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Infrequent transition to direct oral anticoagulants in patients with cancer

Nina Nouhravesh[1], Caroline Sindet-Pedersen[1], Maja Hellfritzsch[2], Ali Akil Al-Alak[1], Thomas Kümler[1, 3], Erik L. Grove[2, 4] & Morten Lamberts[1]

1) Department of Cardiology, Copenhagen University Hospital – Herlev and Gentofte Hospital, 2) Department of Cardiology, Aarhus University Hospital, 3) Steno Diabetes Center Copenhagen, 4) Department of Clinical Medicine, Aarhus University, Denmark

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ABSTRACT

INTRODUCTION. Pharmacokinetic drug-drug interactions (DDIs) are challenging aspects of direct oral anticoagulant (DOAC) therapy in patients with cancer. We evaluated the prevalence of potential DOAC/antineoplastic agent DDIs and the one-year cumulative incidence of switching from low-molecular-weight heparin (LMWH) to a DOAC in patients with cancer.

METHODS. Patients with cancer and an indication of LMWH were included from Herlev and Gentofte Hospital, Denmark, in the 2014-2019 period. Follow-up was initiated when the first dose of LMWH was dispensed. Data were obtained from electronic medical records. One-year cumulative incidence of switching from LMWH to DOAC was estimated using the Aalen-Johansen estimator. Potential DDIs were evaluated using a report from the European Heart Rhythm Association (EHRA) and a review by Hellfritzsch et al.

RESULTS. A total of 161 patients were included with a median age of 70.8 (interquartile range: 64.2-76.1) years. The one-year cumulative incidence of switching from LMWH to DOAC was 32% (95% confidence intervals: 21-43%) in patients eligible for DOACs. Using the EHRA report, a total of 24% of antineoplastic agents were not identified. This percentage decreased to 8% using data from Hellfritzsch et al.

CONCLUSIONS. In patients with cancer, the one-year cumulative incidence of switching from LMWH to DOAC was < 35% in patients eligible for DOAC, revealing a potential for improved anticoagulant treatment. Furthermore, contemporary data elaborated on potential DDIs between DOACs/antineoplastic agents.

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TRIAL REGISTRATION. Not relevant.

Cancer-associated thrombosis (CAT) is an increasingly frequent complication to cancer and antineoplastic therapy, accounting for nearly 30% of all incident cases of venous thromboembolisms (VTE) [1, 2] . In recent years, data from randomised clinical trials have provided evidence for the efficacy of direct oral anticoagulants (DOAC) in patients with CAT [2-5]. Nonetheless, treatment with DOACs for patients with CAT has not yet been implemented routinely in daily clinical practice. Likely explanations include the patient-related costs associated with DOAC treatment, concerns about cancer-specific bleeding risks and potential pharmacokinetic drug-drug interactions (DDIs) between DOACs and antineoplastic agents. DDIs have proven particularly challenging due to a lack of data and specific guidance. For many years, the European Heart Rhythm Association (EHRA) have provided some guidance to assess DDIs with the most common antineoplastic drugs [6, 7]. However, because of

the rapid development of new antineoplastic drugs, these guidelines have rarely been exhaustive. In 2023, Hellfritzsch et al. elaborated significantly on this topic in a comprehensive review assessing a total of 400 specific "DOAC-antineoplastic agents"-pairs for potentially clinically relevant DDIs [8]. Hellfritzsch et al. provided a generic framework for evaluation of the interaction potential for any combination of antineoplastic agents with DOACs, which was endorsed in the newly published Danish Medicines Council guidelines on pharmacotherapy for patients with venous thrombosis and cancer [9].

We aimed to evaluate the one-year cumulative incidence of switching from low-molecular-weight heparin (LMWH) to DOAC in patients eligible for treatment with DOAC and to assess the potential gain from a reclassification of the pharmacokinetic DDIs according to the recent recommendations by Hellfritzsch et al.

