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Mini Review

Direct Oral Anticoagulants (DOACs) in Cancer Related Thromboembolism

Shahid Gilani*

Cancer Centre, University Hospital of North Midlands, Staffordshire, United Kingdom

***Corresponding Author:** Shahid Gilani, Cancer Centre, University Hospital of North Midlands, Staffordshire, United Kingdom.

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Abstract

Cancer patients have an increased risk of venous thromboembolism (VTE) as well as bleeding. For many years Low Molecule Heparin (LMHW) remained standard of care for these patients. Recently Direct Oral Anticoagulants (DOACs) have shown similar efficacy and safety in large randomised control trials. Data from four recent trials done in cancer patients have highlighted importance of the DOACs in cancer patients. DOACs have been found to be simpler to administer with better compliance among cancer patients. However, there are several issues surrounding prescribing DOACs in these patients. Some of them are related to drug-to-drug interactions and others to an increased risk of bleeding in mucosal cancers of gastrointestinal (GI) and urothelial tracts. In this review, the author summarises updated clinical information and presents an easy to use practical guide for treatment of VTE in cancer patients in a flow-sheet manner. It is also suggested to establish a multidisciplinary cancer associated thrombosis clinic for these patients for long term follow-up.

Keywords: Venous Thromboembolism (VTE); Low Molecule Heparin (LMHW); Cancer Associated Thrombosis (CAT); Direct Oral Anticoagulants (DOACs); Gastrointestinal (GI); Deep Vein Thrombosis (DVT); Pulmonary Embolism (PE)

Introduction

Thromboembolism covers arterial thrombosis as well as venous thromboembolism (VTE) including deep vein thrombosis (DVT), pulmonary embolism (PE)[1]. VTE is a significant cause of morbidity and mortality in cancer patients [1]. The incidence is even higher during cancer treatment like chemotherapy [2]. The risk of VTE in cancer patients varies from 0.5% - 20% depending upon the volume and form of cancer [3], these patients also carry a higher risk of recurrent VTE and bleeding during treatment [4].

Comprehensive management of cancer associated VTE is complex and challenging because of increased risk of bleeding as well as recurrent thrombosis [5]. Drug-to-drug interaction is another concern while on systemic anticancer therapy (SACT) [5]. Since the reporting of the CLOT study in 2003 by Agnes Lee, Low Molecular Weight Heparin (LMWH) remained standard of care in the treatment of cancer-associated thrombosis [6-9]. It has long been agreed that for LMWH is more effective and safer than warfarin in cancer patients with reduced incidence of bleeding and decreased incidence of drug-to-drug interactions [6]. LMWH also remained suitable for patients with poor oral intake as well for those undergoing surgery [6-9].

In recent times evidence has been piling up in favour of Direct Oral Anticoagulants (DOACs) for treatment of VTE in cancer patients

[10]. Previous studies have established DOACs as a better option than warfarin to treat acute VTE [10]. More recent randomised controlled trials have shown DOACs comparable to LMWH, exhibiting a similar efficacy and safety profile [5]. Moreover, DOACs have a fixed oral dose and predictable anticoagulation effects [5]. DOACs are administered orally avoiding long term subcutaneous injections which improves patient compliance and satisfaction [11].

DOACs display similar efficacy and safety as LMWH in cancer associated thrombosis in head to head randomised controlled trials [5,13]. This evidence is shown adequately in four recent randomised studies namely Hokusai VTE Cancer [24], SELECT-D [9], ADAM VTE [13] and Caravaggio trials [16]. This defines an important role of DOACs in the treatment of thrombosis in cancer patients. However, bleeding complications remain a concern particularly in those patients who have active gastro-intestinal and genitourinary malignancies [15]. This has led to recent ASCO [12], NICE [17] and NCCN [33] guidelines updates. Clinical practice guidelines across the world are being updated to include the role of DOACs in the treatment of cancer associated thrombosis [5].

Ambulatory cancer patients on chemotherapy are also at increased risk of VTE and may benefit from pharmacological prophylaxis based on innovative randomised control trials like CASSINI [29] and AVERT [30]. In these trials thrombosis risk stratification is performed based on the Khorana score [15]. High risk patients undergoing chemotherapy with a Khorana score of two or higher may be offered thrombo-prophylaxis [26].

Author has reviewed and summarized current evidence and compiled recommendations for treatment of VTE in cancer patients [4,12]. Easy to use flow diagrams are created based on this evidence [4,14-18]. Ongoing and future clinical trial will provide further evidence in this setting. Clinical practice guidelines are being updated to include the role of DOACs in the treatment of thrombosis in cancer patients [5]. Management of cancer associated thrombosis is complex and challenging therefore a longitudinal multidisciplinary cancer associated thrombosis clinic (CAT-Clinic) is suggested for the long-term follow up of these patients [15].

