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Trial Outcomes and Sub-Analyses of Direct Oral Anticoagulants in the Treatment of Cancer-Related Venous Thromboembolism: Interviews with Key Opinion Leaders

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Disclosure: Muñoz Martin has declared no conflicts of interest. Muñoz Martin is a consultant, lecturer, and advisory board member with Sanofi, Celgene, AstraZeneca, Roche, Leo Pharma, Servier, Pfizer, Bristol Myers Squibb, Daiichi, Sankyo, Bayer, Amgen, Rovi, Merck, MSD, Dohme, and Eli Lilly; he co-developed the Tic-Onco genetic risk score for cancer-related venous thromboembolism with his colleague, José Manuel Soria. Young is an honoraria member of Leo Pharma and the Bristol Myers Squibb-Pfizer Alliance; and is the recipient of a Chugai Educational grant from Bayer.

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Interview Summary

EMJ conducted interviews with two key opinion leaders and specialists in the prevention and treatment of cancer-related venous thromboembolisms (VTE). Muñoz Martin is lead developer of the TiC-Onco genetic risk-assessment score, which is used to accurately predict patients' clinical and genetic risk factors for VTE. Preliminary findings from the ONCOTHROMB study, an 18-month observational prospective cohort study, are discussed herein. Young has recently concluded the SELECT-D trial, a large, multicentre randomised study comparing the direct oral anticoagulant (DOAC) rivaroxaban with dalteparin, a low molecular weight heparin (LMWH), to assess alternative anticoagulant therapies to heparin in patients with cancer-related VTE. This article aims to create awareness of underdiagnosis and undertreatment of VTE in these patients, and EMJ spoke with these two world experts to gain their recommendations in addressing this knowledge gap amongst oncologists and haematologists.

INTRODUCTION

Cancer-associated thrombosis (CAT) is a leading cause of morbidity and preventable death.[1] LMWH and DOACs[2,3] are the most widely used prophylactic anticoagulation therapies, based on findings where the relative risk of VTE in this patient group was reduced by approximately 50%.[4] Similar reductions in VTE were observed in studies with parenteral (odds ratio: 0.43; 95% confidence interval: 0.33–0.56) or oral anticoagulants (odds ratio:0.49; 95% confidence interval: 0.33–0.74).[5]

Despite the perceived benefits of thromboprophylaxis, the use of this preventive therapy among ambulatory patients remains low.[6] Improving awareness of how VTE prevalence rates impact morbidity and mortality, and identification of risk factors are crucial in determining the best patient pathways. The balance of thrombosis and bleeding (both major and clinically relevant non-major bleeding), must be weighed up before offering anticoagulation therapies to patients with cancer.[1]

ADVANCING VENOUS THROMBOEMBOLISM RISK ASSESSMENT

VTE risk factors include cancer type, patient clinical and lifestyle factors, and treatment types. "VTE incidence varies widely in different tumours, even within the same patients during the evolution of their cancer journey, so there is a strong need to improve risk assessment methods," Muñoz Martin explained. The Khorana score was introduced in 2008 and is considered the gold standard. It is recommended in guidance by the American Society of Clinical Oncology (ASCO),[7] the International Initiative on Thrombosis and Cancer (ITAC),[8] and the National Comprehensive Cancer Network (NCCN).[9] Score performance can be limited in patients with a high-to-moderate VTE risk. "In high-risk cases, the probability of a VTE event at 6 months is less than 10%, and most oncologists do not use a risk-assessment model."

Medical oncologists may be more comfortable proposing thromboprophylaxis if 'high-risk' is over 20%. Muñoz Martin indicated that many clinicians are still unfamiliar with tools like the Khorana score. "They tend to focus on the cancer but not the VTE risk, and the knowledge that up to 90% of high-risk patients will never develop VTE could explain the lack of any sense of urgency in using risk scores. Raising prediction capability and awareness for oncologists will likely improve treatment rates." Recent randomised clinical trials and meta-analyses showed that thromboprophylaxis has demonstrated safety and efficacy in outpatient settings.[5,10] Nevertheless, the problem of identifying which patient should receive therapy or thromboprophylaxis remains a challenge.

