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Assessment of thrombotic adverse events and treatment patterns associated with varicose vein treatment

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Received: May 28, 2014; Accepted: September 24, 2014; Published Online: November 03, 2014

DOI: <http://dx.doi.org/10.1016/j.jvsv.2014.09.007>

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Objective

This retrospective study assessed varicose vein treatment patterns and associated thrombotic complications in a real-world setting.

Methods

A retrospective study was conducted with health care claims data from Truven Health, covering more than 40 million insured lives per year and representing all U.S. census regions. The study sample included subjects aged ≥18 years with a new diagnosis of varicose veins who had received at least one invasive treatment (eg, surgery, endovenous thermal ablation [radiofrequency or laser], or sclerotherapy [liquid or foam]). The adverse events of interest included a coded diagnosis of deep venous thrombosis (DVT) or pulmonary embolism within 30 days of a claim for invasive treatment. Patients treated between January 1, 2008, and June 30, 2012, were observed for up to 2 years after diagnosis.

Results

There were 985,632 unique subjects diagnosed with varicose veins; of them, a total of 131,887 subjects met all of the study criteria: 63,033 (47.8%) having multiple therapies; 22,980 (17.4%) having laser ablation; 21,637 (16.4%) having radiofrequency ablation; 12,708 (9.6%) having sclerotherapy; and 11,529 (8.7%) having surgery. The mean age of the sample was 52.8 years, ranging from 51.5 years (surgery cohort) to 54.5 years (radiofrequency ablation cohort); 77% of the sample was female, ranging from 71% (radiofrequency ablation cohort) to 92% (sclerotherapy cohort). The mean time to treatment after diagnosis was 105 days, ranging from 75 days (sclerotherapy cohort) to 116 days (radiofrequency ablation cohort). The diagnosed prevalence (percentage of subjects within each treatment cohort) of DVT was as follows: radiofrequency ablation, 4.4%; multiple therapies—same day, 3.4%; laser ablation, 3.1%; multiple therapies—deferred, 2.6%; surgery, 2.4%; and sclerotherapy, 0.8%. For pulmonary embolism, the diagnosed prevalence was as follows: radiofrequency ablation, surgery, and laser ablation, 0.3% each; and multiple therapies—same day, multiple therapies—deferred, and sclerotherapy, 0.2% each.

Conclusions

Thrombotic complications associated with invasive varicose vein treatments in the real-world setting may be higher than what has been reported in clinical trials, particularly in regard to DVT after endovenous thermal ablation therapy. A better understanding of these patterns of adverse events may have an impact on new strategies to safely and effectively manage patients with varicose veins.

Varicose veins can be a source of considerable morbidity and burden to society and the health care system, leading to chronic pain, disability, reduced productivity, and declining health-related quality of life.1, 2, 3, 4 Although varicose veins can be a cosmetic concern, most individuals with varicose veins seek treatment because of symptoms.1

The Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) together have developed clinical practice guidelines for the management of patients with varicose veins and associated chronic venous diseases.1 Treatment options include the following: compression stockings, standard open venous surgery, endovenous thermal ablation (ETA) with laser or radiofrequency energy, and sclerotherapy.1 The SVS/AVF guidelines recommend the CEAP (clinical, etiology, anatomy, and pathophysiology) classification system as a basis for clinical treatment decisions for patients with chronic venous disease.1 Once a decision has been made to intervene on symptomatic varicose veins, the SVS/AVF guidelines favor ETA as the first therapeutic choice (at the time of the development of the guidelines, foam sclerotherapy was not approved by the Food and Drug Administration). More than 300,000 ETA treatments were performed in the United States in 2012, a 450% increase over the last decade due to this minimally invasive approach.5

Each of these treatment methods, however, has inherent risks as well as limitations. Thromboembolic complications are the most serious complications associated with varicose vein treatment, including deep venous thrombosis (DVT), heat- or foam-induced thrombus extension, and pulmonary embolism (PE), with the potential for a fatal event. These complications are infrequently reported in the literature, and their incidence varies widely.6, 7, 8, 9 If they are reported, particularly in randomized controlled trials (RCTs), the incidence may be either an overestimation or underestimation by the statistical phenomenon of an infrequent event within a small sample size.10 Moreover, RCTs have stringent inclusion and exclusion criteria that limit the application to “real-world” experience for these complications. Given these problems with information on the thromboembolic complications of varicose vein treatments, the objective of this study was to assess varicose vein treatment patterns and corresponding thrombotic complications in the real-world setting with a large cohort of patients.



