Haematuria and urinary tract cancers in patients with atrial fibrillation treated with oral anticoagulants

Rasmussen, Peter Vibe; Dalgaard, Frederik; Gislason, Gunnar Hilmar; Brandes, Axel; Johnsen, Søren Paaske; Grove, Erik Lerkevang; Torp-Pedersen, Christian; Münster, Anne-Marie Bloch; Erikson, Marie Schmidt; Pallisgaard, Jannik Langtved; Blanche, Paul; Hansen, Morten Lock

Published in:
European Heart Journal - Cardiovascular Pharmacotherapy

DOI (link to publication from Publisher):
10.1093/ehjcvp/pvaa045

Publication date:
2021

Document Version
Accepted author manuscript, peer reviewed version

This is a pre-copyedited, author-produced version of an article accepted for publication in European Heart Journal - Cardiovascular Pharmacotherapy following peer review. The version of record Peter Vibe Rasmussen, MD, Frederik Dalgaard, MD, Gunnar Hilmar Gislason, MD, PhD, Axel Brandes, MD, DMSc, Søren Paaske Johnsen, MD, PhD, Erik Lerkevang Grove, MD, PhD, Christian Torp-Pedersen, MD, DMSc, Anne-Marie Bloch Münster, MD, PhD, Marie Schmidt Erikson, MD, Jannik Langtved Pallisgaard, MD, PhD, Paul Blanche, PhD, Morten Lock Hansen, MD, PhD, Hematuria and urinary tract cancers in patients with atrial fibrillation treated with oral anticoagulants, European Heart Journal - Cardiovascular Pharmacotherapy, , pvaa045 is available online at: https://doi.org/10.1093/ehjcvp/pvaa045

Title:

Hematuria and urinary tract cancers in patients with atrial fibrillation treated with oral anticoagulants

Authors and affiliation

Peter Vibe Rasmussen, MD[a], Frederik Dalgaard, MD[a], Gunnar Hilmar Gislason, MD, PhD[a,b,c], Axel Brandes, MD, DMSc[d], Søren Paaske Johnsen, MD, PhD[e], Erik Lerkevang Grove, MD, PhD[f,g], Christian Torp-Pedersen, MD, DMSc[h, i], Anne-Marie Bloch Münster, MD, PhD[j], Marie Schmidt Erikson, MD[k], Jannik Langtved Pallisgaard, MD, PhD[a], Paul Blanche, PhD[a,l], Morten Lock Hansen, MD, PhD[a]

a) Department of Cardiology, Herlev-Gentofte University Hospital, University of Copenhagen, Hellerup, Denmark
b) Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
c) The Danish Heart Foundation
d) Department of Cardiology, Odense University Hospital, Odense Denmark
e) Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
f) Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
g) Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark
h) Department of Clinical Investigations and Department of Cardiology, Nordsjaellands Hospital, Denmark
i) Department of Cardiology, Aalborg University Hospital, Denmark
j) Department of Clinical Biochemistry, Hospital of SouthWest Denmark, University of Southern Denmark, Denmark
k) Department of Urology, Herlev-Gentofte University Hospital, Denmark
l) Department of Biostatistics, Copenhagen University, Copenhagen, Denmark

Short title:

Hematuria and the risk of cancer in anticoagulation therapy.

Word count: 4451

Address for correspondence:

Peter Vibe Rasmussen, Department of Cardiology, Herlev-Gentofte University Hospital, Kildegårdsvej 28, 2900 Hellerup, Denmark, E-mail: peter.vibe.rasmussen@gmail.com

Telephone: (+45) 38 67 38 67

Abstract

Aims

Patients with atrial fibrillation (AF) treated with oral anticoagulants (OAC) have an increased risk of bleeding including hematuria. In the general population gross hematuria is associated with urinary tract cancer. Consequently, we aimed to investigate the potential association between gross hematuria and urinary tract cancer in anticoagulated patients with AF.

Methods and results

Using Danish nationwide registers, we included Danish AF patients treated with OACs between 2001 and 2016. Non-parametric estimation and semi-parametric absolute risk regression were used to estimate the absolute risk of urinary tract cancer in patients with- and without gross hematuria.

We included 125,063 AF patients with a median age of 74 years (interquartile range [IQR] 65-80) and a majority of males (57%). The absolute risk of gross hematuria 12 months after treatment initiation increased with age ranging from 0.37 % (95% Confidence Interval [CI] 0.31 – 0.42) to 0.85 % (95% CI 0.75 – 0.96) in the youngest and oldest age groups of $\leq$ 70 years and > 80 years of age, respectively. The 1-year risk of urinary tract cancer after hematuria ranged from 4.2 % (95% CI 2.6-6.6) to 6.5 % (95% CI 4.6-9.0) for patients in age group > 80 years and 71-80 years, respectively. Gross hematuria conferred large risk ratios of urinary tract cancer when comparing patients with- and without hematuria across all age groups.

