

# Anticoagulation Therapy in Cancer Patients with Thrombosis in the Outpatient Sector of Germany (The CERTIFICAT Initiative)—German Practice of Anticoagulation Therapy of Cancer Patients with Thrombosis

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## Abstract

**Objective** This article aims to investigate the reality of anticoagulation treatment for cancer patients with thrombosis in the outpatient sector of Germany.

**Methods** For the analysis period 2012 to 2015, anonymized data from 4.1 million statutory insured patients were analyzed. Cancer patients with incident thrombosis and an outpatient prescription of anticoagulant drugs were identified and evaluated for three subsequent quarters with regard to anticoagulant use.

**Results** A total of 7,313 cancer patients with incident thrombosis (ICD-10: I80\*) were evaluated. About, 90% of patients with thromboses were diagnosed and treated in the ambulatory sector. More than 80% of the prescriptions were issued by general practitioners. And 57% of patients were anticoagulated predominantly (>50% of the time) with different low-molecular-weight heparins (LMWHs), 24% predominantly with vitamin K antagonists (VKAs), and 17% with direct oral anticoagulants (DOACs). Anticoagulants were prescribed for an average of 4.5 months. LMWH had a substantially longer prescription period (90–135 days) than VKA (53 days) or DOAC (47 days). Gastrointestinal bleeding in conjunction with hospitalization was documented in 1.76% of patients with a range of 1.3 to 3% for the different LMWHs.

**Conclusion** The prescription practice documented by this representative and comprehensive evaluation demonstrates an anticoagulation duration in accordance with the guidelines, although the choice of the respective anticoagulant was often not in compliance with the contemporary label or guidelines.

## Keywords

- ▶ anticoagulation therapy
- ▶ thrombosis
- ▶ oncology
- ▶ heparin
- ▶ oral anticoagulants
- ▶ claims data
- ▶ CERTIFICAT

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## Introduction

The risk of deep venous thrombosis (DVT) is estimated to be at least four- to sevenfold higher in patients with cancer compared to those without.<sup>1–3</sup> Superficial venous thrombosis (SVT), too, occurs more often in patients with malignancy.<sup>4,5</sup> Cancer patients with thrombosis have a 2.2-fold increase in mortality compared to those without.<sup>6–8</sup> The individual risk to suffer from venous thrombosis is related to the underlying cancer type and stage as well as several patient-associated and treatment-related factors.<sup>9</sup> Anticoagulation therapy, the cornerstone of thrombosis treatment, is complex because cancer patients are at an increased risk of thrombotic relapse and bleeding compared to those without cancer.<sup>10</sup> Contrary to the general guidelines for thrombosis, low-molecular-weight heparin (LMWH) was recommended initially and for the first 3 to 6 months as treatment of cancer-associated DVTs for many years in Germany.<sup>11</sup> Only recently, direct oral anticoagulants (DOACs) have been recommended as an alternative in some guidelines following the results of recent randomized controlled trials (RCTs).<sup>12,13</sup>

The recommendation of prolonged treatment with LMWH has been based on individual RCTs and meta-analyses demonstrating superiority compared to lead-in with LMWH followed by anticoagulation with vitamin K antagonists (VKAs).<sup>14</sup> These trials showed a significant reduction of more than 40% of recurrences without increase in major bleedings.<sup>14–16</sup> But during the period of the investigation presented here, prolonged treatment of cancer-associated thrombosis (CAT) was not approved for all LMWH agents. In contrast to the recommendation for early treatment, guidelines do not recommend a specific kind of anticoagulant for secondary prophylaxis beyond 3 to 6 months after a thrombotic event of the veins, because valid data from RCTs are missing.<sup>11</sup>

The aim of our study was to elucidate the reality of anticoagulation treatment of patients with CAT in Germany. Our statutory health insurance (SHI) claims database consisted of representative patient data. The methodology of our study and first results were recently reported<sup>17</sup> and confirmed the feasibility of the here-presented detailed analysis of anticoagulation practice in 7,313 cancer outpatients, allowing us to focus on the kind of anticoagulation drugs more deeply, the prescribing physicians, and the adherence to guideline recommendations.<sup>17</sup>

## Methods

### Database

This retrospective study was based on an anonymized database of the Institute for Applied Health Research (InGef, former German Health Risk Institute, HRI) which provides comprehensive information on a representative sample of approximately 4 million insurants, and accounts for approximately 5.5% of the total German population.<sup>18</sup> The sample is age- and sex-adjusted to the German population and has a good overall accordance in terms of morbidity, mortality, and drug usage. Besides demographic information, data records include anonymized core data on insurants and health care providers,

billing information on utilized inpatient and outpatient health services (including diagnoses based on German Modification of the coding system International Statistical Classification of Diseases and Related Health Problems: ICD-10-GM), and prescribed pharmaceuticals (based on German national drug codes: Anatomisch-Technisch-Chemische Einordnung von Wirkstoffen und Arzneimitteln, ATC).

