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CLINICAL PRACTICE

Anticoagulation in patients with atrial fibrillation and active cancer: an international survey on patient management

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Background In patients with active cancer and atrial fibrillation (AF) anticoagulation, thrombotic and bleeding risk still entail uncertainty.

Aim We explored the results of an international survey examining the knowledge and behaviours of a large group of physicians.

Methods and results A web-based survey was completed by 960 physicians (82.4% cardiologists, 75.5% from Europe). Among the currently available anticoagulants for stroke prevention in patients with active cancer, direct oral anticoagulants (DOACs) were preferred by 62.6%, with lower values for low molecular weight heparin (LMWH) (24.1%) and for warfarin (only 7.3%). About 46% of respondents considered that DOACs should be used in all types of cancers except in non-operable gastrointestinal cancers. The lack of controlled studies on bleeding risk (33.5% of respondents) and the risk of drug interactions (31.5%) were perceived as problematic issues associated with use of anticoagulants in cancer. The decision on anticoagulation involved a cardiologist in 27.8% of cases, a cardiologist and an oncologist in 41.1%, and a team approach in 21.6%. The patient also was involved in decision-making, according to ~60% of the respondents. For risk stratification, use of CHA_2DS_2-VASc and HAS-BLED scores was considered appropriate, although not specifically validated in cancer patients, by 66.7% and 56.4%, respectively.

Conclusion This survey highlights that management of anticoagulation in patients with AF and active cancer is challenging, with substantial heterogeneity in therapeutic choices. Direct oral anticoagulants seems having an emerging role but still the use of LMWH remains substantial, despite the absence of long-term data on thromboprophylaxis in AF.

Keywords Anticoagulation • Atrial fibrillation • Direct oral anticoagulants • Cancer • Low molecular weight heparin • Metastasis • Risk stratification • Stroke • Survival • Survey • Warfarin

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Introduction

Atrial fibrillation (AF) is the commonest arrhythmia encountered in clinical practice with an increasing incidence with age.[1] Atrial fibrillation may occur in patients with cancer, with a prevalence of 2.4% at the time of cancer diagnosis and an incidence of 1.8% during the course of the disease.[2]New-onset AF in patients with active cancer appears to be associated with negative prognostic implications, even at short term, with stroke as a possible cause of death.[3] In consideration of the improved and relatively favourable outcome of many types of cancer, it is important to address the AF-associated risk of stroke, and specifically the need of anticoagulation prophylaxis to reduce this risk and to define the patients' selection when its risk–benefit profile can be predicted as favourable.[4] As a matter of fact, the use of anticoagulants for reducing the high risk of AF-associated thromboembolism in cancer patients usually raises concerns related to the risk of bleeding. In patients with cancer, the risk of bleeding may be actually dependent on several factors (e.g. type of cancer, localized bleeding for tumour invasion or tumour metastasis, generalized haemorrhagic diathesis, thrombocytopenia, supratherapeutic levels of INR, also for interaction with chemotherapies, post-surgery and post-radiation tissue damage).[4–6] The availability of direct oral anticoagulants (DOACs) has offered new therapeutic options for long-term treatment, although no specific trials have focused on the challenging scenario of patients with active cancer.[4–8] However, data from registries in specific types of malignancy, such as breast cancer, seem to confirm the safety profile of DOACs also in this type of patients.[9,10] As a result of the generalized concern on bleeding risk, registries such as the EORP-AF long-term general registry highlighted an under-prescription of oral anticoagulants in patients with history of malignancies.[11] The aim of this survey, promoted by the Council of Cardio-Oncology of the European Society of Cardiology (ESC), was to obtain a view of the beliefs, perceptions, and attitudes with a specific focus on the factors considered for prescription of anticoagulants in the management of AF in cancer patients.

Methods

A cross-sectional survey was carried out during the last 3 months of 2019 involving a group of European and non-European physicians, who had previously been engaged in activities of the ESC with interest in AF and/or in Cardio-Oncology. Physicians were enrolled using social media or direct email and were asked to complete the online survey containing 17 questions. The entire questionnaire is reported in detail in the Supplementary material online, *Appendix*. For all the questions only one choice for the answer was allowed. Data were collected anonymously and within the EU General Data Protection Regulation policy. The survey included the widely used scores for stratifying the risk of stroke and bleeding, i.e. the CHA_2DS_2-VASc score [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 years, and sex category (female >65 years)] and the HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly, each item leading to 1 point).[12] According to literature,[13] active cancer was defined as cancer diagnosed within the previous 6 months; recurrent, regionally advanced or metastatic cancer, or cancer for which treatment had been administered within 6 months, or haematological cancer without complete remission.

Data are presented as proportions. Following whole-sample analysis, separate sub-analyses were carried out based on the demographic information provided. Respondents were stratified into subgroups according to age (≤50 or >50 years), sex, cardiologists vs. non-cardiologists, and geographical region (Europe vs. Rest-of-the-World). For the practice setting sub-analysis, all pairwise comparisons between subgroups were performed using a χ^2 test. Statistical significance was considered when the *P*-value was <0.05.

Results

Between October and December 2019, 1146 physicians participated to the online anonymous survey, and 960 of them completed the entire survey with an answer to all the detailed questions on clinical management of AF. The characteristics of respondents are reported in *Figure 1* for the overall group of 1146 physicians and in Table 1 for the 960 physicians who completed the survey. As shown, the larger majority was represented by cardiologists, with very few qualifying themselves as cardio-oncologists. Three quarters of participants were from Europe, and one-third were from Southern Europe. Although the place of work of the majority of respondents was in hospital, one quarter were involved in out-of-hospital cardiology practice. Young physicians were a substantial proportion of respondents.

