Vascular Ehlers-Danlos (vEDS) Patient-Centered Research Conference

CER Factsheets

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Background

Vascular Ehlers-Danlos syndrome (vEDS) is a rare, dominantly inherited condition that affects between 1 in 50,000 and 1 in 250,000 individuals.[1] The condition results from mutations in *COL3A1* and results in premature death as a consequence of arterial and bowel fragility and rare uterine rupture in the context of pregnancy.[1] The median age of death is 51 years of age in a large cohort in which the cause of death was often identified as result of a major complication. The wide distribution of affected organ systems means that affected individuals may require care by clinicians from multiple specialties (geneticists, vascular surgeons, pulmonologists, general surgeons, and obstetricians).

We created the Vascular Ehlers-Danlos Syndrome (vEDS) Collaborative which was funded by PCORI, via the Tier A Pipeline to Proposal award mechanism in October 2017.[2] Through this Collaborative we issued a survey completed by more than 300 affected individuals through which we learned that most patients obtained information about vEDS from the internet, and that nearly 1 in 4 patients has not had a physician explain the diagnosis or management vEDS to them. The rarity of this condition has meant that most individuals are managed in isolation, and indeed only half of patients surveyed have a primary care provider who coordinates their care. Despite this, the majority (90%) are willing to share their medical records for research studies and wish to be updated on research progress. The most common reason cited for this interest in research partnership is to advance research for a treatment and/or cure (86%) and because affected individuals wish to help others learn from their experiences (82%).

Historically, the development of a strategy for care, an approach to treatment, a true understanding of the natural history of the condition, the development of biologically-based effective therapies, and early diagnosis have been restricted. Both large cross-sectional studies and a smaller longitudinal perspective have provided an approach to the "natural history" of the condition (limited by methods of ascertainment and clear indications that not all classes of mutations are appropriately represented)[3-6], they have yet to lead to clear strategies for care, or approaches to biologically-based treatment. In the remaining tenure of the project, the Collaborative will initiate activities to define and prioritize comparative effectiveness research (CER) and patient-centered outcomes research (PCOR) questions that can be best defined within this context.

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FACTSHEET A

Barriers to vEDS Care

vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

Current State

Barriers to care for rare diseases are well documented within the literature and rare disease communities. Patients with vascular Ehlers-Danlos Syndrome (vEDS) are no exception to this. The very nature of a rare disease puts patients at a disadvantage in terms of access to care, access to education, and access to research advancements. We assessed the current literature to understand the landscape of barriers to care in rare disease as well as those currently documented within vEDS specifically (summarized in the table below).

Summary of barriers related to vEDS care:

Physician barriers	• Lack of physician awareness or knowledge around vEDS, and the distinction between EDS and vEDS • Lack of evidence-based care pathways or standards of care for vEDS treatment[1] • Lack of access and/or reluctance to consult vEDS experts
Patient barriers	• Isolation, perception of vEDS as an "invisible illness", and lack of awareness of patient care networks[2,3] • Financial or insurance barriers, including prohibitive travel costs to see specialists • Lack of national organizations to support education, advocacy, and research • Difficulties developing care team relationships (e.g. finding knowledgeable providers, fear about getting appropriate vEDS care, building mutual trust/respect with team) • Lack of guidance on when and how to seek treatment, particularly emergency treatment, for vEDS symptoms; lack of specialized emergency services for vEDS[5]
Barriers to diagnosis	• Diagnosis process can take up to one year; many patients remain undiagnosed • Difficulty navigating the healthcare system (e.g. getting appropriate referrals to geneticists, etc.) • Lack of patient education or pathways about what to do next after diagnosis
Barriers to research	• Lack of research on new treatments • No FDA approved treatments, and limited funding for drug development

Pragmatic Feasibility / Study Design

In order to assess barriers to care in vEDS we propose using a survey study design. The survey will evaluate barriers to care for vEDS patients throughout their clinical course from those they face at diagnosis, to treatment and ongoing care. It will address what the most and least effective learning tools and educational interventions are within the community as well as address ways to improve care coordination. Additionally it will look at the patient and physician communication in both adult and pediatric populations. A survey could help assess the current quality of communication at different stages of care (diagnosis, treatment, management) and identify opportunities for improvement. It will also evaluate how all of the above affect a patient's perceived quality of life.

