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RESEARCH LETTER

Bleeding risk of intramuscular injection of COVID-19 vaccines in adult patients with therapeutic anticoagulation

Dear Editor,

Efficacy and safety of vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was demonstrated,[1,2] however an additional booster dose is recommended in most countries. Intramuscular (IM) injections for patients with therapeutic anticoagulation[3] is a major concerns because of risk of bleeding and muscle hematomas.[4] Regarding anticoagulants, the warning about IM administration is present in the monograph for vitamin K antagonist (VKA), but not for direct oral anticoagulants (DOACs). Evidence supporting IM injection in patients with anticoagulant exists but generally focused on IM influenza vaccination in patients treated with VKA therapy.[3] However, in line with the growing number of patients treated with DOACs, generalizing the conclusions of literature review[3] to patients treated with DOACs receiving IM vaccine was hazardous. Several national guidelines described the practical aspects of IM vaccination in patients treated with anticoagulants.[5-7] Concerning the bleeding risk associated with IM vaccination, Public Health England addressed the specific case of administering COVID-19 vaccine to individuals receiving anticoagulants.[7] These guidelines stated that individuals on stable anticoagulation therapy, including individuals on VKA who are up-to-date with their scheduled INR testing and whose latest INR was below the upper threshold of their therapeutic range, could receive IM vaccination. If there is any doubt, a consultation with the clinician responsible for prescribing or monitoring the individual's anticoagulant therapy is recommended. Overall, for IM route, the injection should be performed in the deltoid muscle,[5] with a fine needle (23-gauge at least)[4,6] and performed by medically trained personnel. A firm pressure, without rubbing, at the injection site should be maintained 2 to 5 min after.[5]

The aim of our study was to evaluate the risk of bleeding events at the site of injection following IM vaccination in patients treated with therapeutic anticoagulation.

We first performed a French multicenter prospective study including adult patients treated with anticoagulant therapy for venous thromboembolism (VTE) between May 2021 and September 2021 in the Georges Pompidou European Hospital (Paris, France) and Brest university hospital center (Brest, France). Consecutive patients were asked to report bleeding events at the site of COVID-19 vaccine injection during a planned follow-up for VTE. All bleeding events were classified according to International Society on Thrombosis and Haemostasis (ISTH) classification.[8,9] The physician collected data from patients using a standardized questionnaire during patient consultation. No exclusion criteria were applied. The study was performed in accordance with the Declaration of Helsinki. The institutional review board of each center approved the study, and anonymous data collection was declared to the appropriate authorities (AnticoVax 20210917152943, CERAPHP.5, IRB registration: #00011928). The patients' non-opposition to the use of their data for research was collected in accordance with the European regulation (General Data Protection Regulation, GDPR). Continuous data were expressed as median with interquartile range [IQR] (25^{th}–75^{th} percentiles). Categorical data were expressed in numbers (*n*) and percentages.

Between May 2021 and September 2021, a total of 348 consecutive patients with anticoagulant therapy received 561 IM injections of COVID-19 vaccines. Characteristics of patients are reported in Table 1. Briefly, median age of patients was 68.4 years (IQR 59.0–76.1) and 65.2% were males. Patients were treated for a first episode of non-provoked VTE (49.1%) or recurrent VTE (35.6%) and for long-term therapeutic anticoagulation in most cases (95.0%). Almost all patients were treated with DOACs (96.6%), 11 (3.2%) patients with VKA and only one (0.2%) with tinzaparin. During the study period, 234 (74.0%) patients had IM vaccination with BNT162b2 (BioNTech/Pfizer), 63 (19.9%) with ChAdOx1 nCov-19 (Oxford–AstraZeneca), 15 (4.7%) with mRNA 1273 (Moderna) and four (1.2%) with Ad26.OV2.S (Johnson & Johnson/Janssen). Overall, patients received 561 IM injections of COVID-19 vaccines of them; among them, 251 (72.1%) had one injection, 91 (26.1%) had two injections and six (1.7%) had three injections. For the majority of patients (86.7%), vaccination took place in vaccination centers (Table 2) and 17.9% of patients had pressure at the injection site during >2 min after the injection and 4.2% skipped an anticoagulant dose before vaccination. After IM injections, a total of three (0.6%) bleeding events were observed, two (0.4%) minor and one (0.2%) clinically relevant non-major bleeding. These three patients were treated with rivaroxaban at the time of IM injection without any further risk factor of bleeding (i.e., age >75 years, presence of renal failure, liver failure, antiplatelet therapy, bleeding history, uncontrolled hypertension).

