I.F.C. Italian Federation of Cardiology

Direct oral Xa inhibitors versus warfarin in patients with cancer and atrial fibrillation: a meta-analysis

Matteo Casula[a,b], Federico Fortuni[a,b], Francesca Fabris[a,b], Sergio Leonardi[a,b], Massimiliano Gnecchi[a,b], Antonio Sanzo[a], Alessandra Greco[c] and Roberto Rordorf[a]

Aims **Patients with cancer are at higher risk of atrial fibrillation, thromboembolic complications and bleeding events compared with the general population. The aim of the present meta-analysis was to compare the efficacy and safety of direct oral Xa inhibitor anticoagulants versus warfarin in patients with cancer and atrial fibrillation.**

Methods **We searched electronic databases for randomized controlled trials comparing direct oral Xa inhibitor anticoagulants and warfarin in cancer patients. The primary efficacy outcome was stroke or systemic embolism. The primary safety outcome was major bleeding. A subgroup analysis was performed to explore the outcome differences between patients with active cancer or history of cancer.**

Results **Three trials with a total of 3029 cancer patients were included in the analysis. There was no statistically significant difference in the risk of stroke or systemic embolism [risk ratio (RR) 0.76; 95% confidence interval (CI) 0.52–1.10] between the two therapeutic strategies. Direct oral Xa inhibitors significantly reduced the incidence of major bleeding compared with warfarin (RR 0.79; 95% CI 0.63–0.99; $P = 0.04$; number needed to treat = 113). These results were consistent both in patients with active cancer and in those with history of cancer.**

Conclusion **In patients with cancer and atrial fibrillation, direct oral Xa inhibitors have a similar efficacy and may be safer compared with warfarin. These results are consistent both in patients with active cancer and history of cancer.**

J Cardiovasc Med 2020, **21**:570–576

Keywords: atrial fibrillation, cancer, oral anticoagulant therapy

[a]Coronary Care Unit and Laboratory of Clinical and Experimental Cardiology, Fondazione IRCCS Policlinico San Matteo, [b]Department of Molecular Medicine, University of Pavia and [c]Division of Cardiology - Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Correspondence to Matteo Casula, MD, Coronary Care Unit and Laboratory of Clinical and Experimental Cardiology, Fondazione IRCCS Policlinico San Matteo Viale Camillo Golgi 19, 27100, Pavia, Italy
Tel: +39 382 5011; fax: +39 382 501640; e-mail: matt.casula@gmail.com

Received 17 April 2020 **Revised** 5 May 2020
Accepted 31 May 2020

Introduction

Patients with cancer are at higher risk of atrial fibrillation compared with the general population.[1–3] Furthermore, cancer per se and anticancer treatments have been associated with thromboembolic complications and increased bleeding risk.[4–6] The best strategy to prevent embolic events in cancer patients with atrial fibrillation has not yet been defined. Considering the frequent need for invasive procedures, drug-to-drug interactions with antineoplastic agents and fluctuations in vitamin K absorption because of common liver function abnormalities, mucositis and diarrhea, antivitamin K anticoagulants have several limitations in this context. Moreover, only about 12% of cancer patients treated with warfarin are able to achieve an international normalized ratio (INR) stably in the therapeutic range.[7–9] Direct oral anticoagulants (DOACs) may represent a valid alternative because of the more predictable dose–response relationship, shorter half-life and fewer drug and food interactions compared with warfarin. Nonetheless, their use in this population has been scarcely investigated. In particular, no randomized controlled trials (RCTs) have directly compared DOACs with warfarin in patients with atrial fibrillation and cancer, even if some post hoc analysis of RCTs[10–12] and observational studies[13–18] have been conducted. Furthermore, to our knowledge, no previous review has ever evaluated outcome differences between patients with active cancer and those with history of cancer. Therefore, the aim of this study was to compare the efficacy and safety of DOACs versus warfarin in patients with cancer and atrial fibrillation. Moreover, we investigated whether there was any difference according to the presence of active cancer or history of cancer. In order to obtain the most stringent estimate of treatment effects, we excluded observational studies from the analyses.

