Direct Oral Anticoagulation in Cancer Patients

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Introduction

Thrombosis is the second leading cause of mortality in cancer patients (Prandoni et al. 2005; Noble and Noble 2006). Venous thromboembolism (VTE) , arterial thromboembolism, and disseminated intravascular coagulation are all possible manifestations of cancer-mediated thrombosis (Levi 2014; Eichinger 2016). Atrial fibrillation (AF) and VTE are two common thromboembolic cardiovascular disease (CVD) largely represented in cancer patients. Several studies showed an increased risk of AF after cancer first diagnosis (O'Neal et al. 2015; Hu et al. 2013; Guzzetti et al. 2002) and VTE is estimated to occur in approximately 20% of cases (Blom et al. 2005; Khorana and Francis 2018; Walker et al. 2013) being one of the leading causes of death in cancer patients receiving chemotherapy (Khorana et al. 2007). Anticoagulation is the main prophylactic and treatment regimen in patients suffering thromboembolic events. A number of risk factors (Mandala et al. 2011) and pathogenetic mechanisms (Falanga et al. 2015) are involved in cancer-mediated thrombosis. Anticoagulation exposes cancer patients to an increased risk of bleeding, especially when compared to anticoagulated non-cancer patients (Hull et al. 2006; Hutten et al. 2000; Meyer et al. 2002; Schulman et al. 2013; Prandoni et al. 2002; Palareti et al. 2000). Therefore, the prophylaxis and treatment management of

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thromboembolic events is challenging in this subset of patients. In general population direct acting oral anticoagulants (DOACs) are preferred over Vitamin K antagonists (VKAs) for treatment of VTE and stroke prevention in AF (Hindricks et al. 2020; Konstantinides et al. 2020). Little is still known about use of DOACs in cancer patients with AF with evidences only available from retrospective, observational and subgroup analysis of randomized clinical trial (RCTs) and no available specific guidelines (Russo et al. 2019a; Deng et al. 2019; Yang et al. 2020). More data are available for treatment with DOACs in VTE cancer patients. However, major guidelines still recommend low molecular weight heparin (LMWH) for VTE treatment in this subgroup of patients (Farge et al. 2016; Kearon et al. 2016; Lyman et al. 2015) with the exception of rivaroxaban and edoxaban who were directly compared with LMWH (Khorana et al. 2018). Due to the more favorable pharmacological profile of DOACs over VKAs and LMWH, deepening the knowledge in this field is mandatory. For this reason, we aim to review the available data on the use of DOACs in AF cancer patients for stroke prevention and for treatment of cancer-mediated thrombosis.

Use of DOACs in AF Cancer Patients

Literature data for the use of DOACs in AF cancer patients are generally lacking. The main RCTs of DOACs have included a small number of patients with cancer due to reduced life expectancy or an excessively high risk of bleeding in patients with malignancies (Connolly et al. 2009; Granger et al. 2011; Patel et al. 2011; Giugliano et al. 2013).

Recently several studies have explored the role of DOACs in this subgroup of patients (Russo et al. 2019a; Deng et al. 2019; Yang et al. 2020).

From the observational and metanalytical results obtained, it was possible to conclude that DOACs could be a valid alternative to VKAs for stroke prevention in AF cancer patients (Russo et al. 2019a; Deng et al. 2019; Yang et al. 2020).

From the systematic review including six studies by Russo (Russo et al. 2019a) and colleagues emerged that efficacy and safety profile of DOACs in AF cancer patients are maintained when compared to that of general population. Specifically, some interesting results emerge from this descriptive analysis: (a) the annual incidence of bleedings, ischemic stroke, and thromboembolic events in AF cancer patients on DOAC therapy is generally small compared with VKAs (range for bleedings:1.2–4.4% (Melloni et al. 2017; Laube et al. 2017); range for ischemic stroke and thromboembolic events: 0–4.9% (Ording et al. 2017; Russo et al. 2018)); (b) the risk of thromboembolic and bleeding events in AF cancer patients is similar to that of non-cancer patients, irrespective of the treatment they are prescribed (DOACs vs VKAs) (Ording et al. 2017); (c) in DOACs patients, the risk of stroke, thromboembolic, and bleeding complications is similar between cancer and non-cancer patients (Melloni et al. 2017; Ording et al. 2017); and (d) when gastrointestinal bleedings occur, clinical characteristics are similar between those occurring on dabigatran and those on warfarin (hospitalization rate, mean nights in hospital,

intensive care unit requirement, transfusion requirement, the need for endoscopic, and surgical intervention) (Russo et al. 2019a; Flack et al. 2017). Details of the studies included in Russo et al. analysis are available in Table 10.1.

