Is VTE Prophylaxis Necessary on Discharge for Patients Undergoing Adrenalectomy for Cushing Syndrome?

Bruna Babic,[1] Amory De Roulet,[1] Anita Volpe,[1] and Naris Nilubol[2]

[1]*Department of Surgery, New York Presbyterian-Queens, Flushing, New York 11355; and* [2]*Endocrine Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892*

ORCiD numbers: 0000-0001-8191-7520 (B. Babic); 0000-0002-7348-7804 (N. Nilubol).

Background: Patients with Cushing syndrome (CS) have an increased risk for venous thromboembolism (VTE). However, it is unclear whether patients undergoing adrenalectomy for CS are at increased risk for postoperative VTE. The aim of this study was to determine the rate of postoperative VTE in patients undergoing adrenalectomy for CS.

Methods: A retrospective analysis of patients in the American College of Surgeons National Surgical Quality Improvement Program database who underwent adrenalectomy from 2005 to 2016 was performed. We compared the clinical characteristics and 30-day postoperative VTE occurrence in patients with and without CS.

Results: A total of 4217 patients were analyzed; 2607 (61.8%) were female and 310 (7.4%) had CS. The overall prevalence of postoperative VTE was 1.0% (n = 45). The rates of VTE were higher in patients with CS (2.6% vs 0.9%; P = 0.007). In the two groups, CS was associated with younger age, increased body mass index, and diabetes mellitus ($P < 0.001$). CS was also associated with longer length of operation and longer hospital length of stay ($P < 0.001$). In the subgroup of patients who had diagnosed VTE, CS was associated with longer length of operation ($P < 0.001$). Rates of laparoscopic vs open surgery were equivalent between patients with and without CS, and VTE events did not differ. The median time to VTE event was 14.5 days (range, 1 to 23 days) in the CS group and 4 days (range, 2 to 25 days) in the group without CS.

Conclusions: The prevalence of postoperative VTE was increased in patients undergoing adrenalectomy for CS. In patients with CS undergoing adrenalectomy, VTE prophylaxis for 28 days should be considered upon discharge.

Endogenous Cushing syndrome (CS) results in chronic glucocorticoid excess. The etiology includes ACTH-dependent and -independent causes. The former is most commonly from a pituitary adenoma [Cushing disease (CD)], whereby excess ACTH from the anterior pituitary results in hypercortisolism, in addition to ectopic sources of excess ACTH production from a

Abbreviations: ACS-NSQIP, American College of Surgeons National Surgical Quality Improvement Program; BMI, body mass index; CD, Cushing disease; CS, Cushing syndrome; DVT, deep-vein thrombosis; ICD-9, *International Classification of Diseases, Ninth Revision*; PE, pulmonary embolism; PTT, partial thromboplastin time; VTE, venous thromboembolism.

nonpituitary tumor. ACTH-independent CS results from excess glucocorticoid production directly from the adrenal glands, and the pathology is associated with unilateral or bilateral disease, as well as benign and malignant disease. Excess cortisol production is associated with increased metabolic complications (obesity, hypertension, diabetes), in addition to increased incidence of cardiovascular and venous thromboembolism (VTE) complications [1, 2].

The pathogenesis of VTE events includes hypercoagulability from increased levels of multiple coagulation factors and von Willebrand factor, as well as decreased fibrinolysis activity via increased plasminogen activator inhibitor-1 (inhibits urokinase plasminogen activator, which is required for cleavage of plasminogen) [2–6]. It has been reported that patients with CD tend to be more hypercoagulable than those with ACTH-independent CS pathology secondary to their coagulation profiles [7]. However, the latter also have increased incidence of VTE events [8], as do those undergoing surgery, although the rates have varied from 0% to 20% [4, 8–11]. The higher rate of VTE has predominantly been shown in individuals with CD undergoing transsphenoidal surgery, whereas individuals with ACTH-independent CS undergoing adrenalectomy have lower rates and no evidence of VTE [8, 10]. A recent analysis of American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) data of all patients undergoing adrenalectomy found a low incidence of VTE, at ≤1.4% overall [12]. This is similar to the general postoperative risk for VTE.

Most of the aforementioned studies have a small population and are predominantly composed of individuals with CD undergoing transsphenoidal surgery. In light of the inherent hypercoagulability of those with CS, the question remains as to whether the subgroup of patients with CS undergoing adrenalectomy have an increased risk for VTE and whether they should receive thromboprophylaxis upon discharge. The aim of this retrospective analysis was to evaluate the incidence and characteristics of VTE events in patients from the ACS-NSQIP database who underwent adrenalectomy and for whom the indication was CS.

