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BRIEF REPORT

Hematuria in anticoagulated patients with atrial fibrillation and urologic cancer

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Abstract

Background: Based on their renal excretion, direct oral anticoagulants (DOACs) may increase the risk of hematuria in patients with atrial fibrillation (AF) and urologic cancer compared with vitamin K antagonists.

Objectives: To examine the risk of bleeding associated with DOAC versus warfarin in patients with AF and urologic cancer.

Methods: We conducted a Danish nationwide cohort study with individually linked registry data on patients with AF and active or a history of urologic cancer. We calculated crude rates per 100 person-years of hospital episodes of major bleeding and hematuria. We then compared rates of hematuria during the year after initial oral anticoagulation filled prescription by treatment regimen using inverse probability of treatment weighting and Cox regression.

Results: The study population included 2615 patients with AF and urologic cancer (6.1% women; median age, 76 years) initiating a DOAC or warfarin. One-year risk of hematuria was 4.8% in the DOAC group and 4.7% in the warfarin group with a corresponding weighted hazard ratio (HR) of 1.21 (95% confidence interval [CI], 0.81-1.81). HRs for hematuria were generally similar in analyses restricted to patients treated with standard-dose DOAC and patients with active cancer. For those with cancer of the kidney, renal pelvis, ureter, and bladder, the HR was 0.82 (95% CI, 0.44-1.54). Results were mirrored for other bleeding events, whereas the risk for intracranial bleeding was lower with DOACs.

Conclusion: In patients with AF and urologic cancer, there was a similar risk of hematuria associated with DOAC and warfarin treatment.

KEYWORDS
anticoagulants, atrial fibrillation, hematuria, urologic neoplasms, warfarin

Essentials

- Anticoagulants may lead to bleeding in patients with atrial fibrillation and urologic cancer.
- Population-based cohort study in Denmark with individual-level linked registry data.
- One-year hematuria risk was 4.8% with direct oral anticoagulants (DOACs) and 4.7% with warfarin.
- Hematuria risk was similar for DOACs and warfarin.

1 | INTRODUCTION

Malignancy increases the risk of cardiovascular events,[1] and cancer concurrent with atrial fibrillation (AF) poses a clinically important challenge because of increased bleeding and thrombotic risk.[2]

Vitamin K antagonists (VKAs) and the direct oral anticoagulants (DOACs) rivaroxaban, dabigatran, apixaban, and edoxaban are used for stroke prevention in AF, with DOACs recommended as first-line therapy in international guidelines.[3-5] Multiple studies of patients with AF receiving DOACs versus VKA for stroke prevention demonstrated comparable bleeding risk in patients with a history of cancer.[6-11] These studies combined different types of cancer, although the bleeding risk may differ by cancer type. Indeed, DOACs in the presence of urologic cancer may particularly increase the risk of hematuria because these drugs are partly cleared renally and may exert a direct effect in the urinary system.[12] Few studies have assessed bleeding outcomes in patients treated with oral anticoagulants with urologic cancer, and none of these specifically included a population of patients with AF.[13,14]

We used Danish nationwide registries with individual-level linked data to compare bleeding risk associated with DOACs versus warfarin in patients with AF and urologic cancer.

2 | METHODS

2.1 | Setting and data sources

The Danish National Health Service provides tax-supported health care to all residents.[15] Individual-level data can be linked across registries by means of the unique civil registration number assigned to all Danish residents at birth or upon immigration.[15] Migration, sex, and vital status are tracked by the Civil Registration System (CRS).[16] The Danish National Patient Registry (DNPR) covers all Danish hospitals and has recorded inpatient discharge diagnoses since 1977 and diagnoses in outpatient clinics since 1995. Diagnoses were coded according to the International Classification of Diseases (ICD), Eighth Revision, until 1993 and according to the ICD, Tenth Revision, starting in 1994.[17] The Danish National Prescription Database (DNPD) records information on outpatient pharmacy prescription claims using the Anatomical Therapeutic Chemical Classification System.[18] The Danish Cancer Registry (DCR) records all incident cancer diagnoses in Denmark with information on morphology, histology, and stage at diagnosis.[19] Codes are provided in Table S1.