Ensuring that patients have access to appropriate information is vital and Young is a strong advocate of case-by-case assessment of ambulatory patients in outpatient settings. Highlighting the recent survey for the European Patient Cancer Coalition (EPCC),[11] she remarked that: "Approximately 72% of patients with cancer did not know they may be at risk of developing clots. There is a massive unmet need." VTE risk information could be incorporated into routine consultations: "Nurses and pharmacists trained in thrombosis and oncology run CAT clinics alongside oncologists in many hospitals in the UK, including Cardiff and Swansea, but UK implementation has generally been slow." Implementation science is key, and Young described the pioneering strategies used in Vermont, USA, where multidisciplinary team members offer patients integrated care in a structured manner, starting with an individual risk assessment of VTE, assessed using electronic health records.[12] "This would be an excellent model for the UK, but finding dedicated nurses and pharmacists to implement the model is tricky." Vital opportunities present during the clinical assessment, at follow-up, and throughout chemotherapy treatment, to inform high-risk patients of VTE risk and help them recognise and manage early warning signs and symptoms.

GENETIC BIOMARKERS AND THE TIC-ONCO SCORE IN VENOUS THROMBOEMBOLISM RISK PREDICTION

Both experts emphasised the importance of a good risk prediction score to establish VTE risk, before considering cancer type. Young uses the Khorana score to assess VTE risk "because it can be easily completed in routine clinic." Tumour site

is particularly important in the decision to offer a DOAC where there is still a lesion *in situ*. Other risk predictors include stage of disease, type of chemotherapy, and certain biomarkers.[13]

Tumour mutations are also important as they prompt different risk scores. "*ROS-1* or *ALK* rearrangement in non-small-cell lung cancer (NSCLC) are associated with a 3- to 5-fold higher risk of VTE compared to the general population of NSCLC. The VTE incidence in this group of patients exceeds 30–40%." Recent findings suggest that a *BRAF* mutation in NSCLC and colorectal cancer may pose a similarly higher risk of VTE.[14] "In contrast, the *IDH* mutations in gliomas [brain tumours] act as a protective factor in VTE, but in hepatobiliary tumours do not confer any protection concerning VTE risk." All these figures suggest that the molecular profile of neoplasms should be incorporated in the risk assessment models to improve the prediction capability.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has improved awareness and increased routine analysis of D-dimer tests.[15] D-dimer is now a validated CAT VTE biomarker,[15-17] and several scores have included it in the risk assessment at cancer diagnosis and throughout the course of the disease. The second cohort of the ONCOTHROMB study is currently underway and includes D-dimer analysis in addition to genomic analysis.[18] Muñoz Martin's team will analyse the genomics of more than 400 patients and compare results with the Khorana score and other clinical scores (CATSCORE, PROTECHT, and CONKO):[19] "This study will clarify whether the addition of different biomarkers to clinical variables will help to improve VTE prediction."

After the publication of a 2014 study that demonstrated that genetic analysis in non-cancer populations could help identify high-risk patients,[20] Muñoz Martin and his colleague, José Manuel Soria, developed the TiC-Onco score.[13] By extending the genomic profile in the ONCOTHROMB study,[18] the prediction of VTE risk was significantly improved and a new model, based on stage, type of tumour, BMI, and extended genetic risk score, was established. Published in 2018, the authors concluded that it was significantly better than the gold standard Khorana score at identifying patients that would benefit from thromboprophylaxis.[13] The four-variable TiC-Onco score was externally validated in an independent cohort of patients from the Vienna CATS study.[21]

