Alignancy has long been recognized as a risk factor for venous thromboembolism (VTE), dating back to the 19th century, when Armand Trousseau diagnosed the syndrome on himself. 1 Although the risk for thromboembolism varies based on patients' cancer type overall, it has been estimated that patients with cancer have a 4- to 7-fold higher risk for thromboembolism than the general population.1-3 Tumor production of hypercoagulable substances (eg, tissue factor and tumor compression of blood vessels) may explain part of the increased risk for VTE associated with malignancy.4 In addition, patients with cancer often have indwelling catheters and receive medications (eg, tamoxifen, bevacizumab, cisplatin, lenalidomide) that increase the risk for thrombosis. 5,6

Low-molecular-weight heparin (LMWH) and sulfated non–anticoagulant LMWH have been shown to suppress tumor growth with and without traditional chemotherapeutic agents.7 In addition, intracellular processes

Background: Malignancy is a significant risk factor for venous thromboembolism (VTE), conferring a 4- to 7-fold increased risk in patients with cancer. Because of its effect on certain tumors, low-molecular-weight heparin (LMWH) has been evaluated as a treatment option for cancer and as an alternative to traditional warfarin therapy in patients with active cancer. LMWH is associated with a reduced recurrence of VTE, fewer adverse bleeding events, and, in some instances, decreased mortality. The American College of Chest Physicians/American Society of Clinical Oncology has recommended LMWH for at least the initial 3 to 6 months when treating VTE in patients with cancer, based on the positive outcomes associated with LMWH.

Objective: The purpose of this study was to evaluate physician prescribing patterns for LMWH or warfarin in patients with acute VTE and active cancer.

Methods: We conducted a retrospective chart review of hospitalized patients at a community teaching hospital with an affiliated regional cancer center located in a rural area of the United States. Patients included in the analysis had an International Classification of Diseases, Ninth Revision code indicative of any cancer type and a concomitant code for any VTE. The primary outcome was the drug prescribed at discharge for the treatment of VTE. Secondary outcomes included specialty of the prescribing physician, adverse bleeding events, and the need for transfusion. VTE treatment regimen was evaluated using the binomial test, and logistic regression analysis was used to determine correlation of the prescriber’s specialty with the patient’s prescribed regimen.

Results: Of 129 patients included in the analysis, 107 (82.9%) were prescribed warfarin compared with 9 (7%) who were prescribed LMWH. Hematologists and oncologists were more likely to prescribe LMWH than general practitioners (odds ratio, 7.8; 95% hazard ratio, 1.5-42). Seven patients had a documented adverse bleeding event and 2 patients required a transfusion. Four of the 7 adverse bleeding events and 1 of the 2 transfusions occurred in the group receiving vitamin K antagonist therapy.

Conclusion: Physicians in our system were significantly more likely to prescribe warfarin for acute treatment of VTE in patients with active cancer—despite consistent evidence and multiple evidence-based guidelines recommending treatment with LMWH in this patient population. This was lower than other observations in Canadian populations but may more accurately represent nonteaching centers in the United States, particularly those in rural areas. Specialists in oncology were significantly more likely to prescribe LMWH than generalists.
affecting cancer cell adhesion and migration have been shown to be inhibited with LMWH products.\textsuperscript{5-12} Enoxaparin has also been shown to suppress cell proliferation in adenocarcinomic epithelial cell lines.\textsuperscript{13} Because of these targeted effects on specific cancer cells, LMWH derivatives are being evaluated not only for their therapeutic effects, but also as drug delivery vehicles for chemotherapy.\textsuperscript{14,15}

Clinically, LMWH has consistently been shown to decrease rates of recurrent VTE with similar or lower rates of major bleeding compared with traditional vitamin K antagonist (VKA) therapy.\textsuperscript{16-20} LMWH may also positively impact survival, particularly for patients with less advanced disease progression, presenting a more favorable prognosis.\textsuperscript{10,21-25} Based on these findings, contemporary guidelines have reached a consensus that patients with cancer should be treated with LMWH long term when diagnosed with VTE.\textsuperscript{26-28}

Despite a large body of evidence, there is still reluctance by physicians to follow guidelines because of subjective fears regarding exposing patients to LMWH for a prolonged period.\textsuperscript{29,30} Two large studies of patients with cancer and VTE, which were based on 2 large databases—the Multicenter Advanced Study for a Thromboembolism Registry (MASTER) and the Computerized Registry of Patients with Venous Thromboembolism (RIETE)—featuring a substantial subgroup of patients with cancer (approximately 20% in each registry), noted that significantly more patients with cancer were treated with LMWH than patients without cancer. Those rates, however, were only 30% and 50%, respectively, compared with patients receiving VKA therapy.\textsuperscript{31,32}

To evaluate the dissemination of evidence-based, clinical recommendations in a community setting, we designed a study to evaluate the prescribing rates of LMWH for the long-term management of VTE in patients with active cancer.

