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Do Direct Oral Anti-Coagulants Actually Trigger More Bleeding in the Treatment of Deep Venous Thrombosis or Pulmonary Embolism in Patients with Cancer?

Emile Ferrari[1], Nathan Heme[1], Florian Asarisi[1], Victoria Ferrari[2], Fabien Squara[1], Sithikun Bun Sok[1] and Pamela Moceri[1]*

[1]Department of Cardiology, University Hospital of Nice, Université Côte d'Azur UR2CA, France

[2]Department of Oncology, Centre Antoine Lacassagne, Nice, France

Introduction

Direct Oral Anticoagulants (DOACs) are now an alternative to Low-Molecular-Weight Heparins (LMWHs) for the treatment of patients with Venous Thromboembolic Disease (DVT-PE) and active cancer [1-4]. Compared with LMWH, the substantial benefit they provide in terms of thromboembolic recurrence is undermined, to different extents, by a fear concerning an increased risk of bleeding (Table 1) [1-5]. This increased risk, which is not reported for all DOACs, is unusual and was not observed in studies validating this class of anticoagulants in conditions other than cancer. The present article aims to understand the reasons for this discordance [6-8].

Lessons from Non-Cancer Studies

In the non-cancer studies validating the use of DOACs in venous thromboembolic diseases, the benefits provided by this class of drugs were obtained essentially by a reduction in the risk of bleeding. In the EINSTEIN-PE, AMPLIFY and HOKUSAI trials, which were specifically designed to demonstrate the non-inferiority of DOACs on the main criterion, namely the recurrence of thromboembolic events, it was indeed, the benefit of the secondary criterion defined by at least one category of bleeds which established the success of DOACs and positioned them as a first-line treatment [9-12]. Table 2 shows the benefit obtained in at least one type of bleeding in the main studies that validated DOACs for use in venous thromboembolic diseases. Of note, in these trials, the comparator was not a LMWH alone but a LMWH followed by international ratio-adjusted warfarin, which was the standard treatment for DVT-PE, apart from cancer patients, before the advent of DOACs. Also, it is important to bear in mind that, in another validated indication, namely non-valvular atrial fibrillation, in more than 72,000 patients included in randomized clinical trials, DOACs have demonstrated a substantial benefit versus warfarin in terms of bleeding risk (except an excess of digestive bleeding for some of them), which has largely contributed to their use as a first-line treatment [13]. Patients with AF included in the above mentioned studies were at higher risk of bleeding that those included in VTE studies, because older and presenting with more comorbidities, somewhat closer, in this aspect, to patients with VTE and cancer.

LMWH in VTE/Cancer Studies

In the studies validating LMWH for cancer DVT-PE, the comparator, after an initial treatment by LMWH, was warfarin [14-18]. These trials, summarized in Figure 1, showed greater efficacy for LMWH in terms of recurrence [RR 0.60 (0.45, 0.80)] but no benefit in terms of bleeding risk [RR 1.07 (0.65, 1.75)]. In the CLOT trial [14], which validated dalteparin, a tendency was even noted towards an increased hemorrhagic risk [RR 1.57 (0.77, 3.18)].

In other words, in non-cancer VTE disease, DOACs trigger less bleeding than warfarin whereas, in cancer-related VTE, LMWHs, which produce as much bleeding as warfarin, would appear to trigger less bleeding than DOACs.

To date, we have no study comparing DOACs *vs.* LMWHs alone in non-cancer-related DVT-PE which could corroborate or disprove this latest result, but, in our opinion, this result is a paradox and deserves discussion. Several explanations can be forwarded to account for this discordance.

1. In the four trials, HOKUSAI VTE Cancer/SELECT-D/ADAM-VTE/CARAVAGGIO, the LMWH was dalteparin [1-4]. This LMWH is characterized by a particular dosage administration since the dose is larger during the 1st month (200 units/kg) than during the remainder of treatment

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Correspondence:
Emile Ferrari, Department of Cardiology, University Hospital of Nice, Université Côte d'Azur UR2CA, 30, Avenue de la Voie Romaine - CS 51069 - 06001 Nice Cedex 1, France, Tel: +33 4 92 03 77 34; Fax: +33 4 92 03 78 79; E-mail: ferrari.e@chu-nice.fr

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Table 1: Bleeding rates in DOACs *vs.* Dalteparin studies in cancer patients.

