OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE
Breast

Safety and Efficacy of Extended Postdischarge Venous Thromboembolism Prophylaxis in Microsurgical Breast Reconstruction

Marek A. Hansdorfer, MD, MS*
Rachel L. Sadowsky, BA*
Sydney R. Horen, MD*
Adan Z. Becerra, PhD†
Deana S. Shenaq, MD*
George Kokosis, MD*

Background: Discharging patients on extended postoperative venous thromboembolism (VTE) prophylaxis is trending in microsurgical breast reconstruction (MBR). This study investigated contemporary bleeding and thromboembolic complications after MBR and reported postdischarge enoxaparin outcomes.
Methods: The PearlDiver database was queried for MBR patients who did not receive postdischarge VTE prophylaxis (cohort 1) and MBR patients discharged with enoxaparin for at least 14 days (cohort 2), then queried for hematoma, deep venous thrombosis (DVT), and/or pulmonary embolism. Concurrently, a systematic review was undertaken to identify studies investigating VTE with postoperative chemoprophylaxis.
Results: In total, 13,541 patients in cohort 1 and 786 patients in cohort 2 were identified. The incidence of hematoma, DVT, and pulmonary embolism were 3.51%, 1.01%, 0.55% in cohort 1, and 3.31%, 2.93%, and 1.78% in cohort 2, respectively. There was no significant difference in hematoma between these two cohorts ($P = 0.767$); however, a significantly lower rate of DVT ($P < 0.001$) and pulmonary embolism ($P < 0.001$) occurred in cohort 1. Ten studies met systematic review inclusion. Only three studies reported significantly lower VTE rates with postoperative chemoprophylaxis. Seven studies found no difference in bleeding risk.
Conclusions: This is the first study utilizing a national database and a systematic review to investigate extended postoperative enoxaparin in MBR. Overall, rates of DVT/PE seem to be declining compared with previous literature. The results of this study suggest that there remains a lack of evidence supporting extended postoperative chemoprophylaxis, although the therapy appears safe in that it does not increase bleeding risk. *(Plast Reconstr Surg Glob Open 2023; 11:e4839; doi: 10.1097/GOX.0000000000004839; Published online 27 February 2023.)*

INTRODUCTION

Postoperative hematoma and venous thromboembolism (VTE) remain significant causes of morbidity and mortality in patients undergoing breast reconstruction after mastectomy.[1–6] Specifically, VTE is the most common cause of mortality in postoperative cancer patients, likely due to hypercoagulable effects from the underlying malignancy coupled with operative time and stress.[7] Previous studies examining breast reconstruction complications have reported hematoma rates of 0.5%–3.6%[1–3] and VTE in up to 1.3% of patients, with the majority (67.1%) of postoperative thrombotic events occurring after discharge from the hospital.[3,6] However, there is a paucity of studies reporting these complication rates since the 2000s, with some authors hypothesizing that VTE rates have decreased in recent years since the advent of strict perioperative prophylaxis

*From the *Division of Plastic and Reconstructive Surgery, Rush University Medical Center, Chicago, Ill.; and †Department of Surgery, Rush University Medical Center, Chicago, Ill.*

Received for publication November 6, 2022; accepted January 12, 2023.

Presented at the 59th Annual Midwest Association of Plastic Surgeons Meeting (MAPS), June 2–5, 2021; 90th Annual American Society of Plastic Surgery Meeting (ASPS), October 29, 2021; American Society of Reconstructive Microsurgery Meeting (ASRM), January 14–18, 2022.

DOI: 10.1097/GOX.0000000000004839

Disclosure: *The authors have no financial interests to declare in relation to the content of this article.*

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

(antithrombotic medications, sequential compression devices, etc).[5]

Some recommendation bodies have attempted to disseminate VTE prophylaxis guidelines for widespread use, such as the American College of Chest Physicians Guidelines for Antithrombotic Therapy for VTE Disease,[8] but the Caprini Risk Assessment Model remains the most commonly employed VTE risk score stratification system.[9,10] The Caprini scoring model has been demonstrated to be a strong predictive measure for perioperative risk of VTE events and selecting high-risk patients who should receive pharmacologic anticoagulation prophylaxis.[9–11] However, few guidelines exist on selecting the appropriate pharmacologic agent for prophylaxis, and there is no current consensus on therapy duration.[5,12]

