# Drug–drug interactions between direct oral anticoagulants and other medications in patients with pulmonary embolism: results from the Lungenembolie Augsburg (LEA)

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# Drug–Drug Interactions Between Direct Oral Anticoagulants and Other Medications in Patients with Pulmonary Embolism: Results from the Lungenembolie Augsburg (LEA)

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## Abstract

**Background and aim** Direct oral anticoagulants (DOACs) are now a well-established class of medication for blood clot prevention and treatment. So far, literature evaluating real-world data on the drug–drug interactions (DDIs) between DOACs and other medications in patients with pulmonary embolism (PE) is limited. This study aims to investigate these interactions in patients with PE to address this and improve patient care.

**Materials and methods** In a retrospective study, patients' medications were recorded upon hospital discharge and reviewed again 3 months later. A clinical decision support system (AiDKlinik® Release 3.5) was initially used to screen for DDIs and drug-related problems. Subsequently, medications were entered into Lexicomp®, a comprehensive drug interaction database, to gain detailed scientific explanations and references for the identified interactions and their mechanisms. Binary logistic random intercept models were used to identify potential risk factors of drug–anticoagulation interactions.

**Results** The 477 included PE patients had a median intake of five drugs. Drug–anticoagulation interactions depended strongly on the number of medications taken ($P$ value $< 0.001$). However, the association was non-linear, resulting in a saturation effect for a higher number of drugs. The odds ratio for having at least one drug–anticoagulation interaction was 0.40 (95% confidence interval 0.17–0.96; $P$ value $= 0.040$) in patients with hypertension.

**Conclusions** The potential for DDIs with DOACs represents a significant concern. By being aware of the most common interactions, risk factors and avoidance strategies, the safety and efficacy of therapy can be optimized.

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## 1 Introduction

In Germany, approximately 60,000–80,000 people suffer from acute pulmonary embolism (PE) every year [1, 2], corresponding to an annual PE incidence of 50–100 per 100,000 inhabitants. Acute PE is a frequent and life-threatening event, and it is most commonly a consequence of deep vein thrombosis. It is the third most frequent cardiovascular syndrome, following myocardial infarction and stroke, with increasing frequencies in recent years [3, 4]. The risk of PE is higher in men, older people and people with certain risk factors (e.g., cancer, surgery, immobility).

The cornerstone of PE treatment is anticoagulation with the aim of reducing mortality, morbidity, recurrence and the occurrence of post-thrombotic syndrome [5]. Direct oral anticoagulants (DOACs) have emerged as a safe and effective alternative to vitamin K antagonists for the treatment and prevention of arterial and venous thrombosis [6, 7]. However, the pharmacological characteristics of patients requiring anticoagulant treatment must be considered. Elderly patients in particular, who often have low body weight and concomitant diseases such as renal or liver failure, have a higher risk of toxicity and drug–drug interactions (DDIs). DDIs are a major challenge, especially in this group of people. In a recent systematic review and meta-analysis that included 31 studies from different countries, estimates of DDI prevalence in people aged 65 years and older ranged from 0.8 to 90.6%. The pooled DDI prevalence was 28.8% (95% confidence interval [CI] 19.3–40.7), but there was considerable heterogeneity ($P < 0.10$; $I^2 = 100\%$; $\text{tau}^2 = 2.13$). These differences may mainly be due to the different DDI identification methods used by the studies [8].

DDIs can occur when two or more pharmaceutical agents are administered simultaneously, resulting in a phenomenon whereby the drugs interact with each other and produce unintended effects. Such interactions can be deleterious, resulting in increased toxicity or decreased efficacy of the drugs involved [9]. Nevertheless, DOACs are now administered as standard therapy in PE patients and are considered relatively safe drugs with a reduced need for monitoring [8–10]. Although there are fewer DDIs with DOAC therapy compared to warfarin, these are of clinical relevance, as DDIs are likely to go unnoticed until a complication occurs [10]. Furthermore, individualized dosing strategies are crucial, and comorbidities such as kidney or liver disease require tailored approaches to balance risks and benefits [11, 12].

So far, literature evaluating real-world data on the occurrence of DOAC DDIs in patients with PE is limited [13]. Therefore, this study in patients with PE focuses on the effects of combining DOACs with other medications that are considered risky in terms of DDIs. The goal of this study is to describe and explain strategies for managing these interactions.

## 2 Study Population

This analysis was based on participants of the 'Lungenembolie Augsburg' (LEA) study, a long-term observational cohort including patients 18 years and older who were treated at the University Hospital Augsburg due to an acute PE. All patients admitted with an incident or recurrent PE, regardless of the underlying disease (e.g., cancer, deep vein thrombosis, chronic obstructive pulmonary disease [COPD]), and who were diagnosed by multidetector computed tomography (CT) pulmonary angiography or ventilation–perfusion lung scanning, were included. The following exclusion criteria applied to the study: no capacity to consent (e.g., dementia, language problems); age < 18 years; no interest in participating in the study.

