New Developments, Data, and Guideline Updates: Direct Oral Anticoagulants for the Treatment of Venous Thromboembolism Associated with Cancer – Interviews with Key Opinion Leaders

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Interview Summary

For this article, EMJ conducted interviews with two key opinion leaders. Harry Gibbs is the Program Director of the Outpatients Program and Deputy Director of General Medicine at The Alfred Hospital, Melbourne, Australia, as well as Adjunct Clinical Associate Professor at Monash University, Melbourne, Australia. He has a particular interest in thrombosis and anticoagulant therapy and is a board member of the Australian and New Zealand Society for Vascular Surgery (ANZSVS). F.A. (Erik) Klok is an Internist Vascular Medicine Specialist at the Leiden University Medical Center, the Netherlands, and holds a position of Visiting Professor at the Center for Thrombosis and Hemostasis, Mainz, Germany. His research interests include the diagnosis, treatment, and long-term complications of venous thromboembolism (VTE), and he is co-chair of the Working Group for VTE at the International Consortium for Health Outcomes Measurement (ICHOM).

In this interview, they discuss the role of direct oral anticoagulants (DOAC) as a treatment for cancer-associated thrombosis (CAT), including updates to the guidelines and the importance of patient-centric care. A discussion of key unmet needs as described by the two experts and a look to the future of anticoagulation in patients with cancer is also included.

INTRODUCTION

CAT is a serious complication that can affect up to 6% of patients with cancer, and is associated with a 2–5-fold increased risk of mortality.[1] Since 2003, low molecular weight heparin (LMWH) has been the standard of care for the management of CAT due to its demonstrated superiority to vitamin K antagonists.[2] However, the need for daily subcutaneous injections over an extended period can exert a significant burden on patients with cancer. DOACs have been used as an oral treatment for thrombosis in the non-cancer setting since 2008 and, more recently, have been shown to be beneficial for CAT in several landmark clinical trials.

The CARAVAGGIO[3] and Hokusai VTE Cancer[4] randomised controlled trials (RCT) both enrolled more than 1,000 patients and demonstrated that apixaban and edoxaban respectively were non-inferior to LMWH for the treatment of CAT. Rates of major bleeding were slightly higher with edoxaban versus LMWH in the Hokusai VTE Cancer study, but no differences were reported in the CARAVAGGIO study. Apixaban was also studied in the smaller ADAM-VTE study[5] (n=300) and was shown to result in fewer VTE recurrences, but similar rates of major bleeding and clinically relevant non-major bleeding compared with LMWH were observed. In the SELECT-D study[6] (n=203), rivaroxaban was associated with lower rates of VTE recurrence, but higher rates of clinically relevant non-major bleeding compared with LMWH.

However, it should be noted that both the ADAM-VTE and SELECT-D studies had relevant methodological limitations. The ADAM-VTE study did not meet its predefined primary endpoint due to lower than anticipated major bleeding rates in both study arms. In addition, fewer patients with gastrointestinal (GI) malignancies were enrolled in this study compared with the Hokusai VTE Cancer study.[5] SELECT-D was designed as a feasibility study, of which the sample size had to be reduced as recruitment was slower than anticipated. Furthermore, after an early signal for rivaroxaban-associated major bleeding in patients with cancer of the oesophagus or gastroesophageal junction was identified, patients with this type of tumour were subsequently excluded from enrolment in the study.[6]

KEY UPDATES TO GUIDELINES ON ANTICOAGULATION FOR PATIENTS WITH CANCER

For many years, the guidelines recommended LMWH as the sole therapy for VTE in patients with cancer. However, with the emergence of data from recent RCTs, the guidelines began to incorporate recommendations for DOACs, initially as a treatment that could be considered and then as a reasonable alternative to LMWH.

In the past 12 months there has been a further important shift in the guidelines. Gibbs highlighted that the CHEST,[7] American Society of Hematology (ASH),[8] and National Comprehensive Cancer Network (NCNN)[9] guidelines were all updated in 2021. He explained: "These three guidelines now favour DOACs over LMWH in the majority of patients and state that LMWH should only be used in specific circumstances." He added that the guidelines recommend caution in patients with unresected GI cancers; this is not a message not to use them, but to be cautious.

Klok noted that national guidelines have also been updated to recommend DOACs, and added: "The most recent guidelines suggest that the DOACs should be the primary treatment for VTE, although there is no international consensus on that because, although they are as good as LMWH in terms of efficacy and safety, there is no evidence that they are better." He also added the caveat that guidelines are published at a slow pace and may not include the most recent data.

