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STATE-OF-THE-ART REVIEW

Atrial Fibrillation and Cancer

Bidirectional Relationship and Potential for Personalized Care



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ABSTRACT

A bidirectional relationship between cancer and atrial fibrillation (AF) is well known. Although systemic inflammation and the effects of cancer treatment significantly increase the risk of AF in patients with cancer, new-onset AF has also been shown to independently predict the risk of active malignancy. With a continued growth in our understanding of the molecular pathogenesis of AF and with the advent of novel anticancer agents with unique cardiotoxic effects, there is a need to study if the management of AF in patients with cancer requires a more “personalized” approach rather than a generalized approach. The current review focuses on the application of “precision cardio-oncology” to the screening, diagnosis, and management of AF in patients with cancer through biomarkers, cardiac imaging, and personalized risk stratification. Through this review, we highlight the growing need to incorporate personalized interventions into clinical studies and analyze the feasibility of integrating these into the routine care of patients with cancer.

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Atrial fibrillation (AF) is one of the most frequently diagnosed arrhythmias, with cancer recognized as an independent risk factor. Increased systemic inflammation, cardiotoxic cancer-directed therapies, and associated comorbidities likely collectively contribute to atrial remodeling, thereby elevating the overall risk of AF among patients with cancer.¹ The risk of stroke has also been shown to be significantly higher among patients with AF and cancer compared with those without a diagnosis of cancer.² Although overall the presence

of cancer increases the likelihood of AF, certain cancer subtypes have a notably increased prevalence of AF. For example, multiple myeloma has demonstrated a strong association with AF, whereas among solid tumors, esophageal cancer appears to be associated with a notably high incidence of AF.¹

Advances in understanding the molecular underpinnings of AF have highlighted the heterogeneity of the disease, facilitating a transition from a generalized therapeutic approach to more individualized management strategies.^{3,4} Similarly, the

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ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug
AF = atrial fibrillation
AI = artificial intelligence
CaMKII = calcium/calmodulin-dependent protein kinase II
CLL = chronic lymphocytic leukemia
CRP = C-reactive peptide
CT = computed tomography
DOAC = direct oral anticoagulant
GDF = growth differentiation factor
IL = interleukin
NT-proBNP = N-terminal pro-B-type natriuretic peptide

adoption of a personalized approach for managing AF in patients with cancer is crucial. Precision cardio-oncology, an emerging discipline at the intersection of cardiology and oncology, aims to deliver tailored diagnostic and therapeutic strategies for managing cardiovascular complications, including arrhythmias, in patients with cancer.⁵ In this review, we explore the diagnosis and management of AF in patients with cancer, with a focus on the integration of pharmacogenetics, biomarkers, advanced cardiac imaging, personalized risk stratification, and the evolving role of precision cardio-oncology in this space.

BIDIRECTIONAL RELATIONSHIP BETWEEN AF AND CANCER

Cancer-related AF is believed to arise from inflammation-induced atrial myopathy, autonomic dysfunction with increased sympathetic activity, and the cardiotoxic effects of cancer-directed therapy (Figure 1).⁶ These therapies may exert direct toxic effects on myocardial tissue or induce a persistent arrhythmogenic substrate, even after treatment cessation.^{7,8} Shared genetic alterations between cancer and AF suggest that new-onset AF may serve as a predictor of active malignancy, positioning AF as a potential biomarker for underlying cancer.^{9,10} It is well known that AF risk is significantly higher among patients with cancer, particularly in esophageal, lung, gastric, myeloma, and lymphoma. Conversely, in patients with AF, the risk of incident cancer is also elevated.¹¹ In a large retrospective analysis, risk was limited to the short term and higher in abdominal and thoracic cancers,¹² whereas another study showed sustained risk beyond 1 year, with a particularly high incidence of colon cancer.¹³ Recent data investigating this bidirectional relationship at a more molecular level do not appear to indicate a causal relationship between AF and cancer.^{14,15}

CLINICAL IMPACT AMONG PATIENTS WITH CANCER

The diagnosis of AF has significant impact on cancer care. AF may limit therapeutic options because of critical drug-drug interactions between antiarrhythmic drugs (AADs) and cancer-directed therapy. For example, AF is the most common reason for discontinuing ibrutinib, a Bruton tyrosine kinase inhibitor used in chronic lymphocytic leukemia (CLL) and other hematological cancers.¹⁶ These

HIGHLIGHTS

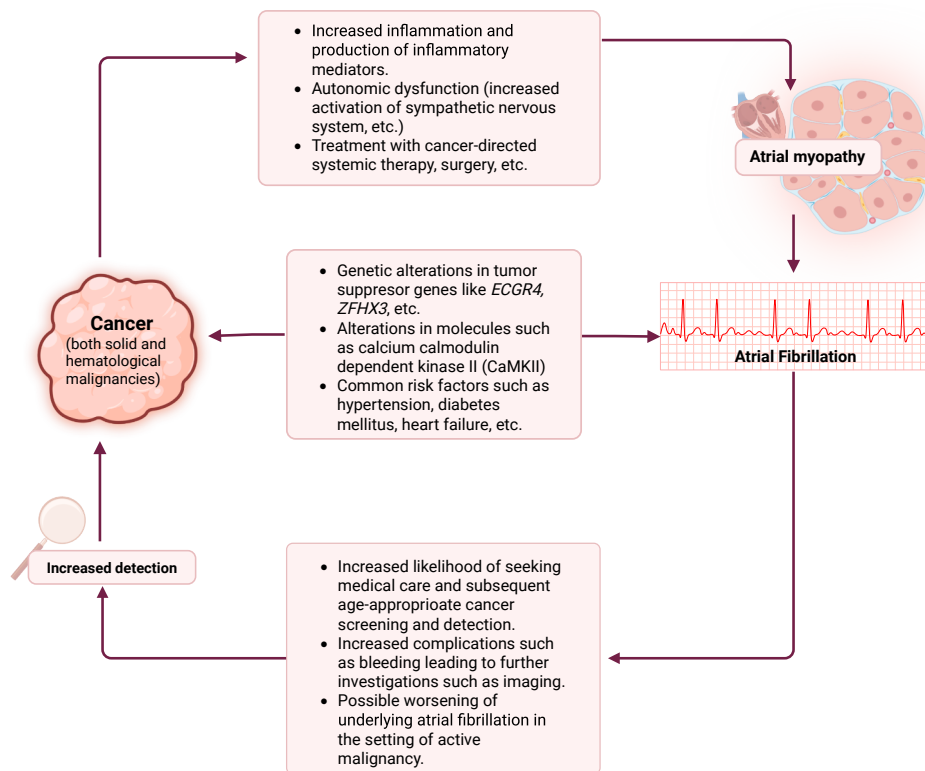
- Cancer and AF share a bidirectional relationship with diagnostic and prognostic implications.
- This review advocates for precision cardio-oncology to personalize AF screening, risk stratification, and management.
- Cancer-specific drug interactions and thromboembolic and bleeding risks demand nuanced, individualized AF treatment strategies.
- Prospective studies should evaluate personalized AF management strategies integrated with genomic, imaging, and biomarker data.