At the University Hospital Augsburg, all suspected PE cases (including inpatient, outpatient, emergency department and intensive care unit patients) were prospectively recorded. Study nurses checked and verified potential cases with the attending physician. Finally, the study nurses visited each PE patient to inform them about the study and deliver the study documents (all in the German language). All patients received comprehensive information on the study. Detailed information on the study design can be found in the published study protocol [14]. The study nurses were trained according to a standard operating procedure (SOP), which contained the exact procedure for patient recruitment, interviews and data collection. After extensive practice in conducting interviews, several training interviews with patients were carried out under the supervision of the principal investigator. The study staff was only deployed for independent patient recruitment and interviewing after successful certification by the principal investigator.

After the patients signed the consent form, the study nurses interviewed the study participants during their hospital stay, using a standardized questionnaire. The interviews covered demographic information, symptoms on presentation, delay in diagnosis, predisposing and PE-provoking factors and comorbidities (e.g., carcinoma, pulmonary and cardiac comorbidity, diabetes mellitus, neuromuscular disease and sleep-disordered breathing). The patients were asked to fill in self-administered questionnaires (EQ-5D and the Hospital Anxiety and Depression Scale). Further data on comorbidities, treatment, complications, laboratory parameters and discharge medication were taken from the medical records.

Participants receive postal questionnaires in the first year after 3, 6 and 12 months (thereafter, every 12 months up to a follow-up period of 60 months) after discharge. In

the follow-up surveys, the participants were asked about employment status, use of medical services, quality of life (Pulmonary Embolism Quality of Life Questionnaire) [15], physical activity, smoking status and current medication intake. The questionnaire was in German. If possible, the questionnaire had to be answered by the patients themselves. Help in completing the questionnaire by relatives or nursing staff was permitted and had to be indicated in the questionnaire.

Baseline recruitment of study participants began on July 1, 2017, and ended on July 11, 2023. The follow-up surveys of participants will be completed at the end of October 2028. A total of 976 participants were recruited. For the present study, all participants were included for whom the baseline data and the data from the consecutively collected 3-month questionnaires were available in the database at the time of the analysis. Thus, 477 patients could be included in the analyses for whom at least a baseline and a 3-month follow-up survey were available (see Supplementary Figure 1).

The study protocol was approved by the Ethics Committee of the Ludwig-Maximilians-Universität München (date of approval: 1 August 2017; reference number: 17–378). The study was performed according to the Declaration of Helsinki. Written informed consent was obtained from each study participant.

## 3 Material and Methods

To identify and analyze the drug-related problems (DRPs) and DDIs, patients' medications were checked at hospital discharge and 3 months after discharge by means of the computerized decision support system (CDSS) AiDKlinik® Drug Information System Release 3.5 (Dosing GmbH, Heidelberg) [16]. This CDSS is a comprehensive drug information system that is scientifically tested and can be used to tailor drug dosages for individual patients. AiDKlinik® provides a comprehensive medication database and safety of drug therapy services as a cloud-based web service. It is an active knowledge system that employs patient data, including laboratory data, to furnish decision support for the treatment of patients [17, 18]. The CDSS AiDKlinik® Release 3.5 is designed to identify and address the following DRPs:

- Interactions
- Dosing in patients with renal insufficiency, taking into account the current clearance
- Prescription of closely related active substances or prescriptions containing the same active substance
- Potentially inadequate medication for elderly patients
- Maximum dose

We chose the CDSS AiDKlinik® because it ranked second overall and performed best in ease of use in a comparison of eight drug interaction databases [19].

After checking medications with the CDSS, patients' medications were entered into a second interaction database (Lexicomp® Drug Interactions © 2024). The Lexicomp® Drug Interactions software [20] was employed to provide a scientific representation and underlying mechanisms of the interactions. The results of DDIs between the two databases exhibited no significant discrepancies. Our categorization of DDIs into three categories—contraindicated/high-risk combinations, clinically serious interactions and potentially clinically relevant moderate risks—was derived from an analysis of both the CDSS and the Lexicomp® drug database.

All prescribed anticoagulants were checked for dosage and scored as follows:

1 = The dosage is correct.

2 = A reduction in dosage is necessary due to renal function.

3 = Dose increase is necessary.

4 = No dosage information.

Next, each DDI between the anticoagulant prescribed for the treatment of PE and the other medication was recorded and subjected to a systematic evaluation. The resulting necessary actions were duly documented and summarized according to the following structured format:

1 = Discontinue

2 = Substance exchange

3 = Factor Xa activity determination

4 = Intensive monitoring for bleeding events (close observation and very frequent assessment of patients' coagulation status to prevent or quickly address bleeding complications; regular inquiry about symptoms such as unusual bleeding or bruising, dizziness, lightheadedness, red or black tarry stools, coughing up or vomiting fresh or dried blood, severe headaches and weakness)

5 = Tight monitoring for bleeding (observation and assessment of the patient's coagulation status at regular intervals to avoid bleeding complications; regular inquiry about symptoms such as unusual bleeding, severe abdominal pain, weakness and the appearance of black tarry stools)

6 = Change of anticoagulant recommended

7 = Close monitoring of International Normalized Ratio (INR) values

### 3.1 Statistical Analysis

Baseline characteristics were presented either as median and interquartile range for continuous variables or as absolute and relative frequencies for categorical variables. Regarding the binary outcome and longitudinal design with measurements at baseline and the 3-month follow-up, a binary logistic random intercept model was used to identify potential

predictors of drug–anticoagulation interactions (at least one interaction vs. no interaction). In this context, age and sex were used as permanent components in the model, while the backward stepwise selection procedure of fixed effects was applied for the remaining predictor variables. The linearity assumption was tested and, if necessary, captured by natural cubic splines for continuous variables. Missing values in variables used in regression models were considered completely at random, which is why a complete case analysis was carried out. In addition, we analyzed the prediction of one or more DDI occurrence according to pharmacological classes (intake of antihypertensive, antidiabetic, antidepressant drugs) instead of medical history.

