BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email editorial.bmjopen@bmj.com

BMJ Open

Protocol for a longitudinal cohort study: Determination of risk factors for the development of first venous leg ulcer in people with chronic venous insufficiency, the VEINS (Venous Insufficiency in South Florida) Cohort

SCHOLARONE™
Manuscripts

Protocol for a longitudinal cohort study: Determination of risk factors for the development of first venous leg ulcer in people with chronic venous insufficiency, the VEINS (Venous Insufficiency in South Florida) Cohort

Joshua Mervis[1], B.A.; Robert S. Kirsner[1], M.D.; Ph.D.; Hadar Lev-Tov[1], M.D.

[1]Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, Florida

*Address for correspondence:**

Hadar Lev-Tov, M.D.
Department of Dermatology & Cutaneous Surgery
University of Miami Miller School of Medicine
1600 NW 10th Avenue, Room 2023A
Miami, FL, 33136
U.S.A.
Phone: 305-243-6734
Email: hlevtov@med.miami.edu

Word Count: 2,570

Reference Count: 26

Figure Count: 1

Table Count: 2

Conflict of Interest: The authors of this protocol have NO conflict of interest to declare.

Prior Presentation: The authors declare that this protocol has NOT been published previously.

Abstract:

Introduction: Chronic venous insufficiency (CVI) affects up to one third of the adult population yet venous leg ulcers (VLU), a significant complication of CVI, only affect 1-2% of adults in the United States. Why some develop VLU and others do not is unclear. VLU have a significant impact on quality of life and are extremely costly and difficult to treat. Moreover, VLU prevalence is increasing, doubling in the last 20 years. In order to characterize the differences between people with CVI and those who ultimately develop VLU, we aim to set up the unique Venous Insufficiency in South Florida (VEINS) cohort.

Methods and analysis: Subjects will be recruited from the University of Miami Hospital and Clinic's vascular lab database, which began in July 2011. Any adult age 18-95 who has had venous reflux detected on duplex ultrasound of the lower extremities is included. Approximately 2,500 patients are already in the database that meet these criteria, with an estimated 2,500 additional potential subjects to be recruited from the vascular lab database over the next five years. Subjects with history of VLU prior to duplex study date will be excluded. Data will be collected via review of the Doppler study report, patient phone interview, and review of the electronic medical record. Subjects will be contacted for follow-up every 3 months for at least 5 years until the study endpoint, development of first VLU (fVLU), is reached. In order to estimate the time from reflux documentation to fVLU, Kaplan Meier survival curves will be constructed. Cox proportional hazard regression models will be constructed to investigate possible risk factors.

Ethics and dissemination: This study is approved by the University of Miami's Institutional Review Board (IRB). We hope to present the results of this study to the scientific community at conferences and in peer-reviewed journals.

Keywords: Venous leg ulcer, Chronic venous insufficiency, primary prevention, cohort study

Strengths and Limitations:

- To our knowledge, this study is the first that seeks to prospectively track development of the fVLU among a population of subjects with CVI.

- The VEINS cohort will describe the natural history of CVI leading to fVLU, reveal specific risk factors for the development of fVLU, and allow for the development of 3- and 5-year predictive models for fVLU occurrence.

- The data obtained from this study will support the development of VLU prevention strategies.

- This study does not address time in relation to initial development of CVI, but rather time from documentation of CVI on venous duplex ultrasound, typically the point at which CVI becomes clinically significant.

Protocol for a longitudinal cohort study: Determination of risk factors for the development of first venous leg ulcer in people with chronic venous insufficiency, the VEINS (Venous Insufficiency in South Florida) Cohort

Introduction

Background:

Chronic ulcers of the lower extremities affect 1-2% of adults in the United States (1-3). Of these ulcers, around 70% are due to venous disease alone, while 20% are due to arterial or mixed arteriovenous disease (2). Venous leg ulcers (VLU) are wounds that typically occur on the lower third of the leg between the ankle and knee, often referred to as the "gaiter area," in the setting of chronic venous insufficiency (CVI). In the United States, roughly a third of the adult population is likely to have CVI, while worldwide prevalence estimates are up to 60% (4). CVI is characterized by sustained ambulatory venous pressure (aka venous hypertension) and by reflux on Doppler ultrasound. Reflux is defined as retrograde blood flow in the lower extremities greater than 0.5 seconds while in the reverse Trendelenburg position without provocation. Typical causes of CVI include obstruction from deep vein thrombosis, valvular defects, which may be acquired or genetic, and ineffective calf muscle pump action (1, 2). The pathophysiology of VLU remains unclear, though various hypotheses implicating pericapillary fibrin cuffing, endovascular trapping of oxygen and nutrients, inflammatory cell infiltrates, cytokine trapping, and metalloproteinase dysregulation have all been areas of extensive research (5-7).

VLU often have a very significant impact on a patient's quality of life (8). Compared with matched controls, patients with VLU have more comorbid conditions, miss more days of work, and use more medical resources (9, 10). While numerous advancements in treatment, such as cellular and acellular skin equivalents and biomaterials, have been made in recent years (1), VLU prevalence seems to be increasing. The estimated prevalence of VLU has doubled in the last 20 years from 0.3% to 0.6% in adults under 65 and is up to 2.2% in adults over 65 (9, 11). European epidemiologic data has shown similar prevalence rates among these age groups, while revealing that VLU prevalence is even higher at 4-5% in individuals older than 80 years (12) and may exceed 12% among certain elderly populations. (13)

Moreover, the costs associated with VLU have been increasing and represent a great burden for both the patient and public health system. Over the last 30 years, the estimated cost of treating a single, chronic VLU has more than tripled to $34,000 today (9, 11). Likewise, the annual cost of VLU treatment in the United States has risen from around $3 billion in 1987 to $15 billion in 2011 ((10).

Rationale:

With an aging population, it is likely that VLU prevalence will continue to rise, with more ulcers occurring in older, sicker patients who are costlier to treat. Despite the significant morbidity, high costs, and continued difficulty in healing of VLU, little attention has been given to primary prevention. Thus, a paradigm shift, away from wholesale investment in advanced interventions and toward prevention, is warranted. The idea that a greater emphasis on VLU prevention is needed is not new, going back to at least 1997 (14). Nonetheless, no studies to

date have focused on prevention of the first VLU (fVLU). Without this data, society and summary guidelines on VLU have not been able to make recommendations regarding primary prevention (1, 2, 15, 16).

Given that the pathophysiology of VLUs is not well-understood, risk factor analysis is a sensible strategy for studying prevention. With the goals of developing a predictive model for ulceration and overall prevention strategy in mind, this study aims to identify risk factors associated with development of the fVLU. While certain risk factors have been described (Table 1), they are based primarily on either retrospective analyses that compared people with any VLU (i.e. first or recurrent) to the general population or on expert opinion.

Furthermore, associations between VLU occurrence and certain medical conditions (17), medications (18, 19), and other parameters (20-22) have been made, but the directionality of the association is not clear. Although these data are informative, they may not be clinically useful. A need exists to distinguish risk factors for CVI and for fVLU, as a only a small minority of patients with CVI proceed to develop a fVLU (23). Particular risk factors specific for the fVLU are not known, and to our knowledge no study has prospectively tracked development of the fVLU.

Therefore, the primary aim of this research is to answer a simple yet extremely complex clinical question: in a patient presenting with signs and symptoms of CVI, what interventions may prevent a fVLU?

Primary Objective

1. Characterize risk factors associated with developing fVLU in people with CVI.

Secondary Objectives

2. Develop 3- and 5-year predictive models for risk of developing fVLU in patients with

     signs and symptoms of CVI.

3. Estimate the incidence of fVLU in people with CVI.

Methods and Analysis:

Geographical Context

 Subjects will represent a diverse group from all over southeastern Florida primarily, with

the vast majority coming from Miami-Dade, Broward, and Palm Beach Counties in the United

States.

Study population

 The VEINS Cohort will include both men and women ages 18-95. Any adult who

has had reflux detected on venous duplex ultrasound of the lower extremities is

potentially eligible. Patients who have undergone venous duplex studies for any

indication will be considered. Exclusion criteria include age under 18, inability to provide

consent over the phone, and history of venous ulcer prior to duplex study date.

Recruitment of Participants

Subjects will be recruited from a database of the University of Miami Hospital and Clinic's vascular laboratory. The database, which goes back to July 2011, will be queried for all patients who were found to have reflux on venous duplex ultrasound of the lower extremities. After reflux has been noted from the duplex study report, the subject's chart will be reviewed in the Electronic Medical Record (EMR) to ascertain basic contact information. For this part of the study, a privacy waiver for recruitment purposes has been approved by the local institutional review board (IRB). The investigators will then call potential subjects by phone. The subjects will provide a verbal phone consent for a phone survey and further chart review of potential risk factors. During the verbal informed consent, all aspects of the study will be reviewed, including: why subjects were selected, researcher goals, procedures, relevant risks, benefits, and subjects' rights. It is anticipated that a large portion of the study population is Spanish speaking. The verbal informed consent and survey have both been translated to Spanish and will be administered by Spanish speaking research staff, with the help of an interpreter as needed. Once consent is obtained and inclusion criteria confirmed, subjects will be enrolled into the cohort.

Sample size

There are approximately 2,500 lower extremity venous duplex ultrasound reports in the database that detected reflux going back to its inception in July 2011. In recent years, approximately 500 duplex studies that find reflux have been performed annually. Thus, over the next 5 years, we expect approximately 2,500 additional subjects will be potentially eligible to

enter the cohort. Given the paucity of data available on the incidence of fVLU, we will attempt

to recruit as many subjects as possible.

