Outpatient Use of Low Molecular Weight Heparin Monotherapy for First-Line Treatment of Venous Thromboembolism in Advanced Cancer

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ABSTRACT

Background. Evidence-based treatment guidelines recommend low molecular weight heparin (LMWH) monotherapy for cancer-associated venous thromboembolism (VTE). This analysis assessed the first-line treatment strategies for VTE in patients with advanced solid tumors.

Methods. Using administrative data from advanced lung, prostate, colon, or breast cancer patients diagnosed between January 2000 and December 2007 at four HMOs with integrated delivery systems, patients with an inpatient or outpatient VTE diagnosed within 2 years after cancer diagnosis and an outpatient purchase of warfarin, LMWH, and/or fondaparinux anticoagulant within 7 days of the VTE diagnosis were identified. First-line outpatient VTE pharmacological treatment and factors independently associated with receipt/non-receipt of LMWH monotherapy were assessed.

Results. Overall, 25% of the 1,089 eligible patients received LMWH monotherapy as primary VTE treatment.

The percentage increased steadily over time from 18% among patients diagnosed in 2000 to 31% among those diagnosed in 2007. Factors associated with LMWH monotherapy included VTE diagnosis year, chemotherapy within 60 days prior to VTE diagnosis, history of VTE prior to cancer diagnosis, and invasive surgery in the 90 days following VTE diagnosis. Colorectal and prostate cancer patients versus lung cancer patients and stage III versus stage IV patients were less likely to be treated with LMWH monotherapy.

Conclusions. Adoption of LMWH monotherapy as initial treatment for cancer-associated VTE was low but increased steadily over the study period. Future studies should explore reasons underlying the underutilization of this preferred evidence-based treatment as well as the comparative effectiveness of LMWH versus warfarin-based anticoagulation in real-world cancer patients with VTE. *The Oncologist* 2012;17:419–427

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INTRODUCTION

Venous thromboembolism (VTE) is a frequent complication in patients with cancer [1, 2]. It is precipitated by tumor growth and inflammatory mechanisms and is also a well-recognized complication of cancer surgery and systemic chemotherapy agents [3]. Anticoagulation therapy decreases the incidence of VTEs (including deep vein thrombosis [DVT] and pulmonary embolism [PE]) in cancer patients.

In July 2003, a randomized controlled trial (RCT) demonstrated that, among cancer patients with VTE, low molecular weight heparin (LMWH) anticoagulation resulted in lower rates of recurrent VTE as compared with warfarin-based therapy [4]. Subsequently, American College of Chest Physicians (ACCP) [5, 6], American Society of Clinical Oncology (ASCO) [7], and National Comprehensive Cancer Network (NCCN) [8] treatment guidelines recommended long-term treatment with LMWH monotherapy (i.e., enoxaparin, tinzaparin, or dalteparin) over warfarin-based therapy for cancer-related VTE [5–8]. Long-term outpatient VTE treatment with the Factor Xa inhibitor fondaparinux also has been used for cancer patients but has not been studied to the same extent as LMWH [9].

Factors other than recurrent VTE prevention may influence the choice of anticoagulant treatment for cancer patients. The high cost of LMWH and fondaparinux monotherapy and prolonged need for daily injections are significant drawbacks for many patients [10]. Warfarin, in contrast, is an inexpensive oral tablet but has a slow-onset-of-effect drawback, necessitating short-term cross coverage with injectable unfractionated heparin, LMWH, or fondaparinux for at least 5 days at the initiation of therapy [5]. Warfarin also has a widely variable anticoagulant response and high drug-drug and drug-diet interaction potential that necessitates regular International Normalized Ratio (INR) monitoring and dosage adjustment for the duration of therapy [5].

Little is known about how physicians and patients weigh the risks and harms for these alternative VTE treatment strategies in advanced cancer [9]. Small studies suggest that, after the publication of the pivotal RCT and the incorporation of LMWH as the preferred treatment strategy in national guidelines, warfarin-based treatment remained the most common strategy [11, 12]. We sought to evaluate utilization of LMWH monotherapy for first-line treatment of VTE in patients with advanced-stage, common solid tumors over time in a large, geographically heterogeneous population.

MATERIALS AND METHODS

Study Design and Setting

We identified patients with advanced breast, colorectal, lung, and prostate cancer who received treatment at one of four Cancer Research Network (CRN) HMOs in the United States. The CRN is a consortium of managed care plans that pool their data in order to evaluate the quality and effectiveness of care across the continuum of cancer prevention, screening, and treatment.