METHODS

Data sources and patient population

We included patients with cancer who collected LMWH from the Thrombosis Unit at Herlev and Gentofte Hospital, Denmark from 2014 through 2019. The indications for LMWH were pulmonary embolism, deep venous thrombosis, atrial fibrillation and splanchnic thromboses. The indication for and initiation of LMWH were devised by the Department of Oncology at Herlev and Gentofte Hospital, which subsequently referred the patients to the Thrombosis Unit to collect future doses free of charge and perform anticoagulant treatment follow-up. Medical records were reviewed to obtain the required data.

Patients were included on the day they collected their first dose of LMWH at the Thrombosis Unit and were followed until switching to DOAC, discontinuation of an antineoplastic regimen, or death – whichever came first. Patients who were not eligible for DOAC treatment based on a high bleeding risk (previous gastrointestinal or intracerebral haemorrhage (three months), active bleeding, central nervous system metastases, low platelet count ($< 50 \times 10^9$/l) and estimated glomerular filtration rate (eGFR) < 30) were excluded, as were patients with mechanic heart valves [6].

Drug-drug interaction

Potential pharmacokinetic DDIs between antineoplastic agents and DOACs were assessed using the 2018 EHRA Practical Guide on DOAC use [7]. This assessment was then repeated using the framework and data provided by the 2023 review by Hellfritzsch et al. [8].

The assessment of potential DDIs between ongoing antineoplastic therapy and DOACs was performed on the day LMWH was collected. Drug combinations were classified as "green", "yellow" or "red", indicating no DDI, potential DDI or significant DDI, respectively. If the antineoplastic agent was not identified in the reports, it was classified as "antineoplastic agent not identified", and a DDI was classified as "unclassifiable" if unknown. A DDI assessment was made between each antineoplastic agent and the three DOACs (apixaban, edoxaban and rivaroxaban). The total DDI assessment for each patient was characterised according to the lowest DDI degree; hence, if a DDI was green for one DOAC, but red for the others, the overall assessment was green. For DDIs classified as "red", we further retrieved information on adverse events including re-thrombosis, major bleedings, clinically relevant non-major bleedings, minor bleedings and stroke.

Outcome

The primary outcome was one-year cumulative incidence of switching from LMWH to DOAC among patients eligible for DOAC. Patients were followed for one year from the inclusion date. The secondary outcome was to assess a potential gain from a reclassification of the drug combinations according to the review by Hellfritzsch et

al.

Baseline characteristics

Baseline characteristics were described at the time of inclusion for the entire cohort and stratified by cancer type, i.e. kidney and urinary tract cancer, gastrointestinal cancer and a group comprised of other cancers. The following baseline characteristics were reported: age, sex, alcohol consumption, smoking, indication of anticoagulant therapy; and comorbidities including ischaemic stroke, chronic obstructive pulmonary disease, hypertension, peripheral arterial disease, heart failure, acute myocardial infarction, chronic kidney disease, previous thromboembolism, and hypercholesterolaemia.

Statistical analysis

Baseline characteristics are presented as frequencies and percentages for dichotomous variables and as median with interquartile range for continuous variables.

The Aalen-Johansen estimator was used to estimate the crude one-year cumulative incidence of switching from LMWH to DOAC. Competing risk of death was accounted for [10]. The pharmacokinetic DDIs were reported in pie charts as counts and percentages according to the assessments made based on the reports from the EHRA and Hellfritzsch et al., respectively.

Supplemental analyses

To assess the distribution of DDIs only in patients treated with an antineoplastic agent, we excluded patients who were not receiving active antineoplastic treatment at inclusion. The assessment was performed as previously described.

Ethics

The study was approved by the legal department at Herlev and Gentofte Hospital including the directors, and chief physicians at the Department of Cardiology (Ref. 19085455). Ethical approval for retrospective register-based analysis is not required in Denmark

Trial registration: not relevant.

RESULTS

Cohort characteristics

The study included 161 patients with a cancer diagnosis treated with LMWH from 2014 through 2019. Among these, the majority of patients had a kidney/urinary tract cancer (31.6%) or a gastrointestinal cancer (40.4%). The median age was 70.8 (interquartile range: 64.2-76.1) years and 49.7% were males. The most frequent indication for LMWH was pulmonary embolism (39.6%) (**Table 1**). In total, 35 patients were excluded due to a high bleeding risk or mechanic heart valve (Supplementary Figure 1).

