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Surgical Thromboprophylaxis in Patients With Head and Neck Cancer: An Economic Model

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Abstract

Objective. To quantify postoperative venous thromboembolism (VTE) incidence in head and neck cancer (HNC) patients, and assess the economic implications of chemoprophylaxis.

Study Design. Retrospective cost-effective analysis.

Setting. Fifty-three health care organizations.

Methods. The TriNetX Research Network was queried to identify the 1-month VTE rate in HNC patients undergoing neck dissection from 2012 to 2022. A literature search provided additional postsurgical VTE rates in HNC patients. Costs of prophylactic heparin and enoxaparin were obtained from a drug wholesaler, and VTE-associated medical costs were sourced from the literature. A break-even analysis determined the absolute risk reduction (ARR) in the VTE rate necessary for a medication to break-even on cost.

Results. In TriNetX, 8193 HNC surgical patients underwent neck dissection, and an additional 1640 patients underwent neck dissection plus free flap reconstruction without chemoprophylaxis. Respective 1-month VTE rates were 1.3% (n = 103) and 2.5% (n = 41). Four additional studies of 1546 postoperative HNC patients not prescribed chemoprophylaxis reported a mean VTE rate of 3.8% (n = 59), ranging from 1.9% to 13.0%. At $8.40 per week, heparin resulted in cost savings if it decreased the VTE rate by an ARR of at least 0.05%, while enoxaparin, at $23.66 per week, needed to achieve a 0.14% ARR. Considering potential added costs from bleeding complications, heparin, and enoxaparin remained cost-effective if chemoprophylaxis did not increase bleeding complications by an absolute risk of more than 2.86% and 2.79%, respectively.

Conclusion. Postoperative VTE rates varied in HNC patients. Despite this, achievable ARRs suggested the potential cost-effectiveness of routine chemoprophylaxis with heparin and enoxaparin.

Keywords

chemoprophylaxis, cost-effective, deep venous thrombosis, head and neck cancer, pulmonary embolism, VTE

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Venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary embolism,[1] is associated with over 100,000 deaths annually in the United States, with 1/3 occurring postoperatively.[2,3] Additionally, after VTE, patients are at elevated risk for recurrence and complications such as venous stasis syndrome, venous ulcers, pulmonary hypertension, and the sequelae of requiring long-term anticoagulation.[4,5] From an economic standpoint, VTE-related patient-level medical cost estimates range from $16,437 to $53,420 annually,[6-8] and, at a population level, VTEs are responsible for $5-10 billion in annual direct medical costs.[9]

The role for chemoprophylaxis to prevent VTEs in Otolaryngology–Head and Neck Surgery continues to be debated, given that the rate of VTE is reported to be lower compared to other specialties.[10-12] Oncologic head and neck surgery may represent a higher-risk subgroup, however reported VTE rates range widely from 0% to 26.3%.[11-23] Proponents of thromboprophylaxis in this setting cite a high prevalence of risk factors for VTE in this population including length of surgery, hypercoagulable state of malignancy, and the presence of other comorbidities, including advanced age, smoking, and chronic pulmonary disease.[24] Conversely, those not in favor note potential bleeding complications associated with chemoprophylaxis, which could lead to hematoma formation and airway compromise.[25,26]

Currently, there are no practice guidelines or consensus for VTE prophylaxis for patients with head and neck cancer (HNC) following surgery. Although the effectiveness and utility of chemoprophylaxis in this setting is unclear, the objective of this study was to determine

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whether its use is justified from an economic perspective. To the authors' knowledge, there are no existing studies of this nature.

Methods

Data Collection

The study sourced data from the TriNetX Research Network,[27] a regularly refreshed, deidentified database with electronic medical records from 100 million patients from over 50 health care organizations. TriNetX is compliant with the Health Insurance Portability and Accountability Act. Because this study utilized deidentified patient records without individually identifiable data, an Institutional Review Board review exemption was granted by the Penn State Human Subjects Protection Office (STUDY00018629).