This was a retrospective, longitudinal, multisite, cohort study to evaluate anticoagulant treatment choices in cancer patients who developed a VTE within 2 years of an advanced

cancer diagnosis. Data were obtained from four integrated health plans of the CRN with a combined membership of approximately 4 million members in 2008. All sites had at least one LMWH agent on formulary during all years of the study. This study was approved by the Kaiser Permanente Colorado (KPCO) Institutional Review Board (IRB), to whom the other study sites ceded IRB oversight.

Patient Population

Using tumor registry data, patients with an initial diagnosis of American Joint Committee on Cancer (AJCC) stage III or IV prostate, colon, non-small cell lung (NSCLC), or breast cancer between January 2000 and December 2007 were identified. At the time of cancer diagnosis, patients were members of Group Health Cooperative or the Kaiser Permanente regions in Colorado, Northern California, and the Pacific Northwest. To be included in this analysis, patients had to have an inpatient or outpatient VTE diagnosis of DVT or PE within 2 years of cancer diagnosis and an outpatient purchase of warfarin, LMWH, and/or fondaparinux anticoagulant within 7 days after the inpatient discharge or outpatient VTE diagnosis date, with no other outpatient anticoagulant purchase or in-office administration between the cancer diagnosis and VTE diagnosis dates. Assessing for an anticoagulant purchase within 7 days was employed to limit false-positive VTE diagnoses in lieu of chart reviewing all potential VTE patients to confirm the diagnosis yet provide for patients who did not receive immediate outpatient pharmacotherapy for their VTE (e.g., patient diagnosed with VTE in the hospital would not receive outpatient treatment until discharged 2 or more days after diagnosis date). Finally, patients were required to have 6 months of continuous eligibility in their respective health plan before cancer diagnosis (allowing for a 30-day gap between premium start dates) to enable assessments of risk profiles and patient characteristics. Patients were followed after VTE diagnosis until death, health plan disenrollment, or 1 year, whichever came first. Case identification within 2 years of cancer diagnosis and a 1-year post-VTE follow-up were employed because it allowed for the capture of consistent data across the largest study population with the available data, with the understanding that 3-year post-cancer-diagnosis mortality in this population would be substantial. For example, a patient diagnosed in December 2007 would be a study case if his/her VTE was identified as far out as December 2009 while still allowing for follow-up through December 2010.

Study Outcomes

The primary outcome was first-line outpatient pharmacological treatment choice for incident post-cancer-diagnosis VTE. First-line treatment was identified based on the anticoagulant treatment strategy purchased by patients at their health plan's outpatient pharmacies within 7 days of the initial VTE diagnosis. Because health plan members in this study can receive subsidized outpatient medications at in-network pharmacies, there is very little use of non-plan pharmacies. Anticoagulant strategies were categorized as LMWH monotherapy (enoxaparin, tinzaparin, and/or dalteparin), fondaparinux monotherapy, or

warfarin-based therapy. Many patients who purchased warfarin also purchased a limited quantity of LMWH or fondaparinux as short-term cross-coverage is necessary until therapeutic warfarin levels are achieved. Patients were considered to have received LMWH monotherapy if they had no evidence of a warfarin purchase in the 7 days after VTE diagnosis. VTE characteristics, VTE risk factors, duration of anticoagulant treatment, VTE recurrence, treatment of recurrence, complications of treatment, and deaths were assessed over the 1-year period following the VTE diagnosis.

Data Sources

The CRN uses a federated database (the Virtual Data Warehouse [VDW]) where data are stored in common data structures across managed care sites [13]. This allows a programmer at one site to develop analytic algorithms that can be run independently at each site to extract the necessary data elements for the study. The VDW records patients' diagnoses captured with International Classification of Diseases (ICD)-9 codes, health services procedure data as captured with Healthcare Common Procedure Coding System [including Current Procedural Terminology (CPT) codes] and Diagnosis-Related Group (DRG) codes, and pharmacy data that are captured with National Drug Codes (NDC). Each CRN site tracks all specific NDCs ever approved for dispensing by its pharmacies. In addition, the VDW includes tumor registry data with information on each patient's cancer site, sequence, diagnosis date, AJCC stage, and dates of initial cancer-related surgery and chemotherapy (where applicable). Each site's VDW data were extracted and transferred to KPCO for analysis.