Although subcutaneous unfractionated heparin remains the most-commonly used anticoagulation prophylactic agent, a few recent studies have compared the efficacy of low-molecular-weight-heparin (LMWH) (ie, enoxaparin sodium) to unfractionated heparin, direct oral anticoagulants, and vitamin K antagonists (ie, warfarin) for thromboprophylaxis and have found lower VTE incidence and fewer complications associated with LMWH.[8,13] Furthermore, The American Society of Clinical Oncology has historically advised initiation of thromboprophylaxis before surgery with continuation for 7–10 days postoperatively.[7] The American Society of Clinical Oncology approved changes to its recommendations in May 2019 after multiple systematic reviews concluded that 28 days ("extended post-operative prophylaxis") of LMWH therapy offered reductions in VTE incidence in postsurgical cancer patients without increasing the risk of bleeding.[14]

The initiation of extended postoperative (14–28 days) VTE prophylaxis can be traced to several recent high-quality studies in multiple surgical specialties reporting on the benefits of prolonged therapy after discharge. The benefits of extended VTE prophylaxis were first documented in colorectal surgery patients with multiple studies corroborating the results of the initial studies.[15,16] Improved outcomes with extended postoperative VTE prophylaxis have also been reported in urology in patients undergoing radical cystectomy,[17] in surgical oncology (oncologic liver surgery),[18] pancreatic surgery,[19] and oncologic gynecologic surgery.[20,21] Since these studies were published, many plastic surgeons have adopted extended postoperative VTE prophylaxis into their clinical protocols. However, there is a relative paucity of literature investigating the benefits of this therapy in plastic surgery,[5] and at the time of publication of this work, only one pilot study exists concerning microsurgical breast reconstruction (MBR).[22]

Takeaways

Question: Is there a benefit (or possibly harm) to VTE prophylaxis after microsurgical breast reconstruction?

Findings: This study investigated VTE rates after microsurgical breast reconstruction with and without VTE prophylaxis.

Meaning: No significant benefit to VTE prophylaxis was observed, although it did not increase risk of hematoma.

The purpose of this study is to (1) report updated hematoma, DVT, and pulmonary embolism (PE) rates in MBR in the era of strict VTE protocols and increased awareness of the morbidity and mortality of these complications and (2) investigate the benefits and/or potential harms of extended postoperative VTE prophylaxis in patients undergoing MBR, when compared with patients who receive VTE prophylaxis only while hospitalized. This work is intended to guide clinical practice and serve as a foundation for further investigation into this domain.

METHODS

Database Query

The first aim of this study utilized the PearlDiver Mariner (version 15, 2021) database. This mixed payer (containing both commercial and public claims patients) contains over 120 million unique patients. STROBE guidelines for reporting epidemiological research findings were adhered to in querying the database and reporting outcomes. The database was queried from 2013 through 2019. The patient cohorts were identified with the use of CPT-4 codes (Table 1). The first cohort consisted of all patients in the database who underwent MBR during the specified period. After identification of these patients, they were filtered for a minimum of 90 days of continuous claims records after their MBR event code to ensure that all postoperative events were captured. These patients were then queried for ICD diagnosis codes of hematoma within 30 days of surgery and DVT and/or PE within 90 days of surgery (Table 2). Logistic regression was utilized to identify patient characteristics and comorbidities that

Table 1. Data Query Codes Utilized

Procedure/Medication	ICD-PCS/CPT/NDC Codes
Microsurgical breast reconstruction (free flap breast reconstruction)	CPT-19364, CPT-S2066, CPT-S0267, CPT-S2068, ICD-0HRV076, ICD-0HRV077, ICD-0HRV078, ICD-0HRV079, ICD-0HRT076, ICD-0HRT077, ICD-0HRT078, ICD-0HRT079, ICD-0HRU076, ICD-0HRU077, ICD-0HRU078, ICD-0HRU079,
Enoxaparin sodium codes	NDC-00075062040, NDC-00075062041, NDC-00075062160, NDC-00075062161, NDC-00075062280, NDC-00075062281, NDC-00075062300, NDC-00075062301, NDC-00075062430, NDC-00075062431, NDC-00075062603, NDC-00075062604, NDC-00075291201, NDC-00075291202, NDC-00075291501, NDC-00075291502, NDC-00075801310, NDC-00075801410, NDC-00075801610, NDC-00075801810, NDC-00075802010, NDC-00075802210

Procedural codes included in the query of the PearlDiver Mariner database.
CPT, Current Procedural Terminology; ICD-PCS, International Classification of Disease Procedure Code; NDC, National Drug Code.

