DR AURÉLIEN DELLUC (Orcid ID : 0000-0003-0227-1245)

DR TZU-FEI WANG (Orcid ID : 0000-0003-2407-9000)

DR CIHAN AY (Orcid ID : 0000-0003-2607-9717)

Article type : Recommendations and Guidelines

Anticoagulation of cancer patients with non-valvular atrial fibrillation receiving chemotherapy: guidance from the SSC of the ISTH

Aurelien Delluc A[1], Tzu-Fei Wang[2], Eng-Soo Yap[3],Cihan Ay[4], Jordan Schaefer[5], Marc Carrier[1], Simon Noble[6]

[1] Department of Medicine, Ottawa Hospital Research Institute at the University of Ottawa, Ontario, Canada.

[2] Division of Hematology, Department of Internal Medicine, Ohio State University Wexner Medical Center, Columbus.

[3] Department of Haematology-Oncology National University Cancer Institute, National University Health System, Singapore.

[4] Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, Comprehensive Cancer Center Vienna, Vienna, Austria.

[5] Division of Hematology and Oncology, University of Michigan, Ann Arbor, Michigan, USA.

[6] Marie Curie Palliative Care Research Centre, Cardiff University, Cardiff, Wales, UK.

Corresponding author:

Simon Noble,

Marie Curie Palliative Care Research Centre

8th Floor Neuadd Meirionydd

Cardiff University

Heath Park

Campus

CF14 4YS

Wales, UK

Email: NobleSI1@wales.nhs.uk

Telephone: 02920687500

Fax: 02920687501

Abstract

Background

Approximately 4% of cancer patients have non-valvular atrial fibrillation (NVAF) and require anticoagulation for prophylaxis against embolic stroke. One third of these may receive

chemotherapy, which will further increase the risk of bleeding and thrombosis. Furthermore, many chemotherapeutic agents interact with commonly used anticoagulants, which may affect their safety and efficacy.

The paucity of data may explain why no guidelines exist to advise on the management of anticoagulation during chemotherapy for patients with NVAF or even which anticoagulant should be used.

Methods

The Scientific and Standardization Committee for Malignancy and Hemostasis of the International Society for Thrombosis and Hemostasis has reviewed the data around NVAF and cancer in order to produce a guidance document to better inform clinicians. Where no data exists, other patient populations or clinical scenarios have been reviewed and cautiously used to develop management suggestions.

Results

Five guidance statements are included. Two statements are recommendations, reflecting a strong guidance statement and three are suggestions reflecting a weak guidance statement.

Conclusion

There is a very little evidence to inform the management of anticoagulation for NVAF during chemotherapy. Most guidance suggestions are extrapolated from other populations. An individualised approach to decision making is essential and should take into consideration the aims of chemotherapy and patient preferences and values. **BACKGROUND:**

Atrial fibrillation is the most common cardiac arrhythmia, affecting approximately 1.5–2% of the general population, increasing by a further 1.8% in the presence of cancer (1). Atrial fibrillation becomes more prevalent with age and increases the overall risk of embolic stroke five-fold (2, 3). Anticoagulation has long been established as the most effective way to prevent

embolic stroke but this is challenging in the cancer setting since it is associated with a higher rate of clinically relevant non-major and major bleeding (4). Cancer patients often have additional risk factors for bleeding, independent of anticoagulation, including thrombocytopenia, use of non-steroidal anti-inflammatory drugs or antiplatelets agents or renal dysfunction (5).