Deng and Yang's working groups separately conducted a meta-analysis of five studies (Deng et al. 2019; Yang et al. 2020) [three post hoc analyses from three RCTs (Melloni et al. 2017; Fanola et al. 2018; Chen et al. 2019), one retrospective propensity score-matched study (Shah et al. 2018), and one retrospective population-based observational data study (Kim et al. 2018)].

The pooled analysis from the three post hoc analyses of the Apixaban Versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE) trial (Melloni et al. 2017), Rivaroxaban Versus Warfarin in Non-valvular Atrial Fibrillation (ROCKET-AF) trial (Chen et al. 2019), and the Edoxaban Versus Warfarin in

Table 10.1 Principal characteristics and results of the studies included in Russo et al. systematic review

References	Study design	Cancer patients on DOACs *n* (%)	Outcomes HR (95% CI)	
Ording et al. (2017)	Restrospective cohort study	1809 (15.2%)	TE events[a,b] *n/N*	**VKA**
				Cancer vs. cancer free
				628/10,046 vs. 2734/49,057 (6.5% vs. 5.8%) HR, 1.0 (0.93–1.1)
				DOACs
				Cancer vs. cancer free
				65/1809 vs. 290/7207 (4.9% vs. 5.1%) HR, 0.80 (0.61–1.1)
			MB[a,c] *n/N*	**VKA**
				Cancer vs. cancer free
				513/10,046 vs. 2025/49,057 (5.4% vs. 4.2%) HR, 1.1 (1.0–1.2)
				DOACs
				Cancer vs. cancer free
				60/10,046 vs. 166/49,057 (4.4% vs. 3.1%) HR, 1.2 (0.92–1.7)

(continued)

Table 10.1 (continued)

References	Study design	Cancer patients on DOACs *n* (%)	Outcomes HR (95% CI)	
Flack et al. (2017)	RE-LY Post hoc analysis	34 (77.2%)	MGIB[d] related to GI cancers (*N* = 44) *n/N*	**Overall** (*N* = 546)
				Dabigatran vs. warfarin
				34/398 vs. W:10/148 (8.5% vs. 6.8%) *P* = 0.6
				Colorectal cancer *N* = 35/44 (79.5%)
				Dabigatran vs. Warfarin
				30/34 vs. 5/10 (88.2% vs. 50.0%) *P* = 0.02
				Gastric cancer *N* = 6
				Dabigatran vs. warfarin
				1/34 vs. 5/10 (2.9% vs. 50%)
Melloni et al. (2017)	ARISTOTLE Post hoc analysis	615 (49.8%)	S/SE[a] *n/N*	**Cancer**
				Apixaban vs. warfarin
				15/615 vs. 14/621 (1.4% vs. 1.2%) HR, 1.09 (0.53–2.26)
				Cancer free
				Apixaban vs. warfarin
				196/8493 vs. 251/8454 (1.3% vs. 1.6%) HR, 0.77 (0.64–0.93)
			MB[a] *n/N*	**Cancer**
				Apixaban vs. warfarin
				24/615 vs. 32/621 (2.4% vs. 3.2%), HR, 0.76 (0.45–1.29)
				Cancer free
				Apixaban vs. warfarin
				303/8493 vs. 430/8454 (2.1% vs. 3.1%) HR, 0.69 (0.59–0.80)

Table 10.1 (continued)