Table 2. Outcome Measure/Complication Codes

Outcome Diagnosis	International Classification of Disease (ICD) Codes
Hematoma	ICD-9: 998.11, 998.12, 998.13, ICD-10: D7801, D7802, D7821, D7822, E3601, E3602, E89810, E89811, G9731, G9732, G9751, G9752, H59111, H59112, H59113, H59119, H59121, H59122, H59123, H59129, H59311, H59312, H59313, H59319, H59321, H59322, H59323, H59329, H9521, H9522, H9541, H9542, I97410, I97411, I97418, I9742, I97610, I97611, I97618, I97620, J9561, J9562, J95830, J95831, K9161, K9162, K91840, K91841, L7601, L7602, L7621, L7622, M96810, M96811, M96830, M96831, N9961, N9962, N99820, N99821
Venous thromboembolism (deep venous thrombosis + pulmonary embolism)	ICD-9: 415.1, 415.11, 415.19, 451.1, 451.2, 451.81, 451.19, 453.4, 453.41, 453.42, 453.8, 453.9, 997.2, 999.2, 997.79 ICD-10: I82.62, I82.72, I82.40, I82.50, I82.49, I82.492, I82.499, I82.621, I82.622, I82.4Y, I82.4Z, I82.41, I82.629, I82.401, I82.402, I82.403, I82.493, I82.4Y1, I82.4Y2, I82.4Y3, I82.4Z1, I82.4Z2, I82.4Z3, I82.623, I82.409, I82.4Y9, I82.4Z9, I26.0, I26.01, I26.02, I26.09, I26.9, I26.90, I26.92, I26.93, I26.94, I26.99

Outcome measure (complication) codes were used to query the Mariner PearlDiver Database.

may be predictive of the complications of hematoma, DVT, and PE.

A second cohort was identified by isolating patients who underwent MBR and, within 3 days of discharge, filled an outpatient prescription for enoxaparin sodium for at least 14 days of total therapy (patients who received more than 28 days of enoxaparin were not excluded). Enoxaparin was selected for analysis, as it is the most reported agent for extended postoperative VTE prophylaxis in the literature and is reported in outcomes databases with J-codes. The national drug code database codes used in the analysis are reported in Table 1. This group was also queried for diagnoses of hematoma and DVT and/or PE within the specified time frames. The ICD-9 and 10 codes queried for outcome measure analysis are listed in Table 2. Demographic information for this cohort was also extracted.

Systematic Review

An experienced medical librarian helped run a comprehensive literature search on June 1, 2021, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] The PubMed/MEDLINE, Scopus, Cochrane Database of Controlled Trials, Cochrane Database of Systematic Reviews, and Google Scholar databases were queried. Both controlled vocabularies (ie, MeSH terms) and keywords were searched. (**See figure, Supplemental Digital Content 1,** which displays the search terms utilized for the systematic review. **http://links.lww.com/PRSGO/C422**.) To refine results, keyword searching was limited to the title or abstract fields in Scopus and the Cochrane databases. There were no restrictions on date range, geography, age of participants, or language of publication. The reproducible search strategy flow diagram is presented in Supplemental Digital Content 2. (**See figure, Supplemental Digital Content 2**, which displays the PRISMA flow diagram outlining the literature search strategy. **http://links.lww.com/PRSGO/C423**.)

Search results were uploaded to Covidence (www.covidence.org), and duplicate results eliminated. Screening of articles for titles and abstracts that met inclusion criteria was conducted by two individuals. Full-text review of articles was then performed with further exclusion based on eligibility criteria, which included articles that were prospective and retrospective reviews with text available in English that investigated the effect of anticoagulants after MBR. Systematic reviews, meta-analyses, and gray literature were excluded unless they also featured a prospective or retrospective cohort of patients. References of the articles meeting the inclusion criteria were analyzed to ensure completeness. (**See figure, Supplemental Digital Content 3**, which displays the summary of articles in systematic review.[10,21,24–31] **http://links.lww.com/PRSGO/C424**.)

Data were extracted using a data abstraction form created in Microsoft Excel (software version 16.16.27, 2021). The data collected from studies included: study location, study period, study design, patient characteristics, number of patients, type of VTE prophylaxis and duration, type of reconstruction flap performed, anticoagulation complications (ie, rate of deep venous thrombosis, pulmonary embolism, hematoma), and clinical outcomes (ie, rate of re-operative hematoma, death).

Statistical data in this study were analyzed with R Studio (software version 1.3.1093, 2021), Microsoft Excel (software version 16.16.27, 2021; Microsoft Corp, Redmond, Wash.), and built-in statistical software contained in the PearlDiver Mariner database. Descriptive statistics such as age, rate of comorbidities, and rate of complications were analyzed for each group in this study. Logistic regression was undertaken to investigate the effect of patient characteristics and comorbidities on the likelihood of developing complications (hematoma/perioperative hemorrhage, DVT, PE).