interactions are largely mediated by impaired cytochrome P450 metabolism or P-glycoprotein inhibition, leading to adverse effects such as QT prolongation or bradycardia.^{17,18} Pharmacogenetic studies are increasingly applied to identify genetic variations in drug metabolism and prevent supra- or subtherapeutic levels of both cancer-directed therapy and cardiac drugs.¹⁸

Variability in the safety and efficacy of AF therapies extends beyond AADs and chemotherapy. Direct oral anticoagulants (DOACs), although widely used, may not be ideal in cancer therapy-induced AF. Among patients with ibrutinib-induced AF, DOACs may increase bleeding risk through P-glycoprotein interactions.¹⁹ These concerns are amplified in the era of targeted therapies, with multiple tyrosine kinase inhibitors demonstrating interactions with AADs and anticoagulants (Table 1).²⁰⁻³⁰

Patients with cancer also face higher bleeding risk with anticoagulation compared with control subjects. The HAS-BLED score is commonly used but does not capture cancer-specific factors such as thrombocytopenia or intracranial metastases.^{31,32} Similarly, the CHA₂DS₂-VASc score may underestimate thromboembolic risk, underscoring the need for cancer-specific risk stratification.³³ Therapy-related factors further complicate anticoagulation; for instance, enzalutamide induces CYP3A4 and inhibits P-glycoprotein, potentially reducing the efficacy of apixaban and rivaroxaban.³⁴ Personalized strategies are essential to mitigate interactions, minimize toxicity, and optimize anticoagulation in patients with cancer and AF.

FIGURE 1 Depiction of a Bidirectional Relationship Between Atrial Fibrillation and Cancer



Bidirectional relationship between cancer and atrial fibrillation (AF). Schematic illustrating how malignancy can precipitate atrial disease and AF, and how AF can, in turn, lead to detection of an underlying cancer. Cancer promotes atrial myopathy and AF through systemic inflammation and release of inflammatory mediators; autonomic dysregulation with heightened sympathetic tone; and direct/indirect effects of cancer-directed therapies (eg, chemotherapy, targeted agents, radiation), culminating in electrical and structural remodeling of the atria. Shared substrates—including tumor-associated or AF-linked genetic alterations (eg, *ECRG4*, *ZFHX3*), signaling pathways such as CaMKII, and common clinical risk factors (hypertension, diabetes, heart failure)—further lower the threshold for AF. Conversely, AF may increase cancer detection via greater health-care contact and age-appropriate screening; evaluation of AF-related complications; and clinical worsening of pre-existing AF in the setting of active malignancy that triggers additional work-up. The figure summarizes proposed mechanisms and clinical pathways discussed in this review and underscores the need for precision cardio-oncology approaches to screening, surveillance, and management.

PATHOPHYSIOLOGY

As indicated above, AF in patients with cancer is the result of a multifaceted interplay of systemic inflammation, autonomic imbalance, direct tumor effects, and comorbidities inherent to malignancy. Systemic inflammation, a hallmark of cancer, is known to promote atrial myopathy through inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor- α .³⁵ These cytokines induce atrial electrical and structural remodeling by disrupting

connexin expression, promoting atrial fibrosis, and prolonging P-wave dispersion, all of which may promote the creation of an arrhythmogenic substrate. In parallel, tumor-associated macrophages may contribute to cardiac remodeling by releasing catecholamines; these macrophage-derived catecholamines have been shown to induce myocardial injury and arrhythmogenesis.³⁶ Cancer-related oxidative stress is another key factor, as excess reactive oxygen species can damage atrial cardiomyocytes and create a substrate for AF.³⁷ Additionally, profibrotic

TABLE 1 Interactions of TKIs With AADs and Oral Anticoagulants

Agents	Targets	Interactions With AADs (Classified per the Vaughan-Williams Classification)	Interactions with Oral Anticoagulants	Mechanisms
Erlotinib	Epidermal growth factor receptor	Increased levels of TKIs with some agents in classes 3 and 4.	Increased levels of warfarin.	CYP3A4 substrate ²⁰
Osimertinib	Epidermal growth factor receptor	Increased levels of AADs with some agents in classes 1b, 1c, 2, 4 and digoxin; increased levels of TKIs with some agents in classes 2 and 4. QTc prolongation with some agents in classes 1a, 1b and 2.	Increased levels of warfarin, rivaroxaban and apixaban.	CYP3A4 substrate; BRCP inhibitor ²¹
Ibrutinib	Bruton tyrosine kinase	Increased levels of AADs with some agents in classes 1a, 2, 3, 4 and digoxin. Increased levels of TKIs with some agents in classes 3 and 4.	Increased effect of warfarin and increased levels and effect of apixaban, rivaroxaban, edoxaban, and dabigatran.	CYP3A4 substrate; P-glycoprotein inhibitor ²²
Imatinib	<i>BCR-ABL</i> , c-KIT, PDGFR, stem cell factor	Increased levels of AADs with some agents in classes 1a, 1b, 1c, 2, 3, 4 and digoxin. Increased levels of TKIs with some agents in classes 2, 3 and 4.	Increased levels and effect of warfarin. Increased levels of rivaroxaban and apixaban.	CYP3A4 substrate and moderate inhibitor; P-glycoprotein substrate ²³
Sunitinib	PDGFR- α , β , VEGFR-1,2,3, FMS-like tyrosine kinase 3, colony-stimulating factor type 1, RET	Increased levels of AADs with some agents in classes 1a, 2, 3, 4 and digoxin. Increased levels of TKIs with some agents in classes 3 and 4. QTc prolongation with some agents in classes 1a, 1c, 2 and 3.	Increased levels of apixaban, rivaroxaban, edoxaban and dabigatran.	CYP3A4 substrate; P-glycoprotein inhibitor ²⁴
Pazopanib	VEGFR-1,2,3, PDGFR- α , β , fibroblast growth factor receptor-1,3, c-KIT, interleukin-2 receptor, inducible interleukin-2 receptor inducible T-cell kinase, leukocyte-specific protein 1 tyrosine kinase, transmembrane glycoprotein receptor tyrosine kinase	Increased levels of propafenone when used concomitantly. Increased levels of TKIs with some agents in classes 1a, 2, 3 and 4. QTc prolongation with some agents in classes 1a, 1c, 2, 3 and 4.	None	CYP3A4 substrate; P-glycoprotein substrate ²⁵
Axitinib	VEGFR-1,2,3	Increased levels of TKIs with some agents in classes 3 and 4.	None	CYP3A4 substrate ²⁶
Lenvatinib	VEGFR-1,-2,-3, fibroblast growth factor receptor-1,-2,-3,-4, PDGFR- α , KIT, RET	Increased levels of TKIs with some agents in classes 2 and 4. QTc prolongation with some agents in classes 1a, 1c and 3.	None	CYP3A4 substrate; P-glycoprotein substrate; breast cancer resistance protein substrate ²⁷
Crizotinib	Anaplastic lymphoma kinase, hepatocyte growth factor receptor, Recepteur d'Or-igine Nantais	Increased levels of AADs with some agents in classes 1a, 1c, 2, 4 and digoxin. QTc prolongation with some agents in classes 1a, 1c and 3. Bradycardia with some agents in classes 2, 4 and digoxin.	Increased levels of warfarin, apixaban, rivaroxaban, edoxaban, and dabigatran.	CYP3A4 substrate and moderate inhibitor; CYP2C9 substrate; P-glycoprotein substrate and inhibitor ²⁸
Ruxolitinib	Janus-associated kinase-1,2	Increased levels of TKIs with some agents in classes 3 and 4. Bradycardia with some agents in classes 1c, 2, 3, 4 and digoxin.	None	CYP3A4 substrate ²⁹
Cabozantinib	Hepatocyte growth factor receptor, RET, VEGFR-1,2,3, KIT, FMS-like tyrosine kinase 3, tyrosine kinase with Ig-like and epidermal growth factor-like domains -2, tropomyosin receptor kinase B, anexelekto receptor tyrosine kinase	Increased levels of AADs with some agents in classes 1a, 2, 3 and digoxin. Increased levels of TKIs with some agents in classes 3 and 4.	None	CYP3A4 substrate ³⁰

