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Review

Cancer-related arterial thromboembolic events

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ABSTRACT

Cancer is associated with a hypercoagulable state and is a well-known independent risk factor for venous thromboembolism, whereas the association between cancer and arterial thromboembolism is less well established. Arterial thromboembolism, primarily defined as myocardial infarction or stroke is significantly more frequent in patients with cancer, independently of vascular risk factors and associated with a three-fold increase in the risk of mortality. Patients with brain cancer, lung cancer, colorectal cancer and pancreatic cancer have the highest relative risk of developing arterial thromboembolism. Antithrombotic treatments should be used with caution due to the increased risk of haemorrhage, as specified in current practice guidelines.

1. Abbreviations

ACS	acute coronary syndrome
AF	atrial fibrillation
ATE	arterial thromboembolism events
BCR-ABL	breakpoint cluster region – abelson murine leukaemia viral oncogene Homolog 1
CATS	cancer and thrombosis study
CDK4/6	Cycline dependent kinase 4/6
CHD	coronary heart disease
CI	confidence interval
CLI	critical limb ischaemia
CNS	central nervous system
CTLA-4	cytotoxic T-lymphocyte antigen 4
CTX	chemotherapy
DXI	direct oral factor Xa inhibitor
EGFR	epidermal growth factor receptor
HR	Hazard ratio
HR+	hormone receptor positive
ICH	intracranial haemorrhage
ICI	immune checkpoint inhibitors
OR	odds ratio
PAD	peripheral artery disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand
PY	Person years
RCT	randomized controlled trial
REGARDS	reasons for geographic and racial differences in stroke
RR	relative risk
SIR	standardised incidence ratio
SMR	standardised mortality ratio
TKI	tyrosine kinase inhibitor
US SEER	United States surveillance epidemiology and end results
VEGF-A	vascular endothelial growth factor A
VEGFR	vascular endothelial growth factor receptor

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2. Introduction

In contrast to venous thromboembolism, the association between cancer and arterial thromboembolic events (ATE), including myocardial infarction, ischaemic stroke or peripheral artey occlusion, is less well established, although an increased risk has been previously reported in patients with cancer, especially for stroke and coronary heart disease (CHD). Moreover, cardiovascular diseases and cancer are more prevalent in the older population and often share the same risk factors. In addition, the risk of ATE in cancer may also be increased by cancer treatments, with chemotherapy, hormonal therapy, tyrosine kinase inhibitors (TKIs) and immunotherapy all conferring a higher risk of arterial complications. This article reviews what is known about the association between cancer and ATE and the implications for therapy. We also cover atrial fibrillation (AF), which although not an ATE itself, is a major risk factor for stroke. The review is restricted to patients with incident ATE following a diagnosis of cancer; the literature concerning ATE as a predisposing factor for the subsequent development of cancer is not discussed. To support this review, a literature search was performed in the PubMed database (see e-supplement).

3. Arterial thromboembolism in patients with cancer: epidemiological considerations

Compared to the general population, a two to six-fold-increased incidence of ATE (myocardial infarction, ischaemic stroke and peripheral arterial occlusion) is observed in patients with cancer (Table 1). Using the US SEER Medicare database, the six-month cumulative incidence of ATE was 4.7% [95%CI: 4.6–4.8%] in patients with cancer compared to 2.2% [95%CI: 2.1–2.2%] in patients without cancer (hazard ratio: 2.2 [95%CI: 2.1–2.3] [1]. Based on the UK Biobank database of 13,972 patients analysed, aged from 40 to 69 years, Duarte et al. reported an adjusted odds ratio (OR) of 1.9 [95% CI 1.2–3.2] for ATE in patients with cancer compared to patients without [2]. More recently, Navi et al. reported that patients with cancer have a six times higher risk of ATE in the first 30 days after a cancer diagnosis than matched controls [3]. In the recent large overview based on analysis of data extracted from the Austrian Association of Social Security Providers Dataset (covering the years 2006–2007), an ATE diagnosis (myocardial infarction, stroke or arterial embolism) was documented in 5.4% of people with cancer compared to 0.9% with an ATE diagnosis in the absence

Table 1
Cancer- related arterial thromboembolism events.

	Population studied	ATE event in cancer population	Main cancer sites with ATE
Zoller et al., 2012 [6,7]	Swedish national data base 1987–2008 (n = 820,491)	At 6 months after cancer diagnosis SIR CHD 1.7 [95%CI: 1.66–1.75]	Small intestine cancer: 2.88 Leukaemia: 2.84 Kidney cancer: 2.65 Lung cancer: 2.56 Metastatic disease: 1.46
		SIR ischaemic stroke 1.6 [95%CI: 1.5–1.6]	CNS cancer: 4.1 Leukaemia: 3 Metastatic disease: 1.5
Navi et al., 2017 [1]	US SEER Medicare database 2002–2011 (n = 279,719)	Cumulative incidence at 6 months after cancer diagnosis 4.7 % [95 %CI: 4.6 %–4.8 %] vs. 2.2 % [2.1 %–2.2 %] in controls (HR: 2.2; 95 %CI: 2.1–2.3)	
Duarte et al., 2017 [2]	UK Biobank (n = 13,972)	OR 1.9 (1.2–3.2)	
Grilz et al., 2018 [8]	Vienna CATS Cohort (n = 1,880) 2003–2013 Median FU 2y	Cumulative incidence at 2 years after cancer diagnosis ATE: 2.6% CHD: 41.7% Stroke: 33.1% PAD: 25%	Lung cancer: HR = 2.3 Kidney cancer: HR = 3.8
	The 2-year cumulative incidence of ATE increased from 1.4% to 12.5% related to the number of associated cardiovascular risk factors	Mortality HR 3.2 [95%CI: 2.2–4.8]	
Navi et al., 2019 [3]	Cohort from REGARDS study and Medicare (n = 4,175) 2003–2007 Beyond 30 days, cancer was not associated with an increased risk of ATE	At 30 days after cancer diagnosis HR(a) 5.8 [95%CI: 2.1–15.9]	Restricted to lung, colorectal, gastric and pancreatic cancer HR 15.6 Metastasis 14.4
Grilz et al., 2021 [4]	Austrian Social Security Database (n = 8,306,244) 2006–2007	RR: 6.88 [95%CI: 4.81–9.84]	Urinary tract cancer Respiratory system cancers Male genital cancers
[5]	Danish registries (n = 1 833 848) 1997–2017	Cumulative incidence at 6 months 1.50 % [95 %CI: 1.47–1.54 %] vs. 0.76 % [95 %CI: 0.75–0.77 %] HR 2.36 [95 %CI: 2.28–2.44]	Bladder (2.49%), lung (2.08%), colorectal 2.08%)
		Mortality HR 3.28 [95% CI: 3.18–3.38]	

ATE: arterial thromboembolism events; CHD: coronary artery disease; CI: confidence level; CNS: central nervous system; HR: hazard ratio; REGARDS: REasons for Geographic and Racial Differences in Stroke; OR: odds ratio; RR: relative risk; SIR: standardised incidence ratio; US SEER medicare database: United States surveillance epidemiology and end results–medicare linked database; Vienna CATS: Vienna cancer and thrombosis study; PAD: peripheral artery disease.