Study design – Overview

This protocol is for a longitudinal cohort study with retrospective and prospective

components. The methodology for building the cohort and following subjects is outlined in

Figure 1. The aim throughout is to identify subjects with venous reflux documented on

ultrasound prior to the development of fVLU. Any subject who reports a history of an ulcer

prior to the date of reflux study will be excluded from the cohort. The retrospective part of the

study will cover all patients currently in the database. If a subject went on to develop a fVLU

subsequent to the time of duplex study (i.e. after reflux was documented but before first

contact by the investigators), he/she will not be followed in any prospective manner. Instead,

only an entry survey will be administered (see below for details) and the subject's participation

will end. The prospective part of this study will include any subject who met inclusion criteria

but has not yet developed a VLU. Regardless of when subjects enter the cohort, they will be

followed prospectively for five years from the beginning of the study or the occurrence of an

ulcer, whichever occurs first. Any subject who begins in the retrospective cohort can continue

into the prospective cohort so long as the fVLU has not developed. Currently, there is no pre-

determined stop date after which new subjects will cease to be recruited for the cohort. New

subjects will continuously be recruited as new patients come through the vascular lab for

venous studies.

End Point and Follow-up

The endpoint of this study is development of fVLU, after which subjects will exit the cohort. If a subject has no history of fVLU, he/she will be contacted by phone for a follow-up survey every 3 months until the development of fVLU. At this time, the intention is that subjects will be followed for at least 5 years.

Data collection and management

In all cases, data will be collected via three sources: venous duplex ultrasound report, phone survey, and patient chart in the EMR. Venous duplex ultrasound reports will be accessed from a secure electronic database housed in the University of Miami Hospital and Clinic's vascular laboratory. For the phone survey, a script with exact wording for all questions and instructions has been created. Data on specific variables of interest will be ascertained from each source as outlined in Table 2.

All data will be entered and stored electronically in REDCap (Research Electronic Data Capture), a secure, web-based application that facilitates creation and management of data collection instruments, monitoring of data quality, and statistical analysis of data (24). This software has commonly been used for epidemiological research, including similar cohort studies (25). All investigators will be trained in data entry by the REDCap study administrator and must demonstrate proficiency with mock patients and data entry before being granted access to data collection forms.

Evaluation of study endpoint – photo of wound

If a subject reports development of fVLU, investigators will seek to obtain a photo in the patient chart or request that the subject submits a picture of the wound via email. While not required by the study protocol, a photograph can help validate that the wound is a VLU. In cases where visual evidence is not available, ulcer validation will be supported by key questions regarding the wound, such as location and duration. Moreover, there is data supporting the ability of patients to correctly self-assess the status of their chronic wounds with up to 97% accuracy when compared to expert evaluation (26).

Pilot Study

A pilot study of 70 potential subjects was carried out. The first 10 venous duplex studies to report reflux from each year of the database's existence (2011-2017) were used. The purpose of this pilot study was to give investigators the chance to determine how well the phone survey and data collection forms performed with a variety of real subjects, and to discuss any changes that should be made. Only minor technical changes in data coding were made. Of the 70 patients that were called, 22 were reached over the phone, 20 of whom enrolled in the study.

Statistical analysis of data

For purpose of analysis the data will be de-identified and exported from Redcap into IBM SPSS Statistics for Windows (IBM Corporation, Armonk, NY, USA). Summary estimate and confidence

intervals will be calculated. In order to estimate the time from venous reflux documentation to fVLU, Kaplan Meier survival curves will be constructed. Cox proportional hazard regression models will be constructed to investigate possible risk factors.

Discussion

The aim of this study is to develop a cohort of patients with proven venous reflux that can be followed prospectively until the development of a venous leg ulcer. In doing so, we hope to shed some light on who, of the millions of people with CVI, is at greatest risk of developing a fVLU. Previous studies have looked at recurrence rates and associated risk factors regarding venous ulcers, but data regarding fVLU is quite limited. In addition, VLU incidence data collected from the cohort will be informative, as the only incidence data available has been inferred from retrospective analyses. The VEINS Cohort study seeks to determine, in a prospective fashion, the roles of traditional CVI risk factors and novel risk or protective factors in the development of fVLU. Where associations are detected, further studies will be pursued that seek to elucidate the nature of the association. Furthermore, in identifying particular risk factors and/or protective factors, we hope to develop a predictive model with risk scores for the likelihood of fVLU development within 3 and 5 years of clinically significant CVI. Of note, this study does not address time in relation to initial development of CVI, but rather time from documentation of CVI on venous duplex ultrasound. Though lead time bias could impact our analyses, lower extremity ultrasounds looking for reflux are typically only performed when CVI

becomes clinically significant, which is usually concurrent with the first time a patient sees a doctor for leg problems.

Implementing early interventions that delay or prevent the development of a chronic and morbid condition is the guiding principle behind these efforts. In doing so, the whole of society benefits both economically and socially from a happier and healthier population.

Potential Benefit to subjects:

While there is no direct benefit to subjects, being asked about their health status by a member of the research team every three months may raise the subjects' awareness of their health. Additionally, if a patient develops an ulcer while in the cohort, he/she will be referred to a wound clinic for appropriate management and wound care.

Ethics and Dissemination:

Ethical aspects

The Primary Investigator has extensive training and experience in clinical research and relevant bioethics. The research staff will include a team of primary researchers that have extensive qualifications and expertise to lead the study. All study staff are trained and routinely re-educated about the ethical conduct of human subject research. There are no anticipated physical, social, legal or economic risks associated with the study. There is minimal risk of breach of confidentiality. No vulnerable populations are specifically targeted in this study. Pregnant women will not be excluded.

Data protection

All subject-specific data will be kept confidential in a password-protected University desktop that can only be accessed by investigators. Study offices are kept locked and are protected by around-the-clock University of Miami security services. All records containing personal health information will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. De-identified collected data may be used for future analysis and publication.

Dissemination

We hope to present the results of this study to the scientific community at conferences and in peer-reviewed journals.

Table 1: Risk factors for VLU (Vivas *et al., 2016)*(1)

Age older than 55 years
Family history of CVI
Higher body mass index
History of pulmonary embolism
History of superficial/deep venous thrombosis
Lower extremities skeletal or joint disease
Number of pregnancies
Parental history of ankle ulcers
Physical inactivity
Ulcer history
Severe lipodermatosclerosis
Venous reflux in deep veins

VLU = venous leg ulcer

CVI = chronic venous insufficiency

Table 2: Variables of interest with corresponding data source

Venous duplex ultrasound report:	Phone survey:	Patient chart:
Study date	Race	Sex
Study indication	Ethnicity	Height
Reflux location(s)	History of VLU (including ulcer start date)	Weight
Reflux time(s)	Limitation of ankle movement	Venous dermatitis
Presence of DVT or superficial vein thrombosis	Mobility (i.e. use of a wheelchair or walker)	Lipodermatosclerosis
	History of DVT or PE	Atrophie blanche
	History of varicose veins	Past medical and surgical history
	History of leg swelling	Ulcer photograph
	Chronic itch of lower extremities	
	Chronic rash of lower extremities	
	Lower extremity vein procedures	
	Lower extremity artery procedures	
	Use of compression on lower extremities	
	Elevation of legs when sleeping	
	Number of pregnancies	
	Other past medical and surgical history	
	Medications	
	Smoking history	
	Exercise	
	Family history of leg ulcers, swelling, or varicose veins	

VLU = venous leg ulcer

DVT = deep vein thrombosis
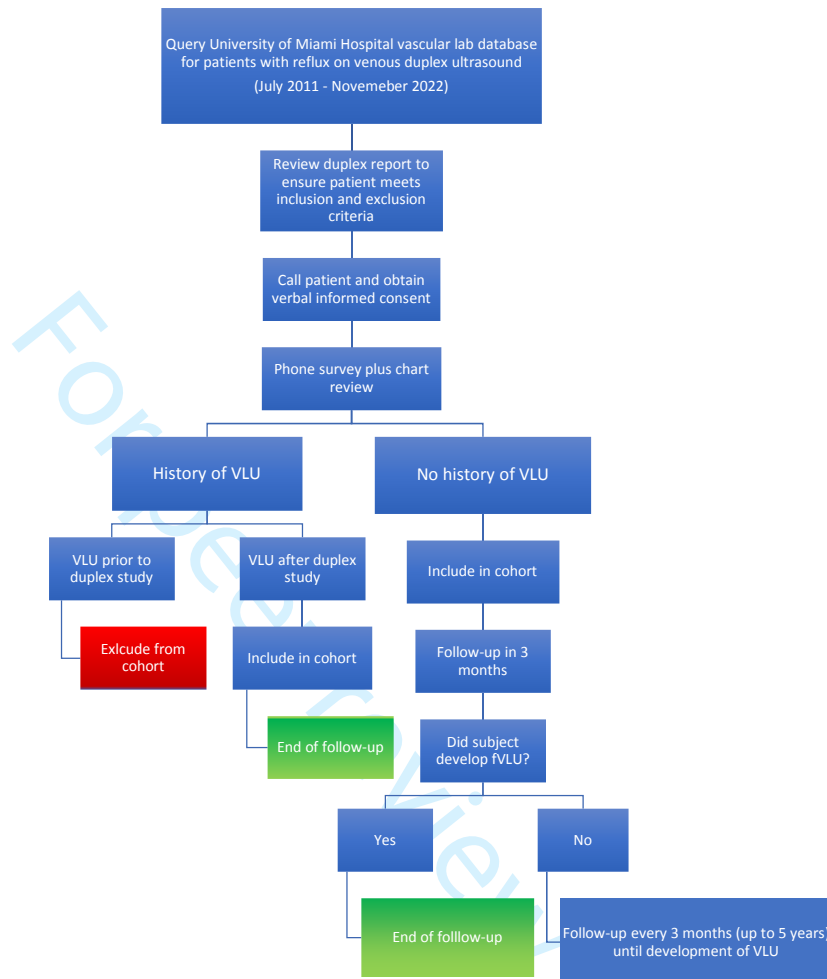
PE = pulmonary embolism

Figure 1: Flowchart outlining the methodology for building the VEINS cohort and following subjects prospectively once they are enrolled

References:

1.   Vivas A, Lev-Tov H, Kirsner RS. Venous Leg Ulcers. Ann Intern Med. 2016;165(3):ITC17-ITC32.

2.   Alavi A, Sibbald RG, Phillips TJ, Miller OF, Margolis DJ, Marston W, et al. What's new: Management of venous leg ulcers: Approach to venous leg ulcers. J Am Acad Dermatol. 2016;74(4):627-40; quiz 41-2.