Conclusion

Gross hematuria was associated with clinically relevant risks of urinary tract cancer in anticoagulated patients with AF. Thus, underlining the importance of meticulously examining anticoagulated patients with hematuria.

Keywords: Anticoagulants; atrial fibrillation; hematuria; bleeding; cancer

Introduction

Patients with atrial fibrillation (AF) are commonly treated with oral anticoagulants (OAC) to mitigate the risk of thromboembolic complications, but concurrently increasing the risk of bleeding.[1] Bleeding complications related to OACs range from nuisance bleedings (e.g. epistaxis, hemorrhoidal bleeding, bruising) to serious and potentially life-threatening bleeding events, such as gastrointestinal bleeding and intracranial hemorrhage, and to a lesser extent, gross hematuria. Existing evidence regarding the safety of OACs has primarily been focused on intracranial- and gastrointestinal bleedings. Consequently, reports concerning incidence and clinical significance of gross hematuria are scarce.[2,3]

In the general population, gross hematuria is considered a strong marker of potentially malignant lesions of the urinary tract, and guidelines recommend thorough clinical evaluation of these patients.[4–7] Reports have indicated that hematuria in patients using antithrombotic agents, including OACs, could potentially also be associated with yet undiagnosed malignant lesions, especially bladder cancer.[6,8–11] However, these studies are either limited by sample size or not designed for quantifying absolute risks.

Thus, using a nationwide study population including Danish AF patients treated with OACs we sought to 1) estimate the risk of gross hematuria and 2) estimate and quantify the 1-year absolute risk of urinary tract cancer after gross hematuria and compare the risk of cancer to patients without gross hematuria.

Methods

Data sources

All the data analyzed and used in the present study were collected from Danish nationwide administrative and clinical registers. With linkage of these healthcare registers, and a unique personal identification number assigned to all Danish residents, it is possible to follow individuals over time with respect to death, emigration, use of prescription medication, and any hospital or outpatient clinic diagnosis or procedure. The Danish health care system is primarily tax-funded and the enrollment in the administrative registers is mandatory and do not require patient consent.

We used the following registers and databases; The Danish Civil Registration System containing information regarding personal identification number, emigration, and date of birth and death. The Danish National Patient Register (DNPR) holding data on all hospital diagnoses, procedures and operations coded according to the international classification diseases 10th revision (ICD-10).[12] The Danish Registry of Medicinal Product Statistics holding information on all medical prescriptions including the dispensing date, the strength of the drug, and package quantity.[13] The Danish Cancer Register containing high-quality data on the incidence of malignancies (and certain precancerous lesions) in the Danish population including date of diagnosis as well as a range of tumor characteristics.[14]

Study population

We included all Danish patients aged between 18 and 100 years with a diagnosis of AF or atrial flutter (in the following both referred to as AF) between January 1, 2001, and December 31, 2015 and followed them up until December 31, 2016. Patients with a redeemed prescription for any OAC

(i.e. warfarin, phenprocoumon, rivaroxaban, dabigatran or apixaban) were included on the date of their first filled OAC prescription after being diagnosed with AF. Edoxaban was not investigated due to later introduction to the market.[15] Patients were excluded at baseline for the following reasons: not permanently residing in Denmark, any diagnosis of urinary tract malignancy before study inclusion, or a cystoscopy or urography (computed tomography urography or magnetic resonance urography) within two years prior to study inclusion. Furthermore, patients were excluded if they had a potentially different indication for treatment with OACs than AF. As such, we excluded patients with a venous thromboembolic event within six months prior to study inclusion or hip/knee surgery within five weeks prior to study inclusion.

Comorbidity and concomitant medication

Patient comorbidities were defined using primary or secondary hospital diagnoses (ICD-10) identified from any hospital and outpatient clinic contacts in a period of five years prior to study inclusion. We included the following comorbidities: diabetes mellitus, previous bleeding episodes including previous episodes of gross hematuria, chronic kidney disease, chronic obstructive pulmonary disease, previous diagnosis of cancer, ischemic heart disease, congestive heart failure, and ischemic stroke. Diabetes mellitus was defined using prescription fillings for medication specific for treatment of diabetes mellitus. **(Supplementary Table 1)**

Concomitant medical therapy was defined as prescriptions filled at any pharmacy in Denmark in a period of 180 days prior to study inclusion. We included treatment with the following drugs: adenosine diphosphate receptor inhibitors, dipyridamole agents, nonsteroidal anti-inflammatory drugs, acetylsalicylic acid, beta-blockers, calcium-channel antagonists, renin-angiotensin-system inhibitors, loop-diuretics, glucocorticoids, and non-loop diuretics. (**Supplementary Table 2)**