Methods



Data source

A retrospective database analysis was conducted with the Truven Health MarketScan Commercial Claims and Encounters Database and the Truven Health MarketScan Medicare Supplemental and Coordination of Benefits Database. Historically, more than 500 million claim records are available in the MarketScan databases. The Commercial Claims and Encounters Database represents the health care experience of active employees and dependents, early (non-Medicare) retirees and dependents, and those who opt to continue coverage through the Comprehensive Omnibus Budget Reconciliation Act (COBRA), a plan that allows employees and their families the ability to continue group health benefits for a limited time after leaving employment. The Medicare database represents Medicare-eligible active and retired employees and their Medicare-eligible dependents from employer-sponsored supplemental plans. These databases contain integrated medical and pharmacy claims data that include inpatient and outpatient medical claims, prescription drug claims, and patient enrollment data. Study data were accessed by procedures compliant with the Health Insurance Portability and Accountability Act of 1996; therefore, informed consent or Institutional Review Board approval was not required. Data from January 2007 through June 2012 were used in this study to allow adequate follow-up over time.



Study design and sample

Eligible subjects met all of the following criteria: (1) received at least one International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) primary or secondary diagnosis code of 454 (ie, 454.0, 454.1, 454.2, 454.8, or 454.9) for varicose veins of lower extremities between January 1, 2008, and June 30, 2012 (enrollment period); (2) at least 18 years of age; (3) received an invasive treatment (eg, surgery, ETA [radiofrequency or laser], or sclerotherapy) during the assessment period; and (4) continuously eligible to receive medical and pharmacy services during the 1-year preindex period and up to 2 years during the postindex period. The index date was defined as the first chronologically occurring diagnosis during the enrollment period. The 1-year period before the index date was referred to as the preindex period and was used to measure patient baseline characteristics; the period after the index date (up to 2 years) was referred to as the assessment period and was used to measure treatment patterns and outcomes. Subjects were excluded from the study if any of the following criteria were met: (1) received an invasive treatment during the preindex period; (2) had no evidence of an invasive treatment during the assessment period (eg, compression stockings only); or (3) received a diagnosis of varicose veins for any site other than the lower extremities during the study period.



Treatment characterization and outcome assessment

Subjects were divided into cohorts based on the type of therapy received during the assessment period. Subjects with evidence of invasive varicose vein treatment during the assessment period were placed in one of the following cohorts on the basis of Current Procedural Terminology (CPT) codes: surgery (CPT codes 37700, 37718, 37722, 37735, 37760, 37765, 37766, 37780, 37785, 37799, 37500, 37761); laser ablation (CPT codes 36478, 36479); radiofrequency ablation (CPT codes 36475, 36476); sclerotherapy (CPT codes 36468, 36470, 36471, S2202); or multiple therapies (includes two or more of the invasive therapies during the assessment period). The multiple therapies cohort was further stratified on the basis of whether the subjects received more than one therapy on the same day (multiple therapies—same day) or on different days (multiple therapies—deferred).