The database was queried using diagnosis (International Classification of Diseases-10) and procedure (Current Procedural Terminology) codes to identify patients with HNC undergoing neck dissection during 2012 to 2022 (refer to Supplemental Data S1, available online for codes). Due to presumed heterogeneity of operative time, complexity, and length of hospitalization within patients coded for neck dissection, they were grouped according to concurrent free flap reconstruction. The free flap subset served as an upper bound for surgical extent and risk. Patients were excluded if they did not have medication recorded on the day of surgery. The presence of a medication denoted that medications and likely other clinical information were reliably abstracted, and filtered for higher-quality data. To prevent loss to follow-up, patients were required to have continued enrollment in the database for the first month postoperatively. Patients who met inclusion criteria were stratified according to whether they received prophylactic anticoagulation, with those who did excluded from the break-even analysis. Demographic and oncologic variables including age, sex, ethnicity, race, and tumor site were collected. The rate of VTE in the 30 days following surgery was determined.

Additional data came from a literature review identifying studies reporting VTE rates following oncologic head and neck surgery. Studies were stratified according to whether patients received prophylactic anticoagulation, with those who did excluded from the break-even analysis. Mechanical prophylaxis alone was not a reason for exclusion.

Cost-Effectiveness Calculations

A break-even equation, originally described by Hatch et al,[28] and validated in the orthopedic literature,[29,30] served as an economic model for cost-effectiveness. The equation yields the absolute risk reduction (ARR) required for a prophylactic measure to break-even in costs (**Figure 1**). The model incorporates costs of prophylactic anticoagulation from a drug wholesaler, the initial rate of VTE before anticoagulation determined by our TriNetX analysis as well as from the literature, and VTE-related medical costs also obtained from the literature. Costs for 1 week of heparin (5000 U thrice daily) and enoxaparin (40 mg once daily) at prophylactic dosage were analyzed, as these are the most commonly prescribed anticoagulants in this setting.[31]

$$S_{total} \times C_t \times VTE_i = (S_{total} \times C_c) + (S_{total} \times C_t \times VTE_f)$$

Solving for VTE_f yields:

$$VTE_f = VTE_i - \frac{C_c}{C_t}$$

Figure 1. Economic model to calculate break-even VTE rate. S_{total} = total annual surgeries, C_t = cost of treating VTE, C_c = cost of chemoprophylaxis, VTE_i = initial VTE rate, VTE_f = break − even VTE rate. ARR = $VTE_i - VTE_f$, or $\frac{C_c}{C_t}$.

Sensitivity analyses were performed to account for variable drug prices, VTE-related medical costs, and VTE rates. Another analysis incorporated potential costs associated with major bleeding complications, with rates of bleeding complications and total excess costs after head and neck oncologic surgery obtained from the literature. TriNetX provided an additional data point on bleeding rates related to chemoprophylaxis by determining the postoperative hematoma rate in patients with and without anticoagulation. All cost estimates were adjusted for inflation and converted to 2022 US dollars via the Consumer Price Index.

Results

Rate of VTE

In TriNetX, we identified 22,133 total patients who underwent neck dissection between 2012 and 2022, with demographics described in **Table 1**. Among this group, 9833 were not prescribed chemoprophylaxis and met inclusion criteria for the break-even analysis: 8193 underwent neck dissection without free flap reconstruction, and 1640 underwent concurrent free flap reconstruction. The 1-month rate of symptomatic VTE was 1.3% (n = 103) in the neck dissection alone cohort, and increased at 2.5% (n = 41) among patients who underwent concurrent free flap reconstruction. Of note, VTE rates were actually greater in the same cohorts of patients who were prescribed anticoagulation; the neck dissection without free flap VTE rate was 2.1% (n = 151 out of 7092 patients), and the concomitant free flap rate was 3.6% (n = 190 out of 5208 patients).

