



# Anticoagulation of Cardiovascular Conditions in the Cancer Patient: Review of Old and New Therapies

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## Abstract

**Purpose of Review** The anticoagulation strategies for various cardiac-specific pathologies including atrial fibrillation are changing. Applying these strategies in patients with concomitant active cancer requires additional considerations. Here, we review the most recent changes in the anticoagulation management of common cardiac diseases and their application in cancer patients.

**Recent Findings** There are a range of indications for therapeutic anticoagulation in cancer patients including venous thromboembolism (VTE), atrial fibrillation/flutter (AF/AFL), prosthetic heart valves, and intracardiac thrombi. Certain cancer therapeutics such as ibrutinib and anthracycline chemotherapy increase the risk of developing AF/AFL and pose unique challenges in anticoagulation management. Anticoagulation decisions for AF/AFL often utilize the CHADS2 or the CHA2DS2-VASc score with annualized stroke risk; however, these risk stratification models may be inadequate in cancer patients. Cancer type, stage, prognosis, and bleeding risk are all relevant when considering whether to initiate therapeutic anticoagulation. Moreover, thrombocytopenia may limit the ability to provide anticoagulation. Subsequent analyses of direct oral anticoagulants (DOACs) show fewer bleeding complications and thromboembolic events compared to warfarin in AF/AFL with apixaban and edoxaban particularly promising in this population for VTE, pulmonary embolism, and AF/AFL. There is a lack of data regarding ablation therapy and left atrial occlusion devices in this population. There is a growing experience of DOACs for intracardiac thrombi. Warfarin is still appropriate for patients with prosthetic heart valves and left ventricular assist devices.

**Summary** Anticoagulation management in the cancer patient can be challenging. DOACs are often a safe alternative to warfarin in cancer-associated DVT/PE and AF/AFL, and may be preferable in certain circumstances. Other cardiac indications for anticoagulation including the presence of a mechanical heart valve remain unchanged and dependent on warfarin or heparin-based products.

**Keywords** Anticoagulation · Cancer · Atrial fibrillation · Cardio-oncology

## Introduction

In the treatment of cardiovascular disease, it is often necessary to prescribe therapeutic anticoagulation. The most common

indications are atrial fibrillation/flutter (AF/AFL) and venous thromboembolism (deep vein thrombosis and pulmonary embolism (DVT/PE)). Other indications include mechanical prosthetic heart valves, left ventricular assist devices, pulmonary hypertension, or intracardiac thrombus. For over half a century, anticoagulation has relied upon vitamin K antagonists (e.g., warfarin, coumarin (VKA)) and/or heparin products (e.g., low molecular weight heparins (LMWH)), but the development of direct oral anticoagulant medications (DOACs) in the past decade has resulted in a dramatic shift in prescribing habits [1, 2]. Due to the decreased need for monitoring, rapid onset of action, reduced drug-drug interactions compared to VKAs, and equivalent or superior efficacy in preventing strokes in AF/AFL trials, direct oral anticoagulants (DOACs) are often considered a better first-line agent for many patients with AF/AFL [3]. DOACs are also now the

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anticoagulant of choice for both the treatment and prevention of DVT/PE.

Active malignancies are frequently associated with thrombophilias and/or coagulopathies [4–7]. The CLOT and LITE trials showed that low molecular weight heparin was superior to warfarin for preventing recurrent VTE, though the newer and larger CATCH trial does cast some doubt on this finding [8–10]. Consequently, there had been some skepticism in using DOACs for the treatment of VTE in cancer patients [11, 12]. Those fears have been attenuated with multiple trials demonstrating the safety and efficacy of DOACs in the treatment of VTE [13–17]. For example, in the Housaki-VTE study, edoxaban, an anti-factor Xa inhibitor, was compared to warfarin in 8292 patients with either pulmonary embolism or deep vein thrombosis and was found to be non-inferior for the prevention of recurrent venous thromboembolism and superior with regard to severe bleeding complications [17]. The recently published SELECT-D trial also demonstrated the safety of using rivaroxaban, another anti-factor Xa inhibitor, in a cohort of unselected cancer patients with newly diagnosed DVT or PE [18]. The risk of recurrent DVT/PE was equivalent between rivaroxaban and LMWH, and bleeding risks were lower in the rivaroxaban arm, with the exception of patients with primary gastrointestinal malignancies where bleeding was higher in the rivaroxaban arm [18]. Despite these trials, the 2018 National Comprehensive Cancer Network (NCCN) guidelines still recommend heparin-based therapies over DOACs for the treatment of thromboembolism in cancer patients [19•, 20, 21].