Baseline characteristics included age, gender, and geographic location. Comorbidity burden was measured by the Charlson Comorbidity Index during the preindex period. Also, the number of unique diagnosis codes and the number of unique prescription classes in the preindex period were calculated as an additional measure of concomitant diagnoses. Disease severity for varicose veins at the time of the index diagnosis date was assigned by the Thomson Reuters Disease Staging classification system. The disease staging criteria use diagnostic findings (based on physical findings, radiologic and laboratory results, and pathologic and operative reports) to classify diseases into stages based on level of severity (for varicose veins of lower extremities: stage 1, no complications; stage 2, local complications [eg, chronic venous insufficiency, stasis ulcers, cellulitis, or DVT]; stage 3, systemic complications [eg, PE, sepsis, respiratory failure, or shock]; stage 4, death).11 Varicose vein treatment pattern metrics that were evaluated in the study included the following: (1) number of days from index diagnosis date to initial treatment; (2) proportion of subjects with symptomatic varicose veins (ICD-9-CM codes 454.0, 454.1, 454.2, 454.8) vs asymptomatic varicose veins (ICD-9-CM code 454.9); and (3) failure rates with initial treatment (defined as a claim for a treatment of interest after a gap of 60 days from the initial procedure). The rate of clinical adverse events (AEs) for each treatment cohort (both percentage of subjects and number of unique AEs) was measured during the 30 days after a procedure. An AE of interest was identified by an ICD-9-CM diagnosis code. The AEs of interest included DVT (453.4, 453.8, 453.9; all of these codes are specific to DVT) and PE (415.1). In addition, a sensitivity analysis on the rates of AEs was performed by excluding patients who may have been at a higher risk of AEs because of evidence of a DVT during the 1 year before diagnosis. Finally, the frequency of death associated with an AE of interest during the 30 days after a procedure was assessed within each treatment cohort by a proxy measure. This proxy measure for death was defined as any of the following criteria during the last month in which medical and pharmacy claims were available during the study period (ie, no evidence of further claims beyond this time period) and also included an AE of interest: a cardiac event including resuscitation (CPT, fourth edition [CPT-4] 92950), defibrillation (CPT-4 92960, 92961), cerebral death (CPT-4 95824), cardiac arrest/failure (ICD-9-CM 427.5), evidence of injection given to stimulate the heart (J0170, J2000), hospitalization (Uniform Billing [UB-92] revenue codes 100-219), emergency room visit (Place of Service code 23; CPT-4 99281-99288; UB-92 revenue codes 450-459, 981), ambulance service (CPT-4 99289-99290, UB-92 revenue codes 540-549), or use of hospice care (Place of Service code 34).



Statistical analysis

Baseline patient characteristics were described by mean ± standard deviation for continuous variables and by counts and percentages for categorical variables. The percentage of subjects with AEs and the number of unique AEs within each treatment cohort were descriptive in nature.



Results

Among 985,632 subjects who had at least one ICD-9-CM primary or secondary diagnosis code for varicose veins (454.0, 454.1, 454.2, 454.8, or 454.9) during the study period, 853,745 subjects did not meet study eligibility requirements and therefore were excluded from the analysis ([Fig](http://www.jvsvenous.org/cms/attachment/2021560530/2041497180/gr1.jpg)). More than 394,500 subjects were identified with varicose veins who did not have any evidence of an invasive treatment during the assessment period (ie, they could have been treated only with compression stockings as part of conservative management).12 These subjects were ultimately excluded from the analysis as they did not meet eligibility criteria. A total of 131,887 subjects met all of the study criteria: 63,033 (47.8%) had multiple therapies; 22,980 (17.4%) had laser ablation; 21,637 (16.4%) had radiofrequency ablation; 12,708 (9.6%) had sclerotherapy; and 11,529 (8.7%) had surgery. Among the subjects who had multiple therapies, a similar number of subjects received multiple therapies either on the same day (multiple therapies—same day, 51.3%) or on different days (multiple therapies—deferred, 48.7%). The mean deferral duration between the first two therapies was 73 days.



Fig

Patient attrition. *ICD-9-CM*, International Classification of Diseases, Ninth Revision, Clinical Modification. aCriteria are not mutually exclusive.

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Demographic characteristics of study subjects are summarized in [Table I](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext#tbl1). The mean age of the sample was 52.8 years, ranging from 51.5 years (for surgery) to 54.5 years (for radiofrequency ablation). A majority of subjects in the overall sample population were female (77%), ranging from 71% (for radiofrequency ablation) to 92% (for sclerotherapy). The mean Charlson Comorbidity Index for each treatment cohort was less than 1. Treatment cohorts were similar in terms of the number of unique diagnoses (range [mean], 10-12) and the number of unique prescription classes (range [mean], 4-5). The top five comorbid conditions were disorders of lipid metabolism (29.1%), other disorders of soft tissues (27.2%), essential hypertension (27.0%), general symptoms (22.3%), and unspecified disorders of joint (21.3%). The top five prescribed drugs/drug classes were opioid combinations (22.1%), nonsteroidal anti-inflammatory agents (17.5%), azithromycin (15.1%), statins (14.3%), and fluoroquinolones (12.5%).