3.   Singer AJ, Tassiopoulos A, Kirsner RS. Evaluation and Management of Lower-Extremity Ulcers. N Engl J Med. 2017;377(16):1559-67.

4.   Rabe E, Guex JJ, Puskas A, Scuderi A, Fernandez Quesada F, Coordinators V. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. Int Angiol. 2012;31(2):105-15.

5.   Liu YC, Margolis DJ, Isseroff RR. Does inflammation have a role in the pathogenesis of venous ulcers? A critical review of the evidence. J Invest Dermatol. 2011;131(4):818-27.

6.   Van de Scheur M, Falanga V. Pericapillary fibrin cuffs in venous disease. A reappraisal. Dermatol Surg. 1997;23(10):955-9.

7.   Falanga V, Kirsner R, Katz MH, Gould E, Eaglstein WH, McFalls S. Pericapillary fibrin cuffs in venous ulceration. Persistence with treatment and during ulcer healing. J Dermatol Surg Oncol. 1992;18(5):409-14.

8.   Green J, Jester R, McKinley R, Pooler A. The impact of chronic venous leg ulcers: a systematic review. J Wound Care. 2014;23(12):601-12.

9.   Ma H, O'Donnell TF, Rosen NA, Iafrati MD. The real cost of treating venous ulcers in a contemporary vascular practice. J Vasc Surg Venous Lymphat Disord. 2014;2(4):355-61.

10.   Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons N. Burden of venous leg ulcers in the United States. J Med Econ. 2014;17(5):347-56.

11.   Kurz X, Kahn SR, Abenhaim L, Clement D, Norgren L, Baccaglini U, et al. Chronic venous disorders of the leg: epidemiology, outcomes, diagnosis and management. Summary of an evidence-based report of the VEINES task force. Venous Insufficiency Epidemiologic and Economic Studies. Int Angiol. 1999;18(2):83-102.

12.   Neumann HA, Cornu-Thénard A, Jünger M, Mosti G, Munte K, Partsch H, et al. Evidence-based (S3) guidelines for diagnostics and treatment of venous leg ulcers. J Eur Acad Dermatol Venereol. 2016.

13.   Marklund B, Sülau T, Lindholm C. Prevalence of non-healed and healed chronic leg ulcers in an elderly rural population. Scand J Prim Health Care. 2000;18(1):58-60.

14.   Maklebust JA, Margolis DJ. Venous leg ulcer risk factors: who will study the problem? Adv Wound Care. 1997;10(2):6, 8.

15.   Burrows C, Miller R, Townsend D, Bellefontaine R, Mackean G, Orsted HL, et al. Best practice recommendations for the prevention and treatment of venous leg ulcers: update 2006. Adv Skin Wound Care. 2007;20(11):611-21; quiz 22-3.

16.   Robson MC, Cooper DM, Aslam R, Gould LJ, Harding KG, Margolis DJ, et al. Guidelines for the prevention of venous ulcers. Wound Repair Regen. 2008;16(2):147-50.

17.   Margolis DJ, Knauss J, Bilker W. Medical conditions associated with venous leg ulcers. Br J Dermatol. 2004;150(2):267-73.

18.   Margolis DJ, Hoffstad O, Isseroff RR. Association between the use of beta-adrenergic receptor agents and the development of venous leg ulcers. Arch Dermatol. 2007;143(10):1275-80.

19.   Bérard A, Kahn SR, Abenhaim L. Is hormone replacement therapy protective for venous ulcer of the lower limbs? Pharmacoepidemiol Drug Saf. 2001;10(3):245-51.

20.   Abbade LP, Lastória S, Rollo HeA. Venous ulcer: clinical characteristics and risk factors. Int J Dermatol. 2011;50(4):405-11.

21.   Robertson L, Lee AJ, Gallagher K, Carmichael SJ, Evans CJ, McKinstry BH, et al. Risk factors for chronic ulceration in patients with varicose veins: a case control study. J Vasc Surg. 2009;49(6):1490-8.

22.   Vlajinac H, Marinkovic J, Maksimovic M, Radak D. Factors related to venous ulceration: a cross-sectional study. Angiology. 2014;65(9):824-30.

23.   Evans CJ, Fowkes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. J Epidemiol Community Health. 1999;53(3):149-53.

24.   Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.

25.   Blumenberg C, Barros AJ. Electronic data collection in epidemiological research. The use of REDCap in the Pelotas birth cohorts. Appl Clin Inform. 2016;7(3):672-81.

26.   Yim E, Van Driessche F, Baquerizo Nole KL, Kirsner RS. Patient self-assessment of chronic wounds. Wound Repair Regen. 2014;22(5):683-4.

BMJ Open

Protocol for a longitudinal cohort study: Determination of risk factors for the development of first venous leg ulcer in people with chronic venous insufficiency, the VEINS (Venous Insufficiency in South Florida) Cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023313.R1
Article Type:	Protocol
Date Submitted by the Author:	03-Aug-2018
Complete List of Authors:	Mervis, Joshua; University of Miami School of Medicine, Dermatology and Cutaneous Surgery Kirsner, Robert; University of Miami School of Medicine, Dermatology and Cutaneous Surgery Lev-Tov, Hadar; University of Miami School of Medicine, Dermatology and Cutaneous Surgery
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Dermatology, General practice / Family practice, Surgery, Cardiovascular medicine
Keywords:	Chronic venous insufficiency, Venous leg ulcer, Longitudinal cohort study, Primary prevention, venous reflux

SCHOLARONE™
Manuscripts

Protocol for a longitudinal cohort study: Determination of risk factors for the development of first venous leg ulcer in people with chronic venous insufficiency, the VEINS (Venous Insufficiency in South Florida) Cohort

Joshua Mervis[1], B.A.; Robert S. Kirsner[1], M.D.; Ph.D.; Hadar Lev-Tov[1], M.D.

[1]Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, Florida

*__Address for correspondence:__

Hadar Lev-Tov, M.D.
Department of Dermatology & Cutaneous Surgery
University of Miami Miller School of Medicine
1600 NW 10th Avenue, Room 2023A
Miami, FL, 33136
U.S.A.
Phone: 305-243-6734
Email: hlevtov@med.miami.edu

Word Count: 2,646

Reference Count: 27

Figure Count: 1

Table Count: 2

Contributorship Statement: All authors, including Joshua S. Mervis, Robert S. Kirsner, and Hadar Lev-Tov, made substantial contributions to the conception and design of this

protocol. All authors have critically read this manuscript and have made their revisions, and they have now all approved this final version for submission. All authors agree to be accountable for the future integrity of this study.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract:

Introduction: Chronic venous insufficiency (CVI) affects up to one third of the adult population yet venous leg ulcers (VLU), a significant complication of CVI, only affect 1-2% of adults in the United States. Why some develop VLU and others do not is unclear. VLU have a significant impact on quality of life and are extremely costly and difficult to treat. Moreover, VLU prevalence is increasing, doubling in the last 20 years. In order to characterize the differences between people with CVI and those who ultimately develop VLU, we aim to set up the unique Venous Insufficiency in South Florida (VEINS) cohort.

Methods and analysis: Subjects will be recruited from the University of Miami Hospital and Clinic's vascular lab database, which began in July 2011. Any adult age 18-95 who has had venous reflux detected on duplex ultrasound of the lower extremities is included. Approximately 2,500 patients are already in the database that meet these criteria, with an estimated 2,500 additional potential subjects to be recruited from the vascular lab database over the next five years. Subjects with history of VLU prior to duplex study date will be excluded. Data will be collected via review of the Doppler study report, patient phone interview, and review of the electronic medical record. Subjects will be contacted for follow-up every 3 months for at least 5 years until the study endpoint, development of first VLU (fVLU), is reached. In order to estimate the time from reflux documentation to fVLU, Kaplan Meier survival curves will be constructed. Cox proportional hazard regression models will be constructed to investigate possible risk factors.

Ethics and dissemination: This study is approved by the University of Miami's Institutional Review Board (IRB). We hope to present the results of this study to the scientific community at conferences and in peer-reviewed journals.

Keywords: Venous leg ulcer, Chronic venous insufficiency, primary prevention, cohort study

Strengths and Limitations:

- To our knowledge, this study is the first that seeks to prospectively track development of the fVLU among a population of subjects with CVI.

- The VEINS cohort will describe the natural history of CVI leading to fVLU, reveal specific risk factors for the development of fVLU, and allow for the development of 3- and 5-year predictive models for fVLU occurrence.

- The data obtained from this study will support the development of VLU prevention strategies.

- This study does not address time in relation to initial development of CVI, but rather time from documentation of CVI on venous duplex ultrasound, typically the point at which CVI becomes clinically significant.