Current recommendations:

Treatment of venous thromboembolism (VTE) in cancer patients:

1. Initial treatment may be started with Low Molecular Weight Heparin (LMWH), Unfractionated Heparin (UFH), fondaparinux or Rivaroxaban. Initial 5 - 10 days of LMWH is preferred over UFH for cancer patients without severe renal impairment (Creatinine Clearance < 30 ml/min).
2. Long term treatment is recommended for at least 6 months with LMWH, Apixaban, rivaroxaban or edoxaban. Vitamin K antagonist (warfarin) may be used if LMWH or Direct Oral Anticoagulants (DOACs) are not available. DOACs are associated with increased risk of major bleeding complications particularly in gastrointestinal or genitourinary malignancies. Therefore, careful consideration is needed in choosing DOACs when mucosal bleeding or drug to drug interactions are likely.
3. Long term anticoagulation beyond 6 months may be offered to selected patients with active metastatic disease or in those receiving chemotherapy with a Khorana score of 2 or higher in prophylaxis.
4. Insertion of inferior vena cava filters may not be offered to all patients with established thrombus or to patients with temporary contraindication to anticoagulation. But they may be offered as adjunct to anti-coagulation in those who have developed an extension of an existing thrombus despite optimal therapy.
5. Patients with primary central nervous system (CNS) malignancy or metastatic brain disease with thrombosis may be offered anticoagulation as for other cancers. Although uncertainties do exist around the selection of patients and the approach of anti-coagulation.
6. Incidental PE or DVT should be treated same way as of symptomatic thrombosis.

7. Treatment of isolated sub-segmental PE or splanchnic or visceral vein thrombi may be considered for treatment on an individual ground.

Prevention of venous thromboembolism (VTE) in cancer patients:

1. Thromboprophylaxis is recommended for hospitalized patients with active cancer and patients undergoing major surgery, in the absence of bleeding and major contraindications. Routine pharmacologic thromboprophylaxis should not be offered to patients admitted in short stay units for chemotherapy or those undergoing minor procedures like stem cell/ bone marrow transplantation.
2. Patients undergoing chemotherapy should not be offered routine pharmacologic thromboprophylaxis. They should have VTE risk stratification based on the Khorana score. High risk patients undergoing chemotherapy with a Khorana score of 2 or higher may be offered thromboprophylaxis with apixaban, rivaroxaban, or Low Molecular Weight Heparin (LMWH), providing there is no increased risk of bleeding or drug to drug interactions. Discussion should take place with the patient about the risks and benefits including the duration of prophylaxis.
3. Patients with multiple myeloma receiving thalidomide or Lenalidomide should be offered pharmacologic prophylaxis with either aspirin or LMWH for low risk patients and LMWH for high risk patients.

Important considerations when prescribing DOACs in cancer patients

It is important to consider concurrent chemotherapy and other drugs when choosing DOACs. There may be drug to drug interaction with Systemic Anti-Cancer Therapy (SACT) and DOACs. Patient can also develop severe thrombocytopenia during chemotherapy. Moreover, the ability to take medications orally is reduced in some patients due to nausea, vomiting or diarrhoea. Particularly, rivaroxaban appears to be absorbed primarily in the stomach therefore it should be avoided in patients being fed through percutaneous endoscopic jejunostomy (PEJ) [32]. One should have to consider stopping or changing anticoagulation due to intolerance, renal impairment, thrombocytopenia, and drug interaction. DOACs can be withheld or bridged with LMWH when a patient is advised 'Nil by mouth' in peri-operative settings, based on VTE versus bleeding risk evaluation. The assessment of bleeding and recurrent thrombosis risk should continue throughout the treatment. Bleeding complications can occur during treatment requiring blood products and/or reversal of anticoagulation. Decision to reverse DOAC induced anticoagulation may only be considered in critical emergencies. In the majority of cases this should not be necessary due to the short half life of DOACs. Choice of anticoagulation drug should be communicated with the patient at all times even in the palliative care setting and in end of life care.