TABLE 1 Baseline characteristics.

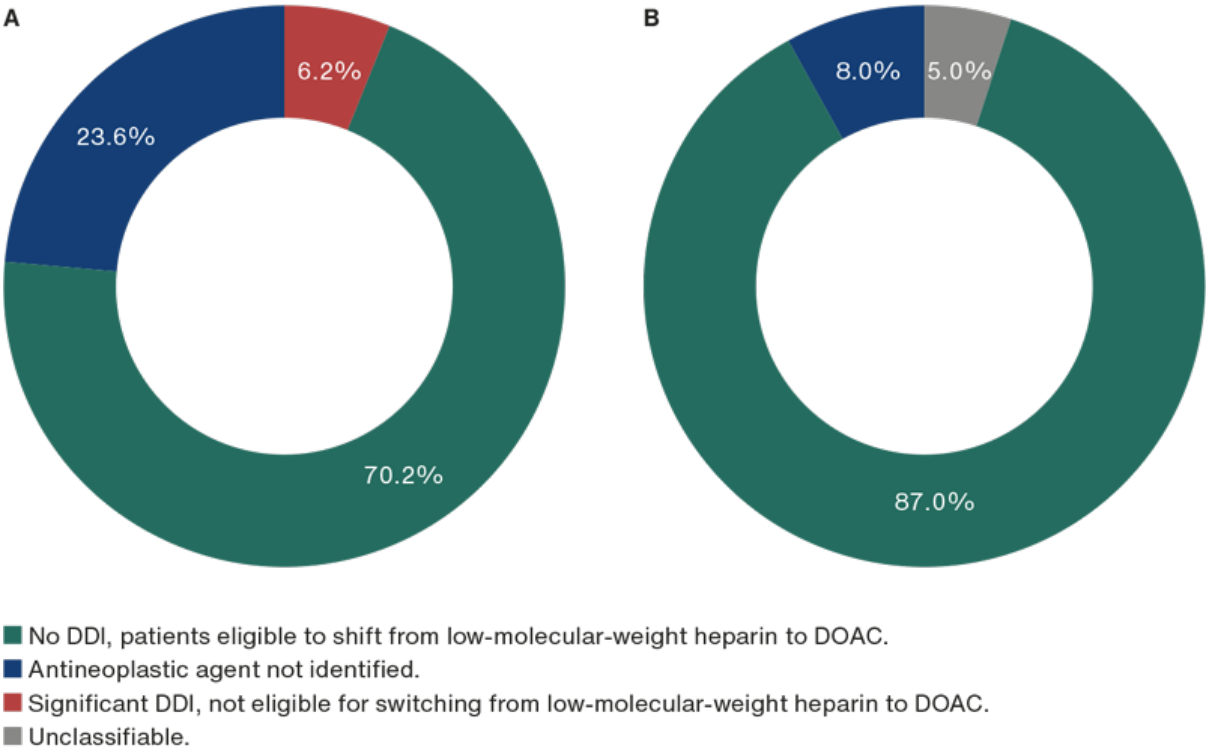
	Kidney and urinary tract cancer (n = 51)	GI cancer (n = 65)	Other cancers (n = 45)	Total (N = 161)
Age, median (IQR), yrs	72.3 (64.8-76.0)	69.3 (64.7-74.3)	72.5 (60.6-77.3)	70.8 (64.2-76.1)
Males, n (%)	29 (56.9)	32 (49.2)	19 (42.2)	80 (49.7)
Alcohol consumption, n (%)				
> 2 units/day	7 (13.7)	6 (9.2)	< 3	-
< 1 unit/day	31 (60.8)	46 (70.8)	27 (60.0)	104 (64.6)
1-2 units/day	11 (21.6)	12 (18.5)	14 (31.1)	37 (23.0)
Smoking, n (%)				
Current smoker	9 (17.6)	8 (12.3)	6 (13.6)	23 (14.4)
Former smoker	18 (35.3)	35 (53.8)	20 (45.5)	73 (45.6)
Never smoked	24 (47.1)	22 (33.8)	18 (40.9)	64 (40.0)
LMWH indication, n (%)				
Pulmonary embolism	20 (40.0)	22 (34.4)	21 (46.7)	63 (39.6)
Deep venous thrombosis	16 (32.0)	15 (23.4)	14 (31.1)	45 (28.3)
Atrial fibrillation	10 (20.2)	11 (17.2)	10 (20.0)	31 (19.5)
Splanchnic thrombosis	< 3 (6.0)	14 (21.9)	< 3	-
Comorbidities, n (%)				
Ischaemic stroke	4 (7.8)	10 (15.4)	6 (13.3)	20 (12.4)
Hypertension	23 (45.1)	29 (44.6)	18 (40.0)	70 (43.5)
Chronic obstructive pulmonary disease	7 (13.7)	4 (6.2)	4 (8.9)	15 (9.3)
Peripheral arterial disease	3 (5.9)	< 3	4 (8.9)	-
Heart failure	6 (11.8)	< 3	4 (8.9)	-
Acute myocardial infarction	6 (11.8)	< 3	< 3	-
Previous venous thromboembolism	9 (17.6)	9 (13.8)	7 (15.6)	25 (15.4)
Chronic kidney disease	7 (13.7)	< 3	< 3	-
Hypercholesterolaemia	8 (15.7)	15 (23.1)	10 (22.2)	33 (20.5)

