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Authors

Lawrence, Peter F
Baril, Donald T
Woo, Karen

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Investigating uncommon vascular diseases using the Vascular Low Frequency Disease Consortium

Peter F. Lawrence, MD, **Donald T. Baril, MD**, **Karen Woo, MD, MS**

Division of Vascular and Endovascular Surgery, Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, Calif

Abstract

Background: Standardized databases such as the Vascular Quality Initiative and National Surgical Quality Improvement Project assess the quality of care related to common vascular surgery procedures, but are not designed for uncommon vascular diseases. We describe a method of assessing uncommon vascular diseases using a multi-institutional collaboration, the Vascular Low Frequency Disease Consortium (VLFDC).

Methods: Uncommon vascular diseases are identified through a systematic literature review. A disease-specific database is developed and tested at a single institution, then refined and circulated to participating VLFDC investigators. Detailed inclusion and exclusion criteria and data point definitions are provided, allowing for standardized data collection across institutions. Each participating institution identifies all patients over a specific time period and enters the data into a VLFDC-provided database. The data are then de-identified and transmitted to our centralized data center for analysis.

Results: Since 2003, the VLFDC has conducted and published nine studies and enrolled 4532 patients, involving 232 institutions and 271 investigators. The studies include renal artery aneurysms, isolated femoral artery aneurysms, spontaneous mesenteric dissection, adventitial cystic disease, carotid body tumors, and vascular Ehlers-Danlos syndrome. Each published study reported on a minimum of 10 times the number of patients collected in previously published studies over the same time period, allowing stronger conclusions to be drawn from the larger sample size. Each study both confirmed previous management principles, which were based on small single-institution experiences, and challenged conventional management paradigms.

Correspondence: Karen Woo, MD, MS, Department of Surgery, University of California Los Angeles, 200 UCLA Medical Plaza, Ste 526, Los Angeles, CA 90095 (kwoo@mednet.ucla.edu).

AUTHOR CONTRIBUTIONS

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Writing the article: PL, DB, KW
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Conclusions: When only small clinical series exist to provide guidance in managing uncommon vascular diseases, and/or where conflicting recommendations are made on the treatment of uncommon vascular diseases, a multi-institutional consortium can provide high-volume standardized data that either confirm or changes prior management principles.

Keywords

Health services research; Uncommon diseases; Multi-institutional

Currently, rare or uncommon vascular diseases are managed using literature that is very limited and not evidence based. At the University of California at Los Angeles (UCLA), uncommon vascular diseases constitute approximately 30% of our tertiary referral center's practice. In managing these uncommon vascular diseases, providers frequently only have guidance from case reports, small case series, and occasionally meta-analyses where the data are collected differently at each institution. Additionally, the literature on low-frequency vascular diseases often describes conflicting management strategies. When larger studies of uncommon vascular disease are published, they often span many years, during which time new diagnostic approaches and new devices have been developed.

The Vascular Low Frequency Disease Consortium (VLFDC) is a model for investigating uncommon vascular diseases, when no single institution has enough patients to provide evidence-based treatment recommendations. The objective of the VLFDC is to compile standardized data from multiple institutions to examine all facets of uncommon vascular diseases, including presentation, diagnosis, optimal treatment strategy, and long-term outcomes. This is in contrast to widely used surgical databases, such as the National Surgery Quality Improvement Project[1] and the Vascular Quality Initiative,[2] whose objective is to improve surgical outcomes by prospectively collecting and sharing data on high-volume vascular procedures, such as open and endovascular abdominal aortic aneurysm repair, carotid endarterectomy, and lower extremity peripheral vascular intervention. The aim of each VLFDC study is to answer questions regarding diagnosis and management of a low-frequency vascular disease that is inadequately addressed in the existing literature.

METHODS

Study topic selection.