Methods
This study was conducted in the United States at a single, regional, referral community teaching hospital with an affiliated regional cancer center located in a rural area. After receiving local institutional review board approval, medical records from January 1, 2005, to December 31, 2009, that were listed with an International Classification of Diseases, Ninth Revision (ICD-9) code for any cancer type and a concomitant ICD-9 code for any VTE, were identified and reviewed. Patients were excluded if they received warfarin prior to admission, were given an inferior vena cava filter, were pregnant, had a documented contraindication to anticoagulation at the time of admission, or died during hospitalization. Patients with duplicate events were only included for their initial event. Additional data collected included patient demographics; cancer type; VTE type; length of time since cancer diagnosis; serum creatinine measurements; international normalized ratio; platelet count at discharge; history of thrombocytopenia or heparin-induced thrombocytopenia (HIT); specialty of the prescriber; and bleeding events prior to or during admission.

The principal outcome of this study was the primary maintenance of anticoagulant prescribed at the time of discharge. LMWH prescribed as a short-term bridge for chronic warfarin therapy was classified as warfarin (VKA group), and LMWH therapy prescribed as the primary maintenance regimen was classified as LMWH (LMWH group). Secondary outcomes included specialty of the prescriber, adverse bleeding events during hospitalization, and whether a contraindication to anticoagulant therapy existed at the time of discharge.

Patients were considered to have an adverse bleeding event if their hemoglobin decreased by more than 2 g/dL in any one 24-hour period during admission, if they required a transfusion of packed red blood cells, or if an adverse bleeding event requiring increased physician monitoring was documented. Patients were considered to have a contraindication to anticoagulant therapy if the provider stated so at the time of discharge, regardless of clinical reasoning.

The binomial test was used to evaluate anticoagulant prescribed at the time of discharge expecting a conservative 70% prescribing rate for warfarin (30% for LMWH). Logistic regression analysis was used to evaluate the correlation of the type of discharging physician with the prescribing of LMWH or warfarin at the time of discharge. Chi-square, Fisher exact test, and the student’s t-test were used when appropriate to evaluate baseline patient demographics. Data analyses were completed using IBM SPSS Statistics, version 21 (IBM Corporation, Armonk, NY).

Results
Of the 244 patients identified based on the inclusion criteria, 115 were excluded (Table 1); 129 patients were included in the study analysis. One hundred seven patients were prescribed warfarin, or warfarin plus LMWH at discharge. Nine patients were prescribed LMWH as the

<table>
<thead>
<tr>
<th>Table 1 Reasons for Patient Exclusion</th>
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<tbody>
<tr>
<td>Exclusion criteria</td>
</tr>
<tr>
<td>Warfarin prior to admission</td>
</tr>
<tr>
<td>Inferior vena cava filter</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Contraindication to anticoagulation</td>
</tr>
</tbody>
</table>
primary treatment for their VTE at time of discharge, and 13 patients were not prescribed any anticoagulants.

The mean age of patients was 62 and 63 years in the LMWH and VKA groups, respectively (Table 2). There were no statistical differences with any variables between the 2 study groups.

Two patients prescribed warfarin had either HIT or a positive HIT antibody test during the time of admission. Of the 9 patients who received LMWH, 1 patient was documented to have “refused warfarin” at the time of their discharge. One patient who received neither LMWH nor warfarin was documented as “intolerant to warfarin”; however, no other contraindications to LMWH or any other anticoagulants were noted.

Significantly fewer patients (n = 9; 7.40%) were prescribed LMWH as their primary anticoagulant at the time of discharge compared with warfarin (n = 107 [82.9%]; P < .0001). Of the patients prescribed LMWH at discharge, 4 (44.4%) were prescribed LMWH by a hematologist/oncologist, and 3 by general practitioners. Only 7 of the 107 patients (6.5%) who were prescribed warfarin were under the care of a hematologist/oncologist. Hematologists/oncologists were therefore 7.8 times more likely (P = .016) to prescribe LMWH than warfarin compared with any general practitioner based on logistic regression analysis of practice specialty in regard to prescribing of LMWH versus VKA (Table 3).

