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REVIEW ARTICLE

Pharmacokinetic drug–drug interactions with direct anticoagulants in the management of cancer-associated thrombosis

Lorenz Van der Linden[1,2] | Thomas Vanassche[3,4] | Eric Van Cutsem[5] | Lucas Van Aelst[3,4] | Peter Verhamme[3,4]

[1]Hospital Pharmacy Department, University Hospitals Leuven, Leuven, Belgium

[2]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

[3]Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

[4]Department of Cardiology, University Hospitals Leuven, Leuven, Belgium

[5]Department of Digestive Oncology, University Hospitals Leuven and KU Leuven, Leuven, Belgium

Correspondence
Lorenz Van der Linden, Hospital Pharmacy Department, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.
Email: lorenz.vanderlinden@uzleuven.be

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Drug–drug interactions (DDIs) are common in cancer management and complicate the choice of anticoagulation in cancer-associated thrombosis. Cancer confers an increased risk of thrombotic events. Also, more bleeding events are observed in those who receive anticoagulation compared to those without cancer. In the treatment of cancer-associated thrombosis, direct oral anticoagulants (DOACs) have been found to be at least as effective as low-molecular weight heparins, which became the standard of care after several trials demonstrated superiority over vitamin K antagonists. Non-inferiority compared to low-molecular weight heparins has been shown for rivaroxaban, edoxaban and apixaban with a signal of fewer recurrent thrombotic events, albeit with an increase in bleeding events. Yet, potentially major pharmacokinetic drug–drug interactions have been identified as a reason to withhold DOACs and to rather choose an alternative. Practical guidance on what constitutes a major pharmacokinetic interaction and/or how to deal with these interactions in clinical practice is limited. Hence, here we have provided a framework to allow clinicians to better deal with pharmacokinetic drug–drug interactions between DOACs and cancer therapies in the management of cancer-associated thrombosis. In this review we have discussed the current literature, how the pharmacokinetic profile links to the label information on DDI, and have provided a practical proposal, applied to a clinical case.

KEYWORDS
anticoagulation, cancer, cancer-associated thrombosis, direct oral anticoagulants, drug–drug interactions

1 | INTRODUCTION

Cancer patients are at increased risk for thromboembolism.[1] Various factors explain the increased susceptibility to clots, including the type, location and staging of the cancer itself. Other determinants such as surgical interventions, indwelling catheters and cancer therapies also play a major role. Cancer-associated thrombosis (CAT) is a prevalent finding in cancer patients.[2] It is the second most common cause of death in cancer patients, following cancer-related death by a large margin.[3] Importantly, the risk of an incidental venous thrombo-embolic event (VTE) is higher in cancer patients than in those without. Moreover, higher risks of both recurrent VTE and bleeding events are observed in cancer patients who receive anticoagulation compared to the general population.[4]

Historically, CAT was treated with the vitamin K antagonist (VKA) warfarin. This treatment paradigm altered a first time after trials comparing VKA with low-molecular weight heparins (LMWH), among which the CLOT trial was the first.[5] A clear benefit was observed in favour of LMWH versus VKA. LMWH-treated patients incurred a similar major bleeding risk, yet LMWH provided superior thrombotic protection compared to VKA. As a result, LMWH have been the standard of care in the

management of CAT up until recently.[6] A second shift in antithrombotic management occurred when direct oral anticoagulants (DOACs) were compared to LMWH. DOACs have proven to be at least as effective as LMWH.[2] Several randomized controlled trials (RCTs) have been performed in this domain, of which the two largest were HOKUSAI VTE CANCER and CARAVAGGIO.[7,8] Currently, we have clinical data on **rivaroxaban**, **edoxaban** and **apixaban** in CAT management. Briefly, non-inferiority was shown in these RCTs with an important signal of fewer recurrent VTE in favour of DOACs with a cost of more bleeding events, mostly explained by a higher risk of gastrointestinal bleeding in patients suffering from gastrointestinal cancers.[9]

Consequently, current guidelines recommend the use of any of the three tested DOACs in the management of CAT, in the absence of contraindications. Multiple guidelines refer to major drug–drug interactions (DDI) as a reason to withhold DOACs and to rather choose an LMWH as an alternative.[10,11] Yet, what a major DDI actually entails has largely remained undefined. Here we would like to provide a framework for clinicians to better deal with weak, moderate and strong interactions between DOACs and cancer therapies in the management of CAT.