2.2 | Design and study population

Using the DNPR and DNPD, we included a cohort of patients with inpatient or outpatient hospital-based diagnoses of nonvalvular AF with a prescription claim for a DOAC or warfarin between August 1, 2011, and June 30, 2018. We excluded experienced users of oral anticoagulants and patients who did not have a prevalent diagnosis of urologic cancer defined as kidney, renal pelvis, ureter, bladder, prostate, testis, and penile cancer recorded in the DCR before their first anticoagulation prescription claim.[18] The index date was defined as the date of initial anticoagulation prescription. We also excluded patients with other indications for oral anticoagulation.

Inpatient and outpatient comorbid diagnoses at index were obtained from the DNPR. With the DNPD, we assessed prescriptions for cardiovascular medication within 90 days before index. We combined covariate information into CHA_2DS_2-VASc and HAS-BLED scores as a measure of baseline stroke and bleeding risk, respectively. We also collected information on cancer-targeted treatment including urologic surgery, chemotherapy, and radiotherapy administered during the 6 months before the index date. Active cancer was defined as a diagnosis of urologic cancer, metastasis, or receipt of chemotherapy or radiotherapy within the previous 6 months.

2.3 | Follow-up and bleeding end points

Bleeding was defined as clinically relevant bleeding events leading to hospital contact and recorded in the DNPR as inpatient or outpatient episodes of hematuria, intracranial bleeding, major bleeding in other anatomic sites, and eventually as a composite of all clinically relevant bleedings (see Table S1 for diagnostic codes). Patients were followed from the index date for 1 year to the first record of a clinically relevant bleeding event regardless of extent and severity, with censoring at emigration, death, or December 31, 2018, whichever came first.

2.4 | Statistical analysis

We described patient characteristics at initial DOAC or warfarin prescription. We accounted for baseline confounding using inverse probability of treatment weighting to obtain estimates that represented the population average treatment effects on pseudo-cohorts of patients treated with DOACs or warfarin with comparable baseline characteristics. Weights were derived using generalized boosted models including information on age, sex, cancer type, cancer stage,

previous stroke, diabetes, hypertension, heart failure, bleeding, and use of lipid-lowering drugs.

We conducted sensitivity analyses for patients with active cancer and for those with a prescription for standard-dose DOAC by reweighting the populations. This approach was used to exclude patients with a potential high bleeding risk at index receiving reduced DOAC dose. Because oral anticoagulant therapy may increase the risk for bleeding from the urinary tract,[13] we also excluded patients with prostate, penile, and testis cancer and reweighted the population of patients with kidney, renal pelvis, ureter, or bladder cancer. Due to few events for bleeding subtypes, we report the composite of all bleeding events and hematuria in the subanalyses. The warfarin and DOAC patients were largely well-balanced across baseline characteristics after propensity score weighting overall and in subgroup analyses, but aspirin use was more common among patients treated with warfarin, even after propensity score weighting. The propensity score distribution demonstrated adequate overlap between the warfarin and DOAC group, with no sign of violation of the positivity assumption with scores approaching zero (data not shown).

We computed weighted cumulative bleeding incidence curves accounting for competing risk of death.[20] We calculated bleeding rates within the unweighted and weighted warfarin and DOAC population and calculated hazard ratios (HRs) using weighted Cox proportional hazards regression.