Potential Study Design Concerns

Study design concerns include self-reported data and recall bias. Survey bias in the form of patients not being molecularly confirmed with vEDS, but rather self-reporting the diagnosis. Creating a survey that uses language which is easily interpretable to the patient (avoids medical jargon) and unambiguous will be important to receiving accurate responses. Another consideration is to ensure our questions are concise and not overabundant, given concerns over 'response fatigue.' Low response rates are often a concern in a survey study, but we feel confident that in our close knit, motivated community we will be able to achieve high response rates. While different distribution methods can be used (mail, online, etc.) we believe an online survey would be the most appropriate and easiest to perform. We will additionally need to decide how data will be stored, coded and analyzed.

Takeaways

Barriers to care remain a significant issue that many patients with vEDS experience. These barriers affect not only patients but caretakers and providers as well. Unfortunately, patients are currently faced with barriers during their workup and diagnosis as well as during their treatment. A lack of funding and research prevents further advancements in disease understanding or new treatment options. Overall, the culmination of these issues likely lead to declined quality of life for patients and poorer disease outcomes. Therefore, this makes addressing these barriers paramount to advancement in vEDS.

Recommendations

Given the information compiled, our workgroup would recommend the following action items:

<u>Short Term Action Items:</u>

1. Increased physician awareness and education about vEDS diagnosis and treatment: consider creation of training modules through Project Echo or other learning management platforms
2. Creation of basic vEDS guidelines: diagnosis and initial work-up, treatment & management, surveillance, exercise recommendations and precautions. These should be published by leading physicians in order to lend guidance and support to local doctors so they may confidently and appropriately care for vEDS patients
3. Development of vEDS patient survey: to further evaluate barriers to care and impact on quality of life within the vascular EDS population

<u>Long Term Action Items:</u>

1. Creation of Centers of Excellence: improving surgical outcomes
2. Telemedicine to improve access to care
3. Emergency crisis line to support patients during critical vEDS symptoms
4. Increased vEDS specific research funding

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FACTSHEET B

Exercise and vEDS

Current State

Regular low-impact physical activity is generally allowed in patients with connective tissues disorders. Daily low intensity exercise can improve aortic health in a mouse model of Marfan syndrome associated aortic aneurysm.[1] Exercise for individuals with Ehlers-Danlos Syndromes, particularly joint hypermobility, has been recommended to stabilize joints and reduce pain, with limited study and broad applicability (non-EDS type specific).[2-4]

However the benefits and risks of exercise for those with vEDS has not been extensively researched, and the recommendations for those with vEDS closely resemble the guidelines for those with Marfan Syndrome and Loey-Dietz Syndrome rather than EDS due to the risk of arterial dissections and ruptures.[5-11] The role of exercise in reducing inflammation and increasing collateral circulation has been studied without focus on vEDS, but the potential benefits may also apply to those with vEDS.[12-16] A study in patients with small abdominal aortic aneurysm (AAA) concluded that exercise was safe in these patients, with no differences observed in aneurysm growth rates after an average of 2 years of participation.[9] Additionally, a review of literature on exercise in patients with thoracic aortic disease (TAD) concluded that there was no unequivocal evidence to indicate that TAD patients should be discouraged from exercise.[17]

Pragmatic Feasibility / Study Design

A preliminary study design would be a survey to assess the types of exercise that individuals with vEDS do right now, and their knowledge and attitudes around daily exercise in patients with arterial health concerns. In addition, a separate survey should be distributed to physicians to assess their understanding of the role of exercise in vEDS and their current recommendations for patients.

Another study design would be a pragmatic trial. This trial could compare patients with vEDS who engage in 30 minutes a day of moderate physical activity vs. those that do not engage in physical activity. This trial would evaluate the risks and benefits of increased physical activity for patients affected by vEDS, and could be conducted within both adult and pediatric populations.