VLFDC study topics are proposed by a member of the consortium who has managed a challenging case of an uncommon vascular disease and found limited published evidence that is unsatisfactory. This leads to the first step of the VLFDC process, a comprehensive literature review. If the literature review reveals that there are inconsistent treatment recommendations, a lack of evidence, and/or small reported sample sizes regarding the proposed disease topic, this suggests that the topic is appropriate for the VLFDC. In some cases of low-frequency diseases, new diagnostic modalities and/or treatments have become available that would also warrant investigation through the VLFDC.

A key point is to determine early in the process whether there are diagnosis and/or procedure codes that can accurately identify the uncommon vascular disease in question. Unless an

institution has a preexisting database that tracks patients with low-frequency vascular diseases, the diagnosis and procedure codes are critical to identifying patients. If no codes exist that are specific to the proposed topic, the study is unlikely to succeed, because participants will be unable to identify patients. We then test the diagnostic and/or procedure codes at UCLA or another VLFDC institution to ensure that the codes are able to identify the intended patients.

Protocol and database development.

The next step in the VLFDC process is to develop the study protocol, including specific aims, hypotheses, inclusion/exclusion criteria, and suggest diagnosis and procedure codes. If we can identify appropriate patients with diagnostic and procedural codes, the study moves to a calculation of sample size and an analytic plan. Each VLFDC study is limited to a maximum of four specific aims and hypotheses, to keep the scope of the data collection reasonable. The sample size goal of a VLFDC study is 10 times the largest published series during the same period of time. In addition, based on the primary outcome, a sample size calculation is performed using previously reported data to ensure that the standard VLFDC goal provides an adequate statistical sample size. If necessary, the sample size goal is increased, based on the calculation. Given the retrospective nature of the studies performed thus far, there have not been defined follow-up periods for the individual studies, but we have aimed to obtain contemporary outcomes, so an appropriate modern review period is defined at the outset of the study.

After the protocol is finalized by the investigators, a disease-specific database is constructed. The foundation of the database is built on the data points that have been reported in the previously published studies and additional data points are derived from the VLFDC study hypotheses specific to each disease topic. Consideration to the retrospective nature of these studies is used as well to optimize the ability of contributing institutions to provide the most complete data possible. Categorical variables with defined response options or continuous variables with discrete values are preferred, versus free text, for ease of data analysis. A data dictionary is created alongside the database, which clearly defines the criteria for each data point and response option, allowing for collection of standardized data.

Single-institution study.

The database is then beta-tested at a single VLFDC institution, usually UCLA, but more recently at collaborating institutions that are familiar with our methodology. In cases where the disease is extremely low frequency, the database may need to be tested at additional institutions to fully assess the proposed data points. Important factors to consider during this step include ease of obtaining data points. Data points that are not typically recorded in the medical record and those without diagnostic or procedural codes are poor candidates for VLFDC studies. In addition, close attention is paid to the time required to completely abstract a case. Every effort is made to construct the study protocol and database such that case abstraction time is no more than 20 minutes per patient. This measure decreases the likelihood of inaccurate or incomplete data submission.

The protocol and database are then refined, based on the single-institution experience, so that all definitions and data points are clear. Once a single-institution study is completed, it is submitted to a local or regional scientific meeting to obtain additional external feedback regarding the study. The protocol and database are then further refined in response to the external feedback. In cases of extremely low-frequency diseases, the single-institution study may not provide adequate sample size for even a local/regional presentation, in which case this step may need to be skipped.

Expansion to a multi-institutional study.

Once the investigators are satisfied that the protocol and database have been optimized, national and international contributors are invited to participate in the multi-institutional stage of the study. All contributors who have previously participated in a VLFDC study or expressed interest in participating in a study are invited, as well as potential contributors who have published on this topic or are known to be experts or referral centers for the study topic.