Approximately one-third of all cancer patients will receive chemotherapy (6). This poses further risks to the safety and efficacy of anticoagulation, depending on the choice of anticoagulant. Firstly, it is well established that many chemotherapeutic agents increase the risk of both arterial and venous thrombosis. Secondly, chemotherapy regimens may independently increase the risk of bleeding, especially those which induce thrombocytopenia (5). The increasing use of targeted anticancer therapies such as tyrosine kinase inhibitors (TKI) and monoclonal antibodies targeting vascular endothelial growth factor (VEGF) can be associated with an increased risk of bleeding due to off-target kinase inhibition resulting in platelet dysfunction (7, 8) or the inhibition of angiogenesis pathways. Finally, all anticoagulants that are licenced for non-valvular atrial fibrillation (NVAF) have potential to interact with some chemotherapy and supportive care drugs, increasing the risk of bleeding or stroke depending on their metabolic pathways.

Chemotherapy can further increase the risk of developing NVAF; cisplatin, melphalan and cyclophosphamide appear to be associated with a risk of 15 to 30% (1). Similarly, monoclonal antibodies (e.g. trastuzumab) and targeted cancer therapies (e.g. ibrutinib) are associated with an increased incidence of NVAF due to their off-target effects (9-11). Compared with those without, cancer patients with new onset NVAF have a 2 fold increased risk of thromboembolism (12).

Clinical decision-making tools to inform anticoagulation in NVAF are well established in the general population and embedded in clinical practice (13-15). Whilst tools such as CHA2DS2-VASC, HAS-BLED and HEMORR2HAGES are validated to stratify according to stroke or bleeding risk in NVAF, they do not take into consideration the additional risks conferred by the malignant state, the heterogeneity of cancer or the varying thrombotic/ bleeding risks associated with chemotherapy. The BleedMAP score is derived from retrospective analysis of 2484 cases of oral

anticoagulant interruptions and is the only bleeding risk tool to include cancer as an independent risk factor (HR, 1.8; 95% CI, 1.0–3.1) (16). There are very little data to accurately quantify the risk of ischaemic stroke due to cancer. One study using Surveillance Epidemiology and End Results (SEER) Medicare linked data of 279,719 patients with a new primary diagnosis of breast, lung, prostate, colorectal, bladder, pancreatic and gastric cancer observed a 1 year stroke incidence up to 6.3% (17). Another study using data of 327,389 newly diagnosed cancer patients showed the risk of stroke differed between different cancers with a 1-year cumulative stroke incidence of 3.6% (prostate), 3.9% (breast), 4.7% (colorectal) and 8.1% (lung) (18).

In summary, the management of anticoagulation regimens in cancer patients receiving chemotherapy is unclear. There are no current guidelines recommendations and wide variation in clinical practice.

Current evidence for anti-thrombotic therapy in non-valvular atrial fibrillation in cancer patients

There are limited data regarding anticoagulation for cancer patients with NVAF receiving chemotherapy. Consequently in formulating these guidance statements, data from other populations or clinical scenarios have been extrapolated and considered in the context of:

- Efficacy (stroke prevention)
- Safety (major bleeding, clinically relevant non major bleeding)
- Drug-drug interactions (chemotherapy and supportive care drugs)
- Patient preference and quality of life

Vitamin K antagonists

Vitamin K antagonists (VKA) such as warfarin reduce the risk of stroke by two-thirds in patients with NVAF when compared to patients on aspirin or placebo (19). However, cancer patients receiving warfarin be it for NVAF or venous thromboembolism (VTE) have worse

anticoagulation control and worse outcomes compared with cancer-free controls, including a six-fold increase in bleeding rates (20-22). Furthermore, the development of cancer in patients on long-term warfarin is associated with a significant reduction in the time in therapeutic range (TTR), particularly within the first six months of cancer diagnosis (23). Moreover, its use is further complicated through food and drug-drug interactions by the following mechanisms:

- Induction or inhibition of cytochrome P450 isozymes
- Displacement of binding from plasma proteins
- Alterations in vitamin K status

Despite these challenges, warfarin has been the mainstay of anticoagulation for NVAF for many years. Warfarin requires frequent monitoring of the INR, which has been shown to have a negative impact on quality of life (24).