Table 2
Acute coronary syndrome in patients with cancer.

	Population studied	ACS event in cancer population	Main cancer sites with ACS
Zoller 2012	Swedish national data base 1987–2008 (*n* = 820,491)	At 6 months after cancer diagnosis SIR CHD 1.7 [95%CI: 1.66–1.75]	Small intestine cancer: 2.88 Leukaemia: 2.84 Kidney cancer: 2.65 Lung cancer: 2.56 Metastatic disease: 1.46
Navi et al., 2017 [1]	US SEER Medicare database 2002–2011 (*n* = 279,719)	Cumulative incidence at 6 months after cancer diagnosis: 2% [95%CI: 1.9–2.0%] vs. 0.7% [0.6–0.7%] in controls	
Duarte et al., 2017 [2]	UK Biobank (*n* = 13,972)	Lung cancer: 8.9% vs. 3.1% OR 2.3 [95%CI: 1.4–3.9]	
Grilz et al., 2018 [8]	Vienna CATS Cohort (*n* = 1,880) 2003–2013 Median FU 2y	Cumulative incidence at 2 years after cancer diagnosis CHD: 41.7%	
[5]	Danish registries (*n* = 1 833 848) 1997–2017	Cumulative incidence at 6 months 0.53 % [95 %CI: 0.51–0.55 %] vs. 0.31 % [95 %CI: 0.30–0.32 %] HR 2.08 [95 %CI: 1.96–2.19]	

ATE: arterial thromboembolism events; CHD: coronary artery disease; CI: confidence level; US SEER Medicare database: United States Surveillance Epidemiology and End Results–Medicare linked database: Vienna CATS: Vienna Cancer and Thrombosis Study; OR: odds ratio; SIR: standardised incidence ratio.

of cancer [4]. Finally, in the Danish National Patient Registry, including 458,462 cancer patients and 1,375,386 comparators (years 1997–2017), the incidence of ATE at 6 months after cancer diagnosis was 1.50% [95%CI: 1.47–1.54%] in cancer patients and 0.76% [95%CI: 0.75–0.77%] in controls, corresponding to a hazard ratio of 2.36 [95%CI 2.28–2.44] [5].

The occurrence of ATE varies by cancer type, with lung, kidney and metastatic cancer bearing the highest risk [1,5–7], correlated with cancer stage. Patients with lung cancer were shown to experience the highest excess risk of ATE, with hazard ratio (HR) of 9.6 [95%CI: 8.4–10.9) at 1 month and 2.2 ([95%CI: 1.9–2.5] at 12 months [1], and an odds ratio of 8.8 [95%CI: 3.8–20.2] [2]. Again, compared to patients without cancer or other cancers, ATE proportion was highest in patients with urinary tract malignancies, with a relative risk (RR) of 7.16 [95%CI: 6.74–7.61] followed by patients with cancer of the respiratory system (RR: 7.12 [95%CI: 6.73–7.54] [4]. Finally, when restricted to participants of the REGARDS cohort with lung, colorectal, gastric, or pancreatic cancers (*n* = 175), the adjusted HR for ATEs in the first 30 days after cancer diagnosis was 15.6 [95%CI: 3.3–73.3] vs. HR 5.8 in the entire cohort [3] (Table 1).

An advanced cancer stage was associated with an increased risk of ATE, (at 6 months, 2.3% incidence at stage 0, compared with 7.7% at stage IV) [1]. In the REGARDS cohort, the adjusted HR for ATE in the first 30 days after cancer diagnosis was 14.4 [95%CI: 4.0–52.2] in participants with known metastatic cancer [3]. In women with breast cancer, factors associated with the occurrence of cardiovascular events were overexpression of HER-2 (HR: 2.6 [95%CI: 1.21–5.56] $P < 0.011$), UICC stage III (or higher stage) tumours more (HR: 5.47 [95%CI: 2.78–10.76] $P < 0.001$) [9].

In the US SEER study, patients with cancer had a > 10-fold increase in ATE in the first month after diagnosis of cancer but the risk returned to pre-cancer levels by one year [1]. The difference in ATE risk between cancer types may be related to associated-classical cardiovascular risk factors that increase the risk of both cancer and ATE, such as hypertension and smoking [3,8]. In women with breast cancer, factors associated with the occurrence of cardiovascular events were pre-existing cardiovascular diseases, including high blood pressure (HR: 1.78 [95%CI: 1.07–2.97], $P = 0.028$) and acute coronary syndrome (ACS) (HR: 5.28 [95%CI: 2.16–12.88] $P < 0.05$] [10]. In the Danish registry study, risk factors for ATE were age > 65y (HR 1.53 [95%CI: 1.43–1.65], previous history of ATE (HR 2.96 (95%CI: 2.77–3.17], distant metastasis (HR 1.21 [95% CI: 1.12–1.30] and chemotherapy (HR 1.47 [95%CI: 1.12–1.61] [5].

Finally, the occurrence of ATE/VTE was associated with poor prognosis [5–7,11], with a threefold increased risk of all-cause mortality (HR for ATE: 3.1 [95%CI: 3.0–3.1] and HR for VTE: 3.2 [95%CI: 2.2–4.8] [1,8]; HR mortality 3.28 [95%CI: 3.18–3.38] [5]).

Key points

- A two to six-fold-increased risk of arterial thromboembolic events is observed in patients with cancer compared to the general population.
- The occurrence of ATE varies by cancer type, with lung, kidney and metastatic cancer having the highest risk.
- Advanced cancer stage is associated with an increased risk of ATE.
- Patients have a > 10-fold increase in ATE in the first month after diagnosis of cancer, with the risk generally declining to pre-cancer levels after one year.
- The occurrence of ATE/VTE is associated with a three-fold increase in the risk of all-cause mortality.

3.1. Acute coronary syndrome in patients with cancer: epidemiological considerations

The proportion of patients with ACS who have active cancer is around 3% [12]. A two to four-fold-increased risk of ACS is observed in patients with cancer compared to the general population (Table 2), with the highest incidence for patients with lung cancer [1,2,12]. Contrasting results regarding in-hospital mortality were reported [13].

The French FAST-MI registry found that in-hospital mortality was not significantly different for patients with a history of cancer compared to those without, either overall (adjusted OR: 1.15 [95%CI: 0.68–1.94]; $P = 0.61$) or in patients with STEMI (adjusted OR: 1.37 [95%CI: 0.69–2.71]; $P = 0.37$) or NSTEMI (adjusted OR: 0.97 [95%CI: 0.41–2.28]; $P = 0.95$). By contrast, in-hospital mortality was reported to be twice as high in patients with an active cancer than in those with a past history or no cancer (11.1% vs. 5.4% and 5.7%, respectively) [12]. Finally, all-cause mortality at five years was higher in patients with a history of cancer (adjusted hazard ratio [HR]: 1.36 [95%CI: 1.08–1.69] $P = 0.008$), whereas five-year cardiovascular mortality did not differ [14].

Key points

- A two to four-fold-increased risk of ACS is observed in patients with cancer compared to the general population.
- The incidence of ACS is higher in patients with lung cancer than in patients without lung cancer.

