

Antithrombotic Therapy in Cancer Patients with Cardiovascular Diseases: Daily Practice Recommendations by the Hemostasis Working Party of the German Society of Hematology and Medical Oncology (DGHO) and the Society for Thrombosis and Hemostasis Research (GTH e.V.)

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Abstract

Keywords

- ▶ cancer
- ▶ atrial fibrillation
- ▶ antithrombotic therapy
- ▶ coronary artery disease
- ▶ platelet disorders

Active cancer by itself but also chemotherapy is associated with an increased risk of cardiovascular disease (CVD) and especially coronary artery disease (CAD) and atrial fibrillation (AF). The frequency of CVD, CAD, and AF varies depending on comorbidities (particularly in older patients), cancer type, and stage, as well as the anticancer therapeutic being taken. Many reports exist for anticancer drugs being associated with CVD, CAD, and AF, but robust data are often lacking. Because of this, each patient needs an individual structured approach concerning thromboembolic and bleeding risk, drug–drug interactions, as well as patient preferences to evaluate the need for anticoagulation therapy and targeting optimal symptom control. Interruption of specific cancer therapy should be avoided to reduce the potential risk of cancer progression. Nevertheless, additional factors like thrombocytopenia and anticoagulation in the elderly and frail patient with cancer cause additional challenges which need

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to be addressed in daily clinical management. Therefore, the aim of these recommendations is to summarize the available scientific data on antithrombotic therapy (both antiplatelet and anticoagulant therapy) in cancer patients with CVD and in cases of missing data providing guidance for optimal careful decision-making in daily routine.

Introduction

According to the World Health Organization (WHO), cardiovascular diseases (CVDs; coronary artery disease, atrial fibrillation [AF], heart failure [HF]) are the leading cause of death worldwide.¹ In 2019, the WHO reported that CVDs were responsible for 32% of deaths, and half of these were due to CAD as the most frequent single disease entity.² This was also reported by the American Heart Association for the United States.³

The prevalence of CAD in cancer patients has increased in recent years, possibly due to improved survival with modern antineoplastic treatments and to similar risk factor profiles of many cancers and CAD.⁴

To improve the outcome of patients with CAD and cancer, both diseases have to be assessed in detail. This involves evaluation of cardiac risk factors, already existing cardiac diseases, and histologic and molecular cancer subtyping, as well as comprehensive staging of the cancer to select the best cancer treatment. Since many oncologic and hematologic disorders have turned from an acute into a chronic condition, the management of comorbidities can become problematic because treatment-related adverse events and drug–drug interaction (DDI) often influence the therapeutic approach in patients with active malignancies and CVD. Besides, tumor cells and platelets maintain a complex crosstalk that on one hand enhances tumor dissemination and on the other hand induces hemostasis abnormalities. Since, apart from cancer progression, thromboembolism represents the leading cause of death next to infections (each 9.2%),⁵ and myocardial infarction (MI) accounted for a fourth of thromboembolic deaths,⁵ primary and secondary prevention strategies are crucial in improving the survival of cancer patients.

However, cardiovascular (CV) death overall and also in cancer patients has declined during the past two decades,⁶ most likely because of increased awareness and application of prevention strategies, efforts which may have mainly benefited from the establishment of interdisciplinary cardio-oncology services in many countries.⁶ Interdisciplinary management (cardiology, hematology, oncology) of cancer patients might be associated with a more favorable CV-related outcome.^{7,8}

AF is a common CV disorder and up to 25% of the population with AF is also affected by cancer.⁹ Only recently, the 2022 ESC guidelines on cardio-oncology published recommendations for the management of patients with acute and chronic coronary artery syndromes as well as of patients with AF receiving anticancer treatment.¹⁰

The aim of these recommendations is to collect the available scientific evidence, including the latest clinical

trials and guidelines, to provide guidance on the management of antithrombotic treatment (both antiplatelet and anticoagulant therapy) in cancer patients with CVD, especially either preexistent or new-onset CAD and AF. Randomized-controlled trials on antithrombotic treatment in oncologic populations with CVD have to be promoted to supply evidence for recommendations in this cardio-oncologic setting.¹¹

Search Strategy

An independent literature search was performed of MEDLINE database on the topic “antithrombotic therapy in cancer patients with CV diseases.” The search terms included *cancer, atrial fibrillation, antithrombotic therapy, anticoagulation and antiplatelet agents, and coronary heart disease* to identify relevant systematic reviews, peer-reviewed clinical trials, and high-quality observational studies from 2000 to March 2023 and guidelines and recommendations from 2010 to March 2023.

Epidemiology

Multiple studies have shown that the incidence of cancer is much higher in patients with CVD compared with the general population.^{12–14} Precise estimates are difficult, but it has been appraised that 20 to 30% of patients with cancer die due to CV causes, irrespective of the time passed after cancer diagnosis.¹⁵

AF is the most common cardiac arrhythmia.¹⁶ An association between AF and malignant disease has been reported, but is incompletely defined and understood.¹⁷ In patients with cancer, the prevalence of AF ranges between 2 and 15%,¹⁸ with higher rates reported for certain classes of antineoplastic drugs, such as alkylating agents, anthracyclines, interferon- α , tyrosine kinase inhibitors (TKIs), or perioperatively, triggered by stress and/or enhanced atrial myopathy.^{19–22}

Available evidence suggests that, in addition to the parameters involved in the CHADS₂ and CHA₂DS₂-VASc scores, active cancer increases the risk of thromboembolism in AF, with particularly high rates of AF in patients with lung cancer, leukemia, and multiple myeloma.^{23,24}

In a prospective study, 28,763 individuals without the history of MI or cancer were followed up for a median of 15.7 years. A total of 1,747 individuals developed MI and 146 developed cancer. Patients with MI had a 46% higher risk of developing cancer compared with those without MI.²⁵

Little is known about how patients with AF and cancer are routinely treated in clinical practice and whether their risk

for embolic or bleeding events is higher than in patients without cancer. Cardiology involvement was less likely to occur among patients with a history of cancer than those without and patients with a history of cancer were less likely to fill prescriptions for anticoagulants than those without cancer. In contrary, cardiology involvement was associated with increased anticoagulant prescription fills and favorable AF-related outcomes in AF patients with cancer (reduced risk of stroke without increased risk of bleeding).²⁶ Another study demonstrated an association of HF and cancer.²⁶

Cancer patients are also at increased risk of stroke.²⁷ Some anticancer therapies have been associated with both thromboembolic complications and increased risk of bleeding events.²⁸ Despite evidence from mechanistic studies that patients with cancer and AF might be at higher risk of stroke and systemic embolism (SE), this was not unambiguously documented in epidemiological and clinical studies. For instance, Atterman et al did not find a statistically significant higher risk for cerebrovascular events in cancer patients who received antithrombotic treatment in a population-based trial with 8,228 patients with cancer and 323,394 without during a 1-year follow-up.²⁹ Pastori et al described a higher or lower risk for ischemic stroke dependent on cancer type in comparison to patients without cancer in a longitudinal cohort study in France with a mean follow-up of 2 years.³⁰ Moreover, stroke in patients with cancer has been associated with worse outcomes, including prolonged hospitalization and disability when compared with cerebrovascular events in patients without cancer.³¹

Antithrombotic, including antiplatelet therapy that is indicated in CVD, poses a challenge between the prevention of thromboembolic events and the occurrence of bleeding. This is of particular interest in disease-associated or cancer-therapy-induced thrombocytopenia (TP). Transient cancer-therapy-induced TP does not protect against thrombosis. Trials on antithrombotic drugs typically exclude patients with active cancer (cancer diagnosed within the previous 6 months, recurrent, regionally advanced or metastatic cancer, and cancer for which treatment had been administered within 6 months and cancer that is not in complete remission³²), ongoing chemotherapy, as well as patients at highest risk for bleeding, including those with TP. The evidence for those patients relies on retrospective observational studies, small subgroups from randomized clinical trials (RCT), registries, case series, or mechanism-based investigations.³³ In the recovery phase of chemotherapy-induced TP, there is a higher risk of major arterial events than in non-oncological patients.³⁴ Moreover, following an acute ischemic or bleeding event, overall mortality and CV mortality are up to four- to fivefold higher in TP patients than in the non-TP counterpart.^{35,36} Data on the true prevalence of TP in patients with cancer and concomitant thrombosis are extremely limited.³⁷ TP is common in hematologic malignancies and is often observed following certain cytotoxic chemotherapies in patients with solid tumors.³⁸ Accordingly, the Flatiron Health Electronic Health Record database of patients with cancer reported a 3-month cumulative incidence of TP of 13% (any grade, platelet count $< 100 \times 10^3/\mu\text{L}$)

in patients with solid tumors. Severe TP (platelet count $< 50 \times 10^3/\mu\text{L}$) occurred in 6% of patients with solid tumors and in 28% of patients with hematologic malignancies receiving chemotherapy.³⁹

Immune-mediated TP (ITP) can be secondary to cancer⁴⁰ and anticancer therapies.⁴¹ Furthermore, the risk to develop cancer seems to be increased in patients with primary ITP (pITP).⁴² Since the incidence of pITP and cancer increases with age, the occurrence of ITP and CVD simultaneously is a relevant problem. In pITP, the risk of a first serious vascular arterial event (MI, stroke) is $\sim 1.5\%$ /year higher than in the general population ($< 1\%$ /year), and appears not to be associated with a specific platelet count threshold.^{35,36} In a retrospective cohort study⁴³ with data from 6,591 pITP patients and 24,275 matched controls, the adjusted incidence rate ratios (IRRs) of overall CVD (1.38; 95% CI, 1.23–1.55; $p < 0.001$), ischemic heart disease (1.21; 95% CI, 1.01–1.44; $p = 0.034$), stroke or TIA (1.39; 95% CI, 1.17–1.66; $p < 0.001$), and HF or LV dysfunction (1.42; 95% CI, 1.12–1.81; $p = 0.004$) were significantly higher in the ITP cohort than in the control. Splenectomy and active steroid treatment were identified as risk factors for CVD.⁴³

Antithrombotic Strategies in Cancer Patients

Cancer patients are very heterogeneous,⁴⁴ but controlling comorbidities and maintaining quality of life is very important.