Direct oral anti-coagulants (DOACs)

Four DOACs are approved and indicated for stroke/systemic embolism prevention in patients with NVAF, although their approval for use varies across countries. These include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban and edoxaban. The advantages of DOACs include predictable pharmacokinetics, and rapid onset and offset, which facilitate the management of anticoagulation in case of invasive procedure. Several trials have demonstrated that DOACs are at least as effective as warfarin in the prevention of stroke/systemic embolism in patients with NVAF (25-28). A meta-analysis of these trials showed that DOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (Relative Risk (RR) 0.81; 95% CI 0.73–0.91; P<0.0001) which was mainly due to a reduction in hemorrhagic stroke (RR 0.49; 95% CI 0.38–0.64; P<0.0001) (29). DOACs also reduced all-cause mortality (0·90, 0·85-0·95; p=0·0003) and intracranial haemorrhage (0·48, 0·39-0·59; p<0·0001), but increased gastrointestinal bleeding (1·25, 1·01-1·55; p=0·04).

Most of these studies excluded cancer patients directly (RELY and ENGAGE studies) or indirectly (ROCKET AF and ARISTOLE studies), by excluding patients with an expected survival less than 1 or 2 years. Therefore, whether these results could be extrapolated to cancer patients is unknown. However, secondary analyses of these studies in patients with or without

a history of cancer, or in patients who developed cancer after enrollment have shed some light on DOAC use in the cancer population. In the ROCKET AF study, the efficacy and safety of rivaroxaban and warfarin in 460 patients with history of cancer were similar to those in patients without cancer (30). In the ATRISTOLE study, the safety and efficacy advantages of apixaban over warfarin in patients without a history of cancer were preserved in those with a cancer history (31). Similarly, a recent analysis of the ENGAGE AF-TIMI 48 trial identified 1153 patients who developed new or recurrent malignancy after randomization and revealed that edoxaban was as effective and safe as warfarin in this subgroup (32).

A recent comparative effectiveness analysis of DOACs versus warfarin in 16,096 cancer patients with AF identified in the MarketScan database showed that the risk of bleeding and ischemic stroke in patients receiving DOACs was similar to that with warfarin, except for apixaban which was associated with a lower risk of bleeding. Furthermore, all DOACs were shown to have reduced risk of VTE complications compared with warfarin (33). As with all retrospective claims database analyses, the results need to be interpreted with caution.

All DOACs are substrates for the excretory permeability glycoprotein (P-gp) system, whilst only apixaban and rivaroxaban are also mainly metabolized via hepatic cytochrome P450 (CYP) 3A4. As such, the use of DOACs concomitantly with drugs that are inhibitors or inducers of P-gp or CYP3A4 might result in variability in the extent of anticoagulation, as well as potentially affecting cancer therapies. This potential drug-drug interaction was taken into account in the HOKUSAI cancer-VTE study, where patients with cancer-associated VTE assigned to edoxaban received a reduced dose when they also received concomitant treatment with potent P-glycoprotein inhibitors (34). Specific attention to potential interactions with cancer therapy should be made when choosing a DOAC for stroke/systemic embolism prevention in NVAF patients with cancer. Where cancer therapies exert strong induction/ inhibition of both P-gp and CYP3A4, it would make sense to observe caution with all DOACs, whilst interaction with P-gp alone should alert caution to just apixaban and rivaroxaban.

One final consideration should be the application of bleeding data from studies comparing DOACs with LMWH for the treatment and secondary prophylaxis of VTE (34, 35). Based on major bleeding data, caution is advised when using DOACs in patients with “luminal

gastrointestinal cancers with an intact primary-or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis or colitis" (36). Intuitively it would seem sensible to observe a similar caution with anticoagulation for NVAF, particularly during chemotherapy when the risk of bleeding is higher.