Potential Study Design Concerns

For the survey design, it is important to differentiate between rehabilitation exercises for injury and regular exercise conducted. The survey should also include any medications (i.e. Beta blockers) currently taken. An assessment of what patients have heard from their physicians should be conducted, and a similar assessment should be conducted for what physicians have told their patients. This is to help determine if physicians' guidelines are consistent with what patients have heard from them. The survey should use multiple choice style questions for ease of data analysis.

For the pragmatic trial design, some important questions to consider are:

- What are the best endpoints to measure (e.g. number of arterial events per year, pain ratings before and after adjustment to exercise, and measures of arterial wall health)?
- What is an appropriate length of time for the study?
- Will the need to actively recruit a group with direction not to exercise be potentially harmful for health of this group?
- What are the effects on blood pressure of isometric and isotonic exercises? Some example questions are: Does performing an isometric exercise of a single limb increase blood pressure? What is the associated effect on blood pressure for different percentages of effort/output of isometric and isotonic exercises? What is the effect of breathing on blood pressure during isometric exercises?
- Can the effect of valsavic maneuvers (sneezing, coughing, grunting force, bearing down while holding breath) be altered with breathing?
- What are the impacts of the various medications (e.g. Beta blockers, etc.) patients take on study results? What is the best way to measure medication usage so that we can appropriately analyze, or are separate trial arms needed for patients who take different medications?

In addition, for both the pragmatic trial and survey designs, definitions of types of exercise should be consistent and clear. The definitions of isometric and isotonic exercises are commonly misused in existing studies. An exercise is isometric if it does not involve moving any limbs. For example, planks are isometric, as is pushing against a wall without moving the body. An exercise becomes isotonic once the limbs are involved in movement. For example, crunches, bicep curls, and pushups are isotonic. This misuse of definitions may contribute towards confusion among both the patient and medical community and should be avoided in these study efforts.

One final consideration is the benefit of a case study design for someone with vEDS who exercises regularly. Their blood pressure taken during exercise and at resting could be documented, as well as their medical images and history gathered and analyzed.

Takeaways

Exercise has been recommended for patients with Ehlers-Danlos syndromes (EDS) to stabilize joints and reduce pain. However, available recommendations and guidelines for vEDS specifically are made based on limited research done for other connective tissue disorders, like EDS and Marfan Syndrome.

Recommendations

- Prior to performing a trial, an assessment of knowledge and attitudes about daily exercise and arterial health is indicated
- Disseminate two surveys: one for individuals with vEDS and one to distribute among vEDS specialists, cardiologists, and vascular surgeons to determine attitudes among physicians as well
- Surveys should be distributed broadly (i.e. in multiple countries) to gather diverse perspectives
- Case studies that compare the exercise levels of people with similar mutations and age, would help assess differences in outcomes (arterial events, joint pain, muscle pain, etc) for different exercise levels
- A pragmatic trial should be sure to assess the effects of isometric exercises as well as isotonic. It should also clearly define these terms
- The pragmatic trial should also take into account outcome variation for different mutation types and current medications usage

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FACTSHEET C

Pregnancy and vEDS

vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

Current State

Women with vascular Ehlers-Danlos syndrome are at increased risk for pregnancy-related complications and pregnancy-related death compared to the general population. The pregnancy related complications include third/fourth degree lacerations and preterm birth. The life-threatening complications include arterial dissection/rupture, uterine rupture and surgical complications. During pregnancy, these women should be cared for by a multi-disciplinary team that includes maternal-fetal medicine specialist, obstetric anesthesiologist, cardiologist, cardiovascular surgeon, neonatologists and geneticists. Additionally, these women should deliver at tertiary care centers due to the high risk nature of these pregnancies. Expert opinion supports Cesarean delivery at 36-37 weeks to avoid uterine rupture, however whether Cesarean is protective for pregnancy-related complications is unknown.

There is limited data on risk factors that are associated with poor pregnancy outcomes in these women. We have insufficient data to determine if the mode of delivery (vaginal versus Cesarean delivery) influences the risk of complications and if timing of delivery influences the risk of complications.

Pragmatic Feasibility / Study Design

Compare the pregnancy-related complications and death between the different types of delivery (vaginal delivery vs Cesarean delivery) leveraging data collected through a natural history study of pregnancy in women with vascular Ehlers Danlos Syndrome.