A website,[3] which has a summary of each study protocol, background information, and documents for IRB submission, and so on, is available to potential investigators so that they may gauge their interest in a study. Each institution that agrees to participate is provided with the protocol, which includes the information typically required for an expedited institutional review board (IRB) application, as well as frequently asked IRB questions. Each participating institution must obtain their own IRB approval, and each institution must agree to maintain secure patient information.

Data entry is performed using a web-based data entry mechanism. A data dictionary, which has been developed by the study principal investigator (PI) and study coordinators, is circulated to all investigation sites, before the study starts, for feedback. In addition, each site is provided with the manuscript generated by the single-institution study. This approach increases the likelihood that the data entered are standardized to the study definitions. Once an individual institution enters all of their data into the VLFDC-provided database, the data are de-identified and transmitted to our centralized data center, where they are analyzed. If there are incomplete data, the primary investigation team reaches out to the contributing PI from the contributing institution to help complete the field. Participating research centers are required to meet their own institutional requirements for security and patient privacy; the VLFDC neither receives nor maintains private health information on any patient.

After data analysis, an abstract is written by the PI from the study results and circulated to the study participants before submission to a national meeting. All participants are encouraged to give feedback on the abstract. Once the abstract(s) is finalized, it is submitted to the appropriate scientific meeting to maximally promote the study and to inform treating physicians about the optimal management of the uncommon disease, which should lead to either confirmation of current practices or changes in practice.

Each VLFDC study typically has a team of investigators that includes individuals from UCLA and other VLFDC institutions. The PI is designated by the team a priori. The PI has the option of presenting the study at the scientific meeting and/or being the first or last

author on the article. Often, owing to the large amount of work invested by a number of people other than the PI, the PI will choose to give another investigator the opportunity to orally present the study at a national meeting and another key investigator will be the last author on the manuscript(s). Currently, authorship is limited to two individuals from each contributing institution who are able to meet the criteria of the journal to which the manuscript is being submitted.

All contributors who participated in the data collection and fulfill the standards of the journal become authors on the manuscript(s). They are encouraged to carefully review the manuscript and provide feedback. When a paper is accepted at a national meeting the presentation is reviewed by all authors before presentation and all authors have unlimited access to the slides used in the presentation. After abstract and full article publication, the PI or another interested investigators also have the opportunity to write additional review articles or evidence summaries on the topic, incorporating the new VLFDC findings. These evidence summaries place the VLFDC findings in the context of previously published literature and may lead to changes in reporting standards, practice guidelines, or appropriate use criteria.

RESULTS

Since 2003, nine studies have been completed, presented at national meetings and published (Table I), six are currently in the data collection phase, and three are under consideration by a peer-reviewed journal. The VLFDC has enrolled 4532 patients, involving 232 separate institutions and 271 investigators. Each published study reported on a minimum of 10 times the number of patients collected over the same time period as the largest previously published series, so strong conclusions could be drawn, owing to the large sample size. Studies often confirmed previous low-volume studies, but also frequently challenged conventional management paradigms which were based on small single-institution experiences. Diseases currently being studied include carotid artery aneurysms and popliteal artery entrapment (Table II). Studies under consideration for the VLFDC include mesenteric aneurysms and primary venous tumors (Table III).

DISCUSSION

Since its inception, the VLFDC research program has resulted in data-supported conclusions and recommendations to help in the management of uncommonly encountered vascular diseases. Before these VLFDC studies, the majority of conclusions regarding treatment of these rare diseases had been based on small case series and even case reports. With the VLFDC, all of the completed studies have been the largest to date for their respective rare disease and have focused on contemporary management rather than spanning excessively long study periods, further strengthening the applicability of their conclusions. Although some of the studies have reaffirmed previously reported conclusions, others have redefined treatment standards and management options.

The first published VLFDC study examined inline aortic reconstruction using cryopreserved aortic allografts (CAA) for the treatment of aortic graft infection after open and

endovascular procedures.[4] The study demonstrated lower early and long-term morbidity and mortality with CAA than other previously reported inline prosthetic and extra-anatomic treatment options establishing CAA as a first-line treatment for aortic infections.

