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ORIGINAL ARTICLE

Anticoagulant medication adherence for cancer-associated thrombosis: A comparison of LMWH to DOACs

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Abstract

Background: Low molecular weight heparin (LMWH) and direct oral anticoagulants (DOACs) are used to treat cancer-associated thrombosis (CAT). It is not clear if patients are less adherent to LMWH compared to DOACs.

Objectives: To compare medication persistence and adherence between LMWH and DOACs.

Patients/Methods: We analyzed Optum's de-identified Clinformatics® Data Mart Database of privately insured adults with cancer diagnosed between January 2009 and October 2015 who were undergoing chemotherapy, immunotherapy, targeted or hormonal therapies; developed CAT; and were treated with an outpatient anticoagulant. The proportion of days covered (PDC) was calculated from the date of anticoagulant prescription until the anticoagulant was switched, stopped, or the study end. Medication adherence was defined as PDC ≥ 80%, ≥95%, and by comparing the mean PDC.

Results: Two propensity-matched groups of 1128 patients were identified. Patient persistence was higher with DOACs compared to LMWH (median 116 days versus 34 days). With adherence defined as PDC ≥ 80%, we found no significant difference (95.6% versus 94.6% adherence with DOACs versus LMWH, $P = .33$). The mean difference of PDC between the two groups was also similar. With medication adherence defined as PDC ≥ 95%, adherence was evident in 73% of DOAC users and 81% of patients on LMWH ($P < .001$). Prescription copayments were higher on average for LMWH compared to DOACs (mean $153.61 versus 40.67; standard deviation $306.74 versus $33.11).

Conclusion: Patients remain on DOACs longer than LMWH, but medication adherence is similar with LMWH.

KEYWORDS

direct-acting oral anticoagulants, duration of therapy, low molecular weight heparin, patient compliance, venous thromboembolism

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1 | BACKGROUND

Venous thromboembolism (VTE) is a leading cause of death among people with cancer.[1] With cancer patients living longer and undergoing more invasive procedures such as central lines, the incidence of cancer-associated thrombosis (CAT) has been increasing over the past two decades. CAT affects up to 8% of all cancer patients.[1] Costs of care in patients with CAT ($49 351) are nearly twice those of patients without ($26 529) and remain significantly higher for years after the index VTE event.[2] Furthermore, CAT reduces patient quality of life and may interrupt cancer directed therapy.[1]

Several studies have shown that, compared to warfarin, using low molecular weight heparin (LMWH) for CAT results in a lower rate of recurrent VTE with a similar rate of major bleeding.[3-8] Anticoagulation options for CAT continue to evolve, with recent clinical trials showing that three of the direct oral anticoagulants (DOACs)—apixaban, rivaroxaban, and edoxaban—may offer an oral anticoagulant option with similar therapeutic efficacy to LMWH for CAT. Some of the studies of the DOACs for CAT showed a potential increased bleeding rate, especially for patients with gastrointestinal malignancies.[9-13] For patients that are candidates for DOAC therapy, one clinical practice guideline favors DOACs for patients without gastric or gastroesophageal lesions;[14] another guideline recommends DOACs and LMWH for long-term anticoagulation for CAT (over vitamin K antagonists), noting caution with DOACs for gastrointestinal and potentially genitourinary malignancies.[15]

Patient adherence, the extent to which patients take the prescribed anticoagulant, is critical for the successful treatment of CAT. It is not clear if patient adherence is improved with the oral DOACs compared to potentially uncomfortable and/or more expensive subcutaneous LMWH therapy. While a patient's adherence to warfarin is easy for clinicians to assess by following a patient's international normalized ratio (INR), providers must rely on refill data and patient report to determine if patients are taking DOACs or LMWH, which are not routinely monitored with drug levels. While it has been suggested that patient persistence, or the duration a patient continues a prescribed anticoagulant, on LMWH is less than oral anticoagulant options,[7] patient adherence has not been well studied. We sought to better understand drug persistence and adherence in a non-trial setting. We compared patients on DOACs and LMWH using pharmacy claims data to assess patient persistence on their initial anticoagulant and the proportion of days covered (PDC), as a surrogate of anticoagulant adherence.

Essentials

- It is not clear if patients are less adherent to low molecular weight heparin (LMWH) compared to direct oral anticoagulants (DOACs) for cancer-associated thrombosis (CAT).
- We evaluated medication adherence among two propensity-matched groups of patients with CAT by comparing the proportion of days covered (PDC).
- Median treatment persistence on DOACs was more than 80 days longer than LMWH.
- Medication adherence was high (~95%) and was similar with LMWH compared to DOACs.