3.2. Ischaemic stroke in patients with cancer

Besides the increased risk of hemorrhagic stroke, ischaemic stroke is also an important neurological complication associated with cancer. The proportion of patients with active cancer who experience an ischaemic stroke ranges from1 to 5%, depending on the type of cancer (Table 3).

Using the US SEER Medicare database to assess the risk of stroke in patients with a new diagnosis of cancer compared to a matched cohort of patients without cancer, the 6-month cumulative incidence of ischaemic stroke was 3.0 in all patients with cancer compared with 1.6 in control patients (HR: 1.9 [95%CI: 1.8–2.0] $P < 0.001$) [1]. Similar results were reported in the Danish registries, with a hazard ratio of 2.39 [95%CI: 2.28–2.50] for patients with cancer [5]. In patients with cancer, the relative hazard of ischaemic stroke at six months was 1.5 [95%CI: 1.4–1.7] for patients with stage 1 disease and 5.2 [95%CI: 5.0–5.4] for patients with stage 4 disease. For lung cancer, the HR for stroke was 7.12 [95%CI: 6.35–7.99] between 0 and 1 month after diagnosis, 5.6%

Table 3
Ischaemic stroke in patients with cancer.

	Population studied	Ischaemic stroke in cancer population	Main cancer sites with stroke
Chen et al., 2011 [15]	Taiwan National Health Insurance data base 1999–2008 (n = 156,267)	HR: 1.43 [95%CI: 1.34–1.51]	Only lung cancer studied
Kuan et al., 2014 [16]	Taiwan National Health Insurance data base 2003–2011 (n = 10,182) Significant risk factors predicting stroke development were age 50 years and older (HR 2.21; P)	HR: 1.49 [95%CI: 1.25–1.78]	Only ovarian cancer studied
Kuan et al., 2015 [17]	Taiwan National Health Insurance data base 2003–2011 (n = 30,786)	HR: 1.11 [95%CI: 1.03–1.19]	Only gastric cancer studied
Navi et al., 2015 [18]	US SEER Medicare database 2001–2009 (n = 327,389) Matched control study	Cumulative incidence rate at 3 months Lung vs. matched controls 5.1% [95%CI: 4.9–5.2%] vs. 1.2% [95%CI: 1.2–1.3%] Pancreatic cancer vs. matched controls 3.4% [95%CI: 3.1–3.6%] vs. 1.3% [95%CI: 1.1–1.5%] Colorectal cancer vs. matched controls 3.3% [95%CI: 3.2–3.4%] vs. 1.3% [95%CI: 1.2–1.4%] Breast cancer vs. matched controls 1.5% [95%CI: 1.4–1.6%] vs. 1.1% [95%CI: 1.0–1.2%] Prostate cancer vs. matched controls 1.2% [95%CI: 1.1–1.3%] vs. 1.1% [95%CI: 1.0–1.2%]	
Navi et al., 2017 [1]	US SEER Medicare database 2002–2011 (n = 279,719) Excess risk of ATE varied by cancer site (greatest for lung cancer), correlated with cancer stage Generally, the elevated risk of ATE had returned to pre-cancer levels by 1 year	Cumulative incidence at 6 months after cancer diagnosis: 3.0 % [95 %CI: 2.9–3.1 %] versus 1.6 % [95 %CI: 1.6–1.7 %] in controls HR: 1.9 [95 %CI:1.8–2.0].	Higher risk in patients with lung cancer
Navi et al., 2019 [3]	Cohort from REGARDS study and Medicare (n = 4,175) 2003–2007	At 30 days after cancer diagnosis HR(a) 5.8 [95%CI: 2.1–15.9]	
Navi et al., 2018 [19]	Cohort from REGARDS study and Medicare (n = 6,602) 2003–2014	At 30 days after cancer diagnosis Adjusted HR: 6.6 [95%CI: 2.7–16.0]	Adjusted HR: > 1 for lung and breast cancer: *Lung*: 20.5, [95%CI: 5.0–83.6] *Breast*: 12.7, [95%CI: 1.8–91.5] but not significantly different from unity for prostate, colorectal, or pancreatic cancer.
[5]	Danish registries (n = 1 833 848) 1997–2017	Cumulative incidence at 6 months 0.87 % [95 %CI: 0.85–0.90 %] vs. 0.43 % [95 %CI: 0.42–0.44 %] HR 2.39 [95 %CI: 2.28–2.50]	
Lun et al., 2022 [20]	Systematic review 41 studies/2,552,121 patients	Pooled incidence of ischaemic stroke at 1 year: 1.3 [95%CI: 1.0–1.58] Pooled cumulative incidence of ICH at 1 year: 0.3 [95%CI: 0.1–0.9]	

ATE: arterial thromboembolism events; CI: confidence interval; HR: hazard raio; ICH: intracranial haemorrhage; REGARDS: REasons for Geographic and Racial Differences in Stroke; US SEER Medicare database: United States surveillance epidemiology and end results–medicare linked database.

[95%CI: 5.4–5.7] at 6 months, and 1.55 [95%CI: 1.39–1.74] between 9 and 12 months [18], highlighting that the risk of ATE is highest in the period immediately after the cancer diagnosis, when cancer activity and treatments are most intense.

In data from the Taiwan National Health Insurance, the incidence of stroke was 1.5 times higher (25.9 versus 17.4 per 1000 person-years) in the lung cancer group compared to a control group without cancer [15] and 1.4 higher in ovarian cancer (Kuan 2014). Moreover, the excess risk observed at 3 months diminished over time and generally returned to pre-cancer diagnosis by 1 year.

Cancer patients with acute ischaemic stroke presented a high rate of recurrent ATE (21% at 1 month, 31% at 3 months and 37% at 6 months). The highest rates of recurrence are observed for patients with adenocarcinoma [21], who present a risk of recurrent ischaemic stroke approximately threefold higher than non-cancer patients without cancer [22].

Cancer-associated ischaemic stroke exhibits a higher mortality rate compared to the general population. For example, it was reported that patients with colorectal cancer and lung and bronchial cancers had the higher rate of death from stroke, with a standardised mortality ratio (SMR) of 1.08 [95%CI: 1.06–1.11] for colorectal cancer and 1.70 [95%CI: 1.65–1.75] for lung cancer [23]. Similarly, in patients with stroke, the presence of malignant pulmonary lesions detected on imaging was associated with all-cause in-hospital mortality (adjusted OR: 3.83; [95%CI: 1.29–9.94] [24]. Finally, in a prospective cohort of patients with embolic stroke of undetermined source in patients with cancer, lung cancer was the primary cancer site which carried the highest risk of ischaemic stroke. In addition, metastatic disease was not associated with one year-related mortality on multivariate analysis, HR 1.13, 95%CI, 0.25–5.13, $P = 0.874$) [25].

In a multicentre international thrombosis registry (RIETE), ischaemic stroke occurred in 63/5717 patients (1.1%) with active cancer over a median follow-up duration of 5.0 months, after diagnosis of cancer. Thirty-day mortality rates were 64% for stroke, 40% for myocardial infarction, 41% for major bleeding and 20% for recurrent pulmonary embolism. In addition, 499/5717 (8.7%) patients experienced recurrent venous thromboembolism [26].