RESULTS

PearlDiver Mariner Database

A total of 13,541 patients who underwent MBR during the specified time period were identified. Patient demographics are presented in Table 3. The number of patients in cohort 1 experiencing the outcome measures of hematoma, DVT, and/or PE with associated rates are presented in Table 4. Logistic regression for this same cohort is presented in Table 5.

Table 3. Demographic Information of Cohort 1 (All MBR Patients)

Variable	Value (%)
Total patients, N	13,541 (100%)
Women	13,524 (99.87%)
Men	17 (0.13%)
Mean age, y	51.72
Age range, y	15–82
Commercial payer	11,828 (87.35%)
Medicaid	688 (5.08%)
Medicare	626 (4.62%)
Government payer	221 (1.63%)
Cash/self-pay	14 (0.10%)
Unknown	164 (1.21%)
Mean length of stay	4.48 d (range: 1–92 d)

Table 4. Outcomes of Patients in Cohort 1 (All MBR Patients) and Cohort 2 (Extended Postoperative Enoxaparin after MBR Patients)

Cohort 1	
Variable	**N (%)**
Total patients	13,541 (100%)
Hematoma/bleeding complications	475 (3.51%)
DVT	137 (1.01%)
PE	74 (0.55%)
Cohort 2	
Variable	**N (%)**
Total patients	786 (100%)
Hematoma/bleeding complications	26 (3.31%)
DVT	23 (2.93%)
PE	14 (1.78%)

A total of 786 patients who underwent MBR and received extended, postdischarge enoxaparin during the specified time were identified. Patient demographics are presented in Table 6. In the database, the first year a patient was prescribed extended postoperative enoxaparin after MBR was 2015 with 78 prescriptions. That number more than doubled by 2019 (n = 175; 124% increase). The number of patients in cohort 2 experiencing the outcome measures of hematoma, DVT, and/or PE with associated rates is presented in Table 4. A side-by-side comparison of outcomes of the two cohorts in the database portion of this study is presented in Table 7, including a statistical comparison with the χ^2 test. Overall, lower rates of both DVT ($P < 0.001$) and PE ($P < 0.001$) occurred in the non-extended prophylaxis group (cohort 1). However, similar rates of bleeding/hematoma occurred in both groups ($P = 0.767$).

Systematic Review

A total of 551 studies were identified through the literature search. After assessing the articles for eligibility, 108 studies remained. After manual review of each of these studies by two individuals, 10 studies were identified to be included in this systematic review.[10,21,24–31] A detailed summary of the 10 studies meeting inclusion criteria in the systematic review is presented in Supplemental Digital Content 1. (**See figure, Supplemental Digital Content 1**, **http://links.lww.com/PRSGO/C422**.) These studies ranged in year of publication from 1995 to 2021. The most

Table 5. Results of Logistic Regression Investigating Patient Characteristics and Comorbidities and Their Effect on the Likelihood of a Patient Experiencing the Outcomes of Hematoma, DVT, and/or PE

Variable	Odds Ratio (95% Confidence Interval)	*P*
Hematoma/perioperative hemorrhage		
Acute blood loss anemia	1.23 (0.83–1.76)	0.275
COPD	1.137 (0.89–1.44)	0.299
CKD	1.61 (0.57–6.37)	0.428
Coagulopathy	1.50 (1.13–1.95)*	0.003*
Diabetes mellitus	1.10 (0.75–1.57)	0.597
HTN	1.25 (1.01–1.53)*	0.039*
Obesity (BMI >30)	0.84 (0.69–1.02)	0.073
Renal failure	1.34 (0.71–2.53)	0.359
Active tobacco use	0.86 (0.70–1.05)	0.146
DVT		
Acute blood loss anemia	1.23 (0.60–2.28)	0.540
COPD	0.87 (0.55–1.35)	0.535
CKD	8.55 (0.31–38.1)	0.371
Coagulopathy	3.07 (2.08–4.53)*	<0.001*
Diabetes	1.52 (0.80–2.92)	0.20
HTN	1.13 (0.77–1.66)	0.548
Obesity (BMI >30)	1.34 (0.94–1.92)	0.104
Renal failure	1.05 (0.26–4.08)	0.936
Active tobacco use	1.33 (0.94–1.90)	0.103
PE		
Acute blood loss anemia	0.74 (0.22–1.82)	0.559
COPD	1.28 (0.71–2.23)	0.408
CKD	11.92 (0.15–22.3)	0.515
Coagulopathy	2.75 (1.56–4.64)	<0.001*
Diabetes	1.91 (0.85–3.86)	0.092
HTN	1.55 (0.91–2.69)	0.115
Obesity (BMI >30)	1.25 (0.77–2.03)	0.367
Renal failure	1.39 (0.17–11.76)	0.742
Active tobacco use	0.80 (0.47–1.30)	0.376

*Denotes statistical significance.
BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HTN, hypertension.