3 | RESULTS AND DISCUSSION

We included 2615 patients with AF (6.1% women; median age, 76 years) and a history of urologic cancer (34% had active cancer) who claimed their first prescription for DOAC (N = 1776) or warfarin (N = 839). Apixaban was the most frequently prescribed DOAC (39%). Prostate cancer accounted for 73% of cancers (Table 1). Patients initiating reduced-dose DOAC (N = 550) versus standard-dose DOAC (N = 1226) were more often women (9.3% vs 4.2%), nearly 10 years older (median age, 83 years vs 74 years), more often had active cancer (38% vs 32%), and had higher prevalence of comorbidity and higher HAS-BLED score.

There were 161 hospital diagnosed bleeding events among DOAC initiators and 70 in warfarin initiators. Weighted 1-year risk of hematuria was similar (4.8% for DOAC users and 4.7% for warfarin users; Figure 1). Weighted rates for hematuria were comparable for DOAC and warfarin users, and the weighted HR was 1.21 (95% confidence interval [CI], 0.81-1.81), and for the combined bleeding end point, the HR was 1.12 (95% CI, 0.85-1.49). There were only eight

TABLE 1 Participant characteristics by anticoagulant prescription claim

	Unweighted population			Weighted population
Characteristic	DOAC cohort	Warfarin cohort	Standardized difference	Standardized difference
Participants	1776	839		
Women	103 (5.8)	57 (6.8)	0.04	0.00
Median age, y	76.0 (70.0-82.0)	76.0 (70.0-82.0)	0.04	0.00
Cancer type[a]				
Kidney	166 (9.3)	107 (12.8)	0.11	0.01
Renal pelvis	110 (6.2)	116 (13.8)	0.25	0.00
Ureter	<5 (...)	<5 (...)	0.00	0.01
Bladder	213 (12.0)	110 (13.1)	0.03	0.00
Prostate	1311 (73.8)	589 (70.2)	0.08	0.00
Testes	91 (5.1)	44 (5.2)	0.01	0.01
Penile	24 (1.4)	10 (1.2)	0.01	0.01
Metastasis[b]	30 (1.7)	21 (2.5)	0.06	0.05
Active cancer	599 (33.7)	317 (37.8)	0.08	0.07
Cancer treatment[b]				
Chemotherapy	72 (4.1)	40 (4.8)	0.03	0.04
Radiation therapy	459 (25.8)	250 (29.8)	0.09	0.06
Surgery	180 (10.1)	85 (10.1)	0.00	0.01
Cancer stage				
Localized	674 (38.0)	329 (39.2)	0.02	0.01
Regional	54 (3.0)	27 (3.2)	0.01	0.01
Distant	83 (4.7)	33 (4.0)	0.04	0.04
Missing/Unknown	965 (54.5)	450 (53.6)	0.01	0.00

(Continues)

TABLE 1 (Continued)