It is important to recognize that the mechanism of thrombus formation is different for DVT/PE and right atrial thrombus compared with thrombus in the arterial circulation (AF/AFL, LV thrombus) [22, 23]. In 2017, Navi et al. examined the Surveillance Epidemiology and End Results (SEER) data and found that the incidence of arterial thromboembolism in cancer patients is double that of matched controls [24]. On sub-analysis, later stage at diagnosis and lung cancer were associated with the most excess arterial thromboembolism [24]. As for DOACs, they are quickly becoming the new standard for stroke prophylaxis in patients with AF as they show superior efficacy in reducing CVA as well as reduced risk of major bleeding including intracranial hemorrhage [25]. Unfortunately, there is a paucity of data regarding the optimal anticoagulation management strategies for cardiac diseases in cancer patients.

In this review, we will discuss the current anticoagulation practices and challenges for several common cardiac conditions in cancer patients (Fig. 1), how they may have recently changed, and gaps in our current knowledge and understanding. We will focus primarily on anticoagulation related to cardiac-specific disease states as there is already a wealth of information regarding the use of anticoagulation in cancer patients for non-cardiac conditions [14, 26].

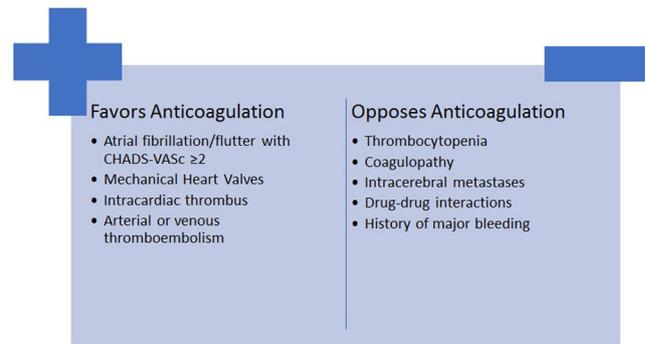


Fig. 1 Anticoagulation challenges in cancer patients

## Atrial Fibrillation/Atrial Flutter

The loss of coordinated atrial activity in both AF and atrial flutter (AFL) leads to relative stasis in the left atrial appendage (LAA) which predisposes to thrombus formation with the potential to dislodge. The CHA2DS2-VASc score, an upgrade of the previous CHADS2 score with superior sensitivity, has become the recommended tool by most major cardiology organizations for determining stroke risk in AF and AFL [3, 27, 28]. A score of 2 indicates a 2.2% risk of stroke per year and is considered the threshold for starting anticoagulation for most patients. The maximum score of 9 points denotes a 15% chance of stroke per year. Of note, active malignancy is not considered an independent risk factor for atrial thrombus formation in AF/AFL in these scoring systems (Table 1) [12, 30]. Regardless of cancer status, anticoagulation is recommended for AF/AFL with a CHA2DS2-VASc of  $\geq 2$  in men and  $\geq 3$  in women if there are no significant contra-indications [31]. It is important to acknowledge that the data from non-cancer populations generally included patients with an excellent 5-year and even 10-year prognosis. Therefore, the cutoff of a CHA2DS2-VASc of  $\geq 2$  is not due to the 2.2% risk in year one, which is a relatively low absolute risk, but the cumulative risk over a 5–10-year window, e.g., patients with AF and a CHA2DS2-VASc score of 2 have an 11% 5-year risk of stroke and 22% 10-year risk. The different CHA2DS2-VASc threshold in women is due to recent studies noting that sex category is only a significant risk factor with higher CHA2DS2-VASc scores [32]. This supports the rationale for long-term anticoagulation, and therefore in cancer patients, it is important to place the stroke risk with AF in the context of their cancer status, stage, response to treatment, and prognosis.