There were an additional thirteen studies reporting VTE rates following oncologic head and neck surgery (**Table 2**). Two[11,15] were excluded because data regarding prophylactic anticoagulation practices were not available. Two more[17,19] were excluded as outliers, reporting VTE rates of 0% and 26.3%. Four[13,16,18,20] articles that met inclusion criteria studied a total of 1546 patients who were not prescribed prophylactic anticoagulation following surgery. The mean rate of symptomatic VTE in these studies was

Table 1. TriNetX Demographics and Cancer Site of Those Who Did Not Receive Prophylactic Anticoagulation

	No chemoprophylaxis (n = 9833)		Chemoprophylaxis (n = 12,300)	
Characteristic	Neck dissection without free flap (n = 8193)	Neck dissection and free flap (n = 1640)	Neck dissection without free flap (n = 7092)	Neck dissection and free flap (n = 5208)
Age at surgery ± standard deviation	62.3 ± 12.8	61.5 ± 12.3	63.2 ± 12.0	62.3 ± 12.1
Sex				
Male	5816 (71%)	1169 (71%)	5117 (72%)	3410 (65%)
Female	2265 (28%)	471 (29%)	1960 (28%)	1770 (34%)
Unknown	112 (1%)	0 (0%)	15 (0%)	28 (1%)
Ethnicity				
Not Hispanic or Latino	6407 (%)	1474 (90%)	4981 (70%)	4416 (85%)
Hispanic or Latino	422 (5%)	71 (4%)	286 (4%)	186 (3%)
Unknown	1364 (17%)	95 (6%)	1825 (26%)	606 (12%)
Race				
White	6030 (74%)	1333 (81%)	5757 (81%)	4158 (80%)
Black or African American	584 (7%)	198 (12%)	468 (7%)	396 (8%)
Asian	316 (4%)	30 (2%)	206 (3%)	198 (4%)
Other[a]	302 (3%)	26 (2%)	302 (4%)	208 (3%)
Unknown	961 (12%)	53 (3%)	359 (5%)	248 (5%)
Cancer site[b]				
C00 lip	170 (2%)	46 (3%)	142 (2%)	112 (2%)
C01 base of tongue	1161 (14%)	204 (12%)	1193 (17%)	693 (13%)
C02 other and unspecified parts of the tongue	1942 (24%)	482 (29%)	1773 (25%)	1777 (34%)
C03 gum	327 (4%)	208 (13%)	357 (5%)	680 (13%)
C04 floor of mouth	457 (6%)	319 (19%)	496 (7%)	926 (18%)
C05 palate	217 (3%)	107 (7%)	222 (3%)	345 (7%)
C06 other and unspecified parts of mouth	1455 (18%)	830 (51%)	1403 (20%)	2455 (47%)
C07 parotid gland	1219 (15%)	87 (5%)	851 (12%)	263 (5%)
C08 other and unspecified major salivary glands	414 (5%)	42 (3%)	291 (4%)	162 (3%)
C09 tonsil	1465 (18%)	91 (6%)	1,312 (18%)	350 (7%)
C10 oropharynx	1045 (13%)	161 (10%)	890 (13%)	555 (11%)
C11 nasopharynx	159 (2%)	20 (1%)	121 (2%)	91 (2%)
C12 piriform sinus	122 (1%)	51 (3%)	94 (1%)	104 (2%)
C13 hypopharynx	194 (2%)	75 (5%)	182 (3%)	226 (4%)
C14 other and ill-defined sites in the lip, oral cavity, and pharynx	342 (4%)	128 (8%)	341 (5%)	431 (8%)
C30 nasal cavity and middle ear	150 (2%)	40 (2%)	108 (2%)	132 (3%)
C31 accessory sinuses	165 (2%)	84 (5%)	164 (2%)	282 (5%)
C32 larynx	1351 (16%)	325 (20%)	1202 (17%)	814 (16%)

[a]Other race includes American Indian or Alaskan Native, or Native Hawaiian or other Pacific Islander due to low counts.
[b]Cancer sites do not add to 100% due to overlapping sites.

3.8% (n = 59), with individual rates ranging from 1.9% to 13.0%. Six studies[12,14,20-23] of 4745 patients prescribed chemoprophylaxis reported an average VTE rate of 1.6% (n = 77), with individual rates ranging from 0.4% to 2.9%.