Exposure and outcome variables

The exposure of interest in the study was a diagnosis of gross hematuria. We defined gross hematuria using diagnostic codes (ICD-10) from either hospital admissions or referrals to outpatient clinics in the DNPR. The primary study outcome was a diagnosis of urinary tract cancer (kidney, renal pelvis, ureter, bladder, urethra) or carcinoma in situ identified in the Danish Cancer Register. Stage Ta tumors in the upper and lower urinary tract were considered benign and not included in the study. Furthermore, we investigated a secondary outcome of a performed endoscopic investigation of the urinary tract defined using procedure codes in the DNPR. (Supplementary Table 1)

Statistical methods

Absolute risks of gross hematuria after OAC initiation were estimated non-parametrically (Aalen-Johansen estimator) in age groups accounting for the competing risk of death. Moreover, the risk of hematuria was also investigated by the concomitant treatment with platelet inhibitors at baseline.

For each age group, we estimated the 1-year risk of urinary tract cancer for two groups of patients for every month during follow-up (t-month): those who have not yet experienced gross hematuria and those who have hematuria precisely at a specific month (t-month) during follow-up. The absolute risks of urinary tract cancer for patients experiencing hematuria were estimated exactly at the time of hematuria using a logistic regression model including age group and time since treatment initiation as covariates modeled via restricted cubic splines. The logistic model was fitted using inverse probability of censoring weighting to handle both competing risk of death and censoring.[16] Moreover, the absolute risks of cancer for patients with hematuria were also estimated using a simpler logistic model with age group as the only covariate, thus averaging any potential

effect of treatment duration. The risk of cancer in patients who had not yet experienced gross hematuria at t-months was estimated using landmarking and the Aalen-Johansen estimator accounting for the competing risk of death. This approach has been described in detail previously.[17]

Risk ratios of urinary tract cancer comparing patients with- and without gross hematuria were calculated as the ratios of the estimated risks in each group with 95 % confidence intervals (95% CI). CIs were estimated using the delta method.

The 1-year probability of having an endoscopy performed after hematuria was estimated with the same methods as for urinary tract cancer as outcome.

Comparison to hematuria in non AF patients

A supplemental analysis was performed in which we matched the patients with gross hematuria in our cohort to patients with hematuria from the background population without AF and treatment with OACs. Patients were matched on sex, age, and calendar year on the day of hematuria. The 1-year risk of urinary tract cancer after hematuria was estimated for both groups and depicted graphically.

Adherence to OACs

The study was performed using on-treatment analyses with right censoring of any patient stopping treatment before experiencing gross hematuria. For defining treatment adherence we relied fully on prescription filling patterns. Treatment periods were calculated throughout the follow-up by dividing the number of tablets dispensed with the estimated daily dose, as done previously.[18,19]

Ethics

This study was conducted without active participation from study subjects and no approval from an ethics committee was required according to Danish law. The study is registered and approved by the data responsible institute (Region Hovedstaden (Approval number: P-2019-358)) in accordance with the General Data Protection Regulation (GDPR).

Results

Study population

A total of 125,063 patients were included in the study. (**Supplementary figure S1)** The median age of the study population was 74 years (Interquartile Range [IQR] 65-80), with a majority of male individuals (57%), having a median CHA_2DS_2-VASc score of 3 (IQR 2-4) and a median HASBLED score of 2 (IQR 1-3). **(Table 1 and Supplementary Table 3**) The majority of patients was treated with vitamin-k antagonists (77%), and to a lesser extent dabigatran (12%), rivaroxaban (5%), and apixaban (6%). Out of the 29,164 patients included in the study in treatment with a direct oral anticoagulant, 10,648 (37%) received the drug in a reduced dose. In the cohort, we identified 1900 cases of hematuria and 769 cases of urinary tract cancer during follow-up. The most common malignant lesions found after hematuria in the anticoagulated AF patients were located to the bladder (77%), kidney (16%), and renal pelvis (5%). **(Supplementary Table 4)**

Risk of hematuria

The absolute risk of hematuria after initiation of OACs increased with age group with risk estimates at 12 months after treatment initiation of 0.37 % (95% CI 0.31 – 0.42), 0.63 % (95% CI 0.56-0.71), and 0.85 % (95% CI 0.75 – 0.96) in the age groups of $\leq$ 70 years, 71-80 years, and > 80 years of age, respectively. **(Figure 1)**

Differences in the risks of hematuria between age groups did not change when looking beyond 12 months after treatment initiation. **(Supplementary figure S2)** The risk of hematuria was accentuated by the use of platelet inhibitors. **(Supplementary figure S3)**

Risk of urinary tract cancer

We found no clear indications that the 1-year absolute risk of urinary tract cancer after gross hematuria was dependent on the time elapsed between OAC initiation and hematuria. **(Figure 2)**

Assuming the risk does not depend on the time of hematuria, the 1-year risks of urinary tract cancer estimated at the time of hematuria were 6.0 % (95% CI 3.9-9.1), 6.5 % (95% CI 4.6-9.0), and 4.2 % (95% CI 2.6-6.6) for patients in age groups <70 years, 71-80 years, and >80 years, respectively. **(Figure 3A)**

Conversely, the averaged 1-year risk of urinary tract cancers in patients who have not experienced hematuria during follow-up was 0.2% (95% CI 0.2-0.2), 0.3% (95% CI 0.2-0.3), and 0.2% (95% CI 0.2-0.2) for AF patients aged < 70 years, 71-80 years, and > 80 years, respectively.