References	Study design	Cancer patients on DOACs *n* (%)	Outcomes HR (95% CI)	
Laube et al. (2017)	Retrospective cohort study	163 (100%)	Stroke	**1 year cumulative incidence (vs. ROCKET-Trial)**
				1.4% (vs. 1.7%) (0–3.4%)
			MB[d]	**1 year cumulative incidence (vs. ROCKET-Trial)**
				1.2% (vs. 3.6%) (0–2.9)
Russo et al. (2018)	Retrospective cohort study	76 (100%)	TE events[e]	0
			MB[d]	**Cumulative incidence**
				3.9%
				Annual incidence
				1.4%
Iannotto et al. (2017)	Case–control study	25 (3.3%)	TE events[f]	**NOACs vs. LDA**
				Incidence rate *n*, (%)
				1 vs. 2 (4–8%)
			MB[d]	**NOACs vs. LDA**
				Incidence rate *n*, (%)
				3 vs. 3 (12% vs. 12%)

DOACs direct oral anticoagulants, *VKA* vitamin K antagonists, *HR* hazard ratio, *CI* confidential interval, *TE* thromboembolic event, *MB* major bleeding, *MGIB* major gastrointestinal bleeding, *GI* gastrointestinal, *S/SE* stroke/systemic embolism, *LDA* low-dose aspirin

[a]Annual incidence

[b]Recurrence of ischemic stroke, VTE, other arterial embolism, or myocardial infarction

[c] Diagnosis of hemorrhagic stroke or GI, lung, or urinary hemorrhage

[d]According to the International Society of Thrombosis and Hemostasis criteria

[e]Ischemic stroke, transient ischemic attack, or systemic embolism

[f]Any documented thrombosis

Patients with Atrial Fibrillation (ENGAGE-TIMI 48) trial (Fanola et al. 2018) in Deng's metanalysis showed that cancer and non-cancer patients have similar efficacy and safety outcome (all $P > 0.05$) (Deng et al. 2019). Moreover, results from the analysis of all studies included showed that cancer patients on DOACs had significantly lower risk of stroke/systemic embolism (S/SE) ($P = 0.04$) and VTE ($P < 0.0001$) with a trend toward a lower rate of ischemic stroke ($P = 0.05$). No significant differences were found in risk of myocardial infarction ($P = 0.26$), all-cause death ($P = 0.39$), and CV death ($P = 0.13$). About safety outcomes, use of DOACs was associated with a decreased risk of intracranial or gastrointestinal bleeding ($P = 0.04$) and a tendency toward statistical significance for a reduced risk of major bleeding (MB) compared with warfarin (RR = 0.73; 95% CI: 0.53–1.00;

$P = 0.05$). Risks of major or clinically relevant nonmajor bleeding (CRNMB) and any bleeding were similar between treatment groups ($P = 0.96$ and $P = 0.39$, respectively) (Deng et al. 2019).

Yang et al. conducted a network meta-analysis (NMA) on the same five studies (Yang et al. 2020; Laube et al. 2017; Fanola et al. 2018; Chen et al. 2019; Shah et al. 2018; Kim et al. 2018) to evaluate and rank anticoagulant strategies in AF cancer patients. The rank score used was the surface under the cumulative ranking area (SUCRA) probabilities: the larger the value, the higher the probability of the endpoint event. The NMA showed no significant differences between DOACs regarding outcome (primary efficacy outcome: S/SE; secondary efficacy outcome: all-cause death; incidental VTE was described too), with all DOACs achieving a better efficacy profile compared with warfarin. Rivaroxaban followed by apixaban ranked the first and second best in lowering risk of S/SE followed by dabigatran and edoxaban and finally warfarin (SUCRAs: 25.2%, 29.3%, 52.3%, 55.8%, 87.4%, respectively) (Yang et al. 2020). In addition, apixaban and dabigatran were associated with the lower probability and the better ranking for VTE occurrence (Yang et al. 2020). Regarding safety outcomes (MB according to the International Society on Hemostasis and Thrombosis (ISTH) criteria (Schulman et al. 2010)), no statistically significant differences were found between treatment groups with the exception of apixaban which was found safer than warfarin (OR 0.39, 95% CI: 0.18–0.79, SUCRA:4.9%) (Yang et al. 2020) .

Table 10.2 shows principal characteristics and results of the five studies included in the abovementioned metanalyses while Table 10.3 summarizes results of Deng and Yang's studies.