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| **Table I**Baseline characteristics |
|  | **Sclerotherapy (n = 12,708)** | **Laser ablation (n = 22,980)** | **Radiofrequency ablation (n = 21,637)** | **Surgery (n = 11,529)** | **Multiple therapies (same day) (n = 32,311)** | **Multiple therapies (deferred) (n = 30,722)** |
| Demographic characteristics |
|  Age, years | 52.9 ± 12.7 | 53.4 ± 13.0 | 54.5 ± 13.2 | 51.5 ± 12.3 | 52.1 ± 12.0 | 52.2 ± 12.0 |
|  Female gender | 11,623 (91.5) | 16,588 (72.2) | 15,307 (70.7) | 8574 (74.4) | 24,035 (74.4) | 24,998 (81.4) |
|  Geographic region |
| Northeast | 2788 (21.9) | 4810 (20.9) | 4203 (19.4) | 2717 (23.6) | 5439 (16.8) | 6105 (19.9) |
| North Central | 5116 (40.3) | 6816 (29.7) | 3924 (18.1) | 3442 (29.9) | 9317 (28.8) | 10,875 (35.4) |
| South | 2808 (22.1) | 8238 (35.9) | 9337 (43.2) | 3073 (26.7) | 10,481 (32.4) | 9469 (30.8) |
| West | 1831 (14.4) | 2623 (11.4) | 3746 (17.3) | 2038 (17.7) | 6352 (19.7) | 3624 (11.8) |
| Unknown | 165 (1.3) | 493 (2.2) | 427 (2.0) | 259 (2.3) | 722 (2.2) | 649 (2.1) |
| Comorbidity in the preindex period |
|  Charlson Comorbidity Index | 0.41 ± 0.91 | 0.62 ± 1.15 | 0.69 ± 1.23 | 0.44 ± 0.95 | 0.43 ± 0.93 | 0.43 ± 0.92 |
|  No. of unique diagnoses | 11.2 ± 7.8 | 11.6 ± 8.4 | 11.9 ± 8.8 | 10.2 ± 7.6 | 10.1 ± 7.4 | 10.6 ± 7.6 |
|  No. of unique prescription classes | 4.9 ± 4.9 | 5.0 ± 5.4 | 5.2 ± 5.7 | 4.3 ± 4.9 | 4.4 ± 4.8 | 4.4 ± 4.8 |
|  Thomson Reuters disease stage |
| 0+ | 3487 (27.4) | 7365 (32.1) | 5634 (26.0) | 2087 (18.1) | 7109 (22.0) | 10,005 (32.6) |
| 1 | 6447 (50.7) | 9571 (41.7) | 10,215 (47.2) | 6764 (58.7) | 16,695 (51.7) | 13,088 (42.6) |
| 2 | 2756 (21.7) | 5961 (25.9) | 5695 (26.3) | 2660 (23.1) | 8444 (26.1) | 7593 (24.7) |
| 3 | 18 (0.1) | 83 (0.4) | 93 (0.4) | 18 (0.2) | 63 (0.2) | 36 (0.1) |
|  Thomson Reuters disease stage[a](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext#tbl1fna) | 1.30 ± 0.46 | 1.39 ± 0.50 | 1.37 ± 0.49 | 1.29 ± 0.46 | 1.34 ± 0.48 | 1.37 ± 0.49 |

Continuous data are presented as mean ± standard deviation and categorical data as number (%).

[a](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext%22%20%5Cl%20%22back-tbl1fna)Excluded subjects with stage = 0 or stage = unknown.