Model results can be interpreted as odds ratios (ORs) for having at least one DDI. *P* values below the threshold of 0.05 were seen as statistically significant. All analyses were performed using the open-source statistical software R (version 4.3.2).

## 4 Results

Table 1 displays the baseline characteristics for the total sample of 477 participants (53.5% males) at hospital discharge. The patients had a median age of 65 years, a median body mass index of 28.3 kg/m$^2$ and a median intake of five drugs. Three percent of patients suffered from a coagulopathy, 14.6% had diabetes mellitus, 10.8% chronic kidney disease and 16.6% cancer. Most of the study participants were treated with apixaban (40.3%), followed by rivaroxaban (30.1%), low molecular weight heparin (17.2%), edoxaban (9%), phenprocoumon (2.5%) and dabigatran (1%).

Specific drug interactions and their frequencies at both baseline and follow-up see supplementary Table 1. The most frequently observed interactions were found for DOACs with metamizole and acetyl salicylic acid (ASA). At discharge and after 3 months, the most frequent DDIs were seen with DOACs. Fewer were seen with phenprocoumon and low molecular weight heparin. There was a decreasing trend in the likelihood of interactions between discharge from hospital and 3 months later (see Supplementary Table 2). Furthermore, the proportions of patients having one DDI, two DDIs and three DDIs decreased between hospital discharge and 3-month follow-up (see Supplementary Table 3).

Based on the prediction model, an existing drug–anticoagulant interaction depends strongly on the number of medications taken (*P* value < 0.001; Table 2). However, the association was non-linear, resulting in a saturation effect for higher numbers of drugs (Fig. 1). The OR for having at least one drug–anticoagulant interaction was 0.40 (95% CI 0.17–0.96; *P* value = 0.040) in patients with hypertension (Table 2). The results from the regression model using antihypertensive, antidiabetic and antidepressant medications

**Table 1** Baseline characteristics of pulmonary embolism patients participating in the LEA cohort study

| Characteristics | Number of patients ($N = 477$) | Number (%) or median (interquartil range)[a] |
|---|---|---|
| Age, years, median (IQR) | 477 | 65 (55; 75) |
| BMI, kg/m$^2$, median (IQR) | 441 | 28.3 (24.9; 32.8) |
| Number of drugs, median (IQR) | 446 | 5 (3; 7) |
| Sex | 477 | |
| Male | | 255 (53.5%) |
| Marital status | 471 | |
| Married | | 299 (63.5%) |
| Single | | 62 (13.2%) |
| Divorced | | 46 (9.8%) |
| Widowed | | 64 (13.6%) |
| Education | 470 | |
| ≤ 9 years | | 199 (42.3%) |
| > 9 years | | 271 (57.7%) |
| Smoking status | 468 | |
| Never | | 247 (52.8%) |
| Ex | | 181 (38.7%) |
| Current | | 40 (8.5%) |
| Alcohol consumption | 469 | |
| None | | 99 (21.1%) |
| Seldom | | 199 (42.4%) |
| Often | | 171 (36.5%) |
| Hypertension | 467 | |
| Yes | | 238 (51.0%) |
| Chronic cardiac insufficiency | 470 | |
| Yes | | 35 (7.4%) |
| Diabetes | 472 | |
| Yes | | 69 (14.6%) |
| Coagulopathy | 471 | |
| Yes | | 14 (3.0%) |
| Depression | 462 | |
| Yes | | 52 (11.3%) |
| Autoimmune disease | 471 | |
| Yes | | 33 (7.0%) |
| Chronic kidney disease | 471 | |
| Yes | | 51 (10.8%) |
| Stroke | 472 | |
| Yes | | 37 (7.8%) |
| Cancer | 471 | |
| Yes | | 78 (16.6%) |
| Anticoagulation | 442 | |
| Apixaban | | 178 (40.3%) |
| Rivaroxaban | | 133 (30.1%) |
| Low molecular weight heparin | | 76 (17.2%) |
| Edoxaban | | 40 (9.0%) |
| Phenprocoumon | | 11 (2.5%) |
| Dabigatran | | 4 (0.9%) |
| At least one interaction | 446 | |
| Yes | | 110 (24.7%) |

*BMI* body mass index, *IQR* interquartile range, *LEA* Lungenembolie Augsburg

[a] Values are number (%) or median (interquartile range) unless otherwise stated in column 1

**Table 2** Results from a binary logistic random intercept model for the prediction of having at least one drug–anticoagulation interaction

| Factor | OR (95% CI) | *P* value |
|---|---|---|
| Age (years) | 0.98 (0.95–1.01) | 0.127 |
| Sex (women) | 0.59 (0.28–1.22) | 0.152 |
| Education (> 9 years) | 0.49 (0.23–1.05) | 0.066 |
| Number of drugs | non-linear | < 0.001 |
| Hypertension (yes) | 0.40 (0.17–0.96) | 0.040 |

Each estimate is presented as OR and 95% CI, and corresponding *P* values

*CI* confidence interval, *OR* odds ratio

rather than medical history can be found in Supplementary Table 4. The results are quite similar (especially for the number of drugs). There was no association with any of the medication groups. This model was worse in terms of the prediction accuracy compared to the model including comorbidities.