### Patients

Between January 2012 and December 2015, cancer patients (ICD-10 GM, chapter C) with initial DVT or SVT (ICD-10 GM I80, exclusive I80.0, I80.20, I80.80) were identified if at least one outpatient prescription of anticoagulation was documented. Patients selected for analysis had not received any anticoagulation therapy or documented thrombosis diagnosis during the four quarters prior to indexing period (“wash-out period”). All patients were followed over a maximum period of four quarters. This constituted the follow-up year. The first quarter with anticoagulation prescription defines the start of observation.

Based on the observation that prothrombotic risk is high in a close temporal context to a new cancer diagnosis and decreasing steadily thereafter,<sup>1,19,20</sup> patients were separated a priori into a normal risk group (NRG) or a high-risk group (HRG). Patients in the NRG had a pre-existing cancer diagnosed more than a quarter prior to incident thrombosis, whereas HRG patients got their cancer diagnosis in the same, previous, or following quarter of incident thrombosis.

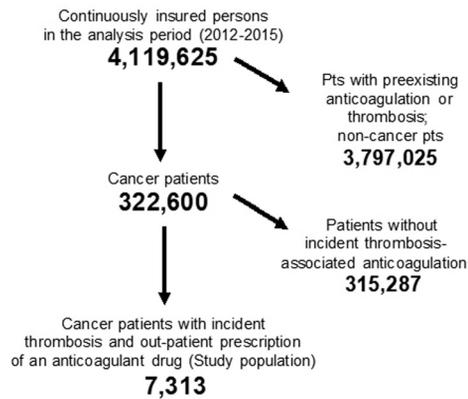
The bleeding prevalence during and after anticoagulation prescription was analyzed for gastrointestinal bleedings combined with inpatient stays. Further details regarding study design can be found in the publication from Schellong et al.<sup>17</sup>

### Data Analysis

For cancer patients with thrombosis, the characteristics for cancer entity, comorbidity, prescribing specialist, and prescribed anticoagulation were analyzed. A descriptive analysis between drug classification based on ATC code of the anticoagulation drugs LMWH, VKA, and DOAC and the six different LMWH drugs (certoparin, dalteparin, enoxaparin, nadroparin, reviparin, tinzaparin) was done. Patients were assigned to a distinct treatment regimen according to the predominant substance. The dominant substance was defined as a share of 51% or higher of the defined daily dose in accordance to the DIMDI (Deutsches Institut für Medizinische Dokumentation und Information) definition during the prescription period.<sup>17</sup>

## Results

From a total of 4,119,625 persons with SHI, 322,600 cancer patients and 91,623 patients with thromboses were identified. Around 90.0% of incident thromboses were diagnosed in the outpatient sector. The study population of 7,313 cancer patients with incident thrombosis and at least one outpatient prescription of an anticoagulant was identified using the defined criteria<sup>17</sup> between 2012 and 2015 (–Fig. 1). Of these, 4,421 patients (60.5%) could be assigned to the NRG and 2,892 patients (39.5%) to HRG.



**Fig. 1** Definition of study population (flow sheet).

### Patient Characteristics

Patient characteristics are given in [Table 1](#).

Most patients suffered from breast or prostate cancers, followed by cancers of the skin, the colon, and the lungs. In about 20% each, (1) metastases of lymph nodes, (2) metastases of the lung and/or gastrointestinal tract, or (3) metastases with other localizations were coded in the study population.

In total, 3% and 17% of the patients were diagnosed with cachexia and renal insufficiency, respectively ([Table 1](#)). Mortality was 16% within 6 months and 26% within 1 year.