The specific contents of the survey will be presented in the following series of figures, with proportions related to the overall number of the 960 respondents. The analysis by groups is not well balanced considering the professional groups, as cardiologists accounted for a higher proportion than other professions (791 vs. 169) and the European respondents represented a higher proportion than the Rest-of-the-World group (725 vs. 235), while the age groups (541 > 50 vs. 419 ≤ 50 years) and sex groups (632 males vs. 328 females) were numerically enough similar. In view of these limitations of the analysis by groups, only the most important and significant results will be reported.

The use of anticoagulants in patients with AF, active cancer, and with a profile at risk of thromboembolism/stroke was analysed, as shown in *Figure 2*, in terms of indications (*Figure 2A*) and in terms of specific preference for the type of anticoagulant agent, specifically low molecular weight heparin (LMWH), warfarin, or fondaparinux (*Figure 2B*). Most of respondents recognized that in patients with active cancer, AF, and a CHA_2Ds_2-VASC score ≥2, oral anticoagulation is indicated if there is no evidence of cerebral metastases (*Figure 2A*) and prioritized the use of DOACs (*Figure 2B*).

The analysis by age group showed some differences in preferences, with respondents ≤50 years slightly less likely to use OAC after checking drug–drug interactions than the older colleagues (70.6% vs. 79.2%, $P = 0.002$), and expressed a relatively higher preference for LMWH at anticoagulant (21.4% vs. 15.5%, $P = 0.02$) or at prophylactic dosages (7.0% vs. 4.1%, $P = 0.049$). The preference for OAC had also revealed differences in terms of profession of respondents (76.1% of cardiologists vs. 66.3% of non-cardiologists, $P = 0.008$) and geographic area (80.9% of Rest-of-the-World vs.72.3% of European responders, $P = 0.009$). Conversely, Europeans expressed a relatively greater preference for LWMH at therapeutic dosages vs. Rest-of-the-World (21.1% vs. 11.9%, $P = 0.002$). Among non-cardiologists, 10.7% expressed a preference for LWMH at prophylactic dosages and this

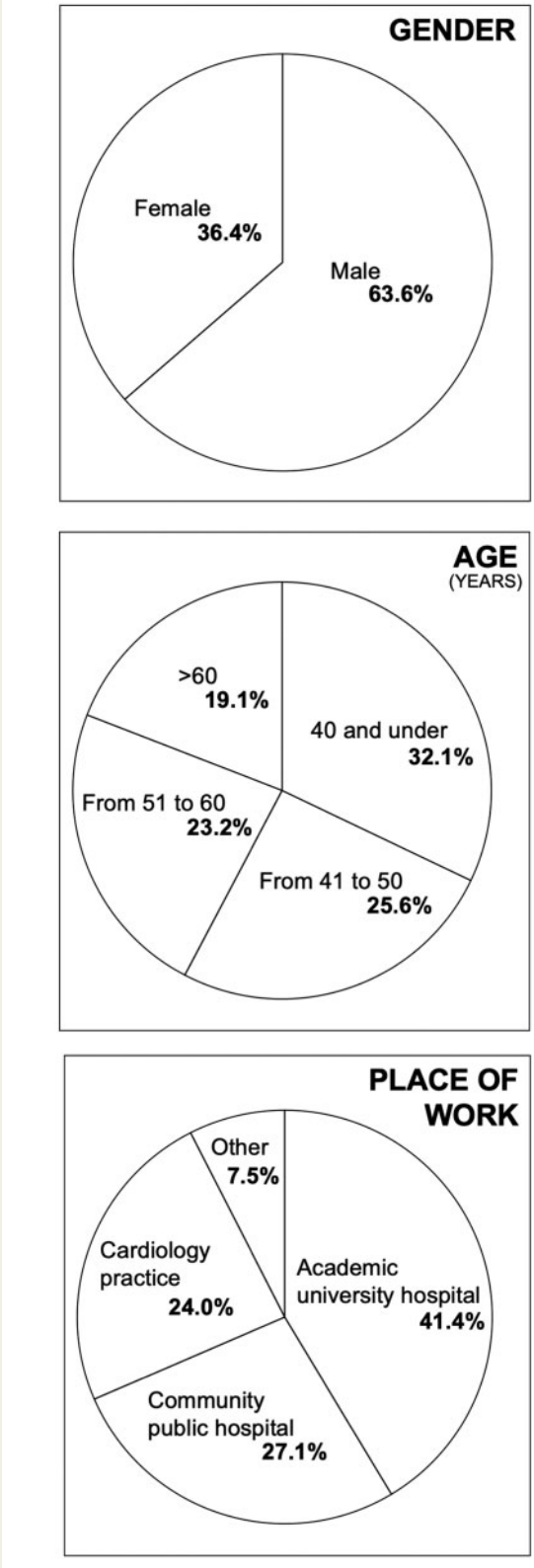

Figure 1 General characteristics of physicians who had access to the survey.

Table 1 Characteristics of the 960 physicians who completed the survey

	N 960	% 100%	
Profession of participants			
Cardiologist	791	82.4%	
Other	169	17.6%	
Oncologist	2	0.2%	
Haematologist	5	0.5%	
Cardio-oncologist	30	3.1%	
Cardiologist in training	34	3.5%	
Oncologist in training	1	0.1%	
Haematologist in training	1	0.1%	
Primary physician	21	2.2%	
Internist	75	7.8%	
Age (years)			
40 and under	287	29.9%	
From 41 to 50	254	26.5%	
From 51 to 60	234	24.4%	
>60	185	19.3%	
Gender			
Male (%)	632	65.8%	
Geographic area			
Europe	725	75.5%	75.5%
Western Europe	106	11.0%	
Eastern Europe	178	18.5%	
Northern Europe	130	13.5%	
Southern Europe	311	32.4%	
Africa	36	3.8%	24.5%
Asia and Oceania	109	11.4%	
North America	17	1.8%	
South and Central America	73	7.6%	
Place of work			
Academic university hospital	389	40.5%	69.0%
Community public hospital	273	28.4%	
Cardiology practice	228	23.8%	23.8%
Other	70	7.3%	7.3%

was observed more frequently in this group than among cardiologists (4.7%, $P = 0.002$).

