awareness for patients, families and health care professionals. We believe an informed and educated population is a critical mediator to improving healthcare both on an individual and system level. This would align with the evidence-based local models of best care for policy makers to improve well-being of AF patients. Finally, we intend to build a sustainable research platform for long-term future collaborations.

This 3-year funded NIHR programme has identified clinical partners in the three LMICs working in AF management who are keen to expand their knowledge in research to bring about changes that will benefit their patients and influence future methods of care. We have been working with our partners/patients to identify their training needs, formulate research questions with local stakeholders to assess need and plan effective and 'value for money' projects.

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*NIHR Global AF Reach Investigators (alphabetical): Ajini Arasalingam, Isabela Bensenor, Peter Brocklehurst, Kar Keung Cheng, Mei Feng, Alessandra Goulart, Sheila Greenfield, Yutao Guo, Mahesan Guruparan, Gustavo Gusso, Wang Hao, Lindsey Humphreys, Balachandran Kumarendran, Kate Jolly, Sue Jowett, Paulus Kirchhof, Emma Lancashire, Deirdre Lane, Dan Lasserson, Xuewen Li, Gregory Y.H. Lip (Co-PI), Trudie Lobban, Paulo Lotufo, Semira Manseki-Holland, David Moore, Krishnarajah Nirantharakumar, Rodrigo Olmos, Alena Shantsila, Isabelle Szmigin, Kumaran Subaschandren, Rajendra Surenthirakumaran, G. Neil Thomas (Co-PI).

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Correspondence:
Prof Gregory Y. H. Lip
Liverpool Centre for Cardiovascular Science,
University of Liverpool and
Liverpool Heart & Chest Hospital,
Liverpool, UK.
Tel: +44 151 600 1876
Email: gregory.lip@liverpool.ac.uk

Prof. Neil Thomas
co-corresponding author
Institute of Applied Health Research
University of Birmingham, UK
Email: g.n.thomas@bham.ac.uk

References

References are available as supplementary material at *European Heart Journal* online.

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Atrial Fibrillation in the Era of Emerging Cancer Therapies

Atrial fibrillation (AF) is becoming a global epidemic and is predicted to affect 6–12 million people in the USA by 2050 and 17.9 million in Europe by 2060.[1–4] Concurrently, with the advent of newer cancer therapies, global cancer survival has dramatically increased, with an expected overall survival of over 18 million persons by 2030.[5] Increasingly, the profile of patients presenting with AF has disproportionately shifted to encompass patients with current or prior cancer diagnoses.

The 'REasons for Geographic and Racial Differences in Stroke' (REGARDS) cohort of nearly 15 500 patients reported a 20% higher adjusted risk of AF in patients with cancer compared to those without cancer.[6] Notably, the incidence of AF was appreciated to be 3.0–4.5 times higher within the first year of a cancer diagnosis compared to later years.[1,7] Conversely, an increased risk of cancer among patients presenting with AF has also been appreciated.[4] For example, in a Danish cohort of 270 000 patients with new-onset AF, the standardized rate incidence ratio of cancer diagnosis was 5.11 in the first 3 months after diagnosis of AF.[8] Similarly, Kim *et al.*[5] reported a 2.6-fold increased incidence of a cancer diagnosis at 1 year after developing AF.

Moreover, the cardiovascular and overall prognosis with AF is worse among cancer patients compared to those without cancer, with a two-fold higher adjusted risk for thromboembolic complications, and a six-fold higher adjusted risk for heart failure,[9] as well as a 10-fold higher risk of adjusted 30-day mortality.[9]

The increased incidence of AF in the setting of malignancy may be due to a variety of factors, including the cancer itself as well as the potential medical and surgical treatments associated with cancer

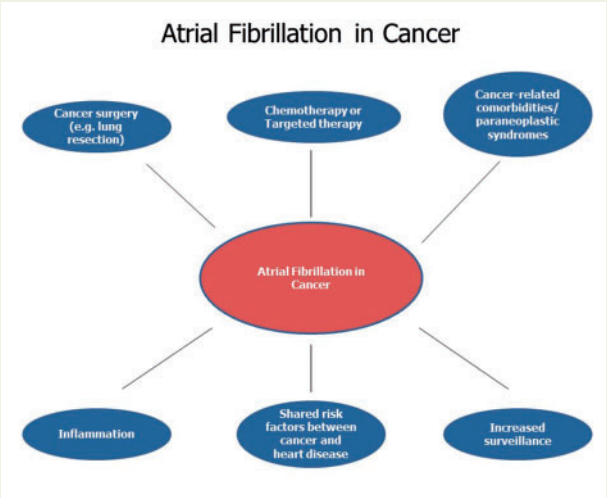

Figure 1 Common risk factors between atrial fibrillation and cancer.