Cancer-related coagulopathy has been implicated as the underlying mechanism in 40% of patients with cancer experiencing an ischaemic stroke [27]. In addition, the incidence of atrial fibrillation, principal cause of cardio-embolic stroke, is also elevated in cancer patients [28]. Moreover, in a subgroup analysis of studies that only included cancer patients with atrial fibrillation, the incidence of ischaemic stroke was 3.3% at one year [95%CI: 2.4–4.6], which was significantly higher than the incidence in patients without AF (1.2% [95%CI: 0.9–1.6] [20].

Key points

- The proportion of patients with active cancer who experience an ischaemic stroke ranges from 1 to 5%.
- Patients with lung cancer have the highest six-month cumulative incidence of ischaemic stroke.
- The elevated risk observed at 3 months after diagnosis decreases over time and is generally no longer detectable beyond 1 year.
- Cancer patients exhibit a risk of recurrence of ischaemic stroke approximately 3-fold higher than non-cancer patients.
- Cancer-associated ischaemic stroke exhibits a higher mortality rate, independently of progression to metastatic disease.

3.3. Peripheral artery disease (PAD) in patients with cancer

Many studies have reported the incidence of cancer diagnosed after a first event of acute (ALI) or chronic limb ischaemia, but few have explored the risk of PAD event, especially following ALI in cancer patients.

In a retrospective cohort of 419 patients with acute limb ischaemia, Tsang et al. [29] reported a prevalence of cancer of 3.8%. Of the 16 cases identified, eight cancers (50%) were present prior to the episode of acute limb ischaemia. Common cancer sites were the urogenital tract ($n = 5$) and the lungs ($n = 5$). In the prospective Vienna Cancer and Thrombosis Study (CATS) (2003–2018), 25% of reported ATE were peripheral arterial events [8]. Again, lung cancer (HR: 2.3 [95%CI: 1.2–4.2] $P = 0.009$), and kidney cancer (HR: 3.8 [95%CI: 1.4–10.5] $P = 0.012$) were associated with a high risk of ATE. In the COPART registry, collecting data on PAD patients hospitalised in four university hospitals in France, the prevalence of known cancer was 15.9%% [30]. In the Danish registry study [5], cancer was a risk factor for PAD (defined as “peripheral arterial occlusion”) with a HR of 2.39 [95%CI: 2.28–2.50]. In this study, patients, with brain tumors were at the highest risk [5].

In a prospective case-control study comprising all Danish citizens undergoing vascular surgery for acute arterial thrombosis between 1986 and 2012 ($n = 7{,}840$), 1,569 (20%) had previously been diagnosed with cancer [31]. Interestingly, histology revealed that occlusions were due to thromboembolism, with no tumour cells identified. The risk of amputation was significantly greater in patients diagnosed with cancer < 24 months prior to admission (HR: 2.0 [95%CI: 1.26–3.19]) [31]. Likewise, in a systematic review of 1,704 patients with ALI presenting after a cancer diagnosis, major amputation was more frequent than in patients with acute limb ischaemia without cancer (7.4% vs. 4.6%; $P < 0.01$) [32]. Moreover, one-year mortality after ALI presentation in patients with cancer was > 50%. In a small cohort study of twenty patients presenting with acute arterial thrombosis who had an underlying malignancy, median survival after the ATE was 2.5 months, with a survival rate was 50% at three months and 17% at one year, compared to 90% and 75% respectively for patients with atherosclerotic-related critical limb ischaemia without cancer [33]. Moreover, in these patients with cancer-associated ischaemia, five out of six thromboembolectomies and two out of three bypass procedures failed [33].

In a retrospective cohort of 116 patients with ALI in Wales, the recurrence rate for arterial thrombosis was reported to be higher in cancer patients (29%) than in the absence of cancer (18%) [34].

Data regarding patients with cancer who present critical limb ischaemia (CLI) are very scarce. An 8-month observational study aims to assess the prevalence of malignant disease in patients presenting with CLI. between January 2002 and June 2003. Of 192 patients admitted with CLI, 22 (11 5%) were found to have an associated malignancy and ten had lung cancer [35].

Key points

- 25% of reported ATE in cancer patients are peripheral arterial events.
- Lung, brain and kidney cancer are associated with a higher risk of PAD.
- The risk of amputation is significantly greater in patients diagnosed with cancer.
- The 1-year mortality after the development of acute limb ischaemia in patients with cancer is > 50%.
- Recurrence of arterial thrombosis appears to be higher in cancer patients.

3.4. Atrial fibrillation in patients with cancer

Active cancer is associated with an increased risk of AF (HR: 1.63 [95%CI: 1.61–1.66]) [36], which varies depending on patient history (including age, pre-existing cardiovascular risk factors or risk factors for other diseases, and previous thoracic surgery), the type of cancer (haematological malignancies, digestive and lung cancer), stage (metastatic cancers), and anticancer treatments [37,38].

Although the association between AF and stroke is well documented in the general population, it is less clear in patients with active cancer and treated with anticancer drugs [37]. On the one hand, in some studies, AF in patients with active cancer is associated with a higher risk of stroke than in cancer patients without AF [20]. On the other hand, other studies have reported patients with AF and cancer to be at lower risk for ischaemic stroke or systemic embolism than patients with AF without cancer (HR: 0.91 [95%CI: 0.89–0.94]) [39].

In patients with AF with CHA_2DS_2-VASc scores of 0 to 2 untreated with anticoagulants newly diagnosed cancer was associated with an increased incidence of stroke, transient ischaemic attack, or systemic ATE compared with matched controls without cancer [40]. The twelve-month cumulative incidence of ATE was 2.13% [95%CI: 1.47–2.99] in 1,411 AF patients with cancer and 0.8% [95%CI: 0.56–1.10] in 4,233 AF patients without cancer, corresponding to a HR of 2.70 [95%CI: 1.65–4.41].

An analysis of the US SEER Medicare database described an increased risk of all-cause death (HR: 2.15 [95%CI: 1.32–3.48]) and cardiovascular death (HR: 3.00 [95%CI: 1.28–7.00]) at one year in women with an AF diagnosis in the 30 days following a diagnosis of breast cancer compared to matched women without breast cancer. The reported causes of cardiovascular death were heart failure (63.3%), systemic embolism (16.7%) and arrhythmias (13.3%) [41]. In this study, the incidence of new-onset AF was 3.3% [95%CI: 3.0–3.5%] at 1 year versus 1.8% [95%CI: 1.6–2.0] in matched non-cancer controls [41].

The impact of cancer on the bleeding risk in patients with AF has been studied in a meta-analysis of 15 studies with 2,868,010 patients of whom 479,571 (16.7%) had cancer. In patients with cancer compared to no cancer, the pooled HR was 1.43 [95%CI: 1.42–1.44] for any bleeding, 1.27 [95%CI: 1.26–1.29] for major bleeding, 1.17 [95%CI: 1.14–1.19] for GI bleeding, and 1.07 [95%CI: 1.04–1.11] for intracranial haemorrhage [39]. In a regression analysis of variables associated with bleeding, the risk of major bleeding was significantly higher in patients with breast cancer or gastrointestinal cancers. Cancer increased the risk of all-cause death 2.00 [95%CI: 1.99–2.02] whereas no association between cancer diagnosis and myocardial infarction or cardiovascular death was observed [39].

