Journal of
Vascular Surgery
Venous and Lymphatic Disorders™

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

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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. (J Vasc Surg: Venous and Lym Dis 2015;3:27-34.)**

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.[1-4] Although varicose veins can be a cosmetic concern, most individuals with varicose veins seek treatment because of symptoms.[1]

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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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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.
2213-333X

http://dx.doi.org/10.1016/j.jvsv.2014.09.007

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.[6-9] 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