Table 6. Demographic Information of Cohort 2 (Extended Postoperative Enoxaparin after MBR Patients)

Variable	Value (%)
Total patients, N	786 (100%)
Women	786 (100%)
Men	0 (0%)
Mean age, y	52.31
Age range, y	27–78
Commercial payer	692 (88.04%)
Medicaid	40 (5.09%)
Medicare	32 (4.07%)
Government payer	0 (0%)
Cash/self-pay	0 (0%)
Unknown	15 (1.91%)
Mean length of stay	4.96 d (range 1–41 d)

Table 7. Comparison of Outcomes of Cohort 1 and 2

Variable	Cohort 1, N (%)	Cohort 2, N (%)	χ^2 Test, P
Total patients	13,541 (100%)	786 (100%)	—
Hematoma/bleeding complications	475 (3.51%)	26 (3.31%)	$P = 0.767$
DVT	137 (1.01%)	23 (2.93%)	$P < 0.001$*
PE	74 (0.55%)	14 (1.78%)	$P < 0.001$*

*$P < 0.05$ indicates statistical significance.

common methodology of these studies was retrospective review (n = 8) with the remaining studies being prospective cohorts (n = 2). One of the retrospective cohort studies also featured a meta-analysis, the data from which were excluded in this systematic review.

Although all the studies featured a control group and at least one experimental group, study designs and interventions (chemoprophylaxis agent, dosing, time of initiation, and duration) were found to be highly variable and heterogenous. Control group interventions also differed, with some studies providing no VTE prophylaxis to control group patients and others using either a single preoperative dose or a shorter duration of VTE prophylaxis compared with the experimental group. Two of the studies stratified patient groups based on Caprini score risk; the score cutoffs for stratification also varied between these studies. Nine of the 10 studies reported VTE rates for study groups as a primary outcome measure, but only one study utilized bleeding complications as a primary outcome measure and did not include any information on VTE rates. Overall, seven of the 10 studies provided a comparison of bleeding complication rates between groups with six of these studies additionally reporting on the rate of bleeding complications requiring operative reexploration (also referred to as "takeback").

In terms of VTE prophylaxis agents investigated, six studies administered enoxaparin to at least one of their experimental groups, four studies involved unfractionated heparin, and four studies investigated low-molecular-weight heparin. Bassiri-Tehrani et al[28] also administered aspirin (81 mg) to "certain" patients in both the control and experimental groups based on senior author experiments. It was unclear how many of the studies also incorporated adjunct VTE prophylaxis measures, such as sequential compression device boots, in their protocols, as most of the studies did not explicitly state they were utilized.

The detection of primary outcome measures (DVT/PE) was not standardized among studies. Presumably, all the retrospective studies reported on symptomatic VTE that were detected in the routine care of patients in the postoperative period. However, some surgeons routinely order postoperative lower extremity duplex ultrasonography to rule out DVT before hospital discharge. One prospective study by Lemaine et al[26] obtained this imaging study for every patient before discharge to capture symptomatic and asymptomatic VTE in both their control and experimental groups.

In terms of efficacy of postoperative VTE prophylaxis, eight of the 10 studies reported a lower rate of VTE in their intervention groups compared with control groups. However, only three of these studies found statistically significant differences. In terms of postoperative bleeding risk, seven of the eight studies comparing bleeding complications in control versus experimental groups found no significant differences in postoperative bleeding complications. The 1995 study by Kroll et al[24] reported a significantly higher risk ($P < 0.01$) of postoperative bleeding with high-dose heparin administration compared with both low-dose heparin therapy and no prophylaxis.

DISCUSSION

This study used the PearlDiver Mariner database to investigate the rates of postoperative hematoma, DVT, and PE in MBR patients discharged on enoxaparin along with a systematic review featuring 10 studies. This is the first study investigating the efficacy of extended postoperative VTE prophylaxis utilizing a database featuring a large cohort of 13,541 patients.