Patients were identified from each site's VDW tumor registry. Patients diagnosed with advanced breast, colorectal, NSCLC, and prostate cancer were linked to administrative data at each site to obtain information on drug utilization, inpatient and outpatient diagnoses, and patient characteristics. The diagnosis codes (primary or secondary) associated with inpatient or outpatient (including emergency department [ED] visit) records were queried for VTEs (ICD-9 codes 415.1, 415.11, 415.19, 451.11, 451.19, 451.2, 451.9, 453.1, 453.2, 453.40, 453.41, 453.42, and 453.8) within 2 years of the advanced cancer diagnosis [14]. For patients with a diagnosis of VTE, administrative records were queried for purchase(s) or in-office administration of anticoagulant(s). Use of outpatient anticoagulant therapy was determined from NDC codes (codes available from corresponding author upon request): (a) in the 6 months prior to cancer diagnosis to ensure patients were not receiving outpatient VTE treatment/prophylaxis; (b) during the 7 days immediately following post-cancer diagnosis (VTE inpatient discharge date/outpatient diagnosis date) to confirm initiation of VTE treatment; (c) following the 7-day confirmation period until end of patient follow-up to measure length of therapy; and (d) in the 7 days immediately following another VTE diagnosis. All anticoagulant purchases within 7 days after VTE inpatient discharge date/outpatient diagnosis date were captured to ensure accurate categorization of treatment strategies. Administrative databases at each site were used to obtain information on patient characteristics, health services utilization,

diagnoses, pharmacy purchases, death date, and dates of plan membership.

Data Analysis

Patients who met the inclusion criteria were categorized into groups based on first-line VTE outpatient treatment (LMWH only, fondaparinux only, or warfarin-based strategies). Patients were further categorized as receiving LMWH monotherapy or not (fondaparinux or warfarin-based therapy). Patient age was determined as of VTE diagnosis date. Risk factors for VTE and other comorbidities were determined based on ICD-9 outpatient diagnoses in the six months prior to the cancer diagnosis of diabetes mellitus, hypertension, heart failure, prior VTE, or prior stroke. Estrogen therapy was determined using NDC codes. Receipt of chemotherapy in the 60 days prior to VTE diagnosis was identified using chemotherapy-specific NDC and procedure codes. Invasive surgery during the 90 days prior to and after VTE diagnosis was identified by querying inpatient encounters, tumor registry, and ambulatory surgery registry datasets with DRG and procedure codes. Morbidity burden was calculated using the "Quan" adaptation of the ICD-9-based Elixhauser morbidity index [15]. Body mass index was determined using the measurements made antecedent but closest to the VTE diagnosis date.

Duration of outpatient anticoagulant therapy was determined by summing the total days of uninterrupted outpatient anticoagulant supplied after the VTE diagnosis for up to 1 year or recurrent VTE, whichever came first. This method does not assess the count of days where the anticoagulant actually was injected/ingested by a patient but only the count of days with a supply of anticoagulant available as reported by the dispensing pharmacist. This analysis was limited to patients with at least 1 year of follow-up after VTE diagnosis. Subanalyses on therapy durations also were performed where only patients with at least 1 year of follow-up after VTE diagnosis and no post-VTE diagnosis surgery were included.

Bleeding events during the 1-year follow-up were identified using ICD-9 and CPT codes from ED visits or inpatient admissions. Venous thromboembolism was categorized as DVT or PE. Recurrent VTE off anticoagulant therapy was defined as both a primary or secondary inpatient or outpatient diagnosis of VTE and a purchase of anticoagulant(s) during the 7 days immediately following that diagnosis occurring at least 90 days after the end of the initial anticoagulant therapy. Recurrent VTE among patients on anticoagulant therapy was not assessable with the administrative datasets available due to a lack of a specific ICD-9 code for VTE recurrence.

Data analyses were performed with SAS 9.1.3 (SAS Institute Inc., Cary, NC) statistical software. No a priori power calculation was performed as all eligible patients were included in this descriptive analysis. Differences in characteristics between the LMWH monotherapy and warfarin-based/fondaparinux treatment groups at baseline and follow-up were compared with results being reported as means, medians, and standard deviations for interval- and ratio-level factors and as percentages for nominal- and ordinal-level factors. Interval- and ratio-level variables were assessed for normality of distribution.

butions, and appropriate tests (e.g., *t*-test and Wilcoxon rank sum) were used to assess differences in values between groups. To assess differences in percentages between groups on nominal- and ordinal-level variables, Pearson's χ^2 tests of association or the Fisher's exact test (as appropriate) were utilized. Multivariate logistic regression with adjustment for clustering by site was performed to ascertain factors independently associated with LMWH monotherapy. Factors with $p \leq .2$ in the bivariate analyses were incorporated into the multivariate analysis.