2 | METHODS

2.1 | Study design

A retrospective cohort study to investigate the effect of anticoagulant class on medication adherence for CAT was performed using Optum's de-identified Cliniformatics® Data Mart. Cliniformatics® Data Mart is a large commercial and Medicare Advantage claims database containing data on more than 61 million privately insured individuals. The database contains linked, de-identified data on inpatient care, outpatient care, prescription claims, and geographic data. This study was determined to be exempt by the University of Michigan Institutional Review Board.

2.2 | Patient selection

We used data from January 2009 through June 2016 (Figure 1). Included patients were over 18 years of age, and had at least one International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code for VTE (Table S1 in supporting information), and at least 12 months of continuous data available prior to their initial diagnosis of VTE, allowing up to a 30-day lapse in insurance coverage. Patients were excluded if they had an outpatient claim for VTE over the 12 months prior to the index VTE diagnosis but a code for a history of VTE (V12.51) was permitted.

A subcohort of patients with active cancer was identified as those patients with at least one ICD-9-CM code for a diagnosis of cancer (Table S2 in supporting information) before the index code for VTE. In addition to a code for cancer, the study cohort was restricted to patients with a simultaneous or subsequent cancer-directed treatment as defined by Healthcare Common Procedure Coding System Codes (HCPCS) code or National Drug Code (NDC) in any position, from inpatient or outpatient claims data (Tables S3 and S4 in supporting information). The HCPCS codes and NDC codes[16] were obtained from the National Cancer Institute and reviewed a priori by the study team. Drugs not thought to be consistent with potential cancer treatment were excluded. Chemotherapy, immunotherapy, targeted and hormonal therapies were included as cancer treatments. If patients had more than one code for cancer on or before their later claim for an episode of VTE (index VTE) they were categorized in the multiple cancer group, otherwise they were grouped by cancer subtype. Codes for both cancer diagnosis and treatment had to occur before the initial code for VTE. We did not require the VTE code to be in close proximity to the cancer diagnosis

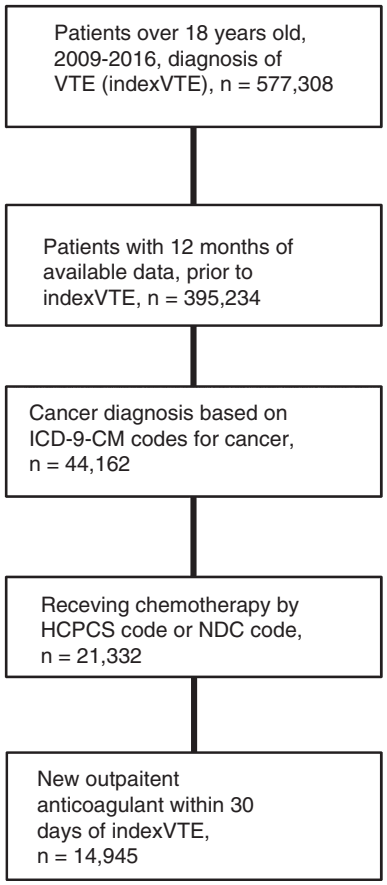

FIGURE 1 Flowchart reflecting initial cohort selection. HCPCS, Healthcare Common Procedure Coding System Codes; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; NDC, National Drug Code; VTE, venous thromboembolism

or treatment codes, as long as the cancer was diagnosed before the VTE event. Included patients were diagnosed with cancer and CAT between January 2009 and October 2015 (when ICD-9 codes were transitioned to ICD-10); medication records were then followed through June 2016.

Ultimately, this cohort of patients with active cancer and a new code for VTE was limited to patients that received a new prescription for an anticoagulant. Anticoagulants were identified by NDC codes and included apixaban, dabigatran, dalteparin, enoxaparin, fondaparinux, rivaroxaban, and warfarin (Table S5 in supporting information). All of the included ICD-9-CM codes had been validated in other studies with high positive and negative predictive values, especially in conjunction with a new anticoagulant prescription.[17-22] Included patients had to have an outpatient prescription claim for an anticoagulant within 30 days of the index VTE. Those with no outpatient claims within this timeframe were excluded. Patients had to have at least 30 days of anticoagulation days supplied to be included. Patients on warfarin or with short prescriptions of LMWH with a prescription for warfarin within ≤ 10 days were excluded for this analysis as these patients were considered to be on warfarin and receiving bridging anticoagulation.