Even with manifest cancer, many patients may have a long-lasting life expectancy due to spontaneously nonprogressive cancer, stable therapy-induced remissions, or improved continuous treatment options. Often these patients are particularly vulnerable, as risk for stroke and SE as well as bleeding may be highest due to active cancer and continued treatment. There are several recent expert reviews on the different antithrombotic treatment strategies, to be considered in cancer patients.^{33,45–50}

Patients with cancer may experience erratic control of international normalized ratio (INR) on treatment with vitamin K antagonists (VKAs) such as warfarin, as both nutritional factors and concomitant medications can influence VKA activity. Intensive INR monitoring and long-lasting action make VKA inconvenient in case of interventions, bleeding, or interfering TP. Direct oral anticoagulants (DOACs) have a shorter duration of action, and a greatly reduced potential risk of interactions with cancer or supportive therapies, which is nicely summarized by Steffel et al.⁵¹

Parenteral anticoagulation with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) is not complicated by interactions with drugs or food. Furthermore, oral or intestinal uptake may be disturbed in cancer patients by nausea, vomiting, diarrhea, or after bowel resections. There is a longstanding clinical experience with LMWH in the primary prevention and treatment of venous thromboembolism (VTE) in cancer patients. But similar to DOAC, their metabolism may be influenced by their renal or hepatic clearance.

Patients who are frail and/or on palliative care (PC)/end-of-life care have an increased risk of CV and bleeding events, mainly due to immobilization and metastatic cancer disease. The vast majority of people followed up in PC are cancer patients.⁵² Data on antithrombotic therapy in this setting are largely limited on cancer patients with VTE. The decision to treat VTE or withhold anticoagulation depends largely on an individual clinician's judgment,⁵³ and not on specific guidelines for the management of cancer-associated thrombosis (CT). The American Society of Clinical Oncology (ASCO) guideline states that anticoagulation at therapeutic doses is of uncertain benefit in patients receiving end-of-life or hospice care and in those with a very limited life expectancy.⁵⁴

Until recently, guidelines recommended LMWH for CT treatment.⁵⁵ There are no relevant data on direct factor Xa inhibitors (DXIs) in the palliative setting. However, caution has been advised in using these anticoagulants in the frail and elderly, with hepatic dysfunction, impaired renal function (no DXIs with creatinine clearance < 30 mL/min), and with potential DDI,^{47,56} all these clinical situations being common in cancer patients in PC.

Clinical relevant non-major bleedings are more common with DXIs than with LMWH in VTE patients with active cancer.⁵⁷ A meta-analysis of 336 patients with metastatic cancers showed LMWH to be more effective than warfarin in the prevention of VTE recurrence (RR = 0.51; 95% CI: 0.35–0.74; $p = 0.0001$) with no increase in the bleeding risk (RR = 1.10; 95% CI: 0.77–1.58; $p = 0.60$).⁵⁸

Prophylactic antithrombotic treatment in patients with AF and/or mechanical heart valve disease is not recommended in end-of-life care due to the increased risk of bleeding and relatively low risk of stroke. However, no studies regarding deprescription (planned reduction or removal of medication) are available.^{59–61} On the other hand, in patients with a recent thromboembolic disease, antithrombotic therapy should be continued and could be deprescribed during the last days to weeks.^{61,62}

Aspirin (ASA) is generally well tolerated and a small tablet that is easy to swallow. However, in stable heart disease, ASA can usually be deprescribed the last month in life or in certain cases even earlier. Since ASA binds cyclooxygenase irreversibly, the effect remains throughout the life cycle of the platelet, which is 7 to 10 days. Thus, the treatment effect lasts for several days after ASA intake was discontinued. In one study, it was shown that there was an overprescription with comedication of both ASA and DOACs.⁶³ The combined therapy of the two antithrombotics was associated with an increased rate of severe bleeding and most patients with stable disease do not require long-term antithrombotic combination therapy.⁶³

In patients with CT and CVD in PC, antithrombotic-shared treatment decisions should be followed on the basis of patient preferences (no treatment, subcutaneous or oral drugs), life expectancy (end-of-life anticipated within 3 months or beyond; using the PRONOPALL score is recommended⁶⁴), contraindications to antithrombotics, evaluation of bleeding risk, the time since VTE diagnosis (more or less than 3 months), and type of VTE (PE or DVT).

Pathophysiology

Cancer and CVD share several common risk factors such as age, sex, genetic predisposition, obesity, sedentary lifestyle, tobacco use, and others. Each of these risk factors has a relatively small contribution to the development of disease, but the combination of several of these factors increases the incidence.⁶⁵ Thus, a close relation between CVD and cancer is not surprising.

Tissue ischemia and necrosis in CAD result in inflammation, angiogenesis, and an increase in tumor necrosis factor (TNF). In HF too, several mediators are secreted from the heart and affected tissues such as TNF, interleukin (IL)-6, IL-1, and vascular endothelial growth factor (VEGF) that in turn affect cancer development and progression. Furthermore, cardiac production of certain biomarkers (e.g., brain natriuretic peptide) may affect tumor growth. These and other mediators elevated in subsets of CVD may contribute to the acceleration of carcinogenesis. In fact, some studies suggested that MI and HF may stimulate the growth of tumors.⁶⁶

Cancer treatment as well as cancer-associated cachexia may enhance cardiac arrhythmias, including AF, but the precise mechanisms remain unclear.⁶⁷

In addition to these links, suggestive of CVD being a risk factor for cancer development and progression, there are several arguments that—the other way around—cancer may increase the risk of CVD. This has been demonstrated very convincingly by the recognition of cardiotoxic effects of anticancer therapies,⁶⁸ which predispose to acute coronary syndromes by causing accelerated atherosclerosis and plaque rupture (e.g., immune checkpoint inhibitors [ICIs], nilotinib), causing vasospasm (e.g., bleomycin, taxanes, and fluoropyrimidines) or coronary thrombosis (e.g., alkylating agents, ICI, immunomodulatory drugs like lenalidomide, and TKIs like ponatinib).^{69–74} In a recent study with up to 40 years of follow-up, 160,000 cancer patients were evaluated; among adolescent and young adult 5-year cancer survivors, it was shown that the cumulative mortality from CVD was 1.4 times greater compared with the general population.¹⁴ Substances secreted from tumor cells promote thrombosis that may lead to thromboembolic phenomena. It has been reported that the incidences of stroke and MI, among others, are increased even before the diagnosis of cancer.⁷⁵ Furthermore, there are several hints, resulting in the hypothesis that advanced stage cancer is also a HF syndrome⁷⁶ with manifestations that occur independent of (and in addition to) the known cardiotoxic effects of anticancer therapies. These manifestations are (1) the presence of a clinical HF-like syndrome and (2) the presence of a high burden of clinically relevant arrhythmias in such patients. The generalized muscle wasting (i.e., sarcopenia) in advanced cancer may relate in a degenerative form of cardiomyopathy with consecutive structural changes in the heart. In a study looking at 177 autopsy reports of cancer patients, it was noted that in 54 cancer patients with cachexia, the average heart weight was 19% lower than in those without cachexia.⁷⁷ There are multiple possible reasons for whole body wasting in cancer, which may also affect the heart of cancer patients. In preclinical models of cancer, cardiac wasting has been

repeatedly observed, and one study also documented this as late-stage phenomenon in a rat cancer model with clinical features of advanced HF.^{78,79} In human cancer patients, reductions of left ventricular (LV) mass have been described in preliminary studies.^{80–82} Multiple cellular wasting processes can affect the structure and function of electrical cells and conduction system pathways of the heart, thereby resulting in an increased arrhythmia risk. In multivariable analyses of 120 unselected patients with non-small cell lung, colorectal, or pancreatic cancer, an 8% prevalence of non-sustained ventricular tachycardia episodes was detected associated with a threefold increased mortality.⁸³

In summary, there is a wide overlap in risk factors for CVD and cancer, explaining at least in part the high incidence of CVD in patients with malignancies. In addition, available evidence suggests an increased risk of cancer in patients with CVD as well as of CVD in patients with cancer.

Antithrombotic Treatment in Patients with Atrial Fibrillation and Cancer

Because of the high incidence of AF in cancer patients, effective and safe treatment strategies for the management of AF in these patients are important:

- To avoid complications of AF, particularly stroke or SE and to reduce CV mortality.
- To avoid complications of antithrombotic treatment, particularly major bleeding.

Careful risk assessment and well-considered choice of antithrombotic therapy are therefore of utmost importance in this vulnerable patient group. Different scores as well as guidelines from working groups exist for risk assessment and to support clinical decision-making in AF.⁸⁴ These tools are well established in the general population and embedded in clinical routine.