Protocol for a longitudinal cohort study: Determination of risk factors for the development of first venous leg ulcer in people with chronic venous insufficiency, the VEINS (Venous Insufficiency in South Florida) Cohort

Introduction

Background:

Chronic ulcers of the lower extremities affect 1-2% of adults in the United States (1-3). Of these ulcers, around 70% are due to venous disease alone, while 20% are due to arterial or mixed arteriovenous disease (2). Venous leg ulcers (VLU) are wounds that typically occur on the lower third of the leg between the ankle and knee, often referred to as the "gaiter area," in the setting of chronic venous insufficiency (CVI). In the United States, roughly a third of the adult population is likely to have CVI, while worldwide prevalence estimates are up to 60% (4). CVI is characterized by sustained ambulatory venous pressure (aka venous hypertension) and by reflux on Doppler ultrasound. Reflux is typically defined as retrograde blood flow in the lower extremities greater than 0.5 seconds after provocation (5). Typical causes of CVI include valvular defects, which may be acquired or genetic, ineffective calf muscle pump action, and obstruction from deep vein thrombosis (1, 2). The pathophysiology of VLU remains unclear, though various observation-based hypotheses implicating pericapillary fibrin cuffing, endovascular trapping of oxygen and nutrients, inflammatory cell infiltrates, cytokine trapping, and metalloproteinase dysregulation have all been areas of extensive research (6-8).

VLU often have a very significant impact on a patient's quality of life (9). Compared with matched controls, patients with VLU have more comorbid conditions, miss more days of work, and use more medical resources (10, 11). While numerous advancements in treatment, such as cellular and acellular skin equivalents and biomaterials, have been made in recent years (1), VLU prevalence seems to be increasing. The estimated prevalence of VLU has doubled in the last 20 years from 0.3% to 0.6% in adults under 65 and is up to 2.2% in adults over 65 (10, 12). European epidemiologic data has shown similar prevalence rates among these age groups, while revealing that VLU prevalence is even higher at 4-5% in individuals older than 80 years (13) and may exceed 12% among certain elderly populations. (14)

Moreover, the costs associated with VLU have been increasing and represent a great burden for both the patient and public health system. Over the last 30 years, the estimated cost of treating a single, chronic VLU has more than tripled to $34,000 today (10, 12). Likewise, the annual cost of VLU treatment in the United States has risen from around $3 billion in 1987 to $15 billion in 2011 ((11).

Rationale:

With an aging population, it is likely that VLU prevalence will continue to rise, with more ulcers occurring in older, sicker patients who are costlier to treat. Despite the significant morbidity, high costs, and continued difficulty in healing of VLU, little attention has been given to primary prevention. Thus, a paradigm shift, away from wholesale investment in advanced interventions and toward prevention, is warranted. The idea that a greater emphasis on VLU prevention is needed is not new, going back to at least 1997 (15). Nonetheless, no studies to

date have focused on prevention of the first VLU (fVLU). Without this data, society and

summary guidelines on VLU have not been able to make recommendations regarding primary

prevention (1, 2, 16, 17).

Given that the pathophysiology of VLUs is not well-understood, risk factor analysis is a

sensible strategy for studying prevention. With the goals of developing a predictive model for

ulceration and overall prevention strategy in mind, this study aims to identify risk factors

associated with development of the fVLU. While certain risk factors have been described (Table

1), they are based primarily on either retrospective analyses that compared people with any

VLU (i.e. first or recurrent) to the general population or on expert opinion.

Furthermore, associations between VLU occurrence and certain medical conditions (18),

medications (19, 20), and other parameters (21-23) have been made, but the directionality of

the association is not clear. Although these data are informative, they may not be clinically

useful. A need exists to distinguish risk factors for CVI and for fVLU, as only a small minority of

patients with CVI proceed to develop a fVLU (24). Particular risk factors specific for the fVLU are

not known, and to our knowledge no study has prospectively tracked development of the fVLU.

Therefore, the primary aim of this research is to answer a simple yet extremely complex

clinical question: in a patient presenting with signs and symptoms of CVI, what are the risk

factors that will help predict development of a fVLU? Once these potential risk factors have

been elucidated, appropriate interventions can then be pursued.

Primary Objective

1. Characterize risk factors associated with developing fVLU in people with CVI.

Secondary Objectives

2. Develop 3- and 5-year predictive models for risk of developing fVLU in patients with

   signs and symptoms of CVI.

3. Estimate the incidence of fVLU in people with CVI.

Methods and Analysis:

Geographical Context

Subjects will represent a diverse group from all over southeastern Florida primarily, with

the vast majority coming from Miami-Dade, Broward, and Palm Beach Counties in the United

States.

Study population

The VEINS Cohort will include both men and women ages 18-95. Any adult who

has had reflux detected on venous duplex ultrasound of the lower extremities is

potentially eligible. Patients who have undergone venous duplex studies for any

indication will be considered. Exclusion criteria include age under 18, inability to provide

consent over the phone, and history of venous ulcer prior to duplex study date.

Recruitment of Participants

Subjects will be recruited from a database of the University of Miami Hospital and Clinic's vascular laboratory. The database, which goes back to July 2011, will be queried for all patients who were found to have reflux of greater than 0.5 seconds on venous duplex ultrasound of the lower extremities. After reflux has been noted from the duplex study report, the subject's chart will be reviewed in the Electronic Medical Record (EMR) to ascertain basic contact information. For this part of the study, a privacy waiver for recruitment purposes has been approved by the local institutional review board (IRB). The investigators will then call potential subjects by phone. The subjects will provide a verbal phone consent for a phone survey and further chart review of potential risk factors. During the verbal informed consent, all aspects of the study will be reviewed, including: why subjects were selected, researcher goals, procedures, relevant risks, benefits, and subjects' rights. It is anticipated that a large portion of the study population is Spanish speaking. The verbal informed consent and survey have both been translated to Spanish and will be administered by Spanish speaking research staff, with the help of an interpreter as needed. Once consent is obtained and inclusion criteria confirmed, subjects will be enrolled into the cohort.

Sample size

There are approximately 2,500 lower extremity venous duplex ultrasound reports in the database that detected reflux going back to its inception in July 2011. In recent years, approximately 500 duplex studies that find reflux have been performed annually. Thus, over the next 5 years, we expect approximately 2,500 additional subjects will be potentially eligible to

enter the cohort. Given the paucity of data available on the incidence of fVLU, we will attempt

to recruit as many subjects as possible.

Study design – Overview

This protocol is for a longitudinal cohort study with retrospective and prospective

components. The methodology for building the cohort and following subjects is outlined in

Figure 1. The aim throughout is to identify subjects with venous reflux documented on

ultrasound prior to the development of fVLU. Any subject who reports a history of an ulcer

prior to the date of reflux study will be excluded from the cohort. The retrospective part of the

study will cover all patients currently in the database. If a subject went on to develop a fVLU

subsequent to the time of duplex study (i.e. after reflux was documented but before first

contact by the investigators), he/she will not be followed in any prospective manner. Instead,

only an entry survey will be administered and the subject's participation will end (see "End

Point and Follow-up" below). The prospective part of this study will include any subject who

met inclusion criteria but has not yet developed a VLU. Regardless of when subjects enter the

cohort, they will be followed prospectively for five years or until the occurrence of an ulcer,

whichever occurs first. Any subject who begins in the retrospective cohort can continue into the

prospective cohort so long as the fVLU has not developed. New subjects will be continuously

recruited as new patients come through the vascular lab for venous studies. We plan to recruit

new subjects for at least five years, though we hope to have the option of extending this

enrollment period and overall study duration depending on availability of resources.

End Point and Follow-up

The endpoint of this study is development of fVLU, after which subjects will exit the cohort. If a subject has no history of fVLU, he/she will be contacted by phone for a follow-up survey every 3 months until the development of fVLU. At this time, the intention is that subjects will be followed for at least 5 years.

Data collection and management

In all cases, data will be collected via three sources: venous duplex ultrasound report, phone survey, and patient chart in the EMR. Venous duplex ultrasound reports will be accessed from a secure electronic database housed in the University of Miami Hospital and Clinic's vascular laboratory. For the phone survey, a script with exact wording for all questions and instructions has been created. Data on specific variables of interest will be ascertained from each source as outlined in Table 2. A comprehensive initial assessment form and a follow-up form have been designed. These forms are quite similar, except that the follow-up form omits questions on unchanging historical and demographic data.

All data will be entered and stored electronically in REDCap (Research Electronic Data Capture), a secure, web-based application that facilitates creation and management of data collection instruments, monitoring of data quality, and statistical analysis of data (25). This software has commonly been used for epidemiological research, including similar cohort studies (26). All investigators will be trained in data entry by the REDCap study administrator and must demonstrate proficiency with mock patients and data entry before being granted access to data collection forms.

Evaluation of study endpoint – photo of wound

If a subject reports development of fVLU, investigators will seek to obtain a photo in the patient chart or request that the subject submits a picture of the wound via secure email. We have developed a protocol for evaluating images received, which involves independent evaluation by two investigators. They will first confirm presence of a wound, then determine if this can be considered a VLU: yes, no, or indeterminate. In cases of disagreement, the case will be presented to a third wound expert (RSK) for final determination. Subjects will then be encouraged to see us in clinic. While a photograph of the wound is an optional step in the study protocol, it can help validate that the wound is a VLU based on location and appearance. In cases where visual evidence is not available, ulcer validation will be supported by key questions regarding wound characteristics, such as location and duration. Moreover, there is data supporting the ability of patients to correctly self-assess the status of their chronic wounds with up to 97% accuracy when compared to expert evaluation (27).

Pilot Study

A pilot study of 70 potential subjects was carried out. The first 10 venous duplex studies to report reflux from each year of the database's existence (2011-2017) were used. The purpose of this pilot study was to give investigators the chance to determine how well the phone survey and data collection forms performed with a variety of real subjects, and to discuss any changes that should be made. Only minor technical changes in data coding were

made. Of the 70 patients that were called, 22 were reached over the phone, 20 of whom enrolled in the study.

Statistical analysis of data

For purpose of analysis the data will be de-identified and exported from Redcap into IBM SPSS Statistics for Windows (IBM Corporation, Armonk, NY, USA). Summary estimate and confidence intervals will be calculated. In order to estimate the time from venous reflux documentation to fVLU, Kaplan Meier survival curves will be constructed. Cox proportional hazard regression models will be constructed to investigate possible risk factors.