(*Figure 1*). For example, in cancer states such as chronic lymphocytic leukaemia, the incidence of AF is increased irrespective of the treatment delivered.[10] Similarly, the incidence of AF during the perioperative period of cancer surgery ranges from 6–28% for lung resection, 4–5% for colectomy, and 9–11% for oesophagectomy.[10,11] Moreover, AF is a known cardiotoxicity of several chemo-, targeted-, and immuno-therapeutics, including anthracyclines, melphalan, ibrutinib, checkpoint inhibitors, and interleukin-2.[12] Broadly, proposed mechanisms driving cancer therapy-related arrhythmogenicity include myocardial ion-channel interactions, excess oxidative stress, fibrosis, and increased levels of inflammatory mediators[11,13] (*Figure 2*). However, more study is needed, particularly with emerging targeted and immune-based therapies.

Although the prognosis of AF is generally worse in cancer patients, specific guidelines directing the treatment of AF in cancer patients are lacking.[5] Nevertheless, the 2019 American College of Cardiology/Heart Rhythm Society (ACC/HRS) update on the management of AF suggested several strategies that may be applicable to cancer patients.[14] As with all patients with AF, management of AF in the setting of cancer should start with a calculation of CHA_2DS_2-VASc score and those with elevated score ($\geq$2 in men and $\geq$3 in women) should be offered anticoagulation.[14] The direct applicability of the CHA_2DS_2-VASc (or the $CHADS_2$) score in cancer patients is uncertain.[15] However, in a recent study, patients with cancer and AF had higher rates of thromboembolism only at low CHA_2DS_2-VAsc scores (0–1) when compared with non-cancer patients.[16] Another study demonstrated that $CHADS_2$ score was insufficient to predict thromboembolic complications in cancer patients with new-onset AF.[17] As such, a scoring system specific to cancer patients may be needed to optimize outcomes.

The most effective anticoagulant(s) to prevent AF-associated thromboembolism in cancer patients remains an area of active investigation. Although low-molecular weight heparin (LMWH) was recommended as the standard of care in treating cancer-associated venous thromboembolic events,[18,19] there is limited high-quality data on the use of LMWH in thromboprophylaxis of AF.[20] Current ACC/HRS guidelines recommend the use of a direct oral anticoagulant (DOAC) over warfarin in DOAC-eligible patients including those with cancer.[13,14] A sub-study of the ENGAGE AF TIMI 48 trial comparing edoxaban to warfarin demonstrated significant improvement in the composite endpoint of ischaemic stroke/systemic embolism/myocardial infarction in patients with active cancer compared to those without malignancy.[21] A sub-analysis of the ARISTOTLE study evaluating patients with a history of active or prior cancer demonstrated superior

Cancer Therapies Associated with Atrial Arrhythmias

Cancer therapy	Drugs/risk factors	General mechanism of action	Arrhythmia mechanism of action
Traditional chemotherapies			
Anthracyclines	Doxorubicin, daunorubicin, idarubicin, epirubicin	Inhibition of DNA/RNA synthesis	Direct cardiotoxicity
Antimetabolites	Fluorouracil, capecitabine	Thymidylate synthase	Myocardial ischemia
Alkylating agents	Cisplatin, Melphalan, Cyclophasphamide, Ifosfamide	Inhibition of DNA/RNA synthesis	Mitochondrial abnormalities, apoptosis, ROS, inflammation
Anti microtubule agent	Paclitaxel, Docetaxel, Gemcitabine, gemcitabinevinorelbine	Block cell division, coronary flow and left ventricular systolic pressure	May be by blocking cell division
Targeted therapies			
Tyrosine kinase inhibitors	Ibrutinib, Sunitinib, Corafenib, Crizotinib, Cetuximab	Inhibition of Bruton's tyrosine kinase, PI3K–Akt pathway	May be through direct kinase inhibition
Immune-based therapies			
Interleukins	Interleukin-2	Immune modulation	Immune mediated
Immune checkpoint inhibitors	Ipilimumab, pembrolizumab, nivolumab, other	Activation of immune system	Immune mediated
Radiation based therapy	Radiation	Direct cellular damage	Myocardial fibrosis

Figure 2 Mechanism of action between cancer therapies and associated atrial fibrillation.

efficacy of apixaban vs. warfarin at preventing the primary endpoint when compared with patients without cancer.[22] Comparative effectiveness data of patients with AF and cancer have consistently shown DOACs to be associated with similar (or lower) risks of bleeding and stroke compared with conventional strategies, such as warfarin.[23]