The validity of the CHA2DS2-VASc and the CHADS2 scores in cancer patients has come under scrutiny. In a recent article by D'Souza et al., patients in a nationwide registry with cancer and AF had higher rates of thromboembolism at low CHA2DS2-VASc scores (0–1) but lower rates with scores of 2+ when compared to non-cancer patients [33•]. In a study from Taiwan, the CHADS2 score lacked power to predict thromboembolism in cancer patients with new-onset AF

**Table 1** CHA<sub>2</sub>DS<sub>2</sub>-VASc score [29]

Number of risk factors*	Annual risk of stroke (%)	Annual risk of stroke/TIA/peripheral emboli (%)
0	0.2	0.3
1	0.6	0.9
2	2.2	2.9
3	3.2	4.6
4	4.8	6.7
5	7.2	10.0
6	9.7	13.6
7	11.2	15.7
8	10.8	15.2
9	12.2	17.4

\*1 point risk assigned for each of the following: age 65–75, hypertension, congestive heart failure, diabetes mellitus, arterial vascular disease, female sex

\*\*2 points assigned for each of the following: age > 75, history of stroke/TIA/arterial thromboembolism

[34]. As such, it remains unclear which scoring system (CHA<sub>2</sub>DS<sub>2</sub>-VASc or CHADS<sub>2</sub>) is preferable in the cancer population [35].

Per the recent AHA/ACC/HRS guideline update, DOACs are now the preferred anticoagulants over VKAs for patients with non-valvular AF/AFL which is defined as patients without either a prosthetic heart valve or significant mitral stenosis (Table 2) [31]. Any other native valvular pathology is not a contraindication to DOAC use. There was initially some hesitation using DOACs for stroke prophylaxis in cancer patients with AF/AFL due to the aforementioned mixed thrombophilic/coagulopathic state of active malignancy and partial exclusion of known cancer patients from the initial DOAC trials, but several recent studies have shown that DOACs in cancer are indeed safe. A sub-analysis of the ARISTOTLE trial looking at 1236 patients with a history of active or prior cancer showed that apixaban offered greater protection than warfarin in preventing the composite endpoint of stroke/systemic embolism, myocardial infarction, and death when compared to patients without cancer [40]. A sub-analysis of the ENGAGE AF-TIMI 48 trial with edoxaban versus warfarin in patients with newly diagnosed cancer or recurrence of remote cancer ( $n = 1153$ ) showed significant improvement in the composite endpoint of ischemic stroke/systemic embolism/myocardial infarction that was not seen in the patients without active malignancy [41]. A retrospective analysis of 16,096 patients with AF/AFL, active cancer, and concomitant oral anticoagulant use suggested similar ischemic stroke rates among the DOACs, with apixaban having lower rates of bleeding [42]. In a large Danish nationwide population-based cohort of patients with AF prescribed a DOAC or warfarin with ( $n = 11,855$ ) or without cancer ( $n = 56,264$ ), the rates of subsequent thromboembolism or

bleeding were not significantly different between DOACs or warfarin regardless of cancer status [43]. It is also important to acknowledge that while LMWH is often a preferred anticoagulant to treat DVT/PE in cancer patients; there are no trials assessing the long-term efficacy and safety of LMWH in patients with AF to prevent thromboembolism [44].

Thrombocytopenia is common in many cancer patients, and it remains uncertain whether low platelets in this context reduces the likelihood of AF-associated thrombus formation. In cancer patients with a high risk of bleeding or where bleeding could have severe consequences (e.g., intracerebral metastases) and overall life-expectancy is limited (< 12 months), forgoing anticoagulation for atrial fibrillation may be a reasonable option even if their CHA<sub>2</sub>DS<sub>2</sub>-VASc score is  $\geq 2$ . Unfortunately, a simple system to assess bleeding risk in cancer patients with AF is lacking. While the HAS-BLED score is frequently utilized, subsequent analyses have shown that it does not possess sufficient predictive power to be used reliably [45, 46]. Moreover, it does not incorporate thrombocytopenia which is a common finding in cancer patients that predisposes to bleeding complications. As such, deferring anticoagulation may be necessary in the setting of thrombocytopenia, though specific thresholds remain controversial. For example, the original DOAC trials excluded patients with platelet values < 90,000–100,000 [47, 48]. In 2012, Saccullo et al. demonstrated safety and efficacy of resuming sub-therapeutic heparin at platelets > 30,000 and warfarin at platelets > 50,000 in patients with chemotherapy-induced thrombocytopenia [49].

### Cancer Treatment-Related AF

Multiple cytotoxic chemotherapies agents and novel targeted agents such as tyrosine kinase inhibitors (TKI) are associated with the development of AF/AFL by various proposed mechanisms [50]. For example, rates of AF are reported as high as 10.3% with anthracycline use. In the setting of stem cell transplantation, rates of AF are reported around 11% if melphalan is used as the preconditioning chemotherapy [51]. Radiation-induced pericarditis is also associated with atrial arrhythmias.