Table 10.2 Results on S/SE and MB of the studies included in Deng and Yeng meta-analysis

References	Study design	Cancer patients/DOACs users with cancer DOAC studied	Outcomes HR, (95%CI)	
Chen et al. (2019)	Rocket-AF Post hoc analysis	640/309 Rivaroxaban	S/SE *n/N*	**History of cancer**
				Rivaroxaban vs. warfarin
				8/307 vs. 16/329 (1.36 vs. 2.71)[a] HR, 0.52 (0.22–1.21)
			MB *n/N*	**History of cancer**
				Rivaroxaban vs. warfarin
				97/309 vs. 96/331 (23.63 vs. 21.59) HR, 1.09 (0.82–1.44)

Table 10.2 (continued)

References	Study design	Cancer patients/DOACs users with cancer DOAC studied	Outcomes HR, (95%CI)	
Shah et al. (2018)	Retrospective cohort study	16,096/6075 Dabigatran (2189) Rivaroxaban (2808) Apixaban (1078)	Ischemic stroke *n*/*N*	**Dabigatran vs. warfarin**
				26/2189 vs. 127/8339 HR, 0.89 (0.56–1.42) *P* = 0.63
				Rivaroxaban vs. warfarin
				16/2808 vs. 59/5673 HR, 0.74 (0.40–1.39) *P* = 0.35
				Apixaban vs. warfarin
				4/1078 vs. 18/2775 HR, 0.71 (0.19–2.60) *P* = 0.6
				Dabigatran vs. rivaroxaban
				9/859 vs. 3/922 7.61 (1.52–38.12) *P* = 0.01
				Apixaban vs. rivaroxaban
				3/1126 vs. 13/2016 HR, 0.52 (0.13–2.17) *P* = 0.37
			SB[b] *n*/*N*	**Dabigatran vs. warfarin**
				70/2189 vs. 329/8339 HR, 0.96 (0.72–1.27) *P* = 0.75
				Rivaroxaban vs. warfarin
				68/2808 vs. 181/5673 HR, 1.09 (0.79–1.50) *P* = 0.59
				Apixaban vs. warfarin
				10/1078 vs. 84/2775 HR, 0.37 (0.17–0.79) *P* = 0.01
				Dabigatran vs. rivaroxaban
				22/859 vs. 22/922 HR, 1.07 (0.50–2.32) *P* = 0.86
				Apixaban vs. rivaroxaban
				10/1126 vs. 43/2016 HR, 0.29 (0.13–0.65) *P* = 0.002

(continued)

Table 10.2 (continued)

References	Study design	Cancer patients/DOACs users with cancer DOAC studied	Outcomes HR, (95%CI)	
Fanola et al. (2018)	ENGAGE AF-TIMI 48 Post hoc analysis	1153/395 Edoxaban	S/SE	**Cancer**
				Edoxaban vs. warfarin
				14/390 vs. 24/395 °(1.43 vs. 2.38) HR, 0.60 (0.31–1.15)
				No Cancer
				Edoxaban vs. warfarin
				282/6645 vs. 313/664 °(1.58 vs 1.77) HR, 0.89 (0.76–1.05)
				P-interaction = 0.25
			MB	**Cancer**
				Edoxaban vs. warfarin
				56/390 vs. 63/395 °(7.92 vs. 8.18) HR, 0.98 (0.68–1.4)
				No cancer
				Edoxaban vs. warfarin
				388/6645 vs. 494/6641 °(2.62 vs. 3.34) HR, 0.98 (0.68–1.4)
				P-interaction = 0.31
Melloni et al. (2017)	ARISTOTLE Post hoc analysis	1236/615 Apixaban	S/SE *n*/*N*	**Cancer**
				Apixaban vs. warfarin
				15/615 vs. 14/621 (1.4% vs. 1.2%) HR, 1.09 (0.53–2.26)
				Cancer free
				Apixaban vs. warfarin
				196/8493 vs. 251/8454 (1.3% vs. 1.6%) HR, 0.77 (0.64–0.93)
			MB *n*/*N*	**Cancer**
				Apixaban vs. warfarin
				24 /615 vs. 32/621 (2.4% vs. 3.2%), HR, 0.76 (0.45–1.29)
				Cancer free
				Apixaban vs. warfarin
				303/8493 vs. 430/8454 (2.1% vs. 3.1%) HR, 0.69, (0.59–0.80)