RESULTS

There were 2,699, 5,977, 13,046, and 2,538 patients diagnosed with advanced breast, colorectal, non-small cell lung, and prostate cancer, respectively, in the participating CRN sites during the study period. A total of 87 (3.2%), 371 (6.2%), 583 (4.5%), and 48 (1.9%) breast, colorectal, non-small cell lung, and prostate cancer patients, respectively, had a VTE for a final study cohort of 1,089 patients with VTE in the setting of advanced cancer. Approximately half of the analytic cohort were men, and half were 65 years or older (Table 1). Although the mean Quan risk score (1.6) indicated that overall patients had modest morbidity burden prior to cancer diagnosis, the vast majority of patients (92%) had at least one VTE risk factor or comorbidity.

Over the entire study period, 25% of patients received LMWH monotherapy as their primary VTE. The proportion treated with LMWH increased steadily each year, reaching 31% by study end (Figure 1). The majority of patients received warfarin-based therapy in all years (74% overall), and a small number received fondaparinux monotherapy (1%) (Table 2). Among patients with at least 1 year of follow-up, the median duration of warfarin treatment was 200 days while concomitant injectable anticoagulant treatment median duration was 15 days. Median duration of injectable anticoagulant monotherapy was 112 days. In subanalyses among patients with at least 1 year of follow-up but no post-VTE diagnosis surgery, the median duration of warfarin treatment was 200 days (interquartile range [IQR] = 100–320, $n = 310$) and concomitant injectable anticoagulant treatment median duration was 14 days (IQR = 7–51, $n = 298$). Median duration of injectable anticoagulant monotherapy was 120 days (IQR = 30–277, $n = 67$).

There were 36 off-therapy recurrent VTEs identified within 1 year of incident post-cancer VTE diagnosis, and the vast majority of recurrent events (97%) were treated with LMWH monotherapy. Over half of the cohort (55%) died during the 1-year follow-up. Additionally, a sizeable number of patients had a post-VTE bleeding diagnosis (34%) during the 1-year follow-up.

Patients who received LMWH monotherapy were younger and were more likely to have been diagnosed with VTE in the latter years of the study period. Patients with NSCLC, AJCC stage IV cancer, or history of prior stroke or VTE and those with invasive surgery in the 90 days following VTE diagnosis were also more likely to receive LMWH monotherapy (Table 3). In multivariable analysis, factors independently associated with increased likelihood of LMWH monotherapy included

Table 1. Baseline cohort patient characteristics: Patients diagnosed with stage IIIB or IV breast, lung, prostate, or colorectal cancer between 2000 and 2007 who had a venous thromboembolic event within 2 years of diagnosis

Characteristic	VTE cohort (N = 1,089)
Mean age ^a (SD, years)	64.9 (± 10.7)
Age ≥ 65 years (n, %)	578, 53%
Male (n, %)	571, 52%
Malignancy (n, %)	
Breast	87, 8%
Colorectal	371, 34%
Non-small cell lung	583, 54%
Prostate	48, 4%
Stage (n, %)	
III	482, 44%
IV	607, 56%
Year of malignancy diagnosis (n, %)	
2000–2002	271, 25%
2003–2005	445, 41%
2006–2007	373, 34%
Risk factors and comorbidities (n, %)	
Diabetes mellitus ^b	135, 12%
Estrogen therapy ^c	46, 4%
Hypertension ^b	339, 31%
Heart failure ^b	30, 3%
Prior history of VTE ^b	53, 5%
Prior stroke ^b	7, <1%
Prior chemotherapy ^d	705, 65%
Invasive surgery prior to VTE diagnosis ^e	201, 19%
Invasive surgery after VTE diagnosis ^f	439, 40%
Mean BMI (SD, n)	29.0 (± 5.4 , 771)
VTE diagnosis made in inpatient setting (n, % yes)	663, 61%
Mean Quan risk score (SD)	1.6 (± 1.5)

^aAs of VTE diagnosis date.

^bDiagnosis from a medical office visit anytime in the 6 months prior to malignancy diagnosis date.

^cBased on a purchase of a prescription anytime in the 6 months prior to VTE diagnosis date.

^dAnytime in the 60 days prior to VTE diagnosis date.

^eAnytime in the 90 days prior to VTE diagnosis date.

^fAnytime in the 90 days after VTE diagnosis date.