AAD = anti-arrhythmic drug; CYP3A4 = cytochrome P3A4; *BCR-ABL* = breakpoint cluster region-Abelson oncogene; c-KIT = c-KIT receptor tyrosine kinase; PDGFR = platelet-derived growth factor receptor; RET = rearranged during transfection; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.

signaling through transforming growth factor- β leads to the activation of atrial fibroblasts and extracellular matrix deposition, exacerbating atrial fibrosis and providing an anatomical substrate for AF.³⁸ Finally, cancer and cancer-directed therapy can perturb cardiomyocyte calcium handling and induce endoplasmic reticulum stress; this combination promotes

electrophysiological instability (eg, abnormal sarcoplasmic reticulum Ca^{2+} release) in atrial cells, ultimately facilitating the development of AF.³⁸ Neurohormonal changes, including increased sympathetic activity, may further augment AF risk. Specific malignancies, such as multiple myeloma and esophageal cancer, show a particularly strong

association with AF, potentially because of their higher systemic inflammatory burden or anatomical proximity to the heart.³⁹

Direct tumor effects may also contribute to the increased risk of AF in cancer. For instance, mediastinal tumors may compress the heart and great vessels, leading to hemodynamic stress and atrial stretching, which may ultimately provoke electrical heterogeneity and atrial ectopy.⁴⁰ Cancer-related anemia, hypoxia, and electrolyte imbalances may further exacerbate the risk by sensitizing the atria to arrhythmogenesis.⁴¹ Mechanisms through which the use of systemic therapy may increase the risk of AF in cancer are highly variable and discussed in the next section.

SYSTEMIC THERAPY AND AF

Several cancer-directed therapies—including chemotherapy, targeted agents, immune checkpoint inhibitors, and cellular therapies—are associated with AF through direct cardiotoxicity or by creating an arrhythmogenic substrate.

CHEMOTHERAPY. AF is a known complication of several chemotherapeutics. Anthracyclines (doxorubicin, daunorubicin) cause oxidative stress, mitochondrial damage, and fibrosis, creating an arrhythmogenic substrate.⁴² Their inhibition of topoisomerase II β , essential for DNA replication and repair, drives anthracycline-induced cardiomyopathy, which may contribute to delayed-onset AF. Cisplatin, a non-cell cycle-specific agent that covalently binds purine bases, is associated with AF in 12% to 32% of patients with urothelial and head and neck cancers.⁴³ Melphalan, which disrupts DNA synthesis and transcription, is used in conditioning regimens for myeloma and carries an AF risk of 7% to 22%.⁴⁴ By contrast, 5-fluorouracil and its oral prodrug capecitabine inhibit thymidylate synthase and DNA nucleotide synthesis but are linked to lower AF rates (0%-1.3% and 1.1%, respectively).^{45,46}

TARGETED THERAPY. Ibrutinib, a Bruton tyrosine kinase inhibitor, is a leading cause of therapy-related AF, enhancing atrial electrical remodeling through C-terminal Src kinase inhibition.⁴⁷ Other tyrosine kinase inhibitors (dasatinib, nilotinib) also increase risk through QT prolongation and ion channel disruption⁴⁸; ibrutinib has the highest incidence, followed by nilotinib, with ponatinib and vandetanib associated with lower rates.⁴⁹ Trastuzumab, a HER2-targeted antibody, is strongly linked to cardiomyopathy but has a low overall AF incidence (0.46%),⁵⁰ although risk rises to ~19% with prior cardiac

disease.⁵¹ Real-world cohorts of patients with breast cancer suggest no AF signal despite increased heart failure risk.⁵² Proteasome inhibitors such as carfilzomib (greater than bortezomib) have been tied to AF, particularly in patients with cardiovascular disease.⁵³ CDK4/6 inhibitors, used in breast cancer, have been associated with excess cardiovascular events and AF-related mortality.⁵⁴

IMMUNOTHERAPY. Immune checkpoint inhibitors may cause cardiovascular immune-related adverse events. A systematic review found AF in 4.6% of treated patients.⁵⁵ Mechanistically, T-cell-mediated inflammation with lymphocytic infiltration of sinoatrial and atrioventricular nodes has been described.⁵⁶ Pharmacovigilance analyses identified AF as the most common immune checkpoint inhibitor-related arrhythmia (576/1,945 cases [0.62%]), with high mortality (26%); fatal events occurred earlier (median onset of 30 days) than nonfatal ones.⁵⁷

CELLULAR THERAPY. Chimeric antigen receptor T-cell therapy, particularly CD19-directed, has been associated with atrial arrhythmias. In a lymphoma cohort (n = 236), 10% developed arrhythmias, with higher risk in patients with prior AF or those receiving CD28 costimulatory domain products.⁵⁸ Some experienced reduced left ventricular function, and anticoagulation was often withheld because of thrombocytopenia or bleeding. A National Inpatient Sample study found AF prevalence of 8.1% in patients undergoing chimeric antigen receptor T-cell therapy (lower than control subjects) but higher rates of atrial tachycardia, ventricular tachycardia, and QT prolongation.⁵⁹

BIOMARKERS

As already known, AF is associated with several well-established risk factors, including hypertension, obesity, diabetes, smoking, alcohol consumption, and valvular heart disease.⁶⁰ However, studies suggest that cancer is an independent risk factor for AF. A new diagnosis of AF or its incidental detection could therefore serve as a clinical indicator of an underlying malignancy.⁶¹ Although identifying an underlying malignancy in patients presenting with new-onset AF is critical, the early detection of AF in individuals with cancer is also important. Timely diagnosis of AF may potentially help mitigate serious complications of AF, such as an elevated risk of stroke, and also inform the personalization of treatment planning for cancer-directed therapies. The emerging field of precision cardio-oncology offers

promising opportunities to leverage biomarkers for the early detection of AF. The biomarkers discussed in this section could be classified as cardiac (N-terminal pro-B-type natriuretic peptide [NT-proBNP], cardiac troponin), inflammatory (C-reactive peptide [CRP], IL-6), cancer-specific (insulin-like growth factor binding protein, CA-125), or mixed (galectin-3, growth differentiation factor 15 [GDF-15], uric acid, micro-RNAs).