The combination of a ICD-9-CM for VTE with a subsequent prescription for an anticoagulant, inferior vena cava (IVC) filter placement, or death has shown a positive predictive value of 0.91 and a negative predictive value of 0.95 in a previous study that most closely mirrors our strategy.[19]

2.3 | Measures

Patient demographics were assessed at the time of the index VTE, and hospital claims were assessed for recent hospitalization (defined as within the 4 weeks prior to the index VTE). Medical claims over the 12 months prior to index VTE were reviewed to assess relevant co-morbidities,[23] tobacco use,[24] and concomitant medications by NDC code. A modified (to exclude cancer) Charlson Comorbidity Index was calculated for each patient.[25] Optum uses a major data syndicator, Knowledge-Based Marketing Solutions (KBM, Richardson, TX) to provide several socioeconomic variables; data are linked to participants in Optum by name, date of birth, address, and phone number. KBM collects data from primary sources, including public records, purchase transactions, census data, and consumer surveys.[26] Socioeconomic variables—insurance type, educational attainment, and household income—were collected for each patient. Although not used in propensity-score matching, prescription copayment data was analyzed post-matching by determining the total copayment cost over the duration of follow-up and averaged to be the cost per 30-day supply of anticoagulant.

Each patient's initial anticoagulant prescription was identified based on anticoagulant class (LMWH or DOACs). Pharmacy claims data were reviewed from the time of the initial anticoagulant was prescribed until the patient stopped anticoagulation, had a prescription for another anticoagulant, or through the end of our study period (June 2016). Within the limitations of our dataset, stopping anticoagulation could be due to a variety of reasons, including death, change of health insurance, or discontinuing the anticoagulant due to physician and/or patient choice.

Stopping anticoagulation for DOACs or LMWH was defined as no claim for an anticoagulant for > 30 days after the end of the days supplied with the most recent anticoagulant prescription. This was to allow a grace period for patients that may have missed doses, been hospitalized (and receiving their anticoagulation from an inpatient stay), or temporarily held (for example, with thrombocytopenia related to chemotherapy), or other situations that would not require them to refill their anticoagulant prior to the end of the number of days supplied.

We calculated the PDC for each patient group. Medication adherence was defined as a PDC ≥ 80%.[27] We also conducted a sensitivity analysis, defining medication adherence as PDC ≥ 95%. Next, we conducted a second sensitivity analysis comparing mean PDC between the two groups to evaluate adherence as a continuous variable. PDC was calculated by dividing the number of days supplied of LMWH or DOAC by the number of days that passed from the date of the initial anticoagulant prescription until the (a) first date a

prescription for an anticoagulant class other than that of initial anticoagulant (anticoagulation switch), (b) end of the study period (June 30, 2016), or (c) patient met criteria for stopping anticoagulation (Table 1), with the date of stopping considered the final day of the days supplied from the most recent prescription. Given that patients admitted to the hospital would likely have their anticoagulant, if continued, supplied by the hospital rather than from their outpatient supply, the days that the patient was admitted to the hospital were excluded from the PDC calculation.[28] This was to avoid potentially biasing the results toward decreased adherence among hospitalized, as patients may not need to refill their medication as soon after a hospital stay.

Patient persistence on anticoagulation was assessed as the time from index VTE to the time of being censored based on one of the above criteria.

While we excluded patients with less than 30 days of outpatient anticoagulation, it was unclear if adherence would differ among patients receiving a longer course of anticoagulation. Therefore, we conducted a third sensitivity analysis that limited the study to patients who received at least 90 days of anticoagulation.

2.4 | Statistical analysis

We compared the baseline characteristics of the LMWH- and DOAC-treated groups using frequency distributions and univariate descriptive statistics. Means and standard deviations were calculated for continuous covariates; counts and proportions were calculated for categorical covariates. We tested statistical imbalance between the two anticoagulant groups using analysis of variance for continuous variables; we used Chi-squared tests for categorical covariates with a sufficient number of patients and Fisher's exact test for categorical covariates with small patient numbers (n ≤ 5).