Characteristic	Unweighted population			Weighted population
	DOAC cohort	Warfarin cohort	Standardized difference	Standardized difference
Comorbidities				
Heart failure	416 (23.4)	258 (30.8)	0.17	0.00
Diabetes	285 (16.0)	149 (17.8)	0.05	0.00
Hypertension	1003 (56.5)	515 (61.4)	0.10	0.00
Stroke	238 (13.4)	103 (12.3)	0.03	0.09
Systemic embolism	<5 (…)	<5 (…)	0.00	0.00
Myocardial infarction	202 (11.4)	118 (14.1)	0.09	0.03
Ischemic heart disease	450 (25.3)	249 (29.7)	0.10	0.04
Cardiomyopathy	43 (2.4)	26 (3.1)	0.04	0.01
Obesity	94 (5.3)	52 (6.2)	0.04	0.00
Hyperthyroidism	32 (1.8)	17 (2.0)	0.02	0.01
Chronic pulmonary disease	285 (16.0)	144 (17.2)	0.03	0.02
Liver disease	5 (0.3)	<5 (…)	0.04	0.04
Renal disease	110 (6.2)	116 (13.8)	0.26	0.00
Previous bleeding	494 (27.8)	214 (25.5)	0.05	0.00
CHA_2DS_2-VASc score				
0	44 (2.5)	17 (2.0)	0.03	0.02
1	231 (13.0)	90 (10.7)	0.07	0.02
2–4	1178 (66.3)	538 (64.1)	0.05	0.01
5+	323 (18.2)	194 (23.1)	0.12	0.01
HAS-BLED score				
0	28 (1.6)	14 (1.7)	0.01	0.01
1–2	764 (43.0)	306 (36.5)	0.13	0.05
3+	984 (55.4)	519 (61.9)	0.13	0.04
Medication				
Apixaban	692 (39.0)	…	…	…
Dabigatran	441 (24.8)	…	…	…
Edoxaban	20 (1.1)	…	…	…
Rivaroxaban	623 (35.1)	…	…	…
DOAC standard dose	1226 (31.0)	…	…	…
DOAC reduced dose	550 (69.0)	…	…	…
Renin-angiotensin inhibitor (ACE/ARB)	683 (38.5)	332 (39.6)	0.02	0.03
Calcium channel blockers	379 (21.3)	26.8 (225)	0.13	0.09
Beta blockers	1100 (61.9)	496 (59.1)	0.06	0.09
Diuretics	557 (31.4)	347 (41.4)	0.21	0.12
Digoxin	352 (19.8)	167 (19.9)	0.00	0.01
Lipid-lowering drugs	599 (33.7)	310 (36.9)	0.08	0.00
Aspirin	516 (29.1)	301 (35.9)	0.15	0.11
Nonsteroidal anti-inflammatory drugs	173 (9.7)	92 (11.0)	0.04	0.06
Amiodarone	50 (2.8)	33 (3.9)	0.06	0.04
Clopidogrel, ticagrelor, prasugrel	184 (10.4)	112 (13.3)	0.09	0.05

Note: Numbers represent the median (interquartile range) or number of patients (%), as indicated; as required by Danish data protection law, counts were suppressed for observations with <5 incidents.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DOAC, direct oral anticoagulant.

[a]Cancer types were are not mutually exclusive.

[b]Recorded during the 6 months before initial prescription claim.