The follow-up examination 3 months after discharge demonstrated that anticoagulant maintenance therapy was continued in accordance with the established guidelines. As anticipated, there was a transition from low molecular weight heparin to DOACs (Fig. 2). Established guidelines [21] recommend that maintenance therapy should be continued for a period of 3–6 months. This was also observed in the patients examined at 3 months after discharge. A comparison of the baseline data with the 3-month follow-up data revealed no tendency among general practitioners to discontinue anticoagulant medication.

The most frequent DDI at discharge was observed between the DOACs and metamizole: a total of 22 patients experienced interactions with apixaban, 18 patients with rivaroxaban and 11 patients with edoxaban. The second most frequently observed interaction was with ASA: 14 patients used apixaban, 13 patients used rivaroxaban and eight patients used edoxaban. Additionally, the combination of low molecular weight heparin with ASA was observed. There are many diseases in which the interaction of these two substances is essential. Nevertheless, this may lead to an undesired DDI. Furthermore, eight additional DDIs were observed between rivaroxaban and ibuprofen, three patients exhibited a DDI between clopidogrel and

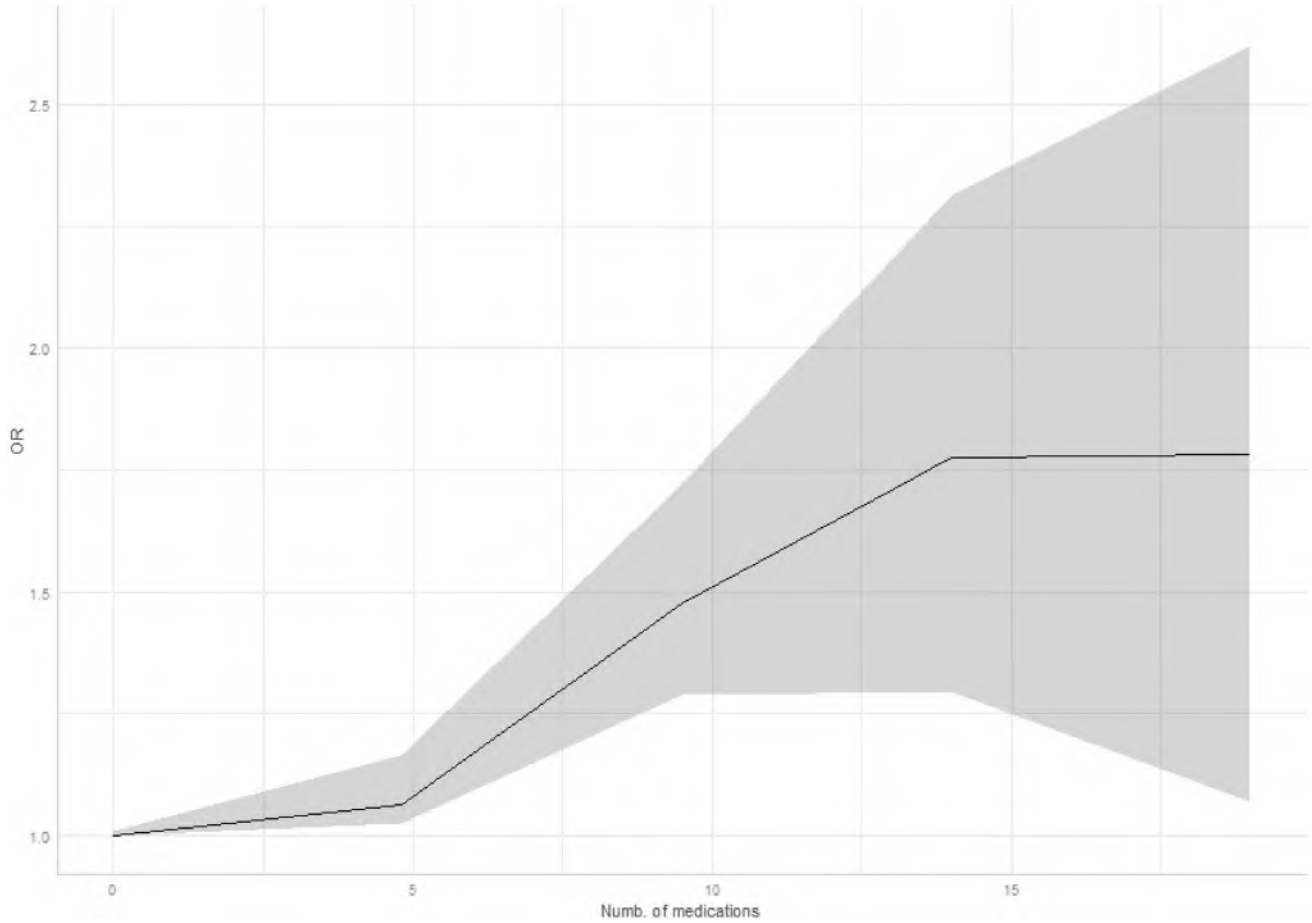


**Fig. 1** Non-linear association between number of medications taken and drug–anticoagulation interaction on the odds ratio (OR) scale