Low Molecular Weight Heparin (LMWH)

There is little evidence to support the use of LMWH for long-term stroke prophylaxis in patients with NVAF regardless of the presence of cancer or not. Data are limited to its use as a perioperative-bridging agent for patients on warfarin (37). Despite demonstrating non-inferiority compared with placebo with respect to stroke events, LMWH bridging was associated with a threefold increase in bleeding compared with placebo (38).

It is a matter of debate as to whether perioperative bridging data are sufficient to justify using LMWH to "bridge" anticoagulation during chemotherapy. In these studies, patients rarely received LMWH for more than two weeks (38). Since many chemotherapy regimens are given over several months, it is difficult to surmise whether long-term use of once daily LMWH for this indication will be effective or safe.

Owing to the paucity of data supporting the use of LMWH to prevent embolic stroke in NVAF, its long-term use for other conditions has also been reviewed. Data from the use of LMWH for treatment of cancer associated VTE give some indication of bleeding risks, assuming similar doses are used for stroke prophylaxis. The use of data form those studies also has the advantage that many patients with metastatic disease who were receiving chemotherapy were included. In a meta-analysis of eight studies comparing LMWH with warfarin, the major bleeding rate with LMWH and warfarin was 4.3% and 4.1% respectively (39).

Clinical decision-making and patient preferences

The heterogeneity of cancer extends beyond the disease, and its stage and treatment. When making decisions about treatment regimens that have competing attributes (in this case the risk of stroke and risk of bleeding) clinicians have a responsibility to consider these within the context of individual patient preferences and values. These are likely to be influenced by

their previous experiences, understanding and wishes for the future. Quality of life studies regarding anticoagulation and cancer have predominantly focused on the treatment and secondary prophylaxis of VTE. These have suggested LMWH to be acceptable within the context of the cancer journey, in part, because patients place most value on anticoagulants that interfere least with their cancer treatment (40-42). However, whilst anticoagulation for VTE may be time limited, for NVAF it is usually indefinite. Arguably convenience in relation to quality of life takes an even greater emphasis when choosing an anticoagulant for NVAF. Most patients on long-term anticoagulation will prefer oral rather than parenteral medication, although they may will be willing to accept parenteral medication in the short term if indicated e.g. during chemotherapy. Studies also suggest that patients place considerable trust in the advice of their clinicians, highlighting the importance of exploring what matters most to patients.

In keeping with the mantra "Primum non nocere", it would be remiss not to consider whether there are situations where the possible benefit from chemotherapy may be less than the harm from more serious complications associated with NVAF, its co-morbidities and complicating stable anticoagulation. The use of adjuvant chemotherapy is standard in many cancer regimens because of established benefits in terms of overall and progression free survival (43). For some cancers however, the survival improvements may only be modest and when balanced against an unfavourable toxicity profile, the role of adjuvant treatments has been controversial (44). In such patients receiving anticoagulation therapy for NVAF, particularly those with high CHA2DS2-VASC, HAS-BLED scores; the increased risk of bleeding, stroke and drug-drug interactions may pose a greater threat to mortality/ morbidity than the benefits afforded by the chemotherapy.

Finally, even when the risk /benefit ratio favours the concomitant use of anticoagulants and SACT, it is important to recognise that the risk profiles of bleeding and stroke are not static entities; they will change over time according to alterations in platelet count, associated co-morbidities and disease response. As such, the use of both chemotherapy and anticoagulation should be regularly evaluated according to changes in treatment plans and clinical status.

Clinical decision making/ choice of DOAC

The initial phase of clinical decision-making will center on i) whether anticoagulation is indicated and ii) the class of anticoagulant to be used. Based on current published data for DOAC use across various indications, it is clear that the four DOACS licensed for NVAF have sufficient clinical differences that it would be remiss to recommend them as a class without considering circumstances which may favor one over another. Table 1 offers a comparative summary of characteristics, which may be considered when choosing one agent over another. For example trial and observational data suggest that apixaban may be safer with respect to GI bleeding risk, whilst rivaroxaban and edoxaban have the strongest phase 4 published data. Furthermore, whilst all DOACS have interaction potential with P-gp, edoxaban arguably has the most robust evidence base with respect to dose reduction in the presence of P-gp drugs, since this was prespecified in ENGAGE-AF and HOKUSAI and HOKUSAI-Cancer studies. However, it should be noted that new data continues to emerge, especially with respect to safety outcomes.