The following questions' group was focused on decision-making in patients with active cancer and AF. *Figure 3A* shows the most important limitations perceived in antithrombotic prophylaxis, mostly related to the lack of controlled/randomized studies and the risk of interactions with chemotherapeutic agents. No significant differences among respondents' groups were noted for these answers. The respondents were also asked to report what physicians, alone or in collaboration, are usually involved in prescription of anticoagulants (*Figure 3B*). As shown, the decision on anticoagulation involved a cardiologist in 27.8% of cases, a cardiologist and an oncologist in 41.1%, and a team approach in 21.6%. The patient was also involved in decision-making, according to ~60% of the respondents (*Figure 3C*).

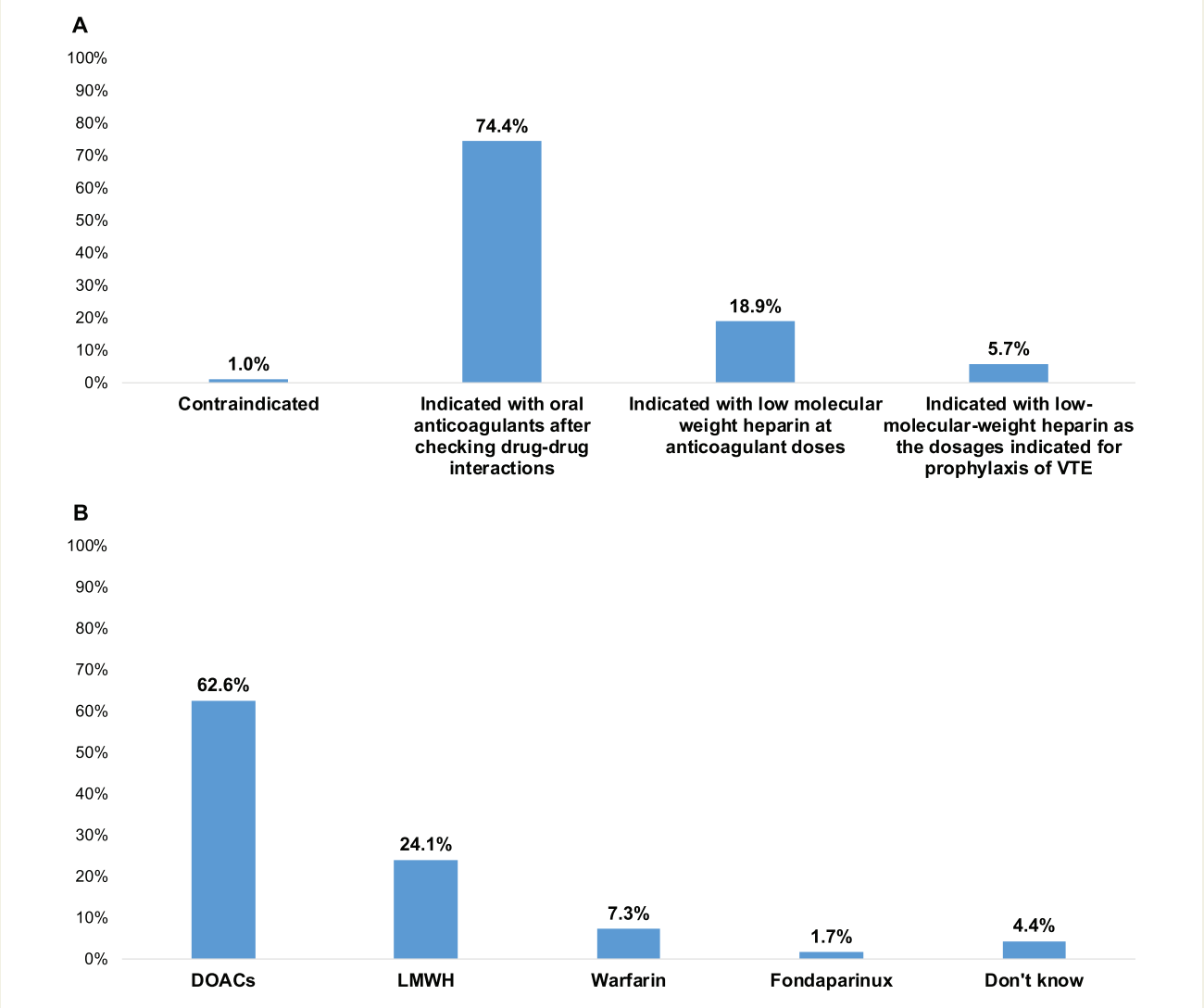

Figure 2 Questions on indications for use of anticoagulants in patients with active cancer and atrial fibrillation. (*A*) In a patient with active cancer, atrial fibrillation, and a CHA_2DS_2-VASc ≥2, with no evidence of cerebral metastases what do you think about anticoagulation? (*B*) In a patient with active cancer with atrial fibrillation and CHA_2DS_2-VASc score ≥2 which anticoagulant treatment is indicated in your view to prevent the risk of stroke? DOACs, direct oral anticoagulants; LMWH, low molecular weight heparin, VTE, venous thromboembolism.

Some differences were found in the answers to this question according to age with only 56.2% of respondents ≤50 years reporting that the patient is always involved in the decision-making compared to 64.7% of the older colleagues ($P = 0.008$). Non-cardiologists reported that decision-making about anticoagulation is the result of a multi-specialist team more often than cardiologists (34.3% vs. 18.8%, $P = 0.001$).

The use of scores for risk stratification for thromboembolism/stroke and for bleeding usually through CHA_2DS_2-VASc and HAS-BLED was analysed in terms of potential limitations (*Figure 4A and B*).