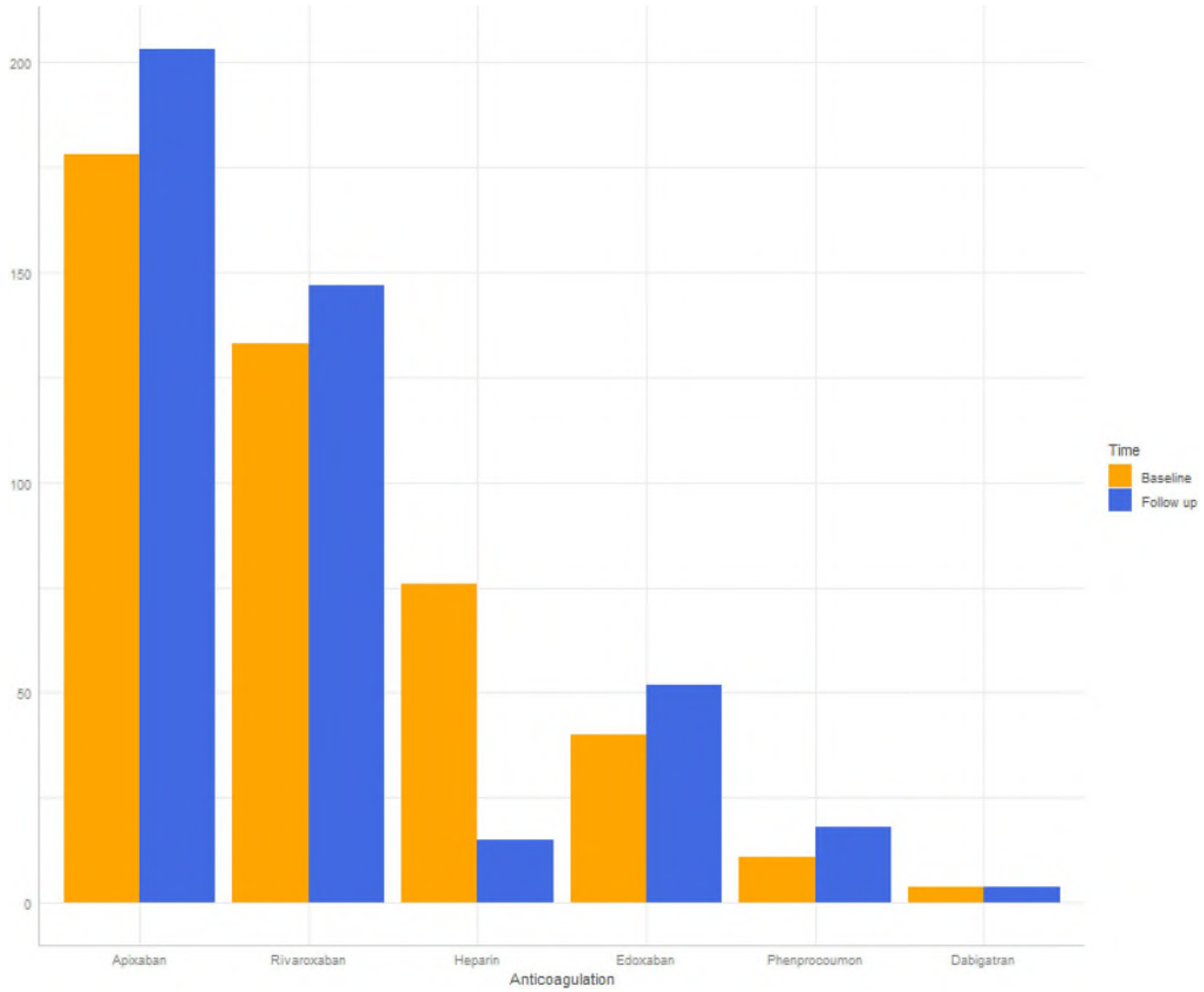


**Fig. 2** Use of direct oral anticoagulants at discharge vs. 3 months follow-up

apixaban, while two patients demonstrated a DDI between clopidogrel and rivaroxaban. One patient was treated with the contraindicated or high-risk combination of apixaban and the low molecular weight heparin tinzaparin. The other interaction partners of the baseline and the follow-up data are summarized in Table 3. Including data of hospital discharge and 3-month follow-up, the following classification was made:

1. *Contraindicated/High-Risk Combinations:* In one case, a patient was treated with the contraindicated and high-risk combination of apixaban and the low molecular weight heparin tinzaparin at discharge. However, this combination was no longer observed after 3 months.

2. *Clinically Serious Interactions:* A total of 31 patients exhibited clinically significant interactions at hospital discharge. The combination of ASA (100 mg) and apixaban ($n = 14$), as well as ASA (100 mg) and rivaroxaban ($n = 13$), were the most prevalent in this category. After 3 months, this combination was less frequently detected, i.e., ten times (apixaban/ASA) and 11 times (rivaroxaban/ASA). Other problematic agents that could lead to clinically serious interactions at discharge were the combinations of rivaroxaban/carbamazepine ($n = 1$), rivaroxaban/amiodarone ($n = 1$) and phenprocoumon/clopidogrel ($n = 1$). The 3-month follow-up data indicated a reduction in the number of patients experiencing this interaction category. However, there were also cases of clinically serious interactions, including apixaban/posaconazole ($n = 1$), edoxaban/carbamazepine ($n = 1$), phenprocoumon/ASA, and phenprocoumon/sulfamethoxazole and trimethoprim ($n = 1$).