Type of bleeding	Bleeding rates DOAC *vs* dalteparin	HR (95% CI)
HOKUSAI		
Major bleeding	6.9% *vs.* 4%	HR 1.77 (1.03 to 3.04)
Clinically relevant non major bleeding	14.6% *vs.* 11.1%	HR 1.38 (0.98 to 1.94)
SELECT-D		
Major bleeding	6% *vs.* 4%	HR 1.83 (0.68 to 4.96)
Clinically relevant non major bleeding	13% *vs.* 4%	HR 3.76 (1.63 to 8.69)
CARAVAGGIO		
Major bleeding	3.8% *vs.* 4%	HR 0.82 (0.40 to 1.69)
Clinically relevant non major bleeding	9% *vs.* 6%	HR 1.42 (0.88 to 2.30)

In the HOKUSAI-Cancer study. There is a higher rate of major bleeding and a tendency for a higher rate of CRNM bleedings versus dalteparin. In the SELECT-D study, CRNMBs were higher with DOAC and there is a trend for a higher rate of major bleeding. These 2 results have raised a lot of fears about the hemorrhagic risk. We note that in the CARAVAGGIO study there is no significant hemorrhagic risk with the DOAC *vs.* Dalteparine.

Table 2: Benefit of DOACs *vs.* Warfarin in at least one type of bleeding in their main studies in non-cancer patients.

Type of bleeding	HR (95% CI)	p
EINSTEIN PE		
Major bleeding	HR 0.49 (0.31-0.79)	P=0.003
AMPLIFY		
Major bleeding	HR 0.31 (0.17-0.55)	P<0.001
Clinically relevant non major bleeding	HR 0.48 (0.38-0.60)	
Major or clinically relevant non major bleeding	HR 0.44 (0.36-0.55)	P<0.001
HOKUSAI		
Clinically relevant non major bleeding	HR 0.80 (0.68-0.93)	P=0.004
Major or clinically relevant non major bleeding	HR 0.81 (0.71-0.94)	P=0.004
Any bleeding event	HR 0.82 (0.75-0.90)	

All non-cancer patient DOAC studies highlighted a benefit regarding bleeding events as compared to LMWH and warfarin

Table 3: Comparison of major bleedings with LMWH *vs.* Warfarin in DVT-PE cancer patients.

Study	LMWH *vs.* VKA	Events		HR (95% CI)	p
		LMWH	VKA		
CANTHANOX	Enoxaparin *vs.* Warfarin	26054	27729	HR 0.44 (0.16 to 1.19)	NS
CLOT	Dalteparin *vs.* Warfarin	19/338	12/335	HR 1.57 (0.77 to 3.18)	NS
MAIN-LITE	Tinzaparin *vs.* Warfarin	7/100	7/100	HR 1.00 (0.36 to 2.75)	NS
ONCENOX	Enoxaparin *vs.* Warfarin	6/67	1/34	HR 3.04 (0.38 to 24.28)	NS
CATCH	Tinzaparin *vs.* Warfarin	12/449	11/451	HR 0.89 (0.40 to 1.99)	NS

In all these studies, LMWH did not bring less bleedings than warfarin

(150 units/kg). Patients in the dalteparin arm in the 4 trials thus «benefitted» from significantly lower doses of LMWH after 30 days, a reduction which undoubtedly impacted the results. In the SELECT trial, this dose reduction was indeed concomitant with a significant drop in the bleeding events after 30 days, as clearly shown by the Kaplan Mayer analysis (Figure 1). On the contrary this decrease in LMWH dosage probably affected the incidence of thromboembolic recurrence. In the CARAVAGGIO trial, this dose reduction at 30-days was immediately followed by a higher recurrence rate in patients treated with dalteparin as also shown in the Kaplan Meyer analysis (Figure 2). In the Hokusai VTE Cancer trial [4], the recurrence rate diverges to the disadvantage of dalteparin a little later than the 30th day, but the discrepancy is clear. Of note: the other protocols using a LMWH (Enoxaparin or tinzaparin), often used "by derogation" do not provide for a drop in dose after 1 month. It is therefore unfounded to think that all LMWHs would bring the same result as dalteparin.

2. In the 4 DOAC/Cancer trials, patients presented active cancer and consequently were treated with anticancer drugs or supportive therapies. Pharmacological interactions between DOACs and anticancer drugs, hormone therapy and supportive therapy are an underestimated issue. Many drugs used in the main cancers treated in these studies have displayed potential interactions with P-glycoprotein and/or cytochrome P450 and, thus may interfere with DOACs [19,20].