Gross hematuria occurred more frequently in men, however, we found no differences in the 1-year risk of urinary tract cancer after hematuria between men and women (P = 0.829). **(Supplementary figure S4)**

When comparing the 1-year risk of urinary tract cancer after gross hematuria in our cohort to a matched sample from the background population with gross hematuria without AF and OAC treatment, we found the risk to be slightly attenuated in OAC treated AF patients. (5.5 % vs. 8.3 %). **(Supplementary figure S5)**

Risk ratios

Comparing patients with- and without gross hematuria we found large risk ratios of urinary tract cancer with risk ratios ranging from 36.3 (95% CI 23.6 – 55.9) to 18.7 (95% CI 11.7 – 29.9) in the youngest and oldest age groups of $\leq$ 70 years and > 80 years of age, respectively. **(Figure 3B)**

Probability of endoscopic investigations after gross hematuria

The 1-year probability of undergoing invasive endoscopic testing after gross hematuria declined with age but was generally high in all age groups ranging from 86.0% (95% CI to 81.1 - 89.8) to 66.5 % (95% CI 61.6 - 71.1) for age groups ≤ 70 years and > 80 years, respectively.

(Supplementary figure S6)

Discussion

In this nationwide cohort of AF patients treated with OACs, we observed that 1) The risk of gross hematuria increased with age, but hospital contact due to hematuria was a relatively uncommon event (< 1% absolute risk during the first year of treatment). 2) The 1-year risks of urinary tract cancer after episodes of gross hematuria were relatively high and clinically relevant in all investigated age groups, bringing further evidence to recommend meticulous clinical examination of gross hematuria in anticoagulated patients.

Bleeding associated with OACs in AF patients has been extensively studied in both randomized clinical trials and observational studies with a primary focus on the potentially life-threatening intracranial hemorrhages and gastrointestinal bleedings with gross hematuria investigated less intensely.[2,18] In an older prospective study the authors were unable to find differences in the occurrence of hematuria between patients treated with OACs and untreated patients.[20] However, more recent and comprehensive evidence has since ascertained an association between the use of antithrombotic medications, including OACs, and hematuria.[10,21] In our study, the risks of hematuria increased with age, however, gross hematuria was still relatively uncommon when comparing to reported risks of gastrointestinal bleeding during OAC treatment.[2,18] However, it should be noted that the risk of hematuria seemed to be accentuated by the concomitant use of platelet inhibitors.

In the general population, gross hematuria is associated with structural lesions of the urinary tract including malignancies, and current guidelines advocate both non-invasive imaging as well as invasive testing (endoscopy) irrespective of the use of antithrombotic medications. [5–7] A few reports

suggest an increased incidence of urinary tract cancers, especially bladder cancer, in anticoagulated patients with hematuria. However, the referenced studies were limited by small sample sizes or were not designed for estimating absolute risks of cancer often necessary for a clinical interpretation of an association. [8–11] In the present study, we included Danish AF patients in treatment with OACs on a nationwide level and found significant absolute risks of malignant lesions associated with gross hematuria in all the examined age groups. Our data support the notion that in an anticoagulated AF population, gross hematuria should be considered a strong marker of potential malignancies of the urinary tract and not merely a consequence of treatment with OACs. Accordingly, these patients should be offered the same diagnostic procedures as patients naïve to antithrombotic agents. Importantly, it has been reported that patients with gross hematuria are not always referred from primary care.[22] However, reassuringly, we found that the probabilities of undergoing invasive testing after gross hematuria were high in the context of the present study.

In several referral series from the general population, the probability of urinary tract cancer after hematuria was reported to be higher (> 10%) than what we currently present (~ 6%). [23,24] Whether this disparity is due to referral bias and selection of patients referred for urology or if treatment with OACs has some influence on the risk of cancer associated with hematuria is unknown. However, when comparing the risk of cancer after hematuria in our cohort with a matched sample from the background population without AF and OACs we found OAC associated hematuria to confer a slightly lower risk of cancer. Nevertheless, the reported risks of cancer after hematuria in anticoagulated patients were still relatively high and very relevant in a clinical context.