Abbreviations: BMI, body mass index; VTE, venous thromboembolism.

year of VTE diagnosis (there was a 21% increased likelihood for every 1 year increase), receipt of chemotherapy in the 60 days prior to VTE diagnosis (39% increased likelihood), history of VTE prior to cancer diagnosis (254% increased likeli-

Figure 1. Low molecular weight heparin venous thromboembolism treatment in advanced cancer patients by year of VTE diagnosis ($n = 1,089$).

Abbreviations: LMWH, low molecular weight heparin; VTE, venous thromboembolism.

hood), and invasive surgery in the 90 days following VTE diagnosis (55% increased likelihood) (Table 4). Conversely, colorectal cancer (50% decreased likelihood compared to NSCLC), prostate cancer (70% decreased likelihood compared to NSCLC), and stage III (51% decreased likelihood compared to stage IV) were independently associated with a lower likelihood of LMWH monotherapy.

DISCUSSION

In an analysis of 24,260 patients diagnosed with advanced solid tumors in four health plans, we found that 1,089 (4.5%) experienced a VTE within 2 years of their cancer diagnoses. Overall, only 1 in 4 received LMWH monotherapy as first-line outpatient treatment during the study period. However, a strong secular trend with increasing use of LMWH monotherapy over time is evident. Specifically LMWH use increased from 18% in 2000 to 31% in 2008, consistent with a moderate effect on practice of the 2003 publication of the pivotal RCT showing greater efficacy of LMWH in preventing VTE recurrence, as well as the subsequent promulgation of guidelines recommending LMWH as the preferred VTE therapy in cancer patients by several national organizations.

Although the observed rate of LMWH monotherapy use for first-line treatment increased steadily throughout the study period, the rate peaked at only 31% in the final year of observation (2008). Other studies of LMWH monotherapy use as first-line VTE treatment in cancer patients have reported lower (19%) [11] or similar (30%) [12] rates of LMWH monotherapy. A medical record review analysis from one anticoagulation clinic in Washington state reported in 2006 that only 19 of 100 cancer patients with a VTE received LMWH monotherapy [11]. A 2008 Italian analysis of 424 cancer-related VTE patients from an anticoagulation registry reported that

129 received LMWH monotherapy [12]. The narrow adherence to guidelines recommending LMWH monotherapy as first-line therapy for VTE are not limited to cancer patients as the ENDORSE study demonstrated that, among patients treated for VTE prevention in the inpatient setting, only 37% received recommended therapy [16]. Together, these findings demonstrate that prescriber and/or patient preference continued to favor warfarin-based anticoagulation whether for financial, personal, or other factors notwithstanding guidelines recommending LMWH therapy.

The pivotal clinical trial demonstrating superiority of LMWH monotherapy for VTE treatment in cancer patients was published in July 2003 [4], and guidelines recommending LMWH monotherapy as first-line therapy [6] were disseminated beginning in 2004 and thus would have been available to inform ~60% of the VTE treatment courses we examined. Cancer patients diagnosed with VTE prior to publication of research documenting the superiority of LMWH monotherapy [4] would not be expected to have received this treatment option. These findings suggest that after 2004 prescribers were either unaware of the guidelines for VTE outpatient treatment in cancer patients or made a conscious decision to ignore the recommendation.

There are numerous reasons why a physician might choose to prescribe a warfarin-based VTE treatment strategy. Warfarin has a long history of use in VTE [6], and anticoagulation monitoring services are used widely in HMOs, resulting in a high level of physician comfort with this therapeutic option [17]. Some evidence suggests that warfarin has antitumor properties [18]. Warfarin's anticoagulant effect can be reversed predictably within hours, perhaps making it preferred when the need for reversal might be reasonably anticipated (e.g., patients at high risk for bleeding) [10]. Furthermore, war-

Outcome	Value
First-line VTE anticoagulant treatment (n, %)	
LMWH only	272, 25%
Fondaparinux only	11, 1%
Warfarin + any injectable anticoagulant	806, 74%
VTE type (n, %)	
Deep vein thrombosis	659, 61%
Pulmonary embolism	430, 39%
Year of VTE diagnosis (n, %)	
2000–2002	218, 20%
2003–2005	420, 39%
2006–2008	451, 41%
Median time days between cancer and VTE diagnoses (IQR) ^a	113 (48–220)
Median length days of warfarin anticoagulant therapy (IQR, n) ^a	200 (100–330, 501)
Median length days of injectable anticoagulant therapy with warfarin cotreatment (IQR, n) ^a	15 (7–61, 501)
Median length days of injectable anticoagulant therapy without warfarin cotreatment (IQR, n) ^a	112 (30–237, 122)
Recurrent VTE ^a off therapy (n, % of total cases)	36, 3%
Recurrent VTE ^a anticoagulant treatment (n, % ^b)	
LMWH only	35, 97%
Fondaparinux only	0, 0%
Warfarin + any injectable anticoagulant	1, 3%
Deceased ^a (n, %)	603, 55%
Bleeding event ^a (n, %)	372, 34%