The CHADS₂ and CHA₂DS₂-VASc scores (–Tables 1 and 2) are well validated to stratify the risk for stroke^{85,86} and recommended.^{84,87,88} In a large nationwide retrospective cohort study in France of 2,435,541 adults hospitalized with AF with a mean follow-up of 2 years, the CHA₂DS₂-VASc score's predictive value was slightly lower in the 16.4% with cancer.³⁰ Patell et al and Hu et al found that the CHADS₂ score was more predictive of risk of stroke in patients with cancer and AF than the CHA₂DS₂-VASc score.^{89,90}

Major bleeding and intracranial hemorrhage rates progressively increase with the HAS-BLED score (–Table 3),⁹¹ a widely used bleeding risk assessment tool with a moderate predictivity but noninferiority to other models.⁹²

A good performance has been shown in the large cohort of different cancer patients by Pastori et al,³⁰ whereas Raposeiras et al describe poor performance.⁹³ The BleedMAP is derived from a retrospective analysis of 2,182 cases of interruptions/replacement of VKAs.⁹⁴ It is the only bleeding risk tool to include cancer as an independent risk factor (hazard ratio [HR]: 1.8; *p* = 0.04), but it has been developed in a very specific clinical scenario and has not been applied in patients taking DOACs.

Table 1 CHA₂DS₂-VASc score

CHA ₂ DS ₂ -VASc	Points (0–9)	
Congestive heart failure	1	
Hypertension	1	
Age ≥75 y	2	
Diabetes mellitus	1	
Stroke or TIA in the past	2	
Vascular disease	1	
Age 65–74 y	1	
Female sex	1	
CHA ₂ DS ₂ -VASc Score	Stroke or SE: 2-y cumulative incidence	
	Recent cancer	No recent cancer
0	1.7	1.2
1	3.2	1.8
≥ 2	7.1	10.9

Table 2 CHADS₂ score

CHADS ₂	Points (0–6)
Congestive heart failure	1
Hypertension	1
Age > 75 y	1
Diabetes mellitus	1
Stroke or TIA in the past	2
CHADS ₂ score	Stroke or SE per 100 patient-years
	Patients with cancer
0	0.5
1	1.7
2	1.9
3	2.0
4	3.8
5	6.4
6	25

Unfortunately, cancer patients have been excluded from most clinical trials; thus, only very limited data exist for decision making. In general, trials have used variable definitions for onco-hematologic patients and inclusion criteria. This is important to consider when interpreting trial results and meta-analysis. Some authors differentiated between patients with solid tumors and patients with hematologic malignancies.⁹⁵ A higher risk for stroke has been described in patients with solid tumors and AF,⁹⁵ particularly for pancreatic cancer, uterine cancer, and breast cancer.³⁰ Bleeding risk by TP may need special attention in patients with hematologic malignancies. These patients receive less frequent

Table 3 HAS-BLED score

HAS-BLED	Points (0–9)
Uncontrolled hypertension	1
Abnormal renal or hepatic function	1 for each
Stroke in the past	1
Bleeding history or predisposition	1
Labile INR (only patients with VKA)	1
Elderly (> 65 y)	1
Interfering drugs or alcohol	1 for each

antithrombotic treatment,¹⁸ and therefore are often under-represented in the analyses of risk–benefit ratios if antithrombotic treatments are analyzed.

Antithrombotic Treatment by Oral Anticoagulants

A similar net benefit of oral antithrombotic therapy, assessed by the composite outcome of ischemic stroke, SE, all major bleedings, and death, has been described for patients with active cancer and for noncancer patients (HR: 0.81).²⁹ But these data have to be interpreted with caution, as patients with cancer receive antithrombotic therapy less frequently than patients without cancer (36.9 vs. 52.5% in a retrospective study of the Swedish Health Registry²⁹) potentially leading to selection bias. Fradley et al¹⁸ found in a monocentric retrospective analysis at the Moffitt Cancer Center, United States, in 2016, that among cancer patients with AF, 259 patients (54.9%) were prescribed antithrombotic treatment (38% warfarin, 54% DOACs, 8% LMWH), and 45.15% were not. Moreover, 44.3% of the 296 patients with a CHA₂DS₂-VASc score ≥ 2 and HAS-BLED score < 3 —thus appropriate for antithrombotic treatment according to existing guidelines—did not receive it. Only 18.3% had platelet values < 50 G/L (see below); other associated factors were current or recent use of chemotherapy, history of bleeding, or perioperative AF.

Patients with AF plus cancer have not been addressed specifically in clinical trials on DOACs. In the pivotal trials evaluating dabigatran (RE-LY) or edoxaban (ENGAGE AF-TIMI 48), patients with “recent malignancy or radiation therapy (within 6 months) and not expected to survive 3 years”⁹⁶ or “patients with active malignancy (diagnosed within 5 years) and patients with current anticancer therapy”⁹⁷ were excluded. The ROCKET AF⁹⁸ and the ARISTOTLE⁹⁹ trials evaluating rivaroxaban and apixaban versus warfarin excluded patients with a life expectancy of less than 2 and 1 years, respectively. Acknowledging this missing group of patients, post hoc data of the corresponding pivotal trials on certain patients with (a history of) cancer have been collected for rivaroxaban¹⁹ and apixaban.⁴⁴ Due to the exclusion criteria of the respective trials that may have excluded patients with the most severe cancers or those with the highest bleeding risk, thus introducing a selection bias, these analyses have limiting value for the general population of patients with AF and cancer.⁴⁴ With these limitations, both trials showed a

similar risk for stroke and SE by antithrombotic treatment and noninferiority of rivaroxaban and apixaban compared with warfarin for the cancer patient group as well as for the noncancer patient group.^{19,44} Interestingly, even patients with a history of cancer showed an increased bleeding risk with antithrombotic therapy compared with noncancer patients in a post hoc analysis of the ROCKET AF trial.¹⁹

The efficacy and safety analysis of edoxaban in patients with active cancer and AF of the ENGAGE AF-TIMI 48 trial followed a different design.⁹⁵ Patients with a new diagnosis of cancer or cancer recurrence during the 2.8 years of follow-up are described post hoc in respect of the clinical outcomes. Nearly 50% of the 1,153 patients suffered from either luminal gastrointestinal or genitourinary malignancies, only 6% from hematological malignancies. The rates of stroke or SE were similar between those with malignancy and those without malignancy. Rates of major bleeding were higher in patients with malignancy, but no statistically significant difference was seen between edoxaban and warfarin (malignancy: 7.92%/year vs. 8.18%/year; HR, 0.98; no malignancy: 2.62%/year vs. 3.34%/year; HR, 0.79).

A very recent meta-analysis identified altogether nine trials with $\sim 225,000$ cancer patients (the aforementioned three post hoc analyses and six retrospective population-based cohort studies) comparing the use of DOACs to warfarin.¹⁰⁰ Gastrointestinal, breast, and prostate cancers were most prevalent. While various definitions for cancer patients were used in the original reports, DOACs as compared with warfarin were associated with a reduced risk of stroke and SE (RR: 0.84 vs. 0.65). DOAC use was related to a significant reduction of the risk of major bleeding (RR: 0.68) and gastrointestinal and intracranial bleeding (RR: 0.64) compared with warfarin.

In one large study that was included in the meta-analysis, 16,096 patients with AF and with actively treated cancer with warfarin, rivaroxaban, apixaban, or dabigatran were matched by age, sex, enrollment date, and drug initiation date. Compared with warfarin, rates of bleeding (HR [95% confidence interval]) were similar in rivaroxaban (1.09 [0.79, 1.39]) and dabigatran (0.96 [0.72, 1.27]) users, whereas apixaban users experienced lower rates (0.37 [0.17, 0.79]). Rates of ischemic stroke did not differ among anticoagulant users. Compared with warfarin, the rate of VTE (HR [95% confidence interval]) was lower among rivaroxaban (0.51 [0.41, 0.63]), dabigatran (0.28 [0.21, 0.38]), and apixaban (0.14 [0.07, 0.32]) users. In head-to-head comparisons among DOACs, dabigatran users had lower rates of VTE than rivaroxaban users; apixaban users had lower rates of VTE and severe bleeding than rivaroxaban users.²⁸ Similar results have recently been reported from the ARISTOPHANES substudy.¹⁰¹ In this large retrospective population-based study, 40,271 patients with a recent diagnosis of cancer (within 6 months before antithrombotic treatment) were included (92% with solid cancers, of whom $\sim 45\%$ received chemotherapy, 7% hormone therapy, 8 and 3% were treated with either radiotherapy or surgery). The risk for major bleeding was lowest for apixaban (HR: 0.58; $p < 0.001$ compared with warfarin, HR: 0.66; $p < 0.001$ compared with

rivaroxaban, HR: 0.83; $p = 0.307$ compared with dabigatran). Apixaban was also shown to have the lowest risk for stroke and SE (HR: 0.59; $p < 0.001$ compared with warfarin), whereas rivaroxaban and dabigatran showed similar results.¹⁰¹

Although existing evidence (though not from randomized controlled studies) points out that DOACs are at least as effective and safe as warfarin in preventing stroke and SE in cancer patients,⁸⁴ relative bleeding risks differ among studies. This may be related to different tumor sites and different cancer patient groups in the trials. More information is needed to better estimate the individual cancer patients, also with reference to specific DOACs.

Anticoagulation by LMWH

LMWH may be more appropriate in patients receiving anti-cancer agents and/or other drugs that interact with p-glycoprotein and/or CYP3A4.^{51,102,103} They may also be preferred if bleeding risk is high, such as in patients with luminal manifestations in gastrointestinal, genitourinary, or lung cancer, or in case of TP (platelet counts < 100 G/L) because of their well-known and defined dose-dependent effects.²² Evidence about their safety profile as compared with VKA or DXI—a subgroup of DOACs—is from studies of cancer-associated VTE for treatment periods up to 12 months.^{104–110} Efficacy and safety of LMWH in AF has not been prospectively evaluated.¹⁰² Thus, LMWHs are not approved for patients with AF. One single-center retrospective study of 762 patients with cancer and AF was published recently¹¹¹: Herein, outcome—after propensity matching—incidence of stroke and SE was significantly higher for LMWH (enoxaparin) compared with DOACs after 1 year (HR: 2.231; $p = 0.012$), with loss of significance after 3 years (HR: 1.565; $p = 0.089$). One-year and 3-year mortality rates were also reported to be significantly higher to LMWH (HR: 1.594; $p = 0.036$ and HR: 1.550; $p = 0.007$). Other arguments that point against the general use of LMWHs in AF are that long-term administration by subcutaneous route is associated with negative implication on quality of life¹¹² and may reduce adherence.¹¹¹

Cancer patients on antithrombotic treatment with active luminal gastrointestinal or genitourinary lesions have the highest incidence of bleeding.¹¹³ Based on data for cancer patients with VTE, LMWH^{107,108} may be considered—at least temporarily—for them, as depicted earlier. Individual risk-benefit ratio has to be thoroughly estimated initially and frequently thereafter.