### Anticoagulation Treatment Groups/Patient Groups

In 60% of the study population, a single ATC code was documented. LMWHs were predominantly prescribed to 4,162 patients (57%), with 63% in the HRG and 53% in the NRG. And 24% of the patients (NRG 24% and HRG 24%) were

**Table 1** Patient characteristics

	Whole study population	Normal-risk group (NRG)	High-risk group (HRG)
<i>n</i>	7,313	4,421	2,892
Mean age (SD), y	70.1 (12.4)	70.1 (11.9)	68.6 (12.9)
Men, %	52.7	52.8	52.6
Breast cancer (C50), %	19.6	22.6	14.9
Prostate cancer (C61), %	15.0	17.8	10.7
Skin cancer (C44), %	13.9	15.4	11.5
Colon cancer (C18), %	10.9	10.5	11.3
Lung cancer (C34), %	9.7	7.5	13.0
Without coded primary (C80), %	10.0	8.8	11.8
Lymph node metastases (C77), %	20.2	17.7	24.1
Lung and/or gastrointestinal metastases (C78), %	22.3	20.4	25.1
Metastases with other localization (C79), %	19.2	19.7	18.4
Renal insufficiency (N18), %	16.8	17.6	15.6
Cachexia (R64), %	3.3	3.0	3.8
Inpatients with GI bleeding, %	1.8	1.6	2.0
1-year mortality, %	26.0	24.3	28.5

Abbreviations: GI, gastrointestinal; SD, standard deviation.

mainly treated with VKA. DOAC was predominant in 17% of the patients (NRG 21% and HRG 12%). In addition, 1.7% of the patients (NRG 1.8% and HRG 1.5%) received several anticoagulant drugs, each one for less than 51% of time share; thus, a dominant anticoagulant could not be defined.

There were differences in the prescription of the specific LMWH: within the LMWH group, most patients received enoxaparin (NRG 31%, HRG 39%), followed by tinzaparin (NRG 10%, HRG 11%) and certoparin (NRG 8%, HRG 8%). Dalteparin, nadroparin, and reviparin were each prescribed to less than 3% of the patients ([Fig. 2](#)).

### Prescription Patterns and Duration of Anticoagulation

Anticoagulant drug prescriptions were issued for a mean time period of 135 (standard deviation [SD] 117, median 119) days or 4.5 months, with 133 (SD 118, median 114) days for NRG patients and 137 (SD 115, median 127) days for those in the HRG.

The prescription period was substantially longer for LMWH than for VKA and DOAC ([Table 2](#)). Within the LMWH group, dalteparin and tinzaparin were prescribed for the longest periods. Reviparin and nadroparin had the shortest prescription periods.

### Prescription Behavior

In the outpatient setting, all anticoagulation drugs—independent of their class—were primarily prescribed by the general practitioner ([Fig. 3](#)). Unlike other LMWH brands and oral anticoagulant drugs, tinzaparin and—less obvious—dalteparin were prescribed more often in both risk groups by specialists in hematology/oncology.