Guidance statements

The guidance statements included in this document are predicated on the following premises:

- For each of the clinical situations described herein, these guidance statements are applicable to an average patient using standard, licenced doses. There may be exceptional circumstances for which these guidance statements do not apply and anticoagulant management, including drug dosing and frequency, would be at the treating physician's discretion.
- The wording 'we recommend' reflects a strong guidance statement, whereby the clinician should adopt the practice in most cases.
- The wording 'we suggest' reflects a weak guidance statement, whereby the clinician may adopt the practice in some cases and that an alternative practice also may be acceptable.

Guidance Statement

1) We recommend individualized anticoagulation regimens after shared decision-making with patients, based wherever possible on risk of stroke, bleeding and patient values.
2) In cancer patients with NVAF already on an anticoagulant regimen before starting chemotherapy, we recommend continuing the same anticoagulation regimen unless there are clinically relevant drug-drug interactions.
    a. In cancer patients on chemotherapies with clinically relevant VKA interactions, we suggest considering a DOAC if no additional drug-drug interactions with DOAC or close monitoring of VKA (target INR between 2 and 3).
    b. In cancer patients on chemotherapies unable to tolerate an oral route of administration (e.g. nausea and vomiting), we suggest the use of parenteral anticoagulation with therapeutic dosing of LMWH with resumption of oral anticoagulation as soon as possible.
3) In cancer patients on chemotherapy with newly diagnosed NVAF, with the exception of patients with luminal gastrointestinal cancers with an intact primary or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis or colitis we suggest the use of a DOAC over a VKA or LMWH as anticoagulant therapy if no clinically relevant drug-to-drug interactions are expected.

Addendum

All authors contributed to the concept, design, data interpretation, writing of the manuscript, and final approval of the submitted version.

Acknowledgements

M. Carrier is the recipient of Tier 2 Research Chair from the University of Ottawa in Cancer and Thrombosis. S. Noble holds a Marie Curie Chair in Supportive and Palliative Care from Cardiff University.

Disclosure

Dr. Aurelien Delluc reports he has participated as a member of Advisory Board for Sanofi Aventis, Leo Pharma, Bayer, and Pfizer/Bristol-Myers Squibb, has received speaker honoraria from Bayer, Pfizer/Bristol-Myers Squibb, LEO Pharma, and is participating in or has participated in a clinical trial within the past two years with Leo Pharma, Bristol-Myers Squibb, Bayer; Dr. Tzu-Fei Wang reports non-financial support from Daiichi Sankyo during the conduct of the study; other from Pfizer/BMS, outside the submitted work; Drs. Eng-Soo Yap participated as a member of an Advisory Board for Novartis and received speaker honorarium from Bayer, Leo Pharma, Novartis and Sanofi; Dr. Cihan Ay reports he has participated as a member of Advisory Board for: Bayer, Daiichi-Sankyo, BMS/Pfizer, and Boehringer Ingelheim has received speaker honoraria from Bayer, Daiichi-Sankyo, BMS/Pfizer, and Sanofi; Dr. Jordan Schaefer reports no conflict interest during the conduct of the study; Dr. Marc Carrier reports he has participated as a member of Advisory Board for: Sanofi Aventis, Leo Pharma, Bayer, Aspen, and Pfizer, has received speaker honoraria from Bayer, Pfizer, LEO Pharma, Sanofi, Boehringer Ingelheim, and Servier, and is participating in or has participated in a clinical trial within the past two years with Leo Pharma, Bristol-Myers Squibb, Bayer, and Octapharma; Dr. Simon Noble reports he has received speaker's bureau fees from Pfizer, Daiichi Sankyo, and Bayer, and advisory board fees from Daiichi Sankyo.

