between OAC and the falsification endpoint was seen, neither in cancer nor in non-cancer patients (HR: 1.12, CI: 0.96–1.31 and HR: 0.98, CI: 0.95–1.01, respectively).

A complete presentation of outcome analyses is shown in [Supplementary material online, Table S3](#).

Discussion

The main finding of our study was that patients with AF, active cancer, and at least intermediate stroke risk, had a lower risk of AE, including death, when treated with OACs. Among patients with AF, we found a net cerebrovascular benefit of OAC treatment during the first year following a cancer diagnosis and with NOACs compared to warfarin. This complements the findings of a recent study, which suggests that anticoagulants are safe to use in AF patients with breast cancer.¹³

The incidences of AF and cancer increase with age, which highlights the importance of studying the overlap between these two common medical conditions in an ageing population. Observational data can indicate associations but not causality and should, therefore, be interpreted cautiously. However, it is a valuable source of information when randomized controlled trials are not available.

Our study reveals that not even half of cancer patients with AF received OAC. This is in line with a previous study showing that up to 60% of AF patients with active cancer were not prescribed anticoagulants according to AF guidelines.¹⁴ The low use of anticoagulants and in its place the use of platelet inhibitors may be due to overappraisal of the risk of excess bleeding among cancer patients during OAC treatment but also factors unaccounted for in health registers, e.g. short life expectancy. Therefore, in this study, we included prognostically important factors like cancer type, chemotherapy, radiotherapy, and metastasis status in the propensity score matching. Sensitivity analyses, e.g. by excluding metastasis status, did not significantly alter the results, but a high proportion of imputed data on metastasis may have undermined this subgroup analysis.

Certain cancer types, especially adenocarcinoma of the pancreas, colon, breast, lung, prostate, and ovary, and the presence of metastases indicating a more advanced cancer stage, have been reported to increase the risk of ischaemic stroke. Incidence has further been seen peaking during the first year after cancer diagnosis.¹⁵ We performed separate analyses on each studied cancer type, but as the subgrouping of patients reduced the number of events, we observed fewer significant associations and mostly in the larger cancer subgroups, which could be related to the limited sample size. However, several cancer-related aspects influencing prognosis, as well as most factors taken into account by clinicians when considering initiation of anticoagulants, were included in the propensity score matching to minimize confounding data. The lack of significant association between treatment and the composite falsification endpoint suggests that unaccounted confounding did not affect the main results to any great extent.

We found that the incidences of ischaemic stroke/intracranial bleeding were comparable in cancer and non-cancer patients. This is in agreement with previous smaller studies including patients with both active cancer and patients with a more distant history of cancer.³ As expected, the mortality was nearly doubled in cancer patients. To adjust the effect of this, we applied competing-risks regression models.

A net benefit of OACs regarding ischaemic stroke, extracranial arterial thromboembolism, all major bleedings, and death, was seen in patients with high estimated stroke risk, regardless of cancer status; in cancer patients, statistical significance was reached also at intermediate stroke risk, which suggests a possibly greater general benefit of OACs.

In cancer patients at low stroke risk, no significant association was seen between OAC and any of the studied outcomes. There are several plausible explanations for this. With fewer events in the low-risk subgroup, the statistical power to detect differences becomes low. A particularly interesting observation was made in a recent study, in which risk stratification according to CHA₂DS₂-VASc seemed less predictable in cancer patients.¹⁶ Our results regarding a higher net benefit of OAC therapy as stroke risk increases seem, however, to be clinically reasonable.

The potential problem of treatment cross-over can be reduced by performing analyses with a limited follow-up time. By doing so we observed a net cerebrovascular benefit of OACs during the year following a cancer diagnosis, even after taking the competing risk of death into account, a result of great interest in a patient group which is affected in several ways.

The safety of NOACs compared to VKA regarding risk of intracranial bleeding has been shown in clinical non-inferiority studies. A systematic review of post-hoc analyses has also come to the same conclusion in AF patients with cancer.¹⁷ Our results confirm these findings by showing a lower risk of ischaemic stroke and the combined endpoint ischaemic stroke and intracranial bleeding with NOAC treatment compared to warfarin.

Our data lacks information about anticoagulation control in VKA-treated patients. However, previous validations have shown a generally good anticoagulation control in Sweden, with an average time in therapeutic range for warfarin of over 75%.¹⁸ Anti-tumoural treatment, which often increases the bleeding risk, can potentially influence anticoagulation treatment in cancer patients. By including chemotherapy and radiotherapy in the propensity score, we took this aspect into account. As emphasized in a recently published guidance on anticoagulants in AF patients receiving chemotherapy, it is of great importance in the clinical setting to consider the dynamic nature of cancer and its treatment.¹⁹

The CLOT study on the treatment of cancer patients with venous thromboembolism showed the benefits of low-molecular-weight heparin (dalteparin) over OAC (coumarin).²⁰ To date, there are no guideline recommendations about prophylactic anticoagulant treatment specifically for AF patients with cancer, which may explain the findings of an Italian study, in which one-third of the patients were prescribed only low-molecular-weight heparins in prophylaxis dosage rather than OAC.¹⁴ In line with the common practice with venous thromboembolism, many clinicians conceivably avoid OACs in favour of parenteral anticoagulants in the presence of AF and cancer. Since our data sources did not make it possible to see the specific indication of prescribed parenteral anticoagulants, we excluded all cancer patients on parenteral anticoagulation as part of a sensitivity analysis; however, the main results remained the same. Neither did exclusion of patients with venous thromboembolism, a common indication for parenteral anticoagulants in cancer patients, result in a significant difference in ischaemic stroke/intracranial bleeding.

Limitations

Being based on register data, this study has several limitations. First, our registers comprise binary data, introducing possible misclassification and residual bias, and lack information about drug compliance. Second, during the follow-up time (up to 12.3 years long), treatment practices and guideline recommendations regarding cancer treatment and stroke prophylaxis in AF changed towards new anti-tumoural drug mechanisms and broader awareness of the role of anticoagulants in avoiding ischaemic stroke. Third, patients with prescriptions for anticoagulants have more healthcare contacts and are more likely to receive diagnoses of concomitant diseases. This could lead to underestimation of comorbidity among untreated patients and thereby exaggerate the benefits of OAC treatment. Fourth, analyses according to treatment at baseline disregard patient cross-over and attenuates associations between treatment and outcomes.

Conclusion

Our results support the hypothesis that patients with AF, active cancer, and elevated stroke risk benefit from treatment with OACs

according to current AF guidelines. We suggest that these patients should be routinely assessed for anticoagulants. Further studies regarding cancer types and stages are warranted.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: A.A. and K.A. report no conflicts of interest. L.F. has received consultancy 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.

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