Key points

- Active cancer is associated with an increased risk of AF.
- AF in patients with active cancer is associated with a twofold higher risk of systemic thromboembolism or stroke.
- In patients with cancer and AF, the risk of major bleeding and of all-cause death increases with the proportion of breast cancer, whereas no association with myocardial infarction and CV death was found.
- Certain anticancer therapies may increase the risk of AF, and thus indirectly increase the risk of stroke.

4. Drug related arterial events

The therapeutic armamentarium in medical oncology has expanded considerably with the introduction of molecularly targeted agents. Molecular targets of these new therapies include hormone receptors, growth factor receptors and their associated protein tyrosine kinases, proteins involved in immune regulation. Target anticancer therapies comprise monoclonal antibodies, receptor antagonists and small molecule TKIs.

With respect to their impact on coagulation, increased rates of VTE and ATE have been reported for anti-hormonal therapy, tamoxifen, the VEGF-antibody bevacizumab, VEGFR-TKIs, and second generation BCR-ABL-inhibitors (Table 4). In addition, substantial rates of thromboembolic events have been reported more recently with immune checkpoint inhibitors (ICI) and for patients with lung cancer and underlying ALK-/ROS-translocations [42].

During anticancer therapy, AF may occur with a frequency of 15–20%. The variability in incidence may be explained by several factors, including the patient's baseline cardiovascular toxicity risk and the AF detection strategies used [37]. Many anticancer drugs have been associated with AF, in terms of incident and recurrent AF [46]). However, the level of evidence is only high for the association of AF with use of inhibitors of Bruton's tyrosine kinase (principally ibrutinib), which carry a $\approx$ 3–4-fold higher risk of AF [46]. In a VigiBase pharmacovigilance analysis, ibrutinib was reported to be associated with increased reporting for supraventricular arrhythmias (reporting OR: 23.1 [21.6 to 24.7]; $P < 0.0001$) [47]. By increasing the risk of AF, ibrutinib also indirectly increases the risk of stroke. In the above VigiBase pharmacovigilance analysis, ibrutinib was also reported to be associated with increased reporting for stroke (reporting OR: 2.2 [95%CI: 2.0–2.5]) [47].

4.1. Hormonal therapy

Tamoxifen is a non-steroidal selective oestrogen receptor modulator whose efficacy depends on the overexpression of hormonal receptors on breast cancer cells. In a post-hoc analysis of seven randomised controlled trials, a higher risk of both VTE and ATE was observed. The incidence of ATE in premenopausal women receiving tamoxifen plus chemotherapy of 1.6% compared with < 0.1% in women receiving chemotherapy alone ($P = 0.03$). In postmenopausal women, in contrast, no increased risk was observed with tamoxifen: incidence rates for ATE were 1.0% for tamoxifen plus chemotherapy, 1.0% for chemotherapy alone and 1.7% for observation only ($P = 0.63$), respectively [48].

4.2. Anti-angiogenic monoclonal antibodies

Bevacizumab, a humanised monoclonal antibody targeting vascular endothelial growth factor A (VEGF-A) is widely used for the treatment of advanced or metastatic colorectal, renal, lung and gynaecological cancers. Use of bevacizumab is associated with an increased risk of ATE, whereas evidence for a change in the risk of VTE is less clear. In the largest meta-analysis comprising 22 randomised clinical trials (RCT) including 20,050 individual patients with different cancers, the RR of ATE in patients treated with bevacizumab compared to control arms was 1.37 [95%CI: 1.10–1.70] [49]. The absolute risk was quantified in an earlier meta-analysis, with an ATE rate of 5.5 per 100 person-years under bevacizumab, compared to 3.1/100 person-years in the controls [50].

In addition to a prothrombotic effect of anti-angiogenic therapies, a higher bleeding risk has been observed in patients receiving VEGF-targeted agents. In patients treated with bevacizumab, haemorrhagic adverse events were observed more frequently

Table 4
Absolute and relative risk of arterial thromboembolism under targeted anticancer therapies.

Treatment	Study type	Setting	*n*	ATE RR [95%CI]	Absolute ATE risk
Hormonal therapy					
Tamoxifen	Post-hoc analysis of 7 RCT [Saphner 1991]	Premenopausal (tamoxifen + CTX vs. CTX alone) Postmenopausal (tamoxifen + CTX vs. CTX alone vs. observation)	2673	–	1.6% vs. 0.0% (P = 0.03) 1.0% vs. 1.0% vs. 1.7% (P = 0.63)
CDK4/6 inhibitors					
	Multicenter, retrospective cohort study [West 2021]	Metastatic breast cancer (palbociclib, ribociclib, abemaciclib)	266	–	3.8% (n = 10 events)
Anti-angiogenic therapy					
Bevacizumab	Meta-analysis [Scappaticci 2007]	Various cancers, Bevacizumab vs. control arms	5 RCT, n = 1745	HR 2.0 [1.10–3.75] P = 0.031	5.5 vs. 3.1/100 PY
	Meta-analysis [Totzeck 2017]	Various cancers, Bevacizumab vs. control arms	22 RCT, n = 20,050	RR 1.37 [1.10–1.70] P = 0.004	–
Ramucirumab	Meta-analysis [Arnold 2017]	Various cancers, Ramucirumab vs. control arms	6 RCT, n = 4996	RR:0.8 [0.5–1.3]	–
VEGFR-TKI	Meta-analysis [Choueiri 2010]	Sorafenib/Sunitinib vs. control arms	10 RCT, n = 10,255	RR: 3.03 [1.15–7.37]	Sorafenib:1.7% Sunitinib: 1.4%
	Meta-analysis [Qi 2014]	VEGFR-TKI vs. control arms	19 RCT, n = 0,711	OR 2.26 [1.38–3.68]	1.5%
EGFR-targeted	Meta-analysis [Petrelli 2012]	Cetuximab, panitumumab, gefitinib, erlotinib vs. control arms	13 RCT, n = 7611	RR: 1.34 [0.94–1.90]	4.5% vs. 3.4%
Immune checkpoint inhibitors					
	Meta-analysis [43]	Inclusion of heterogeneous study types (cohort, RCT)	68 studies, n = 20,273	RCT(n = 3): RR: 1.86 [0.7–4.9]	1.1%
	Cohort study [Moik 2021]	Different cancer types, real world setting	n = 672	–	1.8% [0.7–3.6]
BCR-ABL-targeted TKIs					
	Meta-analysis [44]	2nd generation BCR-ABL-TKIs vs. imatinib	12 RCT including 4,328 patients	OR: 2.81 [2.11–3.73] For 2nd generation versus imatinib	2.3% with imatinib 6.1% with 2nd generation TKIs

Adapted from Moik et al., 2022 [45]. CI: 95% CI: confidence interval; ATE arterial thrombotic events; BCR-ABL: breakpoint cluster region – abelson murine leukaemia viral oncogene homolog 1; CDK4/6: cycline dependent kinase 4/6; CTX: chemotherapy; HR: hazard ratio; HR + : hormone receptor positive; OR: odds ratio; PY person years; RCT: randomized controlled trial; RR relative risk, TKI tyrosine kinase inhibitors; VEGFR: vascular endothelial growth factor receptor; VTE: venous thromboembolism

compared to the control arms based on a meta-analysis of 22 RCTs (n = 14,277), with a relative risk for high-grade bleeding events of 1.60 [95%CI: 1.19–2.15] and an incidence of 2.8% in the bevacizumab group [51].