Seven patients had documented bleeding during admission with only 2 patients requiring transfusion. Four patients were prescribed warfarin and 1 patient was prescribed LMWH for the treatment of VTE at the time of discharge.

### Discussion

A frequently hypothesized reason for the discrepancies between prescribing more efficacious LMWH in patients with cancer and VTE is the increase in cost. For patients without prescription coverage, generic warfarin can be obtained for merely a few dollars each month, whereas LMWH would cost patients thousands of dollars for a 6-month treatment period. For patients without prescription coverage, cost would be an inhibitory deterrent to obtaining the more effective LMWH treatment. Conversely for those with prescription coverage, patient cost may be less of an issue.

A cost-effectiveness analysis published in 2005 found that LMWH provided a quality-adjusted life expectancy of 1.097 quality-adjusted life-years with a cost of $15,329. The vast majority of the cost were attributed to pharmacy costs for LMWH. Although the LMWH enoxaparin is now available as a generic, its costs are still high compared with warfarin therapy. With the early mortality benefit associated with LMWH, it is likely prudent to still preferentially consider it in accordance with current guidelines, when the patient has prescription coverage to offset the drug acquisition cost.

It is well known by clinicians that there is substantial lag time between the publication of new research findings and their incorporation into everyday clinical practice. A literature search using PubMed and the Internet, yielded little to no information regarding the typical lag time from publication, guideline incorporation or bedside use. Several researchers have attempted to measure

### Table 2 Patient Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low-molecular-weight heparin (N = 9)</th>
<th>Vitamin K antagonist (N = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean), yrs</td>
<td>62</td>
<td>63</td>
</tr>
<tr>
<td>Sex, male, %</td>
<td>33.3</td>
<td>40.2</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, %</td>
<td>66.7</td>
<td>72.0</td>
</tr>
<tr>
<td>Black/African American, %</td>
<td>11.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Unknown, %</td>
<td>22.2</td>
<td>27.1</td>
</tr>
<tr>
<td>Type of VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT, %</td>
<td>62.5</td>
<td>58.9</td>
</tr>
<tr>
<td>PE, %</td>
<td>12.5</td>
<td>34.6</td>
</tr>
<tr>
<td>DVT + PE, %</td>
<td>25.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Type of cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast, %</td>
<td>11.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Colon/rectal, %</td>
<td>11.1</td>
<td>9.3</td>
</tr>
<tr>
<td>Esophageal</td>
<td>11.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Gastrointestinal, %</td>
<td>—</td>
<td>10.3</td>
</tr>
<tr>
<td>Hematologic, %</td>
<td>—</td>
<td>10.3</td>
</tr>
<tr>
<td>Lung, %</td>
<td>11.1</td>
<td>33.6</td>
</tr>
<tr>
<td>Other, %</td>
<td>66.7</td>
<td>42.2</td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

### Table 3 Secondary Outcome: Prescribed Agent by Specialty of Prescriber

<table>
<thead>
<tr>
<th>Specialty of prescriber</th>
<th>Low-molecular-weight heparin (N = 9)</th>
<th>Vitamin K antagonist (N = 107)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalist</td>
<td>3</td>
<td>37</td>
<td>—</td>
</tr>
<tr>
<td>Hematologist/oncologist</td>
<td>4</td>
<td>7</td>
<td>7.8 (95% CI, 1.5-41.8)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

*Comparative group.*
the time from translational research to bedside implementa-
tion, but there is no consensus on how to define and measure this process.42 Even measuring the uptake of
clinical trial results leads researchers down the road of
counting publications and citations,35 which has little to
no meaning for those trying to answer the question of
true dissemination to bedside clinical practice.

We present data on a treatment approach that is clearly
known to be beneficial. The CHEST antithrombotic
guidelines incorporated a recommendation to use LMWH
for the initial 3 to 6 months after the diagnosis of acute
VTE in patients with cancer in the 2004 iteration of their
guidelines.36 Contemporary papers have been written on
this issue with directives on how to improve adherence to
guidelines29,37; however, there is still a disconnect be-
tween adherence to long-standing evidence-based recom-
mandations and actual clinical practice.