GI = gastrointestinal; IQR = interquartile range; LMWH = low-molecular-weight heparin.

Drug-drug interaction stratified by the European Heart Rhythm Association and Hellfritzsch et al.

No DDIs (green) were found in 70.2% of patients included when using the EHRA report. This included patients treated with antineoplastic agents but also patients in palliative care receiving no active antineoplastic treatment. Furthermore, 6.2% had a DDI categorised as red and one patient experienced a minor bleeding that did not result in hospitalisation (see details on specific antineoplastic agent in Supplemental Table 1). In 23.6% of patients, the antineoplastic agent was not identified (**Figure 1**). No DDIs were classified as yellow.

FIGURE 1 Distribution of drug-drug interaction (DDI) between the antineoplastic agent and direct oral anticoagulant (DOAC) classified by the European Heart Rhythm Association report (**A**) and by Hellfritzsch et al. (**B**) [7, 8].

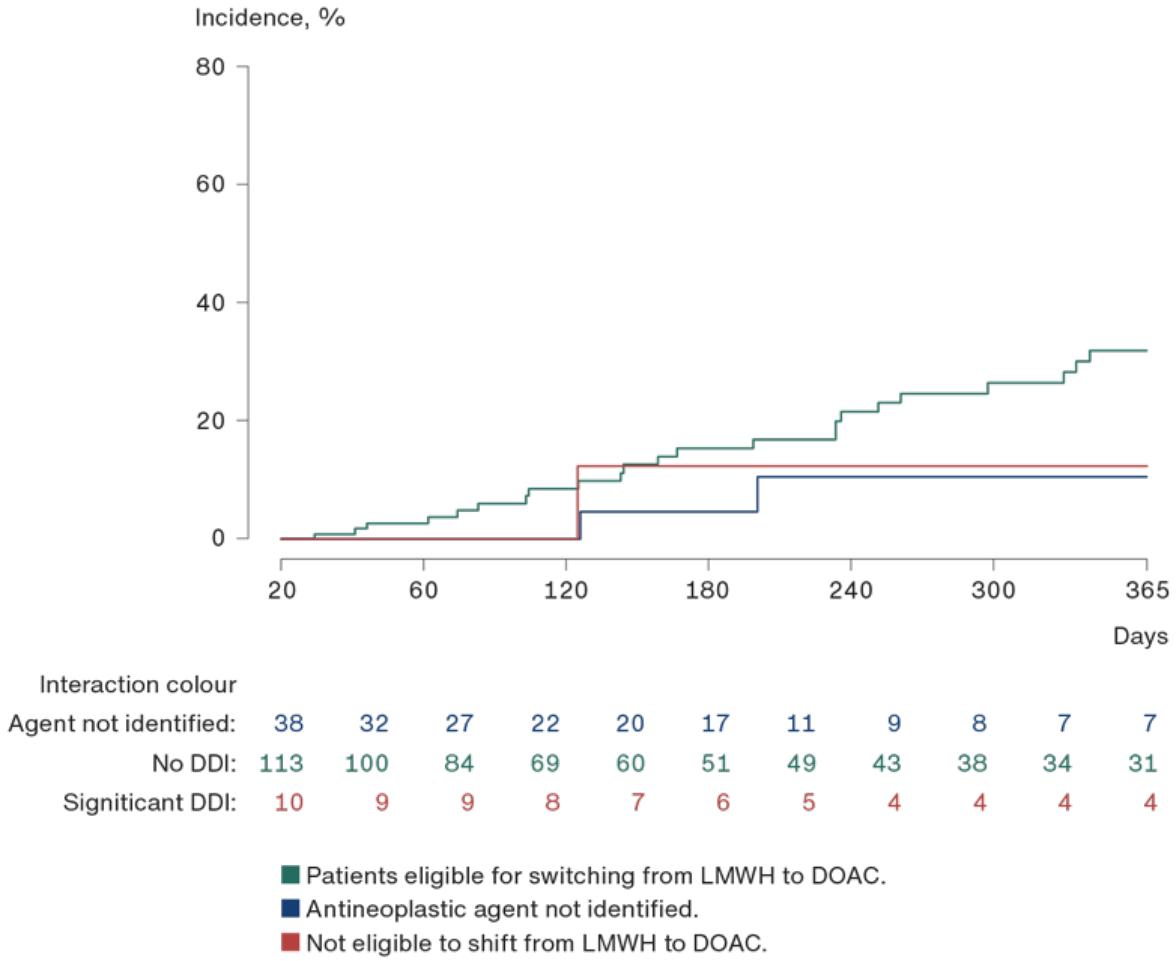


When reclassifying drug combinations according to Hellfritzsch et al., we found no potential DDI (green) in 87.0% of patients. In 8.0% of patients, the antineoplastic drug was not identified; and in 5.0% of patients, the potential DDI was unclassifiable.

One-year cumulative incidence of switching from low-molecular-weight heparin to direct oral anticoagulants

The one-year cumulative incidence of switching from LMWH to DOAC was 32.0% (95% confidence interval (CI): 20.8-43.1%) in patients where no potential interaction was found (green curve), 12.5% (95% CI: 0.0-35.4%) in patients with a potentially significant DDI (red curve) and 10.7% (95% CI: 0.0-24.9%) in patients where the antineoplastic agent was not identified (blue curve) (**Figure 2**).