Historically, the recommended size criteria for surgical repair of an asymptomatic degenerative femoral artery aneurysm (FAA) was when it reached a diameter of 2.5 cm.[5,6] The VLFDC study of degenerative FAA, which was the largest study to date,[7] demonstrated that acute complications did not occur in asymptomatic FAAs that were 3.5 cm or smaller. The study recommended that repair criteria of asymptomatic FAAs be changed to more than 3.5 cm, and chronic intraluminal thrombus should reduce the threshold for repair.

Guidelines for treatment of renal artery aneurysms (RAA)have historically been controversial owing to the limited data in the literature regarding risk of rupture and growth rate. The VLFDC RAA study demonstrated that asymptomatic RAAs rarely rupture (even when >2 cm), the growth rate is 0.086 ± 0.08 cm/year, and calcification does not protect against enlargement.[8] Subsequent to the publication of the multi-institution study of RAA, an evidence summary of RAA was published as a review article including the results of the VLFDC study.[9] The review concluded that the “natural history of RAA is likely more benign than historic reports have suggested, with a low risk of rupture, slow to null rate of growth, and improved survival following rupture.”

Additional completed studies from the VLFDC have included treatment and outcomes of aortic endograft infection,[10] the use of cryopreserved allograft in patients with current or prior angioaccess graft infection,[11] new predictors of complications in carotid body tumor resection,[12] optimal therapy for the treatment of isolated mesenteric artery dissection,[13] treatment for adventitial cystic disease,[14] and a review of patients with vascular Ehlers-Danlos syndrome.[15]

Despite its early and ongoing success, the VLFDC has its limitations, just as larger databases have their limitations. One major limitation is the inability to study diseases for which there is no specified billing or associated procedural code. When this is the case, there is no standardized means by which institutions can identify patients with the proposed study disease, leading to difficulty in identifying patients for study. To date, there have been several proposed topics that have a dearth of literature and a perceived need for further study for there is no searchable *Current Procedural Terminology* or *International Classification of Diseases, 9th* or *10th* edition codes. Unfortunately, given the inability of contributing institutions to appropriately search for patients with these diagnoses, these studies have not been carried forward. Examples of these have included persistent sciatic artery aneurysms and mycotic aneurysms associated with intravesicular Bacillus Calmette-Guérin therapy. Furthermore, although the data points targeted for collection are intended to be commonly recorded data for that disease, medical record keeping is not always complete and missing data points are inevitable. Given the rarity of some of the diseases studied, time periods have been up to 10 years; consequently, there may be some variation in treatment modalities and trends over time. Although this can be accounted for in specific studies, with low sample sizes, adjustment may not be possible for all diseases.

Given its retrospective nature, patients included in VLFDC studies have been treated at physicians' discretion throughout a variety of institutions and over a variety of different specialties. Ultimately, this variation in treatment is beneficial in examining outcomes of varying treatment, but selection bias is inherent in this approach. Despite these limitations, the studies completed thus far have led to strong conclusions and recommendations, based on sample sizes far exceeding any previously completed studies. All completed studies are on diseases that are rare enough that prospective studies over a reasonable time period could not be completed, so retrospective standardized data collection is the highest level of research feasible.

We have recently assembled a VLFDC steering committee consisting of representatives from all major regional, national, and international vascular surgery societies with a diversity of clinical and research expertise. On a quarterly basis, the steering committee will review and approve study proposals that are submitted using a standardized research proposal form. A committee member with the appropriate expertise will guide the PI through each step of the VLFDC process. The steering committee member will work with the PI to refine the protocol and data dictionary, recruit participating investigators, analyze the results, and prepare the abstract, presentation, and manuscript. The steering committee will oversee all projects and ensure that they stay on target and move efficiently through the steps. Additionally, the council was formed to help direct future ideas around the VLFDC, including the possibility of creating prospective databases of some of these rare pathologies, Given the thoroughness and proven success of the data dictionaries used for the retrospective studies, these might be able to be used in the future for prospective studies as well.