Biomarkers such as insulin-like growth factor binding protein and NT-proBNP may provide valuable tools for identifying incidental AF in patients with a diagnosis of cancer. Insulin-like growth factor binding protein has been shown to have a positive association with incident AF risk, and prior studies have also linked the biomarker to several cancers.⁶² Most clinical studies on the role of NT-proBNP in prediction of risk of incident AF have been done among patients undergoing thoracic surgery for lung cancer. In patients undergoing surgical resection for lung cancer, increased NT-proBNP levels either 24 hours before or 1 hour after the surgery appear to be associated with a substantially higher risk of AF (64% vs 5% in patients without increased NT-proBNP; $P < 0.001$).⁶³ A few studies have also attempted to establish cutoff levels of NT-proBNP for prediction of AF in postsurgical patients with cancer. For example, a prior study noted that a cutoff of 182 ng/L was highly predictive of postoperative AF in patients with lung cancer undergoing surgical resection.⁶⁴ There is a need to assess the utility of NT-proBNP in predicting incident AF in all patients with cancer irrespective of type of cancer and modalities of treatment.

Some evidence suggests that elevated cardiac troponin levels may herald new-onset AF or may be a marker of underlying AF in patients with cancer.⁶⁵ Interestingly, existing data also suggest that elevated cardiac troponin I levels may be a marker of chemotherapy-induced cardiotoxicity in patients with cancer.⁶⁶ Perhaps more longitudinal clinical data in this regard may help establish the role of cardiac troponin I levels in predicting the risk of chemotherapy-induced AF as well. Elevated levels of CA-125, a tumor marker used primarily in the follow-up of patients with ovarian cancer, have been linked to new-onset AF in several small studies conducted on patients with decompensated heart failure and in postmenopausal women.^{67,68} Elevated uric acid levels are seen in many cancers, especially hematological malignancies due to spontaneous or therapy-induced tumor lysis syndrome. Intriguingly, hyperuricemia has been linked to not just an increased incidence of cancer and cancer-related

mortality but has also been found to be associated with a larger left atrial size, which may increase risk of AF as well.^{69,70}

A case-control study by Chung et al⁷¹ showed that CRP is elevated in non-postoperative AF patients and that stepwise elevation of CRP correlates with higher AF burden. They also found that CRP levels are higher in persistent than in paroxysmal AF patients.⁷¹ Moreover, the levels of CRP have also been found to decline after ablation in patients with atrial flutter.⁷² On the other hand, several cancers such as colorectal cancer and lung cancer have been found to be associated with an increase in the levels of CRP, which highlights the underlying proinflammatory state in patients with cancer that could also potentially link cancer with AF.^{73,74} Similarly, elevation of IL-6 levels has been found to induce atrial electrical remodeling by the downregulation of cardiac connexins that may increase the risk of AF (indicated by abnormal P-wave dispersion indices).⁷⁵ The role of IL-6 in the progression and therapeutic response of several cancers has been well studied and demonstrated, suggesting the utility of IL-6 as another biomarker that could be studied in predicting the risk of incident AF in cancer patients.⁷⁶

Galectin-3, a member of the β -galactoside-binding lectin family, is yet another biomarker being implicated in the pathogenesis of AF. Galectin-3 levels are known to be elevated in patients with persistent vs paroxysmal AF, predict recurrence after ablation, and contribute to atrial remodeling and fibrosis. Additionally, in preclinical animal models, galectin-3 inhibition also demonstrated reduced AF burden and promoted termination, suggesting a potential preventive therapy for AF progression.⁷⁷ Interestingly, galectin-3 has also been shown to play a multifaceted role in the pathogenesis of multiple cancers, with evidence demonstrating its involvement at various stages of tumor development and metastasis.⁷⁸ These data highlight the need to prospectively investigate and validate the role of galectin-3 as a helpful predictive and prognostic marker for AF among patients with cancer.

GDF-15 is a stress-responsive biomarker associated with several cardiovascular diseases including AF. A prior analysis from the Atherosclerosis Risk in Communities study noted that higher concentrations of GDF-15 were independently associated with incident AF, supporting its potential value as a clinical marker of AF risk.⁷⁹ Additionally, GDF-15 is also a very strong predictor for bleeding among patients with AF and known to play a role in body weight regulation and chronic inflammation in patients with cancer.⁸⁰ It has also been shown to be a reliable cancer-specific

biomarker because of its role in predicting response to platinum chemotherapy and also serving as a diagnostic marker with CA-125 in patients with ovarian cancer.⁸¹ More recently, GDF-15 has also been shown to be a reliable predictor of bleeding among patients with cancer with and without thromboprophylaxis.^{82,83} This highlights the potential of GDF-15 as a biomarker for not only predicting the risk of AF in cancer but also in personalized assessment of bleeding risk among patients with cancer and AF on thromboprophylaxis. Additionally, micro-RNAs are essential modulators of cardiac arrhythmias, influencing electrical remodeling, ion channel dynamics, and fibrosis, and have been shown to serve as noninvasive biomarkers for early arrhythmia risk prediction.⁸⁴ Because micro-RNAs also play an important role in cancer pathogenesis, they carry potential to be investigated as biomarkers for risk prediction of AF in patients with cancer.⁸⁵

Overall, existing studies have indicated a need to study the role of these biomarkers in helping predict the risk of incident AF in patients with cancer using a personalized approach. Further studies aimed at analyzing the clinical applicability of these biomarkers may also help in preventing high-risk patients from being initiated on potentially arrhythmogenic cancer-directed therapies. These biomarkers may also help identify patients who would benefit from closer monitoring for development of AF, with or without initiation of cancer-directed therapy.