Intracranial neoplasms have been excluded from some trials (ROCKET-AF⁹⁸). Data from population-based trials are very limited^{101,113} due to the rarity of cerebral neoplasms and because sites of metastases have not been reported in detail.³⁰ Still, these patients are reported to have a high risk of bleeding¹¹⁴ as well as of stroke and SE.^{113,114} Available evidence confirms an increased risk of intracranial bleeding complications in patients with primary or metastatic brain cancers due to antithrombotic treatment and suggest a lower risk of DOAC than for LMWH.¹¹⁵

When patients have contraindications for long-term anticoagulation, LAA occlusion may be considered for stroke

prevention in patients with cancer and nonvalvular with AF and a life expectancy > 12 months^{87,116} (→ Table 4).

Antithrombotic Therapy in Cancer Patients with CAD with or without AF

Risk factors for CAD in Cancer Patients

In general, the same diagnostic workup, risk mitigation strategies, and treatment modalities are applied to cancer patients as to noncancer patients. Thus, in chronic CAD, CV risk factors will have to be assessed in any cancer patient, including smoking habits, obesity, physical inactivity, arterial hypertension, diabetes mellitus, hyperlipidemia, and significant family history for CVDs.³ Decrease of risk factors (e.g., by smoking cessation, increase of physical activity,¹¹⁷ and the treatment of arterial hypertension, diabetes, and hyperlipidemia) most likely will improve the survival of cancer survivors.

However, cancer patients may be exposed to additional risk factors for CAD development, including radiotherapy^{118–120} and antineoplastic agents (reviewed in Carrillo-Estrada et al⁴), and is open to discussion how much this risk can be decreased (i.e., through reduction of radiation dose or field) without compromising cancer control.

Characteristics of Acute Coronary Syndrome in Patients with Cancer

ACS in cancer patients carries a worse prognosis than in non-cancer patients.^{121,122} In large studies, it was demonstrated that the worse outcome of patients with MI was associated with active but not historical cancer, lower rates of invasive coronary interventions, and higher rates of bleeding complications.^{121,122} Cancer patients were more likely than the general population to have non-ST elevation MI (NSTEMI) than ST elevation MI (STEMI),^{121–123} and they were older and had more comorbidities than their noncancer counterparts.^{121,122}

Whether despite or because of these increased risks, cancer patients are less invasively treated in case of an ACS: they are less likely to receive percutaneous intravenous interventions (PCIs) and coronary angiography, to have a drug-eluting stent (DES) implanted versus a bare metal stent, and to undergo coronary artery bypass graft (CABG).^{121,122} This was associated with a lower rate of drug interventions, such as dual-antiplatelet therapy (DAPT), statins, β -blockers, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARB).¹²² Importantly, the application of such measurements has been demonstrated to be effective in cancer patients.^{122,124}

Management of Patients with Cancer and ACS

Cancer patients are underrepresented in randomized controlled trials (RCTs) investigating management strategies in CAD and ACS. Thus, evidence-based treatment algorithms for this important patient group are missing. Standard acute management of ACS may be associated with a higher rate of death^{121,125,126} and complications in cancer patients, such as bleeding (especially in colon cancer patients) and MACCE (“Major Adverse Cardiac and Cerebrovascular Events,” composite endpoint of all-cause mortality, cardiac complications,

Table 4 Recommendations for the management of AF in cancer patients receiving anticancer treatment¹⁰

Recommendations
CHA ₂ -DS ₂ -VASc and CHADS ₂ score should be considered for risk stratification for stroke/SE taking into account that it may underestimate the actual thromboembolic risk. ^{30,85} The CHADS ₂ score was more predictive of risk of stroke in patients with cancer and AF than the CHA ₂ DS ₂ -VASc score ^{89,90}
Long-term anticoagulation is recommended for stroke/SE prevention in patients with cancer with AF and a CHA ₂ -DS ₂ -VASc score ≥ 2 (men) or ≥ 3 (women) as per the 2020 ESC guidelines for the diagnosis and management of AF ⁸⁷
Long-term anticoagulation with DOACs (preferentially DFXal) should be considered for stroke/SE prevention in patients with cancer with AF and a CHA ₂ -DS ₂ -VASc score = 1 (men) or = 2 (women) as per the 2020 ESC guidelines for the diagnosis and management of AF ⁸⁷
Patients with cancer ^a and AF with a CHA ₂ -DS ₂ -VASc score 0 (men) or 1 (women) may have a higher thromboembolic risk than patients without cancer and may be considered for anticoagulation after consideration of the bleeding risk ⁸⁵
Thromboembolic and bleeding risk reassessment is recommended initially and during follow-up in patients with cancer with AF ^{b,87}
DOAC should be considered in preference to LMWH or VKA for stroke prevention in patients with non-valvular AF (in the absence of mechanical heart valves or moderate-to-severe mitral stenosis) if bleeding risk, DDI, and renal function allow their application ^{19,28,44,95,100,101,218}
LMWH may be considered in patients with certain cancer patients ^c who are not suitable for DOAC ^{d,219}
LAA occlusion may be considered for stroke prevention in patients with cancer and nonvalvular AF and contraindications for long-term anticoagulation with a life expectancy > 12 mo ^{87,116}
Antiplatelet therapy is not recommended for the prevention of stroke or SE prevention in patients with cancer and AF ⁸⁷

^aFactors that may increase thromboembolic risk in patients with cancer including comorbidities (proteinuria >150 g/24 hours, eGFR <45 mL/min/1.73 qm, BMI ≥ 30 kg/qm, thrombophilia), cancer type (pancreatic, gastric, ovarian, brain, lung, multiple myeloma), cancer stage (metastatic disease), anticancer therapies.

^bStroke and bleeding risk may change during both cancer treatment and the course of the underlying disease; reassessment is important to inform treatment decisions and address potentially modifiable bleeding risk factors.

^cPatients receiving cancer treatment, patients diagnosed with cancer in the past 6 months, and patients with progressive or advanced disease.

^dHigh bleeding risk, severe renal dysfunction (CrCl <15 mL/min); DOAC major DDI.

and stroke).^{121,126} This may explain the use of less invasive therapies in cancer versus noncancer patients so far, particularly regarding the use of DAPT and its elevated bleeding risk in patients with TP (see chapter below/above). Nevertheless, cancer patients do benefit from invasive therapies (PCI, CABG) and/or noninvasive drug treatments. This has been shown for PCI,^{126,127} DES,¹²⁵ CABG,¹²⁸ as well as DAPT¹²² (with careful consideration of the bleeding risk), statins,¹²² β -blockers,¹²² and ACE inhibitors/ARB.¹²² DAPT should involve ASA and clopidogrel, instead of other P2Y₁₂ inhibitors (e.g., ticagrelor, prasugrel).

Therefore, careful selection of patients and management within an interdisciplinary team of hematologists/oncologists and cardiologists/cardiosurgeons is recommended in patients with ACS and cancer,⁴ considering all established treatment options for CAD in noncancer patients.

Future additional assessments of CAD risk in cancer patients may include noninvasive methods such as a coronary calcium scan¹²⁹ which is a special computed tomography scan of the heart which is especially helpful in recognizing patients at risk of heart attacks or strokes before they have symptoms and which will be helpful to better select patients in need of invasive procedures.

Cancer Patients with CAD and AF

Given that all patients with CAD are already assigned one CHA₂DS₂-VASc score point for their vascular disease, regardless of any other CHA₂DS₂-VASc criterion, cancer patients with AF will most likely be candidates for anticoagulation as

stroke prevention, as long as cancer-associated bleeding risk is low. The decision to withhold anticoagulation (e.g., DOACs or vitamin K-antagonists [VKA]) and to use ASA only or even to withhold any antithrombotic drug will have to be made based on the individual risk for thromboembolism (e.g., CHA₂DS₂-VASc score) when bleeding risk is considered to be high.

Recommendations for the management of AF and CAD can be found in the recently published 2022 ESC guidelines on cardiooncology¹³⁰ (→Table 5).