Varicose vein treatment pattern metrics are shown in [Table II](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext#tbl2). The length of time to initial treatment ranged from 75 days (for sclerotherapy) to 116 days (for radiofrequency ablation) after the index diagnosis date. A majority of subjects in each treatment cohort had symptomatic varicose veins; all were in the range of 83% to 88%, except for the surgery cohort (76%). Perceived failure rates with initial treatment (excluding the multiple therapies cohort, which could have included treatments received on different days) ranged from 4% (surgery) to 21% (sclerotherapy).

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| **Table II**Treatment patterns |
|  | **Sclerotherapy (n = 12,708)** | **Laser ablation (n = 22,980)** | **Radiofrequency ablation (n = 21,637)** | **Surgery (n = 11,529)** | **Multiple therapies (same day) (n = 32,311)** | **Multiple therapies (deferred) (n = 30,722)** |
| Time to initial procedure, days | 75 ± 114 | 112 ± 129 | 116 ± 129 | 105 ± 126 | 112 ± 123 | 96 ± 109 |
| Symptomatic disease | 10,631 (84) | 19,577 (85) | 18,210 (84) | 8593 (76) | 26,727 (83) | 27,003 (88) |
| Failure rate of initial treatment[a](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext#tbl2fna) | 2603 (21) | 1881 (8) | 1584 (7) | 458 (4) | 5147 (16) | 15,247 (50) |

*SD,* Standard deviation.

Continuous data are presented as mean ± standard deviation and categorical data as number (%).

[a](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext%22%20%5Cl%20%22back-tbl2fna)Defined as a gap of 60 days between consecutive claims for a treatment of interest.

Overall, 10.1% of the sample had at least one AE of interest within 30 days of treatment. The rates of AEs within each treatment cohort at the subject level and procedure level are shown in [Table III](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext#tbl3). A sensitivity analysis on the rates of AEs was performed by excluding patients who may have been at a higher risk of AEs because of evidence of a DVT during the 1-year period before diagnosis to form a “normal-risk” group. Removal of these patients resulted in a 12% reduction in the overall rate of AEs, from 10.1% to 8.9%. This reduction did not affect the relative order of AEs across the treatments ([Table III](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext#tbl3)).

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| **Table III**Adverse events (*AEs*) |
|  | **Sclerotherapy** | **Laser ablation** | **Radiofrequency ablation** | **Surgery** | **Multiple therapies (same day)** | **Multiple therapies (deferred)** |
| No. of subjects | 12,708 | 22,980 | 21,637 | 11,529 | 32,311 | 30,722 |
| No. of procedures | 39,689 | 35,750 | 33,992 | 13,770 | 62,750 | 159,316 |
| Subject-level AEs[a](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext#tbl3fna) (calculated as number of unique subjects with AEs/total number of subjects), n/N (%) |
|  DVT | 104/12,708 (0.82) | 701/22,980 (3.05) | 954/21,637 (4.41) | 277/11,529 (2.40) | 1110/32,311 (3.44) | 795/30,722 (2.59) |
|  PE | 19/12,708 (0.15) | 58/22,980 (0.25) | 68/21,637 (0.31) | 33/11,529 (0.29) | 73/32,311 (0.23) | 75/30,722 (0.24) |
| Procedure-level AEs (calculated as total number of AEs/total number of procedures), n/N (%) |
|  DVT | 228/39,689 (0.57) | 1191/35,750 (3.33) | 1653/33,992 (4.86) | 470/13,770 (3.41) | 1913/62,750 (3.05) | 1645/159,316 (1.03) |
|  PE | 33/39,689 (0.08) | 196/35,750 (0.55) | 196/33,992 (0.58) | 152/13,770 (1.10) | 247/62,750 (0.39) | 236/159,316 (0.15) |

*DVT,* Deep venous thrombosis; *PE,* pulmonary embolism.

These safety metrics were calculated during the 30 days after the invasive procedure.

[a](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext%22%20%5Cl%20%22back-tbl3fna)AEs were not adjusted for variable follow-up times.