To this end we briefly discuss the relevant pharmacokinetics (PK) of DOACs and how the PK profile can be linked to the drug label information on DDI, ending with a practical proposal, which we have applied to a clinical case.

2 | PHARMACOKINETICS OF DOACS USED IN CAT

Randomized controlled trial (RCT) data have been collected in the management of CAT for three DOACs. Accordingly, we will limit the discussion here to the following agents: apixaban, rivaroxaban and edoxaban.[7,8,12] These DOACs concern direct-acting factor Xa inhibitors, with a rapid time to maximal plasma concentration and a rather short half-life of approximately 2, 5 and 11 h, respectively. They are selective for **factor Xa**, reach steady state exposure in about 2 days and after discontinuation, all anticoagulant activity has dissipated in approximately 2 days as well. From a PK point of view, they thus resemble their parenteral comparators, LMWH, more so than the oral VKA.

These three factor Xa inhibitors are orally available, are partially metabolized hepatically and are partially eliminated unchanged by the kidney to differing degrees, from 27% for apixaban to 35% and 50% for rivaroxaban and edoxaban, respectively.[13,14] In contrast to VKAs, DOACs are not characterized by a narrow therapeutic index. For all DOACs, a broad range of on-therapy plasma values has been observed in the landmark trials, albeit based on limited sampling and without measurements at the time of a clinical outcome. Moreover, a partial disconnect between exposure and outcome has been observed, explained largely by patient characteristics, which influence outcome as well.[15–18] Characteristics of relevant DOACs and LMWHs are summarized in Table 1.

Briefly, DOACs have a much lower PK DDI potential compared to VKA. Yet, the risk is not fully absent.[20] As a rule, more DDIs will occur with DOACs than with LMWHs. DOACs are, again to differing degrees, substrate to one or more of the following enzyme systems (**cytochrome P450** [CYP], **P-glycoprotein** [P-gp], **breast cancer resistance protein** [BCRP], **organic anion transporting polypeptides** [OATP]).[13,14] These enzyme systems impact the disposition and/or metabolization (= breakdown) of the DOACs, and hence influence the effective plasma concentration at the pharmacological end target, factor Xa. Only CYP and P-gp-mediated interactions will be discussed

TABLE 1 Summary of the pharmacology of common anticoagulants used in cancer-associated thrombosis.[13,14,19]

	Apixaban	Edoxaban	Rivaroxaban	Dalteparin, tinzaparin
Type	DOAC	DOAC	DOAC	LMWH
Target	Factor Xa	Factor Xa	Factor Xa	Factor Xa, more than thrombin, via AT-III
T_{max}	3–4 h	1–2 h	2–4 h	2–3 h
$T_{1/2}$	~12 h	~8–10 h	5–9 h; older adults: 11–13 h Summarized: 5–13 h	3–4 h (of anti-Xa activity)
F (%)	~50%, oral	~62%, oral	90–100% (food), oral	>90%, s.c.
Renal elimination (unchanged in urine)	27%	50%	35%	Mainly/principal
CYP	15% CYP3A4/5 6% CYP1A2, CYP2J2 Minor contributions of CYP2C18, CYP2C9, CYP2C19	<4% CYP3A4/5	18% CYP3A4/5 14% CYP2J2	/
P-gp	Substrate	Substrate	Substrate	/
BCRP	Substrate	No substrate	Substrate	/
OATP	No substrate	No substrate	Substrate of OAT3	/

Abbreviations: AT-III, antithrombin; BCRP, breast cancer resistance protein; CYP, cytochrome P450; DOAC, direct oral anticoagulant; LMWH, low-molecular weight heparin; OATP, organic anion-transporter poly-protein; P-gp, P-glycoprotein; s.c., subcutaneously.