Patient and public involvement:

Patients and the general public were not involved in the development of the research question, outcome measures, or protocol design.

Discussion

The aim of this study is to develop a cohort of patients with proven venous reflux that can be followed prospectively until the development of a venous leg ulcer. In doing so, we hope to shed some light on who, of the millions of people with CVI, is at greatest risk of developing a fVLU. Previous studies have looked at recurrence rates and associated risk factors regarding venous ulcers, but data regarding fVLU is quite limited. In addition, VLU incidence data collected from the cohort will be informative, as the only incidence data available has been inferred from retrospective analyses. The VEINS Cohort study seeks to determine, in a

prospective fashion, the roles of traditional CVI risk factors and novel risk or protective factors in the development of fVLU. Where associations are detected, further studies will be pursued that seek to elucidate the nature of the association. Furthermore, in identifying particular risk factors and/or protective factors, we hope to develop a predictive model with risk scores for the likelihood of fVLU development within 3 and 5 years of clinically significant CVI. Of note, this study does not address time in relation to initial development of CVI, but rather time from documentation of CVI on venous duplex ultrasound. Though lead time bias could impact our analyses, lower extremity ultrasounds looking for reflux are typically only performed when CVI becomes clinically significant, which is usually concurrent with the first time a patient sees a doctor for leg problems.

Implementing early interventions that delay or prevent the development of a chronic and morbid condition is the guiding principle behind these efforts. In doing so, the whole of society benefits both economically and socially from a happier and healthier population.

Potential Benefit to subjects:

While there is no direct benefit to subjects, being asked about their health status by a member of the research team every three months may raise the subjects' awareness of their health. Additionally, if a patient develops an ulcer while in the cohort, he/she will be referred to a wound clinic for appropriate management and wound care.

Ethics and Dissemination:

Ethical aspects

All aspects of this study, including verbal informed consent, data collection, and photo acquisition, have been approved by the University of Miami Institutional Review Board. The Primary Investigator has extensive training and experience in clinical research and relevant bioethics. The research staff will include a team of primary researchers that have extensive qualifications and expertise to lead the study. All study staff are trained and routinely re-educated about the ethical conduct of human subject research. There are no anticipated physical, social, legal or economic risks associated with the study. There is minimal risk of breach of confidentiality. No vulnerable populations are specifically targeted in this study. Pregnant women will not be excluded.

Data protection

All subject-specific data will be kept confidential in a password-protected University desktop that can only be accessed by investigators. Study offices are kept locked and are protected by around-the-clock University of Miami security services. All records containing personal health information will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. De-identified collected data may be used for future analysis and publication.

Dissemination

We hope to present the results of this study to the scientific community at conferences and in peer-reviewed journals.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Contributorship Statement: All authors, including Joshua S. Mervis, Robert S. Kirsner, and

Hadar Lev-Tov, made substantial contributions to the conception and design of this protocol. All

authors have critically read this manuscript and have made their revisions, and they have now

all approved this final version for submission. All authors agree to be accountable for the future

integrity of this study.

Table 1: Risk factors for VLU (Vivas *et al., 2016)*(1)

Age older than 55 years
Family history of CVI
Higher body mass index
History of pulmonary embolism
History of superficial/deep venous thrombosis
Lower extremities skeletal or joint disease
Higher number of pregnancies
Parental history of ankle ulcers
Physical inactivity
Ulcer history
Severe lipodermatosclerosis
Venous reflux in deep veins

VLU = venous leg ulcer

CVI = chronic venous insufficiency

Table 2: Variables of interest with corresponding data source

Venous duplex ultrasound report:	Phone survey:	Patient chart:
Study date	Race	Sex
Study indication	Ethnicity	Height
Reflux location(s)	History of VLU (including ulcer start date)	Weight
Reflux time(s)	Limitation of ankle movement	Venous dermatitis
Presence of DVT or superficial vein thrombosis	Mobility (i.e. use of a wheelchair or walker)	Lipodermatosclerosis
	History of DVT or PE	Atrophie blanche
	History of varicose veins	Past medical and surgical history
	History of leg swelling	Ulcer photograph
	Chronic itch of lower extremities	
	Chronic rash of lower extremities	
	Lower extremity vein procedures	
	Lower extremity artery procedures	
	Use of compression on lower extremities	
	Elevation of legs when sleeping	
	Number of pregnancies	
	Other past medical and surgical history	
	Medications	
	Smoking history	
	Exercise	
	Family history of leg ulcers, swelling, or varicose veins	

VLU = venous leg ulcer

DVT = deep vein thrombosis

PE = pulmonary embolism

Figure 1: Flowchart outlining the methodology for building the VEINS cohort and following subjects prospectively once they are enrolled

References:

1.   Vivas A, Lev-Tov H, Kirsner RS. Venous Leg Ulcers. Ann Intern Med. 2016;165(3):ITC17-ITC32.

2.   Alavi A, Sibbald RG, Phillips TJ, Miller OF, Margolis DJ, Marston W, et al. What's new: Management of venous leg ulcers: Approach to venous leg ulcers. J Am Acad Dermatol. 2016;74(4):627-40; quiz 41-2.

3.   Singer AJ, Tassiopoulos A, Kirsner RS. Evaluation and Management of Lower-Extremity Ulcers. N Engl J Med. 2017;377(16):1559-67.

4.   Rabe E, Guex JJ, Puskas A, Scuderi A, Fernandez Quesada F, Coordinators V. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. Int Angiol. 2012;31(2):105-15.

5.   Lurie F, Comerota A, Eklof B, Kistner RL, Labropoulos N, Lohr J, et al. Multicenter assessment of venous reflux by duplex ultrasound. J Vasc Surg. 2012;55(2):437-45.

6.   Liu YC, Margolis DJ, Isseroff RR. Does inflammation have a role in the pathogenesis of venous ulcers? A critical review of the evidence. J Invest Dermatol. 2011;131(4):818-27.

7.   Van de Scheur M, Falanga V. Pericapillary fibrin cuffs in venous disease. A reappraisal. Dermatol Surg. 1997;23(10):955-9.

8.   Falanga V, Kirsner R, Katz MH, Gould E, Eaglstein WH, McFalls S. Pericapillary fibrin cuffs in venous ulceration. Persistence with treatment and during ulcer healing. J Dermatol Surg Oncol. 1992;18(5):409-14.

9.   Green J, Jester R, McKinley R, Pooler A. The impact of chronic venous leg ulcers: a systematic review. J Wound Care. 2014;23(12):601-12.

10.   Ma H, O'Donnell TF, Rosen NA, Iafrati MD. The real cost of treating venous ulcers in a contemporary vascular practice. J Vasc Surg Venous Lymphat Disord. 2014;2(4):355-61.

11.   Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons N. Burden of venous leg ulcers in the United States. J Med Econ. 2014;17(5):347-56.

12.   Kurz X, Kahn SR, Abenhaim L, Clement D, Norgren L, Baccaglini U, et al. Chronic venous disorders of the leg: epidemiology, outcomes, diagnosis and management. Summary of an evidence-based report of the VEINES task force. Venous Insufficiency Epidemiologic and Economic Studies. Int Angiol. 1999;18(2):83-102.

13.   Neumann HA, Cornu-Thénard A, Jünger M, Mosti G, Munte K, Partsch H, et al. Evidence-based (S3) guidelines for diagnostics and treatment of venous leg ulcers. J Eur Acad Dermatol Venereol. 2016.

14.   Marklund B, Sülau T, Lindholm C. Prevalence of non-healed and healed chronic leg ulcers in an elderly rural population. Scand J Prim Health Care. 2000;18(1):58-60.

15.   Maklebust JA, Margolis DJ. Venous leg ulcer risk factors: who will study the problem? Adv Wound Care. 1997;10(2):6, 8.

16.   Burrows C, Miller R, Townsend D, Bellefontaine R, Mackean G, Orsted HL, et al. Best practice recommendations for the prevention and treatment of venous leg ulcers: update 2006. Adv Skin Wound Care. 2007;20(11):611-21; quiz 22-3.

17.   Robson MC, Cooper DM, Aslam R, Gould LJ, Harding KG, Margolis DJ, et al. Guidelines for the prevention of venous ulcers. Wound Repair Regen. 2008;16(2):147-50.

18. Margolis DJ, Knauss J, Bilker W. Medical conditions associated with venous leg ulcers. Br J Dermatol. 2004;150(2):267-73.

19. Margolis DJ, Hoffstad O, Isseroff RR. Association between the use of beta-adrenergic receptor agents and the development of venous leg ulcers. Arch Dermatol. 2007;143(10):1275-80.

20. Bérard A, Kahn SR, Abenhaim L. Is hormone replacement therapy protective for venous ulcer of the lower limbs? Pharmacoepidemiol Drug Saf. 2001;10(3):245-51.

21. Abbade LP, Lastória S, Rollo HeA. Venous ulcer: clinical characteristics and risk factors. Int J Dermatol. 2011;50(4):405-11.

22. Robertson L, Lee AJ, Gallagher K, Carmichael SJ, Evans CJ, McKinstry BH, et al. Risk factors for chronic ulceration in patients with varicose veins: a case control study. J Vasc Surg. 2009;49(6):1490-8.

23. Vlajinac H, Marinkovic J, Maksimovic M, Radak D. Factors related to venous ulceration: a cross-sectional study. Angiology. 2014;65(9):824-30.

24. Evans CJ, Fowkes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. J Epidemiol Community Health. 1999;53(3):149-53.

25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.

26. Blumenberg C, Barros AJ. Electronic data collection in epidemiological research. The use of REDCap in the Pelotas birth cohorts. Appl Clin Inform. 2016;7(3):672-81.

27. Yim E, Van Driessche F, Baquerizo Nole KL, Kirsner RS. Patient self-assessment of chronic wounds. Wound Repair Regen. 2014;22(5):683-4.