1. Methods

A. Study Design

A retrospective analysis was performed by using Participant User File from the ACS-NSQIP database, which contains risk-adjusted, surgical outcomes data from initiation of the program in 2005 to December 31, 2016. ACS-NSQIP database comprises preoperative risk factors, along with 30-day postoperative mortality and morbidity outcomes for individuals who have undergone surgical interventions. The database is effective in improving outcomes [13, 14]. Participation is voluntary, and from 2005 to 2016 the number of participating hospitals increased from 121 to 680. The list of participating hospital can be viewed on the American College of Surgeons website [15]. The distribution varies among academic vs private and referral vs regional. The institutional review board of New York-Presbyterian Queens approved the study (#11010916). Data on patients who underwent adrenalectomy were acquired from the following three Current Procedural Terminology (CPT) codes: 60540 (adrenalectomy, partial or complete, or exploration of adrenal gland with or without biopsy, trans-abdominal, lumbar or dorsal), 60545 [adrenalectomy, partial or complete, or exploration of adrenal gland with or without biopsy, trans-abdominal, lumbar or dorsal (separate procedure); with excision of adjacent retroperitoneal tumor], and 60650 (laparoscopy, surgical, with adrenalectomy, partial or complete, or exploration of adrenal gland with or without biopsy, *trans*-abdominal, lumbar or dorsal). No patients underwent image-guided adrenal biopsy.

Individuals who underwent adrenalectomy were further subcategorized according to *International Classification of Diseases, Ninth Revision* (ICD-9) code for CS (255.0) and neoplasm of pituitary gland (237.0, 227.3) for presumed CD that required adrenalectomy. There is no dedicated code for subclinical CS. Control subjects were ICD-9 codes for non-Cushing adrenal pathology and included the following: 255.1/255.10 (hyperaldosteronism), 255.12 (Conn syndrome), 255.2 (adrenogenital disorders), 255.41(glucocorticoid deficiency),

255.6 [medulloadrenal hyperfunction (pheochromocytoma)], 237.3 (neoplasm of uncertain behavior of paraganglia), 211.8 (benign neoplasm of retroperitoneum), and 227.0 (benign neoplasm of other endocrine glands). ICD-9 codes associated with malignant disease, including metastatic disease, were excluded (ICD-9 158, 194.0, and 198.7), as were ICD-9 codes for adrenal pathology that were not specified (ICD-9 255.3, 255.8, and 255.9), blank information, and ICD-9 codes that were not for the previously mentioned control group.

Patient demographic and perioperative characteristics analyzed included age, body mass index (BMI), tobacco use, the American Society of Anesthesiologists physical status classification, wound class, and functional status. Comorbidities included diabetes mellitus and chronic obstructive pulmonary disease. Preoperative biochemical markers abstracted included sodium, blood urea nitrogen, creatinine, albumin, bilirubin, serum glutamic-oxaloacetic transaminase, alkaline phosphatase, white blood cell count, hematocrit, platelets, partial thromboplastin time, and international normalized ratio. The primary occurrence outcome of the study was a diagnosis of VTE, defined as pulmonary embolism (PE) or deep-vein thrombosis (DVT). Secondary outcomes included time to VTE, hospital length of stay, and length of operation. Secondary occurrences of superficial or deep organ infection, wound disruption, pneumonia, renal insufficiency or failure, urinary tract infection, congestive heart failure or myocardial infarction, and cerebrovascular event were analyzed among the groups, as was the prevalence of VTE events in participants undergoing laparoscopic vs open adrenalectomy.

B. Statistical Analyses

A descriptive statistical analysis was performed for the study population. Values were reported as mean (SD) for continuous variables with normal distributions, median (interquartile range) for continuous variables with non-normal distributions, and frequencies (percentage) for categorical variables. Bivariate analysis was performed by using the χ^2 test for differences in proportions and unpaired *t* test or Wilcoxon test to compare differences between means and medians respectively. A two-tailed *P* value < 0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed by using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

2. Results

A total of 8,082 patients underwent adrenalectomy from 2005 to 2016, according to Current Procedural Terminology codes. After exclusion of ICD-9 codes that were not designated in the Methods section, 4217 patients were identified. Female patients made up 61.8% of the group (n = 2607) and 7.4% (n = 310) of patients had CS. There were 3907 patients in the control group. The overall incidence of postoperative VTE was 1.0% (n = 45). Patients with CS had a significantly higher rate of VTE events compared with those without CS [2.6% (n = 8/310) vs 0.9% (n = 37/3907); *P* = 0.007]. Of six patients with CS and VTE, four had PE; two of the four had associated DVT and two had DVT only. Of 37 patients in the control group who had VTE, 23 had PE; 8 of those had associated DVT and 6 had DVT only (Fig. 1).