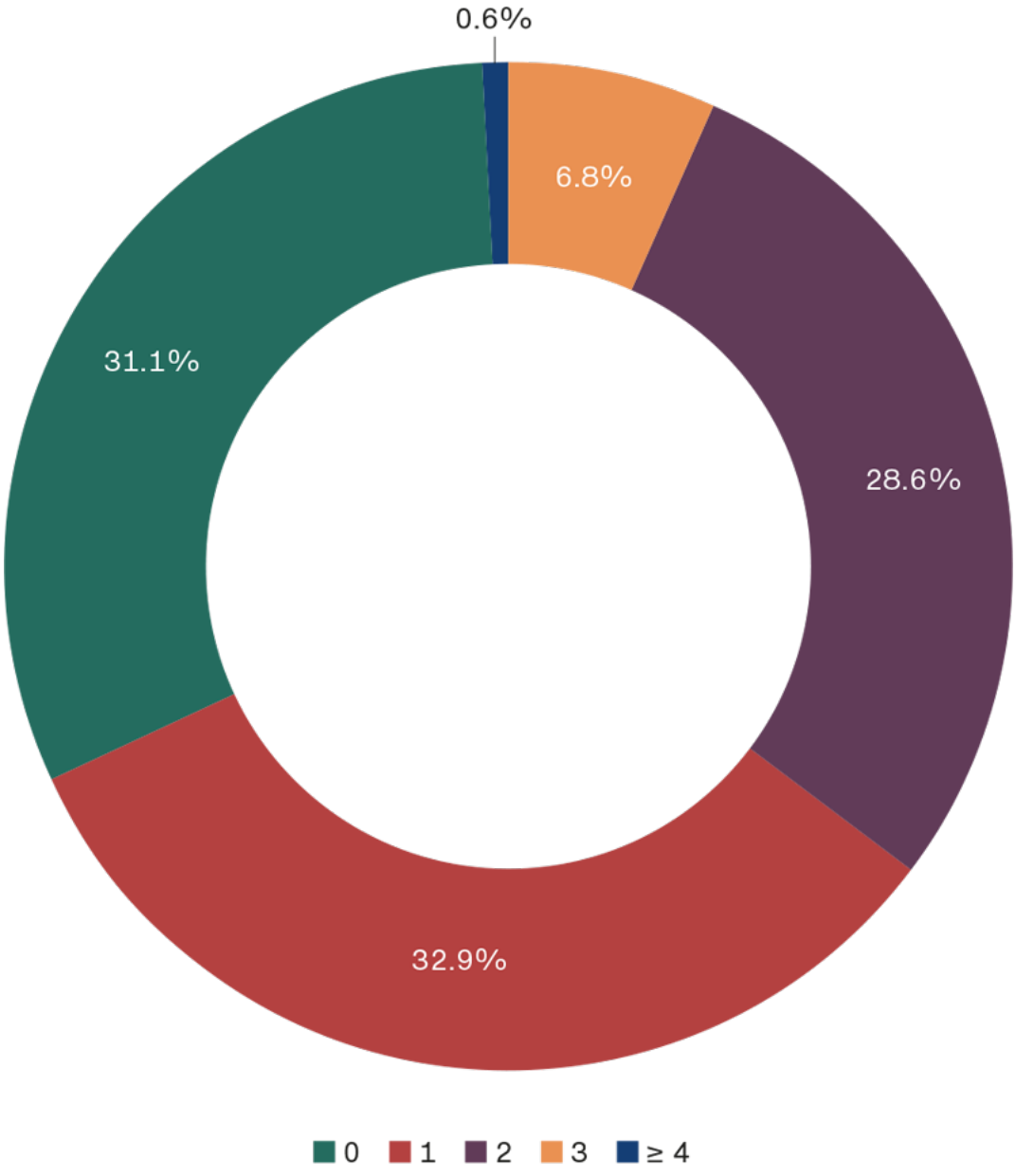
FIGURE 2 One-year cumulative incidence of switching from low-molecular-weight heparin (LMWH) to direct oral anticoagulant (DOAC) stratified by drug-drug interactions (DDI) in patients with cancer-associated thrombosis. Competing risk of death and switching to another antineoplastic regimen were taken into account.



Overview of the number of antineoplastic agents

No active antineoplastic treatment was administered in 31.1% of patients, 32.9% received one type of antineoplastic agent and 28.6% received two types of antineoplastic agents. Finally, approx. 7% received more than three types of antineoplastic agents (**Figure 3**).

FIGURE 3 Distribution of the number of antineoplastic agents used in patients with cancer-associated thrombosis.



Supplemental analyses

The analyses included 111 patients. Using the EHRA report to evaluate DDIs, 56.8% of patients had no potential DDI (green) and 9.0% had a significant DDI (red); and in 34.2% of patients, the antineoplastic agent was not identified (blue). Reclassifying drug combinations according to Hellfritzsch et al. revealed no DDI (green) in 81.1% and unclassifiable DDI (grey) in 7.2%; and in 11.7% of patients, the antineoplastic drug was not identified (Supplemental Figure 2).

DISCUSSION

In a single cardio-oncology centre, we included a total of 197 patients among whom 36 were excluded due to ineligibility for DOAC treatment. Approximately 24% of potential DDIs could not be assessed by the frequently used report from EHRA; when reclassifying DDIs according to Hellfritzsch et al., this proportion was reduced to approximately 8%. Surprisingly, among patients eligible for DOAC treatment, the one-year cumulative incidence of switching from LMWH to DOAC was < 35%.