Despite their efficacy in preventing AF-associated thromboembolic complications, increased scrutiny must be utilized when prescribing DOACs in cancer patients. Cancer patients frequently have thrombocytopenia and other bleeding diatheses. If the bleeding risk is substantial and overall life-expectancy is limited (<12 months), foregoing anticoagulation may be a reasonable choice even at higher CHA_2DS_2-VASc scores.[24] Moreover, frequent drug–drug interactions with cancer therapeutics and/or renal impairment may limit the use of anticoagulants, particularly, the DOACs.[13]

In patients that are unable to tolerate long-term anticoagulation, percutaneous left atrial appendage closure may be an option, however, this procedure has not been specifically studied in the cancer population.[14] In general, the management of AF in cancer patients should follow a shared decision-making model.[20] Though dedicated studies in cancer patients are lacking, AF catheter ablation may be a reasonable option in highly symptomatic patients or those with heart failure with reduced ejection fraction who can tolerate at least short-term anticoagulation.[14] In addition, patients who are overweight or obese should be advised weight loss and combination of risk factor modification is recommended.[14] Finally, it is essential to recognize the potential interactions of antiarrhythmic medications or anticoagulants with different cancer therapeutics in order to minimize toxicity and mitigate risk. Specific details about management of AF and caveats specific to cancer are presented in (*Figure 3*).

In conclusion, AF is an increasingly frequent presenting cardiovascular condition among cancer patients. Shared epidemiology and risk factors contribute to the association between cancer and AF. However, AF may also be a manifestation of cardiotoxicity of specific cancer treatments. The optimal AF management strategy in cancer patients is uncertain due to the lack of dedicated prospective studies in this population. Direct oral anticoagulants represent a convenient and patient-centred anticoagulation strategy to minimize AF-associated thromboembolism, with emerging data supporting their safety and efficacy in the care of cancer patients. Nonetheless, the application of traditional