There were statistical differences in demographic and clinical characteristics between the CS and non-CS groups (Table 1). The non-CS group was older (52.7 vs 47.5 years; *P* < 0.001), had lower rates of diabetes mellitus (*P* < 0.001), and had a lower BMI (30.8 vs 33.4; *P* < 0.001) than the CS group. In addition, the non-CS group had shorter surgery duration (142 vs 191.2 minutes; *P* < 0.001) and shorter length of hospital stay (2 vs 2.4 days; *P* < 0.001). American Society of Anesthesiologists physical status classification and operative wound classification did not significantly differ between the CS and non-CS groups, although the rate of partially dependent functional status was higher in patients with CS than those without CS (*P* < 0.03; data not shown). Demographic and clinical characteristics of patients with a VTE event are shown in Table 2. There were no statistically significant differences between the two groups, although we noted a trend toward longer surgery time in patients with CS compared with those in the non-CS group with VTE.
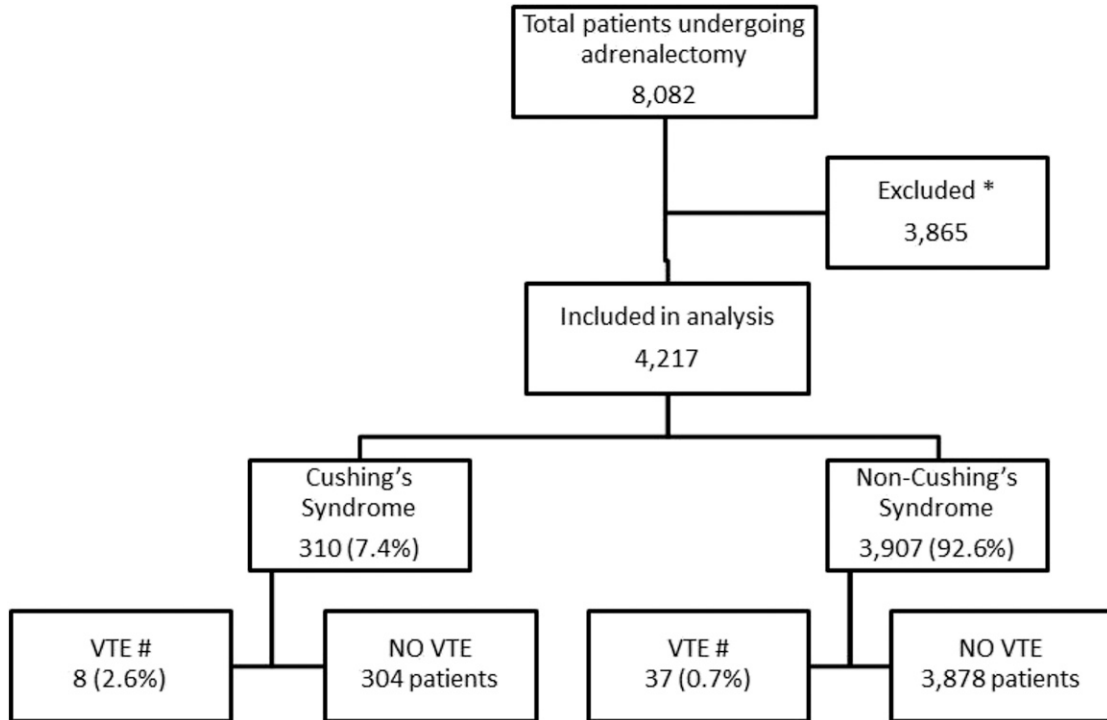
Figure 1. Study design. Total patients undergoing adrenalectomy. After exclusion of patients (*) not designated as control, 4217 patients were included in the final analysis. #VTE includes both DVT and PE that may have occurred in same individual.

Preoperative biochemical parameters were compared between the CS and non-CS groups (Table 3) as well as between the CS vs non-CS group with VTE (Table 4). Table 3 highlights a few statistical differences between the CS and non-CS groups, including higher aspartate aminotransferase and white blood cell count in patients with CS and lower partial thromboplastin time (PTT) in that group (26.2 vs 28.6 seconds; $P < 0.001$). The PTT in patients with VTE did not significantly differ between the CS and non-CS groups, likely because of a type II error. The CS group had a higher white blood cell count in both the overall comparison and among patients with VTE.

There were no statistical differences in postoperative events, aside from PE and DVT (data not shown). These included superficial or deep organ infection, wound disruption, pneumonia, renal insufficiency or failure, urinary tract infection, congestive heart failure or myocardial infarction, and cerebrovascular events. Additionally, the incidence of VTE did not significantly differ between patients with and without CS according to operative approach (laparoscopic vs open adrenalectomy) ($P = 0.8$).

Despite the lack of statistical difference in the time interval from surgery to PE ($P = 0.061$) or DVT ($P = 0.052$), among patients with CS the interval between the day of surgery and VTE diagnosis was longer than in the non-CS group (Fig. 2). Because the average length of stay in patients with CS undergoing adrenalectomy was 3 days, VTE was likely to be diagnosed after discharge.

