

Project Title: Patients with Post-thrombotic Venous Obstruction are More Likely to Undergo Reintervention with Intravenous Ultrasound and Experience Slower Symptom Resolution After Iliac Vein Stenting

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Project IRB Number:

15-00506

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Study Aims:

This study aims to analyze the outcomes of patients with proximal iliac venous lesions based on the presenting symptoms and etiologies of the lesions at the time of index venous stenting procedure. The patients will be drawn from a large single institution, single surgeon database with the aim of changing classification guidelines for patients with what we believe is a new and distinct venous pathology entailing symptoms of compression as well as occlusive suggesting a dually-presenting lesion suggesting both May-Thurner Syndrome with a remote, prior DVT.

Abstract

Objective: Patients undergoing iliac vein stent placement (IVS) for chronic proximal venous outflow obstruction are observed to mainly have two types of stenosis: a more focal stenosis from external compression which was present in every patient, also known as a nonthrombotic iliac vein lesions (NIVL), or a more diffuse stenosis suggestive of post-thrombotic venous obstruction (PTVO) from a remote deep venous thrombosis (DVT) which was present as a concurrent stenosis in some NIVL patients. We assessed the influence of PTVO on outcomes of symptom change and reintervention after IVS.

Methods: A retrospective review of IVS procedures at a tertiary academic medical center from August 2011 to March 2022 is to be performed. Patients are to be divided into two cohorts based on intravascular ultrasound and contrast venography assessment: PTVO and NIVL. Patients with a known history of DVT but no findings of PTVO on intraoperative imaging are to be excluded

from the analysis. Minor reintervention are to be defined as endovenous thermal ablation or sclerotherapy to the same limb of interest as the index procedure. Major reintervention are to be defined as any procedure that includes intravenous ultrasound. Our research group has already analyzed 815 such IVS patients to date, representing patients who underwent IVS from August 2011 to July 2021, with the NIVL group containing 583 patients while the PTVO or “NIVL+” group had an additional 232 patients in it. This analysis will be continued to account for the additional patients who have undergone IVS after July 2021 and will therefore be an even larger, more robust cohort of patients that is estimated to contain by the time of final data collection over 1000 patients undergoing IVS.

Public Health Relevance Statement:

The relevancy of this project to public health is that it might lead to the adoption of a new category with which to classify patients with proximal iliac venous lesions. This new category, which our group has started calling “NIVL+” for its concurrent presentation of compressive symptoms seen traditionally in May-Thurner Syndrome with occlusive symptoms suggesting prior, remote DVT could carry with it differences in outcomes from those with the more traditional etiologies of either NIVL or occlusion from remote DVT.

Being able to definitively identify this distinct pathology and adopt it into the spectrum on which venous disease exists could greatly help vascular specialists both in counseling their patients about operative therapies as well as the actual management of this presentation in terms of postoperative expectations for symptom resolution and the need for future re-interventions.

Environment:

In order to complete such a project, our research group would require a paid research coordinator to obtain from patients in the pre, peri, and postoperative periods such data points including VCSS composite scores, CEAP clinical classification scores, and of course importantly to keep this data such that the changes in responses over time can be studied properly.

In addition to this, we would need the coordinator to be able to have ample time within the operating rooms during the venous stent procedures to obtain information such as the types of stents used, the number of stents used, and whether the stent placement was bilateral or unilateral. In the postoperative period, researchers would be required to monitor each patient for as much as 7 years in order to continue obtaining aforementioned patient reported data such as CEAP and VCSS, but also be able to keep track of patients requiring re-intervention. What is more, the re-interventions themselves are classified as either major or minor based on certain intraoperative criteria including the use of a venogram, which the coordinator would have to consistently record.

In addition, our group is already planning on traveling to and presenting at the 2022 EVS Conference to present findings on a similar topic to this titled “How Prior History of Deep Vein Thrombosis Influences Iliac Vein Stenting,” a study that directly influenced the thought process that led to the conception of this project.