Antithrombotic Therapy in Cancer Patients with CAD and Venous Thromboembolism

VTE, a composite of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent and steadily increasing complication of active cancer¹³¹ with negative impact on quality of life and overall prognosis.^{132,133} Compared with VTE patients without underlying malignancies, patients with CT are at increased risk for both VTE recurrence and major bleeding during anticoagulant therapy.¹³⁴ Depending on tumor-, patient-, and treatment-related factors, the risk of CT is highly variable.¹³⁵ Age is an independent risk factor for CAD, VTE, and cancer.^{136,137} In cancer patients, more than half of VTE events are detected unexpectedly (e.g., by routine imaging studies).^{138,139}

For more than a decade, guidelines have recommended LMWH for the long-term treatment of cancer-associated VTE due to its superior efficacy over VKAs.^{140,141}

Table 5 Recommendations for the management of acute coronary syndromes (ACS) in cancer patients receiving anticancer treatment¹⁰

Recommendations
An invasive strategy is recommended in patients with cancer presenting with STEMI or high-risk NSTEMI-ACS with a life expectancy ≥ 6 mo
A conservative noninvasive strategy should be considered in patients with poor cancer prognosis ^a (e.g., life expectancy < 6 mo) and/or very high bleeding risk presenting with STEMI or NSTEMI-ACS
A temporary interruption of cancer therapy is recommended in patients when cancer therapy is suspected as a contributing cause ^b
A short (1–3 mo in most cases) dual-antiplatelet therapy (DAPT) strategy should be considered in patients with cancer with very high bleeding risk treated with PCI for an ACS ^c
In patients with cancer, thrombocytopenia, and ACS, aspirin is not recommended if platelet count is $< 10,000/\mu\text{L}$
In patients with cancer, thrombocytopenia, and ACS, clopidogrel is not recommended if platelet count is $< 30,000/\mu\text{L}$ and prasugrel or ticagrelor are not recommended if platelet count is $< 50,000/\mu\text{L}$
DAPT with aspirin and ticagrelor or prasugrel may be considered in patients with cancer and ACS undergoing PCI if bleeding risk is low and thrombotic risk is high

^aRelated to advanced cancer stage and/or severe irreversible non-CV comorbidities.

^bAnticancer therapies associated with high risk of ACS (very common [$>10\%$]): capecitabine, paclitaxel, cisplatin, carfilzomib, bevacizumab, ramucirumab, aflibercept, axitinib, sorafenib, pazopanib, cabozantinib, lenvatinib, ponatinib, erlotinib.

^cHigh risk of GI or GU bleeding, significant DDI, severe renal dysfunction ($\text{CrCl} < 30 \text{ mL/min}$), significant liver disease ($\text{ALAT/ASAT} > 2 \times \text{ULN}$), or significant TP (platelet count $< 50,000/\mu\text{L}$).

Real-world data and findings from prospective observational studies indicated, however, that guideline adherence was poor in clinical practice, with significant proportions of cancer patients terminating parenteral LMWH therapy prematurely because of inconvenient subcutaneous dosing, local allergic reactions or soft-tissue hematomas, or increased treatment costs.¹⁴² Following their approval for VTE treatment in primarily noncancer patients, the DXI edoxaban, rivaroxaban, and apixaban have indicated a significantly reduced risk of recurrent VTE for DXI compared with dalteparin in meta-analyses, with reported HRs of 0.62 to 0.66.^{106–108,143–146} While the rate of major bleeding is numerically higher, DXIs are associated with a significantly increased risk of clinically relevant non-major bleeding.¹⁴⁷

Findings from DXI trials have been adopted by updated clinical practice guidelines.^{54,139,148–150} While some favor DXI over LMWH because of their improved efficacy, lower drug expenditures, and increased treatment satisfaction,^{150,151} others prefer LMWH over DXI in patients with (luminal upper) gastrointestinal (GI) cancers.^{139,149} The choice of anticoagulant should be based on a careful assessment of the patient's individual thromboembolic recurrence and bleeding risk, considering tumor type and stage, renal function, potential DDIs, and patient preference.¹⁵²

Since active cancer is considered a strong persistent risk factor for recurrent VTE, continuation of anticoagulation beyond 6 months is recommended in most patients with cancer-associated VTE and noncured malignancies. The optimal type and intensity of anticoagulation in this setting, however, is not clear. Two studies compare lower-dose apixaban (2.5 mg twice daily) with higher-dose apixaban (5 mg twice daily) in CT patients who have completed at least 6 months of anticoagulation.^{153,154} While preliminary findings from the EVE trial suggest similar safety and

efficacy of both apixaban dosages,¹⁵⁵ the API-CT trial is still ongoing.

Although some management algorithms are available for the antithrombotic treatment of patients with CAD and VTE,¹⁵⁶ specific recommendations for patients with cancer-associated VTE who also suffer from CAD are rare and not based on dedicated clinical trials in the population under discussion. These patients, however, were not excluded from RCTs on patients with cancer-associated VTE. Therefore, the following recommendations are derived from current expert consensus statements and clinical practice guidelines for primarily noncancer patients with AF or VTE requiring medical therapy or PCI for CAD^{87,156} (**Table 6**).

Antithrombotic Agents and Cancer-Directed Therapy

There are five major aspects of how antithrombotic treatments can impact cancer treatment.

- Antithrombotic therapy and invasive procedures in cancer patients.
- Antithrombotic agents and TP in cancer patients.
- Antithrombotic agents and cancer therapies with inherent anticoagulant activity.
- Effect of anticancer agents on the activity and metabolism of anticoagulants.
- Effect of antithrombotic treatment on compliance, adherence, and satisfaction with anticancer treatments.

Patients prefer an anticoagulant that does not interfere with their cancer treatment, showing primacy of cancer therapy over any other concomitant disorders.¹⁵⁷ The common goal of all the above five aspects should therefore be that antithrombotic therapy neither requires anticancer therapy

Table 6 Recommendations for the antithrombotic therapy in patients with cancer and CAD and VTE

Recommendations
In patients with chronic CAD receiving anticoagulation for the treatment or secondary prevention of cancer-associated VTE, additional antiplatelet therapy is not required
In patients with cancer-associated VTE undergoing PCI for ACS, full-dose oral anticoagulation with a DXI in combination with a P2Y12 inhibitor (preferably clopidogrel) for 6–12 mo is suggested over full-dose anticoagulation with LMWH in combination with a P2Y12 inhibitor for 6–12 mo. In patients with non-resected luminal GI or genitourinary cancers and a high risk of mucosal bleeding, full-dose LMWH might be the preferred option. ASA may be given periprocedurally for 1–7 d (this could be prolonged for up to 30 d in selected cases with a high risk for stent thrombosis if bleeding is low)
In patients with a history of cancer-associated VTE who have already received > 3–6 mo of full-dose anticoagulation and who require PCI for CAD, dual-antiplatelet therapy with ASA and a P2Y12 inhibitor for the first weeks with reduced dose anticoagulation with apixaban (2 × 2.5 mg daily) or rivaroxaban (1 × 10 mg daily) might be an option when the risk of bleeding is perceived to be high
In patients with a history of cancer-associated VTE who have already received > 3–6 mo of full-dose anticoagulation and who require PCI for CAD, dual-antiplatelet therapy with ASA and a P2Y12 inhibitor for 6–12 mo without concomitant anticoagulation might be an option if the risk of VTE recurrence is perceived to be low

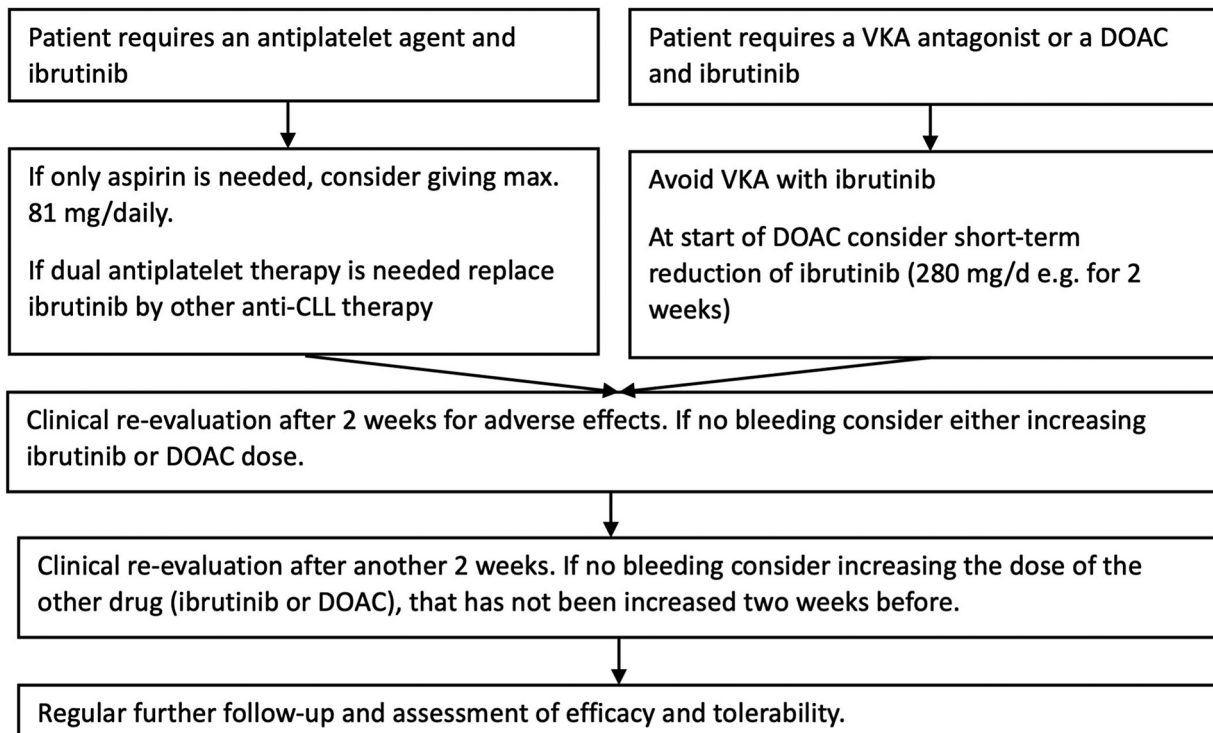
discontinuation nor dose reductions because this may jeopardize cancer treatment results and cause anxiety and reduced quality of life to the patient.