3. The recent study by Demiranda [21], reports a similar 15% interaction rate between the 3 DOACs and anticancer or supportive care agents. It is known that cancer patients receive many medications besides antineoplastic agents and that the risk of drug-drug interaction increases dramatically with the number of co-medications from 14% with 4 drugs to 67% with 11 drugs [22]. Increasing the number of co-medications results in a hugely higher risk of major bleedings but also of thromboembolic events [23]. These drug-drug interactions, all of which are far from having been identified, must have impacted both the bleeding and the thrombotic risks. Most recommendations

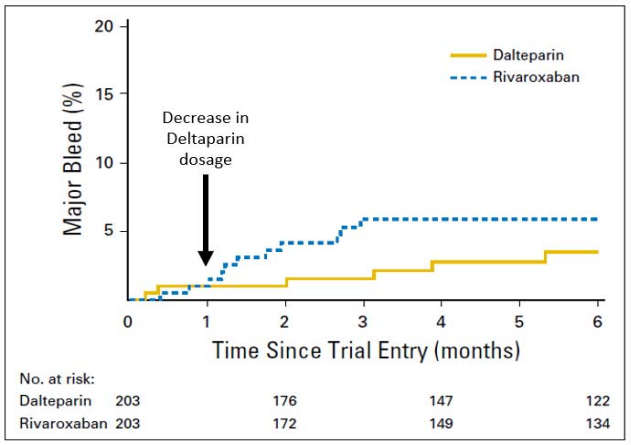

Figure 1: Major bleeding increase in SELECT-D study (Rivaroxaban *vs.* dalteparin).
After 1 month. As soon as dalteparin dosage is decreased KM analysis shows a clear difference in major bleeds.

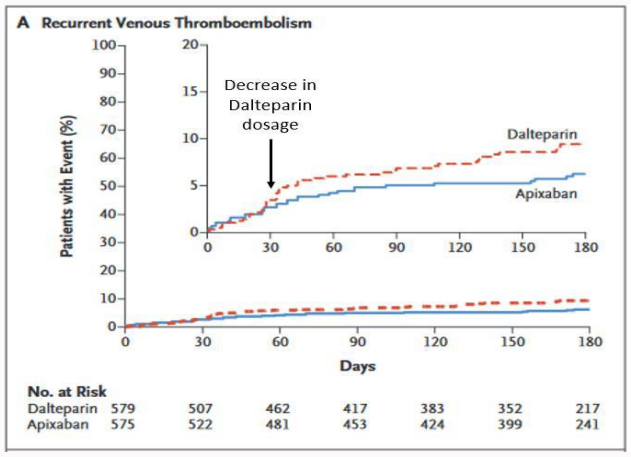

Figure 2: VTE Recurrence after 1 month in dalteparin arm in HOKUSAI cancer study.
After 1 month. As soon as dalteparin dosage is decreased KM analysis shows a clear difference in major bleeds.

that consider DOACs for this indication advocate taking these drug-drug interactions into consideration [24-26], something that was not done in the studies. Indeed, some studies have attempted to take into account the co-administration of treatments which might interact, however the dosage adjustment of the DOAC was not made or was made empirically and certainly was not adapted to precise pharmacological data. In any case, such adaptation to pharmacological data would be very difficult in this context of staggered co-medication as in chemotherapy.

4. In contrast, LMWH pharmacokinetics is not influenced by either P-glycoprotein or cytochrome P450. Therefore there is no fear of drug-drug interactions between LMWH and anticancer drugs. Furthermore, in patients with vomiting induced by anti-cancer treatments, oral administration of DOACs can be problematic. Finally particularly in digestive cancers, surgery may affect DOAC absorption and this may also modify DOAC pharmacokinetics [27]. All of these reasons gave dalteparin an advantage over DOACs.

5. The protocol for the management of anticoagulation in cases of thrombocytopenia occurring during treatment (essentially resulting from chemotherapy) was different between dalteparin and DOACs. For instance, In SELECT and HOKUSAI studies, with dalteparin, a 25% dose reduction was recommended when platelet counts fell below 100 G/l whereas for DOACs the dose remained unchanged despite the same drop in platelet levels (1,2). This signifies that, at the same level of thrombocytopenia, patients in the LMWH arm received a less bleeding anticoagulant treatment than those treated by DOACs. It is clear therefore that this situation could have affected bleeding events in the DOAC group. The exact rate of occurrence of this thrombocytopenia between 50 and 100 G/L induced by chemotherapy is not known. But, given that those below 50 G/L have occurred in about 2.5% of patients, it is certainly far from being negligible.