Biographical Sketches:

Jason Storch, BA will be the Principal Investigator for this study. Jason is a medical student at the Icahn School of Medicine at Mount Sinai located at 1 Gustave Levy Place, New York, NY 10029. He completed his undergraduate degree in Russian and Slavic Studies with minor concentrations in Chemistry and History at Vassar College in 2017 located at 124 Raymond Avenue, Poughkeepsie, NY 12604. Jason has conducted research in the fields of cardiovascular surgery as well as vascular surgery, with his research presented at conferences such as the American Association for Thoracic Surgery Annual Conference (“Ross Procedure Outcomes in Patients Undergoing Surgery Over 20 Years Ago”) as well as the Vascular Annual Meeting (“Iliac Vein Stenting Outcomes for Patients with Superficial Venous Insufficiency Concurrent with Deep Venous Disease”). In addition to that, Jason has had his research work published in such peer reviewed journals as the Journal of American Cardiology (“Prosthesis-Patient Mismatch Between Transcatheter Heart Valves in Transcatheter Aortic Valve Replacement”) as well as the Journal of Vascular Surgery. Jason is also intending to apply for a position at an integrated vascular surgery residency program after completing his medical education at Mount Sinai. In addition to that, for 2 years Jason served as a clinical researcher at the Department of Cardiovascular Surgery at the Icahn School of Medicine at Mount Sinai where he personally oversaw over 15 clinical trials at various phases of completion per FDA guidelines. Given his medical training and experience in vascular surgery outcomes research is well-primed to lead this investigation.

Justin George, MD will be the mentor of the study. Dr. George is an Assistant Professor of Surgery in the Division of Vascular Surgery at the Icahn School of Medicine at Mount Sinai located at 1 Gustave Levy Place, New York, NY 10029. Dr. George obtained his undergraduate degree from Rutgers University located at 57 US Highway 1, New Brunswick, NJ 08901-8554 in 2011 before attending the University of Pennsylvania Perelman School of Medicine located at 3400 Civic Center Blvd, Philadelphia, PA 19104 in 2015. After obtaining his medical degree, Dr. George graduated from the Icahn School of Medicine at Mount Sinai General Surgery Residency Program in 2020 before then graduating from the Fellowship in Vascular Surgery in 2022. Dr. George has published widely vascular surgery in such journals as The Journal of Vascular Surgery (“Higher Surgeon Volume is Associated with Lower Odds of Complication Following TEVAR for Aortic Dissections”) and Vascular and Endovascular Surgery (“Duplex Ultrasound Can Successfully Identify Endoleaks and Renovisceral Stent Patency in Patients Undergoing Complex Endovascular Aneurysm Repair”). Dr. George’s experience in research and growing clinical practice makes him a perfect candidate to be an EVS mentor for this project.

Krystina Choinski, MD will be a co-investigator of the study. Dr. Choinski is a vascular surgery resident at the Icahn School of Medicine at Mount Sinai. Dr. Choinski completed her undergraduate degree at Hamilton College located at 198 College Hill Road, Clinton, NY 13323 in 2015 before completing her medical training at the Albert Einstein College of Medicine located at 1300 Morris Park Ave, The Bronx, NY 10461 in 2020. Dr. Choinski has published widely in vascular surgery journals including the Journal of Vascular Surgery (“Improvement in Thoracic Outlet Syndrome Symptoms After Iliac Vein Stenting for Iliac Vein Proximal Venous Outflow Obstruction”) as well as in Surgical Technology International (“The Feasibility and Applicability of Percutaneous Deep Vein Arterialization in Peripheral Artery Disease”). Dr.

Choinski takes an active role in medical students and early vascular and general surgery residents research output and would be an ideal candidate to be a co-investigator for this study.