Antithrombotic Agents and Cancer Therapies with Inherent Anticoagulant Activity

While it has long been discussed that some anticoagulants may have an anticancer effect, the opposite, the anticoagulant potential of anticancer agents, is less often of an issue. Asparaginase inhibits protein synthesis and causes depletion of pro- and anticoagulant plasma factors, which then may manifest as thrombosis, disseminated intravascular coagulation, or bleeding. The risk of bleeding is lower than the one of thrombosis but still substantial, particularly

with decreasing fibrinogen levels.^{158,159} Careful monitoring of coagulation parameters and target-specific supplementations of deficient coagulation factors (fibrinogen and antithrombin) is recommended.¹⁵⁸

Ibrutinib and acalabrutinib are inhibitors of Bruton's tyrosine kinase (Btk) and used in multiple B cell-mediated lymphoproliferative disorders. Both, however, also act on several platelet signaling pathways and bleeding events ranging from minor mucocutaneous bleeding to life-threatening hemorrhage have been reported.^{160,161} Expert recommendations on anticoagulant dosing while on ibrutinib have been published (→ Fig. 1). The new Btk inhibitor rilzabrutinib has less such antiplatelet activity and is currently undergoing evaluation as a new therapy in ITP.¹⁶²

**Fig. 1** Clinical dosing of antithrombotic agents in patients with ibrutinib.^{160,161}

Effect of Anticancer Agents on the Activity and Metabolism of DOACs (DXI)

The DXI (apixaban, rivaroxaban, and edoxaban) are substrates of P-glycoprotein (P-gp) and to a varying degree of cytochrome 450 3A4 (CYP3A4). The prodrug dabigatran etexilate is also a P-gp substrate based on the limited data in cancer patients and the thrombin inhibitor dabigatran is rarely used in cancer patients. The importance of potential interactions of anticancer agents with DOACs via P-gp or CYP3A4 have been comprehensively reviewed elsewhere,^{163–165} but clinical studies on DDI in cancer patients are virtually missing/rare. Anticancer drug classes with potential class-wide interactions with DOACs include anti-mitotic microtubule inhibitors, most TKIs, and glucocorticoids; in addition, cyclosporine is known to increase plasma edoxaban exposure.¹⁶⁶ There are also potential interactions between DOACs and individual drugs among the topoisomerase inhibitors, anthracyclines, alkylating agents, and hormonal agents. Anticancer drugs with minimal interaction potential are platinum agents, monoclonal antibodies, anti-metabolites. In addition to the possibilities of drug–drug interactions, the timing, dosing (once per week vs. three times daily), and half-life of the anticancer drugs need to be considered.

Despite the large number of potential interactions between DOACs and anticancer agents, there are almost no clinical data or expert recommendations on how to modify DOAC dosing if coadministration cannot be avoided. Switching to LMWH is an option in selected cases. Only the Hokusai VTE Cancer study provides a specific dose recommendation when combining edoxaban with strong P-gp inhibiting agents (–Table 1). There are no such recommendations for apixaban, dabigatran, or rivaroxaban (–Table 7).

Effect of Antithrombotic Treatment on Compliance and Adherence with Anticancer Treatments

Cancer patients usually take not just one but a multitude of drugs; for example, besides their anti-cancer-specific therapy

they may need antiemetics, glucocorticoids, antibiotics, and medications for concomitant diseases. It has long been known that medication adherence drops sharply with the number of treatments.¹⁶⁷ There are numerous reasons on the patients' side, such as forgetfulness, other priorities, lack of information, and emotional factors. If the patient decides to omit doses because he feels he is on “too many pills,” he jeopardizes the efficacy of both his antithrombotic therapy and cancer treatment. Physicians contribute to poor adherence by prescribing a new antithrombotic drug, failing to explain the benefits and side effects of a medication adequately, not giving consideration to the patient's lifestyle or the cost of the medications, and having poor therapeutic relationships with their patients.¹⁶⁷ Any hemato-oncologist prescribing a new anticoagulant should therefore consider not only potential DDI but also whether the number of concomitant medications can be significantly reduced. This will improve adherence and support the success of both anticoagulation and tumor therapy (–Table 8).

Antithrombotic Therapy in Cancer Patients, CVD, and Platelet Disorders

Platelet disorders may occur as quantitative (thrombocytopenia) or qualitative (thrombocytopathy) abnormalities as well as in combined defects, which may clinically lead to or contribute to hemorrhagic diatheses of varying severity. They are very heterogeneous in their genesis and require a careful, usually interdisciplinary risk–benefit evaluation in everyday clinical practice. Typical and frequent thrombocytopathies, for example, occur in patients with advanced renal insufficiency. For the rare inherited platelet disorders (IPDs), there are only casuistic reports for antithrombotic therapy in cardiac disease. Myeloproliferative neoplasms (MPNs) are hematologic diseases in which both quantitative and qualitative platelet disorders are common. In MPN, there is often a marked increase in peripheral platelet counts, seldom observed in patients with solid cancers as well—which may

Table 7 Landmark studies on DOACs for CT and study protocols' recommendations for dose modification in case of DDI^{106–108,143–146}

Drug	Edoxaban	Rivaroxaban	Apixaban
Study	Hokusai-VTE-Cancer ¹⁰⁷	Select-D ¹⁰⁸	Caravaggio and ADAM VTE ^{106,144}
Anticancer or supportive care agents specifically listed as potentially interacting drugs	Tyrosine kinase inhibitors: imatinib, nilotinib, lapatinib, sunitinib, crizotinib, vandetanib Hormonal agents: tamoxifen, enzalutamide, abiraterone Immunomodulating agents: cyclosporine, tacrolimus Supportive care agents: ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin	Specific anticancer agents not listed Supportive care agents: ketoconazole, itraconazole, erythromycin, azithromycin, or clarithromycin	List of interacting drugs provided but no specific anticancer agents listed Supportive care agents: ketoconazole, itraconazole, erythromycin, azithromycin, clarithromycin, etc.
Recommended dose modification	Edoxaban 30 mg once daily	No dose modification recommended	No dose modification recommended

Table 8 General recommendations for antithrombotic agents and cancer-directed therapy

Recommendations
Bleeding is not uncommon in cancer patients and oncologists need to consider patient's age, location and type of tumor, recent surgery, and concomitant use of antithrombotic drugs, including antiplatelet therapy. ¹⁵⁸ Bevacizumab seemed to have a higher bleeding risk in the Hokusai-VTE-Cancer study. ¹⁵⁹ The effect of anticancer agents on the activity and metabolism of DOACs (DXI) is summarized by Steffel et al ⁵¹
The hemato-oncologist should be—if possible—involved in the periprocedural management and anticoagulant decisions of their patients
BTK inhibitors (e.g., ibrutinib) have an anticoagulant potential. Expert recommendations on anticoagulant dosing together with ibrutinib have been published
There are no expert recommendations on potential interactions between DOACs and anticancer agents. Digital drug interaction evaluation tools should be used or a pharmacist should be consulted to inform about potential interactions. Plasma level determination of DOACs may be helpful to diagnose or rule out DDI and to control the DOAC level even when dosing of the anticoagulant drug has been altered
Patients should be instructed about relevant bleeding symptoms and how to manage them at any time. ²²⁰ Simple and comprehensive treatment plans should support patient empowerment

lead to a bleeding tendency in the form of a secondary von Willebrand disease.^{168,169} In addition to quantitative changes in platelet counts, qualitative changes in the sense of thrombocytopeny are also responsible for an increased bleeding tendency in MPNs.¹⁶⁹ All of the aforementioned conditions of platelet disorders require an individual approach to antithrombotic therapy in CVD, which is discussed here.

Antithrombotic Agents and TP

TP is common in cancer patients. Although it can be caused by the underlying disease itself, most often it is the result of myelosuppressive chemotherapy. The risk of chemotherapy-induced TP varies by type of cancer and chemotherapy.^{170,171} Unless patients show bleeding symptoms or are categorized as high risk for bleeding, guidelines do not argue against full-dose anticoagulation in patients with platelet counts $> 509/L$. Expert recommendations suggest a reduced-dose anticoagulation when platelet counts are between 20 and $50 \times 10^9/L$ or even withholding anticoagulants during periods of severe TP ($< 20 \times 10^9/L$).^{172,173} For patients with acute thromboembolism, severe TP, and a high risk of thrombus progression, experts suggest full-dose anticoagulation with platelet transfusion support to maintain a platelet count of ≥ 40 to $50 \times 10^9/L$. Recently, new recommendations have been published by EHA and ESC which provide guidance for antithrombotic therapy in daily hemato-oncology practice.^{10,33} It is the experience of the authors that the platelet-transfusion approach is rarely chosen in daily practice due to high cost, organizational hurdles, and uncertainties to result in maintained target platelet counts.^{173,174}

TP $< 50 \times 10^9/L$ is an excepted contraindication to conventional dosed antithrombotic treatment.^{22,175} As in the pivotal trials of rivaroxaban,⁹⁸ dabigatran,⁹⁶ apixaban,⁹⁹ and edoxaban,⁹⁷ patients with platelet counts $< 90 \times 10^9/L$ (rivaroxaban) or $< 100 \times 10^9/L$ were excluded. A retrospective study from Taiwan reported a statistically not significant benefit (HR: 0.45; 95% CI: 0.16–1.14) of DOACs as compared with warfarin for bleeding events in AF patients with platelet counts $< 100 \times 10^9/L$ (mean: $76 \times 10^9/L$), of whom 24% had cancer.¹⁷⁶ Reduced doses were used in the majority of

patients. Another small study reported about safety and efficacy in 62 patients with moderate TP with reduced doses of apixaban (2.5 mg bid), dabigatran (110 mg bid), or rivaroxaban (15 mg once daily),¹⁷⁷ but defined protocols for dose-reduced regimens of antithrombotic therapy are lacking.