CARDIAC IMAGING

Much of the evidence on cardiac imaging for detecting asymptomatic dysfunction from systemic therapy has focused on trastuzumab and anthracyclines. The role of global longitudinal strain remains uncertain in this space. In the SUCCOUR trial, a global longitudinal strain-based strategy was not superior to an ejection fraction-based approach for detecting chemotherapy-related cardiomyopathy.⁸⁶ Nonetheless, global longitudinal strain remains of interest given its ability to predict AF in other high-risk groups, such as patients with hypertension.⁸⁷ Its utility for predicting AF in cancer patients treated with anthracyclines or other systemic agents remains to be determined. Speckle-tracking echocardiography similarly allows noninvasive assessment of left atrial remodeling and has predicted paroxysmal AF after ischemic stroke.^{88,89} Studying its role in cancer populations is important, particularly in chemotherapy-induced cardiomyopathy, where atrial myopathy is closely linked to AF.⁹⁰⁻⁹²

Echocardiographic parameters have also provided insight into AF pathogenesis in cancer. In 1 study of 53 breast cancer patients treated with adriamycin, cyclophosphamide, and paclitaxel, atrial electromechanical delay predicted AF, likely related to impaired left ventricular relaxation and left atrial conduction.⁹³ A lower left atrial emptying fraction has also predicted postoperative AF in patients undergoing lung or esophageal cancer resection.⁹⁴

Cardiac magnetic resonance imaging offers complementary value. The DECAAF study demonstrated its role in characterizing left atrial remodeling and fibrosis.⁹⁵ T₁ mapping enables quantification of atrial fibrosis.⁹⁶ A prospective study of 381 chemotherapy-naïve cancer patients showed that cancer itself was independently associated with alterations in chamber size and function, with higher native T₁ values compared with control subjects, supporting the role of serial T₁ monitoring for early detection of therapy-related toxicity and arrhythmia risk.⁹⁷ However, more widely available modalities such as strain echocardiography and speckle-tracking echocardiography may suffice to identify left atrial abnormalities to guide therapy decisions.⁹⁸

Cardiac computed tomography (CT) can evaluate chemotherapy-related disease but has a limited role in AF management. Although CT provides volumetric and functional assessment of atria and ventricles, echocardiography remains more practical and avoids radiation. Rarely, CT may detect cardiac metastases in new-onset AF.^{98,99} CT angiography also identifies underlying coronary artery disease in cancer patients, warranting closer monitoring after cardiotoxic therapy.⁹⁹⁻¹⁰¹

Finally, positron emission tomography/CT may have emerging utility. In a cohort of 3,703 cancer patients, atrial fluorodeoxyglucose uptake correlated with atrial inflammation and active AF.¹⁰² Because many cancer patients undergo positron emission tomography/CT for staging or surveillance, incidental atrial uptake should prompt AF evaluation and closer follow-up after cardiotoxic therapies. Prospective studies are needed to clarify the diagnostic role of atrial fluorodeoxyglucose avidity.¹⁰³

PERSONALIZED RISK STRATIFICATION AND MOLECULAR MEDICINE

Several studies have shed light on molecular mechanisms that allude to the biological association between cancer and AF. The increased expression of the esophageal cancer-related gene-4 (*ECRG4*), a tumor suppressor gene, in the atria and conduction system of the heart has been found to play a critical role in

the pathogenesis of AF.¹⁰⁴ Similarly, zinc finger homeobox 3 (*ZFHX3*) is a tumor suppressor gene that has been found to predict survival in several different types of cancers such as non-small cell lung cancer.¹⁰⁵ *ZFHX3* encodes a transcription factor that also has cardiac expression, and at least 2 variants of the gene have been found to be associated with AF.¹⁰⁶

Calcium/calmodulin-dependent protein kinase II (CaMKII) expression levels have been found to be elevated in multiple cancer types. For example, calcium-activated chloride channel anoctamin 1 (*ANO1*) is located within the 11q13 amplicon, which is one of the most frequently amplified chromosomal regions in cancer, amplified in about 15% of all breast cancers. This amplification has been shown to cause overexpression of *ANO1* channels and correlates with disease severity and prognosis. Interestingly, overexpression of *ANO1* causes increased phosphorylation and activity of CaMKII, and primary breast cancer cell lines show an increased expression of *ANO1* and phosphorylation of CaMKII.¹⁰⁷ The role of CaMKII in cell cycle effects, apoptosis and invasion, and metastasis of different cancer types is well known and has even been explored as a biomarker for cancer.¹⁰⁸ CaMKII signaling has been implicated in the pathogenesis of numerous cardiac arrhythmias, especially AF. Increased CaMKII activity by oxidation and phosphorylation has been linked to AF in hypertensive and diabetic animal models and in human patients.¹⁰⁹⁻¹¹¹ Ibrutinib has been shown to increase the expression and phosphorylation of CaMKII, causing both significant electrical and structural remodeling in the heart, leading to increased AF risk.¹¹²

Interestingly, the addition of genetic information has been shown to increase the predictive accuracy of risk prediction scores in patients with AF.¹¹³ Studies have indicated that both monogenic and polygenic factors contribute to the risk of AF in the general population and that these may be responsible for genetic susceptibility to AF.¹¹⁴ Over 100 single nucleotide polymorphisms have been identified through genome-wide association studies and found to be associated with AF.¹¹⁵ Several personalized risk stratification scores for AF such as the polygenic risk scores have also been extensively studied and validated.¹¹⁶ Polygenic risk scores use multiple single nucleotide polymorphisms to identify individuals who are at an increased risk for AF.¹¹⁷ However, there have been concerns regarding the cost-effectiveness of their use for management of patients with AF in the general population. Because the impact of AF on

the prognosis and treatment of patients with cancer is very significant, this may potentially be an avenue where the incorporation of polygenic risk scores into clinical care may be feasible. The clinical utility and cost-effectiveness of these personalized risk stratification scores should be studied in patients with cancer, especially those who are being initiated on potentially cardiotoxic anticancer therapies.¹¹⁸

In addition to genomic data, the addition of cancer-specific variables to personalized risk stratification scores may also further increase their clinical value in the management of AF among patients with cancer. For example, risk prediction scores like the Mayo CLL AF and Italian AF scores are valuable tools for assessing the risk of AF in patients with CLL treated with ibrutinib.¹¹⁹ These models help identify high-risk patients, guiding therapy choices, especially as newer, less cardiotoxic Bruton tyrosine kinase inhibitors like acalabrutinib and zanubrutinib gain prominence. Emerging data also demonstrate the promising role of machine learning and artificial intelligence (AI) in this area. A large study that included 4,600 patients with cancer showed that machine learning was able to identify 4 subgroups of cancer survivors who were at different levels of cardiac event risk. Risk stratification at different levels allows the identification of patients who may benefit from robust and more long-term cardiovascular surveillance.¹²⁰ Another study evaluated the role of an AI-electrocardiogram algorithm to predict AF risk among patients with CLL. Among 754 patients with CLL, patients with an AI-electrocardiogram score of 0.1 or more had a significantly higher risk of AF. The predictive ability of the algorithm remained significant even after adjusting for various factors.¹²¹