To compare medication adherence between the two anticoagulant groups, while minimizing treatment selection bias, we employed a propensity-score matching method. We matched two individuals in separate anticoagulant groups by propensity score. The propensity-score matching enables direct comparisons of the adherence rates accounting for observed confounders. We used logistic regression for estimating propensity score based on the baseline covariates: age, sex, region, Charlson Comorbidity Index, recent (within 4 weeks) hospitalization, history of VTE, type of malignancy, type of medical insurance, region, year of index VTE, and type of thrombosis. Given the minimal overlap of copayment between the two groups, we did not include copayment in the propensity-score matching model. We carried out one-to-one matching using nearest neighbor method with caliper size 0.01 (R package MatchIt version 3.0.2). Here, the caliper size is the maximum standard deviation (SD) of the estimated propensity scores within which two subjects on LMWH or DOAC are identified and matched. A standardized difference of less than 0.1 was used to indicate a negligible difference in the covariates between the groups.[29] We checked covariate balance upon propensity-score matching by paired t-test for continuous covariates and McNemar's test for categorical covariates. The propensity score–matched adherence rate comparison was based on McNemar's test. All statistical tests were two-sided and *P*-value ≤ 0.05 was considered statistically significant. We performed all computations using R version 3.6.1.

For the second sensitivity analysis, we compared medication adherence as evaluated by mean PDC. The mean difference in PDC between matched and unmatched groups was compared; a paired *t*-test was used for comparing mean PDC values.

TABLE 1 Anticoagulation receipt definitions

	Definition
Continued anticoagulation	Patients with evidence of continued anticoagulant use throughout the remaining study period who do not have a claim for an anticoagulant belonging to another anticoagulant class
Anticoagulation switch	Patients with evidence of continued anticoagulant use who submit a claim for an anticoagulant belonging to another anticoagulant class ≥ 1 day from their most recent claim
Stopped anticoagulation	
LMWH	No claim for an anticoagulant >30 days after the end of the days supplied for the last prescription.
DOAC	No claim for an anticoagulant >30 days after the end of the days supplied for the last prescription.

Abbreviations: DOAC, direct oral coagulant; LMWH, low molecular weight heparin.

3 | RESULTS

A total of 2580 patients with active cancer and an episode of CAT were treated with LMWH, compared to 1570 patients treated with DOACs. Before propensity-score matching, we found that 5% of DOAC users were non-adherent to therapy compared to 6% of those anticoagulated with LMWH.

Two propensity score–matched groups of 1128 patients on DOACs and LMWH were compared. Patients were followed for a median of 72 days (interquartile range [IQR]: 30–170 days). Patients remained on DOACs for a median of 116 days (IQR: 57–231 days) compared to a median of 34 days for LMWH (IQR: 30–92 days; Figure 2).

After matching, there were no significant differences between the groups with respect to age, modified Charlson Comorbidity Index score, sex, recent hospitalization, type of thrombosis, type of malignancy, health insurance subtype, region, and history of VTE (Table 2). Furthermore, matching was effective in achieving balance between the two groups by reducing the absolute standardized differences to <0.1 in all covariates (Figure 3, Figure S1 in supporting

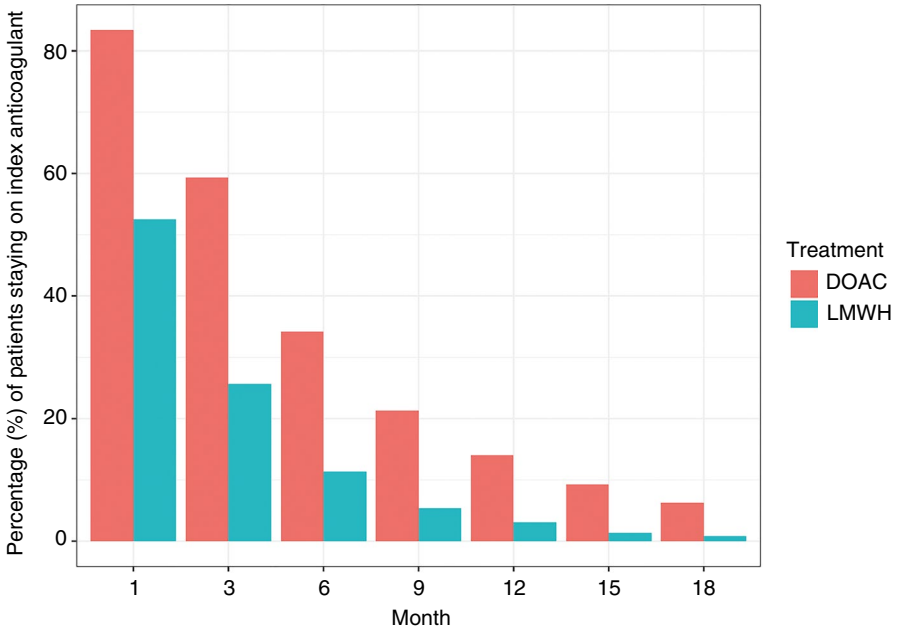

FIGURE 2 Patient persistence by anticoagulant class after propensity score matching. DOAC, direct oral coagulant; LMWH, low molecular weight heparin

information). After matching, the average prescription copayment for 30 days of medication supplied was numerically higher for LMWH treated patients compared to DOAC treated patients (mean $153.61 versus 40.67; SD $306.74 versus $33.11).