Figure 5 shows the results of questions related to decision-making in very specific contexts, such as use of anticoagulants in patients with cerebral metastases and a favourable prognosis (*Figure 5A*) or in patients with first detected AF with subsequent restoration of sinus rhythm (*Figure 5B*).

The answers to the question shown in *Figure 5B* differed according to respondents' age, since indication to OAC only in case of AF recurrence was reported by 17.6% of respondents aged >50 years vs. 25.5% of respondents aged ≤50 years ($P = 0.003$). Moreover, more non-European respondents (11.1%), as compared to Europeans (4.1%), did not consider the use of anticoagulants where patients had reverted to sinus rhythm, despite a significant stroke risk with CHA_2DS_2-VASc ≥2.

Finally, the current role of warfarin (*Figure 6A*) and DOACs (*Figure 6B*) for preventing stroke/thromboembolism in patients with AF and cancer at risk of stroke/thromboembolism, in terms of therapeutic choices according to patient profile, risks, and other factors is shown in *Figure 6*.

In the questions exploring the role of oral anticoagulants, more male respondents (16.9% vs. 10.7% female, $P = 0.001$) and more Non-European respondents (21.7% vs. 12.6% Europeans, *P*-value

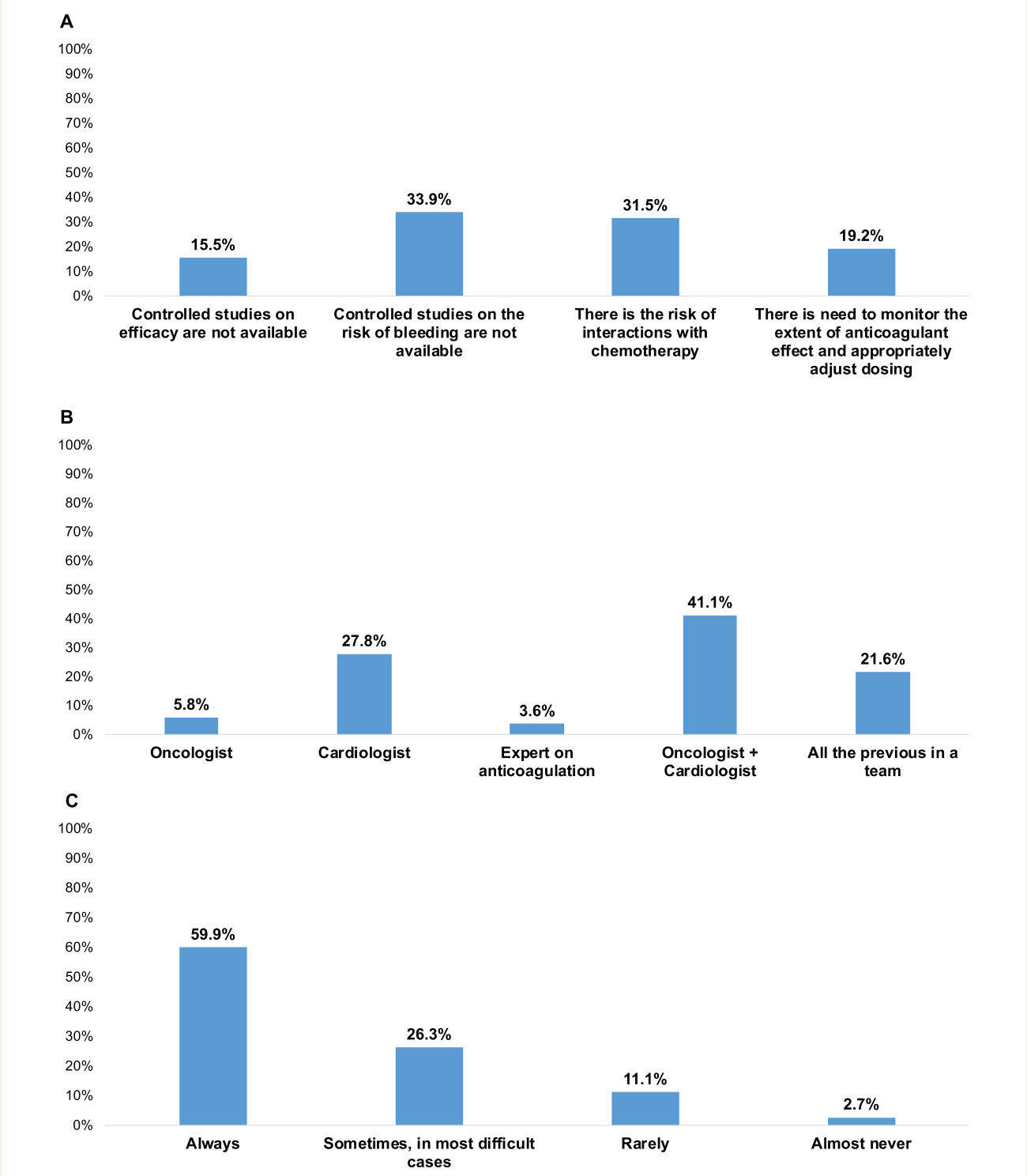

Figure 3 Questions on decision-making in patients with active cancer and atrial fibrillation. (*A*) Which are the most important limitations in the prophylaxis of stroke in patients with active cancer and atrial fibrillation? (*B*) In a patient with active cancer and atrial fibrillation at risk of stroke who usually takes the decision on prescribing or not of anticoagulation in your setting? (*C*) Is the patient involved in decision expressing his/her preferences on the risk and benefit of anticoagulation after appropriate information?