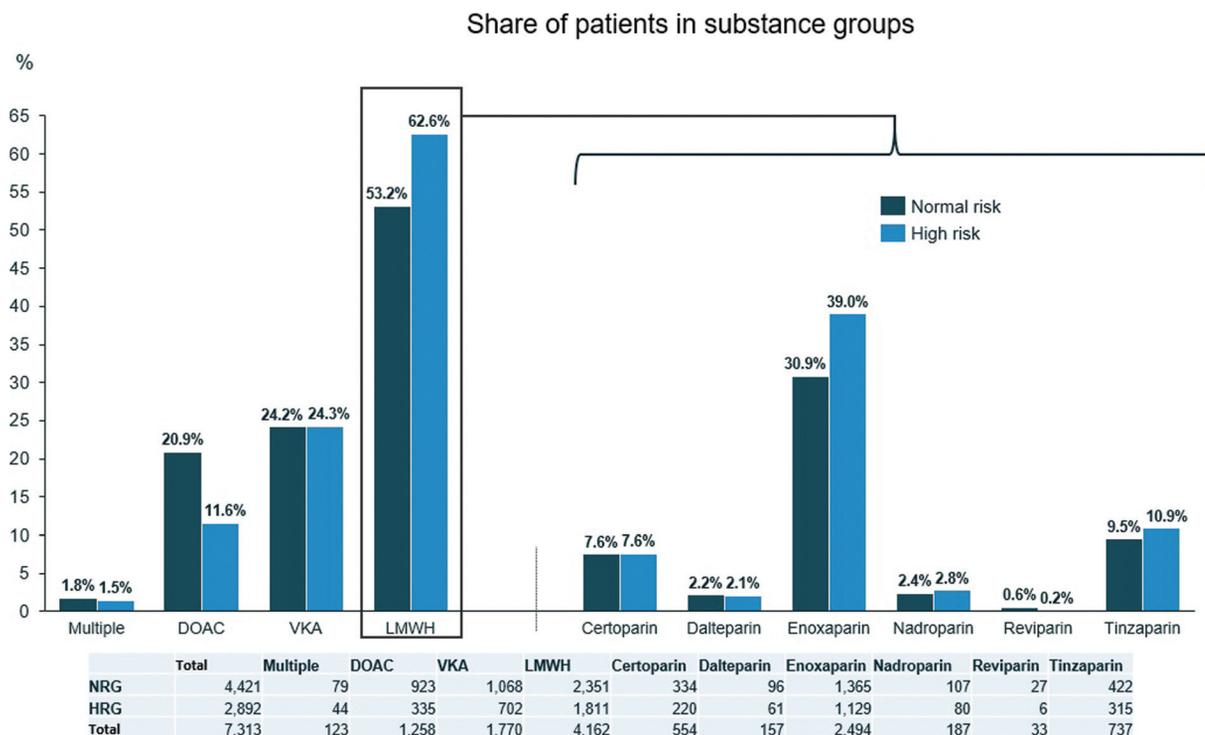


Fig. 2 Patient groups sorted by dominant anticoagulant.

**Bleeding Risks**

A total of 1.76% of patients on anticoagulants were coded as having gastrointestinal bleeding during inpatient care, 1.8% each for LMWH and DOAC, and 1.6% for VKA. When multiple anticoagulants were used, 3.3% of patients were affected (> Fig. 4).

**Discussion**

**Patient Characteristics**

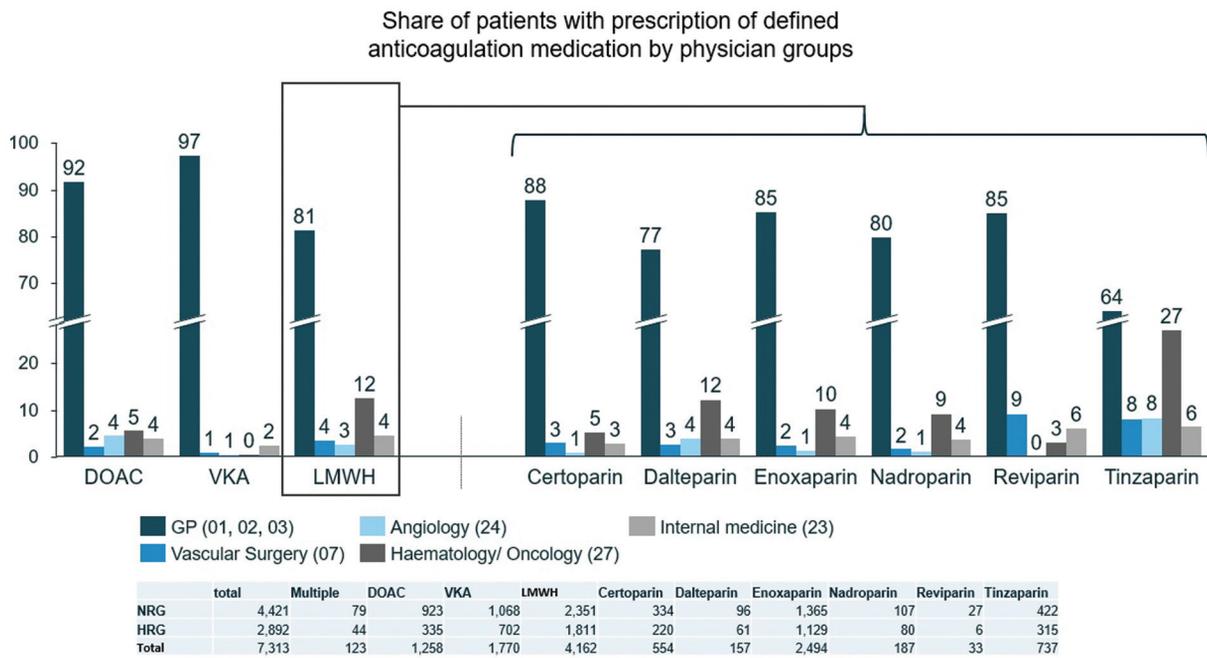
The characteristics of the population with cancer and thrombosis identified in this analysis largely correspond to the care reality and expectations derived from the literature with