here, as their impact can be potentially clinically relevant, compared to those pertaining to DOAC and BCRP or OATP.[14]

Apixaban and rivaroxaban are substrate to both **CYP3A4** and P-gp. As a result, dual, strong inhibitors and inducers of the two enzyme systems are expected to significantly impact exposure of apixaban and rivaroxaban. In contrast, edoxaban is not a major CYP substrate. Only P-gp has been found to play a substantial role in its exposure. As a result, strong inhibitors and inducers of P-gp are expected to have a significant impact on edoxaban's plasma concentrations; CYP3A4 does not play a relevant role in edoxaban's exposure.[13,14,20]

3 | A PK-BASED FRAMEWORK

Both pharmacodynamic (PD) as well as PK interactions are mentioned in the respective package inserts of the three selected DOACs.[21–23] PD interactions occur when a culprit drug impacts the pharmacological effect of the victim drug, e.g., when combining a non-steroidal anti-inflammatory drug with a DOAC or a LMWH, the bleeding risk will increase. PD interactions impact all oral anticoagulants, regardless of the mechanism of action (i.e., VKA, DOAC and LMWH). Here, we will focus on PK DDI. Hereby, the culprit drug will alter the exposure, mostly defined as the area-under-the curve (AUC) of the time–concentration curve and/or the C_{max}, of the victim drug.

The European package inserts provide both direct and indirect guidance on how to apply the PK profiles and subsequently link them to potentially clinically relevant DDIs. Relevant information has been extracted from the inserts and summarized in Table 2. For apixaban and rivaroxaban, dual strong inhibitors should be avoided. For edoxaban, the concomitant use of strong P-gp inhibitors, including others than those investigated in RCTs (i.e., **cyclosporine**, **dronedarone**, **erythromycin** and **ketoconazole**), is discouraged.

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued guidance on how to define the strength of DDI and how to deal with them.[24,25] The thresholds have been translated in the respective package inserts. A strong DDI is defined as one that results in an at least five-fold change of the exposure (i.e., the AUC) of the victim drug. Moderate and weak DDIs impact the AUC by a factor of 2–5 and <2, respectively. This framework also depends on the therapeutic index of the victim drug, where a wide therapeutic window would imply a larger capacity to tolerate deviating plasma values, such as is likely the case with DOACs.[26]

For DOACs, we recommend using a threshold of AUC*2 or AUC/2 as an actionable parameter to evaluate DDIs. First, we prefer using AUC over C_{max}, in part owing to the former's long-standing use in DDI studies. There, the AUC-based framework to interpret the strength of a DDI was initially moulded onto midazolam as the essential CYP3A4 probe, after which its scope was broadened and was adopted subsequently by the FDA and EMA.[26] Also, while largely similar, the AUC was more sensitive than the C_{max} in detecting the impact or a culprit agent such as ketoconazole on the selected DOACs (i.e., $AUC_{ratio} > C_{max,ratio}$).[27–29] Second, assuming linear PK within the used dose range, a doubling of the dose will result in a doubling of the

TABLE 2 Selected information on drug–drug interactions from the Summaries of Product Characteristics of apixaban, rivaroxaban and edoxaban.

	Apixaban	Edoxaban	Rivaroxaban
Dose adjustments (AF, VTE) owing to concomitant treatments	None	Use 30 mg instead of 60 mg in the case of concomitant treatment with cyclosporin, dronedarone, erythromycin or oral ketoconazole.	None
To be avoided, use not recommended	Strong combined inhibitors of CYP3A4 and P-GP: oral ketoconazole, itraconazole, voriconazole, posaconazole, HIV-protease inhibitors (e.g., ritonavir) Inducers such as rifampicin, phenytoin, phenobarbital, St John's wort, carbamazepine if the patient is receiving apixaban for management of acute VTE (DVT/PE).	Strong P-gp inhibitors, other than cyclosporin, dronedarone, erythromycin or ketoconazole (not investigated)	Strong combined inhibitors of CYP3A4 and P-gp: oral ketoconazole, itraconazole, voriconazole, posaconazole, HIV-protease inhibitors (e.g., ritonavir) Inducers such as rifampicin, phenytoin, phenobarbital, St John's wort, carbamazepine, unless the patient can be monitored closely.
Use with caution	Inducers such as rifampicin, phenytoin, phenobarbital, St John's wort, carbamazepine in other indications than acute VTE treatment	Inducers such as rifampicin, phenytoin, phenobarbital, St John's wort, carbamazepine	