Medication adherence, defined as a PDC ≥ 80%, was evident in 96% of DOAC users compared to 95% of patients on LMWH ($P = .33$; Table 2). For our first sensitivity analysis, defining medication adherence as a PDC ≥ 95%, medication adherence was evident in 73% of DOAC users and 81% of patients on LMWH ($P < .001$).

Our second sensitivity analysis, comparing adherence as a continuous variable rather than a dichotomous variable, showed a matched group mean adherence difference between DOAC and LMWH of −0.004 days covered (95% confidence interval [CI]: −0.029 to 0.020; $P = .72$), indicating no significant difference between the two groups.

For our third sensitivity analysis, limiting the study to patients with at least 90 days of outpatient anticoagulation, two propensity-matched groups of 668 patients were compared. Medication adherence was evident for 95% of DOAC users compared to 95% of LMWH users ($P = .90$).

4 | DISCUSSION

This analysis shows that a high proportion of cancer patients are adherent to the anticoagulant class prescribed by their physician, which highlights the importance of choosing the best anticoagulation agent for an individual patient for the management of CAT, not necessarily the most convenient. While the DOACs may be preferred because of the ease of oral administration, adherence does not differ between the DOACs and LMWH. However, by 3 months, more than half of patients initially managed with LMWH will have transitioned to another anticoagulant class (Figure 2), emphasizing that due to cost, a desire to avoid injections, and/or other factors, patient persistence is less with LMWH.

In this study of more than 2200 matched patients with active cancer and an initial episode of CAT, in a non-trial setting, adherence rates in both groups were high. There was no statistically significant difference in adherence between LMWH and DOACs for the primary analysis (defining medication adherence as PDC ≥ 80%). Furthermore, the marginal difference in adherence that was observed is of uncertain clinical significance. When medication adherence was compared by mean PDC (DOAC-LMWH), we again found no significant difference in adherence for DOACs versus LMWH. With a stricter definition of medication adherence (PDC ≥ 95%), we found that medication adherence was actually significantly greater for LMWH compared to DOACs. While medication adherence was overall similar, we did find that patient persistence on LMWH as an initial anticoagulant therapy was significantly shorter than DOACs, consistent with previous research.[7]

The high medication adherence in our study mirrors that seen in clinical trials and argues against the perception that patients will be less adherent with the parenterally administered LMWH compared to the oral DOACs. Approximately 86% of patients on LMWH and edoxaban were adherent to the study treatment compared to 89% on dalteparin monotherapy in the Hokusai VTE-Cancer Trial (defined as taking at least 80% of the prescribed treatment before discontinuation).[9] The median length of treatment in Hokusai VTE-Cancer was 211 days for edoxaban versus 184 for dalteparin; 15% of patients discontinued dalteparin due to the inconvenience of dosing compared to 4% of patients on edoxaban.[9] In the SELECT-D Trial, 22% of patients reported missing doses of dalteparin compared to 27% with rivaroxaban; the median duration of treatment was similar with 5.9 months for rivaroxaban and 5.8 months with dalteparin.[10] In the Caravaggio trial, the median duration of therapy was 178 days

TABLE 2 Characteristics and adherence of patients with cancer-associated thrombosis treated with DOACs versus LMWH before and after propensity-score matching