Table 2 Prescription periods in days

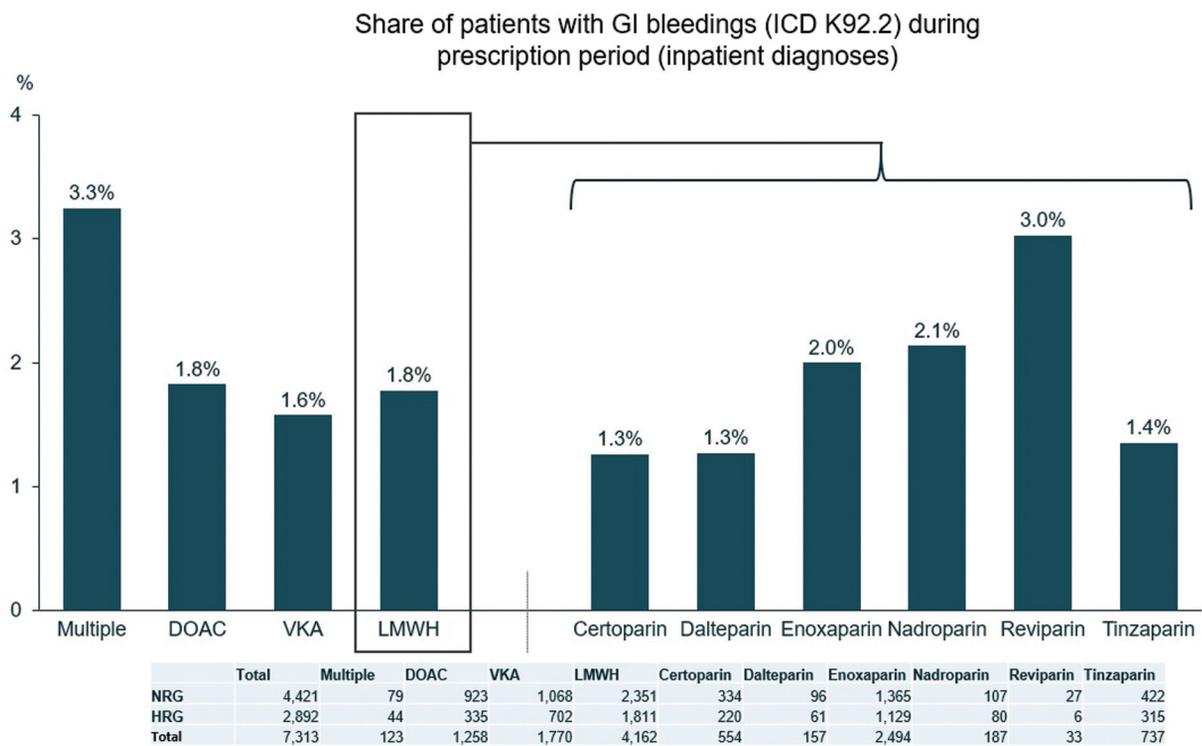
Drug class	Drug	Risk group	Mean	Standard deviation	Median
VKA		NRG	53	58	31
		HRG	62	60	45
DOAC		NRG	47	57	26
		HRG	50	56	36
LMWH	Certoparin	NRG	109	109	58
		HRG	90	91	55
	Dalteparin	NRG	135	117	103
		HRG	135	103	126
	Enoxaparin	NRG	108	101	75
		HRG	119	95	98
	Nadroparin	NRG	103	95	66
		HRG	116	91	90
	Reviparin	NRG	99	105	54
		HRG	96	102	57
	Tinzaparin	NRG	129	102	102
		HRG	127	96	106

Abbreviations: DOAC, direct oral anticoagulant; HRG, high-risk group; LMWH, low-molecular-weight heparin; NRG, normal-risk group; VKA, vitamin K antagonist.

Note: For this analysis the dates of prescription of a particular medication were analyzed. So the data represent the period between the first and last prescriptions a patient received during the observation period.



**Fig. 3** Different anticoagulation prescriptions by physician groups (note: individual patients can receive prescriptions by physicians of different groups over four quarters within the observation period, hence numbers above 100%).