Determine the fetal and/or maternal genetic mutation in COL3A effects on preterm birth and classify preterm birth pathways by premature rupture of membranes, cervical insufficiency and preterm labor. The cervix and fetal membranes are composed of Type 3 collagen and dysfunction collagen has been proposed as the reason for preterm birth.

Potential Study Design Concerns

There are several considerations that may impact study design and validity. First, detailed pregnancy history needs to be collected as there are many confounders for poor pregnancy outcomes and preterm birth beyond just vEDS. Second, pregnancy-related death is a very rare outcome (only about 5.3%), therefore a very large sample size would be needed in order to have adequate power for study findings. Lastly, studies will need to attempt to control for significant potential bias in recruitment and data collection. There is an assumption that the more severe the condition, the more likely to be delivered via Cesarean, which may impact the care that the study population receives and bias the conclusions drawn from a study.

Takeaways

- Pregnancy can be associated with some life-threatening complications for women including arterial dissection, uterine rupture or surgical complications and currently there is no risk-stratification system to know who with vEDS will have one of these complications during pregnancy or who is at higher risk for these complications.
- Women with vEDS may be at increased risk for some adverse outcomes during pregnancy including preterm rupture of membranes and preterm birth, increased frequency of 3rd/4th degree vaginal lacerations, and postpartum hemorrhage.
- We currently do not know the optimal timing and method of delivery (vaginal vs Cesarean) in women with vEDS to have the best possible outcomes.

Recommendations

The first step to create a database to gather more information about modifiable and non-modifiable risk factors associated with poor maternal and pregnancy outcomes in women with vEDS. This can be a retrospective, natural history database where once a pregnancy has been completed, data can be entered. This study could compare pregnancy in women who themselves have a diagnosis of vEDS to women who are not affected but pregnant with a child affected by vEDS.

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FACTSHEET D

vEDS Screening and Surveillance

vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

Current State

There has been a hesitancy to perform surveillance studies in vEDS due to concerns regarding safety of operative repair.

Why perform surveillance?

- Aortic and arterial aneurysms can lead to rupture or dissection, thus prophylactic repair is recommended.[1]
- Elective surgical repairs have better outcomes than emergent surgical repairs in individuals with vEDS and in the population of patients affected by arterial disease.[2,3]

How is surveillance performed?

The imaging "test" for surveillance varies by the anatomic location for surveillance (see table below).

Test	Anatomic location	Pros	Cons	Additional details
Duplex ultrasound	• Carotid/vertebral arteries, upper/lower extremities arteries, mesenteric/renal arteries, aorta and iliac arteries	• No radiation exposure • Cannot be used for the descending thoracic aorta	• Time consuming • Tech/lab dependent • May not be available at all hospitals	• Aortic root and ascending aorta a transthoracic echo is used (similar technology)
Computed Tomography Angiogram (CTA)	• All of the above, plus the entire aorta	• Quick study • Ubiquitous • Can also evaluate the lungs and intestine	• Radiation (cancer concerns) • Contrast induced nephropathy • Contrast allergy	• CT with venous contrast does not give the same resolution for the arteries
Magnetic Resonance Angiogram (MRA)	• All of the above	• No radiation	• Time consuming • Some people experience claustrophobia • Experience needed to get satisfactory imaging • Not used for planning stent graft operations	

What are examples of arterial diseases that have benefited from surveillance?