In contrast, for ramucirumab, a human monoclonal antibody targeting VEGF-R2 used in the treatment of advanced/metastatic colorectal, gastric, and lung cancer, no association with VTE, ATE or bleeding risk was observed in a meta-analysis of six RCTs [52].

4.3. Receptor tyrosine kinase inhibitors targeting VEGFR1/2

A number of tyrosine kinase inhibitors (TKIs) inhibiting the VEGFR1/2- associated receptor tyrosine kinase (although not always specific for this target), have been introduced for the treatment of a range of cancers, including renal cell carcinoma, hepatocellular carcinoma, or gastrointestinal stroma tumours. In a large meta-analysis of RCT including 10 trials (n = 10 255 patients, mostly renal cell carcinoma) risk of ATE was compared between sorafenib or sunitinib and the respective control arms of the studies. The absolute risk of ATE during sorafenib and sunitinib treatment was 1.7% and 1.4%, respectively. Compared to the control arms, a three-fold increase ATE risk was observed (RR: 3.03 [95%CI: 1.15–7.37]) [53]. In another meta-analysis of RCT, treatment with a broader panel of VEGFR-TKIs (pazopanib, sorafenib, sunitinib and vandetanib) was compared to their respective control arms with respect to ATE risk. Overall, the risk of ATE was more than twofold higher in the aggregated VEFGR-TKI arms (OR: 2.26 [95%CI: 1.38–3.68]), with an absolute ATE risk of 1.5% [54].

4.4. Receptor tyrosine kinase inhibitors targeting EGFR

Receptor tyrosine kinase inhibitors targeting epidermal growth factor receptor tyrosine kinase (EGFR) include cetuximab, panitumumab, gefitinib and erlotinib. In a meta-analysis of studies of TKIs targeting EGFR, the risk of VTE and ATE were aggregated from 13 RCTs (n = 7611). The risk of ATE was not significantly elevated in patients treated with these molecules (RR: 1.34 [95%CI: 0.94–1.90]) [55].

4.5. Receptor tyrosine kinase inhibitors targeting BCR-ABL

Imatinib and other TKIs targeting the BCR-ABL oncogene are used for the treatment of chronic myeloid leukaemia and other Philadelphia + haematological malignancies. In a meta-analysis, higher rates of ATE (OR: 3.32 [95%CI: 2.29–4.81]) and a trend towards increased VTE-risk (OR: 2.17 [95%CI: 0.90–5.25]) was observed in patients treated with this class of TKI [56]. Thromboembolic complications seem to be especially pronounced with

ponatinib, with one phase III trial prematurely terminated due to safety concerns over the high rate of ATE (7%) observed [57].

4.6. Immune checkpoint inhibitors

The introduction of immune checkpoint inhibitors (ICIs), using monoclonal antibodies to specifically target and inhibit (i) tumoral immune evasion pathways (programmed cell death protein 1 [PD-1] or its ligand [PD-L1]) or (ii) physiological immunosuppressive pathways (cytotoxic T-lymphocyte antigen 4 [CTLA-4]), has led to revolutionary advances in survival and treatment responses in several tumour types including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, urothelial cancer [58].

An association between ICI use and increased atherosclerosis-related cardiovascular events (myocardial infarction, coronary revascularization and ischaemic stroke) has been reported (HR: 3.3 [95%CI: 2.0–5.5] $P<0.001$) [59]. The rate of progression of total aortic plaque volume (imaging substudy, $n=40$) was higher with ICIs (from 2.1%/year before ICI treatment to 6.7%/year after initiation of ICIs) and was attenuated with concomitant use of statins or corticosteroids [59]. In a meta-analysis that included 48 RCTs ($n=29,592$, treated for 6.6–32.8 months), ICI use was associated with an increased risk of immune-related cardiovascular adverse events including myocarditis, pericardial diseases, heart failure, dyslipidemia, myocardial infarction, and cerebral arterial ischaemia with higher risks for cerebral arterial ischaemia (OR: 1.56 [95%CI: 1.10–1.20]) and myocardial infarction (OR: 1.51 [95%CI: 1.01–2.26]). In studies with a median follow-up ranging from 3.2 to 32.8 months, the cumulative incidence of cardiovascular adverse events ranged from 3.2‰ for myocarditis [95%CI: 2.0–5.1] to 19.3‰ for dyslpidemia [95%CI: 6.7–54.1] [60].

A meta-analysis of RCTs compared the thromboembolic risk between patients treated wi th ICIs or the relevant control treatment [43]. The relative risk was 1.08 [95%CI: 0.60–1.90] for VTE and 1.86 [95%CI: 0.7–4.9] for ATE. However, the absolute rates of reported thromboembolic events in included studies were very low and this study must therefore be interpreted with caution. In addition, certain methodological limitations to the analysis have been identified [61]. Moreover, 45 out of the 113 eligible studies were excluded from this analysis because they did not explicitly report rates of VTE and ATE as adverse events, and it is possible that this meta-analysis underestimates event rates. Recent retrospective studies focusing on the risk of thromboembolism have reported high rates of VTE (from 4.1% to 16.2%) and ATE (from 1.8 to 4.6%) in patients treated with ICIs [61]. The most recent evidence indicates that rates of VTE in patients receiving ICIs may indeed be higher than originally reported in RCTs [62].

Key points

- Treatment with tamoxifen is associated with a higher risk of both VTE and ATE.
- Treatment with bevacizumab is associated with a higher risk of ATE.
- Treatment with sorafenib and sunitinib is associated with a threefold higher risk of ATE during treatment.
- Treatment with EGFR-targeted agents (cetuximab, panitumumab, gefitinib, erlotinib) are associated with a higher risk of ATE.
- Treatment with ICIs is associated with a threefold higher risk of atherosclerosis-related cardiovascular events (myocardial infarction, coronary revascularisation and ischaemic stroke.
- Treatment with ICIs is associated with an increased risk of immune-related cardiovascular adverse events including myocarditis, pericardial disease and heart failure.
- Treatment with ibrutinib, and possibly other inhibitors of Bruton's tyrosine kinase is associated with an increased risk of AF, and indirectly with an increased risk of stroke.

5. Current guidelines on treatment of cancer-related arterial events

Although treatment of VTE in patients with cancer has received considerable attention in the scientific literature and is largely documented [63,64], little is known about the management of cancer-associated ATE. Currently, there are no specific recommendations for the treatment of cancer-related ATE from evidence-based guidelines. It is possible that the occurrence of ATE in cancer patients may involve other mechanisms than just a mechanism of hypercoagulable state due to the malignancy. For this reason, the relevant treatment options for venous thrombosis in cancer patients can be taken as a basis for treatment decision-making, with the important caveat that they may not be fully and directly applicable to the management of ATE.