Jenny Chen, BA will be a co-investigator of the study. Jenny is a medical student at the Icahn School of Medicine at Mount Sinai located at 1 Gustave Levy Place, New York, NY 10029. Jenny completed her undergraduate degree in 2021 from Dartmouth College located in Hanover, New Hampshire before starting her medical training at the Icahn School of Medicine at Mount Sinai in New York City. Jenny has published extensively in vascular research, including in the Journal of Vascular Surgery (“Hypercoagulable States Among Patients Undergoing Vein Stent Placement for Chronic Iliofemoral Vein Obstruction”). She will also be presenting her findings at the upcoming EVS Conference 2022 (“How Prior History of Deep Vein Thrombosis Influences Iliac Vein Stenting”). Jenny offers a comprehensive understanding of data analytics and management which makes the processing and interpretation of complex large data sets much more manageable, her skills make her a great candidate for co-investigator.

Halbert Bai, MPH will be a co-investigator of the study. Halbert is a medical student at the Icahn School of Medicine at Mount Sinai located at 1 Gustave Levy Place, New York, NY 10029. Halbert previously completed his undergraduate degree at the University of Pennsylvania in 2018. After his undergraduate degree, Halbert obtained his Masters in Public Health from Yale University in 2020. Halbert has published widely on topics pertaining to vascular surgery including in the Journal of Vascular Surgery Venous and Lymphatic Disorders (“Patients with active venous leg ulcers at the time of iliac vein stenting require more reoperations”) and has presented his works at such conferences as the Vascular Annual Meeting (“Comparison of Iliofemoral Vein Stenting in Octogenarians and Older to the Younger Population”). As such, Halbert is an ideal candidate as co-investigator on this study.

Anna B. Williams will be a co-investigator of the study. Anna is currently an undergraduate student at Dartmouth College.

Rami O. Tadros, MD will be a co-investigator of the study. Dr. Tadros is a Professor of Surgery in the Division of Vascular Surgery at the Icahn School of Medicine at Mount Sinai located at 1 Gustave Levy Place, New York, NY 10029. Before joining Mount Sinai as faculty, Dr. Tadros completed his integrated vascular surgery residency at Mount Sinai in 2013. Prior to this, he obtained his medical training at Ross University School of Medicine and his undergraduate degree at Saint Xavier University. Dr. Tadros has published extensively on various aspects of vascular surgery including carotid artery surgery in the Journal of Vascular Surgery Cases, Innovations, and Techniques (“Rapid progression of carotid artery atherosclerosis and stenosis in a patient with a ventricular assist device”) as well as on aortic surgery in the Journal of Vascular Surgery (“Higher Surgeon Volume is Associated with Lower Odds of Complication Following TEVAR for Aortic Dissections”). Dr. Tadros has also conducted research clinical trials before including industry-sponsored trials analyzing aneurysmal progression in arterial dissections. He would make an ideal candidate as a co-investigator on this study.

Windsor Ting, MD will be a co-investigator of the study. Dr. Ting is a Professor of Surgery in the Division of Vascular Surgery at the Icahn School of Medicine at Mount Sinai located at 1

Gustave Levy Place, New York, NY 10029. Dr. Ting previously graduated from the Tufts University School of Medicine located at 145 Harrison Ave, Boston, MA 02111 in 1979 before completing his residency in General Surgery and a fellowship in Thoracic Surgery both at Columbia-Presbyterian Medical Center located at 630 W. 168th Street, New York, NY 10032. Dr. Ting has published widely in preeminent vascular surgery journals including the Journal of Vascular Surgery (“Secondary interventions after iliac vein stenting for chronic proximal venous outflow obstruction”) as well as the Journal of the American College of Surgeons (“Quality of care and outcomes in coronary revascularization—are there any differences between mandatory and voluntary reporting?”). He has also spoken at many national and international conferences, including most recently at the 2022 Vascular Annual Meeting, specializing on the management of complex venous lesions. Dr. Ting would make an excellent candidate for co-investigator for this study.

Research Budget:

This study will require a budget of 25,000.00\$ This budget will be allocated for a research coordinator who will oversee the logistical aspects of the study referenced in detail above in the Environment section. While 25,000.00\$ would not fully support this researcher financially, it would go a long way in helping to ensure we are able to adequately obtain, maintain, and preserve the data needed to bring this study into full fruition.