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TABLE 1 Clinical characteristics of the vaccinated patients with anticoagulant therapy

	Patients ($n = 348$)	Available data
Age, years - median (IQR)	68.4 (59.0–76.1)	348
Male - *n* (%)	227 (65.2)	348
BMI – kg/m², median (IQR)	27.4 (25.0–31.0)	328
Plasma creatinine, µmol/L - median (IQR)	79.0 (68.0–93.0)	143
History of thrombosis - *n* (%)		
First episode of non-provoked VTE	170 (49.1)	346
First episode of provoked VTE	53 (15.3)	
Recurrent VTE	123 (35.6)	
Duration of anticoagulation		
Long term anticoagulation	324 (95.0)	341
3–6 months of anticoagulation	17 (5.0)	
Anticoagulant therapy - *n* (%)		
VKA	11 (3.2)	346
Apixaban 10.0 mg BID	4 (1.4)	
Apixaban 5.0 mg BID	87 (25.0)	
Apixaban 2.5 mg BID	54 (15.6)	
Rivaroxaban 20 mg OD	114 (32.9)	
Rivaroxaban 10 mg OD	75 (21.7)	
Tinzaparin 175 UI/kg per day	1 (0.2)	
Antiplatelet therapy - *n* (%)	5 (1.5)	339
Comorbidities - *n* (%)		
Hypertension	126 (36.3)	347
Atrial fibrillation	13 (3.7)	347
Stroke	5 (1.4)	347
Coronary syndrome or heart failure	11 (3.2)	347
Kidney failure	13 (3.7)	347
Liver dysfunction	1 (0.3)	347
Non-metastatic cancer	44 (12.7)	347
Metastatic cancer	12 (3.5)	347
Chronic inflammatory disease	14 (4.0)	347
History of major bleeding	6 (1.7)	347
History of clinically relevant non-major bleeding	8 (2.3)	347
Anemia	14 (4.0)	347
Thrombocytopenia	2 (0.6)	347
COVID−19 vaccine type - *n* (%)		
BNT162b2	234 (74.0)	316
ChAdOx1 nCoV−19	63 (19.9)	
mRNA 1273	15 (4.7)	
Ad26.OV2.S	4 (1.2)	
Vaccine doses administered - *n* (%)		
1	251 (72.1)	348
2	91 (26.1)	
3	6 (1.7)	

Abbreviations: BID, twice daily; BMI, body mass index; IQR, interquartile range; OD, once daily; VKA, vitamin K antagonist; VTE, venous thromboembolism.

TABLE 2 Precautions used at the time of intramuscular vaccination and bleeding events after in patients with anticoagulant therapy

Vaccination - *n* (%)	Dose of vaccination ($n = 561$)	Available data
Vaccination center	327 (86.7)	377
General practitioner	33 (8.8)	
Pharmacist	17 (4.5)	
Pressure at the injection site during >2 min	82 (17.9)	457
Anticoagulant dose skipping	22 (4.2)	528
Bleeding events - *n* (%)	3 (0.6)	561
Minor bleeding	2 (0.4)[a]	
Clinically relevant non major bleeding	1 (0.2)[b]	
Major bleeding	0 (0.0)	

[a]Two patients had minor bleeding events after IM vaccination. Patient #1 was a 53-years-old man treated with rivaroxaban 20 mg OD for long-term therapeutic anticoagulation. After IM injection with ChAdOx1 nCoV-19 vaccine, he developed a 3-cm superficial subcutaneous hematoma at the site of injection. Patient #2 was a 43-years-old man treated with rivaroxaban 10 mg OD for long-term therapeutic anticoagulation. After IM injection with BNT162b2 vaccine, he developed a 2-cm superficial subcutaneous hematoma at the site of injection. Both patients had no DOAC-skipping dose and no pressure at the injection site during >2 min.