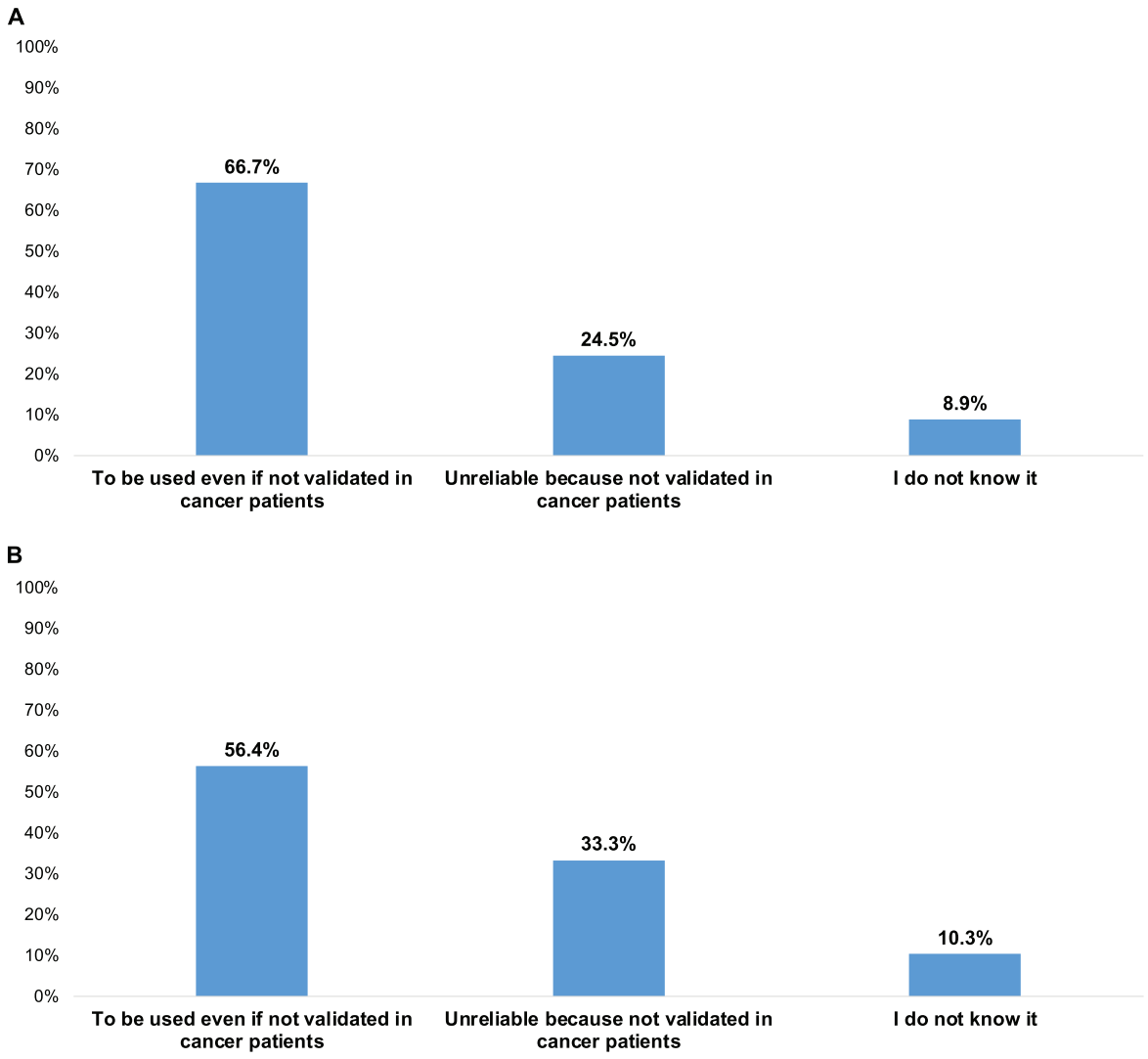

Figure 4 Questions on risk stratification using scores for the risk of thromboembolism/stroke and for the risk of bleeding. (*A*) What do you think about the use of the CHA_2DS_2-VASc score in oncology patients with atrial fibrillation? (*B*) What do you think about use of the HAS-BLED score for the risk of bleeding in oncology patients with atrial fibrillation?

0.001) reported to prefer using warfarin as it allowed the therapeutic effect to be measured by monitoring the INR. Moreover, more female respondents (24.7% vs. 17.4% male, $P = 0.007$) and relatively more Europeans (22.2% vs. 12.8%, $P = 0.002$) reported that they would consider warfarin as a second choice as compared to LMWH at therapeutic doses.

With regard to the role of DOACs, relatively more Europeans than Non-Europeans reported that, in their opinion, DOACs can be used in all cancer types, with the exception of non-operable gastrointestinal cancers (48.4% vs. 37.4%, $P = 0.003$).

Discussion

The present survey, carried out in a large sample of participants, highlights that there is a large heterogeneity with regard to decision-making for anticoagulation in patients with active cancer and AF, with differences in perceptions and beliefs than can be interpreted in view of the absence of direct, solid evidence for many aspects of AF management in this specific context.[5,6,14]

With regard to the specific type of anticoagulants that can be prescribed to patients at risk of stroke, it is clear that the availability of DOACs actually widens the therapeutic possibilities in this setting, especially in consideration of the limitations of warfarin in terms of food and drugs interactions, and the variation of the anticoagulant effect, mediated by vitamin K and liver function. Despite the lack of dedicated trials, there are data on DOACs derived from *post hoc* analysis of randomized trials and observational studies.[4,15–19] The interpretation of studies from the literature including cases of active cancer should be differentiated from studies including cases of remote cancer.[15–20] In the ISTH (International Society on Thrombosis and Haemostasis) guidance document on DOACs in the treatment