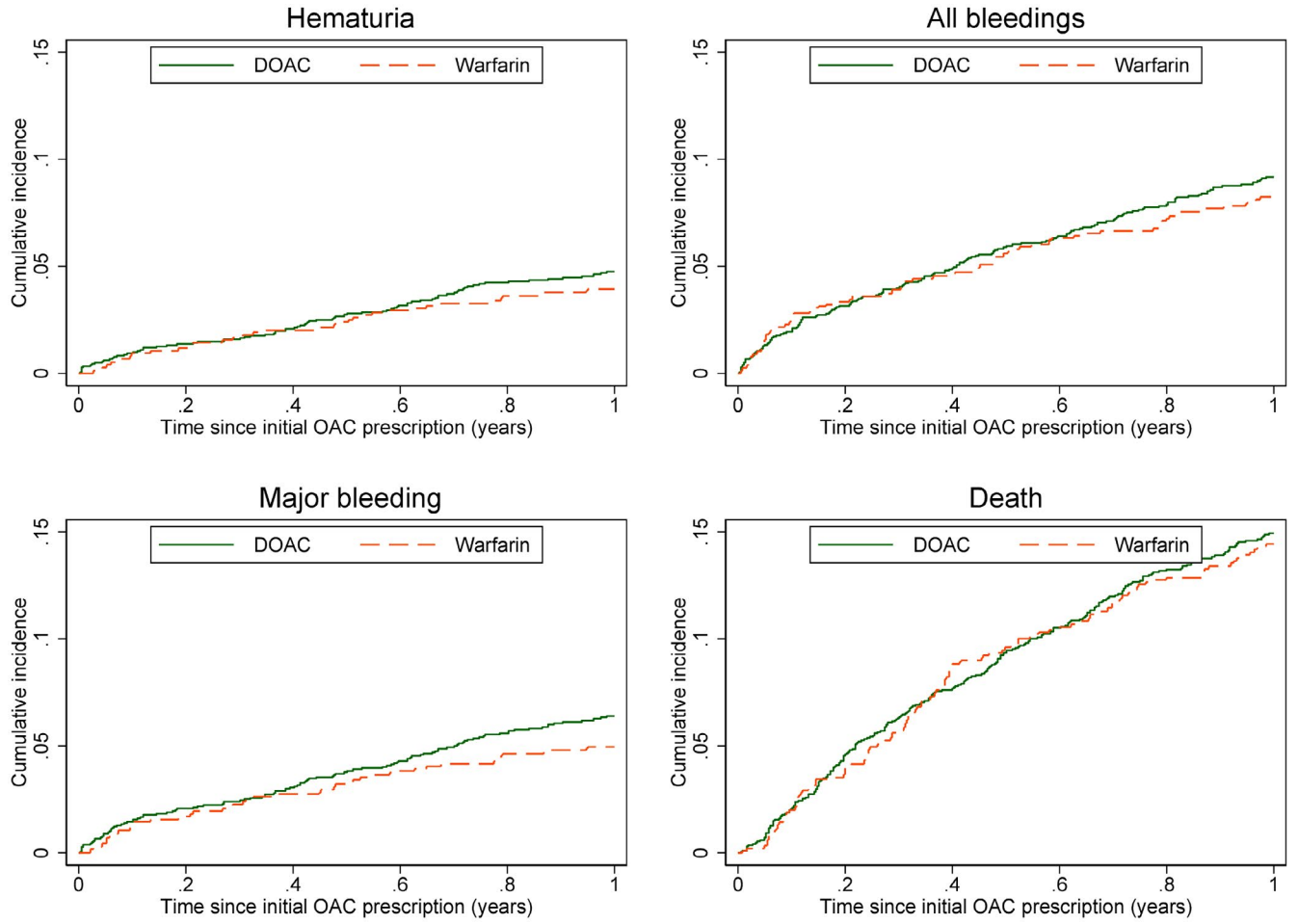

FIGURE 1 1-year risk of bleeding in patients with atrial fibrillation and urologic cancer. Graphs show the weighted cumulative incidences during the one-year follow-up of (top left) hematuria, (top right) all bleeding events, (bottom left) major bleeding, and (bottom right) death. DOAC, direct oral anticoagulant; OAC, oral anticoagulant

cases of intracranial bleeding in each group, favoring DOAC with a HR of 0.44 (95% CI, 0.16-1.19). In sensitivity analyses that were restricted to patients treated with standard dose DOAC vs warfarin, the HR was 1.29 (95% CI, 0.83-2.02) for hematuria and 1.34 (95% CI, 0.91-1.97) for major bleeding (Table 2). Incidences of death were similar for patients initiating DOACs (14.8%) and warfarin (14.7%).

The weighted hematuria rates were higher for patients with active cancer than in the overall cohort, but the HR slightly lower; weighted HR was 1.14 (95% CI, 0.64-2.01). These results were mirrored in the composite of all bleedings, HR was 1.11 (95% CI, 0.72-1.70). Among patients with cancers located in the kidney, renal pelvis, ureter, or bladder, rates and HRs showed no or an inverse association with DOACs compared with warfarin (HR, 0.82; 95% CI, 0.44-1.54 for hematuria; and HR, 0.99; 95% CI, 0.64-1.53) for the composite bleeding end point (Table 2).

In this large, nationwide cohort study including patients with AF and history of urologic cancer, we demonstrated comparable 1-year bleeding risks for patients initiating DOAC and warfarin therapy. There was no clinically important difference in bleeding risk for the subgroup of patients with active cancer. In analyses restricted to patients with cancers of the kidney, renal pelvis, ureter, or bladder, we also found similar or lower risk of hematuria in those treated with DOACs compared with warfarin, but the scarcity of events resulted in imprecise HR estimates.