Many of the combinations used are necessary for certain indications or are even described in guidelines. Therefore, they should not be criticized here, but the clinician should

**Table 3** Frequency of observed drug–drug interactions at hospital discharge and 3 months later, underlying mechanisms and associated risks

| Interaction partners | Discharge | 3 months follow-up | Mechanism | Outcome | Classification |
|---|---|---|---|---|---|
| Apixaban * metamizole | 22 | 19 | CYP3A4 inducer/P-gp inducer (moderate) | May moderately increase the risk of thrombosis | Potentially clinically relevant moderate interaction |
| Rivaroxaban * metamizole | 18 | 7 | CYP3A4 inducer/P-gp inducer (moderate) | May moderately increase the risk of thrombosis | Potentially clinically relevant moderate interaction |
| Edoxaban * metamizole | 11 | 4 | CYP3A4 inducer/P-gp inducer (moderate) | May moderately increase the risk of thrombosis | Potentially clinically relevant moderate interaction |
| Apixaban * acetyl salicylic acid | 14 | 10 | Additive bleeding risk | Increased bleeding risk | Clinically serious interaction |
| Rivaroxaban * acetyl salicylic acid | 13 | 11 | Additive bleeding risk | Increased bleeding risk | Clinically serious interaction |
| Edoxaban * acetyl salicylic acid | 8 | 11 | Additive bleeding risk | Increased bleeding risk | Potentially clinically relevant moderate interaction |
| Low molecular weight heparin * acetyl salicylic acid | 9 | 1 | Additive bleeding risk | Increased bleeding risk | Potentially clinically relevant moderate interaction |
| Phenprocoumon * acetyl salicylic acid | 0 | 1 | Multiple mechanisms | Increased major and minor bleeding risk | Clinically serious interaction |
| Rivaroxaban * ibuprofen | 8 | 1 | Additive bleeding risk | Increased bleeding risk | Potentially clinically relevant moderate interaction |
| Apixaban * ibuprofen | 0 | 1 | Additive bleeding risk | Increased bleeding risk | Potentially clinically relevant moderate interaction |
| Apixaban * clopidogrel | 3 | 2 | Additive bleeding risk | Increased bleeding risk | Potentially clinically relevant moderate interaction |
| Rivaroxaban * clopidogrel | 2 | 1 | Additive bleeding risk | Increased bleeding risk | Potentially clinically relevant moderate interaction |
| Phenprocoumon * clopidogrel | 1 | 0 | Additive bleeding risk | Increased bleeding risk | Clinically serious interaction |
| Apixaban * low molecular weight heparin | 1 | 0 | Additive bleeding risk | Increased bleeding risk | Contraindicated/high-risk combination |
| Apixaban * amiodarone | 1 | 0 | Weak CYP3A4 inhibitor/P-gp inhibitor | Increased bleeding risk | Potentially clinically relevant moderate interaction |
| Rivaroxaban * amiodarone | 1 | 0 | Weak CYP3A4 inhibitor/P-gp inhibitor | Increased bleeding risk | Clinically serious interaction |
| Rivaroxaban * carbamazepine | 1 | 1 | Strong CYP3A4 inducer/P-gp inducer | Increased risk of thrombosis | Clinically serious interaction |
| Edoxaban * carbamazepine | 0 | 1 | Strong CYP3A4 inducer/P-gp inducer | Increased risk of thrombosis | Clinically serious interaction |

Lexicomp® Drug Interactions © 2024

*CYP* cytochrome P450, *P-gp* P-glycoprotein

be made aware of possible complications of the interaction of the listed active substances.

3. *Potentially Clinically Relevant Moderate Interaction:* At hospital discharge, this interaction category was identified 93 times, whereas in the 3-month follow-up, it was identified 55 times. The most prevalent combination that elicited this interaction was apixaban/metamizole, occurring 22 times at discharge and 19 times after 3 months. Another observed interaction was that between rivaroxaban and metamizole, which occurred 18 times at discharge and seven times at follow-up. The combination of edoxaban and metamizole was observed 11 times at discharge and four times at follow-up. Low molecular weight heparin was given nine times at discharge and only once at follow-up. The patients were treated with low molecular weight heparin under clinical monitoring, and this was replaced at follow-up by phenprocoumon ($n = 4$), apixaban ($n = 11$), rivaroxaban ($n = 16$) and edoxaban ($n = 3$). A total of eight instances of edoxaban/ASA were identified at discharge, and 11 times at follow-up. Similarly, the combination of rivaroxaban and ibuprofen was observed eight times at discharge and only once at follow-up. Another interaction identified was apixaban/clopidogrel, which was detected three times at discharge and only twice at follow-up. Rivaroxaban/clopidogrel was identified twice at discharge and only once at follow-up. Table 3 presents a

comprehensive overview of all occurring interactions and their respective assessments.