Break-Even Analysis

According to our institution's drug wholesaler, the cost to the hospital for a 1-week supply of heparin 5000 U ranged from $8.40 to $82.11. One week of enoxaparin 40 mg costs $23.66 to $210.49. Additional information regarding route, frequency of administration, and price per dose is presented in **Table 3**. After adjustment for inflation, VTE-related medical costs, including those incurred on an inpatient, outpatient, and pharmacy basis, are reported to range from $16,437 to $53,420.[6-8]

At $8.40 per week, the lowest cost available for purchase, heparin was determined to be cost-effective if

Table 2. Overview of Existing Studies Analyzing VTE Rates in Head and Neck Oncologic Surgery

Author	Year	Study type	Prophylactic anticoagulation	Number of patients	Number of VTE	VTE rate, %
Thai	2013	Retrospective	No	134	8 (2 confirmed, 6 suspicious)	5.8
Clayburgh	2013	Prospective	No	100	13	13.0
Shuman	2012	Retrospective	No	1,092	21	1.9
Bahl	2014	Retrospective	No	220	17	7.7
			Yes	287	6	2.1
Chen	2008	Retrospective	Yes	1591	12	0.8
Ali	2015	Retrospective	Yes	413	12	2.9
Lodders	2015	Retrospective	Yes (94% of patients)	233	1	0.4
Ong	2017	Retrospective	Yes	1953	43	2.2
Garritano	2013	Retrospective	Yes	268	3	1.1
Kakei[a]	2015	Retrospective	No	133	35	26.3
Gavriel[a]	2013	Retrospective	No	450	0	0
			Yes	568	0	0
Hennessey[b]	2012	Retrospective	Data unavailable	93,663	1860	2.0
Innis[b]	2009	Retrospective	Data unavailable	542	5	0.9
Overall no chemoprophylaxis (4 studies)			No	1546	59	3.8
Overall chemoprophylaxis (6 studies)			Yes	4745	77	1.6

Abbreviation: VTE, venous thromboembolism.
[a]Two studies excluded as outliers.
[b]Two studies excluded due to unavailable data regarding prophylactic anticoagulation. Excluded studies are painted gray.

Table 3. Costs of VTE Prophylactic Agents

Drug	Dose	Route of administration	Frequency	Price per dose, $	Price per week, $
Heparin	5000 U	SQ	TID	0.40-3.91	8.40-82.11
Enoxaparin	40 mg	SQ	QD	3.38-30.07	23.66-210.49

Abbreviations: mg, milligrams; QD, once daily; SQ, subcutaneous; TID, three times daily; U, units; VTE, venous thromboembolism.

its ARR is at least 0.05%. At the lowest cost of $23.66 per week, enoxaparin would be cost-effective with an ARR of at least 0.14%. A sensitivity analysis was performed to account for varying medication costs (**Table 4**). The lowest cost of treating VTE ($16,437) was held constant for this analysis. When obtained at their highest listed prices ($82.11 for heparin and $210.49 for enoxaparin per week), the ARR necessary to break-even increased to 0.50% and 1.28%, respectively.

Given VTE cost estimates varied from $16,437 to $53,420, an additional sensitivity analysis altered VTE-related medical costs (**Table 5**). The least expensive prices of heparin and enoxaparin were held constant for this analysis. The justification for selecting the least expensive medication prices was based on their availability for purchase through the drug wholesaler. It was assumed that most institutions could acquire these medications at comparable prices and would opt for the most economical choice when possible. The ARR for heparin was 0.05% for the lowest cost of VTE described in the literature, and

Table 4. Cost-Effectiveness of Chemoprophylactic Agents at Varying Drug Costs

Drug	Cost of drug, $	Initial VTE rate, %	Final VTE rate, %	ARR, %
Heparin	8.40	3.8	3.75	0.05
5000 U TID	20.00	3.8	3.68	0.12
	40.00	3.8	3.58	0.24
	60.00	3.8	3.43	0.37
	82.11	3.8	3.3	0.50
Enoxaparin	23.66	3.8	3.66	0.14
40 mg QD	75.00	3.8	3.34	0.46
	125.00	3.8	3.04	0.76
	175.00	3.8	2.74	1.06
	210.49	3.8	2.52	1.28

Assumes conservative cost for treating VTE ($16,437) obtained from the literature.
Abbreviations: ARR, absolute risk reduction; QD, once daily; TID, three times daily; U, units; VTE, venous thromboembolism.