Antithrombotic Therapy in ITP

Antithrombotic therapy in cancer patients with TP is challenging. As relevant data on this important aspect are extremely rare, we decided to include exemplarily data on primary and secondary immune thrombocytopenia. Despite decreased platelet counts, there is an increased risk of thrombotic complications due to the abnormally enlarged and hyperactive platelets in ITP, together with an antibody-mediated damage to the endothelium.^{43,178}

Although there is an increasing awareness of the problem of ITP and CVD, published cases with cooccurrence of ITP and CVD complications such as CAD, acute MI, or AF are very rare. The practical management of this situation is challenging because there are no clear guidelines and because treatments such as revascularization, anticoagulation, and antiplatelet drugs carry their own risks, which may be exacerbated by the inherent bleeding tendency of ITP. In the retrospective cohort study cited earlier,⁴³ 3.6% ($n = 236$) of the 6,591 ITP patients were on an antiplatelet agent and 1.6% ($n = 108$) on warfarin. Further data on detailed use, efficacy, and side effect rates of these antithrombotic therapies were unfortunately not published.

There is no high-quality evidence for antithrombotic management of CVD in patients with ITP. On a casuistic basis and using small case series, the administration of antithrombotic therapies in CVD below a threshold platelet count of $30 \times 10^9/L$ to $50 \times 10^9/L$ is discouraged.¹⁷⁹ There are also no evidence-based guidelines for the treatment of thrombocytopenic patients with manifest CAD concerning antiplatelet therapy, as clinical trials with antiplatelet drugs have excluded patients with thrombocytopenia.¹⁸⁰

To better understand the clinical practice of antithrombotic therapy in ITP in above-mentioned situations, a survey was sent to ITP specialists and general hemato-oncologists

worldwide by Pishko et al.¹⁸¹ Four hypothetical clinical scenarios were queried in which antithrombotic therapy might be considered in a patient with ITP:

1. ASA in symptomatic stable CAD.
2. DAPT for coronary stent implantation.
3. Anticoagulation for AF.
4. Anticoagulation for VTE.

For each of these scenarios, a potential bleeding history was discussed, varying in severity from asymptomatic to mild mucocutaneous bleeding to severe gastrointestinal bleeding.

The most common response to the above four scenarios was a minimum platelet count of $50 \times 10^9/L$ for both groups of physicians, regardless of bleeding severity. In the presence of a bleeding history, a significant number of responders increased their minimum platelet count recommendations. Interestingly, the original hypothesis of this study—that ITP specialists would recommend antithrombotic therapy at a lower platelet threshold—was not confirmed. Consistently, a platelet count of $50 \times 10^9/L$ was the most common response for ASA treatment, DAPT, and therapeutic anticoagulation.¹⁸¹

A previously conducted survey of patients with chemotherapy-induced TP also found that the majority of hematologists recommend a minimum platelet count of $50 \times 10^9/L$ for therapeutic anticoagulation.¹⁸² This is also in line with the recommendations of the International Society on Thrombosis and Haemostasis (ISTH), which recommends a minimum platelet count of $50 \times 10^9/L$ for therapeutic anticoagulation in patients with chemotherapy-induced TP.¹⁸³ Overall, all of these recommendations are based on low-quality evidence and expert opinion. In **Table 9** you will find the recommendations for antithrombotic therapy in ITP.

A large retrospective analysis of the U.S. National Inpatient Sample (NIS) database from 2000 to 2014 identified 37,695 ITP patients who had suffered an acute MI and were hospitalized.¹⁸⁴ In this study, more ITP patients were treated with PCI and stenting procedures than with CABG. The reason for this is probably due to the fact that CABG in ITP is associated with a known higher bleeding tendency and is therefore performed less frequently. Remarkably, PCI with stenting nevertheless proved to be an independent predictor of mortality in these ITP patients. In the past, CABG was usually preferred to PCI in ITP patients because it achieved

better results in all types of lesions and the control of antiplatelet drugs after the procedure was easier to manage than PCI.¹⁸⁵ A review demonstrated that both PCI and CABG can be successfully performed in patients with ITP.¹⁸⁶ However, both procedures are associated with an increased risk of bleeding in ITP compared with the general population. Thrombolytic therapy is usually considered contraindicated in ITP patients because of the high risk of bleeding.¹⁸⁷

As for DAPT, it seems to be a safe approach if the platelet count remains above $30 \times 10^9/L$ and the patient is not bleeding.¹⁸⁷ Regarding the choice of antiplatelet drugs in DAPT, the combination of aspirin and clopidogrel is more preferred because clopidogrel has fewer bleeding complications compared with other P2Y12 inhibitors. New data showed that ADP inhibitors may have an advantage over ASA in terms of bleeding risk.^{188,189} The extent to which these data are transferable to the ITP patient population needs to be investigated in future studies.

More CV complications were observed in patients who required transfusions. The last aspect in particular is important, as hospitalized ITP patients receive significantly more platelet transfusions anyway.¹⁹⁰ In general, platelet transfusion is used more frequently in ITP patients with acute MI to control bleeding risks during antithrombotic therapy.^{191–193} In a meta-analysis, it was clearly demonstrated that, in general, in patients with acute MI, the use of blood transfusions increases the risk of death by 12%, regardless of the hemoglobin level.¹⁹⁴ The data mentioned above thus emphasize the cautious use of transfusions in ITP. According to the current recommendations on ITP management, transfusions should therefore be administered only in life-threatening situations.¹⁹⁵

Antithrombotic Therapy in Patients with MPN and CVD

The classic three entities of *BCR-ABL1*-negative MPN include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF).¹⁹⁶ In MPN patients, arterial and venous thromboembolic events (ATE/VTE) occur frequently and have a significant impact on morbidity and mortality. An up to 10-fold higher incidence of such complications compared with the healthy population has been reported.^{197–200} Arterial thrombosis (AT) is responsible for about two-thirds of all severe thrombotic events in MPN,

Table 9 Recommendations for antithrombotic therapy in TP for different degrees of TP and various bleeding tendency (according to WHO bleeding grade) and three different scenarios of cardiac disease: (a) TP and symptomatic stable CAD, (b) TP and PCI, (c) TP and AF

TP with	Platelets $> 50 \times 10^9/L$ and WHO °0, I	Platelets $30–50 \times 10^9/L$ and WHO °0, I	Platelets $20–30 \times 10^9/L$ and WHO °0, I	Platelets $< 20 \times 10^9/L$ and WHO °0, I
(a) Stable CAD	ASA	ASA	Individual decision	Individual decision
(b) PCI ⁵	ASA	ASA	ASA	Individual decision
(c) AF	Full-dose anticoagulation DOACs/VKA	Reduced-dose anticoagulation DOAC/LMWH	Prophylactic dose LMWH	Anticoagulation not recommended

Abbreviations: ASA, acetylsalicylic acid; CAD, coronary artery disease; DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparins; PCI, percutaneous coronary intervention; TP, thrombocytopenia; VKA, vitamin-K antagonists; WHO, bleeding grade.

making it one of the major causes of mortality in MPN.^{201,202} The most common here are ischemic stroke, transient ischemic attack (TIA), acute MI, and peripheral artery occlusion. MPN patients with venous or arterial thrombosis or with a history of CV events are the so-called high-risk MPN patients with a high risk of recurrence for whom cytoreduction is recommended in addition to antithrombotic therapy, which can reduce the recurrence rate.²⁰³

According to data from the ECLAP (European Collaboration on Low-Dose Aspirin in Polycythemia vera) trial, treatment with 100 mg of ASA per day in primary prevention reduced the risk of the combined endpoint of nonfatal MI, nonfatal stroke, PE, severe VTE, or death from CV causes compared with placebo (relative risk, 0.40; 95% confidence interval, 0.18–0.91; $p = 0.03$).²⁰⁴ However, all-cause mortality and CV mortality were not significantly reduced by ASA. The incidence of major bleeding episodes was not significantly increased with low-dose ASA at 100 mg per day.

The international and retrospective PRISM (Preventing Ischemic Stroke in Myeloproliferative Neoplasms) cohort study included 597 MPN patients who had suffered either a TIA ($n = 270$) or an ischemic stroke ($n = 327$).²⁰⁵ Treatment included ASA, oral anticoagulants, and cytoreductive drugs as secondary prevention. After an observation period of 5 years, the incidence of acute MI was 3.74% and for TIA or stroke it was 1.80%. Since similar event frequencies are also expected in the general population, it can be concluded that the benefit–risk profile of antithrombotic and cytoreductive treatment in MPNs is favorable.

In recent decades, platelet inhibition and anticoagulation with VKA has been the treatment of choice for preventing ATE/VTE recurrences in MPN patients. Hernández-Boluda et al reported a 2.8-fold risk reduction for recurrence with VKA treatment in 150 ET and PV patients with ATE/VTE.²⁰⁶

With regard to anticoagulation with DOACs, there are only a few studies in MPN, but all of them suggest good efficacy with adequate safety. Ianotto et al retrospectively reported two arterial thromboembolic events but no VTE recurrences in a cohort of 25 DOAC-treated MPN patients.²⁰⁷ However, three major and two minor bleeding events were observed with DOACs. Fedorov et al reported preliminary data on relapse rates and bleeding complications in 22 DOAC- and 31 VKA-treated MPN patients.²⁰⁸ During a short follow-up period of 8 months, the number of arterial and venous thromboembolic recurrences (DOAC, $n = 5$, vs. VKA, $n = 6$) and bleeding complications (DOAC, $n = 5$, vs. VKA, $n = 11$) was not significantly different.