### Ibrutinib-Induced AF

AF associated with ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor used in the treatment of multiple malignancies including chronic lymphocytic leukemia, mantle cell lymphoma, Waldenström's macroglobulinemia, and even refractory graft vs. host disease [52]. In the phase 3 RESONATE trial, rates of AF associated with ibrutinib were reported at 5% compared to 0.5% for ofatumumab. Subsequent studies have suggested higher rates of AF with ibrutinib ranging from 10 to 16% [53–56]. In a recent meta-analysis, the relative risk of new-onset atrial fibrillation compared to alternative therapies was 3.85 (1.97–7.54) [57]. One possible mechanism may be related

to reduced phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT) activity; however, this remains an active area of investigation [58, 59]. Nonetheless, the etiology may due to an off-target effect as rates of AF are thus far substantially lower with the second-generation BTK inhibitor acalabrutinib [60].

Ibrutinib has been shown to increase the risk of major bleeding complications via effects on platelet aggregation resulting from inhibition of the glycogen VI collagen-activation pathway [61, 62]. Subsequent investigations have confirmed the inherent coagulopathic properties of ibrutinib [63]. This risk is enhanced in the setting of VKAs such as warfarin [64]. For example, 4 subdural hematomas (2%) were reported in the safety analysis of a phase 2 study of 111 patients with refractory mantle cell lymphoma treated with ibrutinib [64]. All events were following falls or trauma, and all these patients were taking aspirin or warfarin when the incident occurred. Following this, warfarin use was excluded from most clinical trials with ibrutinib, and the European Medicine Agency (but not the FDA) explicitly advises avoidance of concomitant ibrutinib and warfarin [65, 66]. DOACs and heparin analogs are currently being used as alternative anticoagulants without definitive evidence of elevated risks of subdural hematomas or other severe bleeding [67, 68].

Complicating the management of AF/AFL in these patients is the pharmacology of ibrutinib, which is a substrate of CYP3A4. Amiodarone, diltiazem, and verapamil are significant inhibitors of CYP3A4, and as such their co-administration must be weighed with the consequences on increased ibrutinib serum concentrations [69]. Ibrutinib also is P-glycoprotein inhibitor, which means it will elevate the levels of P-glycoprotein dependent on the anti-arrhythmic digoxin, which is prone to toxic arrhythmias when levels are highly elevated [69].

### Limitations of DOACs for AF/AFL and DVT/PE

While there are many indications and advantages of DOACs, there are some critical limitations that must be

addressed. Firstly, the use of most DOACs in patients with Stage 4–5 kidney disease with or without dialysis is still controversial, though a recent large retrospective study of end-stage renal disease (ESRD) patients with AF on either apixaban or warfarin ( $n = 25,523$ ) implied that apixaban is non-inferior and possibly superior to warfarin in such patients [70]. Of note, apixaban is the only DOAC considered acceptable for use in ESRD patients based on recent AHA/ACC/HRS guideline updates [31]. Rivaroxaban, despite being FDA approved for CrCl < 50 mL/min down to ESRD is not recommended by the latest guideline updates in patients with CrCl < 15 mL/min due to lack of clinical studies in this population [31]. Secondly, there is significant potential for drug-drug interactions and no readily available method to determine if prescribed doses are safely therapeutic. While all DOACs interact with the P-glycoprotein system, dabigatran is most susceptible to these effects. Apixaban and rivaroxaban are metabolized via the CYP3A4 degradation pathway and caution must be exercised with the concomitant use of CYP3A4 inducers [71]. Certain anti-cancer agents such as ibrutinib are also metabolized by this system and this may affect the choice of anticoagulation for these patients [72]. Finally, available antidotes and/or reversal agents for DOACs remains limited. Idarucizumab has been available for dabigatran reversal for several years, and andexanet alfa was recently approved as an antidote for rivaroxaban and apixaban though currently has limited availability [73]. There is no approved reversal agent for edoxaban, but recent animal data using andexanet alfa is encouraging [74].