5.1. Acute coronary syndrome (ACS)

Consensus statements for the management of ACS in cancer patients have recently been proposed by the European Society for Cardiology (ESC) and the Acute CardioVascular Care Association [65,66].

The choice and duration of anti-platelet drugs should be individualised depending on the type, stage and management of cancer, and the need for chemotherapy and/or cancer surgery after ACS. Thrombocytopenia due to cancer or cancer therapy is encountered in about 10% of cancer-related ACS [67].

In cancer patients with STEMI, parenteral anticoagulation during PCI should be unfractionated heparin, which allows close therapeutic monitoring in order to decrease the risk of bleeding complications.

The choice of invasive over conservative management of patients with ACS and active cancer is not supported by dedicated recommendations and guidelines. Observational data have shown that ACS patients with cancer are less likely to receive guideline-recommended medications for ACS, with optimal medical therapy being prescribed in only one-third of them [68]. A less frequent use of percutaneous coronary intervention with drug-eluting stents in patients with a history of cancer admitted for ACS has been reported [69]. Thrombocytopenia secondary to chemotherapy or to haematological malignancies could explain the decreased use of coronary stents, with a higher risk of stent thrombosis due to the need to limit the duration of dual anti-platelet therapy [70]. Patients with cancer had increased rates of in-hospital all-cause death (RR: 1.74 [95%CI: 1.22–2.47]), cardiac death (RR: 2.44 [95%CI: 1.73–3.44]) and bleeding (RR: 1.64 [95%CI: 1.35–1.98]) as well as one-year all-cause death (RR: 2.62 [95%CI: 1.2–5.73]) and cardiac death (RR: 1.89[95%CI: 1.25–2.86) in ACS studies with or without percutaneous coronary interventions [70]. Another relevant challenge is the increased bleeding risk in cancer patients, which limits the use of antithrombotic therapies after ACS and PCI [71].

5.2. Ischaemic stroke

Reperfusion therapy, intravenous thrombolysis and endovascular thrombectomy are the mainstay of acute management of

patients who have experienced an ischaemic stroke [72]. The use of tPA in cancer patients can be complicated by several factors including thrombocytopenia, impaired coagulation, and the need for additional monitoring.

A systematic review comprising 18 retrospective studies of the safety and efficacy of mechanical thrombectomy in cancer patients concluded that endovascular thrombectomy was safe in cancer patients with acute ischaemic stroke, however, with higher mortality at 90 days and lower 90-day functional independence in cancer patients compared to non-cancer patients [73]. Intravenous thrombolysis was not associated with a significant increase in the incidence of intracerebral hemorrhage (OR: 1.35 [95%CI: 0.85–2.14]), nor with a significant increase in all-cause mortality (OR: 1.26 [95%CI: 0.91–1.75]) in cancer patients compared to patients without cancer. On the other hand, the extent of improvement measured with the modified Rankin Scale following intravenous thrombolysis was similar between cancer and non-active cancer stroke patients (OR: 0.72 [95%CI: 0.35–1.49]). Therefore, intravenous thrombolysis appeared to be safe and effective in patients with ischaemic stroke and concomitant cancer [74].

Regarding antithrombotic drugs, the most recent guidelines for the prevention of stroke recurrence in the general population have been published by the American Heart Association (AHA) and American Stroke Association (ASA) in 2021 [75]. Regarding cancer, the AHA/ASA practice guidelines only focused on ischemic stroke or TIA in the setting of AF and state that it is reasonable to consider anticoagulation with DXIs in preference to warfarin for stroke prevention [75].

The TEACH trial compared the 12-month incidence of bleeding events, stroke and death between patients with malignant tumours treated with aspirin or heparin who had experienced an acute ischaemic stroke cerebral infarction. No significant difference was observed in the cumulative incidence of these events between the two groups of patients [76]. The subgroup analysis of the NAVIGATE ESUS randomised trial comparing rivaroxaban to aspirin [77] found that, although the incidence of recurrent ischaemic stroke was higher in patients with cancer than in those without, incidence did not differ between patients treated with aspirin and those receiving rivaroxaban in either group. The same pattern was observed for all-cause mortality. Aspirin was safer than rivaroxaban with respect to the risk of major bleeding. In light of all of the above, we can conclude that, for the secondary prevention of cancer-related stroke, anticoagulant therapy should be feasible, but its predicted benefit has not yet been explicitly demonstrated. For this reason, treatment decisions in this setting should be taken on a case-by-case basis. In the absence of an embolic source, anti-platelet therapy is preferably indicated as a first line treatment in patients with malignancy and ischaemic stroke [78]. Since cancer-related stroke is closely related to hypercoagulability, anticoagulant regimen should be discussed in case of stroke recurrence [79,80].

5.3. Peripheral artery disease

There are no specific recommendations regarding treatment of PAD in patients with cancer. Guidelines for the management of PAD in the general population have been published by the ESC and the European Society for Vascular Surgery (EVAS) in 2018 [81].

5.4. Atrial fibrillation in cancer patients

The management of AF in patients with active cancer should follow the 2020 ESC guidelines for the diagnosis and management of AF [82] and the more recent ESC guidelines on cardio-oncology [65]. The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) have also published guidelines on anticoagulation of cancer patients with non-valvular AF receiving chemotherapy [83]. Little is known about the predictive performance of AF ischaemic (CHA_2DS_2-VASc) and hemorrhagic (HASBLED) risk scores in patients with active cancer [65]. The use of directly-acting oral anticoagulants for AF has not been evaluated in dedicated RCTs in patients with active cancer. Several post-hoc analyses of subgroups of patients with cancer in the phase III randomised clinical trials (ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48) [84] and a meta-analysis [85] examined the use of direct oral anticoagulants in comparison with warfarin in AF patients with a history of malignancy. Treatment with directly-acting oral Factor Xa or thrombin inhibitors (DXIs/DTIs) was associated with reduced risks of systemic embolism or any stroke (RR: 0.65 [95%CI: 0.52–0.81] $P = 0.001$), ischaemic stroke (RR: 0.84 [95%CI: 0.74–0.95] $P = 0.007$) and haemorrhagic stroke (RR: 0.61 [95%CI: 0.52–0.71] $P = 0.0001$) compared to treatment with vitamin K antagonists (VKAs). Moreover, treatment with DXIs/DTIs was associated with a significantly reduced risks of major bleeding (RR: 0.68 [95%CI: 0.50–0.92] $P = 0.01$) and intracranial or gastrointestinal bleeding (RR: 0.64 [95%CI: 0.47–0.88] $P = 0.006$). Little data are available on the risk of procedural complications during LAA closure in patients with active cancer [86]. At a follow-up of 1.8 ± 1.1 years, ischaemic stroke occurred in 2 (3.6%) patients with bleeding complications in five (9.1%) patients. Device-related complications occurred in six (10.9%) patients, with four (7.3%) with device thrombosis. Patients with a life expectancy > 1 year, with symptomatic AF despite medical therapies and/or with contraindication to antiarrhythmic drugs should be considered for invasive interventional therapies for AF [86].