Previous studies have demonstrated that a large pro-
portion, and in some instances the majority of prescri-
biers, do not adhere to the recommendation to use LMWH
for the initial acute treatment of VTE in patients with
active cancer. LMWH prescribing rates increased from
32% to 60%, approximately, during the 3 to 5 year peri-
od following the 2004 CHEST guidelines in a Canadian
patient population.31,32 Similar to our study, Rahme and
colleagues observed a higher rate of LMWH prescribing
among oncologists compared with general practitioners;
however, their logistic regression model did not show a
significant difference40 as did our study. This is likely due
to the higher rate (59%) of prescribing in their study by
general internists/practitioners compared with no
LMWH prescribed by generalists in our study.

The complexity of this issue drove Johnson and col-
leagues to evaluate the reasons physicians may not ad-
here to the recommendation to prescribe LMWH for
these patients.30 Key findings were that physicians strug-
gled with the appropriateness of this recommendation
with concerns ranging from increased patient burden to
individual patient prognosis. Although physicians may
not adhere to this recommendation for a variety of rea-
sons, the result is the same: the patient often receives
warfarin instead of LMWH despite the evidence favor-
ing the latter.

Despite these known barriers, we expected to see
higher rates of LMWH prescriptions in our cohort in a
community teaching hospital, but the rates of LMWH
prescribing for acute VTE in patients with active cancer
were abysmally low. This study indicates that specialists
(oncologists) who should be more familiar with evi-
dence-based recommendations in patients with cancer
did indeed prescribe LMWH almost 8-fold more often
than their general practitioner colleagues. A qualitative
study looking at the way physicians make decisions in
this patient population also identified a similar trait
among oncologists compared with general practitioners.30
This could also be explained by specialists being more
likely to exhibit traits of an “innovator” or “early adopt-
er” as defined by Berwick,41 suggesting that they are more
likely to be early utilizers of novel therapies.

Although previous registry data have estimated sub-
stantially higher LMWH prescribing rates in this popu-
lation,31,32 our data may more accurately represent “real-
world” prescribing rates in a typical, community Ameri-
can healthcare setting, particularly in rural areas. There
are real barriers to prescribing LMWH that include ac-
cess and medication acquisition cost that are difficult to
identify, even in qualitative “think aloud” studies. These
types of health disparities, such as access to specialists
and prescription drug coverage, are observed more often
in rural areas.42 Likewise, these data are consistent with
the observation by Rahme and colleagues that showed a
correlation between residing in a rural area and being
prescribed VKAs instead of LMWH.40

Limitations
The limitations of our current study include the retro-
spective nature of the observations that were recorded. In
addition, our LMWH group was small and comprised
only 7% of our total patient population. Taking the pri-
mary outcome we evaluated into consideration, this
demonstrated a significant difference in prescribing
choice for our patient population. The cancer type was
more widely distributed, which prevented any meaningful
interpretations between the malignancy type and pre-
scribing patterns of physicians. Although this is a limita-
tion, given that some malignancies have a much higher
rate of thrombosis than others, it is unlikely this weighs
on the decision of prescribers because clinicians may dis-
regard evidence-based guideline recommendations.

Conclusion
We evaluated prescribing patterns of physicians in
regard to evidence-based treatment recommendations
for patients with active cancer and acute deep vein
thrombosis and/or pulmonary embolism.

Similar to previous studies, we observed a very low
rate of adherence to guideline recommendations, which
was more pronounced in our rural geographic area than
in previous Canadian studies. To our knowledge, con-
temporary data in a US patient population are not avail-
able, which suggests the possibility that this large dis-
crepancy may not be limited to only our rural area.

Evidence demonstrates that patients with cancer and
acute VTE treated with LMWH have a lower recur-
rence of VTE, lower mortality rates, and decreased ad-
verse bleeding when compared with traditional warfarin

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therapy. Hematologists and oncologists are more likely than their generalist colleagues to follow evidence-based treatment guidelines when prescribing LMWH in this patient population.

Acknowledgments

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Author Disclosure Statement

Dr Stewart serves on the Speaker’s Bureau for Janssen Pharmaceuticals. Dr Rikhye, Dr Odle, Dr Bossaer, and Dr Flores reported no conflicts of interest.

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