The database query revealed hematoma, DVT, and PE rates of 3.51%, 1.01%, and 0.55%, respectively, in patients undergoing MBR. Although the rate of hematoma is similar to previous studies on this topic, the rates of DVT/PE in this study seem to be lower than those of previous studies.[1–3] This may be explained by improved, stricter VTE prophylaxis protocols that include pre-, intra-, and often postoperative VTE pharmacological prophylaxis as well as adjunct measures such as sequential compression devices. The widespread use of the Caprini risk assessment model may have influenced these results, as it aides in ensuring that high-risk patients receive appropriate pre- and intraoperative (but not postoperative) VTE prophylaxis. The effect of several patient factors/comorbidities on rates of hematoma, DVT, and PE was also investigated and included in the logistic regression analysis. Before the study, it was hypothesized that factors such as tobacco use and obesity would have a significant effect on patients' likelihood of developing postoperative bleeding and/or thrombotic complications. However, the only factor that was found to have a significant effect was the presence of coagulopathy (for hematoma, DVT, and PE), along with hypertension increasing the likelihood of hematoma.

Interestingly, higher rates of DVT and PE were found in the extended postoperative enoxaparin group (2.93% and 1.78%, respectively). This may be due to a higher likelihood of patients with an increased baseline risk for VTE to receive prophylactic therapy, although this was not investigated in this study. However, hematoma rates were similar in the extended postoperative enoxaparin group compared with the entire MBR group ($P = 0.767$), findings consistent with those of the 2014 study by Vedovati et

al[15] and the 2019 study by Ohta et al,[16] which were prospective studies investigating extended postoperative thromboprophylaxis in colorectal surgery patients.

Patients in the database were first noted to receive extended postoperative enoxaparin after MBR in 2015, the timing of which likely corresponds to the first study in a surgical specialty (colorectal surgery) to report on the benefits of this therapy in 2014.[15] The number of MBR patients receiving the extended enoxaparin therapy is likely to continue to increase based on the current author's anecdotal experience, despite an absence of level I evidence on the efficacy and safety of this agent in plastic surgery patients. The findings in the current study highlight the need for prospective, randomized trials on the efficacy and safety of extended postoperative enoxaparin in both MBR and plastic surgery procedures more generally.

The systematic review in this report covered both retrospective and prospective cohort studies dating back to 1995 through 2021 with a range of chemoprophylactic agents investigated. Currently, enoxaparin appears to be the most-commonly prescribed agent for extended postoperative VTE prophylaxis. To the current author's knowledge, there are two studies within plastic surgery specifically investigating extended postoperative VTE prophylaxis with no systematic reviews or meta-analyses published to date. However, no prospective studies on extended enoxaparin have been published to date in microsurgical deep inferior epigastric perforator flap reconstruction (currently the most common method of breast reconstruction in the United States[2]). Study designs in the systematic review were variable, and no two studies included an identical protocol (agent, duration, etc). This is likely responsible for the anecdotal observation that plastic surgical postoperative VTE prophylaxis has minimal standardization and varies from surgeon to surgeon based on personal experience. Only two studies in the systematic review[24,25] found statistically lower rates of VTE with the administration of extended postoperative VTE prophylaxis. The 2008 prospective study by Chung et al[25] reported a dramatic reduction in VTE from 17.2% without therapy to 3.2% ($P = 0.01$) with 6 days of postoperative enoxaparin in transverse rectus abdominis muscle flap patients. This stands in significant contrast to the other prospective study in the review, the 2011 study by Lemaine et al,[26] which found a higher, albeit insignificant, difference in the rate of VTE using postoperative dalteparin (LMWH) (3.4%) compared with no VTE events in their group without chemoprophylaxis ($P = 0.12$). Furthermore, in accordance with previous studies in other surgical specialties,[15–20] most of the studies in this review (7 of 8 studies) found no significant difference in postoperative bleeding complications with extended postoperative VTE prophylaxis. This conclusion, along with the findings in the PearlDiver Mariner database, suggests that postoperative VTE chemoprophylaxis seems to be safe and does not increase the risk of postoperative bleeding.

One of the studies included in the systematic review, the 2018 study by Laws et al,[10] investigated patient compliance with the LMWH VTE prophylaxis protocol instituted in their study. Interestingly, they found that only 60.5% of the patients in the study were compliant with pre- and postdischarge LMWH administration. They reported factors significantly associated with noncompliance to be bilateral procedure, undergoing breast reconstruction versus nonreconstruction, and procedure duration greater than 4 hours. Age, weight, cancer stage, Caprini score, and need for axillary dissection during mastectomy were not found to be significant factors[10] affecting compliance.