Methods

The present study was conducted following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[19]

Data sources, search strategy and eligibility criteria

We searched MEDLINE, EMBASE and Cochrane electronic databases up to September 2019 for original data

DOI:10.2459/JCM.0000000000001041

from RCTs, published in peer-reviewed journals, in English language, that compared the efficacy and safety outcomes of DOACs versus warfarin in patients with cancer and atrial fibrillation. The keywords searched included 'atrial fibrillation', 'AF', 'nonvalvular atrial fibrillation', 'malignancy', 'cancer', 'anticoagulant', 'warfarin', 'vitamin-K antagonist' (VKA), 'direct oral anticoagulant', 'novel oral anticoagulant', 'oral thrombin inhibitors', 'oral factor Xa inhibitors', 'dabigatran', 'rivaroxaban', 'apixaban' and 'edoxaban'. The references of all identified articles were reviewed to look for additional studies of interest. Two investigators independently conducted the search and the study selection (M.C. and F.Fa.); the disagreements were solved by consensus.

Data extraction and quality assessment

Data were extracted by the first author and were assessed for completeness and accuracy by a second reviewer (F.Fo.). The extracted data were collected in a dedicated electronic database and included: study details, patients characteristics, medications, cancer site, atrial fibrillation form (i.e. paroxysmal or persistent), risk scores ($CHADS_2$, CHA_2DS_2-VASc and HAS-BLED), safety and efficacy outcomes (complete details on the extracted data are available in the Supplemental Digital Content – data extracted, http://links.lww.com/JCM/A291). The quality of the included RCTs was assessed using the Cochrane risk of bias assessment.[20]

Outcomes

The primary efficacy outcome was stroke or systemic embolism. The secondary efficacy outcomes were ischemic stroke, myocardial infarction, venous thromboembolism (VTE), all-cause death and cardiovascular death. The primary safety outcome was major bleeding; secondary safety outcomes were major or clinically relevant nonmajor bleeding, intracranial bleeding, fatal or life-threatening bleeding and any bleeding. Outcome events were defined based on the definition used in each original trial. Furthermore, the net clinical benefit was estimated as the sum of stroke, systemic embolism and major bleeding.

Statistical analysis

The extracted data were analyzed using the open-source statistical software ProMeta 3 and Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The heterogeneity across the included studies was evaluated by using the Cochrane Q, Tau^2 and I^2 statistics. I^2 index describes the percentage of total variation across the studies that is because of heterogeneity rather than chance. I^2 values of 25, 50, and 75% were attributed to small, moderate, and large amounts of heterogeneity. Considering the non-negligible clinical heterogeneity across the included studies, the effect size was estimated using a random-effect model as risk ratio (RR) and relative 95% confidence interval (CI). For the endpoints that differed significantly in the two groups (i.e. $P < 0.05$), absolute risk reduction (ARR) or increase and number needed to treat (NNT) or to harm (NNH) were calculated. A subgroups analysis was performed to assess the consistency of our results between patients with active cancer and those with history of cancer, as defined in the included studies (Table 1). A leave-out-one sensitivity analysis was performed to evaluate the influence of each study on the pooled results. Moreover, two sensitivity analyses based on fixed effect model and incidence rate ratio were performed. A univariate meta-regression was conducted to examine the impact of age, BMI, female sex, $CHADS_2$, CHA_2DS_2-VASC, HAS-BLED scores, use of ACE inhibitors or angiotensin receptor blockers, aspirin, beta blockers, prior use of VKA, prevalence of diabetes, heart failure, arterial hypertension, prior stroke, transient ischemic attack (TIA) or systemic embolism, type of atrial fibrillation, cancer site and follow-up duration on the outcomes of interest. According to the Cochrane handbook[20] considering the small number of studies included in the analysis the publication bias was not evaluated.

Table 1 **Study characteristics**

First author	Year of publication	Original trial	Number of patients with cancer	Treatment	Control	Primary efficacy outcome	Primary safety outcome	Active cancer definition	Median follow-up (years)
Chen	2019	ROCKET AF	640	Rivaroxaban (20 mg or 15 mg OD)	Warfarin	All-cause stroke or SE	Major or CRNMB	'Actively treated cancer' (if receiving cancer treatment with hormonal or ChT agents)	1.9
Melloni	2017	ARISTOTLE	1236	Apixaban (5 mg or 2.5 mg b.i.d.)	Warfarin	Stroke or SE	MB (ISTH)	'Active (or recent) cancer' (active or treated within the past 1 year)	1.8
Fanola	2018	ENGAGE AF-TIMI 48	1153	Edoxaban (60 mg or 30 mg OD)	Warfarin	Time to 1st stroke or SE	MB (ISTH)	Postrandomization 'new or recurrent malignancy'	2.8

b.i.d., bis in die; ChT, chemotherapy; CRNMB, clinically relevant nonmajor bleeding; ISHT, international society of thrombosis and haemostasis; MB, major bleeding; OD, once a day; SE, systemic embolism.