Abbreviations: AF, atrial fibrillation; CYP, cytochromes P450; DVT, deep venous thrombosis; HIV, human immunodeficiency virus; NSAID, non-steroidal anti-inflammatory drug; PE, pulmonary embolism; P-gp, P-glycoprotein; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VTE, venous-thromboembolic event.

exposure in a given patient. Based on the current label information, which in turn was informed by DDI studies, no concomitant therapy should hence be used that results in a doubling or halving of the AUC. This also implies that when a DDI results in an increase of the AUC of less than two-fold, this should in and of itself not lead to any therapeutic change.[19]

We acknowledge that this is a conservative approach, bearing in mind the EMA/FDA framework to interpret the strength of DDIs. Moreover, we have reassuring data from several RCTs. A double dose (and hence exposure) only increased the major bleeding risk by approximately 0.1%, 0.1% and 1.14% in EINSTEIN CHOICE, AMPLIFY EXT and ENGAGE TIMI-AF 48, respectively.[30–32]

4 | SOURCES

Multiple sources might be consulted to assess whether a certain DDI might be clinically relevant and hence actionable. Regarding pharmacokinetic DDIs with DOACs in the management of CAT, we have selected the following sources as they might contain relevant information and/or are commonly used in daily clinical practice: package inserts, (protocols of) the landmark trials, prescriber software and online databases.

4.1 | Package inserts

In general, package inserts are not a reliable source of specific information pertaining to those DDIs whereby cancer therapies might act as culprits and hence could influence the DOAC's exposure and thus clinical outcome.[21–23] Yet, as mentioned above, package inserts do *indirectly* provide a framework to allow us to better interpret potential DDIs with cancer therapies.

4.2 | Trial protocols

Studies that are specifically designed to investigate the impact of interacting drugs on clinical outcomes are the preferred source to assess clinical relevance of a DDI. Yet, they are limited in the domain of cancer management. Trial protocols do not provide much information either regarding potential regarding interactions with cancer therapies, beyond what is already known from the package inserts. For example, in SELECT-D and CARAVAGGIO, no specific guidance was provided on how to deal with concomitant cancer therapies in combination with rivaroxaban and apixaban respectively.[8,12] In HOKUSAI VTE CANCER, the investigators did provide an additional list of cancer therapies that were considered to act as P-gp inhibitors. The authors recommended to reduce the daily edoxaban dose to 30 mg in those patients.[7]

As CARAVAGGIO did not identify any cancer therapy on the excluded drug list, the concomitant use with apixaban was implicitly permitted. To further explore the impact of concomitant cancer therapies on multiple clinical outcomes, a post hoc analysis was conducted. This analysis also evaluated the effects of various CYP3A4/P-gp inhibitors and inducers, with an overwhelming majority of culprit agents classified as mild to moderator inhibitors or inducers. Encouragingly, no significant associations were observed between DDIs involving apixaban and clinical outcomes.[33] Although it cannot be definitively concluded that no interactions occurred in single patients, these findings suggest that on average these DDIs did not significantly alter the clinical outcomes in this post hoc analysis.

4.3 | Prescriber support: software and online databases

Clinicians can consult multiple (online) sources. In many settings, a majority of prescriptions will be generated using prescribing software, frequently provided as part of a computerized order entry system (CPOE) which in turn might incorporate additional relevant information from up-to-date online databases. The latter might also be consulted separately. Summary papers might provide additional support. From a pragmatic point of view, we recommend to also apply that hierarchy when interpreting DDIs concerning DOACs and cancer therapies (or supportive therapies): CPOE, then online databases and finally summary papers.