Table 10.2 (continued)

References	Study design	Cancer patients/DOACs users with cancer DOAC studied	Outcomes HR, (95%CI)	
Kim et al. (2018)	Retrospective cohort study	1651/388[d] Dabigatran (140) Apixaban (138) Rivaroxaban (110)	S/SE *n*/*N*	**NOACs vs. warfarin** 9/388 vs. 40/388 (1.3 vs. 5.5)[a] *P* = <0.001
			MB *n*/*N*	**NOACs vs. warfarin** 8/388 vs. 36/388 (1.2 vs. 5.1)[a] *P* = <0.001

DOAC direct oral anticoagulants, *MB* major bleeding, *S/SE* stroke/systemic embolism, *SB* severe bleeding, *CI* confidential interval
[a]Events per 100-patient years
[b]Subarachnoid hemorrhage, intracerebral hemorrhage, gastrointestinal bleeding requiring transfusion and not trauma related
[c]Annualized event rate (100-patient/year)
[d]Propensity scored matched with 388 warfarin users

Table 10.3 Principal results of the metanalysis exploring safety and efficacy of DOACs versus warfarin in cancer patients with AF

References	Studies included (*n*, reference)	Outcomes [a]RR/OR, (95% CI)	
Deng et al. (2019)		Efficacy outcome	**S/SE**
			RR, 0.52 (0.28–0.98)
			Ischemic stroke
			RR, 0.63 (0.4–1.0)
			VTE
			RR, 0.37 (0.22–0.63)
			MI
			RR, 0.75 (0.45–1.25)
			All-cause death
			RR, 0.81 (0.49–1.32)
			CV death
			RR, 0.71 (0.45–1.1)
		Safety outcome	**MB**
			RR, 0.73 (0.53–1.0)
			MB or CRNMB
			RR, 1.00 (0.86–1.17)
			Intracranial or gastrointestinal bleeding
			RR, 0.65 (0.42–0.98)
			Any bleeding
			RR, 0.93 (0.78–1.10)

(continued)

Table 10.3 (continued)

References	Studies included (*n*, reference)	Outcomes [a]RR/OR, (95% CI)		
Yang et al. (2020)		Efficacy outcome	**S/SE**	**Dabigatran**
				0.6 (0.18–1.80)
				Apixaban
				0.48 (0.17–1.30)
				Rivaroxaban
				0.47 (0.18–1.2)
				Edoxaban
				0.71 (0.11–4.5)
			VTE	**Dabigatran**
				0.24 (0.07–1.00)
				Apixaban
				0.12 (0.05–0.52)
				Rivaroxaban
				0.56 (0.25–2.0)
			All-cause death	**Dabigatran**
				0.43 (0.10–1.8)
				Apixaban
				0.72 (0.24–2.00)
				Rivaroxaban
				0.62 (0.21–1.80)
				Edoxaban
				1.1 (0.24–4.8)
		Safety outcome	**MB**	**Dabigatran**
				0.64 (0.25–1.4)
				Apixaban
				0.39 (0.18–0.79)
				Rivaroxaban
				0.65 (0.30–1.20)
				Edoxaban
				0.78 (0.21–2.9)
		SUCRA[b]	**S/SE**	**Rivaroxaban**
				25.2%
				Apixaban
				29.3%
				Dabigatran
				52.3%
				Edoxaban
				55.8%
				Warfarin
				87.4%
			VTE	**Apixaban**
				0.1%
				Dabigatran
				33.3%
				Rivaroxaban
				66.7%
				Warfarin
				100%
			MB	**Apixaban**
				4.9%
				Rivaroxaban
				47.1%
				Dabigatran
				47.3%
				Edoxaban
				62.4%
				Warfarin
				88.4%

Table 10.3 (continued)

References	Studies included (*n*, reference)	Outcomes [a]RR/OR, (95% CI)

DOAC direct oral anticoagulant, *AF* atrial fibrillation, *S/SE* stroke systemic embolism, *VTE* venous thromboembolism, *MB* major bleeding, *CRNMB* clinically relevant non major bleeding, *CV* cardiovascular, *MI* myocardial infarction, *SUCRA* surface under the cumulative ranking area, *CI* confidential interval

[a]RR in Deng's results, OR in Yeng results

[b]NOACs are listed near the corresponding outcome from the better SUCRA to the worst

VTE in Cancer Patients: Are the DOACs Always the Best Choice?

VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication of cancer, and its prevention and treatment is a challenge because of the drug interactions and varieties of coexisting comorbidities (Khorana 2010). According to a large observational cohort study, the incidence of VTE in active cancer patients is 5.8 per 100 person-years (Cohen et al. 2017). Cancer patients are usually in a state of hypercoagulability that results from various factors, including the type of malignancy, extent of disease, patient age, antitumor treatment, and the presence of coexisting diseases (Zwicker et al. 2007). The highest rate of VTE was observed among patients receiving systemic cancer therapy for tumors of the pancreas, stomach, or lung (Khorana et al. 2007; Blom et al. 2006; Chew et al. 2006; Lyman et al. 2013). VTE is an important cause of death in cancer patients as it is second only to tumor progression (Khorana et al. 2007). VTE can lead to a series of comorbidities, such as longer hospitalization, higher risk of bleeding, and delay or discontinuation of chemotherapy, which may affect patients' quality of life and prognosis (Carrier and Lee 2014). For these reasons, the choice of the best anticoagulation therapy is mandatory for this group of patients.

Primary Prevention of VTE in Cancer Patients

Pharmacological prophylaxis can reduce VTE incidence, but it may also increase the risk of bleeding (Agnelli et al. 2009; Khorana et al. 2017). According to existing research, the most commonly used anticoagulant drugs are LWMH and warfarin. Many large RCTs have demonstrated the efficacy and safety of anticoagulants to reduce the incidence of VTE events in ambulatory cancer patients. The PROTECHT study, involving 1150 patients, has shown that nadroparin reduces the incidence of VTE events without significantly increasing bleeding risks (Agnelli et al. 2009). The SAVE ONCO study involving 3212 patients has shown similar results using the ultra-LMWH semuloparin (Agnelli et al. 2012). However, current guidelines do not recommend the routine thromboprophylaxis in patients receiving chemotherapy (Lyman et al. 2015; https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf) . A systematic review published in the Cochrane Library has indicated some positive results for thromboprophylaxis, but routine thromboprophylaxis is not

indicated in ambulatory cancer patients, and the evaluation of the risks and benefits is necessary before its prescription in high-risk patients (Di Nisio et al. 2016). The risk differs among cancer patients, and the Khorana risk score allows for identification of patients with cancer at increased risk for VTE (Khorana et al. 2008).

In recent years, DOACs have played an increasingly important role in clinical practice (Russo et al. 2015, 2019a, b; Russo et al. 2020a, b, c, d). DOACs have been shown to be safe, effective, and well tolerated for VTE among non-cancer patients (Agnelli et al. 2013; Prins et al. 2013). RCTs comparing DOACs with placebo have been performed for primary prophylaxis in cancer patients with inconstant results for the incidence of VTE events and bleeding complications (Khorana et al. 2019; Carrier et al. 2019). Studies of thromboprophylaxis with LMWH in ambulatory patients with cancer have demonstrated that anticoagulation is associated with a significant relative risk reduction in VTE, but current clinical guidelines do not recommend routine outpatient VTE prophylaxis (except for multiple myeloma and select high-risk solid tumors), because the overall benefit-to-risk profile in an unselected patient population is uncertain (Khorana et al. 2019; Carrier et al. 2019). CASSINI trial (Khorana et al. 2020) is a randomized clinical study that compares the efficacy and safety of rivaroxaban with placebo in the prevention of VTE in high-risk ambulatory patients with cancer receiving systemic cancer therapy, as determined by the validated Khorana risk score. This study confirms the benefit of rivaroxaban in thromboprophylaxis, but only after determining the risk/benefit of anticoagulation in high-risk patients with cancer (Khorana et al. 2020).

Also, apixaban was tested in this setting in the AVERT trial (Carrier et al. 2019). Apixaban therapy resulted in a significantly lower rate of VTE than placebo among intermediate-to-high-risk ambulatory patients with cancer who were starting chemotherapy. The rate of MB episodes was higher with apixaban than with placebo (Carrier et al. 2019).