Table 2 Population characteristics

Original trial	Age (years)	Female (%)	BMI (kg/m^2)	Prior stroke, TIA or SE (%)	Hypertension (%)	Heart failure (%)	Prior use of VKA (%)	ASA (%)	PAF (%)	$CHADS_2$	CHA_2DS_2-VASc	HAS-BLED
ROCKET AF	72.2	39.7	28.2	54.7	90.5	62.5	62.4	36.5	17.6	3.5	–	2.8
ARISTOTLE	70.3	35.2	–	19.5	87.5	35.4	57.2	30.9	–	2.1	3.4	1.7
ENGAGE AF-TIMI 48	72.1	37.6	28.7	28.3	93.6	57.4	59.0	–	25.4	2.8	4.3	2.5

ACEi, ACE inhibitors; ARBs, angiotensin receptor blockers; ASA, aspirin; BB, beta blockers; PAF, paroxysmal atrial fibrillation; SE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin K antagonists.

Results

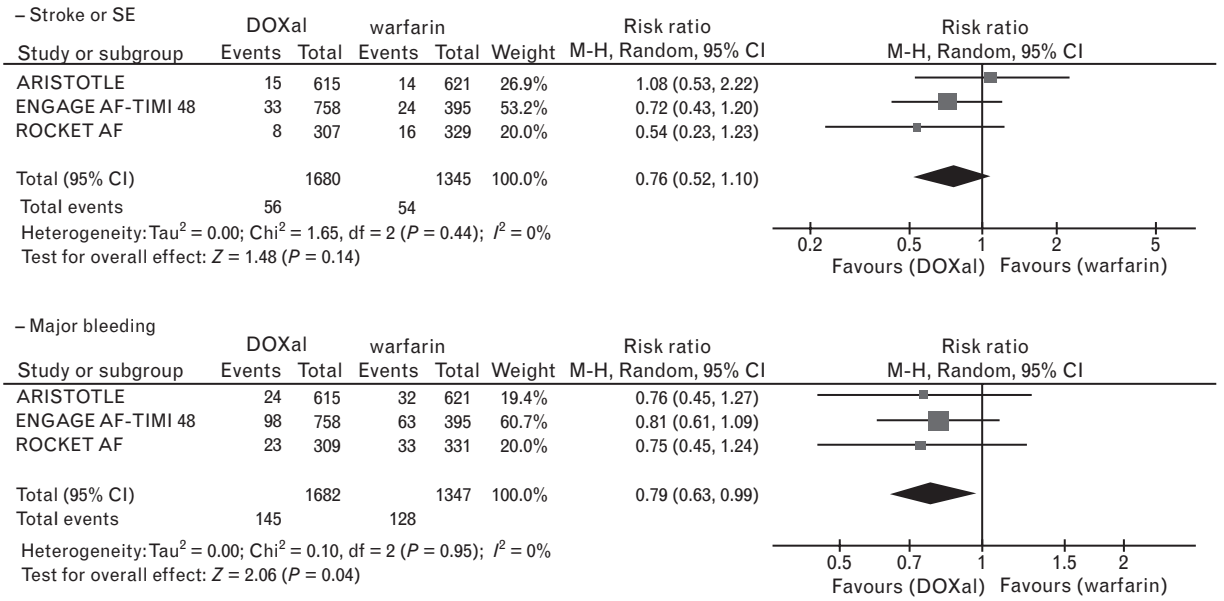
Included studies

Four hundred and fifty-two records were retrieved through database searching and 35 studies were assessed as full text for potential eligibility. Three post hoc analysis of three RCTs[10–12] on direct Xa oral inhibitors were included in the final analysis (Figure S1 – Supplemental Digital Content, http://links.lww.com/JCM/A291). No data regarding cancer patients on dabigatran were found. Characteristics of the included studies and patients are presented in Table 1 and Table 2, respectively (for more details see Supplemental Digital Content Table S1 and Table S2, http://links.lww.com/JCM/A291). Mean age for the included population was 75.6 ± 1.2 years, and 32% were women. Mean follow-up period was 2.2 ± 0.6 years. Mean $CHADS_2$ score was 2.9 ± 0.6 and the mean HAS-BLED score was 2.6 ± 0.4. Table S3 (Supplemental Digital Content, http://links.lww.com/JCM/A291) presents the frequencies of the different cancer sites in the included studies. The most common cancer sites were prostate (23%), gastrointestinal tract (22.2%), breast (12.1%) and genitourinary tract (10.6%). The risk of bias assessment showed high quality for all the studies included.