A propensity score-matched study from Korea reported a higher proportion of cancer events occurring in patients with hematuria during the first months after initiation of treatment with OACs.[9] Interestingly, we were not able to reproduce this finding. Whether this is a consequence of differences in study populations and referral patterns is unknown. Moreover, differences in study designs makes a direct comparison to our results difficult.

Treatment with OACs often requires complex risk-benefit considerations given the hazards associated with an increasing bleeding risk. Nevertheless, in patients with a clear clinical indication, OACs are associated with improved patient outcomes.[25] Due to the increasing prevalence of AF, and the associated treatment with OACs, the management of bleeding complications in AF patients including gross hematuria is likely to become more frequent in the future.[26]

Our findings strongly emphasize that hematuria should not be regarded as merely a consequence of treatment with OACs, and current guidelines recommending both non-invasive and invasive diagnostic procedures seem appropriate.[6,7]

Strengths and limitations

The major limitations of the current study are all inherent to the observational study design. Data on potential risk factors and clinical variables such as obesity, previous urinary tract infections handled in primary care, and tobacco use were not available. No biochemical data on international standardized ratio or hemoglobin were available.

Furthermore, the treatment with OACs was based on prescription filling patterns and adherence to the drug was assumed when the tablets were available for consumption. The main exposure of the study (gross hematuria) was based on hospital admissions and outpatient clinic visits. Thus, patients

with gross hematuria without a subsequent hospital contact risk not being included in the study and our estimates of hematuria occurrence are possibly subject to some degree of underestimation.

However, with a study design using administrative healthcare registers with complete nationwide coverage, we were generally able to minimize selection bias and able to examine a research question very difficult to include in a clinical trial. Moreover, using a nationwide cohort, our study population is more likely to represent the full spectrum of patients treated with OACs encountered in daily clinical practice contrasting the strict inclusion criteria of clinical trials. The Danish registers employed are generally of high quality and have been used and validated extensively for research purposes.[12,27–31]

Conclusion

In this nationwide observational cohort study including all AF patients in Denmark treated with OACs we were able to describe clinically significant absolute risks of urinary tract cancer associated with gross hematuria. The present study brings further evidence to support that hematuria in anticoagulated AF patients should not be dismissed as merely a consequence of treatment with OACs. Oppositely, all eligible patients should be examined for a potential malignant underlying cause.

Acknowledgements and Funding

This work was supported by an unrestricted grant from Bristol-Myers Squibb (Denmark) and Pfizer (Denmark) [No grant number available].

Conflicts of interest

PVR, FD, ME, JLP, AMB, and PB declare no conflicts of interests. AB has received consulting fees from Bayer, Bristol-Myers Squibb, and MSD. GG has received grants from Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, and Bayer. ELG has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, MSD, Portola Pharmaceuticals and Roche, and research grants from Boehringer Ingelheim. SPJ has received speaker honoraria from Bayer, Bristol-Myers Squibb, and Pfizer, has participated in advisory board meeting for Bayer, Bristol-Myers Squibb and Pfizer, and received research grants from Bristol-Myers Squibb and Pfizer. CTP has received support from Bayer not related to this study. MLH has received grants and speaker honoraria from Bristol-Myers Squibb.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.

2. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet Lond Engl* 2014;**383**:955–962.

3. Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GYH. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ* 2016;**353**:i3189.

4. Jones R, Latinovic R, Charlton J, Gulliford MC. Alarm symptoms in early diagnosis of cancer in primary care: cohort study using General Practice Research Database. *BMJ* 2007;**334**:1040.

5. Kaag MG, Raman JD. Clinical guidelines: Clearing murky water - a guideline-based approach to haematuria. *Nat Rev Urol* 2016;**13**:243–244.

6. Nielsen M, Qaseem A, High Value Care Task Force of the American College of Physicians. Hematuria as a Marker of Occult Urinary Tract Cancer: Advice for High-Value Care From the American College of Physicians. *Ann Intern Med* 2016;**164**:488–497.

7. Babjuk M, Burger M, Compérat EM, Gontero P, Mostafid AH, Palou J, Rhijn BWG van, Rouprêt M, Shariat SF, Sylvester R, Zigeuner R, Capoun O, Cohen D, Escrig JLD, Hernández V, Peyronnet B, Seisen T, Soukup V. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ) - 2019 Update. *Eur Urol* 2019;**76**:639–657.

8. Ripley TL, Havrda DE, Blevins S, Culkin D. Early evaluation of hematuria in a patient receiving anticoagulant therapy and detection of malignancy. *Pharmacotherapy* 2004;**24**:1638–1640.

9. Yu HT, Kim T-H, Uhm J-S, Kim J-Y, Pak H-N, Lee M-H, Joung B. Clinical Significance of Hematuria in Atrial Fibrillation With Oral Anticoagulation Therapy. *Circ J Off J Jpn Circ Soc* 2017;**81**:158–164.