3. Discussion

Individuals with CS are more likely to have VTE events than those without CS [16]. This retrospective review of data from ACS-NSQIP showed a significant increase in the incidence of VTE events in patients with CS undergoing adrenalectomy compared with that in patients without CS. Because the incidence of VTE events in the CS group was almost threefold higher than that in the non-CS group and VTE events occurred up to 23 days after surgery in

Table 1. Demographic Characteristics of All Patients Undergoing Adrenalectomy According to CS Status

Variable (Total: n = 4217)	CS (n = 310)	Non-CS (n = 3907)	*P* Value
Mean age, (SD), y	47.5 (14.1)	52.7 (13.2)	<0.001
Mean BMI (SD), kg/m^2	33.4 (8.7)	30.8 (7.6)	<0.001
Diabetes mellitus, n (%)	74 (23.9)	485 (12.4)	<0.001
Tobacco use, n (%)	72 (23.2)	953 (24.4)	0.65
COPD, n (%)	13 (4.2)	171 (4.4)	0.88
ASA class, n (%)			0.33
1	2 (0.7)	45 (1.2)	
2	94 (30.3)	1355 (34.8)	
3	191 (61.6)	2236 (57.3)	
4	23 (7.4)	262 (6.7)	
Wound class, n (%)			0.12
1	263 (85.4)	3373 (86.4)	
2	38 (12.3)	492 (12.6)	
3	7 (2.3)	39 (1.0)	
Outcomes			
Mean length of operation (SD), min	191.2 (103.7)	142.0 (68.4)	<0.001
Median hospital length of stay (IQR), d	2.4 (1.0–4.0)	2.0 (1.0–3.0)	<0.001
PE, n (%)	4 (1.3)	23 (0.6)	0.12
Median time from surgery to PE (IQR), d	4.5 (1.0–14.5)	4.0 (2.0–6.0)	0.61
DVT, n (%)	4 (1.3)	14 (0.4)	0.01
Median time from surgery to DVT (IQR), d	15.5 (4.5–23.5)	5.5 (5.0–12.0)	0.52
Operative approach, n (%)			0.73
Laparoscopic adrenalectomy	270 (87.1)	3376 (86.4)	
Open adrenalectomy	40 (12.9)	531 (13.6)	

Abbreviations: ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

patients with CS undergoing adrenalectomy, our data support postdischarge thromboprophylaxis for 28 days in these patients.

Those with CS are inherently more hypercoagulable [4, 17, 18] than those who do not have CS or those with chronic excess glucocorticoid exposure. However, the question remains: Should individuals undergoing adrenalectomy for CS be discharged with VTE thromboprophylaxis? Other high-risk populations are currently recommended to have thromboprophylaxis upon discharge. These include individuals undergoing operative intervention for malignancy [19] and those undergoing high-risk orthopedic surgery, for whom widespread postoperative discharge thromboprophylaxis has been prescribed for the past two decades [20, 21]. Although a few small studies have previously addressed this issue in patients with CS, there has not been a large database with which to evaluate this given the overall small volume of adrenalectomy compared with other common operations [9, 10]. Boscaro *et al.* [10] showed a decrease in the incidence of VTE after operative intervention (from 20% to 6%) with postoperative thromboprophylaxis. Using the ACS-NSQIP database allowed us to assess more patients compared with other databases. Data from ACS-NSQIP have identified complications more reliably than have data from other databases [12, 22], and ACS-NSQIP reliably captures the incidence of VTE. Although Sood *et al.* [12] showed an overall low VTE incidence in patients undergoing adrenalectomy from the ACS-NSQIP database (at 1.1% and 1.4% when the operation was performed by general surgeons and urologists, respectively), they did not stratify individuals according to indication. Consistent with our study, they found that ~30% of the VTE events occurred after discharge.

Others have proposed various means to address which patients may need thromboprophylaxis. Zilio *et al.* [16] found several risk factors associated with increased VTE in those with CS and assigned a scoring system. Age >69 years and reduced mobility had highest the highest ORs, at 25.6 and 27.7 respectively, because such each would have a score of 2. Severe infection, midnight plasma cortisol level > 3.15 times the upper limit of normal, shortened

Table 2. Demographic Characteristics of Patients Undergoing Adrenalectomy with a VTE According to CS Status

