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RECOMMENDATIONS AND GUIDELINES

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

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1 | BACKGROUND

Atrial fibrillation is the most common cardiac arrhythmia, affecting approximately 1.5% to 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 antiinflammatory drugs or antiplatelet 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. First, it is well established that many chemotherapeutic agents increase the risk of both arterial and venous thrombosis. Second, chemotherapy regimens may independently increase the risk of bleeding, especially those that induce thrombocytopenia.[5] The increasing use of targeted anticancer therapies such as tyrosine kinase inhibitors 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 licensed for 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 two-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] While 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 few data to quantify the risk of ischemic stroke due to cancer accurately. One study using Surveillance Epidemiology and End Results (SEER) Medicare linked data of 279 719 patients with a new primary diagnosis of breast,

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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 among 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 guideline recommendations and wide variation in clinical practice.

1.1 | Current evidence for antithrombotic 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

1.1.1 | Vitamin K antagonists

Vitamin K antagonists (VKAs) 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, particularly within the first 6 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 international normalized ratio, which has been shown to have a negative impact on quality of life.[24]

1.1.2 | Direct oral anticoagulants

Four direct oral anticoagulants (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 metaanalysis of these trials showed that DOACs significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0.81; 95% CI 0.73-0.91; $P < .0001$), which was mainly due to a reduction in hemorrhagic stroke (RR 0.49; 95% CI 0.38-0.64; $P < .0001$).[29] The DOACs also reduced all-cause mortality (0.90, 0.85-0.95; $P = .0003$) and intracranial hemorrhage (0.48, 0.39-0.59; $P < .0001$), but increased gastrointestinal bleeding (1.25, 1.01-1.55; $P = .04$).

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 in database analyses, the results need to be interpreted with caution.

All DOACs are substrates for the excretory permeability glycoprotein (P-gp) system, while 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-gp inhibitors.[34] Specific attention to potential interactions with cancer therapy should be paid 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, while 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 low-molecular-weight heparin (LMWH) for the treatment and secondary prophylaxis of VTE.[34,35] On the basis of 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.

1.1.3 | Low-molecular-weight heparin

There is little evidence to support the use of LMWH for long-term stroke prophylaxis in patients with NVAF regardless of the presence or nonpresence of cancer. 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 three-fold 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 2 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 from those studies also has the advantage that many patients with metastatic disease who were receiving chemotherapy were included. In a metaanalysis of eight studies comparing LMWH with warfarin, the major bleeding rate with LMWH and warfarin was 4.3% and 4.1%, respectively.[39]

1.2 | 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 course, in part, because patients place most value on anticoagulants that interfere least with their cancer treatment.[40–42] However, while anticoagulation for VTE may be time limited, for NVAF it is usually indefinite. Arguably convenience in relation to quality of lifehas 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 well be willing to accept parenteral medication in the short term if indicated, for example, 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 when the possible benefit from chemotherapy may be less than the harm from more serious complications associated with NVAF, its comorbidities, 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 unfavorable 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 favors the concomitant use of anticoagulants and SACT, it is important to recognize that the risk profiles of bleeding and stroke are not static entities; they will change over time according to alterations in platelet count, associated comorbidities, 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.

1.3 | Clinical decision making/choice of DOAC

The initial phase of clinical decision making will center on (a) whether anticoagulation is indicated and (b) the class of anticoagulant to be used. On the basis of 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 that 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 gastrointestinal bleeding risk, while rivaroxaban and edoxaban have the strongest phase 4 published data. Furthermore, while 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

TABLE 1 Comparison of different attributes of different DOACs when considering anticoagulation for NVAF in patients with cancer

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%	+	+	++	++	++

Abbreviations: CAT, cancer-associated thrombosis; CYP3A4, Cytochrome P450 3A4; DOACs, direct oral anticoagulants; NVAF, non-valvular atrial fibrillation; P-gp, P glycoprotein; RCT, randomized control trial.

HOKUSAI-Cancer studies. However, it should be noted that new data continue to emerge, especially with respect to safety outcomes.

1.3.1 | 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, licensed 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 an alternative practice also may be acceptable.

1.4 | 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 international normalized ratio 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.

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CONFLICT OF INTERESTS

Dr. Aurelien Delluc reports he has participated as a member of the 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 2 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; another from Pfizer/BMS, outside the submitted work; Dr. Eng-Soo Yap participated as a member of an Advisory Board for Novartis and received speaker honoraria from Bayer, Leo Pharma, Novartis, and Sanofi; Dr. Cihan Ay reports he has participated as a member of the Advisory Board for Bayer, Daiichi-Sankyo, BMS/Pfizer, and Boehringer Ingelheim; and has received speaker honoraria from Bayer, Daiichi-Sankyo, BMS/Pfizer, and Sanofi; Dr. Jordan Schaefer reports no conflict of interest during the conduct of the study; Dr. Marc Carrier reports that he has participated as a member of the 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 2 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.

AUTHOR CONTRIBUTIONS

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

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