6. In the four above-mentioned trials, the reduction of the absolute risk in terms of thromboembolic events was spectacular… may be too much. In the SELECT trial (2), the absolute reduction in thromboembolic recurrence rate was 7% (11% with dalteparin *vs.* 4% with rivaroxaban: HR 0.43, CI 0.19 to 0.99). In the HOKUSAI VTE Cancer trial (4), it was 3.4% (11.3% with dalteparin *vs.* 7.9% with edoxaban: HR 0.71, CI 0.48 to 1.06) In ADAM-VTE it was 5.6% (6.3% with dalteparin versus 0.7% with apixaban: HR 0.09, 95% CI 0.01 to 0.78) (3). In the CARAVAGGIO trial, the absolute reduction of the recurrence rate was 2.3% (7.9% with dalteparin *vs.* 5.6% with apixaban: HR 0.63, CI 0.37 to 1.07) [1]. This improvement, although not strictly statistically significant in all studies, is far from the results in non-cancer trials. In SELECT and HOKUSAI, this "super-efficacy" came at a price, namely a 2.4% increase in the absolute risk bleeding (3% *vs.* 5.4% and 3.2% *vs.* 5.6%, respectively, in SELECT and HOKUSAI). Of note, in CARAVAGGIO study, apixaban after the first week came off best with a lower absolute benefit than rivaroxaban in terms of recurrence in the SELECT trial but with no serious bleeding over-risk. If the findings of the SELECT and HOKUSAI studies would have been the conclusion of a phase II dose research study, and given that bleeding risk constitutes an integral feature in the results, the tendency would certainly have been to choose a lower dose for the subsequent phase III study.

7. In the same perspective, the need for a loading dose as validated in studies outside of cancer should be confirmed in this high bleeding risk population.

Finally, the dosage twice a day in this population at high risk of thrombosis and bleeding could, more than usual, be a pharmacological advantage by reducing peak plasma levels and therefore the risk of bleeding.

In thousands of patients included in the non-cancer VTE trials, DOACs gave rise to considerably less bleeding than warfarin initiated with a short period of heparin therapy. In cancer-related VTEs, LMWHs, which trigger at least as much, bleeding as warfarin, would paradoxically appear to produce less bleeding than DOACs. This incoherent finding should lead us to review the conditions in which DOACs have been assessed in cancer-related DTV-PE. Indeed, the evaluation procedure is very different from that used for non-cancer-related DVT-PE. All the aforementioned elements lead us to believe that in the published studies it was not 2 anticoagulant molecules that were compared but 2 anticoagulant treatment strategies. Also, it is possible that adapting the doses and protocols of the DOACs to this particular condition could give better results for the bleeding risk.

Indeed, in this high-risk population, it is surely necessary

to rethink the simple administration scheme which has been so successful with DOACs and attempt to identify ways and means of optimizing their results. For instance: The following modifications of the administration scheme could be considered.

- A reduction of the dose after 1 month as with dalteparin (especially for Rivaroxaban and Edoxaban),
- DOACs to be initiated only after the end of the anticancer drugs administration especially when drug-drug interactions are to be expected.
- Different protocol designs for bleeding risk situations, e.g. by switching to LMWH during procedures entailing hemorrhagic risk.
- Management of DOACs dosages according to DOACs blood concentrations in high-risk situations involving drug-drug interactions.
- Adjustment of DOAC dosages to the thrombogenicity of the cancer (as advocated preventively in the same cancer context by the Khorana score)
- Adjustment of DOAC dosages to the thrombogenicity of anticancer treatment
- Promote the dosage regimens in 2 doses per day in view of the results of Apixaban

Conclusion

Treating DVT-PE in the presence of cancer is a major challenge, with a higher risk of both recurrence and bleeding than in treatment of non-cancer related DVT-PE.

The higher bleeding rate observed for DOACs as compared with other anticoagulants regimen was not observed in the large-scale randomized trials validating DOACs in non-cancer population. This possibly indicates that DOACs were not used optimally and should incite us to devise means of enhancing the benefit/risk ratio in this specific population.

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