6. Proposals of the expert group

6.1. Acute coronary syndrome

We recommend to apply the consensus statements for the management of ACS in cancer patients proposed by the European Society for Cardiology (ESC) and the Acute CardioVascular Care Association [65,66], especially:

- the use of aspirin and clopidogrel as the first-choice anti-platelet drugs in cancer patients with a recent cancer diagnosis (< 12 months) or other risk factors for bleeding;
- a shorter DAPT duration in patients at high bleeding risk;
- in patients with cancer, thrombocytopenia, and ACS, clopidogrel is not recommended if the platelet count is < 30,000/μL and prasugrel or ticagrelor are not recommended if the platelet count is < 50,000/μL.

Expert panel ranking: 3.91 out of 4.00.

6.2. Stroke

- In case of AF related ischaemic stroke, we recommend applying the guidelines for the prevention of stroke recurrence in the general population published by the American Heart Association (AHA) and American Stroke Association (ASA), especially the use of anticoagulation with DXIs. Expert panel ranking: 3.88 out of 4.00
- In all patients with non-embolic ischaemic stroke, we suggest anti-platelet therapy with aspirin, as a first line treatment. Expert panel ranking: 3.70 out of 4.00
- In case of recurrent stroke in patients treated by anti-platelet agent, we suggest looking for atrial fibrillation (discuss cardiac implantable monitor) and discussing anticoagulant treatment after careful evaluation of the haemorragic risk.

Expert panel ranking: 3.74 out of 4.00.

6.3. Peripheral arterial disease

The available data do not permit the recommendation of a specific treatment regimen in patients with PAD and cancer. Therefore, in line with the 2018 ESC/ESVC general recommendations for treatment of PAD should be applied. In particular:

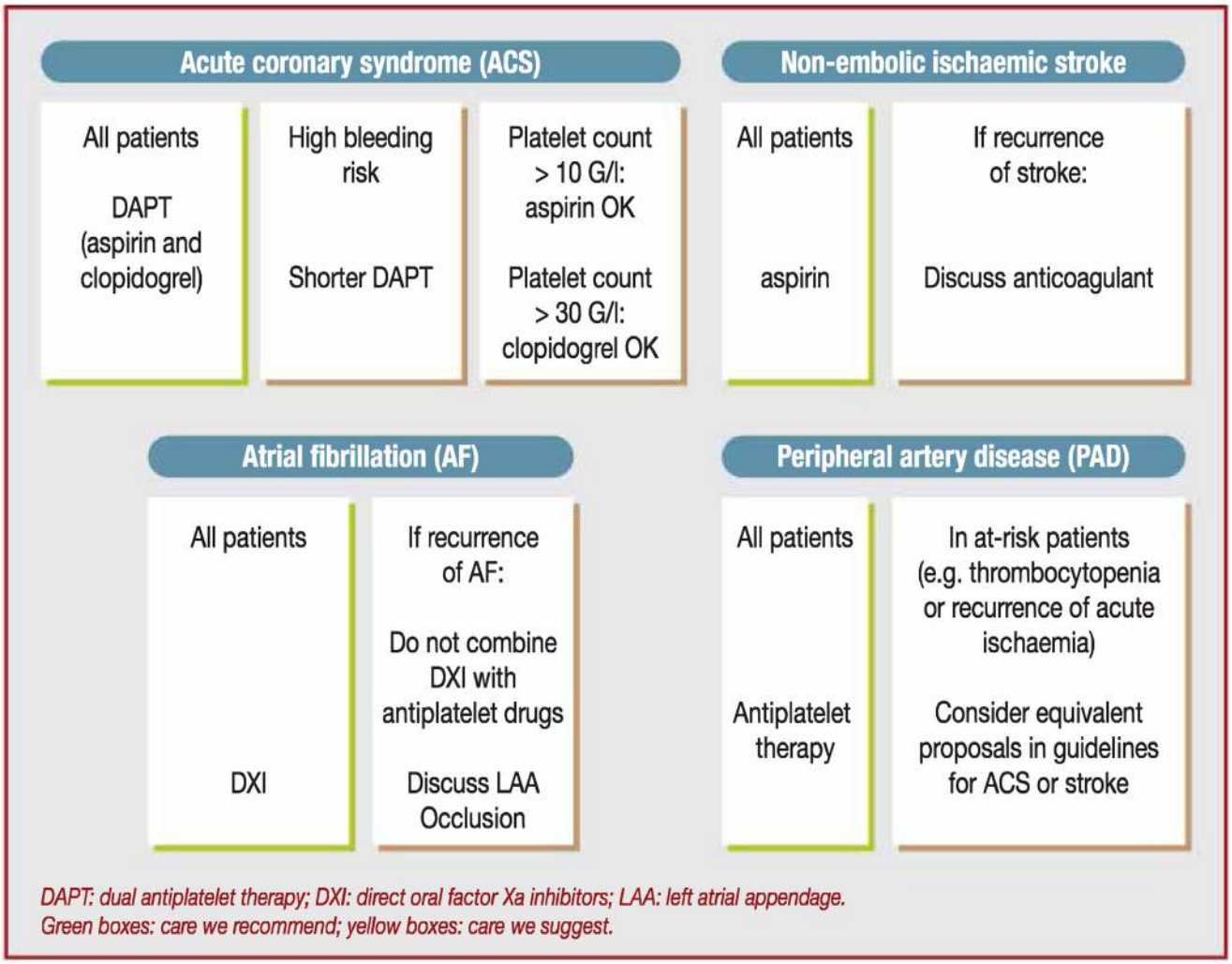
- We recommend single anti-platelet therapy in all patients
- In specific conditions, such as thrombocytopenia or recurrence or acute limb ischaemia, we suggest to discuss proposals regarding acute coronary syndrome or stroke

Expert panel ranking: 3.81 out of 4.00.

6.4. Atrial fibrillation

We recommend applying the 2020 ESC guidelines for the diagnosis and management of AF [82] and the ESC guidelines on cardio-oncology [65], especially:

- we recommend reassessing the thromboembolic and bleeding risk during follow-up in patients with cancer and AF. Expert panel ranking: 3.88 out of 4.00;
- we recommend using the CHA2DS2-VASc score for risk stratification for stroke/systemic thromboembolism, taking into account that it may underestimate the actual thromboembolic risk. Expert panel ranking: 3.88 out of 4.00;
- we recommend using DXIs/DTIs for stroke prevention in preference to LMWH and VKA (excluding in patients with mechanical heart valves or moderate-to-severe mitral stenosis) in patients without a high bleeding risk, significant drug–drug interactions, or severe renal dysfunction. Expert panel ranking: 3.79 out of 4.00;
- we suggest considering treatment with LMWH in patients with active cancer and AF who are not suitable for treatment with DXIs. Expert panel ranking: 3.79 out of 4.00;
- we suggest considering LAA occlusion for stroke prevention in patients with cancer with AF and contraindications for long-term anticoagulation with a life expectancy ≥ 12 months. Expert panel ranking: 3.83 out of 4.00.



Central Illustration.

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Appendix C. Supplementary material

Supplementary material associated with this article can be found in the online version available at https://doi.org/10.1016/j.acvd.2023.11.007.

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