References

1. Tufano A, Galderisi M, Esposito L, Trimarco V, Sorriento D, Gerusalem G, et al. Anticancer Drug-Related Nonvalvular Atrial Fibrillation: Challenges in Management and Antithrombotic Strategies. Semin Thromb Hemost. 2018;44(4):388-96.

2. Flegel KM, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. Lancet. 1987;1(8532):526-9.

3. Wolf PA, Dawber TR, Thomas HE, Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology. 1978;28(10):973-7.

4. Johnstone C, Rich SE. Bleeding in cancer patients and its treatment: a review. Annals of palliative medicine. 2018;7(2):265-73.

5. Avvisati G, Tirindelli MC, Annibali O. Thrombocytopenia and hemorrhagic risk in cancer patients. Crit Rev Oncol Hematol. 2003;48(Suppl):S13-6.

6. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA: a cancer journal for clinicians. 2016;66(4):271-89.

7. Shatzel JJ, Olson SR, Tao DL, McCarty OJT, Danilov AV, DeLoughery TG. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. J Thromb Haemost. 2017;15(5):835-47.

8. Tullemans BME, Heemskerk JWM, Kuijpers MJE. Acquired platelet antagonism: off-target antiplatelet effects of malignancy treatment with tyrosine kinase inhibitors. J Thromb Haemost. 2018;16(9):1686-99.

9. Wang SY, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP, et al. Cardiovascular events, early discontinuation of trastuzumab, and their impact on survival. Breast cancer research and treatment. 2014;146(2):411-9.

10. Brown JR, Moslehi J, O'Brien S, Ghia P, Hillmen P, Cymbalista F, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017;102(10):1796-805.

11. Wiczer TE, Levine LB, Brumbaugh J, Coggins J, Zhao Q, Ruppert AS, et al. Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. Blood Adv. 2017;1(20):1739-48.

12. Hu YF, Liu CJ, Chang PM, Tsao HM, Lin YJ, Chang SL, et al. Incident thromboembolism and heart failure associated with new-onset atrial fibrillation in cancer patients. Int J Cardiol. 2013;165(2):355-7.

13. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006;151(3):713-9.

14. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100.

15. D'Souza M, Carlson N, Fosbol E, Lamberts M, Smedegaard L, Nielsen D, et al. CHA2DS2-VASc score and risk of thromboembolism and bleeding in patients with atrial fibrillation and recent cancer. European journal of preventive cardiology. 2018;25(6):651-8.

16. Tafur AJ, McBane R, 2nd, Wysokinski WE, Litin S, Daniels P, Slusser J, et al. Predictors of major bleeding in peri-procedural anticoagulation management. J Thromb Haemost. 2012;10(2):261-7.

17. Navi BB, Reiner AS, Kamel H, Iadecola C, Okin PM, Elkind MSV, et al. Risk of Arterial Thromboembolism in Patients With Cancer. J Am Coll Cardiol. 2017;70(8):926-38.

18. Navi BB, Reiner AS, Kamel H, Iadecola C, Elkind MS, Panageas KS, et al. Association between incident cancer and subsequent stroke. Annals of neurology. 2015;77(2):291-300.

19. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine. 2007;146(12):857-67.

20. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller 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(17):3078-83.

21. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Patient characteristics associated with oral anticoagulation control: results of the Veterans AffaiRs Study to Improve Anticoagulation (VARIA). J Thromb Haemost. 2010;8(10):2182-91.

22. Rose AJ, Sharman JP, Ozonoff A, Henault LE, Hylek EM. Effectiveness of warfarin among patients with cancer. J Gen Intern Med. 2007;22(7):997-1002.