Efficacy outcomes

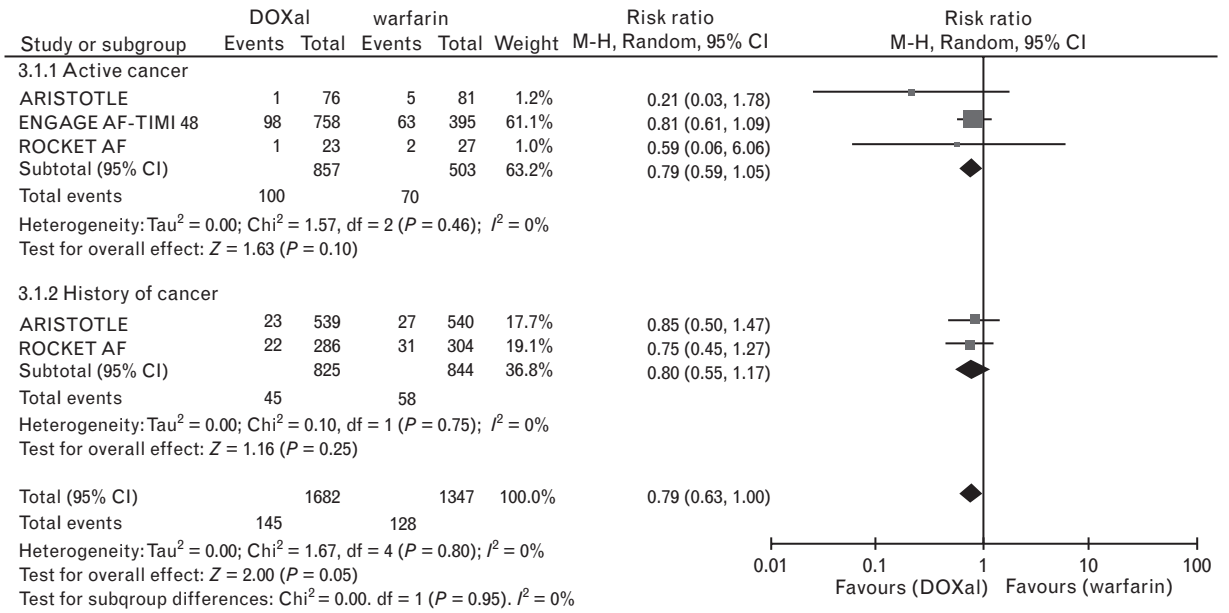
All the three studies included reported data on the efficacy primary outcome. There was no statistically significant difference in the risk of stroke or systemic embolism (RR 0.76; 95% CI 0.52–1.10) in cancer patients treated with direct oral Xa inhibitors versus warfarin (Fig. 1). The risk of ischemic stroke, myocardial infarction, VTE, all-cause death and cardiovascular death were also not significantly different in patients with cancer treated with direct oral Xa inhibitors versus those treated with warfarin (Table S4 – Supplemental Digital Content, http://links.lww.com/JCM/A291). These results were consistent across patients with active cancer and those with history of cancer (Figure S2, Supplemental Digital Content, http://links.lww.com/JCM/A291) and, overall, across the performed sensitivity analyses (Table S5 and S6 – Supplemental Digital Content, http://links.lww.com/JCM/A291). The meta-regression did

Fig. 1



Stroke or systemic embolism and major bleeding in patients with cancer [direct oral Xa inhibitors (DOXal) versus warfarin].

Fig. 2



Major bleeding in subgroups (active cancer and history of cancer) [direct oral Xa inhibitors [DOXal] versus warfarin].

not show any significant impact of age, BMI, female sex, risk scores, concomitant drugs, medical history, cancer site and follow-up duration on the effect size.

Safety outcomes

Direct oral Xa inhibitors significantly reduced the risk of major bleeding compared with warfarin in the study population [RR 0.79; 95% CI 0.63–0.99; $P = 0.04$ (Fig. 1); NNT 113]. This finding was consistent between subgroups of patients with active cancer or history of cancer ($Chi^2 = 0{,}00$; $P = 0.95$) (Fig. 2) and, overall, across the performed sensitivity analyses (Tables S5 and S6 - Supplemental Digital Content, http://links.lww.com/JCM/A291). Direct oral Xa inhibitors significantly reduced also intracranial bleeding in the cancer population (RR 0.12; 95% CI 0.02–0.63; $P = 0.013$; NNT 68) compared with warfarin. No statistically significant differences were found for all the other safety secondary outcomes (Table S4 – Supplemental Digital Content, http://links.lww.com/JCM/A291). As for the efficacy outcomes, all the performed meta-regressions did not show any significant impact of the potential moderators on the effect size.