For further information regarding the VLFDC, please visit http://surgery.ucla.edu/vlfdc.

CONCLUSIONS

When only small clinical series exist to provide guidance in managing uncommon vascular diseases, and/or where conflicting recommendations are made on the treatment of uncommon vascular diseases, a multi-institutional consortium can provide high-volume standardized data.

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ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter, retrospective analysis
- **Key Findings:** Studies using the Vascular Low Frequency Disease Consortium platform have both challenged conventional management paradigms and also often confirmed previous management principles that were based on small single-institution experiences.
- **Take Home Message:** When only small clinical series exist to provide guidance in managing uncommon vascular diseases, and/or where conflicting recommendations are made on the treatment of uncommon vascular diseases, a multi-institutional consortium can provide high-volume standardized data that either confirms or changes prior management principles.

Table I.

Completed Vascular Low Frequency Disease Consortium (VLFDC) studies

Title	No. of institutions	No. of patients	Conclusions
The use of CAA for aortic reconstruction in the United States[1]	14	220	CAA should be considered a first-line treatment for aortic infections.
The current management of isolated degenerative FAAs is too aggressive for their natural history[2]	8	182	Repair criteria of asymptomatic FAAs should be changed to >3.5 cm, and chronic intraluminal thrombus should reduce the threshold for repair.
The contemporary management of RAA[3]	16	760	Asymptomatic RAAs rarely rupture (even when >2 cm), growth rate is 0.086 ± 0.08 cm/y, and calcification does not protect against enlargement.
Treatment and outcomes of aortic endograft infection[4]	19	206	Prosthetic graft replacement after explanation is associated with higher reinfection and graft-related complications and decreased survival compared with autogenous reconstruction.
Cryopreserved venous allograft is an acceptable conduit in patients with current or prior angioaccess graft infection[5]	20	457	Cryopreserved vein was associated with higher patency and a lower cost per day of graft patency.
New predictors of complications in carotid body tumor resection[6]	16	332	Distance to base of skull and tumor volume, when used in combination with the Shamblin grade, better predict bleeding and cranial nerve injury risk.
Medical therapy and intervention do not improve uncomplicated isolated mesenteric artery dissection outcomes over observation alone[7]	12	227	Asymptomatic patients with isolated mesenteric artery dissection may be observed and followed up with intermittent imaging. Symptomatic isolated mesenteric artery dissection without evidence of ischemia does not require anticoagulation and may be treated with antiplatelet therapy or observation alone.
A multi-institutional experience in adventitial cystic disease[8]	14	47	Surgical repair, consisting of cyst excision with arterial reconstruction or bypass alone, provides the best long-term symptomatic relief and reduced need for intervention to maintain patency.
A Multi-Institutional Experience in Vascular Ehlers-Danlos Syndrome[9]	11	173	The study highlights the importance of establishing a precise diagnosis by confirming a causative COL3A1 mutation.

CAA, Cryopreserved aortoiliac allograft; *FAA* femoral artery aneurysm; *RAA*, renal artery aneurysms.

Table II.

Vascular Low Frequency Disease Consortium (VLFDC) studies in progress

Carotid artery aneurysm
Popliteal artery entrapment
Venous aneurysms
Middle aortic syndrome in the pediatric population
Middle aortic syndrome in adults
Inferior vena cava reconstruction for treatment of leiomyosarcoma
Aortic graft infection

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Table III.

Proposed future Vascular Low Frequency Disease Consortium (VLFDC) studies

Mesenteric artery aneurysm
Primary venous tumors
Nutcracker syndrome
Iliac artery endofibrosis
Thoracic outlet syndrome—arterial, venous, and neurogenic