Table 5. Cost-Effectiveness of Chemoprophylactic Agents at Varying Costs of Treating VTE

Drug	Cost of treating VTE, $	Initial VTE rate, %	Final VTE rate, %	ARR, %
Heparin 5000 U TID	16,437	3.8	3.75	0.05
	20,000	3.8	3.76	0.04
	25,000	3.8	3.77	0.03
	30,000	3.8	3.77	0.03
	35,000	3.8	3.78	0.02
	40,000	3.8	3.78	0.02
	45,000	3.8	3.78	0.02
	53,420	3.8	3.78	0.02
Enoxaparin 40 mg QD	16,437	3.8	3.66	0.14
	20,000	3.8	3.68	0.12
	25,000	3.8	3.71	0.09
	30,000	3.8	3.72	0.08
	35,000	3.8	3.73	0.07
	40,000	3.8	3.74	0.06
	45,000	3.8	3.75	0.05
	53,420	3.8	3.76	0.04

Assumes low available costs of 5000 U heparin ($8.40) and 40 mg enoxaparin ($23.66) for 1 week.
Abbreviations: ARR, absolute risk reduction; QD, once daily; TID, three times daily; U, units; VTE, venous thromboembolism.

Table 6. Cost-Effectiveness of Chemoprophylactic Agents at Varying Initial VTE Rates

Drug	Study	Initial VTE rate, %	Final VTE rate, %	ARR, %
Heparin 5000 U TID	TriNetX neck dissection	1.3	1.25	0.05
	Shuman	1.9	1.85	0.05
	TriNetX free flap	2.5	2.45	0.05
	Average[a]	3.8	3.75	0.05
	Thai	5.8	5.75	0.05
	Bahl	7.7	7.65	0.05
	Clayburgh	13.0	12.95	0.05
Enoxaparin 40 mg QD	TriNetX neck dissection	1.3	1.16	0.14
	Shuman	1.9	1.76	0.14
	TriNetX free flap	2.5	2.36	0.14
	Average[a]	3.8	3.66	0.14
	Thai	5.8	5.66	0.14
	Bahl	7.7	7.56	0.14
	Clayburgh	13.0	12.86	0.14

Assumes conservative cost for treating VTE ($16,437) obtained from the literature.
Assumes low available costs of 5000 U heparin ($8.40) and 40 mg enoxaparin ($23.66) for 1 week.
Abbreviations: ARR, absolute risk reduction; QD, once daily; TID, three times daily; U, units; VTE, venous thromboembolism.
[a]Mean VTE rate of all studies including head and neck oncologic surgery patients who did not receive prophylactic anticoagulation.

0.02% for the most expensive. For enoxaparin, the ARR was 0.14% and 0.04% for the same range of costs, respectively.

To account for the wide range of reported VTE rates in our TriNetX analysis and include studies from the literature, an additional sensitivity analysis was performed on varying initial VTE rates. The lowest available prices of chemoprophylactic agents and VTE-related medical expenditures were held constant for this analysis. Heparin and enoxaparin were found to break-even if they achieved ARRs of 0.05% and 0.14%, and therefore, they were cost-effective at the initial VTE rates reported by our TriNetX analyses as well as all 4 included studies from the literature (**Table 6**).

There were 24 studies identified in the literature reporting the rates of bleeding complications in head and neck oncologic surgery. Two[32,33] were excluded, as they did not specify which patients received chemoprophylaxis. Among 3946 patients studied who were prescribed prophylactic anticoagulation, the mean rate of bleeding complications was 2.2% (n = 86) (**Table 7**).[19,32-34] This can be compared to an average bleeding rate of 1.1% (n = 26) in 2265 patients who were not prescribed chemoprophylaxis. The differences in bleeding rates between patients prescribed anticoagulation and those who were not in the literature ranged from no significant differences to 1.7% (**Table 7**).