Both experts agreed that many physicians were using DOACs to treat CAT even before the guidelines were updated. This early adoption was likely driven by patient preference for oral medications over injections, as many patients find it difficult to inject themselves daily in the long-term. It is also supported by data from the GARFIELD-VTE registry,[10] which demonstrated that physicians were using DOACs in patients with cancer before the publication of the CARAVAGGIO study. Although the extent to which DOACs are currently being used in the treatment of CAT is unknown, Klok noted that it is likely that the majority of patients in this setting are now initiating treatment with DOACs, and that this is very different from 5 years ago. Gibbs added: "Thrombosis physicians are very experienced with DOACs and will be comfortable

using them upfront in patients with cancer. Anecdotally, in Australia, medical oncologists are also beginning to use them, although potentially less extensively than thrombosis physicians."

Gibbs and Klok both emphasised the need for real-world evidence on the use of DOACs in CAT. They highlighted that some small studies have been published and these have begun to inspire confidence in the use of DOACs beyond the RCT setting. However, real-world evidence remains limited, and the impact of the COVID-19 pandemic on the collection and publication of real-world data was acknowledged. Klok felt that many cancer institutes and thrombosis experts will now be conducting these types of studies and that more real-world data will be published in the near future. He added that Phase IV and post-marketing studies are useful, as they indicate the rate of complications in real life. This is expected to be higher than in clinical trials due to the exclusion of the highest risk patients from RCTs.

DECISION-MAKING IN DIFFICULT CLINICAL SITUATIONS

Although DOACs are suitable for the majority of patients with CAT, there are clinical situations where the optimal treatment approach remains uncertain. Klok emphasised that patients with cancer and VTE are a very heterogeneous group, and the patients with the highest risk of complications tend to either not be included in clinical trials or are included in only small numbers. In particular, patients with very low platelet counts, severe renal insufficiency, or brain metastases are largely excluded from clinical trials, and these patients pose the greatest dilemma in terms of clinical decision-making.

It is well-established that some cancer types may have an increased risk of bleeding associated with anticoagulation, including GI, brain, and urogenital tumours,[11] and both experts stressed the need for caution when using DOACs in these patients. In the Hokusai VTE Cancer study, the majority of major bleeding occurred in patients with GI cancer.[12] However, a more recent analysis of these patients identified the presence of advanced cancer and low haemoglobin levels, but not resection status, as significant risk factors for bleeding.[13] Gibbs stated: "This gives us some reassurance in using DOACs in patients who have not had a GI cancer resected."

Extremes of body weight were also discussed as an area of uncertainty in the use of DOACs. In particular, it remains unclear as to whether DOACs should be used or whether the dose should be adjusted in patients with extremely low body weight,[14] a situation that can be common in patients with advanced cancer or following certain cancer treatments.

Caution should also be applied in patients with renal or hepatic impairment, as DOACs are both renally excreted and hepatically metabolised.[14] In patients with severe liver dysfunction or significant chronic kidney disease, there is the potential for drug accumulation and increased bleeding. Gibbs noted: "There is some evidence supporting the use of these drugs at low levels of renal and liver function;[15-17] however, in more extreme cases, e.g., Stage 5 chronic kidney disease, then these drugs probably shouldn't be used." Furthermore, Klok emphasised that patients with moderate to severe renal insufficiency were excluded from the RCTs of DOACs in CAT and, therefore, LMWH remains the standard of care for these patients.

Gibbs also described how physicians may be less comfortable using DOACs in certain situations, and that LMWH remains a valid alternative for some patients: "Trials and guidelines have given us confidence that DOACs can be used in the great majority of patients with CAT. However, through years of practical experience with LMWH, physicians have become comfortable with making minor dose adjustments in response to different clinical situations. We can't do this with DOACs as we don't have the confidence or experience to make minor changes to the recommended dosage. There are times when we can fall back on LMWH as a tried and true approach, and there is no harm in doing that."

POTENTIAL IMPACT OF DRUG–DRUG INTERACTIONS

Drug–drug interactions (DDI) were highlighted as an important consideration for DOACs, with Gibbs emphasising that "DDIs are much more important in cancer than in other VTE situations given the large numbers of anti-cancer drugs,

particularly immunotherapies, coming into clinical practice quickly."