For the potentially clinically relevant moderate interactions described in point 3 above, the same note applies as described in point 2, "Clinically Serious Interactions." The combinations described are necessary for many indications.

Supplementary Table 5 presents an overview of whether the interactions identified using AiDKlinik® and categorized using Lexicomp® are based on area under the curve (AUC) variations of the substrate when exposed to the inducer/inhibitor, or on the outcome and therapeutic management of the DDI.

## 5 Discussion

Given the potential for life-threatening consequences of PE, it is of paramount importance to enhance therapy with DOACs (for the mechanisms of action of the individual anticoagulants, see the supplementary material), thereby ensuring the safety of patients. In the present analysis, this issue could be examined by meticulously recording and evaluating drug-related issues with real-world data from the LEA study. The patients under study were older PE patients, who are typically required to take a substantial number of medications. In general, it was observed that the probability of interactions increased with an increase in the number of prescribed medications. It was noticeable that fewer interactions were found for the indication of hypertension.

A DDI can alter the efficacy or toxicity of one or both interacting drugs. Pharmacokinetic interactions refer to the effects that one drug has on the absorption, distribution, metabolization or excretion of another drug. These interactions can lead to altered drug levels in the body and thus affect the efficacy or safety of the medication [22]. Pharmacodynamic DDIs occur when the pharmacological effect of one drug is altered by that of another drug in a combination regimen [23].

### 5.1 DDIs Involving Apixaban

The combination of apixaban and the low molecular weight heparin tinzaparin is contraindicated according to the prescribing information for both substances [24], because the concomitant use of apixaban with other anticoagulants is associated with an elevated risk of bleeding.

The concomitant use of ASA with apixaban has been demonstrated to elevate the risk of bleeding in patients with atrial fibrillation from 1.8 to 3.4% per year [26, 27]. A randomized control trial, which was prematurely discontinued due to bleeding events, revealed an increased risk of major bleeding in high-risk acute coronary syndrome patients when apixaban was administered in combination with ASA [28]. However, the concomitant administration of these drugs is not contraindicated unless there is active bleeding [26]. It is therefore imperative that the physician closely monitors the patient's tendency to bleed [29, 30]. Many of the combinations used are necessary for certain indications or are even described in guidelines. For example, triple therapy, which includes combination of dual antiplatelet therapy and anticoagulation (e.g., in patients after percutaneous coronary intervention with stenting and with concomitant atrial fibrillation), represents a specific example of such a risky but recommended combination [31].

In pharmacokinetic studies with healthy volunteers, the AUC of apixaban (25 mcg single dose) increased by 1.3- to 1.7-fold when combined with strong cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors: ketoconazole, posaconazole, itraconazole, cobicistat and ritonavir [32] [33] [34]. The United States (US) prescribing information for apixaban includes recommendations for dose adjustment when the drug is combined with drugs that strongly inhibit CYP3A4 and also inhibit P-gp [24]. In contrast, the Canadian product monograph states that any use with such inhibitors is contraindicated [25].

### 5.2 DDIs Involving Rivaroxaban

ASA has been demonstrated in several studies to enhance the efficacy of rivaroxaban [35, 36]. In contrast, one study in healthy volunteers found that there were no pharmacokinetic or pharmacodynamic interactions between ASA and rivaroxaban [37]. Nevertheless, it is of utmost importance to carefully weigh the expected risks and benefits of this combination. The US [36] and Canadian [35] package leaflets for rivaroxaban advise caution and increased monitoring for signs of bleeding when rivaroxaban is used concomitantly with an antiplatelet agent. In patients at risk of developing ulcerative gastrointestinal disease, it may be appropriate to consider implementing appropriate prophylactic treatment (e.g., proton pump inhibitors).

The use of non-steroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, has been found to increase the rate of major bleeding with rivaroxaban by 50%, while the suppression of thromboembolic events remains unchanged. The use of NSAIDs is also associated with an increased risk of adverse and toxic effects when combined with rivaroxaban [29, 36]. A comprehensive risk–benefit assessment should be performed in all patients prior to the concomitant use of these agents. The risks are likely to depend on the NSAID dose and the expected duration of use [36]. When rivaroxaban and NSAIDs are used concomitantly, patients should be

advised about the increased risk of bleeding and monitored closely for signs and symptoms of bleeding.

It has been demonstrated that carbamazepine is a potent inducer of CYP3A4 [38–40]. Furthermore, it has been observed that the concurrent use of rivaroxaban and P-gp inducers may result in an increase in serum concentrations of rivaroxaban [41–43]. It is therefore recommended that the concomitant use of rivaroxaban and strong inducers of CYP3A4 and P-gp should be avoided [41]. Additionally, in a case–control study, patients with atrial fibrillation treated with DOACs (31.3% rivaroxaban) in combination with phenytoin or carbamazepine exhibited a higher risk of stroke or systemic embolism than patients treated with DOACs without these drugs [40].