There were an additional 7092 patients in TriNetX who underwent neck dissection without free flap reconstruction for HNC who received anticoagulation, 1.4% (n = 101) of which experienced a postoperative hematoma. This was compared to a hematoma rate of just 0.7% (n = 55 out of 8193) in a similar cohort of patients who were not prescribed anticoagulation. Furthermore, among 5208 anticoagulated patients who underwent neck dissection plus free flap reconstruction, the hematoma rate was 3.9% (n = 204), compared to 2.7% (n = 44 out of 1640) in patients who did not receive prophylactic anticoagulation.

A final analysis was conducted by factoring the additional cost of bleeding complications associated with chemoprophylaxis into the overall cost of chemoprophylaxis (**Table 8**). It has been estimated that cervical neck hematoma results in excess costs of $21,518.43 per complication, adjusted for inflation.[32] The least expensive drug prices and cost of treating a VTE, as well as the 3.8% VTE rate based on the literature review, were held constant for this analysis. It was determined that heparin and enoxaparin would be cost-effective if they did not increase the absolute risk of bleeding by more than 2.86% and 2.79%, or add $615.63 or $600.37 per patient prescribed chemoprophylaxis, respectively. Once the increased bleeding rate and associated costs attributed

Table 7. Overview of Existing Studies Analyzing Rates of Bleeding Complications in Head and Neck Oncologic Surgery

Author	Year	Study type	Prophylactic anticoagulation		Number of patients	Number of bleeding events	Bleeding complication rate, %
Gavriel	2013	Retrospective		Yes	568	11	1.9
				No	450	1	0.2
Barton	2018	Systematic review (21 studies)		Yes	3378	75	2.2
				No	1815	25	1.4
Shah-Becker[a]	2018	Retrospective	The exact number of patients who received prophylactic anticoagulation unclear, but stated antithrombotics had no effect on bleeding risk		32,071	1098	3.4
Haapio[a]	2018	Retrospective	The exact number of patients who received prophylactic anticoagulation unclear, but stated antithrombotics had no effect on bleeding risk		591	31	5.0
Overall chemoprophylaxis (22 studies)				Yes	3946	86	2.2
Overall no chemoprophylaxis (22 studies)				No	2265	26	1.1

[a]Patients excluded from overall rows due to unavailable data regarding prophylactic anticoagulation. Excluded studies are painted gray.

to heparin or enoxaparin surpass these rates, these medications require unattainable VTE ARRs of over 3.8% to break-even, and therefore result in added costs. In all included studies as well as our TriNetX analysis, the differences in bleeding complication rates between patients prescribed and not prescribed prophylactic anticoagulation were below these thresholds. Consequently, both medications maintained cost-effectiveness.

Discussion

The American College of Chest Physicians guidelines for prevention of VTE in the surgical setting do not specifically address head and neck surgery.[35] Postoperative chemoprophylaxis in patients with HNC is debated due to a lack of high-quality data, the wide range of reported VTE rates, and the fine balance between thrombotic and bleeding complications.[24,36] Furthermore, performing studies with sufficient power to determine the efficacy of VTE prophylaxis is a challenge, and randomized controlled trials would likely place high-risk patients at an unwarranted risk of suffering a VTE. Although the study of VTE in head and neck oncologic surgery is difficult, it is important to consider the economic burden of VTE, or conversely that of unnecessary prescriptions on the patient and health care system. Despite variable VTE rates across studies, the available price of chemoprophylaxis was low. We found that prophylactic heparin and enoxaparin have the potential to be cost-effective across a range of VTE rates, medication prices, VTE-related medical costs, and costs associated with bleeding complications.

This break-even analysis explores the ARR necessary at varying VTE rates and costs of the drugs to prevent a VTE, of treating a VTE, and of bleeding complications to have a net zero cost to the system. One of the major determinants of whether a drug is cost-effective is the price at which it is obtained. At the lowest prices available to our hospital, both heparin and enoxaparin are very cost-effective, requiring ARRs of just 0.05% and 0.14%, respectively, to break-even. Institutions strive to order the cheapest medications available and stay on contract whenever possible, so these are likely reflective of the costs at which these drugs are most frequently obtained. At their most expensive prices, heparin and enoxaparin would need to achieve increased ARRs of 0.50% and 1.28% in order to break-even, respectively. These required ARRs are still less than the TriNetX initial VTE rates (1.3% for neck dissection and 2.5% for concurrent free flap) and mean VTE rate reported in the literature (3.8%), and are therefore potentially achievable.