Klok noted: "Patients should be reassured that DOACs are not expected to influence the efficacy or safety of anti-tumour drugs; however, it is possible that anti-tumour drugs may potentially affect the performance of anticoagulants. This is an issue that is not yet resolved."

Gibbs highlighted that an advantage of DOACs is that they have few DDIs, and studies performed so far have not identified any significant problems. For example, in an analysis of data from the CARAVAGGIO study, concomitant administration of anti-cancer drugs did not affect the risk of VTE recurrence or major bleeding in patients treated with apixaban.[18] Klok also described a recent study that demonstrated no significant interactions between dexamethasone and DOACs in patients hospitalised with COVID-19.[19] Although this was only a small study, it is particularly interesting given that dexamethasone is believed to potentially interact with DOACs. Despite the supporting data obtained so far, it was noted that there is the potential for multiple minor DDIs to have an additive effect on the efficacy and safety of DOACs, and that this may be particularly relevant in the context of cancer where patients may be receiving multiple concomitant treatments.

Gibbs discussed the possibility of predicting the risk of DDIs in individual patients. He commented that it would be good to have an accurate test that could provide a good indication of potential therapy failure or bleeding; however, therapeutic drug monitoring for DOACs is not particularly helpful due to the broad range of values observed within a patient population. In the future, the genetic profiling of polymorphisms in metabolic enzymes and efflux transporters may be useful to predict DDIs in individual patients.

TREATMENT OF INCIDENTAL VENOUS THROMBOEMBOLISM

Both experts highlighted that incidental VTEs are discovered quite commonly in patients with cancer due to the need for frequent imaging for staging and to assess progression in this context. Sub-analyses from the CARAVAGGIO and Hokusai VTE Cancer studies indicated that patients with cancer with incidental VTE have a considerable risk of recurrence and, therefore, they should receive anticoagulant treatment rather than observation.[20,21] However, a numeric, but not statistically significant, lower risk of recurrence combined with an increased risk of major bleeding was observed in incidental cases compared with symptomatic patients in both studies.[20,21] Gibbs commented that this increased risk of bleeding may be because screening tests are performed more frequently for cancers with a higher risk of bleeding (e.g., GI cancers) and, therefore, these types of cancers may be over-represented in a cohort of patients with incidental VTE. He further added: "If there is a reason not to use anticoagulants, it may be reasonable to stop anticoagulation at some stage as the recurrence rate is lower."

A ROLE FOR DIRECT ORAL ANTICOAGULANTS AS PROPHYLAXIS

The role of VTE prophylaxis in ambulatory, non-hospitalised patients with cancer was discussed by both experts. Two RCTs have evaluated the benefits of prophylaxis with a DOAC in patients with cancer and a high risk of VTE (Khorana score: ≥2), with conflicting results for the primary endpoints. In the AVERT study,[22] apixaban treatment resulted in a significantly lower rate of VTE episodes compared with placebo, albeit with higher rates of major bleeding episodes.

In contrast, in the CASSINI study,[23] rivaroxaban treatment did not lead to a significantly lower incidence of VTE or death due to VTE during the trial period. Klok also highlighted that many high-risk patients are not currently receiving prophylaxis. "Guidelines recommend that in patients with a high Khorana score, prophylaxis may be considered, preferably with a DOAC, but this is not common practice in many countries," Klok stated.

Questions also remain as to how to identify the patients who are likely to benefit from prophylaxis and how to minimise overtreatment. The Khorana score[24] was noted to be the most commonly used algorithm for assessing risk, but it was acknowledged that it has many limitations. Other scoring systems have also been developed that can be used to predict risk, but so far none have been able to definitively guide treatment.

TREATING THE PATIENT, NOT THE CLOT

The importance of patient-centric and empathic care was strongly emphasised by both experts. Klok stated: "Each patient with cancer is unique, with their own genetic profile, phenotype, and clinical presentation. We need to stop thinking about which patient should receive which drug, and instead think about the overall cancer journey for each patient." He highlighted that treatment may need to be adjusted over time depending on the changing clinical situation. For example, patients receiving chemotherapy agents associated with GI side effects should potentially switch to LMWH.

Klok also stressed the importance of knowing when to stop anticoagulation in patients receiving end-of-life care: "We have very little evidence for when treatment should be ended, but it is an important conversation to have with the patient to establish their priorities in their final months or weeks of life. Most patients die receiving drugs and we should ask why this is the case." He postulated that patients near end-of-life may not need to receive the best possible anticoagulation regimen. Instead, better outcomes may be achieved by stopping anticoagulation in the months before death to reduce the treatment burden and the risk of bleeding. Any thromboses that do occur could then be treated symptomatically.