Variable	CS (n = 6)	Non-CS (n = 29)	P Value
Mean age, (SD), y	56.3 (14.1)	53.9 (14.6)	0.72
Mean BMI (SD), kg/m^2	34.8 (9.8)	34.5 (7.9)	0.93
Diabetes mellitus, n (%)	0 (0.0)	5 (17.2)	0.37
Tobacco use, n (%)	4 (66.6)	5 (17.2)	0.03
COPD, n (%)	0 (0.0)	3 (10.3)	0.56
ASA class, n (%)			0.33
1	0 (0.0)	1 (3.5)	
2	2 (33.3)	10 (34.5)	
3	4 (66.7)	17 (58.6)	
4	0 (0.0)	1 (3.5)	
Wound class, n (%)			0.89
1	5 (83.3)	24 (82.8)	
2	1 (16.7)	4 (13.8)	
3	0 (0.0)	1 (3.5)	
Outcomes			
Mean length of operation (SD), min	258.3 (150.5)	141.8 (70.5)	0.04
Median hospital length of stay (IQR), d	4.0 (2.0–6.0)	5.0 (1.0–20.0)	0.94
PE, n (%)	4 (66.6)	23 (79.3)	0.60
Median time from surgery to PE (IQR), d	4.5 (1.0–14.5)	2.0 (2.0–4.0)	0.61
DVT, n (%)	4 (66.6)	14 (48.3)	0.66
Median time from surgery to DVT (IQR), d	4.5 (1.0–15.5)	5.0 (2.0–12.0)	0.52
Operative approach, n (%)			0.80
Laparoscopic adrenalectomy	5 (1.8)	24 (0.7)	
Open adrenalectomy	1 (2.6)	5 (0.9)	

Abbreviations: ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

PTT, and history of cardiovascular events each receive 1 point [16]. In their patient population, a score of ≥3 carried a high risk for VTE. Specifically, those with a score of 3 had a 46% risk for VTE and individuals with a score ≥4 had an even higher risk (85%). Although that study did not specifically address the postoperative population, it does offer insight to which individuals may be at high risk and can be applied to the postoperative patient.

The ACS-NSQIP does not document data plasma cortisol. In our study, the PTT was shortened in patients with CS vs those without; however, PTT did not differ among those who had a VTE event (Table 4), nor did postoperative infections (data not shown). PTT is known to be low in those with CS

Table 3. Preoperative Biochemical Comparison Between Patients With CS and Those Without CS

Variable (Total: n = 3790)	CS (n = 310)	Non-CS (n = 3907)	P Value
Mean sodium (SD), mmol/L	139.7 (9.2)	137.9 (16.3)	0.07
Median BUN (IQR), mg/dL	15 (11–19)	14 (11–18)	0.18
Median creatinine (IQR), mg/dL	0.82 (0.70–1.00)	0.89 (0.70–1.05)	0.14
Median albumin (IQR), g/dL	4.0 (3.5–4.4)	4.0 (3.7–4.4)	0.64
Median bilirubin (IQR), mg/dL	0.40 (0.3–0.6)	0.5 (0.3–0.7)	0.03
Median AST (IQR), U/L	22.0 (18.0–29.0)	20.0 (16.0–27.0)	<0.001
Median alkaline phosphatase (IQR), U/L	79.0 (60.0–95.0)	72.0 (56.0–91.0)	0.006
Mean WBC count (SD), K/µL	9.4 (3.4)	7.5 (3.2)	<0.001
Mean hematocrit (SD), %	40.2 (6.3)	39.4 (6.5)	0.04
Mean platelet count (SD), K/µL	271.9 (89.9)	260.8 (88.9)	0.04
Median PTT (IQR), s	25.9 (22.6–29.6)	28.0 (25.0–30.6)	<0.001
Median INR (IQR)	0.95 (0.90–1.00)	1.0 (0.90–1.04)	0.02

Abbreviations: AST, aspartate aminotransferase; BUN, blood urea nitrogen; INR, international normalized ratio; IQR, interquartile range; WBC, white blood cell.

Table 4. Preoperative Biochemical Comparison of Patients With a VTE Event in the CS Group vs the Non-CS Group

Variable	CS (n = 6)	Non-CS (n = 29)	P Value
Mean sodium (SD), mmol/L	142.7 (3.2)	139.5 (2.6)	0.01
Median BUN (IQR), mg/dL	24.0 (16.0–25.0)	17.0 (13.0–20.0)	0.19
Median creatinine (IQR), mg/dL	0.95 (0.90–1.10)	0.80 (0.74–1.10)	0.47
Median albumin (IQR), g/dL	3.6 (2.9–4.1)	3.8 (3.2–4.3)	0.52
Median bilirubin (IQR), mg/dL	0.65 (0.30–0.90)	0.30 (0.20–0.40)	0.22
Median AST (IQR), U/L	19.0 (18.0–35.0)	20.5 (15.0–26.0)	0.68
Median alkaline phosphatase (IQR), U/L	74.0 (42.0–48.6)	82.0 (61.0–92.0)	0.97
Mean WBC count (SD), K/μL	12.6 (2.6)	7.9 (2.4)	<0.001
Mean hematocrit (SD), %	42.9 (7.9)	38.6 (4.5)	0.07
Mean platelet count (SD), K/μL	303.3 (116.2)	301.2 (95.3)	0.96
Median PTT (IQR), s	25.6 (24.5–96.0)	28.2 (24.1–30.0)	0.95
Median INR (IQR)	0.93 (0.90–1.00)	1.0 (1.0–1.1)	0.20

Abbreviations: AST, aspartate aminotransferase; BUN, blood urea nitrogen; INR, international normalized ratio; IQR, interquartile range; WBC, white blood cell.