	Before matching		After matching	
	LMWH n = 2580	DOAC n = 1570	LMWH n = 1128	DOAC n = 1128
Age (years), mean (SD)	61.7 ± 12.9	67.7 ± 12.7	65.4 ± 11.8	65.8 ± 13.0
Copayment per 30-day supply ($), mean USD (SD)	155.38 ± 362.87	44.64 ± 46.14	153.61 ± 306.74	40.67 ± 33.11
CCI Score,[a] mean (SD)	1.9 ± 1.8	2.0 ± 2.0	2.0 ± 1.9	1.9 ± 1.9
Male sex no. (%)	1144 (44.3)	708 (45.1)	510 (45.2)	513 (45.5)
Recently hospitalized no. (%)	495 (19.2)	218 (13.9)	165 (14.6)	164 (14.5)
History of VTE no. (%)	196 (7.6)	102 (6.5)	61 (5.4)	64 (5.7)
Region no. (%)				
South Atlantic, Middle Atlantic, New England	1062 (41.2)	627 (39.9)	458 (40.6)	452 (40.1)
East North and South Central	535 (20.7)	331 (21.1)	256 (22.7)	255 (22.6)
Mountain, Pacific	421 (16.3)	284 (18.1)	194 (17.2)	191 (16.9)
Unknown	8 (0.3)	2 (0.1)	1 (0.1)	2 (0.2)
West North and South Central	554 (21.5)	326 (20.8)	219 (19.4)	228 (20.2)
Insurance no. (%)				
HMO	515 (20.0)	274 (17.5)	199 (17.6)	193 (17.1)
EPO, IND, PPO	400 (15.5)	253 (16.1)	173 (15.3)	169 (15.0)
OTH	427 (16.6)	505 (32.2)	311 (27.6)	330 (29.3)
POS	1238 (48.0)	538 (34.3)	445 (39.5)	436 (38.7)
Malignancy no. (%)				
CNS	101 (3.9)	25 (1.6)	23 (2.0)	22 (2.0)
Breast	376 (14.6)	371 (23.6)	224 (19.9)	209 (18.5)
Gastrointestinal	559 (21.7)	242 (15.4)	208 (18.4)	206 (18.3)
Genitourinary	271 (10.5)	281 (17.9)	174 (15.4)	176 (15.6)
Gynecologic	103 (4.0)	32 (2.0)	27 (2.4)	30 (2.7)
Hematologic	306 (11.9)	186 (11.9)	129 (11.4)	123 (10.9)
Lung	311 (12.1)	149 (9.5)	113 (10.0)	130 (11.5)
Other[b]	903 (35.0)	427 (27.2)	345 (30.6)	356 (31.6)
Index VTE type no. (%)				
Lower extremity DVT	984 (38.1)	717 (45.7)	492 (43.6)	466 (41.3)
Pulmonary embolism	994 (38.5)	601 (38.3)	451 (40.0)	453 (40.2)
Upper extremity DVT	200 (7.8)	83 (5.3)	73 (6.5)	82 (7.3)
IVC/RV/PV	56 (2.2)	19 (1.2)	14 (1.2)	15 (1.3)
Multiple VTE types	682 (26.4)	386 (24.6)	292 (25.9)	305 (27.0)
Other/unspecified	182 (7.1)	108 (6.9)	68 (6.0)	64 (5.7)
Non-adherence no. (%)	152 (5.9)	72 (4.6)	61 (5.4)	50 (4.4)

Abbreviations: CCI, Charlson Comorbidity Index; CNS, central nervous system; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; EPO, exclusive provider organization; HMO, health maintenance organization, IND, indemnity; IVC, inferior vena cava; LMWH, low molecular weight heparin; OTH, other; POS, point of service; PPO, preferred provider organization; PV, portal vein; RV, renal vein; SD, standard deviation; USD, United States dollar; y, years.

[a]Modified to exclude cancer.

[b]Other includes cardiac, genitourinary, multiple cancers, metastatic, neuroendocrine, other thoracic, other abdominal, sarcoma, or unspecified cancers.

for apixaban compared to 175 days for dalteparin ($P = .15$); approximately 7% of patients on apixaban received less than 80% of the planned treatment compared to 9% of patients on dalteparin.[13] In the ADAM VTE trial,[11] 62% of patients assigned to apixaban completed the study protocol compared to 54% of patients assigned to dalteparin; 4% of apixaban treated patients refused further treatment