In the AVERT,[22] CASSINI,[23] and TiC-Onco trials,[21] patients with pancreatic cancer experienced very high rates of VTE: between 20 and 30%. Neoplasms have the highest VTE incidence, and guidelines suggest primary thromboprophylaxis when receiving chemotherapy in outpatient settings and when there is a low risk of bleeding.[10] Up until 2018, only high-risk patients were considered for ambulatory thromboprophylaxis in the clinical guidelines. However, "after publication of AVERT and CASSINI in 2019, the ASCO,[24] and Spanish Society of Medical Oncology (SEOM)[10] guidelines started to recommend thromboprophylaxis in intermediate-risk patients with a Khorana score of 2 points." In these patients, thromboprophylaxis is effective, but Muñoz Martin emphasised that bleeding risk should be carefully considered. "Our group is working on a specific risk assessment model of bleeding for patients with cancer based on big data technology, machine learning, and natural language processing, and we hope to obtain the first results during this year."

DIRECT ORAL ANTICOAGULANTS AS ALTERNATIVES TO HEPARIN IN THE TREATMENT OF VENOUS THROMBOEMBOLISM: THE ADAM VTE, CARAVAGGIO, AND HOKUSAI VTE TRIALS

In patients with cancer who have already developed VTE, DOACs are convenient for patients,[25] and those currently evidenced in VTE and cancers are apixaban, edoxaban, and rivaroxaban.[26] Young's team generally offer patients LMWH if they are at high risk of VTE, then DOAC as appropriate once they are more stable. "It is quite common to switch between both types of treatment at any time in the CAT pathway, depending on clinical need; LMWH was shown to be superior to warfarin in 2003[26] for the treatment of pulmonary embolism and deep vein thromboses in cancers, but warfarin is still used in low-income countries due to its affordability." Young also noticed that, in practice, around one in five patients had stopped their LMWH injections before 6

months due to practical concerns surrounding subcutaneous administration and cost.

The ADAM VTE trial was a superiority trial to assess whether oral apixaban is associated with a significantly lower rate of major bleeding compared with subcutaneous dalteparin, in the treatment of patients with active cancer and confirmed acute VTE. The study investigators concluded that patients treated with apixaban experienced low rates of major bleeding (0% versus 1.4%; p=0.138) and significantly lower VTE recurrence rates (0.7% versus 6.3%; p=0.0281) than those treated with dalteparin.[27] This conclusion is supported by the Caravaggio trial,[28] which also assessed recurrence of VTE and major bleeding in patients with cancer and confirmed VTE. This trial concluded non-inferiority of apixaban to dalteparin in preventing recurrent VTE (5.7% versus 7.9%; p<0.0001 for non-inferiority), without increasing the risk of major bleeds.[29] Interestingly, both studies showed a similar gastrointestinal (GI) major bleeding and clinically relevant non-major bleeding rate, both at the upper and lower GI tract, with apixaban and dalteparin.[27,28,30]

The Hokusai VTE trial was designed to determine a composite of the rate of recurrent VTE and major bleeding in patients with cancer-associated VTE treated with either edoxaban or dalteparin. The results show non-inferiority in the composite endpoint (12.8% versus 13.5%; p=0.006). However, when assessed separately, recurrent VTE was observed only numerically less frequently (7.9% versus 11.3%; p=0.09) and major bleeding occurred significantly more frequently (6.9% versus 4.0%; p=0.04) with edoxaban than with dalteparin.[29]

Taken together, these trials support the use of DOACs in patients with cancer and VTE, and it is clear that further trials are required to confirm these findings as well as to increase awareness among healthcare professionals of different treatment options for these patients.

DIRECT ORAL ANTICOAGULANTS AS ALTERNATIVES TO HEPARIN IN THE TREATMENT OF VENOUS THROMBOEMBOLISM: THE SELECT-D TRIAL

Young developed the SELECT-D trial[25] to assess whether rivaroxaban, an oral factor Xa inhibitor, would offer a better alternative to the standard 6-month LMWH regimen for patients at risk of VTE.