First, a CPOE is preferred, simply because it is always active when a prescription is being made or altered. It is crucial, however, to evaluate which DDI databases feed the prescribing software. This can be discussed with the information technology (IT) and/or hospital pharmacy department.

Secondly, online databases are a good adjunct to the CPOE. They are interactive, generally provide a rationale for their recommendations and refer to relevant and up-to-date literature. For example, in our hospital (University Hospitals Leuven, Leuven, Belgium) we commonly consult the online databases of Stockley's Drug Interactions and UpToDate. If there is no direct information on a certain DDI combination, we suggest to look for phase 1 DDI studies with the culprit agent. Commonly one finds data on the impact of a specific cancer therapy on probes (e.g., **midazolam** for CYP3A4 and **digoxin** for P-gp). If there is no impact on midazolam, then it is very unlikely that there will be an impact on CYP-mediated metabolization of the DOACs apixaban and rivaroxaban. Conversely, if a cancer therapy has been found to strongly alter exposure to relevant probes, this should be taken into consideration, particularly in the case of a strong impact on both CYP3A4 and P-gp.

Thirdly, recent guidelines, statement or position papers and excellent reviews can provide health care with a comprehensive overview. For example, we recommend the Statement of the American Heart Association on cardio-oncology drug interactions.[34] There they provide a nuanced yet practical summary on how to deal with common and/or clinically relevant DDI in the cancer setting. Yet, we do not recommend to rely solely on the DDI tables of said publications. By definition, they are dated upon publication given the rapidly evolving field, not interactive and frequently the result of expert opinion. For

example, the DDI table in the appendix of the recent ESC Cardio-Oncology guideline provides succinct information for DOACs.[10] There they mention that **doxorubicin**, **enzalutamide** and **imatinib** are *strong inhibitors of CYP3A4 and/or P-gp*; however, they are not. For example, imatinib is rather a moderate inhibitor of CYP3A4 with no meaningful impact on P-gp.[35] In addition, while doxorubicin is a recognized substrate of both CYP and P-gp, there is no real evidence in defence of its potential as an inhibitor.[36,37] On the contrary, if anything, it is expected to induce – not inhibit – CYP enzymes.[36] Finally, enzalutamide is a known CYP inducer.[38]

5 | FIVE CONSIDERATIONS

In our centre, we take into account the following five considerations when dealing with PK DDIs that concern DOACs when used in the management of CAT. Our proposal is summarized in Figure 1.

(1) We use an up-to-date CPOE to alert us to and to further evaluate the DDI. In our setting we have access to online databases as well. The validity of the CPOE should be confirmed by the IT and/or hospital pharmacy department to ensure the involvement of trained personnel as well as the use of appropriate databases.[39]