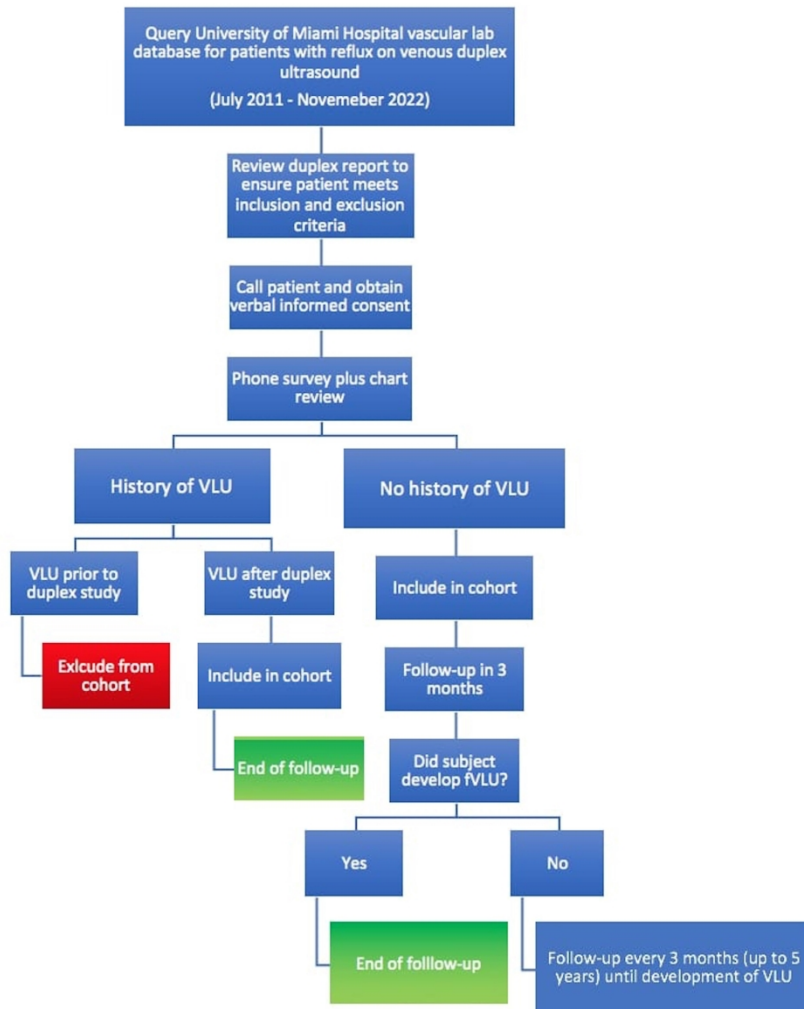Figure 1: Flowchart outlining the methodology for building the VEINS cohort and following subjects prospectively once they are enrolled

309x337mm (300 x 300 DPI)

BMJ Open

Protocol for a longitudinal cohort study: Determination of risk factors for the development of first venous leg ulcer in people with chronic venous insufficiency, the VEINS (Venous Insufficiency in South Florida) Cohort

SCHOLARONE™
Manuscripts

Protocol for a longitudinal cohort study: Determination of risk factors for the development of first venous leg ulcer in people with chronic venous insufficiency, the VEINS (Venous Insufficiency in South Florida) Cohort

Joshua Mervis[1], B.A.; Robert S. Kirsner[1], M.D.; Ph.D.; Hadar Lev-Tov[1], M.D.

[1]Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, Florida

*Address for correspondence:

Hadar Lev-Tov, M.D.
Department of Dermatology & Cutaneous Surgery
University of Miami Miller School of Medicine
1600 NW 10th Avenue, Room 2023A
Miami, FL, 33136
U.S.A.
Phone: 305-243-6734
Email: hlevtov@med.miami.edu

Word Count: 2,646

Reference Count: 27

Figure Count: 1

Table Count: 2

Conflict of Interest: The authors of this protocol have NO conflict of interest to declare.

Prior Presentation: The authors declare that this protocol has NOT been published

previously.

Contributorship Statement: All authors, including Joshua S. Mervis, Robert S. Kirsner,

and Hadar Lev-Tov, made substantial contributions to the conception and design of this

protocol. All authors have critically read this manuscript and have made their revisions, and they have now all approved this final version for submission. All authors agree to be accountable for the future integrity of this study.

Abstract:

Introduction: Chronic venous insufficiency (CVI) affects up to one third of the adult population yet venous leg ulcers (VLU), a significant complication of CVI, only affect 1-2% of adults in the United States. Why some develop VLU and others do not is unclear. VLU have a significant impact on quality of life and are extremely costly and difficult to treat. Moreover, VLU prevalence is increasing, doubling in the last 20 years. In order to characterize the differences between people with CVI and those who ultimately develop VLU, we aim to set up the unique Venous Insufficiency in South Florida (VEINS) cohort.

Methods and analysis: Subjects will be recruited from the University of Miami Hospital and Clinic's vascular lab database, which began in July 2011. Any adult age 18-95 who has had venous reflux detected on duplex ultrasound of the lower extremities is included. Approximately 2,500 patients are already in the database that meet these criteria, with an estimated 2,500 additional potential subjects to be recruited from the vascular lab database over the next five years. Subjects with history of VLU prior to duplex study date will be excluded. Data will be collected via review of the Doppler study report, patient phone interview, and review of the electronic medical record. Subjects will be contacted for follow-up every 3 months for at least 5 years until the study endpoint, development of first VLU (fVLU), is reached. In order to estimate the time from reflux documentation to fVLU, Kaplan Meier survival curves will be constructed. Cox proportional hazard regression models will be constructed to investigate possible risk factors.

Ethics and dissemination: This study is approved by the University of Miami's Institutional Review Board (IRB). We hope to present the results of this study to the scientific community at conferences and in peer-reviewed journals.

Keywords: Venous leg ulcer, Chronic venous insufficiency, primary prevention, cohort study

Strengths and Limitations:

- To our knowledge, this study is the first that seeks to prospectively track development of the fVLU among a population of subjects with CVI.

- The VEINS cohort will describe the natural history of CVI leading to fVLU, reveal specific risk factors for the development of fVLU, and allow for the development of 3- and 5-year predictive models for fVLU occurrence.

- The data obtained from this study will support the development of VLU prevention strategies.

- This study does not address time in relation to initial development of CVI, but rather time from documentation of CVI on venous duplex ultrasound, typically the point at which CVI becomes clinically significant.

Protocol for a longitudinal cohort study: Determination of risk factors for the development of first venous leg ulcer in people with chronic venous insufficiency, the VEINS (Venous Insufficiency in South Florida) Cohort

Introduction

Background:

Chronic ulcers of the lower extremities affect 1-2% of adults in the United States (1-3). Of these ulcers, around 70% are due to venous disease alone, while 20% are due to arterial or mixed arteriovenous disease (2). Venous leg ulcers (VLU) are wounds that typically occur on the lower third of the leg between the ankle and knee, often referred to as the "gaiter area," in the setting of chronic venous insufficiency (CVI). In the United States, roughly a third of the adult population is likely to have CVI, while worldwide prevalence estimates are up to 60% (4). CVI is characterized by sustained ambulatory venous pressure (aka venous hypertension) and by reflux on Doppler ultrasound. Reflux is typically defined as retrograde blood flow in the lower extremities greater than 0.5 seconds after provocation (5). Typical causes of CVI include valvular defects, which may be acquired or genetic, ineffective calf muscle pump action, and obstruction from deep vein thrombosis (1, 2). The pathophysiology of VLU remains unclear, though various observation-based hypotheses implicating pericapillary fibrin cuffing, endovascular trapping of oxygen and nutrients, inflammatory cell infiltrates, cytokine trapping, and metalloproteinase dysregulation have all been areas of extensive research (6-8).

VLU often have a very significant impact on a patient's quality of life (9). Compared with matched controls, patients with VLU have more comorbid conditions, miss more days of work, and use more medical resources (10, 11). While numerous advancements in treatment, such as cellular and acellular skin equivalents and biomaterials, have been made in recent years (1), VLU prevalence seems to be increasing. The estimated prevalence of VLU has doubled in the last 20 years from 0.3% to 0.6% in adults under 65 and is up to 2.2% in adults over 65 (10, 12). European epidemiologic data has shown similar prevalence rates among these age groups, while revealing that VLU prevalence is even higher at 4-5% in individuals older than 80 years (13) and may exceed 12% among certain elderly populations. (14)

Moreover, the costs associated with VLU have been increasing and represent a great burden for both the patient and public health system. Over the last 30 years, the estimated cost of treating a single, chronic VLU has more than tripled to $34,000 today (10, 12). Likewise, the annual cost of VLU treatment in the United States has risen from around $3 billion in 1987 to $15 billion in 2011 ((11).

Rationale:

With an aging population, it is likely that VLU prevalence will continue to rise, with more ulcers occurring in older, sicker patients who are costlier to treat. Despite the significant morbidity, high costs, and continued difficulty in healing of VLU, little attention has been given to primary prevention. Thus, a paradigm shift, away from wholesale investment in advanced interventions and toward prevention, is warranted. The idea that a greater emphasis on VLU prevention is needed is not new, going back to at least 1997 (15). Nonetheless, no studies to

date have focused on prevention of the first VLU (fVLU). Without this data, society and

summary guidelines on VLU have not been able to make recommendations regarding primary

prevention (1, 2, 16, 17).

Given that the pathophysiology of VLUs is not well-understood, risk factor analysis is a

sensible strategy for studying prevention. With the goals of developing a predictive model for

ulceration and overall prevention strategy in mind, this study aims to identify risk factors

associated with development of the fVLU. While certain risk factors have been described (1)

(Table 1), they are based primarily on either retrospective analyses that compared people with

any VLU (i.e. first or recurrent) to the general population or on expert opinion.