[17], and a low PTT has been associated with increased incidence of thromboembolism secondary to increased thrombin production [23]. Although our study showed a statistically significantly shorter PTT in patients with CS than in the non-CS group, this difference was not seen in the two groups according to occurrence of a VTE event. This is likely due to type II statistical error from a small sample size. In our population, there was no difference in age, BMI, or presence of diabetes mellitus in those with or without CS and a VTE. However, functional status differed among those with a VTE event and CS, who were more likely to be partially dependent before surgery. Additional risks for VTE in patients with CS in this cohort included a trend toward significantly longer operation times.
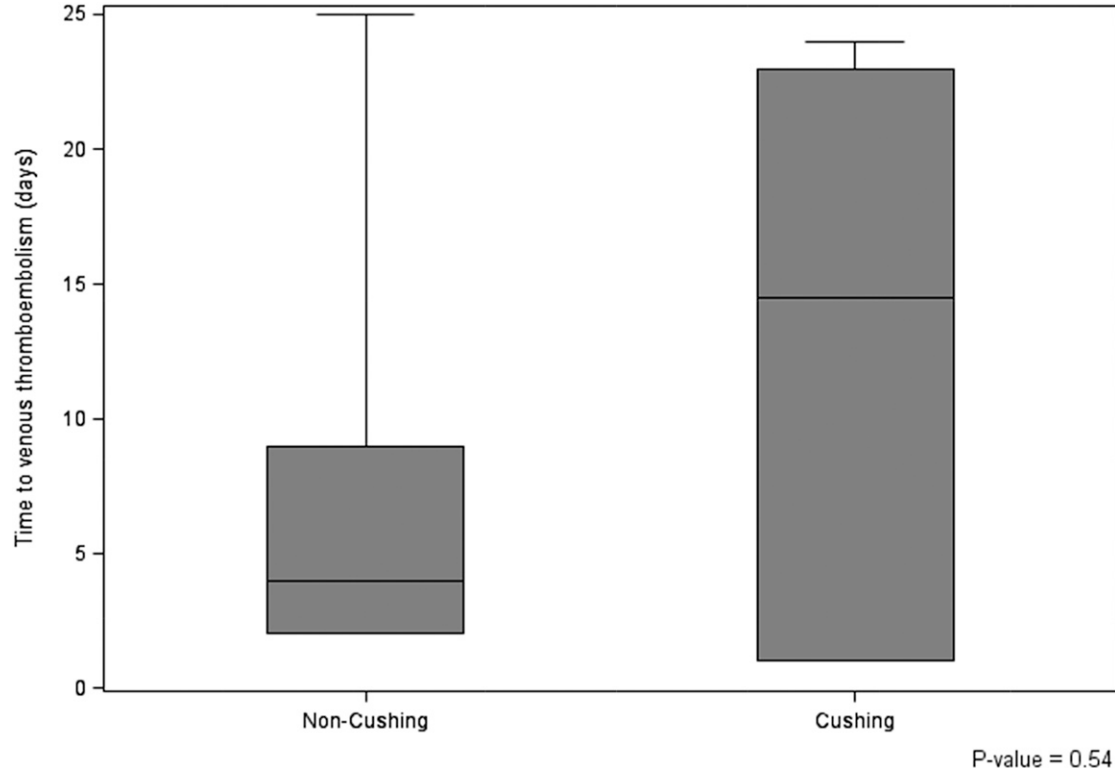

Figure 2. Time to VTE in d. The median time of VTE event was 14.5 d (range, 1 to 23 d) in patients with CS compared with 4 d (range, 2 to 25 d) in patients without CS. Box, IQR; line, median; bars, date range.

Individuals who have undergone surgery for CS show marked improvement in several parameters postoperatively. A meta-analysis of 37 studies shows that most have improvement in not only metabolic complications (including diabetes mellitus, hypertension, and obesity) and emotional stability [11, 24] but also in the hypercoagulability profile. This is evident by decreased coagulable factors and von Willebrand factor, as well as improvement in fibrinolysis as shown by decreased plasminogen activator inhibitor-1 [9, 18]. Despite the latter, individuals who undergo surgery are still at risk for postoperative VTE, especially in those who have persistent abnormal coagulation profile after surgery [9, 10]. Boscaro *et al.* [10] extend postoperative prophylaxis until the coagulative profile normalizes. Because of the hypercoagulability associated with CS, it is plausible that the reversal of hypercortisolism before surgery can reduce the perioperative risk for VTE. However, a multicenter study from Europe with >1100 patients showed that preoperative medical treatment of hypercortisolism did not result in a decreased prevalence of VTE [25].