Research Plan:

Significance:

The hypothesis of this study is that patients with proximal iliac vein lesions presenting with symptoms of both compressive and occlusive components have lower rates of symptom resolution and higher rates of re-operations following index venous stent operation than those patients with only compressive findings found in pathologies like May-Thurner Syndrome. The significance of this is challenging the conventional classification system that reports patients’ venous etiology as either compressive in classically defined NIVL morphology or occlusive in the more PTVO definition. Our study seeks to show there exists a distinct pathology which we have termed “NIVL+” which entails of concurrent etiologies of both the compressive and occlusive nature. Proving the existence of this new distinct diagnosis within iliac venous disease could help the vascular surgeon community better counsel their patients on the rates of successful venous stent procedures in terms of symptom resolution and the need for re-intervention in the long term postoperatively.

Innovation:

After iliac vein stenting, patients with PTVO experienced a slower reduction of VCSS in the first two postoperative years versus patients with only NIVL and were more likely to undergo reintervention. These differences in outcomes could reflect that there exists an until now unclassified pathology that combines both symptoms of compressive disease like May Thurner Syndrome with occlusive symptoms suggesting remote, prior DVT. Such pathology results in worse outcomes after venous stenting and should be listed as a distinct pathology that should be listed separately from PTVO or simply NIVL. We believe that innovation is needed in the move away from using the blanket term NIVL, which we believe is oversimplifying our patients complex venous disease by failing to properly define these patients with symptoms of both compressive and occlusive etiology.

Research Strategy:

This study will be carried out as a retrospectively analyzed, prospectively maintained database of patients undergoing IVS from August 2011 to July 2021.

Patients will be divided into two cohorts, PTVO and NIVL, based on perioperative IVUS and contrast venography assessment. Postoperatively, data points will include major re-interventions or minor procedures, Clinical Assessment Score (CAS) in relation to baseline assessment at various intervals of time, and VCSS scores at interval timepoints. The venous clinical severity score (VCSS) will be used to compare patient disease severity before and after IVS.

Statistical Analysis Plan:

One-tailed independent samples t-tests and chi-squared tests will be used to compare continuous variables and categorical variables, respectively. Logistic regression models will be used to determine the univariate and multivariate odds ratio (OR) of minor and major reintervention. Kaplan Meier analysis with a log-rank test will be used to assess reintervention-free survival. The alpha will be set to 5%.

Tables:

These tables represent only the research which has already been undertaken and interpreted and do not represent the entire vein database which our project will utilize and put forward towards presentation at the EVS 2022 Conference.

Table I: Outcomes in 873 patients undergoing iliac vein stenting using univariate and multivariate analyses for reinterventions.

Note - DVT = Deep vein thrombosis, CEAP =

Clinical-Etiological-Anatomical-Pathophysiological, VCSS = Venous Clinical Severity Score, CAS = Clinical Assessment Score

	Variable	Group 1 (%)	Group 2 (%)	P-value	
		n=290	n=583		
Demographics and Comorbidities	Age (Mean \pm SD)	64.0 (14.1)	60.2 (12.3)	<0.001*	
	Gender	Female	166 (58.0)	324 (55.6)	0.538
		Male	120 (42.0)	259 (44.4)	
	Diabetes	86 (29.7)	106 (18.2)	<0.001*	
	Hypertension	170 (58.6)	274 (47.0)	0.002*	
	Coronary artery disease	45 (16.1)	50 (9.4)	0.007*	
	Cancer	45 (16.0)	46 (8.3)	0.001*	
	History of Smoking	No	220 (75.9)	469 (80.4)	0.14
Yes		70 (24.1)	114 (19.6)		
Perioperative	CEAP Class (Mean (SD))	3.6 (1.1)	3.4 (1.0)	0.043*	
	CEAP Class	C0	5 (1.7)	3 (0.5)	0.031*
		C1	0 (0)	3 (0.5)	
		C2	17 (5.9)	34 (5.8)	
		C3	146 (50.3)	346 (59.3)	
		C4	79 (27.2)	137 (23.5)	
		C5	11 (3.8)	23 (3.9)	
	C6	32 (11.0)	37 (6.3)		
	Number of Stents (Mean (SD))	2.4 (1.0)	2.2 (0.9)	0.008*	
Bilateral Stents	152 (52.4)	398 (68.3)	<0.001*		
Preop VCSS Composite (Mean(SD))	10.1 (4.5)	10.5 (3.6)	0.194		