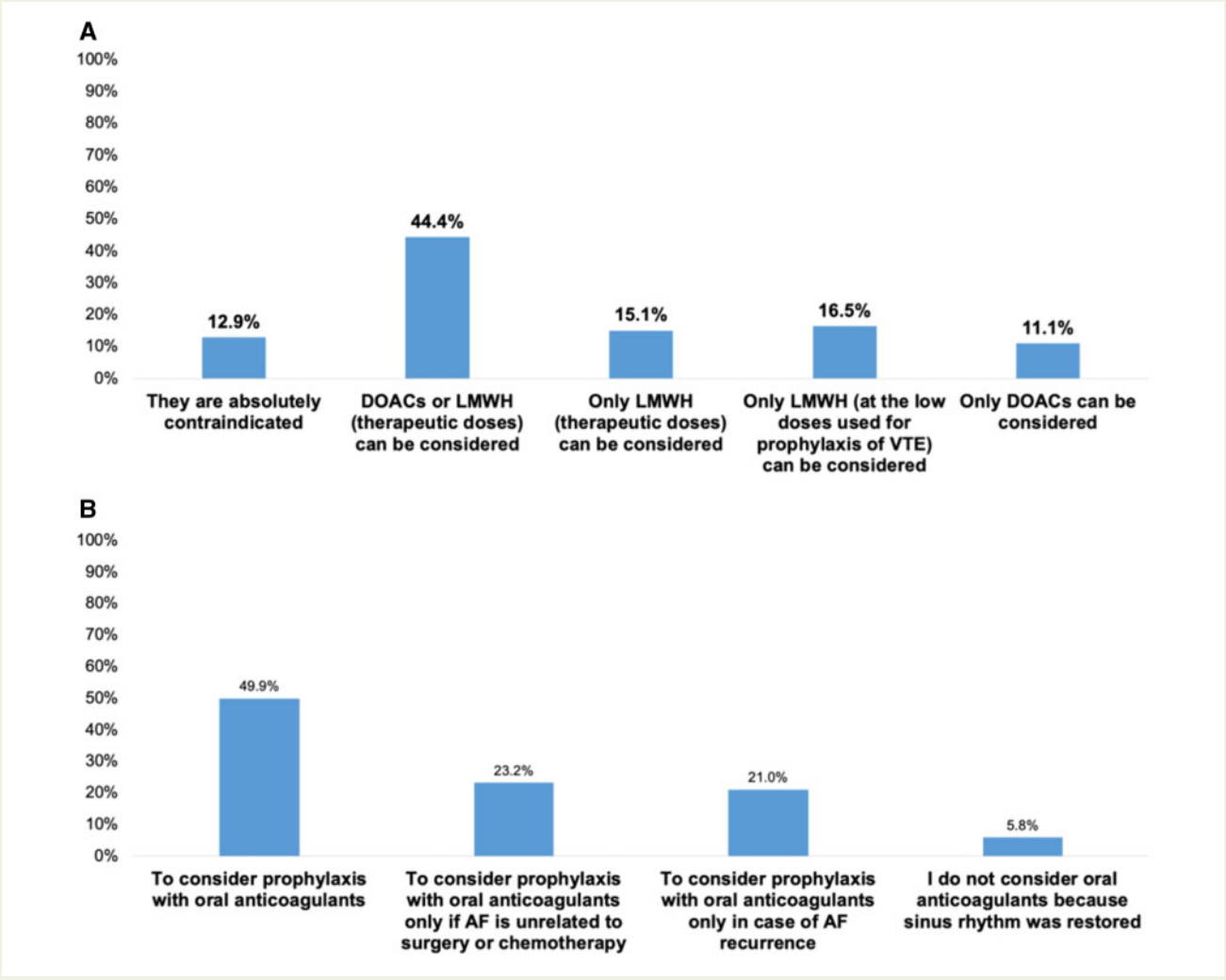

Figure 5 Questions on decision-making for anticoagulants in specific clinical scenarios (brain metastasis and first detected atrial fibrillation with resumption of sinus rhythm). (*A*) What do you think about the use of oral anticoagulants for atrial fibrillation in patients with stable brain metastases and prognosis better than 6 months? (*B*) In a patient with active cancer with first detected atrial fibrillation with subsequent resumption of sinus rhythm what is your decision-making if CHA_2DS_2-VASc is ≥2? AF, atrial fibrillation; DOACs, direct oral anticoagulants; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

of cancer-associated venous thromboembolism,[13] active cancer is defined as cancer diagnosed within the previous 6 months, recurrent, regionally advanced or metastatic cancer or cancer for which treatment had been administered within 6 months or haematological cancer that is not in complete remission.

As highlighted by our survey, active cancer is a setting where some physicians (20% of our respondents), may consider LMWH for stroke prevention, a treatment that although it has been tested and validated in venous thromboembolism,[21–24] has no known efficacy and risk–benefit at long term for prophylaxis of systemic embolism and stroke in AF patients. The analysis by groups showed some differences in the preference for the anticoagulant regimen, including some use of LMWH even only at prophylactic doses, to be interpreted in terms of some background uncertainty, even if the differences by subgroups never exceed a 10% variation in proportion of preferences. The results of this survey underline the need for defining a standard treatment to be applied in daily practice in patients with active malignancies, taking into account that active cancer is not per se an absolute contraindication to anticoagulation at appropriate doses.[20,25–27] In view of the differences between venous and arterial thromboembolism, controlled studies should be performed before defining a specific role of LMWH, for long-term prevention of stroke and systemic thromboembolism in AF. Moreover, while LMWH could be considered for short-term use, its use at long term appears limited by impaired quality-of-life and may cause poor adherence to therapy and local complications.