Our study had several limitations. The sample size is small for the number of individuals undergoing adrenalectomy for CS despite a large number of patients undergoing adrenalectomy. In addition, 43% of the data had to be excluded because of ICD-9 coding for malignancy or unspecified or indeterminate reasons for why an individual underwent adrenalectomy. It is likely that in this group of excluded patients there were both patients who had surgery for CS and/or had a VTE event. Despite the exclusion of the data or lack of identification of certain patients who should have been classified as having CS, this would likely have increased the incidence and even further supported the need for thromboprophylaxis. The study also excluded individuals with ICD-9 codes for metastatic or malignant disease so as not to confound interpretation of the results, as many patients with malignant tumors are inherently hypercoagulable. In addition, using this database, we are unable to obtain regimens used for perioperative and inpatient VTE prophylaxis. Additionally, we are unable to assess whether any patients were discharged on postoperative prophylaxis. But given the lack of recommendations, the number would likely be very small. The incidence of patients with VTE was possibly underreported once patients were discharged.

Despite the limitations, our data support VTE prophylaxis on discharge for patients undergoing adrenalectomy for CS. The natural pathophysiology portends to the overall higher incidence of VTE in these individuals and, as can be seen in the retrospective review, smokers, patients with longer operations, and those who are partially dependent may be at higher risk and would likely benefit from thromboprophylaxis on discharge. The specific regimen for VTE prophylaxis would need to be determined, with recommendation toward dosing based on BMI [26].

4. Conclusion

We recommend that patients with CS undergoing adrenalectomy continue VTE prophylaxis for 28 days because of a higher rate of VTE and a delayed onset of VTE presentation.

Acknowledgments

References and Notes

1. Etxabe J, Vazquez JA. Morbidity and mortality in Cushing's disease: an epidemiological approach. *Clin Endocrinol (Oxf).* 1994;**40**(4):479–484.
2. Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK,

Sonino N, Vance ML, Giustina A, Boscaro M. Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab*. 2003;**88**(12):5593–5602.

3. Kastelan D, Dusek T, Kraljevic I, Polasek O, Giljevic Z, Solak M, Salek SZ, Jelcic J, Aganovic I, Korsic M. Hypercoagulability in Cushing's syndrome: the role of specific haemostatic and fibrinolytic markers. *Endocrine*. 2009;**36**(1):70–74.

4. Van Zaane B, Nur E, Squizzato A, Dekkers OM, Twickler MT, Fliers E, Gerdes VE, Büller HR, Brandjes DP. Hypercoagulable state in Cushing's syndrome: a systematic review. *J Clin Endocrinol Metab*. 2009; **94**(8):2743–2750.

5. Coelho MC, Santos CV, Vieira Neto L, Gadelha MR. Adverse effects of glucocorticoids: coagulopathy. *Eur J Endocrinol*. 2015;**173**(4):M11–21.

6. Koutroumpi S, Daidone V, Sartori MT, Cattini MG, Albiger NM, Occhi G, Ferasin S, Frigo A, Mantero F, Casonato A, Scaroni C. Venous thromboembolism in patients with Cushing's syndrome: need of a careful investigation of the prothrombotic risk profile. *Pituitary*. 2013;**16**(2):175–181.

7. Tirosh A, Lodish M, Lyssikatos C, Belyavskaya E, Feelders RA, Stratakis CA. Coagulation profile in patients with different etiologies for Cushing syndrome: a prospective observational study. Hormone *Metabol Res*. 2017;**49**(5):365–371.

8. Stuijver DJ, van Zaane B, Feelders RA, Debeij J, Cannegieter SC, Hermus AR, van den Berg G, Pereira AM, de Herder WW, Wagenmakers MA, Kerstens MN, Zelissen PM, Fliers E, Schaper N, Drent ML, Dekkers OM, Gerdes VE. Incidence of venous thromboembolism in patients with Cushing's syndrome: a multicenter cohort study. *J Clin Endocrinol Metab*. 2011;**96**(11):3525–3532.

9. Manetti L, Bogazzi F, Giovannetti C, Raffaelli V, Genovesi M, Pellegrini G, Ruocco L, Iannelli A, Martino E. Changes in coagulation indexes and occurrence of venous thromboembolism in patients with Cushing's syndrome: results from a prospective study before and after surgery. *Eur J Endocrinol*. 2010;**163**(5):783–791.