Conclusion

The management of VTE in cancer patients is complex and challenging. The majority of current guidelines recommend LMWH as the first line treatment for the initial and long-term management of VTE in cancer patients. However, emerging data from recent randomised controlled trials favour the use of DOACs in this setting. Therefore DOACs are reasonable alternate for patients without an increased risk of bleeding. Although DOACs are convenient and attractive oral options which may increase acceptability to patients, improve patient satisfaction and compliance. However, still many questions remain unanswered. Cancer patients pose unique challenges for anticoagulation in VTE. Many factors need to be considered before choosing the optimal antithrombotic approach. These challenges revolve around active cancer disease, chemotherapy related thrombocytopenia, brain metastases, venous catheter associated thrombosis, low-weight patients, poor oral intake, liver and renal insufficiency, gastrointestinal and urothelial cancers. The management of thrombosis in cancer patients is truly an example of personalised medicine. Addressing these issues in a longitudinal, multidisciplinary cancer associated clinic (CAT Clinic) may be a practical solution.

Treatment of cancer associated thrombosis (CAT)

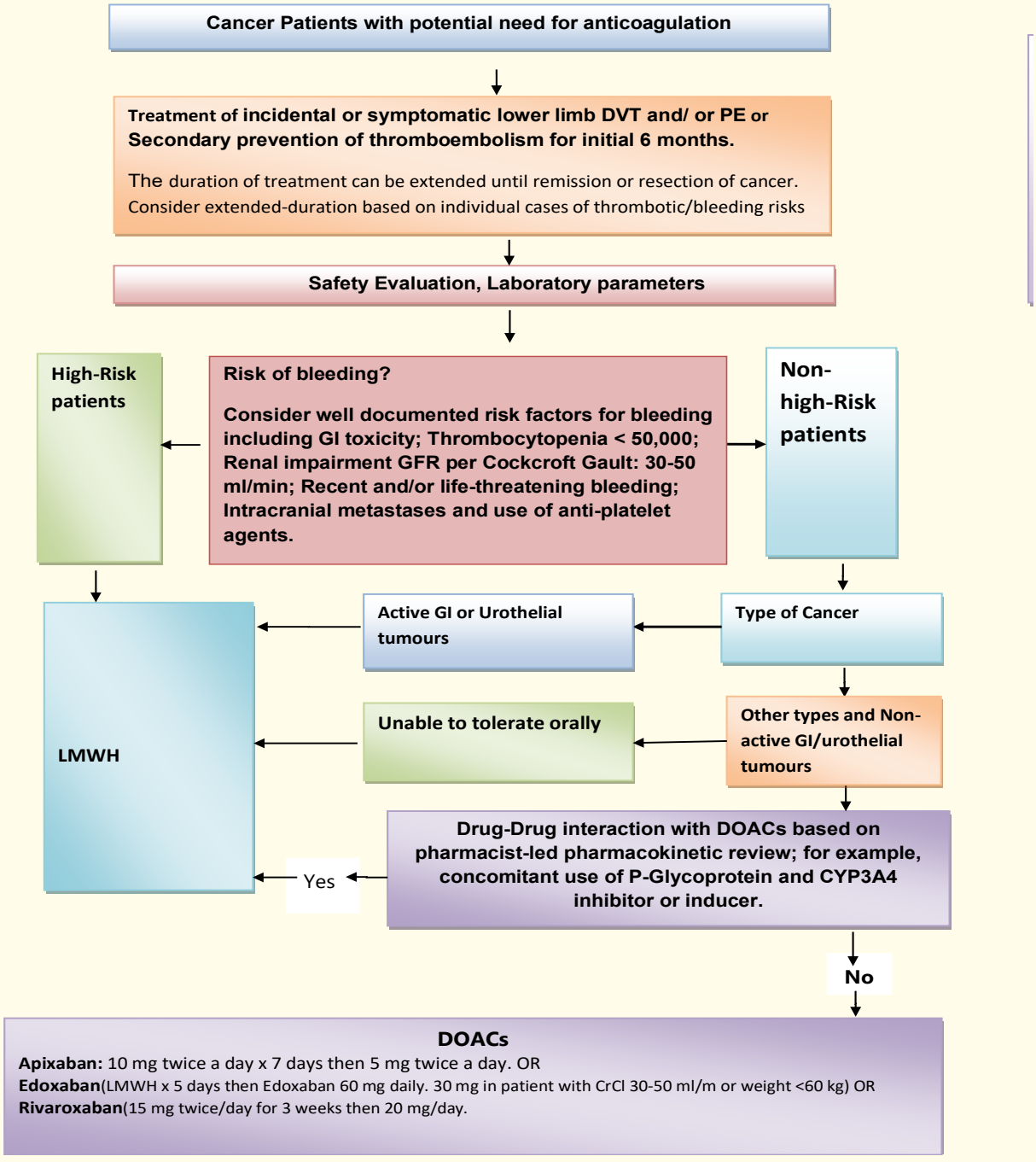

Figure 1: Treatment of Cancer Associated Thrombosis (CAT).