Furthermore, associations between VLU occurrence and certain medical conditions (18),

medications (19, 20), and other parameters (21-23) have been made, but the directionality of

the association is not clear. Although these data are informative, they may not be clinically

useful. A need exists to distinguish risk factors for CVI and for fVLU, as only a small minority of

patients with CVI proceed to develop a fVLU (24). Particular risk factors specific for the fVLU are

not known, and to our knowledge no study has prospectively tracked development of the fVLU.

Therefore, the primary aim of this research is to answer a simple yet extremely complex

clinical question: in a patient presenting with signs and symptoms of CVI, what are the risk

factors that will help predict development of a fVLU? Once these potential risk factors have

been elucidated, appropriate interventions can then be pursued.

Primary Objective

1. Characterize risk factors associated with developing fVLU in people with CVI.

Secondary Objectives

2. Develop 3- and 5-year predictive models for risk of developing fVLU in patients with signs and symptoms of CVI.

3. Estimate the incidence of fVLU in people with CVI.

Methods and Analysis:

Geographical Context

Subjects will represent a diverse group from all over southeastern Florida primarily, with the vast majority coming from Miami-Dade, Broward, and Palm Beach Counties in the United States.

Study population

The VEINS Cohort will include both men and women ages 18-95. Any adult who has had reflux detected on venous duplex ultrasound of the lower extremities is potentially eligible. Patients who have undergone venous duplex studies for any indication will be considered. Exclusion criteria include age under 18, inability to provide consent over the phone, and history of venous ulcer prior to duplex study date.

Recruitment of Participants

Subjects will be recruited from a database of the University of Miami Hospital

and Clinic's vascular laboratory. The database, which goes back to July 2011, will be

queried for all patients who were found to have reflux of greater than 0.5 seconds on

venous duplex ultrasound of the lower extremities. After reflux has been noted from the

duplex study report, the subject's chart will be reviewed in the Electronic Medical

Record (EMR) to ascertain basic contact information. For this part of the study, a privacy

waiver for recruitment purposes has been approved by the local institutional review

board (IRB). The investigators will then call potential subjects by phone. The subjects will

provide a verbal phone consent for a phone survey and further chart review of potential

risk factors. During the verbal informed consent, all aspects of the study will be

reviewed, including: why subjects were selected, researcher goals, procedures, relevant

risks, benefits, and subjects' rights. It is anticipated that a large portion of the study

population is Spanish speaking. The verbal informed consent and survey have both been

translated to Spanish and will be administered by Spanish speaking research staff, with

the help of an interpreter as needed. Once consent is obtained and inclusion criteria

confirmed, subjects will be enrolled into the cohort.

Sample size

There are approximately 2,500 lower extremity venous duplex ultrasound reports in the

database that detected reflux going back to its inception in July 2011. In recent years,

approximately 500 duplex studies that find reflux have been performed annually. Thus, over the

next 5 years, we expect approximately 2,500 additional subjects will be potentially eligible to

enter the cohort. Given the paucity of data available on the incidence of fVLU, we will attempt

to recruit as many subjects as possible.

Study design – Overview

This protocol is for a longitudinal cohort study with retrospective and prospective

components. The methodology for building the cohort and following subjects is outlined in

Figure 1. The aim throughout is to identify subjects with venous reflux documented on

ultrasound prior to the development of fVLU. Any subject who reports a history of an ulcer

prior to the date of reflux study will be excluded from the cohort. The retrospective part of the

study will cover all patients currently in the database. If a subject went on to develop a fVLU

subsequent to the time of duplex study (i.e. after reflux was documented but before first

contact by the investigators), he/she will not be followed in any prospective manner. Instead,

only an entry survey will be administered and the subject's participation will end (see "End

Point and Follow-up" below). The prospective part of this study will include any subject who

met inclusion criteria but has not yet developed a VLU. Regardless of when subjects enter the

cohort, they will be followed prospectively for five years or until the occurrence of an ulcer,

whichever occurs first. Any subject who begins in the retrospective cohort can continue into the

prospective cohort so long as the fVLU has not developed. New subjects will be continuously

recruited as new patients come through the vascular lab for venous studies. We plan to recruit

new subjects for at least five years, though we hope to have the option of extending this

enrollment period and overall study duration depending on availability of resources.

End Point and Follow-up

The endpoint of this study is development of fVLU, after which subjects will exit the cohort. If a subject has no history of fVLU, he/she will be contacted by phone for a follow-up survey every 3 months until the development of fVLU. At this time, the intention is that subjects will be followed for at least 5 years.

Data collection and management

In all cases, data will be collected via three sources: venous duplex ultrasound report, phone survey, and patient chart in the EMR. Venous duplex ultrasound reports will be accessed from a secure electronic database housed in the University of Miami Hospital and Clinic's vascular laboratory. For the phone survey, a script with exact wording for all questions and instructions has been created. Data on specific variables of interest will be ascertained from each source as outlined in Table 2. A comprehensive initial assessment form and a follow-up form have been designed. These forms are quite similar, except that the follow-up form omits questions on unchanging historical and demographic data.

All data will be entered and stored electronically in REDCap (Research Electronic Data Capture), a secure, web-based application that facilitates creation and management of data collection instruments, monitoring of data quality, and statistical analysis of data (25). This software has commonly been used for epidemiological research, including similar cohort studies (26). All investigators will be trained in data entry by the REDCap study administrator and must demonstrate proficiency with mock patients and data entry before being granted access to data collection forms.

Evaluation of study endpoint – photo of wound

If a subject reports development of fVLU, investigators will seek to obtain a photo in the patient chart or request that the subject submits a picture of the wound via secure email. We have developed a protocol for evaluating images received, which involves independent evaluation by two investigators. They will first confirm presence of a wound, then determine if this can be considered a VLU: yes, no, or indeterminate. In cases of disagreement, the case will be presented to a third wound expert (RSK) for final determination. Subjects will then be encouraged to see us in clinic. While a photograph of the wound is an optional step in the study protocol, it can help validate that the wound is a VLU based on location and appearance. In cases where visual evidence is not available, ulcer validation will be supported by key questions regarding wound characteristics, such as location and duration. Moreover, there is data supporting the ability of patients to correctly self-assess the status of their chronic wounds with up to 97% accuracy when compared to expert evaluation (27).

Pilot Study

A pilot study of 70 potential subjects was carried out. The first 10 venous duplex studies to report reflux from each year of the database's existence (2011-2017) were used. The purpose of this pilot study was to give investigators the chance to determine how well the phone survey and data collection forms performed with a variety of real subjects, and to discuss any changes that should be made. Only minor technical changes in data coding were

made. Of the 70 patients that were called, 22 were reached over the phone, 20 of whom

enrolled in the study.

Statistical analysis of data

For purpose of analysis the data will be de-identified and exported from Redcap into IBM SPSS

Statistics for Windows (IBM Corporation, Armonk, NY, USA). Summary estimate and confidence

intervals will be calculated. In order to estimate the time from venous reflux documentation to

fVLU, Kaplan Meier survival curves will be constructed. Cox proportional hazard regression

models will be constructed to investigate possible risk factors.

Patient and public involvement:

Patients and the general public were not involved in the development of the research question,

outcome measures, or protocol design.

Discussion

The aim of this study is to develop a cohort of patients with proven venous reflux that

can be followed prospectively until the development of a venous leg ulcer. In doing so, we hope

to shed some light on who, of the millions of people with CVI, is at greatest risk of developing a

fVLU. Previous studies have looked at recurrence rates and associated risk factors regarding

venous ulcers, but data regarding fVLU is quite limited. In addition, VLU incidence data

collected from the cohort will be informative, as the only incidence data available has been

inferred from retrospective analyses. The VEINS Cohort study seeks to determine, in a

prospective fashion, the roles of traditional CVI risk factors and novel risk or protective factors in the development of fVLU. Where associations are detected, further studies will be pursued that seek to elucidate the nature of the association. Furthermore, in identifying particular risk factors and/or protective factors, we hope to develop a predictive model with risk scores for the likelihood of fVLU development within 3 and 5 years of clinically significant CVI. Of note, this study does not address time in relation to initial development of CVI, but rather time from documentation of CVI on venous duplex ultrasound. Though lead time bias could impact our analyses, lower extremity ultrasounds looking for reflux are typically only performed when CVI becomes clinically significant, which is usually concurrent with the first time a patient sees a doctor for leg problems.

Implementing early interventions that delay or prevent the development of a chronic and morbid condition is the guiding principle behind these efforts. In doing so, the whole of society benefits both economically and socially from a happier and healthier population.

Potential Benefit to subjects:

While there is no direct benefit to subjects, being asked about their health status by a member of the research team every three months may raise the subjects' awareness of their health. Additionally, if a patient develops an ulcer while in the cohort, he/she will be referred to a wound clinic for appropriate management and wound care.

Ethics and Dissemination:

Ethical aspects

All aspects of this study, including verbal informed consent, data collection, and photo acquisition, have been approved by the University of Miami Institutional Review Board. The Primary Investigator has extensive training and experience in clinical research and relevant bioethics. The research staff will include a team of primary researchers that have extensive qualifications and expertise to lead the study. All study staff are trained and routinely re-educated about the ethical conduct of human subject research. There are no anticipated physical, social, legal or economic risks associated with the study. There is minimal risk of breach of confidentiality. No vulnerable populations are specifically targeted in this study. Pregnant women will not be excluded.

Data protection

All subject-specific data will be kept confidential in a password-protected University desktop that can only be accessed by investigators. Study offices are kept locked and are protected by around-the-clock University of Miami security services. All records containing personal health information will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. De-identified collected data may be used for future analysis and publication.

Dissemination

We hope to present the results of this study to the scientific community at conferences and in peer-reviewed journals.