10. Wallis CJD, Juvet T, Lee Y, Matta R, Herschorn S, Kodama R, Kulkarni GS, Satkunasivam R, Geerts W, McLeod A, Narod SA, Nam RK. Association Between Use of Antithrombotic Medication and Hematuria-Related Complications. *JAMA* 2017;**318**:1260–1271.

11. Avidor Y, Nadu A, Matzkin H. Clinical significance of gross hematuria and its evaluation in patients receiving anticoagulant and aspirin treatment. *Urology* 2000;**55**:22–24.

12. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–490.

13. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;**39**:38–41.

14. Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health* 2011;**39**:42–45.

15. Pottegård A, Grove EL, Hellfritzsch M. Use of direct oral anticoagulants in the first year after market entry of edoxaban: A Danish nationwide drug utilization study. *Pharmacoepidemiol Drug Saf* 2018;**27**:174–181.

16. Scheike TH, Zhang M-J, Gerds TA. Predicting cumulative incidence probability by direct binomial regression. *Biometrika* 2008;**95**:205–220.

17. Rasmussen PV, Dalgaard F, Gislason GH, Brandes A, Johnsen SP, Grove EL, Torp-Pedersen C, Dybro L, Harboe L, Münster A-MB, Pedersen L, Blanche P, Pallisgaard JL, Hansen ML. Gastrointestinal bleeding and the risk of colorectal cancer in anticoagulated patients with atrial fibrillation. *Eur Heart J* 2020;ehz964.

18. Lamberts M, Staerk L, Olesen JB, Fosbøl EL, Hansen ML, Harboe L, Lefevre C, Evans D, Gislason GH. Major Bleeding Complications and Persistence With Oral Anticoagulation in Non- Valvular Atrial Fibrillation: Contemporary Findings in Real- Life Danish Patients. *J Am Heart Assoc* 2017;**6**:e004517.

19. Olesen JB, Lip GYH, Kamper A-L, Hommel K, Køber L, Lane DA, Lindhardsen J, Gislason GH, Torp-Pedersen C. Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease. *N Engl J Med* 2012;**367**:625–635.

20. Culclasure TF, Bray VJ, Hasbargen JA. The significance of hematuria in the anticoagulated patient. *Arch Intern Med* 1994;**154**:649–652.

21. Bhatt NR, Davis NF, Nolan WJ, Flynn RJ, McDermott T, Thomas AZ, Manecksha RP. Incidence of Visible Hematuria Among Antithrombotic Agents: A Systematic Review of Over 175,000 Patients. *Urology* 2018;**114**:27–32.

22. Nieder AM, Lotan Y, Nuss GR, Langston JP, Vyas S, Manoharan M, Soloway MS. Are patients with hematuria appropriately referred to Urology? A multi-institutional questionnaire based survey. *Urol Oncol Semin Orig Investig* 2010;**28**:500–503.

23. Edwards TJ, Dickinson AJ, Natale S, Gosling J, Mcgrath JS. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. *BJU Int* 2006;**97**:301–305.

24. Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. *J Urol* 2000;**163**:524–527.

25. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation. *Ann Intern Med* 2007;**146**:857.

26. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, Ferranti SD de, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation* 2017;**135**:e146–e603.

27. Rix TA, Riahi S, Overvad K, Lundbye-Christensen S, Schmidt EB, Joensen AM. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. *Scand Cardiovasc J SCJ* 2012;**46**:149–153.

28. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open* 2016;**6**:e012832.

29. Rasmussen PV, Dalgaard F, Hilmar Gislason G, Torp-Pedersen C, Piccini J, D'Souza M, Ruwald MH, Pallisgaard JL, Hansen ML. Amiodarone treatment in atrial fibrillation and the risk of incident cancers: A nationwide observational study. *Heart Rhythm* 2020;**17**:560–566.

30. Rasmussen PV, Skov MW, Ghouse J, Pietersen A, Hansen SM, Torp-Pedersen C, Køber L, Haunsø S, Olesen MS, Svendsen JH, Melgaard J, Graff C, Holst AG, Nielsen JB. Clinical implications of electrocardiographic bundle branch block in primary care. *Heart Br Card Soc* 2019;**105**:1160–1167.

31. **Validation of the Danish Cancer Registry** https://sundhedsdatastyrelsen.dk/-/media/sds/filer/registre-og-services/nationale-sundhedsregistre/sygedomme-laegemidler-og-behandlinger/cancerregisteret/valideringsrapport-cancerregisteret-english-abstract.pdf?la=da. (Accessed 16 April 2020)

Figure legends

Figure 1

Absolute risk of gross hematuria after initiation of oral anticoagulants during the first 12 months of treatment depicted by age groups. The X-axis depicts months in treatment and the y-axis shows the risk in percentage.