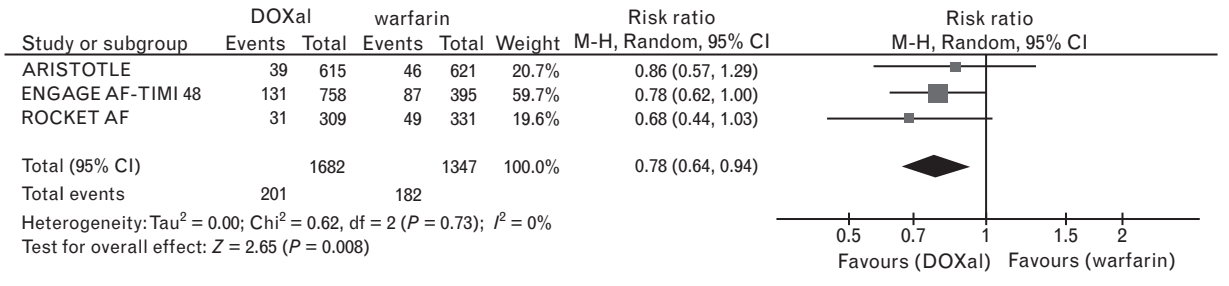
Subgroup analysis

Our findings were consistent between patients with active cancer and those with history of cancer for all the studied outcomes (Figure S2 and S3 – Supplemental Digital Content, http://links.lww.com/JCM/A291).

Net clinical benefit

The risk for the composite of stroke, systemic embolism or major bleeding was significantly lower for patients with atrial fibrillation and cancer treated with direct oral Xa inhibitors compared with those treated with warfarin [RR 0.78; 95% CI 0.64–0.94; $P = 0.008$ (Fig. 3); NNT 64].

Fig. 3



Net clinical benefit [direct oral Xa inhibitors (DOXal) versus warfarin].

Discussion

Our study-level meta-analysis pooled data from three post hoc analyses of RCTs[10–12] comparing the efficacy and safety of direct oral Xa inhibitors versus warfarin in patients with atrial fibrillation and cancer. The analyses showed that the use of direct oral Xa inhibitors exerts similar protection against thromboembolic events compared with warfarin but is associated with a lower risk of major bleedings. As demonstrated for the general population,[10–12] direct oral Xa inhibitors reduced also the risk of intracranial bleeding in cancer patients. These results were consistent both in patients with active cancer and in those with history of cancer and led to a significantly higher net clinical benefit of direct oral Xa inhibitors compared with warfarin (NNT 64).

Our finding could be explained by the fact that warfarin has several limitations compared with DOACs, which are magnified in patients with cancer and atrial fibrillation. As a matter of fact, chemotherapeutic drugs have strong pharmacologic interaction with warfarin and cancer patients have often liver function abnormalities, mucositis and diarrhea leading to fluctuations in vitamin K absorption.[7–9] Indeed, it has been reported that in the real world, only around 12% of patients with cancer treated with warfarin are able to obtain an INR stably in the therapeutic range.[7] DOACs, because of a more predictable dose–response relationship, shorter half-life and the less important drug and food interactions compared with warfarin, can overcome many of these drawbacks. Nevertheless, no clinical or pharmacokinetic data are yet available on the interactions between DOACs and most antineoplastic drugs as summarized in the European Heart Rhythm Association practical guide on the use of nonvitamin K antagonist oral anticoagulant for atrial fibrillation.[21]

We conducted for the first time a subgroup analysis to evaluate any differences in the incidence of safety and efficacy outcomes between patients with active cancer and those with history of cancer. This analysis confirmed that our findings were consistent in both populations for all the studied outcomes. Although further dedicated studies are needed, our data suggest a more favorable net clinical benefit of DOACs compared with warfarin in both active cancer patients and those with history of cancer.