Patients with stomach and oesophageal cancer were initially included, but then excluded near the trial end as a precautionary measure following a Data and Safety Monitoring Committee (DSMC) review. Young reported that bleeding rates with rivaroxaban in comparison with dalteparin seemed non-significantly higher in patients with oesophageal cancers and upper GI cancers. "When considering treatment of VTE in people with colorectal (lower GI) cancers, considerations should always be made via an individualised assessment, including having an *in situ* lesion or not." The Hokusai VTE Cancer trial was first presented around the same time as SELECT-D and results were similar.[27] "Both arms in SELECT-D[25] demonstrated the propensity for major bleeds from GI cancers and bleeding from the GI tract." The recurrent 6-month cumulative VTE risk with rivaroxaban was lower than expected at 4%, compared with the predicted overall VTE rate of 10%.[25] Death as a competing risk factor was not shown to alter the results in a sensitivity analysis, as many patients taking part in the study were extremely ill.[25]

The DSMC closed the second randomisation due to low recruitment. "Patients were deciding not to be randomised for another 6 months, and consultants did not want their patients to be allocated placebo after 6 months of anticoagulation, despite a lack of evidence for continuation or not, and the guidelines then recommended 3–6 months treatment duration." Young continued: "Before SELECT-D [12 months],[31] two 'duration of anticoagulation' trials in patients with cancer had failed, one of which did not recruit any patients. Instead of non-inferiority, we achieved superiority in reducing VTE with rivaroxaban, so our pilot became a full study. In the second randomisation, despite low numbers, in 92 patients thrombogenic signals remained at 12 months. There was a trend towards an ideal 12-month treatment time frame in comparison to 6 months, setting a preliminary foundation for further trials." Since publication of SELECT-D, awareness around treatment of VTE with DOAC is much greater: "The impact has been positive." Both Young and Muñoz Martin

agreed that future trials should extend beyond 6 months, as more longitudinal data are needed.[32]

PRESCRIBING CHALLENGES

Young described some of the challenges around prescribing DOACs when treating VTE in patients with cancer, particularly in patients experiencing nausea and vomiting. "Some patients cannot absorb oral medication. LMWH can be prescribed, and once symptoms improve and where appropriate they can switch back to a DOAC as part of their care pathway. If the tumour is still present, DOACs would not be prescribed, but if the cancer has been resected, if it suited the patient and all risks were explained, then they may." Muñoz Martin currently favours the twice-daily apixaban regimen over other DOACs in patients with GI cancer, based on ADAM VTE[27] and Caravaggio[28,30] trials results, which suggest a different bleeding profile of apixaban relative to other DOAC, in line with LMWH outcomes (though no head-to-head studies have been conducted).[27,28,30] Several hypotheses have been proposed to explain these different bleeding risks (once- versus twice-daily dose and blood–plasma concentration).

Systematic risk assessment and timely risk management methods are crucial to providing the best clinical care. On considering the impact of both of their trials on future prescribing regimens, Young reiterated that healthcare professionals need to listen to patients, have good communication skills, and implement shared decision making from the very beginning, while Muñoz Martin emphasised the need to think carefully about the choice of anticoagulant in relation to tumour type and other clinical characteristics.

IMPROVING TREATMENT UPTAKE AND ADHERENCE

Young emphasised the need to address the current lack of continuity of CAT care as part of the cancer pathway. She remarked on an important All-Party Parliamentary Thrombosis Group (APPTG) report,[33] published in 2020, advocating nurse and pharmacist-led pathways, such as those in Vermont, USA, where patients' CAT care is personalised throughout.[12] Muñoz Martin suggested that adherence to therapy is generally good, but adherence to prophylaxis is not. He maintained that oncologists are best placed to discuss treatment options as they have close, regular patient contact. "DOAC can improve adherence to treatment and prophylaxis as has been shown in the Caravaggio and Hokusai trials; thromboprophylaxis inpatients are receiving anticoagulation routinely, but in outpatient settings there is a large capacity for improvement."