The ARR necessary to break-even also varied based on the costs required to manage and treat VTE. Decreasing VTE-related medical costs increased the ARR necessary for cost-effectiveness. However, it was unlikely that this was clinically significant for heparin or enoxaparin, as it resulted in ARR differences of just 0.03% for heparin and 0.10% for enoxaparin over the range of VTE-related

Table 8. Cost-Effectiveness of Chemoprophylactic Agents Accounting for Potential Bleeding Complications

Drug	Cost of drug, $	Cost per bleeding complication, $	Increased rate of bleeding complications[a]	Cost of bleeding complication attributed to chemoprophylaxis per patient, $	Initial VTE rate, %	Final VTE rate, %	ARR, %
Heparin 5000 U TID	8.40	21,518.43	0.7% (TriNetX neck dissection)	150.63	3.8	2.83	0.97
	8.40	21,518.43	1.1% (Average[b])	236.70	3.8	2.31	1.49
	8.40	21,518.43	1.2% (TriNetX free flap)	258.22	3.8	2.18	1.62
	8.40	21,518.43	1.7% (Gavriel)	365.81	3.8	1.52	2.28
	8.40	21,518.43	2.86% (Breakeven rate)	615.63	3.8	0.00	3.8
Enoxaparin 40 mg QD	23.66	21,518.43	0.7% (TriNetX neck dissection)	150.63	3.8	2.74	1.06
	23.66	21,518.43	1.1% (Average[b])	236.70	3.8	2.22	1.58
	23.66	21,518.43	1.2% (TriNetX free flap)	258.22	3.8	2.09	1.71
	23.66	21,518.43	1.7% (Gavriel)	365.81	3.8	1.43	2.37
	23.66	21,518.43	2.79% (Breakeven rate)	600.37	3.8	0.00	3.8

Assumes conservative cost for treating VTE ($16,437) obtained from the literature.
Assumes low available costs of 5000 U heparin ($8.40) and 40 mg enoxaparin ($23.66) for 1 week.
The 3.8% VTE rate is the mean based on the literature review.
Abbreviations: ARR, absolute risk reduction; QD, once daily; TID, three times daily; U, units; VTE, venous thromboembolism.
[a]The increased rate of bleeding complications column denotes the difference in the rate of bleeding complications in patients prescribed chemoprophylaxis compared to those who were not.
[b]Mean increased bleeding rate of all included studies from the literature.

medical costs. Therefore, both heparin and enoxaparin have the potential to result in cost savings independent of VTE-related medical costs.

In our study, heparin and enoxaparin had the opportunity to break-even on cost across a wide range of initial VTE rates. In fact, chemoprophylaxis would have likely been cost-effective in our TriNetX analysis as well as all included studies.[13,16,18,20] A systematic review by Cramer and colleagues recommended using the Caprini Score for VTE to stratify patients based on risk.[18,37] In our study, patients who underwent more extensive surgery (free flaps) had a greater risk of VTE compared to those who underwent neck dissection, and therefore VTE prophylaxis has an additional opportunity to achieve cost-effectiveness in these higher-risk patients. Interestingly, we found that chemoprophylaxis may be cost-effective even in those patients classified as lower risk.