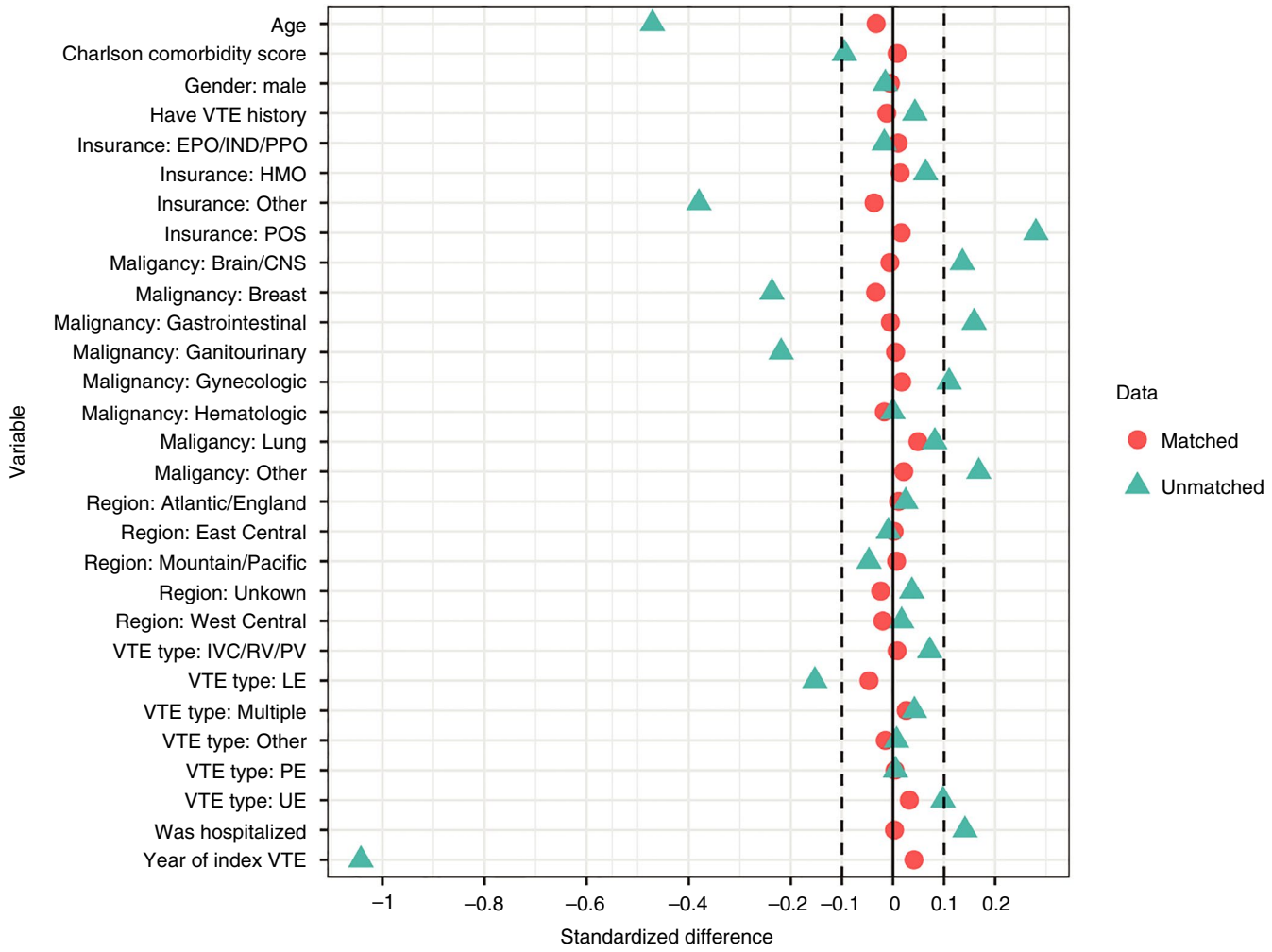

FIGURE 3 Standardized difference plot. Dashed lines represent a standardized difference of −0.1 and 0.1. CNS, central nervous system; EPO, exclusive provider organization; HMO, health maintenance organization, IND, indemnity; IVC, inferior vena cava; LMWH, low molecular weight heparin; OTH, other; POS, point of service; PPO, preferred provider organization; PV, portal vein; RV, renal vein; UE, upper extremity; VTE, venous thromboembolism.

compared to 16% with dalteparin. Our study suggests that adherence may be similar in a non-trial, real-world setting. However, we observed a more striking difference in medication persistence, with DOAC users continuing their initial therapy on average more than 100 days longer than LMWH.

The distinction between adherence and persistence is important. While patients may be less willing or financially able to take extended durations of LMWH (persistence), our data do not suggest that they are significantly less likely to take the medication once prescribed (adherence), when controlling for other variables. Considering that a higher bleeding rate is anticipated among patients first starting anticoagulant therapy,[30] as patients predisposed to bleeding manifest clinically, the shorter half-life of LMWH may be preferred to DOACs for some patients. Again, fewer drug interactions, lower bleeding rates for gastrointestinal cancers,[12] fewer absorption issues, and more extensive experience are some reasons LMWH may be preferred to a DOAC for some patients. Our findings generally do not suggest that anticipated medication adherence should influence initial anticoagulant selection for CAT. For patients initially managed with LMWH, clinicians should be aware that many patients may elect to change anticoagulants within the first 90 days of therapy.