Postoperative	Days of Follow-up (Mean(SD))	748.9 (709.3)	746.8 (654.1)	0.97
	Days from Surgery to Reoperation (Mean(SD))	300.4 (362.8)	313.9 (382.1)	0.742
	Number of Reoperations	2.0 (1.4)	1.8 (1.2)	0.171
	Postop VCSS Composite (Mean(SD))	6.9 (4.0)	6.3 (3.1)	0.026*
	VCSS change Post-op (Mean(SD))	3.0 (3.2)	4.0 (3.2)	<0.001*
	VCSS change 1 year (Mean(SD))	3.7 (3.8)	4.5 (3.7)	0.04*
	VCSS change 2 year (Mean(SD))	3.0 (4.1)	4.4 (3.4)	0.003*
	VCSS change 3 year (Mean(SD))	3.7 (4.9)	4.5 (3.9)	0.288

Table II: Unadjusted and adjusted odds ratios for both major and minor reinterventions among 546 patients undergoing iliac vein stenting.

Note - OR = Odds ratio

Major Reinterventions				
	Model	OR	P-value	95% CI
Group 2 vs Group 1	Unadjusted	0.27	<0.001*	(0.13, 0.54)
	Adjusted	0.29	<0.001*	(0.18, 0.47)
Postoperative Minor Procedures				
Group 2 vs Group 1	Unadjusted	5.47	<0.001*	(2.83, 11.34)
	Adjusted	5.26	<0.001*	(3.33, 8.59)

Bibliography:

1. Azirar S, Appelen D, Prins MH, Neumann MH, de Feiter AN, Kolbach DN. Compression therapy for treating post-thrombotic venous obstruction. *Cochrane Database Syst Rev*. 2019;9(9):Cd004177.
2. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23 Suppl 1):I4-8.
3. Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, et al. The post-thrombotic venous obstruction: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*. 2014;130(18):1636-1661.
4. May R, Thurner J. The Cause of the Predominantly Sinistral Occurrence of Thrombosis of the Pelvic Veins. *Angiology*. 1957;8(5):419-427.
5. Cockett FB, Thomas ML. The iliac compression syndrome. *Br J Surg*. 1965;52(10):816-821.
6. Raju S, Neglen P. High prevalence of nonthrombotic iliac vein lesions in chronic venous disease: a permissive role in pathogenicity. *J Vasc Surg*. 2006;44(1):136-143; discussion 144.
7. Yamaki T, Nozaki M, Sakurai H, Takeuchi M, Soejima K, Kono T. High peak reflux velocity in the proximal deep veins is a strong predictor of advanced post-thrombotic sequelae. *J Thromb Haemost*. 2007;5(2):305-312.
8. Asbeutah AM, Riha AZ, Cameron JD, McGrath BP. Five-year outcome study of deep vein thrombosis in the lower limbs. *Journal of Vascular Surgery*. 2004;40(6):1184-1189.
9. Prandoni P, Frulla M, Sartor D, Concolato A, Girolami A. Vein abnormalities and the post-thrombotic venous obstruction. *J Thromb Haemost*. 2005;3(2):401-402.
10. Roumen-Klappe EM, den Heijer M, Janssen MC, van der Vleuten C, Thien T, Wollersheim H. The post-thrombotic venous obstruction: incidence and prognostic value of non-invasive venous examinations in a six-year follow-up study. *Thromb Haemost*. 2005;94(4):825-830.
11. Roumen-Klappe EM, Janssen MC, Van Rossum J, Holewijn S, Van Bokhoven MM, Kaasjager K, et al. Inflammation in deep vein thrombosis and the development of post-thrombotic venous obstruction: a prospective study. *J Thromb Haemost*. 2009;7(4):582-587.
12. Johnson BF, Manzo RA, Bergelin RO, Strandness DE, Jr. Relationship between changes in the deep venous system and the development of the post-thrombotic venous obstruction after an acute episode of lower limb deep vein thrombosis: a one- to six-year follow-up. *J Vasc Surg*. 1995;21(2):307-312; discussion 313.
13. Beebe HG, Bergan JJ, Bergqvist D, Eklof B, Eriksson I, Goldman MP, et al. Classification and grading of chronic venous disease in the lower limbs. A consensus statement. *Eur J Vasc Endovasc Surg*. 1996;12(4):487-491; discussion 491-482.
14. Masuda E, Ozsvath K, Vossler J, Woo K, Kistner R, Lurie F, et al. The 2020 appropriate use criteria for chronic lower extremity venous disease of the American Venous Forum, the Society for Vascular Surgery, the American Vein and Lymphatic Society, and the Society of Interventional Radiology. *J Vasc Surg Venous Lymphat Disord*. 2020;8(4):505-525.e504.
15. Wen-da W, Yu Z, Yue-Xin C. Stenting for chronic obstructive venous disease: A current comprehensive meta-analysis and systematic review. *Phlebology*. 2016;31(6):376-389.