A recently published retrospective study compared the efficacy and safety of both types of anticoagulants in 71 MPN cases with arterial and ATE/VTE from a cohort of 782 MPN patients.²⁰⁹ Forty-five of 71 ATE/VTE (63.4%) MPN patients were treated with VKA and 26 (36.6%) with DOACs. The duration of anticoagulation therapy ($p = 0.984$), the number of patients receiving additional ASA ($p = 1.0$), and the proportion of patients receiving cytoreductive therapy ($p = 0.807$) did not differ significantly between the VKA and DOAC groups. During anticoagulation therapy, significantly more recurrences occurred with VKA ($n = 16$) compared with

DOAC treatment ($n = 0$, $p = 0.0003$). Over the entire median observation period of 3.2 years (i.e., also the periods without anticoagulation, 0.1–20.4 years), the ATE/VTE recurrence-free survival did not differ significantly between the two anticoagulants ($p = 0.2$). No significant differences were observed between VKA and DOAC for all bleeding events ($p = 0.516$) and especially for major bleeding events ($p = 1.0$).

In an international study (MPN-DOACs study), the incidence and risk factors for thrombotic and bleeding complications were retrospectively assessed in 442 MPN patients treated with a DOAC for AF or VTE.²¹⁰ After a median interval of 4.4 years (0.4–9.6 years) since MPN diagnosis, DOACs were prescribed in 203 patients with AF (45.9%) and 239 patients with VTE (54.1%). In MPN patients, 10 serious thrombotic events were reported with DOACs after a follow-up of 1.7 years (0.8–3.1 years) (2.1% events per patient/year). Thus, the incidence rate (IR) of ischemic cerebrovascular events (ICVEs) is comparable to the IR of SE reported in non-MPN patients with AF, where the IR of ICVE during primary prophylaxis with VKAs or DOACs is 1.2 to 1.8% and 1.0 to 1.4% per patient/year, respectively. However, part of this effectiveness in preventing ICVE may also be due to the concomitant use of hydroxyurea (82%), which is known to have a protective effect on ICVE recurrences in MPN patients with prior ICVE.²⁰³ Overall, 14 major hemorrhagic events were observed in the 203 MPN patients with AF, mainly in the gastrointestinal tract, representing an annual major bleeding rate of 3%. Among the four DOACs, dabigatran was more frequently associated with bleeding than the other three DOACs (7/26, 27% vs. 43/416, 10%, $p = 0.01$). Of note, patients who experienced bleeding were more likely to have a diagnosis of myelofibrosis ($p = 0.005$).

The multicenter, noninterventional and prospective REVEAL study investigated the incidence of bleeding during antithrombotic therapy in 2,510 patients with polycythemia vera.²¹⁰ The bleeding rate in patients receiving ASA alone was 1.40 per 100 patient-years, whereas the combination of ASA plus anticoagulant was associated with a significantly higher bleeding incidence of 6.75 per 100 patient-years. It did not matter whether the anticoagulant warfarin or a DOAC was given in addition to ASA. Clinically relevant was the observation that during periods of thrombocytosis (>600 G/L), the risk of bleeding was significantly increased (HR: 2.25; 95% CI: 1.16–4.38; $p = 0.02$). This is consistent with the fact that secondary von Willebrand's syndrome is more common in MPN with increasing platelet counts and especially with platelets $>1,000$ G/L.²¹¹ Conversely, this means that when platelets are high, the bleeding tendency is significantly reduced under cytoreduction. Therefore, cytoreduction in high-risk MPN and antithrombotic therapy reduces not only thromboembolic events but also the bleeding tendency^{212,213} (→ Table 10).

Antithrombotic Therapy in Patients with Inherited Platelet Disorders and CVD

Although several case reports on thromboembolic complications in patients with Glanzmann thrombasthenia, Bernard-Soulier syndrome, or MYH9-associated TP are available,

Table 10 Recommendations for antithrombotic therapy in MPN for different degrees of thrombocytopenia with various bleeding tendency (according to WHO bleeding grade) and three different scenarios of CVD: (a) MPN and symptomatic stable CAD, (b) MPN and PCI, (c) MPN and AF

MPN and	Platelets normal with cytoreductive therapy and WHO °0, I	Platelets slightly increased up to $600 \times 10^9/L$ and WHO °0, I	Platelets $600-1,000 \times 10^9/L$ and WHO °0, I	Platelets $> 1,000 \times 10^9/L$ and WHO °0, I, II
(a) Stable CAD	ASA	ASA	ASA	ASA individual decision
(b) PCI	ASA	ASA	ASA	ASA individual decision
(c) AF	Full-dose anticoagulation DOACs/VKA	Full-dose anticoagulation DOACs/VKA	Reduced-dose anticoagulation DOAC/LMWH	Prophylactic-dose anticoagulation LMWH, individual decision

Abbreviations: ASA, acetylsalicylic acid; CAD, coronary artery disease; DOACs, direct oral anticoagulants; LMWH, low molecular weight heparins; MPN, myeloproliferative neoplasms; PCI, Percutaneous coronary intervention; VKA, vitamin-K antagonists; WHO, bleeding grade.

data on the long-term management of patients with congenital platelet dysfunction are scarce. Usually, anticoagulation in a therapeutic dose with UFH or LMWH is administered for acute VTE. In the SPATA-DVT study, a patient with Glanzmann thrombasthenia and DVT received a therapeutic dose of enoxaparin for 3 months without bleeding complications.²¹⁴ Thus, temporary anticoagulation seems possible in patients with IPD without a significant increase in the risk of bleeding. However, long-term anticoagulation can disproportionately increase the risk of bleeding. On the basis of the available data, we suggest that, depending on the genesis, localization, and extent, therapeutic anticoagulation should also be administered in the first 3 months after an acute VTE. To adjust the anticoagulation regimen in patients with IPD, the further course of treatment should consider the type of thrombosis, the bleeding tendency of each patient, the efficacy of the treatment, and the individual risk of VTE recurrence. Reduced doses of NMH or DOACs may be appropriate for long-term anticoagulation if bleeding symptoms occur during therapeutic anticoagulation.

Risk Assessment for Bleeding in Patients with Platelet Disorders

Different bleeding assessment tools (BATs) are available to help in assessing the risk of bleeding based on the medical history. The WHO and the ISTH-BAT scores are the most commonly used.²¹⁵ Both assess the bleeding risk according to acute and historic bleeding symptoms. The resulting score correlates with the risk of future spontaneous and provoked bleeding.²¹⁶ It should be noted that additional hemorrhagic risks due to asymptomatic disorders of hemostasis could additionally increase the risk of bleeding. This is reflected in the IMPROVE bleeding risk score by including liver and kidney function as well as platelet count. A combined risk assessment for bleeding and thrombosis in ITP patients (TH2 risk assessment score) was presented in a retrospective study.²¹⁷ The TH2 risk assessment score evaluated two risk factors for thrombosis (risk factor for thrombosis and thrombosis risk of ITP treatment) and bleeding (platelet count $< 20 \times 10^9/L$ and current major bleeding). The TH2 score was developed to aggregate the net risk of thrombosis or bleeding in patients with TP who have a distinct indication

for anticoagulation. This score is designed to help clinicians to make an integrated decision about the use of anticoagulation.

Conclusion

CVDs are concerning issues which impact prognosis of patients with cancer. Cancer patients are at high risk for both ischemic and bleeding events due to dysregulation of their hemostatic system. Therefore, antithrombotic treatment decisions should be based on risk and benefit assessments, and the selection of anticoagulation type and dosage should take into account anticoagulant efficacy, bleeding risk assessment, renal or hepatic function, DDI, clinical setting, convenience of use, cost, and patient preference. Because of the unique risk profile of patients with cancer, management of CVD requires special considerations as compared with patients without cancer. A common complication in patients with cancer is TP (either due to underlying malignancy or the toxicity of cancer-directed therapy), with additional challenges in clinical decision making in patients with cancer who develop both thrombosis and TP, as TP increases the risk of bleeding without conferring protection against thrombosis.⁴⁶ For cancer patients with TP $< 50 \times 10^9/L$, one should consider reduced-dose anticoagulation and with $< 20 \times 10^9/L$ even withholding anticoagulants completely. All hematologists should be familiar with the new EHA and ESC recommendations.

Recent advances in cancer treatment, including many targeted therapies, have led to an improved prognosis for patients with malignancy. Arrhythmias, particularly AF, are becoming a more common adverse reaction in patients with active cancer on anticancer drugs.

AF management in active cancer is largely derived from guidelines for AF patients without cancer, although it is probably not entirely adequate.¹⁰ In most cases, the culprit anticancer drug can be continued. Although not validated in patients with active cancer, the CHA2DS2-VASc and HAS-BLED scores may be used in addition to more specific parameters in patients with active cancer such as platelet count and cancer location. DOACs are usually preferred to VKA.

Another important issue is how patients with cancer and CVD who are frail or on PC should be addressed, also because

polypharmacy causes additional possible DDI. In these patients, treatment decisions should be followed on the basis of patient preferences (no treatment, subcutaneous, or oral anticoagulants), life expectancy (end-of-life anticipated within 3 months or beyond; for estimating 3-month survival in PC cancer patients, using the PRONOPALL score is recommended⁶⁴), contra indications to anticoagulants, evaluation of bleeding risk, the time since VTE diagnosis (over or under 3 months), and the type of VTE (PE or DVT). All decisions should be taken following a discussion and agreement with the patient and family.

The future direction of antithrombotic treatment should be focused on how to reduce bleeding rates while on antithrombotic therapy without compromising efficacy.

Authors' Contributions

S.P., H.R.: conceived and planned the project, wrote parts of the manuscript, completed and revised the whole manuscript; S.K., L.H., M.G., A.M., T.B., F.L., R.S.A.: wrote paragraphs of the manuscript and revised the manuscript; D.D., G.T.: revised the manuscript and added relevant aspects to the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

SP and MG have no conflict of interest.

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