**Fig. 4** Share of patients with gastrointestinal bleeding (ICD K92.2) with anticoagulant prescription according to the dominant prescription group.

regard to age, gender, distribution of underlying cancers, and comorbidities,<sup>21</sup> and thus confirm that the dataset is representative. Unexpectedly, the third most common cancer in the study population proved to be nonmelanoma cancers of the skin or appendages (C44). Usually, these cancer types are excluded from studies of cancer-associated venous throm-

boses. These skin cancers in parallel with the more common breast and prostate cancers are frequent, often diagnosed in a more elderly population, and show a prolonged cancer course. Despite the relatively low prothrombotic potential of these cancers—of ten times demonstrated for cancers of the breast or prostate—the factors mentioned together with

others may result in the predominance observed here for skin cancers as well.

It is well known that cancer patients suffering a venous thromboembolism (VTE; DVT and/or pulmonary embolism [PE]) have an increased risk of dying.<sup>6,9,22</sup> Our data with a 1-year mortality of more than 25% demonstrate that this is true for this cancer patient population with DVT and/or SVT as well, and are in line with the less recognized negative prognostic impact of SVT.<sup>7,8</sup>

### Guideline Conformity of Anticoagulation Treatment

Within the first months of treatment, about 40% of patients got prescriptions for at least two different classes of anticoagulant drugs in noncompliance to contemporary (2012–2015) recommendations favoring prolonged single-class LMWH. The ambulatory prescription period of more than 4.5 months is in line with the recommendation of at least 3 to 6 months of anticoagulation treatment for CAT.<sup>11</sup>

### Approval Status of Prescribed Anticoagulant Drugs

During the data capture period (2012–2015), only dalteparin was explicitly approved for prolonged application in cancer patients; however, the contemporary AWMF (Association of Scientific Medical Societies in Germany) guideline did not recommend a specific LMWH.<sup>11</sup> The differences in LMWH approval are not reflected by the prescription behavior. All brands of LMWH available in Germany at that time were prescribed, but the explicitly licensed drug was only to a small extent. The different frequencies of use of the individual LMWH mostly correspond with the market distribution at that time, with enoxaparin first, followed by tinzaparin and certoparin.

### Prescribers

All kinds of anticoagulant drugs were primarily prescribed by general practitioners, followed by specialists in hematology and oncology. This subgroup of internists prescribed dalteparin and especially tinzaparin more often. This may be due to the awareness of the favorable study result in CAT<sup>15</sup> and/or the approval status of dalteparin. With regard to tinzaparin, there was a lively discussion in the oncological community around the presentation of the CATCH-study results, which demonstrated a positive risk–benefit ratio for tinzaparin as compared to VKA.<sup>16</sup>

### Differences in the Two Risk Groups

Dividing the CAT patients into two groups a priori depending on whether they had an already pre-existing or a newly diagnosed cancer proved to be meaningful: HRG showed an increased mortality rate and the NRG showed a higher proportion of breast and prostate cancer patients—cancers that are well known for a relatively low risk of venous thromboses. The documented prescription patterns seem to indicate a similar risk categorization by the treating physicians. This may explain why HRG patients were more often (62.6%) treated mainly with LMWH as compared to the NRG (52.2%). Concordantly, HRG patients were less often treated with DOAC (11.6 vs. 20.9%).

Unlike today,<sup>23,24</sup> during the investigation period there were no results from RCTs available demonstrating the effective and safe use of DOAC as an alternative to LMWH in cancer patients with venous thromboses. Thus, the relatively common prescription of DOAC was unexpected. However, this finding is in line with the results of a survey done in 2014 of hematologists and phlebologists. According to this survey, 22% of VTE cancer patients were treated with oral anticoagulant drugs (VKA or DOAC) within the first 3 months; 31 and 33% received VKA and DOAC, respectively, in the 3 to 6 months of treatment period.<sup>25</sup>

### Bleeding

Our analysis confirms the known risk of gastrointestinal bleeding events of 1.5 to 2.0% in connection with a hospital stay.<sup>26</sup> There was a tendency toward lower bleeding events for LMWH with higher median molecular weight (certoparin, dalteparin, tinzaparin); LMWH with lower molecular weight and higher renal elimination rates (enoxaparin, nadroparin, reviparin) showed a trend toward more bleeding events. But the low patient numbers and the design of our study do not allow for a robust statement to be extracted. There is no evidence that the broad use of LMWH and DOAC outside the approved use resulted in an increased bleeding risk. In patients with multiple anticoagulant drugs but without a dominant substance, there was a relatively high rate of gastrointestinal bleeding. This may have been occurred by chance; however, an alternative explanation may be that this group represents medically complex patients difficult to anticoagulate continuously and with whom it was not possible to establish a dominant anticoagulant.