The advantages of using thromboprophylaxis to prevent VTE need to be carefully considered alongside the potential risk of bleeding complications. Research examining the bleeding risk associated with chemoprophylaxis in head and neck oncologic surgery has yielded mixed results. In 1 study involving 1018 patients, those who were prescribed chemoprophylaxis had a significantly higher risk of hematoma and bleeding, nearly 10 times greater than those who were not on such medication (1.90% vs 0.22%).[19] However, other studies by Shah-Becker and colleagues found no significant differences in bleeding complications between patients who received chemoprophylaxis and those who did not.[32,33] Additionally, a systematic review by Barton et al, which included 21 studies on postoperative anticoagulation after free flap reconstruction in HNC, showed that the rates of hematomas were similar regardless of the anticoagulant of choice or protocol followed. This similarity included patients who did not receive any anticoagulation.[34]

In our economic analysis, we factored in the potential costs associated with bleeding complications. We determined that, in order to result in added costs to the patient and health care system, heparin and enoxaparin would need to increase bleeding rates by more than 2.86% and 2.79%, respectively. However, across all the included studies and TriNetX analysis, patients prescribed anticoagulation either did not experience an increased risk of bleeding or had an increased risk that was below these established thresholds. As a result, the cost-effectiveness of these medications was maintained across a range of bleeding rates and associated costs.

This break-even analysis is useful for the determination of cost-effectiveness of VTE prophylaxis because it provides data that would be unattainable in a clinical trial. For example, imagine the hypothetical ARR of heparin is 0.05%. In the setting of a clinical trial, assuming $P < .05$ and power of 80%, a sample size of 2,310,512 would be required to detect this difference. Likewise, if the hypothetical ARR of enoxaparin is 0.14%, a sample size of 287,764 would be necessary to determine the same result.

The large sample size and inclusion of multiple studies reporting VTE rates in this analysis increased the generalizability of findings. However, it is crucial to clarify that from this study and literature review, definitive statements for or against the use of chemoprophylaxis in head and neck oncologic surgery are unable to be made. While this study suggests achievable ARRs for chemoprophylactic agents to break-even on costs or result in cost savings, prospective studies are necessary for actual ARR and efficacy determination. We analyzed the economic implications of VTE and its prevention, determining the necessary ARR for chemoprophylaxis to break-even on costs. Our study did not aim to assess the efficacy of VTE prophylaxis, which would be challenging with a retrospective design. VTE rates were actually higher in patients prescribed anticoagulation in our TriNetX analysis. There was likely a component of selection bias in those who did not receive anticoagulation, as they may have had inherent characteristics that made them less likely to suffer VTE. Currently, the decision to prescribe chemoprophylaxis is multifactorial and should be tailored to patient-specific factors on a case-by-case basis. Additional limitations are that patients in included studies were often grouped despite potential differences in patient and procedure-specific factors that may have impacted the overall VTE rate. We addressed this by creating a free flap cohort and varying the initial VTE rate in a sensitivity analysis. Underdiagnosis and underreporting may also lead to an underestimated true VTE rate.[13,16] If the true VTE rate is higher than we have reported, it would further support chemoprophylaxis cost-effectiveness. Furthermore, VTE prophylaxis may not completely eliminate the risk of VTE, and conversely, patients without anticoagulation may still face bleeding complications,[24,32,33] potentially affecting our cost estimations. Our economic model is also not without limitations. Drug prices are likely to vary from 1 institution to another and are also dependent on the dose and length of prescription. The same applies for costs of treating VTE and bleeding complications, therefore we performed sensitivity analyses accounting for these possible differences and utilized medication costs from a wholesaler available to many institutions. Finally, this assessment of the cost-effectiveness of anticoagulant and associated bleeding risk versus the cost of VTE poses uncertain implications for patient well-being. Shared-decision making frameworks or quality-adjusted life years could enhance the determination of patient-centered or high-quality care.

Conclusion

Reported rates of VTE in HNC surgical patients were variable. Prophylactic heparin and enoxaparin were available at inexpensive prices. The results of our break-even analysis found that even if the risk of VTE is relatively small in this population, heparin and enoxaparin can be

cost-effective across a range of drug prices, costs of treating VTE, and costs of bleeding complications, with the potential for cost savings.

Author Contributions

F. Jeffrey Lorenz, concept design, data collection, reviewing data analysis, writing the manuscript, presentation; **Brandon J. Martinazzi**, concept design, reviewing data analyses, critical editing of the manuscript, and final approval; **Neerav Goyal**, concept design, reviewing data analyses, critical editing of the manuscript, and final approval.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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