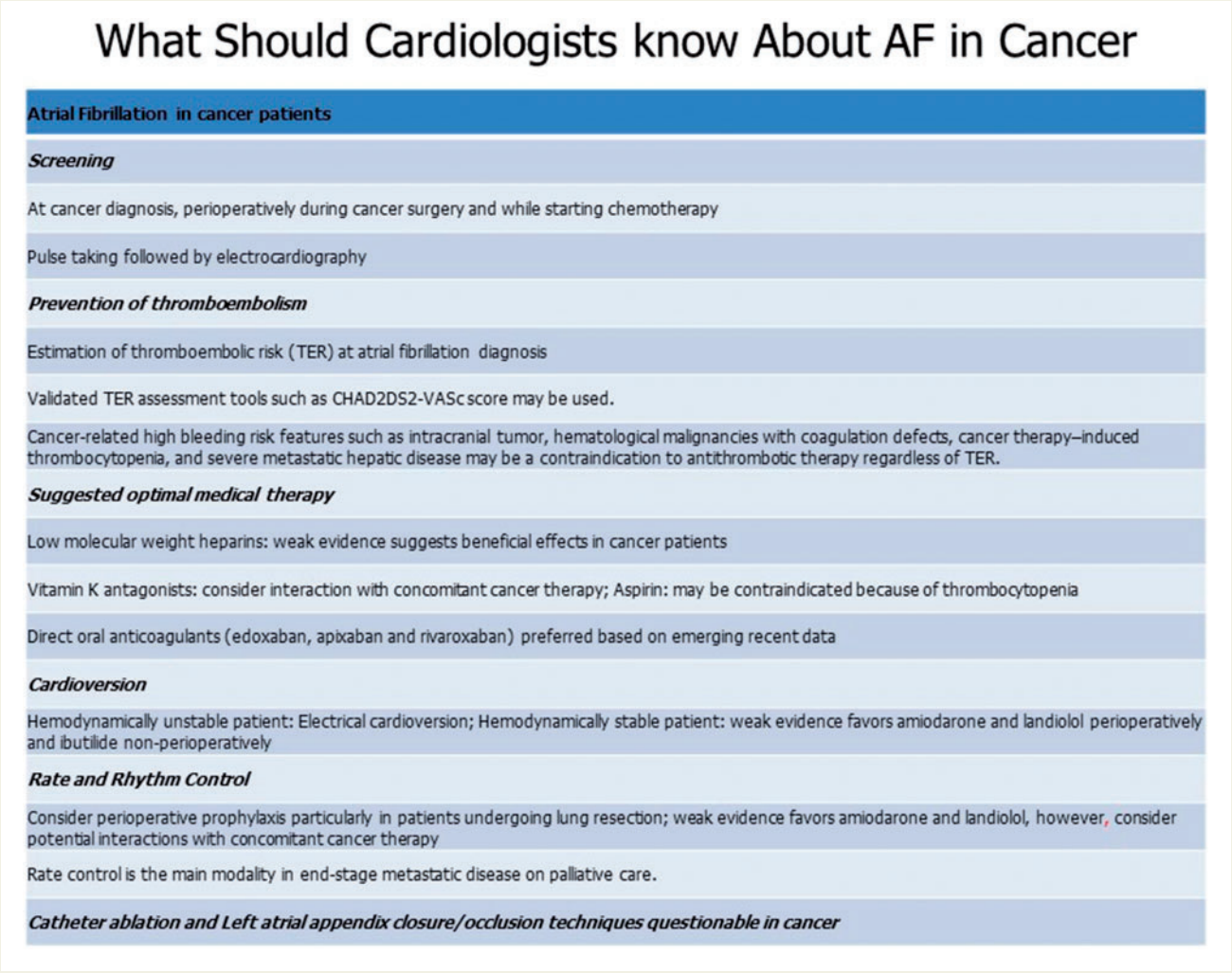

Figure 3 Management of atrial fibrillation in cancer.

risk scores to determine the likelihood of AF-associated thromboembolism may not be sufficient in this population.

It is evident that the management of AF in cancer patients can be challenging and is best accomplished with a longitudinal multidisciplinary approach with frequent clinical assessment by cardio-oncology specialists.

*Both authors contributed equally.

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References

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Corresponding author:
Avirup Guha*, MD FACC RPVI
Clinical Assistant Professor of Cardiology
Harrington Heart and Vascular Institute
Case Western Reserve University
University Hospitals Samaritan Medical Center
350 Hillcrest Drive, Upper Level
Ashland, Ohio-44805, USA
Phone: 419-289-9800
Email: avirup.guha@uhhospitals.org


Amit K. Dey*, MD
National Heart,
Lung and Blood Institute, NIH,
Building 10-CRC Room 5-5232,
Bethesda, MD


Hani Jneid, MD
Division of Cardiology,
Michael E. DeBakey VA Hospital,
Baylor College of Medicine,
Houston, TX


Javier Pinilla Ibarz, MD PhD
Division of Cardiology,
University of South Florida,
Tampa, FL


Daniel Addison, MD
Cardio-Oncology Program,
Division of Cardiology,
Ohio State University,
Columbus, OH


Michael Fradley, MD
Division of Cardiology,
University of South Florida,
Tampa, FL

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Oral Anticoagulation in patients with non-valvular atrial fibrillation and a CHA_2DS_2-VASc score of 1

A current opinion of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Council on Stroke

Background

Current ESC guidelines recommend the initiation of oral anticoagulation (OAC); preferably non-vitamin K antagonist oral anticoagulants (NOACs) or vitamin K antagonists (VKAs) in atrial fibrillation (AF) patients with a CHA_2DS_2-VASc score $\geq$2 for lowering the individual stroke risk, while an OAC approach in individuals with a CHA_2DS_2-VASc score of 0 is not recommended.[1]

However, OAC in patients presenting with a CHA_2DS_2-VASc of 1 (CHA_2DS_2-VASc of 2 in women) remains a challenging approach in clinical practice and physicians need to carefully balance the individual benefit of reducing thromboembolic risk with OAC against the potential harm due to an increase in bleeding risk in this patient population.

In the current opinion statement of the ESC Working Group of Cardiovascular Pharmacotherapy and the ESC Council on Stroke, the authors summarize the currently available evidence in this field.[2] Most importantly, an easily applicable approach for a personalized refinement of the individual thromboembolic risk in patients with AF and a CHA_2DS_2-VASc score of 1 that guides clinicians through the question whether to anticoagulate or not, is provided.

Focus on, doing no harm

The assessment of patients' individual risk for major bleeding is a key prerequisite for initiation of OAC. The HAS-BLED score mirrors a widely validated and accepted tool for this purpose. Based on the individual bleeding risk of 0.59–1.51% per year in HAS-BLED score of 1 and an annual thromboembolic risk of 0.6–1.3% in CHA_2DS_2-VASc of 1, physicians are not able to draw a definite conclusion concerning the net benefit of OAC in relevant patients. Therefore, a general recommendation for OAC therapy in these individuals is not justified and patients that benefit from OAC need to be identified using a personalized approach. In contrast, patients with a HAS-BLED score of 2 (or even higher) an OAC should not be initiated in intermediate thromboembolic risk patients based on an annual bleeding rate of 1.88–3.20% per year.[3–6]