The numbers of deaths associated with AEs of interest within each treatment cohort are shown in [Table IV](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext#tbl4). There were no deaths associated with AEs in the sclerotherapy cohort. The frequency of AE-associated death was highest for subjects experiencing a PE in the laser ablation and both multiple therapies cohorts (range, 2.7%-4.1%), followed by subjects experiencing thrombophlebitis or DVT in the surgery cohort (2.4% and 2.2%, respectively), PE in the radiofrequency ablation cohort (1.5%), and DVT in the laser ablation cohort (1.0%).

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| **Table IV**Deaths associated with adverse events (*AEs*) |
|  | **Sclerotherapy (n = 12,708)** | **Laser ablation (n = 22,980)** | **Radiofrequency ablation (n = 21,637)** | **Surgery (n = 11,529)** | **Multiple therapies (same day) (n = 32,311)** | **Multiple therapies (deferred) (n = 30,722)** |
| Death,[a](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext%22%20%5Cl%20%22tbl4fna) number of subjects/number of subjects with AE (%) |
|  DVT | 0 | 7/701 (1.0) | 9/954 (0.9) | 6/277 (2.2) | 9/1110 (0.8) | 4/795 (0.5) |
|  PE | 0 | 2/58 (3.4) | 1/68 (1.5) | 0 | 3/73 (4.1) | 2/75 (2.7) |

*CPT-4*, Current Procedural Terminology, fourth edition; *DVT*, deep venous thrombosis; *ICD-9-CM*, International Classification of Diseases, Ninth Revision, Clinical Modification; *PE,* pulmonary embolism; *UB-92*, Uniform Billing, Form 92.

[a](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext%22%20%5Cl%20%22back-tbl4fna)The frequency of death associated with an AE of interest during the 30 days after a procedure was assessed by a proxy measure. This proxy measure for death was defined as any of the following criteria during the last month in which medical and pharmacy claims were available during the study period (ie, no evidence of further claims beyond this time period): a cardiac event including resuscitation (CPT-4 92950), defibrillation (CPT-4 92960, 92961), cerebral death (CPT-4 95824), cardiac arrest/failure (ICD-9-CM 427.5), evidence of injection given to stimulate the heart (J0170, J2000), hospitalization (UB-92 revenue codes 100-219), emergency room visit (Place of Service code 23; CPT-4 99281-99288; UB-92 revenue codes 450-459, 981), ambulance service (CPT-4 99289-99290, UB-92 revenue codes 540-549), or use of hospice care (Place of Service code 34).



Discussion

The purpose of our study was to demonstrate the relationship of the various treatments for varicose veins with the complications of DVT and PE in a real-world large population of patients. Data from clinical trials indicate that varicose vein treatments are generally associated with low complication rates.6, 7, 8, 9

In a meta-analysis of available varicose vein treatments (39 studies with a combined total of 8285 participants), local complications (eg, superficial phlebitis, bruising, and skin pigmentation) were common but mostly minor; DVT and PE were infrequently reported.6 The authors concluded, however, that the quality of evidence in the review was low (limited by small sample size, short-term follow-up, and use of surrogate outcomes).6 A randomized clinical trial (500 participants) comparing all four treatments (laser ablation, radiofrequency ablation, foam sclerotherapy, and surgical stripping) also indicated that treatments had relatively low thromboembolic complication rates, with two patients developing major complications: one patient had a DVT and PE after foam sclerotherapy, and one patient had a DVT after surgical stripping.8 Other reported complications were mostly minor, including phlebitis, hyperpigmentation, paresthesia, infection, and hemorrhage.8 A study by Dermody et al10 used meta-analytic techniques to assess the incidence of venous thromboembolic events in RCTs and case series. A total of 12 RCTs and 19 case series investigating ETA were included in the analysis, as well as 12 RCTs and six case series investigating nonproprietary foam preparations (total number of limbs treated with endovenous laser ablation, radiofrequency ablation, and foam sclerotherapy was 12,095, 1750, and 3788, respectively). The meta-analytic technique, which provided a point estimate of event incidence with a 95% confidence interval, showed that the incidence of venous thromboembolic events (including DVT, PE, and endovenous heat-induced thrombosis [EHIT]) was low (generally <1%) and comparable across treatment modalities and study types.10A Cochrane review by Nesbitt et al7 indicated a potential difference in treatment-related AEs. In this review (13 studies with a combined total of 450 participants) comparing ETA (laser or radiofrequency) and foam sclerotherapy with conventional surgery, minor and major complications appeared greater after surgery than after ETA. No major complications were reported for ETA (either laser or radiofrequency). There was not enough evidence to comment on foam sclerotherapy. Again, the authors concluded overall that data were insufficient and of limited quality to provide any recommendations for clinical practice.7