We evaluated what can be, at present, the most important limitations in decision-making in this clinical context. The lack of randomized controlled studies was considered an important drawback by one-third of respondents. An additional limitation is related to drug interactions with chemotherapies. It is noteworthy that the lack of solid evidence on efficacy is perceived as having a

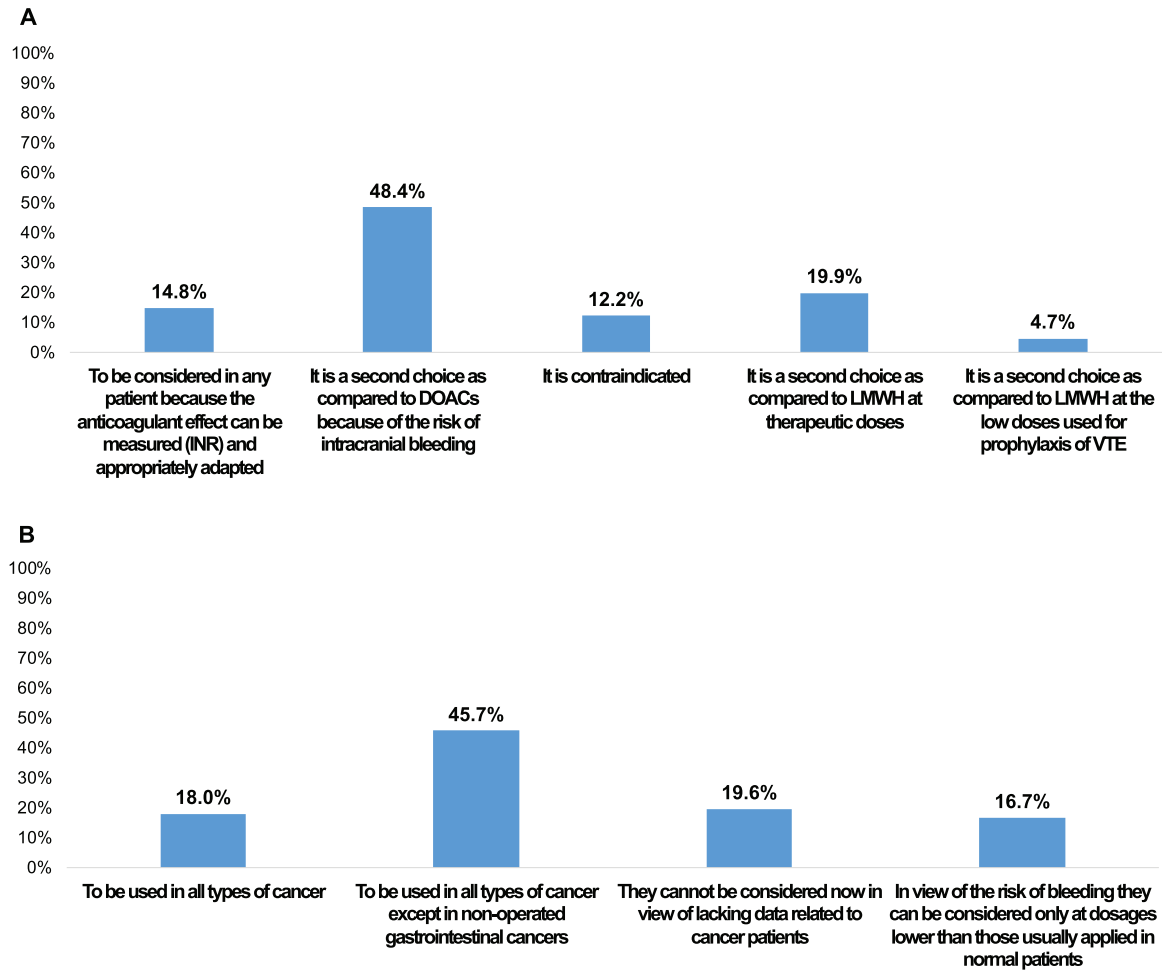

Figure 6 Questions on the role of warfarin (*A*) and direct oral anticoagulants (*B*) in the prevention of stroke/thromboembolism in atrial fibrillation patients with active cancer. (*A*) What role for warfarin in patients with active cancer and atrial fibrillation at risk of stroke? (*B*) What role for direct oral anticoagulants in patients with active cancer and atrial fibrillation at risk of stroke? AF, atrial fibrillation; DOACs, direct oral anticoagulants; INR, International Normalized Ratio; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

lower impact as compared to the lack of evidence on safety, in terms of haemorrhagic risk. One out of five respondents considered that in this specific setting, there is a need to monitor the extent of anticoagulant effect and properly adjust anticoagulants dosing.[28,29]

Moreover, the challenges of anticoagulant therapy in cancer patients are highlighted by the evidence that more than 40% of respondents expressed preference for a decision on patient antithrombotic regimen taken together by a cardiologist and an oncologist or by a team and less frequently by a cardiologist alone or by an oncologist alone. Particularly non-cardiologists reported that the choice about anticoagulation is more frequently taken within a multispecialist team. This is in line with the need for cooperation in decision-making, taking into account the specific patient profile with regard to the risk of stroke, co-morbidities, the specific type and stage of cancer involved and other clinical variables.[4–6,14,30] A study by O'Neal *et al.*[31] reported that involvement of cardiologists in decision-making related to AF management in patients with cancer increased the proportion of patients with appropriate prescription of anticoagulants and was associated with favourable AF-related outcomes (reduced risk of stroke without increased risk of bleeding). Moreover, our survey shows that in ∼60% of cases, the patient is always involved in decision-making with expression of personal preferences after appropriate information on the risk and benefits of anticoagulants, also if significantly younger responders perceive that the patient participates less frequently in the therapeutic choice than their older colleagues. Only rarely, there is no patient involvement in the decision-making process. This approach is perfectly in agreement with the concept of patient engagement especially in a setting with a problematic risk–benefit ratio and the need to share with the patient the final decisions, taking into account his/her values and preferences.[32,33] When decision-making is used, it results in greater medication adherence and this is an important aspect for reducing stroke risk in patients with AF and active cancers.