Outside of cancer, DOACs have already been evaluated in several other conditions associated with an increased thrombotic and hemorrhagic risk and in which warfarin has known limitations. A recent meta-analysis evaluating the efficacy and safety of DOAC versus vitamin K antagonists in the elderly ($\geq$75 years) observed a significant reduction in systemic embolism in favor of DOACs versus vitamin K antagonists. In the same analysis, DOACs reduced the risk of intracranial bleeding, hemorrhagic stroke, and fatal bleeding.[22] Although, there are very few randomized data in patients with chronic kidney disease (CKD), in two recent meta-analyses of observational studies, DOACs showed a significant reduction in stroke and systemic embolism in patients with atrial fibrillation and CKD, as well as a reduction in major bleeding, when compared with warfarin.[23,24] The Food and Drug Administration approved the use of reduced-dose dabigatran (75 mg twice daily) in patients with atrial fibrillation and a creatinine clearance of 15–29 ml/min, as well as the use of apixaban (5 mg twice daily) in stable atrial fibrillation patients on hemodialysis.[25] A further category of patients with atrial fibrillation at increased thrombotic risk are those with concomitant vascular disease. These patients, whether they have coronary artery disease (CAD) or peripheral artery disease (PAD), are usually also treated with antiplatelet therapy after an acute event or percutaneous intervention, increasing their bleeding risk.[26,27] In patients with atrial fibrillation and concomitant CAD, recent systematic reviews and meta-analyses showed the superiority of a DOAC-strategy in relation to a vitamin K antagonist-strategy with regard to the risk of bleeding.[28–30] Only a few patients with PAD were enrolled in ROCKET-AF[31] and ENGAGE AF-TIMI 48.[32] The incidence of major or clinically relevant nonmajor bleeding was higher for patients with PAD who were treated with rivaroxaban than with warfarin. On the other hand, among patients receiving edoxaban or warfarin, there was no interaction between treatment and PAD status with regard to major bleeding.[33] Our results, alongside the previous considerations, highlight that DOACs could be considered at least as effective and perhaps safer than warfarin even in complex patients such as the elderly and patients with CKD, CAD or PAD.

Many issues are still unsettled in the management of anticoagulant therapy in patients with atrial fibrillation and cancer and there are no guidelines concerning the use of DOACs in this population. Cancer patients are extremely heterogeneous, and this impacts the choice regarding the best anticoagulation strategy. Different types of cancer lead to different risks of thromboembolic and bleeding events; tumor staging, time from cancer diagnosis and antitumoral drugs may also influence these risks.[34] There is evidence that some novel antineoplastic drugs themselves (e.g. ibrutinib) are independent risk factors for the development of incident atrial fibrillation.[35] In this context also drug interactions play a role of paramount importance in the choice of the specific anticoagulant drug. Considering the high number of variables involved, we think that further studies are needed in order to optimize the stratification of thromboembolic and bleeding risk and to define the best anticoagulant strategy for each patient. The currently available tools, apart from $HEMORR_2HAGES$ score, do not consider whether a neoplastic disease is present, and no one considers its characteristics. The ability of the

$CHADS_2$ and CHA_2DS_2-VASc scores to predict cerebral ischemic events in cancer patients with atrial fibrillation is still under investigation.[36–38] To our best knowledge, no bleeding risk stratification tool has been validated in this specific population even if $HEMORR_2HAGES$ and ABC scores, in addition to the HAS-BLED score, are frequently used for this purpose. Moreover, close attention must be paid to certain high-risk features, such as intracranial metastases, severe thrombocytopenia, or actively bleeding high-risk cancer.[39] In a real-world study, among 394 cancer patients with confirmed atrial fibrillation diagnosis, only 155 patients (40%) were treated with anticoagulant therapy (21.9% with oral anticoagulants and 78.1% with low-molecular-weight heparin).[40] The general under-prescription reported in this study highlights the safety concerns in the anticoagulation management of these patients in the clinical practice, requiring further targeted studies.

Despite the open questions mentioned above, taking into account the results of our analysis and the limitations of warfarin in patients with cancer, direct oral Xa inhibitors may represent an alternative option safer and at least as effective as warfarin in this population. Moreover, our results add important information suggesting that the efficacy and safety of direct oral Xa inhibitors are similar in patients with active cancer and those with inactive cancer. Dedicated RCTs and real-world studies are needed to shed light on this topic.

Limitations

Our study has some limitations. First, we chose to include in our analysis only data from RCTs introducing an intrinsic selection bias. Trial populations are indeed strictly selected, and the external validity of their results is not guaranteed. This limitation is particularly important for the post hoc analysis of the ROCKET AF trial in which patients with a life expectancy of less than 2 years were excluded. However, we think that the overall consistence of our results also in the active cancer population (i.e. patients who mostly developed cancer after their enrollment in the RCT) can mitigate this limitation. Second, we had no access to the individual patient data, and therefore, conducted a study-level analysis to evaluate the outcomes. Third, patients across the included studies were heterogeneous and this may result in uncontrolled confounding. Further studies are, therefore, needed in order to better define the more appropriate strategy for each patient within a high inter-individual heterogeneity. This high heterogeneity and the limited data available prevented us from performing a subgroup analysis to evaluate outcomes in different types of cancer and to evaluate the effect of different drugs and doses. Moreover, considering the small number of included studies, the results of the meta-regressions conducted to examine the impact of potential moderators on the effect size are limited. The protocol of this systematic review and meta-analysis was not prespecified. The inclusion of three post hoc analyses of RCTs limits the extent of our results to the entire cancer population with atrial fibrillation. Finally, no data were available on the use of dabigatran for patients with atrial fibrillation and cancer, so we could not extend our analysis to the direct oral thrombin inhibitors.