Our study is one of the first large real-world studies to evaluate varicose vein treatment patterns and thrombotic complications over time and to involve all practitioners who perform ETA procedures. The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) has also published results related to thromboembolic events after ETA.13 However, the NSQIP, which is a database used to monitor surgical outcomes and to improve quality measures, is restricted to procedures carried out by surgeons. Because it is hospital based, the NSQIP data do not include procedures done in a physician's office, a site to which many ETA cases are migrating. Because our current claims-based study does not have the same level of restrictive inclusion and exclusion criteria of an RCT, these findings are intended to provide a better representation of the presence of serious AEs in real-world clinical practice.

The largest treatment cohort in our current study was subjects receiving multiple treatments for varicose veins. This use of multiple treatments is not atypical in clinical practice (eg, ETA combined with phlebectomy or sclerotherapy, either concomitantly or sequentially).1 Although multiple treatments were used, there did not appear to be an additive effect with multiple treatments on the coded presence of AEs.

Among the two most commonly used individual treatment options for ablating the saphenous vein in this study (ie, laser ablation and radiofrequency ablation), the proportion of subjects with evidence of DVT ranged from 3.1% to 4.4%. The DVT rates were higher than those quantified in previous studies ([Table V](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext#tbl5)).7, 8, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 However, PE, a serious and potentially fatal complication, was an infrequent occurrence (range of subjects among all treatment cohorts, 0.2%-0.3%). Other rates of thrombotic complications reported in the literature are shown in [Table V](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext#tbl5).7, 8, 14, 15, 16,17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31

|  |
| --- |
| **Table V**Rates of thrombotic complications reported in the literature |
|  | **Sclerotherapy** | **Laser ablation** | **Radiofrequency ablation** | **Surgery** |
| DVT | 0%-5.7%8, 25 | 0%-1%7, 8, 14, 15, 16, 17, 18, 19 | 0%-1%7, 8, 16, 19, 20, 21, 22, 23, 24,[a](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext%22%20%5Cl%20%22tbl5fna) | 0.2%-5.3%8, 27, 28, 29, 30, 31 |
| PE | 0%-0.8%8, 25 | 0%-0.3%7, 8, 18 | 0%-0.04%7, 8, 16, 20 | 0%-0.2%8, 27, 29, 31 |

*DVT,* Deep venous thrombosis; *PE,* pulmonary embolism.

[a](http://www.jvsvenous.org/article/S2213-333X%2814%2900175-9/fulltext%22%20%5Cl%20%22back-tbl5fna)Another study reported DVT in 18% of patients (16% of limbs; 12 of 73); all patients (n = 66) received venous duplex ultrasound scanning after the procedure.26

Compared with a single-center, real-world study, the rates of AEs identified in our current analysis were considerably higher. Marsh et al16 conducted a retrospective analysis in the United Kingdom, and the reported DVT rates were 0.7% and 1% in subjects treated with radiofrequency ablation and laser ablation, respectively. Only one patient (0.04%) developed a PE in the radiofrequency ablation group. An analysis of venous thromboembolic events after ETA, conducted with the NSQIP database (2005-2009), revealed a higher incidence (1.6%) of thromboembolic events but only two PE events among 3874 patients.13 The rates observed in our study are noteworthy, especially because only AEs that are clinically significant are generally coded in administrative claims databases. In addition, the sensitivity analysis did not show any major differences in the trends of reported AEs among the study cohorts, further supporting the study findings. Given the relatively higher incidence of thrombotic complications observed in the current database analysis, particularly DVT associated with ETA treatment, the results warrant further investigation.