Our study findings also highlight the difference in medication copayments between the two anticoagulant classes we studied. We found that when controlling for other factors, patients on LMWH are paying on average more than $100 more per month compared to DOACs for their anticoagulants. This finding favors the DOACs for patients that are otherwise candidates for such treatment, especially considering the substantial financial burden already associated with cancer treatment. The added cost of LMWH may contribute to the lower patient persistence on LMWH relative to DOACs. Interventions at the health-care policy and system level should be considered to try to mitigate potential financial barriers to patients receiving optimal care based on clinical factors. Until that time, clinicians should remain cognizant of the costs patients may be paying for their anticoagulant medications.

Strengths of this study include the use of pharmaceutical claims with two well-matched cohorts, all newly starting anticoagulation, using a conservative definition for CAT. We conducted several

sensitivity analyses that support our study findings. Limitations include the retrospective design, the potential for unadjusted confounding variables and selection bias inherent to a retrospective claims analysis, and that there may be limitations in generalizability. Despite propensity score matching, it is worth noting that patients with worse prognoses (eg, more advanced cancer) may be more likely to be prescribed LMWH than DOACs. Such patients with shorter longevity and duration of follow-up may bias the results toward greater adherence in the LMWH group. Including patients with short follow-up periods, as short as 30 days, could bias the study results toward higher rates of adherence. However, we would expect this to influence both treatment groups equally. The use of propensity score matching may limit the inclusion of extremes of both anticoagulant cohorts and accordingly the results are most applicable to patients that are candidates for both LMWH and a DOAC.

Some trials regarding the use of DOACs in CAT were published after the time of our study. While these results may inform patient selection, we do not expect them to impact patient medication adherence. We were not able to adjust for stage of cancer/disease. It is possible that patients with more advanced disease were more likely to get LMWH, and this may influence adherence and/or persistence. The study was only of privately insured individuals and therefore may not be generalizable to other populations. We were also not able to fully match on copayments. One might expect that the higher copayments for the LMWH group would bias the results toward lower adherence in this group compared to the DOACs, which had a lower average copayment. Consistent with other studies, we primarily defined adherence as a PDC ≥ 80% but it is not clear what non-adherence rate would be clinically significant. Interestingly, when using a stricter definition of medication adherence of a PDC ≥ 95%, patients on LMWH were significantly more adherent compared to LMWH. It is not clear if this is due to confounding with patients with higher risk clots, for whom adherence may be more important, being more likely to receive LMWH. Further research is needed to understand what level of adherence is clinically relevant and to prospectively evaluate if adherence may be greater with LMWH.

In conclusion, we found a similarly high rate of LMWH and DOAC adherence for patients with CAT. Anticipated differences in medication adherence should not guide anticoagulant selection for many patients with CAT, as adherence seems similar with LMWH compared to DOACs. Recognizing that costs may be higher and medication persistence may be less with LMWH, clinicians should regularly re-assess the optimal anticoagulant for their patient in clinical follow-up. Larger studies should be conducted to confirm these findings and explore the role of copayment in anticoagulation persistence/adherence.

CONFLICTS OF INTEREST

Geoffrey Barnes—honoraria: Pfizer/BMS, Janssen, Portola, AMAG Pharmaceuticals; research funding: Blue Cross Blue Shield of Michigan, BMS, Pfizer, NHLBI. Marc Carrier—research funding: BMS, Pfizer, Leo Pharma; honoraria: Bayer, BMS, Pfizer, Leo Pharma, Sanofi, Servier. Michael Dorsch—honoraria (in the past 2 years): Jansen; research funding: Amgen, NIH/NIA, AHRQ, American Heart Association. Jennifer J. Griggs—consulting role: Anglona Corporation; research funding: NIH/NCI. Suman Sood—consulting or advisory role: Bayer. Mengbing Li—research funding: partly supported by the start-up funds from Michigan Institute for Data Science (MIDAS). Zhenke Wu—research funding: partly supported by the National Cancer Institute of the NIH under award number P30CA046592 through the Cancer Center Support Grant (CCSG) Development Funds from the Rogel Cancer Center, and an investigator award from Michigan Precision Health Initiative, and start-up funds from Michigan Institute for Data Science (MIDAS). No other conflicts of interest are reported.

AUTHOR CONTRIBUTIONS

Jordan K. Schaefer, Mengbing Li, Zhenke Wu, Michael Dorsch, Jennifer J. Griggs, and Suman L. Sood: designed research, collected analyzed data, and wrote the paper. Tanima Basu collected and analyzed the data. All authors revised the paper and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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