Similarly, Gibbs recognised that treatment can be stressful for patients with a terminal diagnosis or for patients who are uncertain as to whether their treatment will be curative. He added that the burden of treatment can be significant, and that the patient's wishes should always be included in the decision-making process.

Klok also discussed the need to revise existing endpoints in CAT studies: "We need to look beyond current endpoints of recurrence of VTE, bleeding, and mortality and identify patient-relevant endpoints that allow us to measure the impact of complications for patients with cancer, e.g., quality of life, pain, dyspnoea, fear, or anxiety. The impact of a recurring thrombosis may be different to the impact of bleeding and patients may not be able to balance the risk of thromboses versus the risk of bleeding when making treatment decisions if they don't understand the different impacts of these complications." In order to address this need, the ICHOM has established a working group to identify a minimum set of health outcomes that are relevant for patients with VTE.

A LOOK TO THE FUTURE

Both experts noted that the optimal intensity and duration of anticoagulation treatment in patients with cancer is unclear and is the focus of ongoing studies. It was highlighted that in non-cancer thrombosis, long-term, low-intensity DOAC use is efficacious and safe,[25,26] but in the setting of CAT, the risk–benefit profile of long-term anticoagulation is unknown. This question is currently being addressed by the API-CAT study,[27] which is evaluating whether a regimen of extended treatment with a half-dose of apixaban has an acceptable risk of VTE recurrence and bleeding.

The development of inhibitors to Factors XI and XII were also highlighted as being of particular interest, with both experts noting that these drugs may theoretically be associated with less bleeding than other anticoagulants. Klok commented: "For those categories of patients with the highest rates of bleeding with existing anticoagulant drugs, it will be extremely interesting to see whether those patients may benefit from or have a better outcome when treated with novel Factor XI inhibitors. The Factor XI inhibitor, abelacimab, is currently being investigated in a Phase III trial in patients with cancer-associated VTE."[28]

Klok also discussed the need to better predict and prevent thromboses from occurring in patients with cancer. "The holy grail is that no patient with cancer develops a blood clot," he said. In particular, the potential role of biomarkers measured in liquid biopsy samples was highlighted as a means of identifying risk factors for VTE in patients with cancer.

Gibbs also added that artificial intelligence and machine learning have the potential to define risk and inform treatment decisions more accurately than is currently possible. He noted that existing scoring systems, such as the CHA_2DS_2-VASc score, use only a small number of parameters, whereas, in reality, a far larger number of factors will influence the risk of thrombosis. Each factor alone may only have a minor effect, but these

could be significant when combined into a more sophisticated scoring system. He hypothesised that advanced technologies could easily combine a large number of characteristics from a patient's electronic medical record to give a far more nuanced risk assessment.

Klok concluded: "In 10 years, I expect many of our current questions will be answered, and we will be much better at preventing blood clots." He also highlighted that many of these topics will be discussed at the International Conference on Thrombosis and Hemostasis in Cancer (ISTH), which will be held in May 2022.

CONCLUSION

In recent years, robust evidence has emerged from RCTs supporting DOACs as a treatment option for patients with CAT. The two experts interviewed for this article described how these data have informed major updates to international and national guidelines, and how DOACs are now being routinely implemented in clinical practice. Although DOACs are recommended for the majority of patients with CAT, there remain some clinical situations where there is a degree of uncertainty regarding their use. This includes cancer types associated with an increased bleeding risk, extremes of body weight, renal and hepatic impairment, and the use of concomitant anti-cancer therapies. In addition, evidence to support the use of DOACs as a treatment for incidental VTE or as prophylaxis in ambulatory patients with cancer is currently limited. Ongoing real-world studies and subgroup analyses from large RCTs are expected to address some of these knowledge gaps and give physicians confidence that the data from RCTs is generalisable to their clinical practice. Both of the experts interviewed here also stressed the importance of having an empathic clinical practice and treating the patient rather than the disease. This includes consideration of the overall patient journey, where the choice of treatment may vary over time, and also incorporation of the patient's wishes into all treatment decisions. Looking ahead, it is hoped that advanced technologies combined with a broader range of anticoagulant treatment options may enable us to predict and prevent the majority of thromboses in patients with cancer in the near future.

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