Amiodarone may also elevate the serum concentrations of rivaroxaban. In a prospective observational study of patients with atrial fibrillation treated with rivaroxaban, the concomitant use of amiodarone was found to significantly increase the risk of bleeding, as evidenced by a hazard ratio of 2.17 (95% CI 1.32–3.56) [44]. In a retrospective study of patients with non-valvular atrial fibrillation treated with an oral anticoagulant without a vitamin K antagonist ($n$ = 91,330; 59% rivaroxaban), the use of amiodarone was associated with a 1.4-fold increase in the incidence rate ratio for major bleeding [45]. A case–control study revealed a significantly elevated risk of bleeding in patients treated with rivaroxaban and amiodarone (OR 1.68, 95% CI 1.14–2.49) [40]. The mechanism of this interaction is likely inhibition of P-gp, a transporter responsible for the distribution of rivaroxaban. It is also possible that weak inhibition of CYP3A4 by amiodarone may contribute to this phenomenon.

### 5.3 DDIs Involving Edoxaban

In the case of edoxaban combined with carbamazepine, the assessment is less critical. In a retrospective study, two out of six patients who were administered rifampin (600–900 mg daily) or carbamazepine (400–600 mg daily) with edoxaban (30–60 mg daily) exhibited a serum trough level of edoxaban that was lower than expected based on data from edoxaban clinical trials [34]. The suspected primary mechanism of this interaction is the induction of P-gp-mediated edoxaban efflux. Therefore, it can be reasonably assumed that all P-gp inducers would interact in a similar manner. Consequently, it is advisable to avoid the simultaneous administration of edoxaban and P-gp inducers if possible. In the event that concomitant use is unavoidable, it is important to note that the efficacy of edoxaban may be reduced.

### 5.4 DDIs Belonging to All DOACs

All substances belonging to the DOAC class utilized for the treatment of PE have been found to interact with the active substance metamizole. The mechanism of action of this NSAID is based on steric inhibition of cyclooxygenase (COX), which also synthesizes prostaglandin thromboxane. Analogous to other inducers of CYP3A (rifampicin, carbamazepine), a moderate reduction in the exposure of apixaban or edoxaban is also anticipated from metamizole after at least 3 days of treatment. In the long term, this combination should be used with increased monitoring of the anticoagulant effect. For patients requiring high apixaban or edoxaban maintenance doses, apixaban should be replaced by another form of anticoagulation. Conversely, an analgesic alternative to metamizole can be used if it is sufficiently effective.

Another noteworthy interaction is the combination of DOACs, specifically apixaban or rivaroxaban, with clopidogrel, a P2Y12 inhibitor. Apixaban has no effect on the inhibition of platelet aggregation [28] or the prolongation of the bleeding time induced by clopidogrel. In contrast, clopidogrel exerts no influence on the anticoagulation inhibition exerted by apixaban. However, it has been demonstrated that P2Y12 inhibitors may enhance the adverse/toxic effect of apixaban. Clopidogrel has no effect on the kinetics of rivaroxaban, yet in some patients, the bleeding time was found to be prolonged. The manufacturer of apixaban recommends against the use of this combination due to an increased risk of bleeding complications [28]. In the event that the combination of clopidogrel and rivaroxaban cannot be avoided, increased monitoring for bleeding complications is essential.

### 5.5 Strengths and Limitations

One of the strengths of this study is that the DDIs in PE patients could be examined at two different time points. In addition to the complete recording of the medications taken, extensive phenotyping of the PE patients was available. Additionally, a clinical decision support system (AiDKlinik® Release 3.5) and a comprehensive drug interaction database Lexicomp® were used to identify and explain the mechanisms of the DDIs. Limitations of the study include that no information about non-prescription adjunctive medications was available, despite the fact non-prescription medications and medicinal plants such as garlic, ginkgo or St John´s wort, which is a potent enzyme inducer [45], may influence hemostasis [46] and interact with anticoagulant therapy [45]. Furthermore, no information about whether the symptoms of the interactions actually occurred in individual patients was available in the present study, and there was no information on whether patients with DDI did or did not have a bleeding occurrence or thrombosis recurrence during follow-up. It is also important to note the significant heterogeneity of

agreement between different interaction checkers [47]. For example, while AiDKlinik® is effective at identifying DDIs, it may lead to over-alerting and has limitations in specificity compared to other databases [19]. Also, it cannot be ruled out that data on possible predictors were not assessed in this study. Finally, the results may not be generalizable to other patient groups.

## 6 Conclusions

The potential for DDIs with DOACs is of great concern. However, knowledge of the most common interactions, risk factors and avoidance strategies can optimize the safety and efficacy of therapy. Involving a pharmacist in therapy-relevant decisions during hospital stay could optimize the medication process and improve treatment, particularly for multimorbid elderly patients with polypharmacy.

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## Declarations

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**Conflict of Interest** Klaus Peter Schmelzer, Dennis Freuer, Simone Fischer, Thomas M. Berghaus, Jakob Linseisen and Christa Meisinger declare that they have no potential conflicts of interest that might be relevant to the contents of this article.

**Authors' Contributions** KPS: Conceptualization, data curation, analysis, software, investigation, methodology, project administration, resources, supervision and writing. DF: Data curation, analysis, visualization and writing. SF: Reviewing and editing. TMB: Reviewing and editing. JL: Reviewing and editing. CM: Project administration, supervision, writing, reviewing and editing.

**Data Availability Statement:** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics Approval** The study protocol was approved by the Ethics Committee of the Ludwig-Maximilians-Universität München (date of approval: 1 August 2017; reference number: 17–378).

**Consent to Participate** Written informed consent was obtained from each study participant.

**Consent for Publication** Not applicable.

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