23. Ambrus DB, Reisman JI, Rose AJ. The impact of new-onset cancer among veterans who are receiving warfarin for atrial fibrillation and venous thromboembolism. Thromb Res. 2016;144:21-6.

24. Noble SI, Finlay IG. Is long-term low-molecular-weight heparin acceptable to palliative care patients in the treatment of cancer related venous thromboembolism? A qualitative study. Palliative medicine. 2005;19(3):197-201.

25. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51.

26. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093-104.

27. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-92.

28. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-91.

29. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-62.

30. Chen ST, Hellkamp AS, Becker RC, Berkowitz SD, Breithardt G, Fox KAA, et al. Efficacy and Safety of Rivaroxaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation and a History of Cancer: Observations from ROCKET AF. European heart journal Quality of care & clinical outcomes. 2018.

31. Melloni C, Dunning A, Granger CB, Thomas L, Khouri MG, Garcia DA, 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(12):1440-8.e1.

32. Fanola CL, Ruff CT, Murphy SA, Jin J, Duggal A, Babilonia NA, et al. Efficacy and Safety of Edoxaban in Patients With Active Malignancy and Atrial Fibrillation: Analysis of the ENGAGE AF-TIMI 48 Trial. Journal of the American Heart Association. 2018;7(16).

33. Shah S, Norby FL, Datta YH, Lutsey PL, MacLehose RF, Chen LY, et al. Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. Blood Adv. 2018;2(3):200-9.

34. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med. 2018;378(7):615-24.

35. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With

Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Oncol. 2018:Jco2018788034.

36. Khorana AA, Noble S, Lee AYY, Soff G, Meyer G, O'Connell C, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost. 2018.

37. Steinberg BA, Peterson ED, Kim S, Thomas L, Gersh BJ, Fonarow GC, et al. Use and outcomes associated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Circulation. 2015;131(5):488-94.

38. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. N Engl J Med. 2015;373(9):823-33.

39. Vedovati MC, Giustozzi M, Verdecchia P, Pierpaoli L, Conti S, Verso M, et al. Patients with cancer and atrial fibrillation treated with doacs: A prospective cohort study. Int J Cardiol. 2018.

40. Noble S, Matzdorff A, Maraveyas A, Holm MV, Pisa G. Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology. Haematologica. 2015;100(11):1486-92.

41. Noble S, Prout H, Nelson A. Patients' Experiences of LIving with CANcer-associated thrombosis: the PELICAN study. Patient preference and adherence. 2015;9:337-45.

42. Seaman S, Nelson A, Noble S. Cancer-associated thrombosis, low-molecular-weight heparin, and the patient experience: a qualitative study. Patient preference and adherence. 2014;8:453-61.

43. Partridge AH, Burstein HJ, Winer EP. Side effects of chemotherapy and combined chemohormonal therapy in women with early-stage breast cancer. Journal of the National Cancer Institute Monographs. 2001(30):135-42.

44. Chovanec M, Hanna N, Cary KC, Einhorn L, Albany C. Management of stage I testicular germ cell tumours. Nature reviews Urology. 2016;13(11):663-73.

DOAC	Once or twice a day	Renal elimination	Hepatic elimination	CYP3A4 interaction	P-gp substrate	Strength of RCT data for CAT	Strength of real world data for cancer and NVAF	Bleeding risk in cancer/ NVAF
Apixaban	b.d.	27%	73%	+	+	+	+	+
Dabigatran	b.d.	80%	20%	-	+	+	+	++
Edoxaban	o.d.	50%	50%	-	+	+++	++	++
Rivaroxaban	o.d.	35%	65%	+	+	++	++	++

Table 1: Comparison of different attributes between different DOACs when considering anticoagulation for NVAF in the patients with cancer

NVAF=non valvular atrial fibrillation, CAT=cancer associated thrombosis, RCT=randomised control trial, P-gp =P glycoprotein, CYP3A4= Cytochrome P450 3A4