Conclusion

In patients with cancer and atrial fibrillation, direct oral Xa inhibitors have similar efficacy and may be safer compared with warfarin. These results are consistent both in patients with active cancer and history of cancer. No data fulfilling our inclusion criteria were available on the use of dabigatran in patients with cancer and atrial fibrillation.

Acknowledgements

I thank Antonietta Loi for giving me the opportunity to conceive this work. Authors' contributions: The first author had the first idea for this work, designed the protocol, conducted the search and study selection, collected and analyzed data, drafted this manuscript and decided to submit it for publication. F.Fa. conducted search study selection, assessed for completeness and accuracy of data extracted and revised critically the manuscript. F.Fo. solved disagreement in the study section, assessed for completeness and accuracy of data extracted, reviewed statistical analysis and revised critically the manuscript. All the authors critically analyzed the data and revised the manuscript with important intellectual contributions and approved its final version before submission.

Conflicts of interest

There are no conflicts of interest.

References

1 Conen D, Wong JA, Sandhu RK, *et al.* Risk of malignant cancer among women with new-onset atrial fibrillation. *JAMA Cardiol* 2016; **1**:389–396.
2 Saliba W, Rennert HS, Gronich N, Gruber SB, Rennert G. Association of atrial fibrillation and cancer: analysis from two large population-based case-control studies. *PLoS One* 2018; **13**:e0190324.
3 Kim CH, Al-Kindi SG, Oliveira GH. Atrial fibrillation and cancer—validation in the real world. *JAMA Cardiol* 2017; **2**:343.
4 Zamorano JL, Lancellotti P, Rodriguez Muñoz D, *et al.* 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines. *Eur Heart J* 2016; **37**:2768–2801.
5 Felicetti F, Fortunati N, Brignardello E. Cancer survivors: an expanding population with an increased cardiometabolic risk. *Diabetes Res Clin Pract* 2018; **143**:432–442.
6 Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JGP, Büller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol* 2000; **18**:3078–3083.
7 Rose AJ, Sharman JP, Ozonoff A, Henault LE, Hylek EM. Effectiveness of warfarin among patients with cancer. *J Gen Intern Med* 2007; **22**:997–1002.
8 Vranckx P, Valgimigli M, Heidbuchel H. The significance of drug–drug and drug–food interactions of oral anticoagulation. *Arrhythmia Electrophysiol Rev* 2018; **7**:55–61.