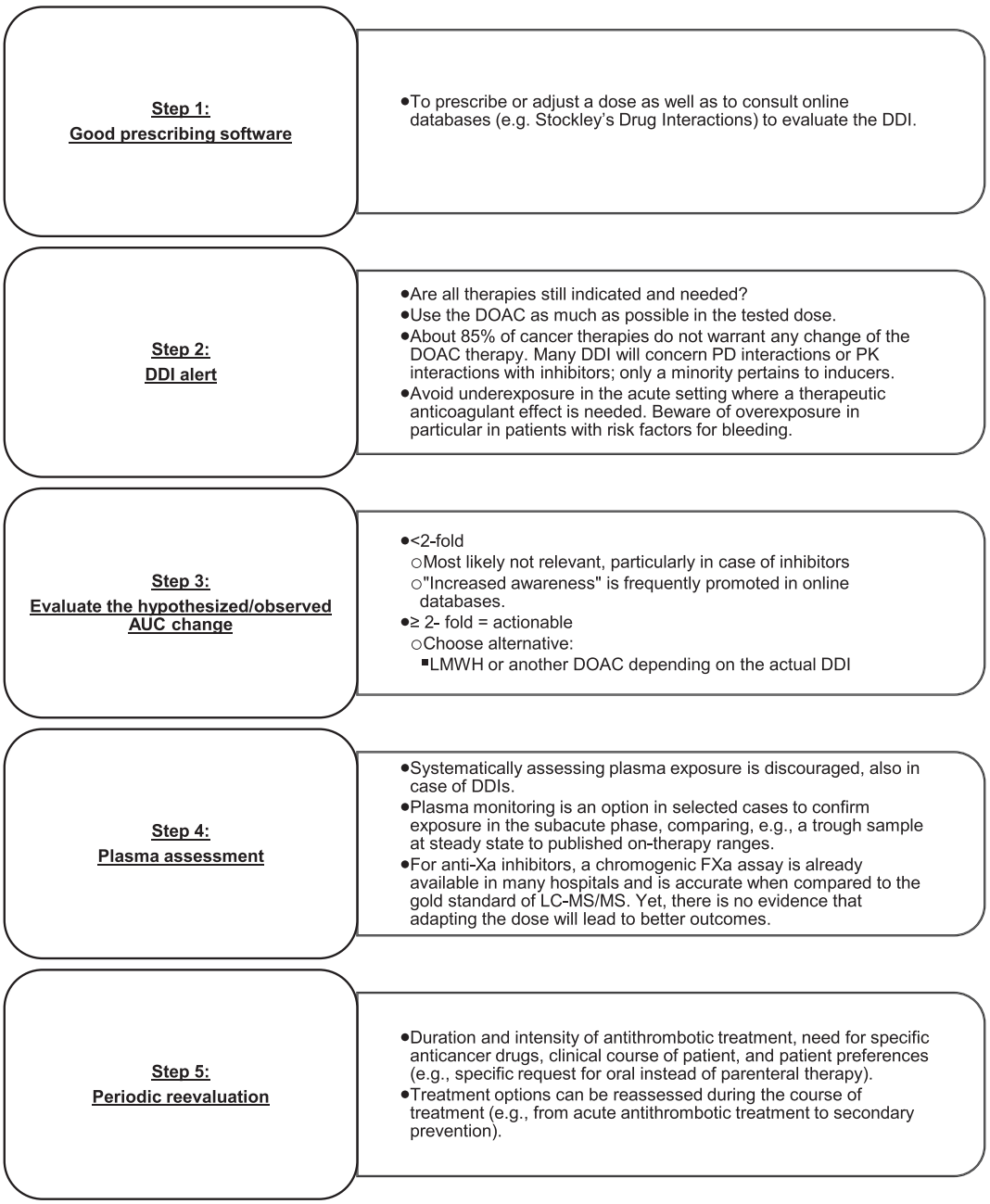

FIGURE 1 Five considerations on the appraisal of pharmacokinetic drug–drug interactions with direct oral anticoagulants in the management of cancer-associated thrombosis. AUC, area under the curve; DDI, drug–drug interaction; DOAC, direct oral anticoagulant; LC–MS/MS, liquid chromatography with tandem mass spectrometry; LMWH, low-molecular weight heparin; PD, pharmacodynamic; PK, pharmacokinetic.

(2) When alerted to a DDI, the indications of both culprit and victim agents should be (re)assessed. Importantly, in acute VTE management, we aim to avoid underexposure, while taking into account risk factors for bleeding in all VTE patients.[40,41] (3) We apply the AUC/2 or AUC*2 paradigm to interpret the relevance of a PK interaction with a DOAC. Reassuringly, about 85% of cancer therapies do not warrant any change to the DOAC therapy.[42] (4) Plasma assessment can be performed to exclude DOAC overexposure or underexposure when combined with a strong inhibitor or inducer respectively. Importantly, there is no evidence at this time that adjusting the DOAC dose in response to measured levels will actually lead to better clinical outcomes.[16,17] Others have promoted adjusting the dose based on measurements and/or expected drug interactions.[43] In general, we advise caution and do not promote this practice systematically. While the observed ranges from landmark trials can be used to interpret an individual patient's exposure, there are no data in support of altering the dose in response to these ranges to improve clinical outcome. We hence err on the side of caution and rather opt to choose an alternative in this situation. (5) Finally, the patient is monitored throughout follow-up to allow for a periodic re-evaluation of the treatment regimen. When dealing with difficult cases, in-house expertise can be consulted throughout each of the five above considerations.