### Interruption and Bridging in AF/AFL

For patients with AF on anticoagulation requiring surgery, it is recommended to stop anticoagulation for procedures with at least moderate bleeding risk. Based on results from the

**Table 2** Direct oral anticoagulants used in atrial fibrillation/flutter

	Dabigatran [36]	Apixaban [37]	Rivaroxaban [38]	Edoxaban [39]
Mechanism of action	Direct thrombin	Factor Xa	Factor Xa	Factor Xa
Typical dosing	150 mg bid	5 mg bid	20 mg daily	60 mg daily***
Renal impairment (GFR 15–50 mL/min)	150 mg bid*	5 mg bid**	15 mg daily	30 mg daily
Elimination half-life	12–17 h	7–15 h	5–12 h	12 h
Renally cleared	80%	27%	36%	50%
Interaction potential	P-GLP (potent)	P-GLP, CYP3A4	P-GLP, CYP3A4	P-GLP, CYP3A4 (minimal)
Use in ESRD	No	Yes	No	No
FDA approved reversal agent	Idarucizumab	Andexanet alfa	Andexanet alfa	None

*bid*, twice daily; *P-GLP*, P-glycoprotein; *GFR*, glomerular filtration rate; *FDA*, US Food and Drug Administration; *ESRD*, end-stage renal disease; \*reduce to 2.5 mg bid if 2 of the following: age > 80, weight < 60 kg, serum Cr > 1.5; \*\*for GFR 15–30, reduce dose to 75 mg bid; \*\*\*avoid use in GFR > 95 due to decreased efficacy with superior renal clearance

BRIDGE trial, it is no longer recommended to provide temporary treatment with heparin products due to an increased risk of bleeding without a reduction in the risk of thromboembolism [75]. The 2017 ACC Expert Consensus Decision Pathway informs that in certain subgroups taking warfarin with a CHA<sub>2</sub>DS<sub>2</sub>-VASc of  $\geq 5$ , bridging with heparin products may still be considered [76]. No patients taking DOACs for AF/AFL require bridging, but the timing of DOAC cessation will depend on creatinine clearance and inherent bleeding risk of the procedure. This interruption/bridging strategy cannot be readily applied to patients anticoagulated for other reasons; however, as many of the other indications require stricter adherence to continuous anticoagulation.

### Left Atrial Appendage Occlusion Devices

Patients with a history of severe bleeding, especially while on anticoagulation, may not be the best candidates for long-term anticoagulation strategies. Currently, the only option available to negate the need for long-term anticoagulation in the setting of AF is LAA occlusion or ligation. The Watchman device is FDA approved for reducing long-term anticoagulation requirements in AF/AFL patients [77]. Procedural placement of a Watchman device uses access from a femoral vein and a trans-atrial septal puncture with the device physically obstructing the appendage inlet. Following the procedure, the device must endothelialize into the appendage to prevent thrombus formation on the device itself. During this process, the patient must be treated with both anticoagulation as well as antiplatelet agents [78]. Recipients in the intervention group of the PREVAIL trial were placed on low-dose aspirin and therapeutic warfarin for 45 days after device implantation. After follow-up TEE was performed to confirm an appropriate seal of the LAA, 92.2% of the 269 patients in the trial were transitioned to clopidogrel and full-dose aspirin for another 5 months followed by full-strength aspirin alone. The remaining patients remained on warfarin until a seal could be confirmed via TEE; however, 1.7% of enrolled patients has persistent LAA leak even after 6 months [78]. There are some data suggesting that in warfarin intolerant patients, 6 months of clopidogrel and lifelong aspirin after Watchman placement is potentially beneficial in reducing the anticipated number of ischemic strokes [79]. This procedure may be an option for a select group of cancer patients desiring cessation of anticoagulation due to excess bleeding risk, such as in patients with high intracranial bleed risk and a similar ischemic stroke risk. For example, a breast cancer patient with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 7 with relatively stable cerebral metastases might be reasonable to consider for Watchman placement. However, more studies are needed to test the outcomes of placing LAA occlusion devices in such patients.