The present study carries several limitations. Although the PearlDiver Mariner database is extensive and features a diverse sample of patients from the entire United States with both commercially and publicly insured patients, it is retrospective in nature. Furthermore, data depend on the accuracy of coding and the types of codes selected for reimbursement. It also requires patients to have continuous claims in order to capture all events in the postoperative period. Insurance databases are only able to capture outpatient prescriptions; therefore, only patients who definitively received a prescription for outpatient enoxaparin after discharge could be identified. It is likely that some of the patients in the general MBR cohort received postoperative enoxaparin that was administered while the patients were admitted (and discontinued prior to discharge), and the effect of this therapy could not be investigated. There is also an inability to measure injection compliance as well as appropriateness of dosing associated with database studies. Finally, due to the inclusion criteria of cohort 2, patients who did not fill their enoxaparin prescription until 2 or 3 days after discharge had an interrupted period of VTE prophylaxis. While the inclusion criteria were specified to increase the number of patients, this noncompliance phenomenon may have further contributed to the higher rate of VTE observed in cohort 2. The heterogeneity in study design, procedure type, VTE prophylaxis protocols, and pharmacotherapy agents used in the systematic review limits the generalizability of the findings from these studies. There were also only two prospective studies that met inclusion criteria, one of which did not report on bleeding or hematoma complications postoperatively. None of the studies investigated or reported the effect of other factors that may significantly increase a patient's risk of postoperative VTE, such as duration of surgery, prior personal history of VTE, or coexisting pro-thrombotic/coagulopathic conditions. Underlying coagulopathy was found to have a significant effect on developing hematoma, DVT, and PE in the PearlDiver Mariner database, which underscores the importance of identifying these patient characteristics in future studies investigating surgical VTE prophylaxis.

CONCLUSIONS

This is the first study utilizing a national database to investigate extended postoperative enoxaparin in MBR. Contemporary rates of postoperative bleeding complications seem comparable to historical rates, but the rates

of DVT and PE seem to be decreasing with the advent of strict VTE prophylaxis protocols. Tobacco and obesity did not influence postoperative bleeding, DVT, or PE, whereas coagulopathy increased the risk of all three of these complications. Based on a systematic review, most studies have not found a definitive benefit to postoperative VTE prophylaxis in lowering the risk of DVT/PE. However, most studies have found no significant difference in the risk of bleeding with this therapy. Further prospective, randomized controlled trials are needed in plastic surgery, including in MBR, to definitively determine the benefits and potential harms of extended postoperative VTE prophylaxis in these domains.

George Kokosis, MD
1725 W Harrison Street
Suite POB 425
Chicago, IL 60612
E-mail: george_kokosis@rush.edu