10. Boscaro M, Sonino N, Scarda A, Barzon L, Fallo F, Sartori MT, Patrassi GM, Girolami A. Anticoagulant prophylaxis markedly reduces thromboembolic complications in Cushing's syndrome. *J Clin Endocrinol Metab*. 2002;**87**(8):3662–3666.

11. Ritzel K, Beuschlein F, Mickisch A, Osswald A, Schneider HJ, Schopohl J, Reincke M. Clinical review: Outcome of bilateral adrenalectomy in Cushing's syndrome: a systematic review. *J Clin Endocrinol Metab*. 2013;**98**(10):3939–3948.

12. Sood A, Majumder K, Kachroo N, Sammon JD, Abdollah F, Schmid M, Hsu L, Jeong W, Meyer CP, Hanske J, Kalu R, Menon M, Trinh QD. Adverse event rates, timing of complications, and the impact of specialty on outcomes following adrenal surgery: an analysis of 30-day outcome data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). *Urology*. 2016;**90**: 62–68.

13. Hall BL, Hamilton BH, Richards K, Bilimoria KY, Cohen ME, Ko CY. Does surgical quality improve in the American College of Surgeons National Surgical Quality Improvement Program: an evaluation of all participating hospitals. *Ann Surg*. 2009;**250**(3):363–376.

14. Khuri SF, Daley J, Henderson W, Hur K, Demakis J, Aust JB, Chong V, Fabri PJ, Gibbs JO, Grover F, Hammermeister K, Irvin G III, McDonald G, Passaro E Jr, Phillips L, Scamman F, Spencer J, Stremple JF; National VA Surgical Quality Improvement Program. The Department of Veterans Affairs' NSQIP: the first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. *Ann Surg*. 1998;**228**(4):491–507.

15. American College of Surgeons. ACS NSQIP Participant Use Data File. www.facs.org/quality-programs/ acs-nsqip/participant-use. Accessed 9 November 2018.

16. Zilio M, Mazzai L, Sartori MT, Barbot M, Ceccato F, Daidone V, Casonato A, Saggiorato G, Noventa F, Trementino L, Prandoni P, Boscaro M, Arnaldi G, Scaroni C. A venous thromboembolism risk assessment model for patients with Cushing's syndrome. *Endocrine*. 2016;**52**(2):322–332.

17. van der Pas R, Leebeek FW, Hofland LJ, de Herder WW, Feelders RA. Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. *Clin Endocrinol (Oxf)*. 2013;**78**(4):481–488.

18. van Zaane B, Stuijver DJ, Squizzato A, Gerdes VE. Arterial and venous thrombosis in endocrine diseases. *Semin Thromb Hemost*. 2013;**39**(5):489–495.

19. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, Samama CM. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; **141**(2 Suppl):e227S–e277S.

20. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;**133**(6 Suppl):381s–453s.

21. Forster R, Stewart M. Anticoagulants (extended duration) for prevention of venous thromboembolism following total hip or knee replacement or hip fracture repair. *Cochrane Database Syst Rev.* 2016;**3**: CD004179.

22. Cima RR, Lackore KA, Nehring SA, Cassivi SD, Donohue JH, Deschamps C, Vansuch M, Naessens JM. How best to measure surgical quality? Comparison of the Agency for Healthcare Research and Quality Patient Safety Indicators (AHRQ-PSI) and the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) postoperative adverse events at a single institution. *Surgery.* 2011;**150**(5):943–949.

23. Korte W, Clarke S, Lefkowitz JB. Short activated partial thromboplastin times are related to increased thrombin generation and an increased risk for thromboembolism. *Am J Clin Pathol.* 2000;**113**(1): 123–127.

24. Neychev V, Steinberg SM, Yang L, Mehta A, Nilubol N, Keil MF, Nieman L, Stratakis CA, Kebebew E. Long-term outcome of bilateral laparoscopic adrenalectomy measured by disease-specific questionnaire in a unique group of patients with Cushing's syndrome. *Ann Surg Oncol.* 2015;**22**(Suppl 3): S699–S706.

25. Valassi E, Franz H, Brue T, Feelders RA, Netea-Maier R, Tsagarakis S, Webb SM, Yaneva M, Reincke M, Droste M, Komerdus I, Maiter D, Kastelan D, Chanson P, Pfeifer M, Strasburger CJ, Tóth M, Chabre O, Krsek M, Fajardo C, Bolanowski M, Santos A, Trainer PJ, Wass JAH, Tabarin A; ERCUSYN Study Group. Preoperative medical treatment in Cushing's syndrome: frequency of use and its impact on postoperative assessment: data from ERCUSYN. *Eur J Endocrinol.* 2018;**178**(4):399–409.

26. Vandiver JW, Ritz LI, Lalama JT. Chemical prophylaxis to prevent venous thromboembolism in morbid obesity: literature review and dosing recommendations. *J Thromb Thrombolysis.* 2016;**41**(3): 475–481.