### Cardioversion

Many patients are first diagnosed with AF/FL under situations of stress such as during chemotherapy or surgery. Elective cardioversion is often attempted to minimize the arrhythmia burden once the stressor has been removed, e.g., completed chemotherapy course [80]. Without anticoagulation, the incidence of thromboembolic events in the period following cardioversion is remarkably higher [81]. In order to safely perform either chemical or electrical cardioversion, patients must be at minimal risk for having a LAA thrombus. Patients with new-onset AF for < 48 h or those on uninterrupted anticoagulation for at least 3–4 weeks may undergo cardioversion without additional testing. For all other patients (including those individuals who may have had prior undiagnosed episodes of AF), transesophageal echocardiogram (TEE) is necessary to exclude atrial thrombus. After cardioversion, patients must be maintained on anticoagulation for at least 4 weeks as thrombus formation frequently occurs during the period following chemical or electrical cardioversion due to atrial stunning [3, 28, 82–84]. This recommendation is applied to all patient populations, including those with active cancer. DOACs have successfully been used in place of warfarin for the post-cardioversion anticoagulation with equivalent non-inferior efficacy and bleeding risk at 30 days as shown in the EMANATE (apixaban), ENSURE-AF (edoxaban), and X-VERT (rivaroxaban) [85–87]. Of note, high risk of bleeding was exclusion from all 3 trials, and in ENSURE-AF active cancer requiring treatment was also an exclusion criterion.

Forgoing anticoagulation in patients with new-onset AF/AFL of < 48 h in duration remains quite controversial. The FinCV study identified the rate of CVA or TIA following 7660 cardioversions performed following < 48 h of persistent atrial fibrillation [88]. Of these, 4715 patients received no pre- or post-procedural anticoagulation. The incidence within 30 days of definite thromboembolic events in the entire cohort was 0.7% and 0.2% in those deemed low-risk patients. A later analysis demonstrated a low rate of thromboembolism in patients under the age of 75 years treated with electrical cardioversion within 12 h of arrhythmia onset [89]. While this practice is currently a 2B indication in the latest American College of Cardiology (ACC) guidelines, most experts strongly recommend 4 weeks of anticoagulation in every patient undergoing an elective cardioversion procedure regardless of the arrhythmia duration [28].

Some populations may warrant extra care to ensuring no LAA thrombus is present prior to DCCV. In a recent article by El-Am et al., cardiac amyloidosis patients had a substantially higher chance of cardioversion cancellation due to the presence of LAA thrombus on TEE, with 46% of these cancellations occurring despite receiving therapeutic anticoagulation for  $\geq 3$  weeks or having AF/AFL duration of < 48 h. There was also

a higher rate of procedural complications compared to control patients, including ventricular arrhythmias and severe bradyarrhythmias requiring pacemaker placement [90].

## Ablation

Ablations are a component of the management algorithm for atrial arrhythmias; however, success rates are highly dependent on the arrhythmia etiology. Typical atrial flutter ablation carries a success rate of about 95%, but there is a high incidence of subsequent AF in these patients [91–93]. Success rates for ablation of atrial fibrillation are more modest at 60–80% and AF ablation strategies are not considered protective against subsequent stroke [28, 94, 95]. Expert consensus statements strongly recommend continued anticoagulation based on CHA2DS2-VASc score regardless of perceived success of ablation [96, 97]. Ablation has not been specifically studied in cancer patients and cancer patients were underrepresented in the original ablation studies. These procedures are not often performed in patients with active cancer, in part due to the transient inflammation associated with cancer and the mandatory 3 months of anticoagulation after the procedure. Nevertheless, research is needed to determine the potential role and benefits of this treatment modality in cancer patients with AF and other arrhythmias.

## Prosthetic Heart Valves

There are an increasing number of patients with pre-existing prosthetic heart valves that later develop cancer. Anticoagulation requirements for heart valves vary depending on the type and location. Bioprosthetic valves in any position do not require long-term anticoagulation, though 3 months of post-procedure warfarin and life-long low-dose aspirin are considered reasonable [98]. All mechanical heart valves require life-long warfarin with variations in the recommended target INR and perioperative bridging strategy depending on the type of mechanical valve, location of the valve, and other comorbidities [98, 99]. There has been some literature supporting the use of therapeutic LMWH for a possible “extended bridging” during periods of prominent thrombocytopenia or elevated bleeding risk; however, randomized trials to evaluate the safety of this approach are lacking [49]. For perioperative bridging in patients with mechanical heart valves in which LMWH is used, ESC guidelines specifically recommend measuring anti-factor Xa levels to ensure optimal dosing [99]. In cancer patients with increased risk of bleeding, using anti-Xa levels will likely better optimize the risk:benefit by ensuring optimal dosing.

The use of DOACS for mechanical heart valves was briefly explored in the RE-ALIGN trial which compared use of dabigatran vs. warfarin in mechanical heart valves, but this

trial was stopped early due to an excess rate of stroke and major bleeding in the dabigatran arm to the point that the trial was stopped early [100]. As such, DOACS are not recommended for anticoagulation in the setting of prosthetic heart valves.