### Limitations

The analysis of SHI claims data has inherent limitations. When using this kind of analysis, validity is directly related to the validity and granularity of the underlying coding system as well as to the quality of coding in clinical practice. The coding quality may be even less for common symptoms such as cachexia (R64).

We analyzed prescriptions in the outpatient sector of the German health care system. These data allow statements to be extracted about prescribed and dispensed medication, but not about patient adherence and persistence with the medication. Furthermore, the last prescription of an anticoagulant drug cannot be equated with the duration of medication, as the size of packages is not coded, and some packages—especially those for DOAC and VKA—may contain up to 100 daily dosages. This may at least in part explain the reduced prescription period for the two oral anticoagulant classes. Information about those patients transferred from hospital to ambulatory care cannot be extracted from the data set as the inpatient medication of anticoagulant drugs is included in the lump sum (diagnosis related groups) and patients receive no separate prescription. Thus, it remains unclear whether ambulatory follow-up prescriptions in the outpatient sector follow the recommendations at discharge or were newly established by the outpatient prescriber. Incident thromboses were diagnosed by 90% of the overall

population in the outpatient sector. Results of the survey mentioned above show that in cancer patients as well, most cases of VTE are diagnosed and treated out of hospital.<sup>25</sup> Thus, it is very suggestive that anticoagulant treatment analyzed for the study population in a substantial extend was initiated in the outpatient sector.

Due to the coding system, a clear-cut differentiation between DVT and SVT was not possible. Both kinds of venous thromboses occur more often in cancer than in noncancer patients. In contrast to DVT, there is a gap of knowledge and data with regard to frequency and impact of SVT.<sup>5,7,8</sup> Frequently, SVTs are accompanied by DVT.<sup>4</sup> When planning this study cancer patients with incident PE (I26) were excluded because of the unclear meaning and therapeutic consequence of a steadily increasing proportion of asymptomatic or incident PEs diagnosed in the context of investigations for cancer staging in the investigated period.<sup>27,28</sup> In addition, no statements can be extracted related to anticoagulation intensity and treatment efficacy as there are no specific codes for recurrences of thromboses. Due to coding shortcomings, the possibilities of a more differentiating bleeding characterization are limited.

Nevertheless, analyses of SHI big data allow extracting insight into the care reality. Unlike RCTs or within application monitoring studies or phase IV studies, there is no decisive selection of licensed or recommended treatments or patient characteristics.

## Conclusion

This analysis uses the most comprehensive data set in Germany on anticoagulation treatment in cancer patients with thromboses. Due to the methodology, there is no risk of bias. The analysis shows that the prescriptions were primarily dispensed by general practitioners. The duration of anticoagulation treatment is guideline-conform and considers patient prognosis, but surprisingly the selection of anticoagulant drugs meets neither evidence nor approval status of the investigation period.

## Key Findings

- This analysis of a representative sample of routine data of 4 million statutory insured persons in Germany allows us to describe the care reality in the ambulatory sector of anticoagulated cancer patients with acute thrombosis.
- Around 90% of thromboses were diagnosed and treated in the outpatient sector.
- Prescriptions in the ambulatory sector were predominantly issued by general practitioners.
- Despite a lack of evidence during the observation period, 40% of affected cancer patients were predominantly treated with oral anticoagulants.
- The duration of prescriptions of 3 to 6 months was predominantly compliant with guidelines.
- Bleeding complications, as assessed by gastrointestinal bleed in connection with hospitalization, occurred in 1.76% of patients.

## What Is Known about This Topic?

- The risk of deep or superficial venous thrombosis is distinctly elevated in cancer patients and connected with a worse survival prognosis as compared to noncancer patients.
- Anticoagulation with low-molecular-weight heparin is the guideline-recommended treatment initially and for the first 3 to 6 months in cancer-associated deep venous thrombosis.

## What Does This Paper Add?

- In Germany, outpatients with cancer-associated thrombosis are predominantly treated by general practitioners.
- Anticoagulation treatment duration is in accordance with the choice of anticoagulant drug, often in noncompliance with the guidelines or label.

### Funding

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### Conflict of Interest

The authors declare that they have no conflict of interest.

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