Figure 2

Plots of 1-year absolute risks of urinary tract cancer for patients who have experienced hematuria in treatment (blue) estimated with cubic restricted splines (knots at quantiles), versus patients who have not yet experienced hematuria (red). The y-axis depicts absolute 1-year risks of urinary tract cancer (%) with 95% confidence intervals. The X-axis depicts time in anticoagulation treatment in months.

Figure 3

A: Forest plot depicting the absolute 1-year risk of urinary tract cancer in patients with gross hematuria, estimated at the time of hematuria, averaged over time in anticoagulation treatment. The X-axis depicts absolute 1-year risks of urinary tract cancer in percentage with 95 % confidence intervals with age groups on the y-axis.

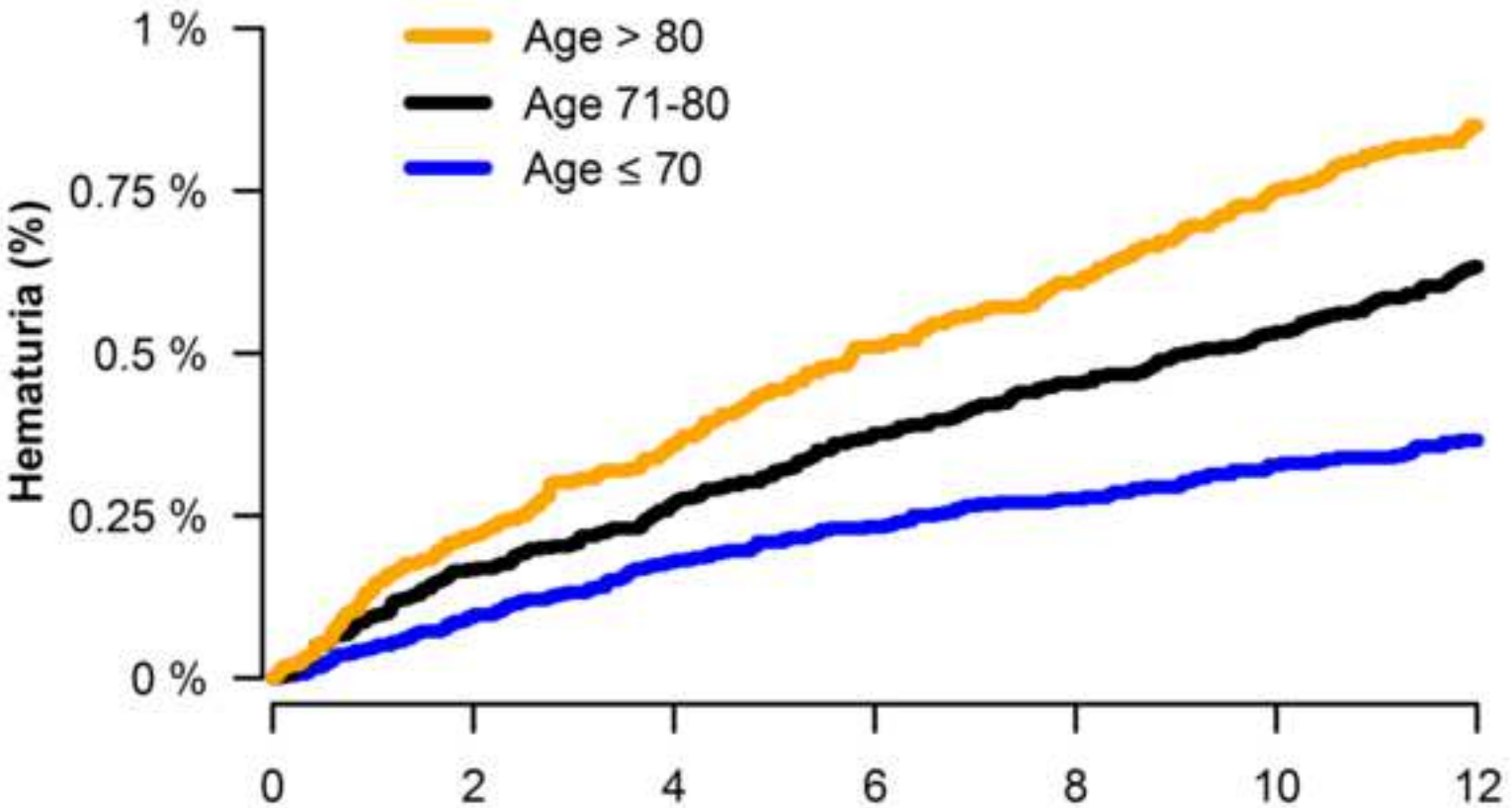
B: Forest plot depicting the risk ratios of urinary tract cancer between patients with- and without gross hematuria by age group. The x-axis illustrates the risk ratios with 95% confidence intervals with age groups on the y-axis.