Young's team has support staff who are trained in counselling: "Wellbeing is a particularly important consideration, as many people with cancer and VTE may become anxious and/or depressed. Within a holistic assessment, preferably in the presence of a caregiver, anxiety can be flagged, and if people are on a cancer pathway they know exactly where to go and who to talk to, and adherence [to VTE therapy] can be improved."

IMPROVING THE CANCER-RELATED VENOUS THROMBOEMBOLISM LANDSCAPE

Young and Muñoz Martin agreed that their trial results will impact future clinical trial designs, and that more head-to-head trials with anticoagulant therapies are required; however, this is unlikely due to drug patents expiring. "Clinicians now have a greater choice of anticoagulants with the introduction of DOACs,[31] though their safety and efficacy must be carefully considered, particularly among high-risk groups." The SELECT-D trial was instrumental in setting a 12-month treatment trend.[31] Young also identified a need for further research around incidental pulmonary embolism, stating that: "Alarmingly, mortality rates in these patients mirror those seen in patients with symptomatic VTE." Establishing an evidence base in this area is extremely important.[31]

Medical training around VTE should also be developed. Muñoz Martin considers that trainees in medical oncology need additional support around VTE in the first years of their medical fellowship. "In a 2017 survey of more than 200 medical oncologists in Spain,[34,35] more than 90% agreed that VTE risk is a relevant complication

in patients with cancer and 93% expressed a need for more medical education in the cancer-associated thrombosis field. Despite this, neutropenic fever is assessed, and prophylaxis is provided much more often than VTE,[36] even with an average clinical rate of only 3% in clinical trials." Young and Muñoz Martin agreed that clinical guidelines are also difficult to implement as there are so many; local solutions sometimes take priority with healthcare managers. Solutions include tailoring guidance to each specific area of practice via robust clinical policies and ensuring the cost effectiveness of resultant recommendations.[5]

CONCLUSION

VTE risk remains an important concern within oncology and haematology. Important take-home messages include the need to consider VTE risk during patient consultations and to adopt the use of recommended and validated risk assessment scores. Vermont-style CAT clinic models may improve VTE detection rates and be used to raise standards in care and education. Technology could also be used more readily, e.g., electronic alerts for those at high risk of VTE could be featured in patient record systems to improve information flow. The discovery of genetic biomarkers may offer new hope around accurate assessment, improved diagnosis, and personalised treatment of cancer-related VTE. Many clinical benefits could also be achieved by educating healthcare professionals on VTE risk during their foundation years.

Clinical trials supporting the use of DOACs in the treatment of VTE are increasing awareness of the condition in patients with cancer. The ADAM-VTE and Caravaggio trials demonstrated a benefit of apixaban over dalteparin in reducing VTE recurrence without increasing the risk for major bleeding,[27,29] and the Hokusai VTE trial showed a similar result with edoxuban versus dalteparin in the composite primary endpoint.[27] The results of the SELECT-D trial demonstrated that rivaroxaban is an effective alternative to LMWH for the treatment of VTE in cancer, showing reduced rates of recurrent VTE compared with LMWH, but increased bleeding.[25,28]

Oral administration of DOACs may be more favourable than daily subcutaneous injections, but caution should always be used when prescribing anticoagulation treatments to patients with specific tumours, particularly those on the oesophageal or GI lumen wall. Clinicians are encouraged to study the diverse safety and efficacy profiles of DOACs and to use the latest clinical guidance to support their clinical use. The use of DOAC is recommended in high-risk patients and may also be beneficial in moderate-risk patients if bleeding risk is sufficiently low.

It is clear that there is an unmet need in both diagnosis and treatment of patients with cancer at risk of VTE. Further education for healthcare professionals and patients is required in order to improve diagnosis, increase the use of prophylaxis for and treatment of VTE, and ultimately, save lives.

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