High-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH provided there are no significant risk factors for bleeding and no drug interactions (Lyman et al. 2015). Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms (Lyman et al. 2015).

At present, no anticoagulant is approved for routinely primary thromboprophylaxis in outpatients with cancer.

Treatment of VTE in Cancer Patients

In the general population, the efficacy and safety of DOACs in the long-term therapy of VTE were demonstrated in six large randomized trials (RECOVER I-II; EINSTEIN-TVP, EINSTEIN-TEP; AMPLIPHY; HOKUSAI TEV). Post hoc analysis and meta-analysis suggested efficacy and safety of DOACs in patients with

cancer, but these patients were underrepresented, not well identified for the type of oncological diagnosis and treatment, and finally the definition of "active cancer" varied greatly from one study to another.

Recent randomized trials have investigated the efficacy of DOACs among cancer patients with VTE (Agnelli et al. 2020; Raskob et al. 2018; Young et al. 2018; McBane et al. 2020). These trials have some limitations: one was a pilot trial (Young et al. 2018), whereas another small trial was prematurely terminated (McBane et al. 2020). Moreover, the two large studies were noninferiority trials and not powered to evaluate the safety of DOACs in this setting (Agnelli et al. 2020; Raskob et al. 2018). The Table 10.4 summarizes the most important characteristics of these studies.

Furthermore, a sub-analysis of the HOKUSAI-VTE cancer study has evaluated the occurrence of the composite outcome, recurrent VTE, or MB in subgroups based on adjudicated cancer diagnoses, including those with gastrointestinal, lung, urogenital, breast, hematological, and gynecological cancer. In the gastrointestinal cancer group, the benefit–risk trade-off requires careful evaluation because edoxaban was associated with an absolute 9.2% increase in MB compared with dalteparin. The absolute risk of recurrent VTE was 3.9% numerically lower with edoxaban. Oral edoxaban is an attractive alternative to subcutaneous dalteparin for the treatment of the majority of patients with cancer-associated VTE, including those with urogenital, lung, breast, hematological, and gynecological cancer (Mulder et al. 2020).

Based on the currently available evidence, the guidelines of European Society of Cardiology and of American Society of Clinical Oncology (Konstantinides et al. 2020; Lyman et al. 2015) recommend that patients with VTE and cancer, particularly those with gastrointestinal cancer, should be encouraged to continue LMWH for 3–6 months. This also applies to patients in whom oral treatment is unfeasible due to problems of intake or absorption, and to those with severe renal disease. In all other cases, the choice between LMWH and edoxaban or rivaroxaban (the publication of the CARAVAGGIO trial on apixaban in this setting is subsequent to the guidelines) is left to the discretion of the physician and the patient's preference. Owing to the high risk for recurrence, patients with cancer should receive indefinite anticoagulation after a first episode of VTE. Renal function and drug–drug interaction should be checked prior to using a DOAC.

Discussion

Compared to warfarin , DOACs have a more predictable anticoagulant effect with a more favorable pharmacological profile, so that they are the first-line anticoagulant treatment proposed in the general population affected by AF and VTE (Hindricks et al. 2020; Konstantinides et al. 2020). Cancer patients are a subgroup of patients with a delicate balance between hemorrhagic and thrombotic risk, so it is essential to choose the right anticoagulation and the time to start it; on the other hand,

Table 10.4 Principal characteristics of the most important RCTs about the treatment of venous thromboembolism (deep venous thrombosis and pulmonary embolism) in cancer patients