Table 1 **Baseline characteristics**	N = 125,063
Male sex (%)	70,889 (57)
Age (median [IQR])	74 (65-80)
Comorbidity	
Heart failure (%)	22,612 (18)
Ischemic heart disease (%)	18,939 (15)
Ischemic stroke (%)	18,682 (15)
Previous cancer (%)	11,360 (9)
COPD (%)	13,619 (11)
Diabetes Mellitus (%)	14,745 (12)
Chronic kidney disease (%)	4802 (4)
Previous bleeding episodes (%)	8018 (7)
Previous hematuria (%)	538 (0.4)
CHA_2DS_2-VASc (%)	
0 – 1	19,996 (16)
2	23,760 (19)
3	28,944 (23)
> 3	52,363 (42)
Medication	
Vitamin-K antagonist (%)	95,899 (77)
Dabigatran (%)	14,643 (12)
Rivaroxaban (%)	6657 (5)
Apixaban (%)	7864 (6)
Betablocker (%)	84,720 (68)
Calcium Antagonist (%)	38,794 (31)
Dipyrimidole agent (%)	4199 (3)
ASA (%)	53,254 (43)
ADP-inhibitor (%)	8751 (7)

NSAID (%)	19,758 (16)
Glucocorticoids (%)	10,777 (9)

Abbreviations: IQR, InterQuartile Range; ASA, acetylsalicylic acid; ADP-Inhibitor, Adenosine diphosphate receptor inhibitor; NSAID, Nonsteroidal anti-inflammatory drugs; OAC, Oral anticoagulant therapy; GI, Gastrointestinal; COPD: Chronic obstructive pulmonary disease

Figure 1



At Risk				
Age ≤ 70:	47172	45317	36965	32205
Age 71-80:	44338	41726	34524	30918
Age > 80:	33553	29910	23600	20390

Figure 2

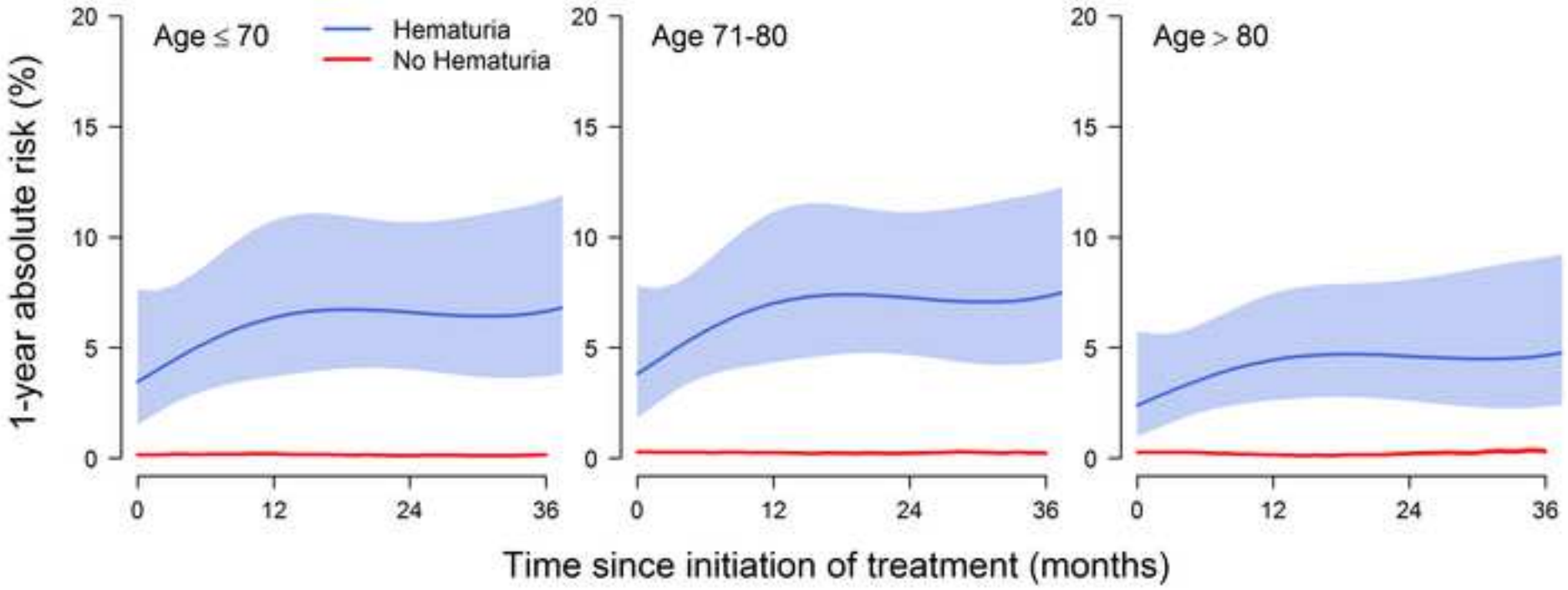


Figure 3