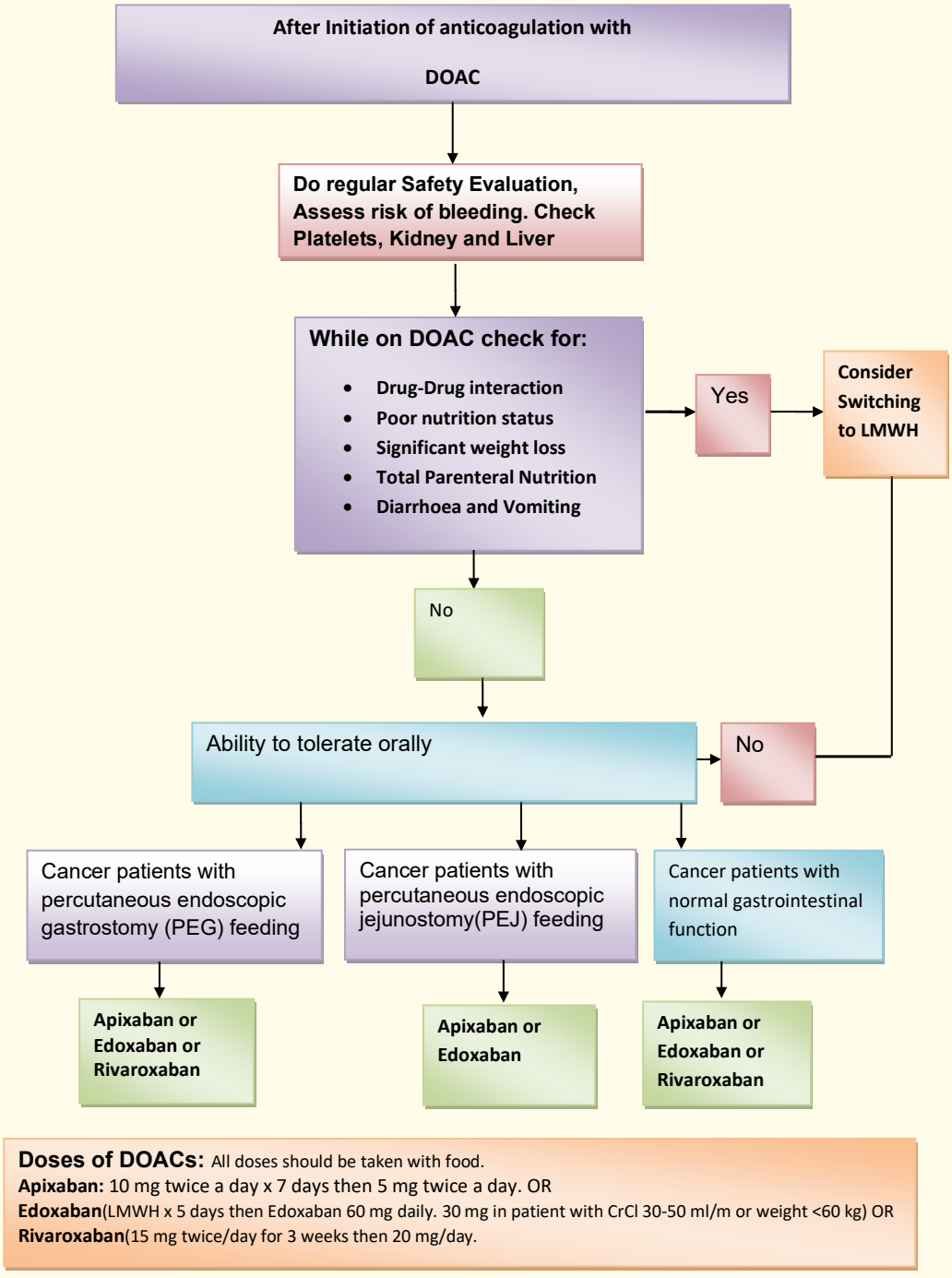

Figure 2: Treatment of Cancer Associated Thrombosis (CAT).