6 | CASE DISCUSSION

A 79-year-old male patient takes enzalutamide in the management of refractory prostate cancer. He presents to the emergency department with de novo fatigue, dyspnoea and tachycardia. A diagnosis of pulmonary embolism is made, and the prescriber would like to administer apixaban, based on the CARAVAGGIO data.[8] Enzalutamide is a potent CYP inducer, for multiple iso-enzymes, and a mild P-gp inhibitor. Apixaban is a substrate to both CYP and P-gp.

The abovementioned approach was applied to this case. (1) The CPOE alerts us to a potential interaction. (2) The regimen is assessed and it is concluded that the patient will need both the anticoagulation and the anti-cancer therapy. (3) This concerns a PK interaction whereby due to induction there might be underexposure in the acute management of CAT. Based on the post hoc analysis of CARAVAGGIO on concomitant cancer therapies, this combination would have been allowed in the RCT.[33] Conversely, in the worst-case scenario, the interaction might result in more than halving of apixaban's AUC. When consulting the package insert of apixaban, it is indeed stated that concomitant use with strong (dual) inducers should be avoided, particularly in the acute management of a VTE as underexposure might lead to insufficient treatment of the clot. Online databases also recommend to choose an alternative. Edoxaban might be a theoretical alternative, as its exposure is less dependent on CYP and more on P-gp. The case is discussed with an expert in vascular medicine. A consensus was reached here that the safest choice would be to provide an LMWH in the acute phase (i.e., first 3–6 months). (4) No plasma monitoring was done. (5) In the long term (i.e., beyond 3–6 months) a DOAC could be provided instead of LMWH. Here it is argued to rather prefer edoxaban to apixaban.

Apixaban in the long term, even when overall exposure might be reduced, might also be effective. At the moment we have reassuring data from EINSTEIN CHOICE and AMPLIFY Extended that a lower dose in secondary VTE prevention provides similar thrombotic protection compared to a higher dose.[30,31] Two trials are currently ongoing, the API-CAT and EVE trials, where such data are being gathered on apixaban in the long-term management of CAT.[44,45]

In sum, when following the proposal as worked out above (Figure 1), the rationale would be to avoid underexposure in the acute phase. Hence, LMWH should be considered for initial treatment.

7 | CONCLUSION

Apixaban, rivaroxaban and edoxaban are recommended in the management of venous thrombosis in cancer. Drug–drug interactions do occur, but frequently do not require therapy changes. In the case of a major PK DDI (i.e., AUC/2 or AUC*2), an alternative therapy (e.g., LMWH) should be considered. Here, we have provided a framework to support clinicians in daily clinical practice.

7.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2020/21.[46,47]

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript. The first draft was written by the first author (Lorenz Van der Linden) and the other authors reviewed, edited and provided input during multiple rounds. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

L.V.D.L. reports grants from Daiichi Sankyo and Pfizer and has received personal fees from Amgen, Bayer, BMS/Pfizer, Daiichi Sankyo, Sanofi Aventis and Servier. T.V.A. reports personal fees for consultancy services and/or participation in speakers' bureau or advisory board from BMS/Pfizer, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Sanofi Aventis, and Servier. E.V.C. declares participation to advisory boards for Abbvie, ALX, Amgen, Array, Astellas, Astrazeneca, Bayer, Beigene, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, GSK, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Mirati, Novartis, Nordic, Pierre Fabre, Pfizer, Roche, Seattle Genetics, Servier, Takeda, Terumo, Taiho, Zymeworks and research grants from Amgen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier paid to the institution. P.V. is co-holder of the Bayer Chair in Cardiovascular Medicine at the University of Leuven. He has received consulting fees from Bayer, Daiichi Sankyo,

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DATA AVAILABILITY STATEMENT

Not applicable.

ORCID

Lorenz Van der Linden https://orcid.org/0000-0001-5195-1891

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