^aWithin 1 year after post-cancer incident VTE diagnosis.
^bPercentage of recurrences.
Abbreviations: IQR, interquartile range; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

farin is inexpensive and does not require daily self-injection [5]. Limited empirical evidence does suggest that LMWH not being covered by insurance (49%) (not applicable in our cohort as the vast majority had a pharmacy benefit for LMWH), physician preference for warfarin (32%), and patient refusal of self-injection (14%) are the most salient factors in the choice of warfarin-based VTE treatment strategy [11].

On the other hand, the 2004 and 2008 ACCP guideline recommendations for use of LMWH monotherapy as first-line

Table 3. Study outcomes with patients who received LMWH versus other anticoagulant treatment by patient characteristics

Characteristic	First-line VTE anticoagulant category		p-value
	LMWH only (n = 272)	Warfarin-based/fondaparinux (n = 817)	
Age			.031
≥65 years	129, 22%	449, 78%	
<65 years	143, 28%	368, 72%	
Gender			.451
Female	148, 26%	423, 74%	
Male	124, 24%	394, 76%	
Malignancy			
Breast	20, 23%	67, 77%	.655
Colorectal	71, 19%	300, 81%	.001
Non-small cell lung	174, 30%	409, 70%	<.001
Prostate	7, 15%	41, 85%	.089
Stage			<.001
III	89, 18%	393, 82%	
IV	183, 30%	424, 70%	
VTE diagnosis from the inpatient setting			.276
Yes	158, 24%	505, 76%	
No	114, 27%	312, 73%	
Year of VTE diagnosis			<.001
2000–2002	33, 15%	185, 85%	
2003–2005	98, 23%	322, 77%	
2006–2008	141, 31%	310, 69%	
Risk factors and comorbidities			
Diabetes mellitus			.715
Yes	32, 24%	103, 76%	
No	240, 25%	714, 75%	
Estrogen therapy			.859
Yes	12, 26%	34, 74%	
No	260, 25%	783, 75%	
Hypertension			.002
Yes	79, 23%	260, 77%	
No	193, 26%	557, 74%	
Heart failure			.828
Yes	8, 27%	22, 83%	
No	264, 25%	795, 75%	
Prior history of VTE			<.001
Yes	26, 49%	27, 51%	
No	246, 24%	790, 76%	

(continued)

Table 3. (Continued)

Characteristic	First-line VTE anticoagulant category		p-value
	LMWH only (n = 272)	Warfarin-based/fondaparinux (n = 817)	
Prior stroke			.004
Yes	5, 71%	2, 29%	
No	267, 25%	815, 75%	
Received chemotherapy			.059
Yes	189, 27%	516, 73%	
No	83, 22%	301, 78%	
Invasive surgery prior to VTE diagnosis			.614
Yes	53, 26%	148, 74%	
No	219, 25%	669, 75%	
Invasive surgery after VTE diagnosis			.013
Yes	127, 29%	312, 71%	
No	145, 22%	505, 78%	
Mean BMI (n, SD)	28.7 (210, ± 5.1)	29.1 (561, ± 5.4)	.678
Mean Quan risk score (SD)	1.6 (± 1.5)	1.6 (± 1.5)	.984
Death			<.001
Yes	184, 31%	419, 69%	
No	88, 18%	398, 82%	
Bleeding post-VTE diagnosis			.452
Yes	98, 26%	274, 74%	
No	174, 24%	543, 76%	
Recurrent VTE			.241
Yes	6, 17%	30, 83%	
No	266, 25%	787, 75%	
Warfarin monotherapy			NA
Yes	0, 0%	576, 71%	
No	272, 100%	241, 29%	
Fondaparinux			NA
Yes	0, 0%	27, 3%	
No	272, 100%	790, 97%	
LMWH type ^a			.005
Dalteparin	8, 3%	0, 0%	
Enoxaparin	264, 97%	213, 99%	
Tinzaparin	0, 0%	1, <1%	

^aAmong patients receiving LMWH.
Abbreviations: LMWH, low molecular weight heparin; NA, not applicable; VTE, venous thromboembolism.