PERSONALIZED RISK ASSESSMENT FOR STROKE

Patients with cancer are at an increased risk of stroke due to the underlying hypercoagulable state, and this risk is further heightened by AF. Bungo et al¹²² performed a large retrospective analysis of 101,185 individuals in the Surveillance, Epidemiology, and End Results database, of whom 48,242 had lung, colon, breast, or prostate cancer and 52,943 did not. They noted that the stroke incidence was significantly higher in the group of patients with cancer, with 2.96 strokes per 100 person-years compared with 2.38 strokes per 100 person-years in the noncancer group (incidence rate ratio: 1.25; 95% CI: 1.18-1.31; $P < 0.01$). The study proposed a modified CHA₂DS₂-VASc score, incorporating cancer as a risk factor, called the

cancer-modified CHA₂DS₂-VASc score. This model outperformed the traditional CHA₂DS₂-VASc score, as demonstrated by a net reclassification index of 12.2% and an improved Akaike Information Criterion score. Cox regression analysis showed that cancer increased the HR for stroke by 8.5% (HR: 1.085; 95% CI: 1.029-1.144; *P* = 0.0027), comparable with age >75 years and female sex. These findings suggest that cancer is an independent risk factor for stroke in AF patients, warranting its inclusion in stroke risk prediction models.¹²²

ANTICOAGULATION AND BLEEDING RISK ASSESSMENT

The management of anticoagulation among patients with cancer and AF is particularly challenging. As discussed above, patients with cancer and AF are associated with variable but significantly increased thromboembolic risk.¹²³ These patients are also at increased risk of bleeding, particularly those with thrombocytopenia caused by bone marrow invasion or therapy-related myelosuppression or those with cancers prone to bleeding, such as gastrointestinal or genitourinary malignancies.¹²⁴

Traditional risk prediction tools like CHA₂DS₂-VASc and HAS-BLED scores, widely used for estimating thromboembolic and bleeding risks, respectively, in the general AF population, may have limited applicability among patients with cancer. This is primarily because these scores do not sufficiently account for cancer-specific factors. For instance, a large cohort study demonstrated that the HAS-BLED score may significantly underestimate the bleeding risk in patients with cancer-associated AF.^{125,126} Therefore, there is a critical need to devise and use more robust, cancer-specific tools for accurate stratification of thromboembolism and bleeding.

A proposed recommendation by the European Society of Cardiology guidelines on cardio-oncology is the TBIP decision tool, for Thrombosis, Bleeding, Interactions, and Patient, that provides a structured approach for decision-making when offering anticoagulation to patients with venous thromboembolism and cancer.¹²⁷ This approach may also be applicable to patients with cancer and AF where thromboprophylaxis is being considered. The TBIP approach includes the following:

1. Thrombotic risk: Incorporating both cancer-related and AF-specific risks.
2. Bleeding risk: Evaluating factors such as tumor location, thrombocytopenia, and recent or ongoing hemorrhagic events.

3. Drug interactions: Assessing potential interactions between anticoagulants, cancer-directed therapies, or AADs.
4. Patient preferences: Considering patient values and access to therapies.

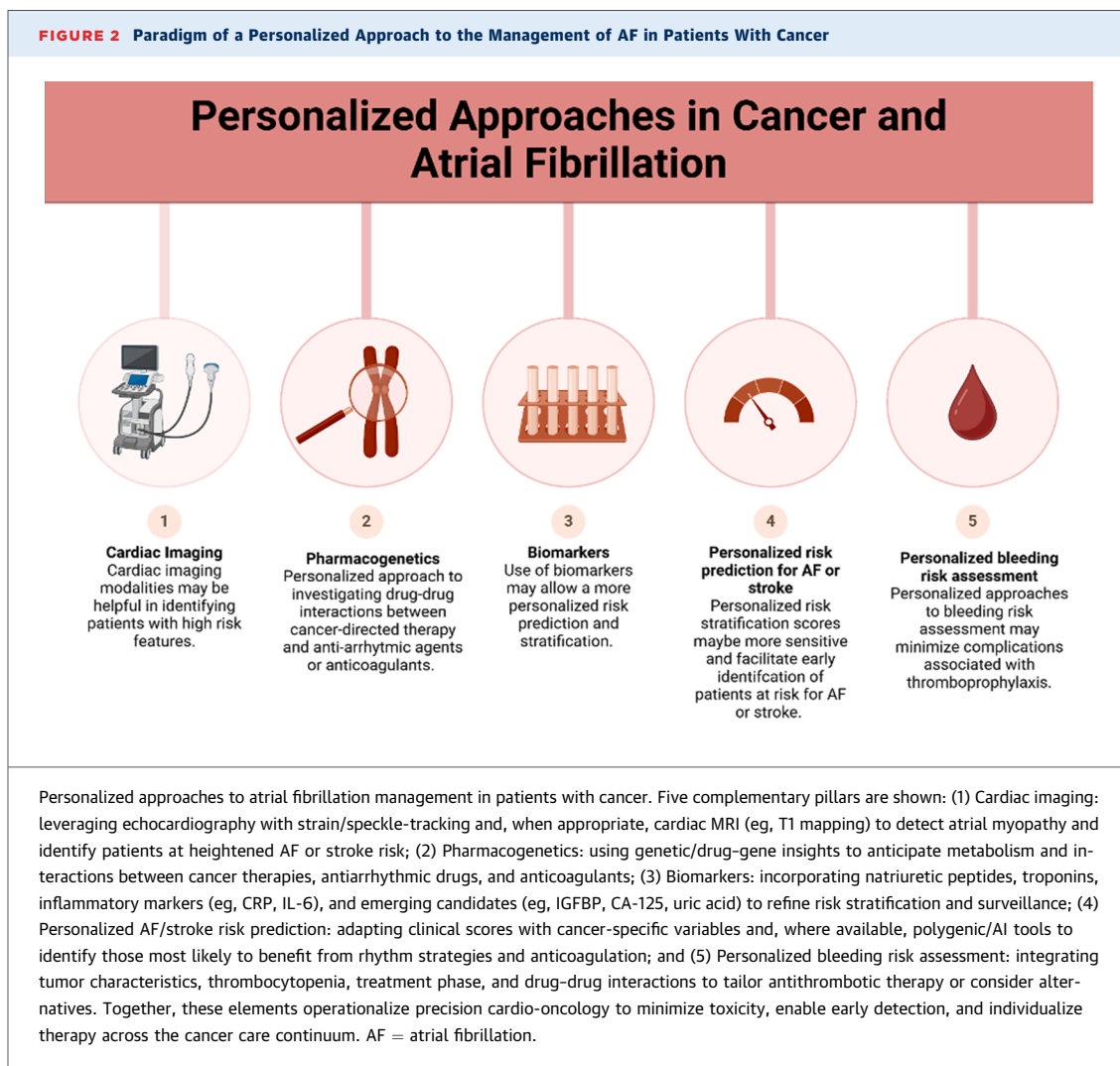
In patients with high bleeding risk, such as those with gastrointestinal or genitourinary cancers, low-molecular-weight heparin may generally be preferred. DOACs may be used in patients without significant drug-drug interactions or bleeding risks. Dose adjustments, wherever necessary, may be made (eg, with suboptimal renal function). Despite promising data with the use of DOACs and low-molecular-weight heparin, vitamin K antagonists remain the standard of care for thromboprophylaxis in valvular AF.¹²⁸ Anticoagulation is contraindicated among patients with active hemorrhage, severe thrombocytopenia, or evolving intracranial lesions. Among these patients, alternatives like left atrial appendage occlusion may be considered in the appropriate clinical context.¹²⁹ Frequent reassessments of anticoagulation regimens are essential, especially during active cancer-directed therapy, because patient parameters and therapy plans may continue to evolve. In this regard, a multidisciplinary cardio-oncology team is paramount for providing comprehensive care to these patients. Thrombocytopenia, renal function, and physician and patient preference are some other key factors to consider regarding the use of anticoagulants among patients with cancer.¹³⁰

Figure 2 demonstrates the paradigm of personalized approach to the management of AF in patients with cancer.