EHIT is a well-recognized complication of ETA therapy.16, 32 However, the clinical significance of EHIT is not well understood. Current consensus guidelines recommend routine postprocedural duplex ultrasound scanning to monitor for EHIT and to exclude any thrombotic complications.1 Despite a low femoral DVT rate reported in the literature, a thrombus extension rate (ie, from the great saphenous vein into the femoral vein and deep venous system) ranging from 2.3% to 7.8% was reported after ETA therapy.15, 18, 19, 20

Varicose vein treatments are generally considered to have a low risk of DVT. A low rate of DVT after ligation and stripping has been described in a range of 0.15% to 0.6%,27, 28, 30 although a prospective study conducted by van Rij et al31suggested that the incidence was higher than previously thought (5.3%). Similarly, the incidence of DVT after ETA (laser or radiofrequency) reported in the literature has generally been low (up to 1%),14, 15, 17, 19, 20, 21, 22, 23, 24 although one study reported a rate as high as 18% in patients after radiofrequency ablation therapy.26 The discrepancy may be due to whether the diagnosis of DVT was clinical or by duplex ultrasound.31 At any rate, reports of relatively high DVT rates outside the typical range suggest caution and are consistent with our study findings that the rates of DVT associated with ETA (laser and radiofrequency) in the real-world setting are higher than what is generally reported in the literature.

This is the first study to provide real-world incidence from a large reliable source in the United States of AEs associated with invasive varicose vein treatments; however, results should be interpreted in regard to the limitations of this study. Our data are derived from a large claims database that is representative of the U.S. commercially insured population and rely on diagnostic codes in the absence of more detailed clinical factors. Therefore, the actual rates of AEs may be underestimated because AEs that are of minimal clinical significance are not likely to be coded. Although we think this is a study strength, particularly for health care decision makers, it is a limitation that cannot be ignored from a clinical perspective. Our study was primarily descriptive, and as such, we did not control for baseline differences across the cohorts. An evaluation of observed differences indicates that certain cohorts have moderate differences in age and comorbidities, which may contribute to the propensity of having these AEs. These factors, along with those that could not be acquired in claims data, may attenuate the findings of this study. In addition, we measured AEs that occurred within 1 month of treatment, but it cannot be confirmed within the context of this study if the treatments unequivocally contributed to the AEs.

Furthermore, the sclerotherapy treatment cohort included subjects receiving both liquid and foam sclerotherapy. In the United States, both forms of sclerotherapy (liquid and physician-compounded foam) are predominantly used for treatment of uncomplicated varicose veins (ie, those not associated with incompetence), minor varicose veins, or thread veins; therefore, the observed minimal venous thromboembolism rate in this study is understandable. Our inability to distinguish between the use of physician-compounded foam for minor thread veins and great saphenous vein treatments should be noted. In the United States, physician-compounded foam sclerotherapy is unapproved; also, liquid sclerotherapy is approved only for reticular and spider veins and is not covered by most insurance providers for treatment of the great saphenous vein or small saphenous vein.



Conclusions

This study demonstrated that thrombotic complications associated with invasive varicose vein treatments in the real-world setting may be higher than what is reported in clinical trials, particularly in regard to DVT after ETA therapy. A better understanding of these patterns of AEs may have an impact on new strategies to safely and effectively manage patients with varicose veins. These findings highlight the need for further investigation on this topic and its impact in clinical practice.



Author contributions

Conception and design: ME, AR, DW

Analysis and interpretation: TO, ME, AR, KB, DW

Data collection: ME, AR

Writing the article: AR, KB

Critical revision of the article: TO, ME, AR, KB, DW

Final approval of the article: TO, ME, AR, KB, DW

Statistical analysis: ME, AR

Obtained funding: ME, DW

Overall responsibility: DW



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This study was funded by BTG International Ltd.

Author conflict of interest: T.F.O. is a consultant for BTG, Tactile Medical, and Covidien. M.E., A.R., and K.B. are employed by Xcenda, a consulting firm that received funding for the writing of this manuscript. D.W. is a full-time employee of BTG International Ltd and has shares in the company.

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