Contributorship Statement: All authors, including Joshua S. Mervis, Robert S. Kirsner, and

Hadar Lev-Tov, made substantial contributions to the conception and design of this protocol. All

authors have critically read this manuscript and have made their revisions, and they have now

all approved this final version for submission. All authors agree to be accountable for the future

integrity of this study.

Table 1: Risk factors for VLU

Age older than 55 years
Family history of CVI
Higher body mass index
History of pulmonary embolism
History of superficial/deep venous thrombosis
Lower extremities skeletal or joint disease
Higher number of pregnancies
Parental history of ankle ulcers
Physical inactivity
Ulcer history
Severe lipodermatosclerosis
Venous reflux in deep veins

VLU = venous leg ulcer

CVI = chronic venous insufficiency

Table 2: Variables of interest with corresponding data source

Venous duplex ultrasound report:	*Phone survey:*	*Patient chart:*
Study date	Race	Sex
Study indication	Ethnicity	Height
Reflux location(s)	History of VLU (including ulcer start date)	Weight
Reflux time(s)	Limitation of ankle movement	Venous dermatitis
Presence of DVT or superficial vein thrombosis	Mobility (i.e. use of a wheelchair or walker)	Lipodermatosclerosis
	History of DVT or PE	Atrophie blanche
	History of varicose veins	Past medical and surgical history
	History of leg swelling	Ulcer photograph
	Chronic itch of lower extremities	
	Chronic rash of lower extremities	
	Lower extremity vein procedures	
	Lower extremity artery procedures	
	Use of compression on lower extremities	
	Elevation of legs when sleeping	
	Number of pregnancies	
	Other past medical and surgical history	
	Medications	
	Smoking history	
	Exercise	
	Family history of leg ulcers, swelling, or varicose veins	

VLU = venous leg ulcer

DVT = deep vein thrombosis

PE = pulmonary embolism

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1: Flowchart outlining the methodology for building the VEINS cohort and following subjects prospectively once they are enrolled

References:

1.   Vivas A, Lev-Tov H, Kirsner RS. Venous Leg Ulcers. Ann Intern Med. 2016;165(3):ITC17-ITC32.

2.   Alavi A, Sibbald RG, Phillips TJ, Miller OF, Margolis DJ, Marston W, et al. What's new: Management of venous leg ulcers: Approach to venous leg ulcers. J Am Acad Dermatol. 2016;74(4):627-40; quiz 41-2.

3.   Singer AJ, Tassiopoulos A, Kirsner RS. Evaluation and Management of Lower-Extremity Ulcers. N Engl J Med. 2017;377(16):1559-67.

4.   Rabe E, Guex JJ, Puskas A, Scuderi A, Fernandez Quesada F, Coordinators V. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. Int Angiol. 2012;31(2):105-15.

5.   Lurie F, Comerota A, Eklof B, Kistner RL, Labropoulos N, Lohr J, et al. Multicenter assessment of venous reflux by duplex ultrasound. J Vasc Surg. 2012;55(2):437-45.

6.   Liu YC, Margolis DJ, Isseroff RR. Does inflammation have a role in the pathogenesis of venous ulcers? A critical review of the evidence. J Invest Dermatol. 2011;131(4):818-27.

7.   Van de Scheur M, Falanga V. Pericapillary fibrin cuffs in venous disease. A reappraisal. Dermatol Surg. 1997;23(10):955-9.

8.   Falanga V, Kirsner R, Katz MH, Gould E, Eaglstein WH, McFalls S. Pericapillary fibrin cuffs in venous ulceration. Persistence with treatment and during ulcer healing. J Dermatol Surg Oncol. 1992;18(5):409-14.

9.   Green J, Jester R, McKinley R, Pooler A. The impact of chronic venous leg ulcers: a systematic review. J Wound Care. 2014;23(12):601-12.

10.   Ma H, O'Donnell TF, Rosen NA, Iafrati MD. The real cost of treating venous ulcers in a contemporary vascular practice. J Vasc Surg Venous Lymphat Disord. 2014;2(4):355-61.

11.   Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons N. Burden of venous leg ulcers in the United States. J Med Econ. 2014;17(5):347-56.

12.   Kurz X, Kahn SR, Abenhaim L, Clement D, Norgren L, Baccaglini U, et al. Chronic venous disorders of the leg: epidemiology, outcomes, diagnosis and management. Summary of an evidence-based report of the VEINES task force. Venous Insufficiency Epidemiologic and Economic Studies. Int Angiol. 1999;18(2):83-102.

13.   Neumann HA, Cornu-Thénard A, Jünger M, Mosti G, Munte K, Partsch H, et al. Evidence-based (S3) guidelines for diagnostics and treatment of venous leg ulcers. J Eur Acad Dermatol Venereol. 2016.

14.   Marklund B, Sülau T, Lindholm C. Prevalence of non-healed and healed chronic leg ulcers in an elderly rural population. Scand J Prim Health Care. 2000;18(1):58-60.

15.   Maklebust JA, Margolis DJ. Venous leg ulcer risk factors: who will study the problem? Adv Wound Care. 1997;10(2):6, 8.

16.   Burrows C, Miller R, Townsend D, Bellefontaine R, Mackean G, Orsted HL, et al. Best practice recommendations for the prevention and treatment of venous leg ulcers: update 2006. Adv Skin Wound Care. 2007;20(11):611-21; quiz 22-3.

17.   Robson MC, Cooper DM, Aslam R, Gould LJ, Harding KG, Margolis DJ, et al. Guidelines for the prevention of venous ulcers. Wound Repair Regen. 2008;16(2):147-50.

18. Margolis DJ, Knauss J, Bilker W. Medical conditions associated with venous leg ulcers. Br J Dermatol. 2004;150(2):267-73.

19. Margolis DJ, Hoffstad O, Isseroff RR. Association between the use of beta-adrenergic receptor agents and the development of venous leg ulcers. Arch Dermatol. 2007;143(10):1275-80.

20. Bérard A, Kahn SR, Abenhaim L. Is hormone replacement therapy protective for venous ulcer of the lower limbs? Pharmacoepidemiol Drug Saf. 2001;10(3):245-51.

21. Abbade LP, Lastória S, Rollo HeA. Venous ulcer: clinical characteristics and risk factors. Int J Dermatol. 2011;50(4):405-11.

22. Robertson L, Lee AJ, Gallagher K, Carmichael SJ, Evans CJ, McKinstry BH, et al. Risk factors for chronic ulceration in patients with varicose veins: a case control study. J Vasc Surg. 2009;49(6):1490-8.

23. Vlajinac H, Marinkovic J, Maksimovic M, Radak D. Factors related to venous ulceration: a cross-sectional study. Angiology. 2014;65(9):824-30.

24. Evans CJ, Fowkes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. J Epidemiol Community Health. 1999;53(3):149-53.

25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.

26. Blumenberg C, Barros AJ. Electronic data collection in epidemiological research. The use of REDCap in the Pelotas birth cohorts. Appl Clin Inform. 2016;7(3):672-81.

27. Yim E, Van Driessche F, Baquerizo Nole KL, Kirsner RS. Patient self-assessment of chronic wounds. Wound Repair Regen. 2014;22(5):683-4.
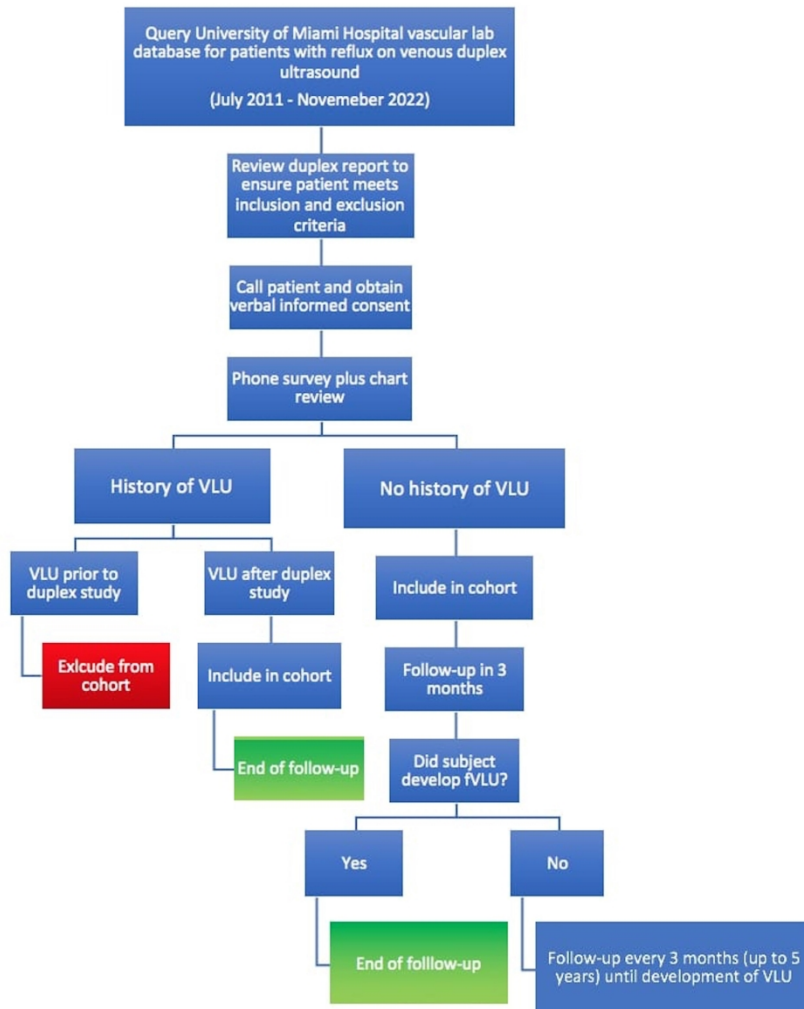
Figure 1: Flowchart outlining the methodology for building the VEINS cohort and following subjects prospectively once they are enrolled

309x337mm (300 x 300 DPI)