## Intracardiac Thrombi

Though there is significant focus on LAA thrombi in the setting of AF and AFL, other cardiovascular disease states can lead to thrombi formation in other cardiac chambers. The most common problem in the cancer population is thrombus in the right atrium as a result of central indwelling catheters positioned too deep and extending into the right atrium. Either via direct physical trauma or the effect of toxic chemotherapy infused directly on to the right atrial endocardium, irritation and damage to the endocardium leads to potential for thrombus formation. Other thrombi in transit in the right heart chambers are typically treated as a pulmonary embolism, and therefore DOACs can be appropriate in these patients. Thrombi in transit can be found in the right atria or right ventricle and rarely within a patent foramen ovale. Treatment is individualized, but a thrombus in the interatrial septum presents a risk of catastrophic thromboembolic stroke and is often taken for immediate surgical embolectomy [101]. Nevertheless, routine closure of patent foramen ovale is not recommended [102].

There are little data regarding the optimal strategy for treating line-related intracardiac thrombus. It is generally accepted that anticoagulation with warfarin should be immediately started and the catheter should eventually be removed or replaced when it is safe to do so [103]. There may be a role for treating catheter-related thrombi with DOACs; however, data is still lacking.

Left ventricular thrombi are often encountered following a large anterior infarct that involves the apex. The exposed necrotizing myocardium and akinetic scar tissue can foster thrombus formation which can occasionally lead to systemic embolization [104]. At present, warfarin is still considered the mainstay of treatment, though per the 2014 American Heart Association/American Stroke Association guidelines, it is appropriate to consider DOACs and heparin for patients with known LV thrombi who do not tolerate vitamin K antagonists due to non-hemorrhagic side effects [102].

## Other Indications for Anticoagulation

There are multiple other indications for anticoagulation that may be encountered in oncology patients including chronic thromboembolic pulmonary hypertension, left ventricular assist devices, and left ventricular non-compaction. The mainstay of anticoagulant therapy remains warfarin with no significant data to support the use of other agents aside from bridging with heparin analogs. Anticoagulation strategies for such

patients will need to be individually tailored with the input of a cardiologist or preferably cardio-oncologist.

## Future Directions

Anticoagulation for cardiac conditions will continue to evolve for all indications, but there are several areas that are likely going to be of more focused interest. The first is likely the use of left atrial occlusion devices. These devices have a high potential to be life-saving and even cost-saving, but in their current form, they are rarely used in cancer patients due to the requirement for concomitant anticoagulation and antiplatelet therapy. Second, atrial fibrillation ablation, while in its current form is not viewed as protective from subsequent stroke, this may be reconsidered as techniques improve. Third, in light of the data from Navi et al., a new or perhaps modified CHA2DS2-VASc score for cancer patients should be developed to better determine stroke risk in these patients [24]. Lastly, mechanical prosthetic heart valves are going to continue to evolve in both their makeup and anticoagulation requirements [105]. Maintaining strict VKA/heparin use for these valves is terribly limiting for patients and often dangerous. As a result, future research is needed to develop novel valve structure and prosthetic material to permit less strict anticoagulation requirements.

## Conclusions

The interaction of cardiovascular diseases, anticoagulation, and active cancer creates a complicated mixture of thrombophilic and coagulopathic mechanisms. Anticoagulation in cancer patients with thrombophilic cardiac diseases is a difficult challenge with increased potential bleeding risk and also prognosis must be factored into the equation regarding initiation versus avoidance of therapeutic anticoagulation. Unfortunately, there are few dedicated studies evaluating these issues. While it is likely that DOACS have the potential to replace warfarin and LMWH in the most common of these cardiac conditions, there are no clear recommendations to guide this approach. Additional studies will be needed to determine the safety of DOACs in the setting of cardiac disease and cancer. It is clear this is an area of cardio-oncology with many opportunities for further research and investigation.

## Compliance with Ethical Standards

**Conflict of Interest** Isaac B. *rhea* declares that he has no conflict of interest. Alexander R. Lyon has received research funding from Pfizer and has received compensation from Servier, Pfizer, Novartis, Roche, Takeda, Boehringer Ingelheim, Amgen, Clinigen Healthcare, Ferring Pharmaceuticals, Eli Lilly, Bristol-Myers Squibb, Eisai, and Stealth

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**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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