We hypothesized that urologic cancer types, and particularly those located in the urinary tract, may be prone to bleeding in relation to DOAC treatment.[13] Whereas warfarin is mainly cleared through hepatic metabolism and excreted renally, DOACs are cleared both renally and through the liver.[12] However, we did not observe any clinically relevant difference in risk of hematuria between DOAC and warfarin initiators. In patients with cancers of the kidney, renal pelvis, bladder, or ureter, the HR point estimates showed no or an inverse association with DOAC compared with warfarin, though imprecisely measured. Similar findings have been demonstrated in a review of other patient populations.[13] Apixaban may be associated with a reduced risk of major bleeding compared with other DOACs, such as dabigatran.[21] Therefore, specific DOACs may be differentially associated with bleeding risk.

Several factors, such as variations in dosing, drug levels, and clearance, concurrent administration of aspirin, nonsteroidal anti-inflammatory drugs, other antiplatelet therapy, invasive or pharmacologic anticancer therapy or radiotherapy may potentially affect

TABLE 2 Bleeding rate in patients with urologic cancer and atrial fibrillation by anticoagulant type

Outcome	OAC group	Bleeding events, n	Unweighted rate per 100 person-years (95% CI)	Weighted rate per 100 person-years (95% CI)	Weighted HR (95% CI)	Standard DOAC dose Weighted HR (95% CI)
All urological cancer patients						
All bleedings	DOAC	161	10.77 (9.23-12.57)	10.67 (9.14-12.53)	1.12 (0.85-1.49)	1.12 (0.82-1.53)
	Warfarin	70	9.60 (7.60-12.14)	9.43 (7.43-12.13)	Ref	Ref
Hematuria	DOAC	84	5.47 (4.41-6.7)	5.38 (4.35-6.72)	1.21 (0.81-1.81)	1.29 (0.83-2.02)
	Warfarin	33	4.44 (3.15-6.24)	4.41 (3.14-6.38)	Ref	Ref
Major bleeding	DOAC	112	7.36 (6.12-8.86)	7.31 (6.08-8.86)	1.30 (0.91-1.85)	1.34 (0.91-1.97)
	Warfarin	42	5.68 (4.20-7.69)	5.59 (4.13-7.75)	Ref	Ref
Intracranial bleeding	DOAC	8	0.51 (0.25-1.02)	0.47 (0.24-1.05)	0.44 (0.16-1.19)	0.34 (0.10-1.11)
	Warfarin	8	1.05 (0.53-2.11)	1.08 (0.54-2.47)	Ref	Ref
Active cancer						
All bleedings	DOAC	66	14.16 (11.13-18.03)	13.66 (10.72-17.65)	1.11 (0.72-1.70)	NA[a]
	Warfarin	31	12.08 (8.50-17.18)	12.16 (8.45-18.28)		
Hematuria	DOAC	39	8.08 (5.90- 11.05)	7.58 (5.57-10.58)	1.14 (0.64-2.01)	
	Warfarin	18	6.88 (4.34-10.92)	6.59 (4.13-11.14)		
Kidney, renal pelvis, ureter, or bladder cancer						
All bleedings	DOAC	52	14.70 (11.20-19.29)	14.59 (11.04-19.63)	0.99 (0.64-1.53)	NA[a]
	Warfarin	33	14.23 (10.12-20.01)	14.42 (10.15-21.11)	Ref	
Hematuria	DOAC	22	5.90 (3.88-8.96)	5.99 (3.95-9.50)	0.82 (0.44-1.54)	
	Warfarin	16	6.72 (4.12-10.96)	7.31 (4.46-12.81)	Ref	

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; OAC, oral anticoagulant.