9 Lee Y-J, Park J, Uhm J-S, *et al.* Bleeding risk and major adverse events in patients with cancer on oral anticoagulation therapy. *Int J Cardiol* 2016; **203**:372–378.
10 Chen ST, Hellkamp AS, Becker RC, *et al.* Efficacy and safety of rivaroxaban vs. warfarin in patients with nonvalvular atrial fibrillation and a history of cancer: observations from ROCKET AF. *Eur Hear J - Qual Care Clin Outcomes* 2019; **5**:145–152.
11 Melloni C, Dunning A, Granger CB, *et al.* Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and a history of cancer: insights from the ARISTOTLE Trial. *Am J Med* 2017; **130**:1440.e1–1448.e1.
12 Fanola CL, Ruff CT, Murphy SA, *et al.* Efficacy and Safety of Edoxaban in Patients With Active Malignancy and Atrial Fibrillation: Analysis of the ENGAGE AF - TIMI 48 Trial. *J Am Heart Assoc* 2018; **7**:e008987; doi:10.1161/JAHA.118.008987.
13 Ording AG, Horváth-Puhó E, Adelborg K, Pedersen L, Prandoni P, Sørensen HT. Thromboembolic and bleeding complications during oral anticoagulation therapy in cancer patients with atrial fibrillation: a Danish nationwide population-based cohort study. *Cancer Med* 2017; **6**:1165–1172.
14 Laube ES, Yu A, Gupta D, *et al.* Rivaroxaban for stroke prevention in patients with nonvalvular atrial fibrillation and active cancer. *Am J Cardiol* 2017; **120**:213–217.
15 Russo V, Rago A, Papa A, *et al.* Use of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with malignancy: clinical practice experience in a single institution and literature review. *Semin Thromb Hemost* 2018; **44**:370–376.
16 Ianotto J-C, Couturier M-A, Galinat H, *et al.* Administration of direct oral anticoagulants in patients with myeloproliferative neoplasms. *Int J Hematol* 2017; **106**:517–521.
17 Shah S, Norby FL, Datta YH, *et al.* Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. *Blood Adv* 2018; **2**:200–209.
18 Kim K, Lee Y-J, Kim T-H, *et al.* Effect of nonvitamin K antagonist oral anticoagulants in atrial fibrillation patients with newly diagnosed cancer. *Korean Circ J* 2018; **48**:406.
19 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PLoS Med* 2009; **6**:e1000097.
20 Higgins JP, Green S. In: Higgins JP, Green S, editors. *Cochrane handbook for systematic reviews of interventions*. Chichester, UK: John Wiley & Sons Ltd; 2008.
21 Steffel J, Verhamme P, Potpara TS, *et al.* The 2018 European Heart Rhythm Association Practical Guide on the use of nonvitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018; **39**:1330–1393.
22 Silverio A, Di Maio M, Prota C, *et al.* Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation [published online ahead of print, 2019 Dec 12]. *Eur Heart J Cardiovasc Pharmacother* 2019;vz073; doi:10.1093/ehjcvp/pvz073.
23 Andò G, Capranzano P. Nonvitamin K antagonist oral anticoagulants in atrial fibrillation patients with chronic kidney disease: a systematic review and network meta-analysis. *Int J Cardiol* 2017; **231**:162–169.
24 Malhotra K, Ishfaq MF, Goyal N, *et al.* Oral anticoagulation in patients with chronic kidney disease. *Neurology* 2019; **92**:e2421–e2431.
25 Ferrari F, da Silveira AD, Martins VM, Franzoni LT, Zimerman LI, Stein R. Direct-Acting Oral Anticoagulants in Atrial Fibrillation: What's New in the Literature [published online ahead of print, 2020 Apr 23]. *Cardiol Rev* 2020;10; doi:10.1097/CRD.0000000000000312.
26 Valgimigli M, Bueno H, Byrne RA, *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2018; **39**:213–260.
27 Aboyans V, Ricco J-B, Bartelink M-LEL, *et al.* 2017 ESC Guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2018; **39**:763–816.
28 Gargiulo G, Goette A, Tijssen J, *et al.* Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of nonvitamin K antagonist oral anticoagulant-based randomiz. *Eur Heart J* 2019; **40**:3757–3767.
29 Fortuni F, Ferlini M, Leonardi S, *et al.* Dual versus triple therapy in patients on oral anticoagulants and undergoing coronary stent implantation: a systematic review and meta-analysis. *Int J Cardiol* 2018; **273**:80–87.
30 Lopes RD, Hong H, Alexander JH. Antithrombotic therapy after acute coronary syndrome and/or percutaneous coronary intervention in atrial fibrillation: finding the sweet spot. *Eur Heart J* 2019; **40**:3768–3770.
31 Patel MR, Mahaffey KW, Garg J, *et al.*, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**:883–891.
32 Giugliano RP, Ruff CT, Braunwald E, *et al.*, ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; **369**:2093–2104.
33 Stacy ZA, Richter SK. Direct oral anticoagulants for stroke prevention in atrial fibrillation: treatment outcomes and dosing in special populations. *Ther Adv Cardiovasc Dis* 2018; **12**:247–262.
34 Navi BB, Reiner AS, Kamel H, *et al.* Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol* 2017; **70**:926–938.
35 Fradley MG, Gliksman M, Emole J, *et al.* Rates and risk of atrial arrhythmias in patients treated with ibrutinib compared with cytotoxic chemotherapy. *Am J Cardiol* 2019; **124**:539–544.
36 Patell R, Gutierrez A, Rybicki L, Khorana AA. Usefulness of CHADS2 and CHA2DS2-VASc scores for stroke prediction in patients with cancer and atrial fibrillation. *Am J Cardiol* 2017; **120**:2182–2186.
37 D'Souza M, Carlson N, Fosbøl E, *et al.* CHA 2 DS 2 -VASc score and risk of thromboembolism and bleeding in patients with atrial fibrillation and recent cancer. *Eur J Prev Cardiol* 2018; **25**:651–658.
38 Hu YF, Liu CJ, Chang PMH, *et al.* Incident thromboembolism and heart failure associated with new-onset atrial fibrillation in cancer patients. *Int J Cardiol* 2013; **165**:355–357.
39 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**:1336–1349.
40 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.