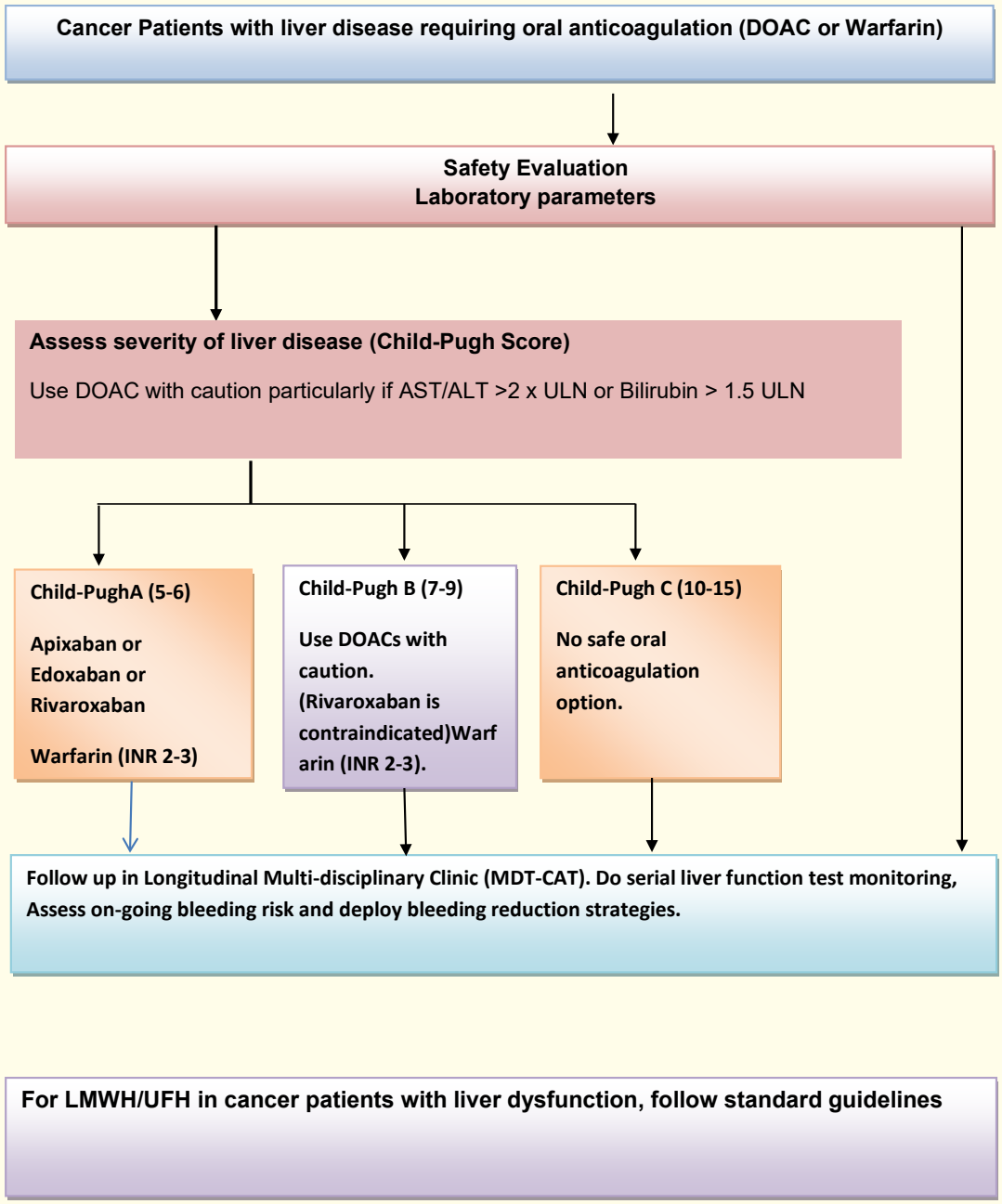

Figure 3: Dose modification of DOACs in Hepatic Insufficiency.

Dose modification of DOACs in Renal Insufficiency(Table)

Cr Cl (Use Cockroft Gault Creatinine Clearance instead of eGFR).	**Rivaroxaban**	**Edoxaban** (Needs 5 days of parenteral anticoagulation)	**Apixaban**
Cr Cl > 90 ml/min	15 mg twice a day for 21 days, and then 20 mg daily thereafter	60 mg daily. But for patients weighing <60 kg 30 mg once daily.	10 mg twice a day x 7 days then 5 mg twice a day
Cr Cl> 50-90 ml/min		Same as above	Same as above
Cr Cl> 30-50 ml/min	20 mg daily	30 mg daily	Same as above
Cr Cl>15-30 ml/min	20 mg daily but consider 15 mg OD if bleeding risk is high	Not recommended	Use with caution
Cr Cl< 15 ml/min	Not recommended	Not recommended	Not recommended

For LMWH/UFH in cancer patients with renal impairment, follow standard guidelines.

Figure 4: Dose modification of DOACs in Renal Insufficiency.

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