[a]Too few events to calculate HRs for subgroups of patients initiating standard DOAC dose.

bleeding risk in patients with AF and comorbidities, such as cancer. It has previously been demonstrated that DOACs may be a safe choice compared with vitamin K antagonists in patients with cancer in general, also for those with active cancer.[11,22,23] However, only little evidence supports the treatment choice for patients initiating anticoagulant therapy in patients with urologic cancer.[14] Our study demonstrated similar risk of bleeding after initiation of DOACs or warfarin for patients with AF and history of urologic cancer as well as in those with active urologic cancer. In our sensitivity analysis that only considered patients initiating standard-dose DOAC by excluding patients at potentially high bleeding risk initiating reduced-dose DOAC, the HR estimates were essentially similar to the overall analysis. This finding does not support that patients with a high baseline bleeding risk drives a potential bleeding association with DOACs. Patients with active cancer also had similar relative bleeding risk as in the overall cohort.

Our nationwide cohort included all patients with AF and prevalent urologic cancer who were new users of oral anticoagulants in Denmark, which has a tax-supported and uniformly organized health care system.[17] The positive predictive value of the registry-based AF diagnosis has been shown to be >90%.[24] All prescription claims are recorded in the DNPD.[18] The majority of cancers are histologically verified in the DCR, and this registry is nearly complete and valid due to mandatory reporting throughout the Danish health care system.[19] Identification of patients in this national setting with health care free of charge, and the tracking of patients using the CRS allowed unselected patient inclusion and complete follow-up.[16] Still, there are limitations to consider. Due to the registry-based design, we lacked information on anticoagulants dispensed at hospitals, adherence and persistence, and lifestyle factors. Choice of anticoagulant therapy in patients with active cancer or at high bleeding risk may depend on patient and physician preference, cancer type, stage, and time since cancer diagnosis. We lacked information on compliance with anticoagulant treatment during follow-up. We accounted for baseline confounding by means of our weighted analysis, which considered measured imbalance between treatment groups in the comparative analyses on observed covariates. Only hospital recorded bleeding events were included with no information on extent and we did not have information on procedures that could indicate severe bleeding. Furthermore, the validity of the bleeding codes in the DNPR may vary by bleeding sites and severity.[17] Coding of hematuria is likely relevant if the initial examination at hospital has ruled out obvious conditions causing hematuria. Therefore, we likely did not capture all patients referred to the hospital with hematuria if an underlying disease is coded. This may result in an underestimation of the true hematuria risk. However, we do not expect the hematuria coding to differ for patients treated with DOACs versus warfarin.

In conclusion, we observed no clinically relevant difference in 1-year risk of hematuria or other bleeding events associated with

DOACs compared with warfarin in patients with AF and a history of or active urologic cancer. Additional analyses are warranted to confirm our findings in larger populations.

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RELATIONSHIP DISCLOSURE

All authors have completed the International Committee of Medical Journal Editors Form for Disclosure of Potential Conflicts of Interest. MS reports personal fees from Bayer, outside the submitted work. ELG has received speaker honoraria or consultancy fees from 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. GYHL reports consultancy and speaker fees from BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo outside the submitted work; no fees received personally. TBL reports grants from the Obel Family Foundation, and personal fees from Bayer AG, Pfizer, Bristol Meyer Squibb, MSD, and Bohringer Ingelheim, outside the submitted work. PBN reports personal fees from Bayer, and personal fees and nonfinancial support from Daiichi-Sankyo and BMS/Pfizer, outside the submitted work. The other authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

AO: conceptualization, methodology, investigation, formal analysis, writing—original draft preparation, review and editing, and project administration. MS: conceptualization, methodology, investigation, writing—original draft preparation, and review and editing. FS: methodology, investigation, data curation, resources, formal analysis, software, validation, visualization, writing—original draft preparation, and review and editing. ELG: conceptualization and writing—review and editing. GYHL: conceptualization and writing—review and editing. TL: conceptualization, methodology, investigation, funding acquisition, resources, writing—original draft preparation, and review and editing. PN: conceptualization, methodology, investigation, supervision, data curation, resources, formal analysis, software, validation, visualization, writing—original draft preparation, and review and editing.

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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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