	n (DOAC/LMWH groups)	Mean age, years (DOAC/LMWH groups)	Male% (DOAC/LMWH groups)	Type of tumor	Metastasis (DOAC/LMWH groups)	Prior VTE (DOAC/LMWH groups)	DOAC group	Control group	Recurrent VTE (events)			Major bleeding (events)		
									DOAC	LMWH	Risk ratio (95% CI)	DOAC	LMWH	Risk ratio (95% CI)
Young et al. (Meyer et al. 2002) SELECT-D TRIAL	203/203	67/67 (median)	57/48	Colorectal, lung, breast cancer	58/58	NR	Rivaroxaban 15 mg BID for 3 weeks, followed by 20 mg QD for 6 months.	Dalteparin (CLOT protocol) for 6 months.	8/203	18/203	0.44 (0.20–1.00)	11/203	6/203	1.83 (0.69–4.86)
Raskob et al. (Hutten et al. 2000) HOKUSAI-VTE CANCER STUDY	522/524	64.3/63.7	53.1/50.2	Colorectal, lung, breast, gynecologic and hematologic malignancies	52.5/53.4	9.4/12	Edoxaban 60 mg QD (for 6 months) after at least 5 days of concomitant Dalteparin	Dalteparin (CLOT protocol) for 6 months.	41/522	59/524	0.70 (0.48–1.02)	36/522	21/524	1.72 (1.02–2.91)
McBane et al. (Schulman et al. 2013)	150/150	64.4/64.0	72/73	Colorectal, lung, pancreatic and hepatobiliary	65.3/66.0	5.4/8.1	Apixaban 10 mg BID for 7 days followed 5 mg BID for 6 months	Dalteparin (CLOT protocol) for 6 months.	1/145	9/142	0.11 (0.01–0.85)	0/145	2/142	0.20 (0.01–4.04)
Agnelli et al. (Hull et al. 2006) CARAVAGGIO TRIAL	576/579	67.2/67.2	50.7/47.7	Lung, breast, genitourinary	67.5/68.4	7.8/10.5	Apixaban 10 mg BID for 7 days followed 5 mg BID for 6 months	Dalteparin (CLOT protocol) for 6 months.	32/576	46/579	0.70 (0.45–1.08)	22/576	23/579	0.96 (0.54–1.71)

RCT randomized controlled trial, *DOAC* direct oral anticoagulants, *LMWH* low molecular weight heparin, *VTE* venous thromboembolism, *CI* confidence interval, *CLOT* Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant therapy for the prevention of recurrent venous thromboembolism in patients with cancer trial

particular attention is needed for the greater risk of bleeding of the cancer patients during anticoagulant treatment compared to the general population (Hull et al. 2006; Hutten et al. 2000; Meyer et al. 2002; Schulman et al. 2013; Prandoni et al. 2002; Palareti et al. 2000; Hindricks et al. 2020). Especially for AF cancer patients, evidences are rare and sparse. There are no RCTs available that directly compare DOACs to warfarin in this subgroup of patients and results emerge only from retrospective analysis of RCTs (Melloni et al. 2017; Flack et al. 2017; Fanola et al. 2018; Chen et al. 2019) and from very small studies (Russo et al. 2018, 2019a; Deng et al. 2019; Yang et al. 2020; Laube et al. 2017; Shah et al. 2018; Kim et al. 2018; Ianotto et al. 2017). However, in August 2019, the ISTH guidelines recommended the use of DOAC over VKAs and LMWH in cancer patients receiving chemotherapy with newly diagnosed NVAF (Delluc et al. 2019) with the exception of patients with gastrointestinal cancer or the presence of gastrointestinal abnormalities that can lead to gastrointestinal bleeding events. More evidence is currently available on the use of DOACs in VTE cancer patients. Rivaroxaban, edoxaban, and recently apixaban were compared directly with LMWH for the treatment of VTE in cancer patients, demonstrating noninferiority in lowering the rate of VTE recurrence but with some concern for bleeding events (Khorana et al. 2019; Carrier et al. 2019; Raskob et al. 2018). Indeed, a higher risk of CRNMB mainly driven by gastrointestinal bleeding events was evidenced with DOAC in cancer patients and VTE, but such events were almost entirely referable to gastrointestinal cancer patients, which is why guidelines still suggest the use of LMWH in patients with gastrointestinal tumors or gastrointestinal abnormalities that may increase the risk of bleeding events.

Conclusion

DOACs are a revolutionary anticoagulation treatment. Several preliminary evidences suggest their effectiveness and safety in AF cancer patients but RCTs should improve these findings. Currently it is better defined their role in VTE cancer patients even if some concern still remains for their safety profile especially in gastrointestinal malignancies and above all for thromboprophylaxis for which no defined recommendations are available due to the paucity of targeted evidences.

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