SPECIAL CONSIDERATIONS FOR MANAGEMENT OF AF IN PATIENTS WITH CANCER

As discussed above, both underlying malignancies and cancer-directed therapy may contribute to the arrhythmogenesis of AF among patients with cancer, which may have a significantly detrimental impact on overall outcomes among these patients.^{10,131-134} Here, we discuss some special considerations relevant to the clinical management of AF in patients with cancer.

There are evolving discussions regarding the appropriate use of rate vs rhythm control strategies in the management of patients with AF in general. These decisions may be even more challenging to make among special patient populations, such as those with cancer. For asymptomatic patients with cancer-related AF, a rate control strategy is generally

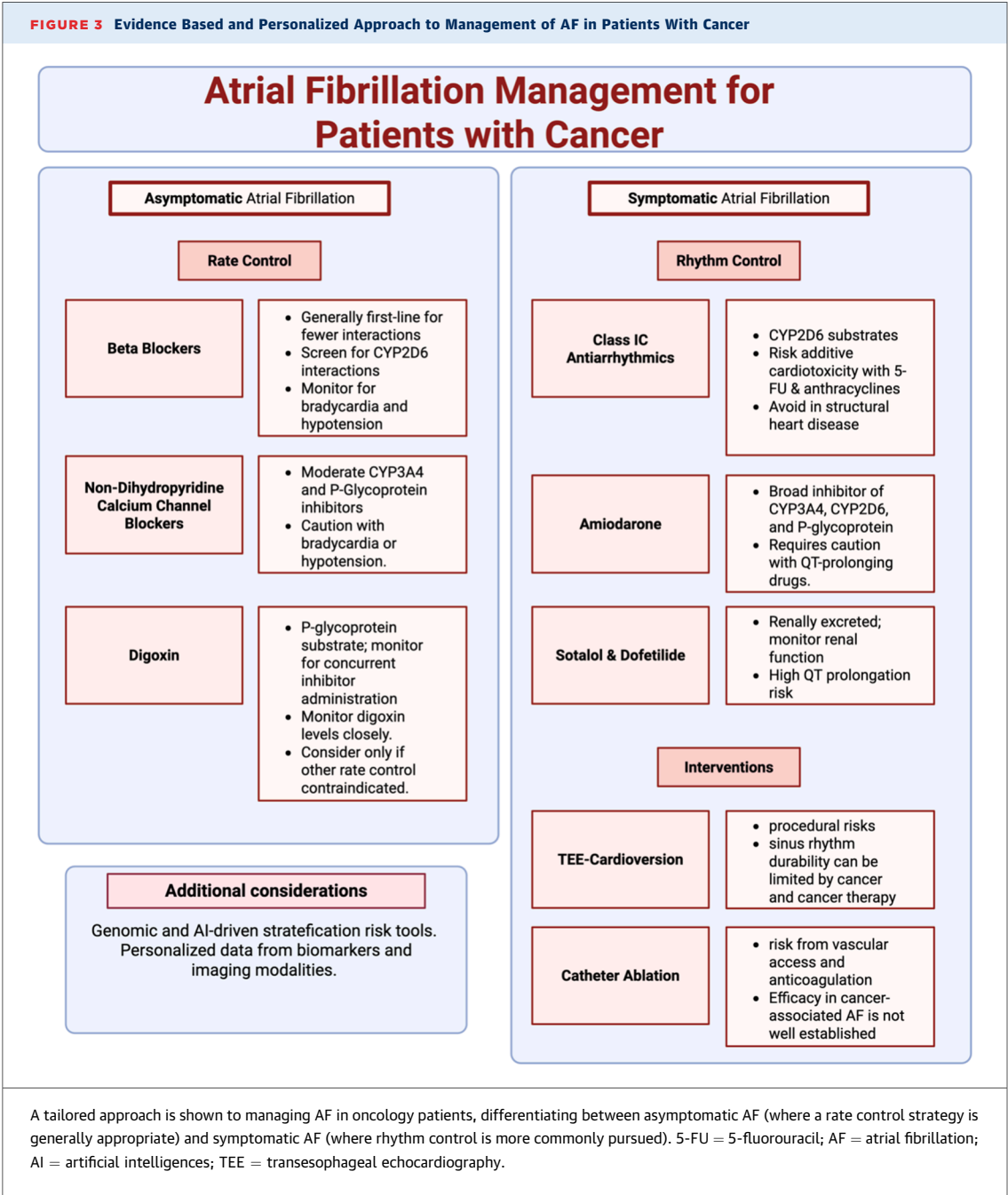
FIGURE 2 Paradigm of a Personalized Approach to the Management of AF in Patients With Cancer

avored. Beta-blockers are typically the agents of choice because of their efficacy and relatively benign interaction profile; however, caution is warranted when considering nondihydropyridine calcium channel blockers and digoxin. Many systemic therapies may inhibit cytochrome P450 3A4 and P-glycoprotein pathways, potentially elevating plasma concentrations of these agents, thereby increasing the risk of toxicity.^{131,135} Structured medication reconciliation and interdisciplinary consultations with clinical pharmacologists are crucial in identifying and mitigating these drug-drug interactions.¹³⁶

In symptomatic patients, or in those in whom AF exacerbates underlying heart failure, a rhythm control strategy may be indicated. Although early rhythm control has shown promise in reducing adverse outcomes in the broader AF population, its benefit in the context of active cancer treatment

remains uncertain because of the persistent proarrhythmic milieu induced by ongoing oncological therapies.^{131,137} The selection of antiarrhythmic medications in these patients must be approached with caution—not only because of the potential for QT prolongation and other electrophysiological disturbances but also because of the risk of significant pharmacokinetic interactions with cancer treatments.¹³⁸

Anticoagulation strategies further complicate the management of AF in cancer patients. Although the CHA2DS2-VASc score is routinely used to assess stroke risk in the general AF population, its predictive accuracy may be diminished in patients with cancer, who often experience additional bleeding risks related to thrombocytopenia and other treatment-induced coagulopathies.^{139,140} Studies have highlighted the relative safety and efficacy of