EVS Mentor Letter of Support:

To the EVS Research Seed Grant Committee,

My name is Justin George, MD and I am writing this letter in support of the project “Patients with Post-thrombotic Venous Obstruction are More Likely to Undergo Reintervention with Intravenous Ultrasound and Experience Slower Symptom Resolution After Iliac Vein Stenting” proposed by Jason Storch. As an EVS member and junior faculty within the Division of Vascular Surgery at the Icahn School of Medicine at Mount Sinai, I have undertaken many projects and seen them through to completion, and if given the opportunity by this committee, this project will be no different. Our team, assembled by Jason Storch and I and supported under the guidance of senior faculty surgeons and fellow EVS members Dr. Windsor Ting and Dr. Rami Tadros, has the ability and experience to produce and present top quality research.

This project is of particular importance both to me and the Mount Sinai vascular division as a whole. Our vein stent registry is one of the most robust and well maintained in the country and our venous research group has already presented findings at various conferences nationwide while publishing our manuscripts in top journals like The Journal of Vascular Surgery. If given the opportunity to continue our work with support and funding from the EVS Research Seed Grant, we can continue to grow and to build on our successes, especially in this unique and previously under-researched topic of nonthrombotic iliac vein lesions (NIVL). This project could help add insight into the diagnosis and classification of iliac vein lesions and help us in the vascular surgery community lend greater specificity and nuance to our patients in the counseling of their lesions. In addition, understanding the differences in outcomes between traditional NIVL lesions and those with the distinct pathology that our group has identified as “NIVL +” could help shape the diagnosis of venous disease and have real ramifications in the diagnosis and treatment of venous disease.

Given the very large practices specializing in management of venous disease, our group here at Mount Sinai is uniquely poised to be a leader in the understanding, diagnosing, and treating this new etiology of iliac venous disease and this research group is the perfect group to undertake the initial clinical research of it. With well over 250 combined articles published, our group represents a great collection of talent from all stages of the medical ladder, from undergraduates and medical students to residents and junior faculty to senior attending surgeons. It is my sincere belief that if given the support from the EVS Research Seed Grant, great work can and will be completed and it with that belief that I give my fullest degree of support to this project which I myself will be the chief EVS mentor on.

Please do not hesitate to contact me if there are any questions on this esteemed committee regarding this project. Thank you.

Sincerely,

Justin George, MD

Assistant Professor of Surgery and Radiology

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