Table 4. Factors independently associated with receipt of LMWH monotherapy for VTE management

Characteristic ^a	Odds ratio	95% confidence interval
Age ≥ 65 years		
Yes	0.81	0.60–1.09
No	referent	
Sex		
Male	0.90	0.66–1.24
Female	referent	
Year of VTE diagnosis	1.21	1.13–1.30
Malignancy		
Breast	0.58	0.32–1.06
Colorectal	0.50	0.35–0.70
Prostate	0.30	0.13–0.68
Non-small cell lung	referent	
Stage		
III	0.49	0.36–0.68
IV	referent	
Reception of chemotherapy		
Yes	1.39	1.01–1.92
No	referent	
Prior hypertension		
Yes	0.88	0.63–1.22
No	referent	
Prior history of VTE		
Yes	3.54	1.92–6.52
No	referent	
Invasive surgery in the 90 days following VTE diagnosis date		
Yes	1.55	1.13–2.12
No	referent	

C-statistic = 0.73.

^aIncludes all variables with a $p \leq .02$ in bivariate analysis plus patient sex and is adjusted for the clustering of patients by CRN site.

Abbreviations: LMWH, low molecular weight heparin.

VTE treatment in cancer patients are grade 1A evidence indicating a strong recommendation supported by high-quality evidence that is applicable to most patients [5, 6]. Although bleeding and mortality outcomes were equivalent, clinical trial

data from Lee and colleagues found that the risk of recurrent VTE is reduced by >50% with LMWH treatment of VTE in cancer patients [4]. This is an important outcome because cancer patients with VTE are more likely than a non-cancer patient to experience a recurrent VTE, and recurrent VTE is a substantial burden on both the patient and the healthcare system [19]. Furthermore, warfarin therapy interacts with many chemotherapy agents [20] and INR control is more difficult in cancer patients [21]. Cancer patients frequently require invasive procedures, and coordination of warfarin therapy interruption for these procedures is notoriously challenging [5]. Finally, there is evidence to indicate that terminally ill cancer patients

prefer daily LMWH injections to the rigors and uncertainties of warfarin therapy [22].

We found that the duration of warfarin anticoagulant treatment in our cohort varied from ~3 to 11 months whereas LMWH monotherapy varied from ~1 to 8 months. Guidelines suggest anticoagulant treatment duration from 3 to 6 months for DVT, from 6 to 12 months for PE, and indefinite if cancer is still present after treatment end [5–8]. We did not find appreciably different durations of treatment in patients with a PE versus a DVT (data not shown). We found that patients who received warfarin had more *days supply* of treatment than those who received LMWH monotherapy. Durations did not differ appreciably when limiting this analysis to patients who did not have post-VTE diagnosis surgery. The implications of this are unclear because administrative data do not identify whether a patient actually ingested/injected their anticoagulant but suggest that, in the real world, patients are more likely to be persistent with warfarin therapy. The variation in our results is not surprising as guideline recommendations for first-line treatment were not adhered to widely in our cohort; the general uncertainty surrounding the optimal length of VTE anticoagulation therapy and the extenuating circumstances of cancer care (e.g., surgery, radiation treatment, and complications) are likely to make real-world VTE treatment inconsistent [23].

The overall rate of off-therapy VTE recurrence in our cohort was low, but there was a trend toward a higher rate among patients receiving warfarin-based therapy. The recurrence rates we identified were lower than those reported by Lee and colleagues (i.e., ~8% and 16% in LMWH- and warfarin-receiving patients, respectively) [4]. This may be reflective of the patient populations studied whereby cancer types with higher incidence of recurrence were included in their study and they exclusively used dalteparin LMWH treatment whereas our patients received primarily enoxaparin [4]. In addition, we used administrative data to identify recurrence whereas the RCT employed objective medical tests (including ultrasound and radio-imaging, as appropriate) on all of their suspected recurrences [4]. Finally, our definition of recurrent VTE limited events to those that likely occurred off anticoagulant therapy, whereas all recurrences were reported by Lee and colleagues. Our study was not powered specifically to detect differences in VTE recurrence, but the numerically higher percentage of VTE recurrence in patients who had received warfarin-based therapy supports the findings of Lee and colleagues especially when considering that the median lengths of LMWH monotherapy treatment identified in our cohort were considerably lower than guideline recommendations [5–8].