Until recently, the exclusion of patients with cancer from DOAC trials left LMWH as first-line treatment [11-14], but emerging evidence from large randomised trials has proved similar or reduced incidence of recurrent VTE in patients treated with DOAC and patients treated with LMWH, without a significant increase in major bleedings [2-5]. As hypothesised recently and now shown in this study, physicians remain hesitant to prescribe DOAC to patients with cancer, even in the absence of a high bleeding risk and pharmacokinetic DDIs [8]. The underlying causes for this are speculative. However, the complexity of this patient population in terms of cancer-specific bleedings risks and pharmacokinetic DDIs may be difficult to evaluate in a busy clinical setting. The assessment of a potential switch from LMWH to DOAC is time consuming; and, as shown by the data presented herein, this patient population often receives multiple antineoplastic agents with a need for several individual risk assessments. In addition, such assessments are frequently required as antineoplastic regimens tend to change.

Furthermore, practical guidelines and reports published by medical societies have rarely been exhaustive, posing yet another challenge to the assessing physician [6, 7]. In conjunction, these challenges may potentially predispose physicians towards avoiding DOAC treatment in patients with CAT. A recent review by Hellfritzsch et al. assessed 400 DOAC/antineoplastic agent combinations. When applying these data to our patient population, we found that nearly 90% of patients were, at least from a DDI perspective, eligible for treatment with at least one type of DOAC [8]. These findings are thought provoking in the sense that LMWH generates significant healthcare costs and burdens patients due to the need for self-injections. Of note, a study by Noble et al. found efficacy and safety to be favoured over convenience of administration [15]. However, randomised clinical trials comparing DOAC with LMWH demonstrated efficacy and safety [2-5]. Furthermore, several studies of quality of life have favoured DOAC [5, 16]. The combination of these findings points toward an anticoagulation strategy guided by shared clinical decision-making considering patient preferences; a notion also recognised by the 2022 Cardio-Oncology Guidelines from the European Society of Cardiology [17].

Limitations

This study was limited by its design as a single-centre study. However, the Thrombosis Unit at Herlev and Gentofte hospital manages all patients selected for LMWH treatment at this hospital and is one of the major cardio-oncology sites in Denmark. The study population was included from 2014 through 2019, with clinical decision-making reflecting former practice. New antineoplastic agents and new indications for their use challenge analyses like the current one due to their historical nature. Moreover, in Denmark LMWH is free of charge for patients and dispensed by the hospital, whereas DOACs are purchased by patients at local pharmacies and only partly reimbursed. This notion may ultimately influence both the physician's and the patient's choice of pharmacotherapy.

Clinical implications

Managing patients with CAT is challenging due to the complications inherent to their cancer disease and especially the antineoplastic agents used. The current landscape provides comprehensive data on the use of DOACs in patients with CAT and is optimistic towards the use of DOAC in this setting. Data from this study presented the experience from a dedicated thrombosis unit at a cardio-oncology centre, highlighting the proportion of patients in whom DOACs can be used.

Perspectives

Clinical practice is often affected by local and regional differences; hence, nation-wide real-life studies addressing use of DOACs in patients with cancer and risk of DDIs are highly relevant, especially in the current landscape in which the Danish Medicines Council report has introduced national recommendations on oral anticoagulants for patients with CAT [9]. Moreover, the rapid development of new antineoplastic agents and new indications for their use calls upon prospective data collection, which will allow insights into contemporary data [18].

CONCLUSIONS

This study demonstrated a potential for improved anticoagulant treatment with DOACs, reporting a one-year cumulative incidence of switching from LMWH to DOAC that was lower than 35% in patients eligible for switching. We also found that the newly published review by Hellfritzsch et al. enabled classification of approximately 90% of potential DDIs between antineoplastic agents and DOACs, which is considerably higher than what was possible according to previous medical society recommendations.

Correspondence *Nina Nouhravesh*. E-mail: nina.nouhravesh@regionh.dk

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