In clinical practice, scores for risk stratification are currently the key reference for guiding patient management in AF, as stressed by

consensus guidelines.[34,35] The CHA_2DS_2-VASc score is designed to identify low thromboembolic risk patients and has been recognized as the most reliable guide to anticoagulation,[34] provided that absolute contraindications are excluded. According to our survey, this score is considered the reference for decision-making in patients with AF and active cancer by around two-thirds of respondents, while a minority considers this score unreliable because it has not been validated in the specific setting of cancer patients. Anyway, the scope of this score is not to identify high-risk patients, but rather to identify low-risk patients in whom anticoagulation should be avoided. In this perspective, the reservations related to specific clinical contexts, such as cancer, chronic kidney disease, and very advanced age, where the risk of thrombosis is further increased, should prompt further studies focused on patients assessed as 'low-risk' by the traditional CHA_2DS_2-VASc score.[14,36]

The criticism that emerges from our survey about the use of the HAS-BLED score is even greater with one-third of respondents stating that it is unreliable in the setting of cancer. In the literature, the HAS-BLED score has been selected as the most satisfactory score for estimating the risk of bleeding and has been validated in large cohorts, but without a specific focus on cancer patients.[34,37] A series of disease-related factors in cancer may actually increase markedly the risk of haemorrhages and clinically should be taken into consideration.[4,5,20] However, the HAS-BLED score has been introduced for identifying the risk of bleeding and increasing the level of commitment for correcting all the modifiable risk factors. As clearly stressed in consensus guidelines, it should not be used for denying anticoagulation in patients at risk, provided that no absolute contraindications are present.[34,35] The definition and validation of bleeding scores specifically designed for the cancer setting is probably very difficult and problematic in view of the specific aspects related to some type of cancers and other oncological aspects (i.e. gastrointestinal location, cerebral metastasis, thrombocytopenia, etc.) that suggest the need for an individualized approach.[4,5,14]

For DOACs, the reduced risk of intracranial bleeding as compared with warfarin, the rapid onset and offset of action and the availability of reversal agents for some DOACs[7,38] may constitute the basis for the preference for these agents in the very challenging setting of a patient with stable brain metastasis and prognosis longer than 6 months. In this setting, some physicians considered the use of LMWH, despite the lack of data on long-term prevention of arterial thromboembolism.[5,20]

The occurrence of a first episode of AF is commonly perceived as associated with a lower risk of stroke and this erroneous perception may lead to under-prescription of oral anticoagulants.[39] Similarly, conversion to sinus rhythm may be erroneously perceived as associated with a lower risk of stroke[8,14] and in our survey this occurred more frequently among non-European physicians, although only in a minority. However, our survey highlights that an enhanced dissemination of knowledge on guidelines is needed on this topic, in order to improve effective implementation for stroke prevention strategies.

For many years, warfarin has been the only reference for stroke prevention in AF, but according to our survey, for ~50% of the respondents, mainly females and European respondents, it is currently a second choice. DOACs are preferred, mainly by European physicians, also in patients with cancer, with the exception of inoperable gastrointestinal cancers which predispose to a high risk of bleeding.

In order to reduce the risk of bleeding, underdosing of DOACs is sometimes applied in daily practice, but this strategy should be considered inappropriate in view of the unknown risk–benefit profile of these regimens that were not tested in trials. In general practice, off-label doses corresponding to underdosing were associated with increased risk for adverse cardiovascular events and mortality.[40,41] In particularly challenging situations related to patients with malignancies, dosing the effect or the concentrations of DOACs may be considered, specifically when knowledge of the actual effect is needed for defining the extent of pharmacological interactions or in case of urgent need for surgery or invasive procedures.[42]

The present survey has some inherent limitations due to the scarce representation of oncologists among the respondents. This highlights the need for creating collaborative networks in the field of Cardio-Oncology, despite the variable organization of single centres, targeted to promote a multidisciplinary approach based on team work, both in research and patient care.[30,43]

Conclusions

Surveys provide a quick feedback for evaluating the perceptions and knowledge of the medical community in complex clinical scenarios. Our survey, promoted by the Council of Cardio-Oncology and mainly targeted to cardiologists belonging to the ESC, highlights that management of AF patients with active cancer requires challenging decision-making. In fact, there is substantial heterogeneity in therapeutic choices, particularly with regard to the role of LMWH, not currently validated for AF thromboprophylaxis. In the absence of data from randomized controlled trials, multidisciplinary discussions are highly recommended. The final decision on prescription of anticoagulants should consider the individual patient characteristics, specifically the type and extension of the tumour, drug–drug interactions, the presence of metastases, the expected outcome, and patients' preferences. Overall, in AF patients with active cancer, DOACs are currently preferred over warfarin. However, differences were noted regarding perceptions and behaviours across different groups of physicians, which underscore the need for educational and research initiatives on this complex topic and require a multidisciplinary approach based on team work, both in research and patient care.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Dedication

This manuscript is in memoriam of our great friend Professor Maurizio Galderisi, Professor of Internal Medicine at the University of Naples, who participated with his typical enthusiasm to the planning of this survey. He was one of the founders of the Council of Cardio-Oncology of the ESC and was its Communication Officer. We recently said good-bye to the 'gentle giant' of Cardiology, Echocardiography, and Cardio-Oncology, who died of COVID-19 disease. Ciao Maurizio.

Conflict of interest: G.B. reports speaker's fees of small amount from Bayer, Boehringer, Biotronik, Boston, and Medtronic outside the submitted work. T.L.F. reports speaker's fees of small amount from Bayer, Daiichi, Bristol BMS, Philips, Menarini, Amgen, Janssen-Cilag, Merck Sharp & Dohme, and Teva outside the submitted work. P.V.d.M. received speaker fees and/or grants from Astra Zeneca, Ionis, Vifor Pharma, Novartis, Pfizer, and Servier outside the submitted work. J.L.Z. reports speaker's fees from Pfizer, Daichii, and Amgen. J.J.B. reports speaker fees from Abbott and Edwards Lifescience; the Department of Leiden University Medical Center, The Netherlands, has received unrestricted research grants from Abbott, Edwards Lifescience, Bayer, GE Healthcare, Medtronic, Boston Scientific, and Biotronik outside the submitted work. All other authors declared no conflict of interest.

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