REFERENCES

1. Liao EC, Taghinia AH, Nguyen LP, et al. Incidence of hematoma complication with heparin venous thrombosis prophylaxis after TRAM flap breast reconstruction. *Plast Reconstr Surg.* 2008;121:1101–1107.
2. Rochlin DH, Sheckter CC, Pannucci C, et al. Venous thromboembolism following microsurgical breast reconstruction: a longitudinal analysis of 12,778 patients. *Plast Reconstr Surg.* 2020;146:465–473.
3. Subichin MP, Patel NV, Wagner DS. Method of breast reconstruction determines venous thromboembolism risk better than current prediction models. *Plast Reconstr Surg Glob Open.* 2015;3:e397.
4. Sullivan SR, Fletcher DRD, Isom CD, et al. True incidence of all complications following immediate and delayed breast reconstruction. *Plast Reconstr Surg.* 2008;122:19–28.
5. Pannucci CJ, Dreszer G, Wachtman CF, et al. Postoperative enoxaparin prevents symptomatic venous thromboembolism in high-risk plastic surgery patients. *Plast Reconstr Surg.* 2011;128:1093–1103.
6. Momeni A, Fox JP. Venous thromboembolism after surgical treatment of breast cancer. *Ann Plast Surg.* 2018;80:188–192.
7. Guo Q, Huang B, Zhao J, et al. Perioperative pharmacological thromboprophylaxis in patients with cancer: a systematic review and meta-analysis. *Ann Surg.* 2017;265:1087–1093.
8. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE Disease: CHEST guideline and expert panel report. *Chest.* 2016;149:315–352.
9. Cronin M, Dengler N, Krauss ES, et al. Completion of the updated Caprini risk assessment model (2013 Version). *Clin Appl Thromb Hemost.* 2019;25:1076029619838052.
10. Laws A, Anderson K, Hu J, et al. Implementation of a venous thromboembolism prophylaxis protocol using the Caprini risk assessment model in patients undergoing mastectomy. *Ann Surg Oncol.* 2018;25:3548–3555.
11. Kim NE, Conway-Pearson L, Kavanah M, et al. Standardized risk assessment and risk-stratified venous thromboembolism prophylaxis for patients undergoing breast operation. *J Am Coll Surg.* 2020;230:947–955.
12. Pannucci CJ, Bailey SH, Dreszer G, et al. Validation of the Caprini risk assessment model in plastic and reconstructive surgery patients. *J Am Coll Surg.* 2011;212:105–112.
13. Amin AN, Lin J, Ryan A. Need to improve thromboprophylaxis across the continuum of care for surgical patients. *Adv Ther.* 2010;27:81–93.
14. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol.* 2020;38:496–520.
15. Vedovati MC, Becattini C, Rondelli F, et al. A randomized study on 1-week versus 4-week prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer. *Ann Surg.* 2014;259:665–669.
16. Ohta H, Miyake T, Shimizu T, et al. The impact of pharmacological thromboprophylaxis and disease-stage on postoperative bleeding following colorectal cancer surgery. *World J Surg Oncol.* 2019;17:110.
17. Pariser JJ, Pearce SM, Anderson BB, et al. Extended duration enoxaparin decreases the rate of venous thromboembolic events after radical cystectomy compared to inpatient only subcutaneous heparin. *J Urol.* 2017;197:302–307.
18. Kim BJ, Day RW, Davis CH, et al. Extended pharmacologic thromboprophylaxis in oncologic liver surgery is safe and effective. *J Thromb Haemost.* 2017;15:2158–2164.
19. Hashimoto D, Nakagawa S, Umezaki N, et al. Efficacy and safety of postoperative anticoagulation prophylaxis with enoxaparin in patients undergoing pancreatic surgery: a prospective trial and literature review. *Pancreatology.* 2017;17:464–470.
20. Guntupalli SR, Brennecke A, Behbakht K, et al. Safety and efficacy of apixaban vs enoxaparin for preventing postoperative venous thromboembolism in women undergoing surgery for gynecologic malignant neoplasm: a randomized clinical trial. JAMA Netw Open. 2020;3:e207410.
21. Marques de Marino P, Rial Horcajo R, Garcia Grandal T, et al. Thromboprophylaxis in gynecologic cancer surgery: is extended prophylaxis with low molecular weight heparin justified? *Eur J Obstet Gynecol Reprod Biol.* 2018;230:90–95.
22. Pittelkow EM, DeBrock WC, Mailey B, et al. Evaluation of an extended-duration chemoprophylaxis regimen for venous thromboembolism after microsurgical breast reconstruction. *Plast Reconstr Surg Glob Open.* 2021;9:e3741.
23. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8:336–341.
24. Kroll SS, Miller MJ, Reece GP, et al. Anticoagulants and hematomas in free flap surgery. *Plast Reconstr Surg.* 1995;96:643–647.
25. Chung MS, Yoon H, Son B, et al. The efficacy of enoxaparin for the prevention of a pulmonary thromboembolism in a skin-sparing mastectomy with immediate reconstruction in breast cancer. *J Breast Canc.* 2008;11:125–132.
26. Lemaine V, McCarthy C, Kaplan K, et al. Venous thromboembolism following microsurgical breast reconstruction: an objective analysis in 225 consecutive patients using low-molecular-weight heparin prophylaxis. *Plast Reconstr Surg.* 2011;127:1399–1406.
27. Pannucci CJ, Wachtman CF, Dreszer G, et al. The effect of postoperative enoxaparin on risk for reoperative hematoma. *Plast Reconstr Surg.* 2012;129:160–168.
28. Bassiri-Tehrani B, Karanetz I, Bernik SF, et al. The timing of chemoprophylaxis in autologous microsurgical breast reconstruction. *Plast Reconstr Surg.* 2018;142:1116–1123.
29. Keith JN, Chong TW, Davar D, et al. The timing of preoperative prophylactic low-molecular-weight heparin administration in breast reconstruction. *Plast Reconstr Surg.* 2013;132:279–284.
30. Kim NE, Conway-Pearson L, Kavanah M, et al. Standardized risk assessment and risk-stratified venous thromboembolism prophylaxis for patients undergoing breast operation. *J Am Coll Surg.* 2020;230:947–955.
31. McKean AR, Knox J, Nanidis T, et al. Reducing postoperative venous thromboembolism in DIEP free flap breast reconstruction: extended pharmacological thromboprophylaxis within an enhanced recovery programme. *J Plast Reconstr Aesthet Surg.* 2021;74:2392–2442.