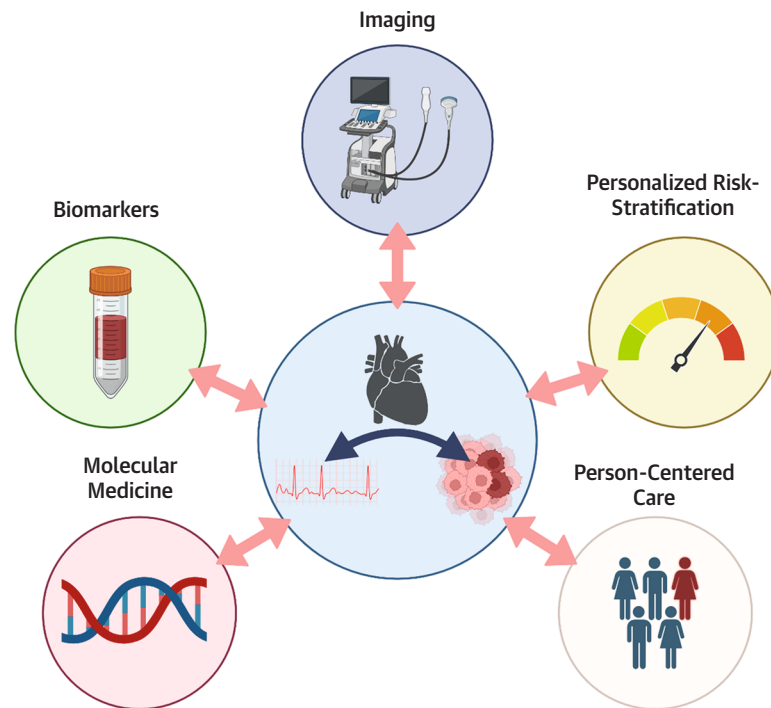


DOACs in this setting; however, the potential for interactions with agents metabolized by CYP3A4 or affected by P-glycoprotein must be carefully weighed.¹⁴⁰⁻¹⁴²

A comprehensive, multidisciplinary approach is paramount when managing AF in the context of cancer. Cardiologists, oncologists, and pharmacists should work collaboratively to individualize therapy, balancing the benefits of arrhythmia control and stroke prevention against the risks of bleeding and

adverse drug interactions¹³¹ (Figure 3). Continuous monitoring, whether with traditional electrocardiogram surveillance or emerging wearable technologies, can facilitate early detection of arrhythmic events and guide timely intervention, while also allowing for dynamic adjustments in therapy as the patient's oncological regimen evolves.¹⁴³

The challenges are further compounded by the advent of novel cancer therapies, including immune checkpoint inhibitors and next-generation tyrosine

CENTRAL ILLUSTRATION Personalized Management of Atrial Fibrillation in Cancer:
A Precision Cardio-Oncology Framework

Grewal US, et al. JACC Clin Electrophysiol. 2026;12(1):183-199.

kinase inhibitors, which have been associated with unique electrophysiological side effects. For example, although ibrutinib has a well-documented association with increased AF incidence, newer agents with greater selectivity may mitigate this risk, yet the overall impact on long-term arrhythmia outcomes remains an area of active investigation.¹⁴⁴⁻¹⁴⁶

The management of AF in patients with cancer necessitates an individualized, nuanced approach that addresses the dual challenges of cancer-directed therapies and arrhythmia management. Careful selection of rate or rhythm control strategies, judicious use of anticoagulation, and rigorous attention to drug-drug interactions are essential to optimizing outcomes in this high-risk patient population.^{147,148} Additionally, recent data have highlighted the role of novel cardioprotective agents such as sodium glucose cotransporter-2 inhibitors in preventing systemic therapy-related cardiotoxicity (including cardiac arrhythmias such as AF).^{149,150} The use of these novel agents should be prioritized and incorporated into the care of patients with AF and cancer wherever appropriate. Further studies are needed to identify

patients who are most likely to benefit from these therapies and if their benefits also extend to patients without comorbid type 2 diabetes mellitus.

**PRECISION CARDIO-ONCOLOGY:
THE WAY FORWARD**

The emerging field of precision cardio-oncology focuses on integrating molecular, genetic, and clinical data to enhance cardiovascular care in cancer patients. This personalized approach addresses the unique challenges of managing cardiovascular complications, including AF, in oncology. With the evolving understanding of the relationship between AF and cancer, several patient- and cancer-specific parameters have demonstrated a clear role for individualized care. As highlighted before, the risk of AF varies significantly by cancer type, being notably higher among esophageal, lung, stomach, myeloma, and lymphoma cancers.¹¹ Epidemiological data from the United States have also highlighted a disproportionately higher rise in cardiovascular mortality among older patients as well as male

patients with AF and cancer compared with female and younger patients.¹⁵¹ The care of older patients with cancer is further complicated by practical challenges such as nutrition, frailty, and bleeding risk.¹⁵² These data strengthen the case for adopting personalized approaches in the care of AF in cancer.

Moreover, advances in genomics and biomarkers offer new avenues for risk stratification and treatment. Genetic variants linked to AF susceptibility, identified through genome-wide association studies, and cancer-specific biomarkers can refine predictive algorithms.¹²⁹ Biomarkers such as troponins, natriuretic peptides, and inflammatory cytokines provide clinically relevant insights into cardiotoxicity and AF progression. AI and machine learning tools also hold promise for analyzing complex datasets to predict individualized risk profiles.¹⁵³ These technologies can integrate multimodal data, including genetic, imaging, and clinical parameters, to identify high-risk patients and guide tailored management strategies. AI-driven algorithms could also facilitate earlier detection of AF, allowing timely interventions.¹⁴⁸ Advances in pharmacogenomic analysis also have significant implications for personalizing cardiovascular therapies, particularly anticoagulation. Knowledge of genetic polymorphisms affecting warfarin metabolism (eg, CYP2C9, VKORC1) or DOAC efficacy can inform anticoagulant choice and dosing, mitigating risks of sub- or supratherapeutic anticoagulation.¹⁵⁴

Overall, personalized therapeutic strategies offer clear advantages over a “one-size-fits-all” approach, enabling safer and more effective cardio-oncology care for patients with AF and cancer. Continued

investigations and implementation of personalized models in clinical practice remain essential (**Central Illustration**).

CONCLUSIONS

A personalized approach to the management of AF in patients with cancer would not only allow care teams to devise strategies to prevent potential drug-related toxicities or adverse events but would also enable the selection of the most suitable treatment regimen for the patients. Use of novel biomarkers and cardiac imaging techniques would help identify patients at high risk for development of AF with or without initiation of chemotherapeutic drugs. Personalized risk stratification and robust cardiovascular surveillance in these patients would improve treatment tolerability, overall quality of life, and long-term outcomes. There is a growing need to incorporate precision cardio-oncology-based interventions into clinical studies and analyze the feasibility of integrating these into the routine care of patients with cancer.

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- KEY WORDS** atrial fibrillation, cancer, cardio-oncology