[b]One patient had clinically relevant non major bleeding events after IM vaccination. Patient #3 was a 63-year-old woman treated with rivaroxaban 10 mg OD for long-term therapeutic anticoagulation. After IM injection with BNT162b2 vaccine, she developed a large superficial subcutaneous hematoma that spread all the way up her arm, leading her to consult her treating physician. She had no DOAC-skipping dose and no pressure at the injection site during >2 min.

We next performed a request in the French national pharmacovigilance database (authorization protocol number: CNIL-1922081) to identify cases of bleeding events at the site of injections following COVID-19 vaccine in patients under therapeutic anticoagulation. In France, 69 089 410 doses of COVID-19 vaccine were administered between December 27 2020 and June 30 2021. A total of 13 bleeding events at the injection site in patients with therapeutic anticoagulation were reported. All of these events were classified as minor bleeding according to ISTH criteria. Hence, these bleeding events correspond to a spontaneous notification rate of 0.19 cases (95% confidence interval, CI, 0.09–0.29) reported per million of doses administered in France.

Based on our prospective cohort and on the pharmacovigilance database, our results suggest a very low risk of bleeding event at the site of vaccine injection. Thus, to our knowledge, this is the first study assessing IM vaccination in patients treated with therapeutic anticoagulation with a large proportion of DOACs. At the beginning of the COVID-19 vaccination campaign, two strategies could be considered for patients treated with DOACs: either not to discontinue or to consider discontinuing DOAC on the day of the injection.[10] The skipping strategy may apply to DOACs because of their favorable pharmacokinetics properties with shorter half-life and shorter C_{max}

compared to VKA.[11] For example, the French Working Group on Perioperative Hemostasis (GIHP) proposed not to administer DOAC the evening before and the morning of procedures at low bleeding risk.[12] This could be applied to patients at low thrombosis risk, especially those at high bleeding risk. In the prospective Dresden NOAC registry,[11] authors analyzed peri-interventional safety data from 2179 DOAC-treated patients and classified IM injections as minor procedures. Twenty-nine bleeding events were observed after 641 minor procedures (4.5%, 95% CI 3.1–6.4). No major bleeding was reported after IM injection. Authors concluded that for non-major invasive procedures, rate of complication was low and fatal complications seem to be very rare. However, the proportion of patients who underwent IM injection without holding DOACs was not reported. Only 4.2% of patients included in the present study had skipping dose strategy suggesting that IM vaccination in DOAC patient without skipping dose is safe. The value of firm compression >2 min is necessarily questioned by the small proportion of patients in whom it was performed (17.9%) but given its safety, it cannot be ruled out that it may have prevented some minor bleeding. In the present study, we showed 7 months later only 0.19 cases per million of doses of COVID-19 vaccines administered, confirming again the safety of IM injection of vaccine under therapeutic anticoagulation. One limitation of our study is that the size of the needle for COVID-19 vaccine was not reported.

Overall, in patients receiving therapeutic anticoagulation, IM vaccination against COVID-19 appears to be safe, in particular in patients treated with DOACs, and may not require a skipping dose strategy. While a reminder of general precautions is useful at a time of mass vaccination campaigns, our data support the statement that therapeutic anticoagulation is not a contraindication for being vaccinated against COVID-19.

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CONFLICT OF INTEREST

All authors have nothing to disclose with the present study.

AUTHOR CONTRIBUTION

NG, LK, CLB, BE, AG, SC, BB, TM, OS, CT, BP and FC included the patients. NG, LK, CLB, BE, CA, WA, TM, OS, CT, BP and FC generated the data NG and LK performed biostatistics analyses NG, LK and BP wrote the manuscript NG, LK, OS, BP and FC supervised the study All authors reviewed the manuscript.

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