Patients who had an invasive surgery in the 90 days following VTE diagnosis had a 50% increased likelihood of receiving LMWH monotherapy. Management of warfarin therapy interruption for surgery is difficult; thus, possible physician awareness of upcoming surgery at the time of VTE diagnosis may have guided physicians to choose LMWH monotherapy because interrupting LMWH therapy is less complicated than interrupting warfarin therapy [5]. In addition, patients with a history of VTE prior to cancer diagnosis or who had recently received chemotherapy were more likely to receive LMWH

monotherapy. This may reflect an acuity judgment by physicians who perceived these patients to be higher risk and, thus, preferentially prescribed LMWH monotherapy instead of warfarin. Supporting this notion, we found that the vast majority of recurrent VTEs were treated with LMWH monotherapy. The desire to avoid drug-drug interactions in patients receiving chemotherapy and warfarin may also explain in part the preference for LMWH monotherapy in these patients [20, 24].

We found that patients with colorectal and prostate cancer were much less likely than patients with NSCLC to have received LMWH. Physicians may be more likely to prescribe LMWH monotherapy in NSCLC patients because of increased awareness of vascular events in these patients [25, 26]. We found that patients with stage III cancer diagnosis and increasing age were less likely to receive LMWH. It is unclear why stage IV patients were more likely to receive LMWH. Current NCCN guidelines recommend LMWH or warfarin for stage III whereas ASCO and ACCP guidelines specifically recommend LMWH, so some confusion may be present when physicians are prescribing anticoagulation for stage III patients [5–8].

Having prescription drug coverage (as the vast majority of our patients had) should theoretically limit cost as a barrier to prescribing long-term LMWH monotherapy. However, the differential cost between brand and generically available drugs may continue to pose a barrier of sufficient magnitude to influence prescribing decisions. Our study was conducted in four integrated HMOs where patients may not have faced financial barriers to outpatient prescription drugs that patients in fee-for-service plans could have encountered prior to the introduction of Medicare Part D. For HMO patients, the costs of warfarin and LMWH most likely were subsidized throughout the study period, thus decreasing financial disincentive as a barrier to utilization of LMWH. Similarly, HMO physicians were free to prescribe LMWHs, and no guidelines discouraging LMWH therapy existed during the study period. During the study period, all LMWHs and fondaparinux were branded agents and required a brand copayment whereas warfarin was available as a generic or branded agent and required a copayment corresponding to the dispensed agent. However, we were unable to identify patient copayments for anticoagulants because this information is not routinely captured in the VDW. The relatively low uptake of LMWH therapy even in the later years of our study, however, is consistent with the prior studies that have examined this issue outside of the context of managed care plans.

Although the validity of our findings is strengthened by the large cohort of study patients with validated, advanced cancer and the use of data obtained from four geographically diverse HMOs over a 9-year time frame, there are important limitations. We used an algorithm to detect VTE based on diagnoses and pharmacy data, but we were unable to validate the diagnoses with manual chart review. However, we did use ICD-9 codes that were sensitive and specific to actual VTE and confirmed the diagnoses with purchases of anticoagulants within 7 days of diagnosis [27]. We were not able to comprehensively assess all potential factors that may have influenced anticoagulant treatment choice. Nevertheless, we did examine numer-

ous factors and found several related to LMWH monotherapy use in a model with a reasonable fit of the data (C -statistic = 0.73). Patients in the early years of the study potentially had longer follow-up than those in the latter years. Although this may have impacted our ability to detect all recurrent VTEs, anticoagulant adverse effects, and death, it had no bearing on our ability to determine first-line VTE treatment because all patients had at least 1 year of follow-up after VTE diagnosis.

SUMMARY

We found that, notwithstanding evidence of superior clinical efficacy to warfarin from the RCT published by Lee and colleagues in 2003 [4], LMWH monotherapy for management of VTE was adopted by only a minority of advanced cancer patients treated in integrated health plans. It is unclear whether anticoagulant choice is driven by patient or provider preferences, but it is encouraging that the rate of LMWH monotherapy use as first-line therapy increased dramatically from the early to latter years of the study. Future studies should explore the reasons underlying the underutilization of this preferred, evidence-based treatment. Additionally, future studies should be conducted on the comparative effectiveness of LMWH versus warfarin-based anticoagulation in routine on-

cology practice settings. In this manner, whether quality improvement efforts to increase use of LMWH or, alternatively, persistent use of warfarin therapy is justified based on clinical effectiveness can be determined.

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