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Scientific editorial

Management of cancer-associated venous thromboembolism from diagnosis to treatment: State of the art and remaining unmet needs

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Venous thromboembolism (VTE) is a common complication encountered by patients with cancer. Although the risk of VTE is modest (1 to 2 per 1000) in the general population, patients with cancer are at a particularly high risk of developing VTE [1]. The 6-month risk of VTE in patients with cancer is 12-fold higher, and up to 23-fold higher for those receiving chemotherapy, when compared to patients without cancer [2]. Furthermore, the cumulative incidence of VTE has been increasing over the last two decades in this patient population. Hence, patients and health care providers need to be aware of the underlying risk of cancer-associated venous thromboembolism (CAT). A recent international patient-centered survey has reported that a majority of respondents were not aware of their risk of CAT and up to 70% never received education about the signs and symptoms of CAT [3]. Similarly, a survey of community cancer centers has reported that a large majority of patients with cancer never had documentation of their underlying risk of VTE [4]. This lack of awareness of CAT is problematic as it can lead to delays in seeking medical attention when signs and symptoms of CAT are developing.

Avoiding delays in diagnosis and prompt initiation of anticoagulant therapy in those with confirmed events are important to minimise morbidity and mortality associated with VTE in this patient population [5,6]. Patients with CAT need initiation of anticoagulant therapy which is associated with a higher risk of recurrent events and bleeding complications in patients with cancer [7]. Hence, venous and arterial thromboses have been reported to be the second leading cause of death in patients with cancer [5]. Furthermore, a new diagnosis of CAT is also associated with an increase in resource utilisation and all-cause health care costs [6]. In order to avoid the morbidity and mortality associated with CAT, it is important to adopt an integrated cancer care approach with collaboration from a multidisciplinary team in order to tailor anticoagulant therapy based on the type of VTE (e.g., catheter-related thrombosis, severity of pulmonary embolism, recurrent or index VTE, etc.), patient characteristics (e.g., frail and elderly, impaired renal or liver function, thrombocytopenia, etc.), type of cancer (e.g., brain tumors, etc.), and anticancer treatment in combination with patient's preferences (e.g., palliative care, etc.).

Over the last few years, significant progresses have been made to enhance the diagnosis and treatment of CAT. Many prospective cohort studies, randomised controlled trials, and clinical practice guidelines have been published to assess and summarise the different management strategies in patients with cancer and VTE [8,9]. In this issue of the *Archives of Cardiovascular Diseases*, members of the Investigation Network On Venous ThromboEmbolism (INNOVTE), under the aegis of the French Clinical Research Infrastructure Network (F-CRIN) are providing a summary of the current literature and practical clinical guidance on the diagnosis and management of nine CAT-related topics that are clinically important and particularly challenging for clinicians. Although the available data from studies and randomised controlled trials provide an excellent

Abbreviations: CAT, cancer-associated thromboembolism; DXI, direct factor Xa inhibitor; F-CRIN, French Clinical Research Infrastructure Network; FXI, factor Xa inhibitor; INNOVTE, Investigation Network On Venous ThromboEmbolism; LMWH, low-molecular weight heparin; VTE, venous thromboembolism.

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scaffold for health care providers to establish their treatment plans, many challenges frequently occurring in clinical practice are difficult to address due to the paucity of data. Hence, the authors of the different manuscripts are providing pragmatic clinical guidance based on shared decision making and individualised management plans tailored on patients' needs and expectations, to maximise adherence and patients' engagement in their own care.

Despite the important breakthroughs on the use of parenteral low molecular weight heparin (LMWH) and direct oral factor Xa inhibitors (DXIs) for the prevention and management of CAT, many unmet needs remain. Although LMWHs have a short half-life, minimal drug-to-drug interactions and are not dependent on gastrointestinal absorption, they remain parenteral anticoagulant regimens requiring daily subcutaneous injections which can be costly and limit adherence and persistence to anticoagulation [10]. Similarly, DXIs have many advantages including oral administration, fixed dosing without monitoring requirements and no drug-to-food interactions, but they may be associated with a higher risk of bleeding complications with certain cancer types (e.g., gastrointestinal, genitourinary), potential drug-to-drug interactions with medications affecting the cytochrome 3A4 and P-glycoprotein and they are dependent on renal and hepatic function for elimination and metabolisms [11]. Hence, important knowledge gaps remain unanswered including optimal management in high-risk subgroups, concerns about drug-drug interactions, and management of patients with severe renal impairment.

Future research on the diagnosis and management of CAT needs to focus on the identified unmet needs. Studies including patients with specific types of VTE (e.g., catheter-related thrombosis), patients' characteristics (e.g., thrombocytopenia, severe renal dysfunction, etc.) and high-risk types of cancer (e.g., brain tumors) are desperately needed. The new generation of anticoagulants inhibiting Factor XI (FXI) may also help to address many of the current knowledge gaps. FXI inhibitors have the potential to be as effective as DXIs and safer than LMWHs. FXI is a key component of the intrinsic coagulation pathway and it can attenuate thrombosis without disrupting hemostasis, making it a potentially extremely attractive target especially for patients with cancer and VTE [12,13]. Several FXI inhibitors are currently being investigated in clinical trials, including antisense oligonucleotide (fesomersen), monoclonal antibodies (osocimab and abelacimab) and small molecule FXIa inhibitors (milvexian and asundexian). The monoclonal antibodies inhibiting FXI may be particularly appealing for the management of CAT. Their long half-life allows for once monthly dosing which could potentially improve adherence and persistence to anticoagulation, and the parenteral administration avoids dependence on gastrointestinal absorption, or renal and liver function for clearance and metabolism [11,14]. Furthermore, given that catheter-related thromboses are initiated by activation of FXII in the contact pathway, FXI inhibitors may be particularly effective for their prevention or treatment. Two phase III randomised controlled trials are underway to evaluate the efficacy and safety of abelacimab for the management of CAT (lower limb proximal deep vein thrombosis and pulmonary embolism). The ASTER and MAGNOLIA trials (NCT05171049 and NCT05171075) compare abelacimab to apixaban (a DXI) or dalteparin (a LMWH) for the management of CAT, respectively. In both trials, abelacimab is administered intravenously for the first dose followed by monthly subcutaneous administration for a total of six months. If the low bleeding potential of FXI inhibition is confirmed while preserving the efficacy, they may provide a safer anticoagulant option for patients with CAT.

In conclusion, in this special edition of *Archives of Cardiovascular Diseases*, members of INNOVTE provide a much-needed comprehensive summary of the evidence along with pragmatic and practical clinical guidance on the diagnosis and management of CAT-related challenging topics. The manuscripts also highlight important unmet needs and knowledge gaps that can help prioritise the research agenda to optimize clinical care for this patient population.

Disclosure of interest

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