- The evaluation of the aortic root and ascending aorta in individuals with heritable thoracic aortic disease; when aortic root aneurysms are detected, surgical repair is offered.[4]
- Aortic root and ascending aortic aneurysms: These are surveilled in individuals with heritable thoracic aortic disease and when they reach recommended sizes, repair is offered.[4] Of note, this is not a common manifestation of disease in vEDS
- Abdominal aortic aneurysms (AAA): When abdominal aortic aneurysms reach 5.5 cm in diameter, surgical repair is recommended. The Screening Abdominal Aortic Aneurysms Very Efficiently (SAAAVE) Act was introduced on January 1, 2007 by Medicare covering AAA screening at the time of enrollment in Medicare for men with a history of smoking. The current recommendations by the USPSTF is a one-time screening by abdominal ultrasound for men with a history of smoking or anyone with a family history of AAA. The recent Society for Vascular Surgery (SVS) guidelines recommends extending the recommendation to include women 65 to 75 years of age with a history of tobacco use.[5-7] Overall, mortality from ruptured AAA has decreased over the last 2 decades[8] and a recent meta-analysis demonstrated an overall decrease in AAA prevalence worldwide with a prevalence ranging from 2.2% in the United States to 6.7% in Australia.
- Aortic dissection: Dissection of the descending thoracic aorta is followed by surveillance imaging. If the aorta enlarges to 5.5-6 cm the repair is performed.[9]
- It is important to remember that vEDS is unique as multiple arteries can be involved with aneurysms and dissections or both. It is also important to remember that not all aneurysms/dissections are treated with surgery as it depends on their location and size.[10-13]

How are arteries and aorta affected and managed?

Impact for and Management for the Arteries	
Arterial dissection	• Dissection of arteries in vEDS can occur without symptoms and are detected by surveillance exams. • Carotid and vertebral arteries dissections can occur without symptoms but can also be associated with stroke. These are usually treated with medications (antiplatelet therapy, anticoagulation, or both). • Mesenteric arteries dissections are treated with medications (antiplatelet therapy, anticoagulation, or both) unless symptomatic (occlusion or rupture) • Renal arteries dissections are treated with medications such as antiplatelet therapy, anticoagulation, or both unless symptomatic (occlusion leading to drug resistant hypertension). Rupture usually will need surgery but there are cases in which medical management (blood pressure control usually with beta blockers if tolerated, stopping antiplatelet therapy, stopping anticoagulation therapy, bed rest, blood transfusion) was successful • Common iliac arteries dissections are treated with medications (antiplatelet therapy) unless symptomatic (narrowing of the artery causing leg pain with walking, occlusion or rupture). If surgery is needed, they can be treated with surgery (stent grafts or bypass operation) • External iliac arteries dissections are treated with medications such as antiplatelet therapy unless symptomatic (narrowing of the artery causing leg pain with walking, occlusion or rupture). If surgery is needed, they can be treated with surgery (stent grafts or bypass operation)

Arterial ruptures	• Ruptures in medium sized arteries are likely fatal without treatment (surgery): mesenteric, renals, iliacs • Can occur in the setting of aneurysm or dissection or both • Small unnamed arterial branch ruptures can be managed with medications (blood pressure control usually with beta blockers if tolerated, stopping antiplatelet therapy, stopping anticoagulation therapy, bed rest, and blood transfusion if needed). These usually present as a "hematoma" and is frequently self-limited

Impact and Management for the Aorta (Less commonly involved than the arteries in vEDS.[2,14])	
Aortic dissection	• The management of aortic dissections depends on the location. The dissections are divided by site of origin of the tear: Ascending thoracic aorta (type A), descending thoracic aorta (type B), and abdominal aorta • Dissection starting in the ascending thoracic aorta (type A aortic dissection) can extend into the aortic arch, descending thoracic aorta, abdominal aorta, and even the iliac arteries • Ascending thoracic aortic dissection (type A aortic dissection) needs emergent open surgical repair due to high risk mortality. This operation does not repair the descending thoracic or abdominal aorta • Descending thoracic aortic dissection (type B aortic dissection) and abdominal aortic dissection can usually be managed with medical management (blood pressure control with beta blockers, and antiplatelet therapy) in the early phase. However, if the weakened aorta becomes an aneurysm, there is an increased risk for rupture and the patient may benefit from surgical repair of the aorta, usually with an open operation to replace the aorta. • Surgery using stent grafts is usually not recommended since the tissues are too weak.
Aortic rupture	• Common sites: Ascending thoracic aorta, descending thoracic aorta, abdominal aorta • These are fatal without treatment (surgery with open replacement of the ruptured aorta or stent graft placement). • Can occur in the setting of aneurysm, dissection, or both

What are the unknowns about vEDS screening and surveillance?

- How often should surveillance be performed?
- What is the best modality for surveillance in individuals with vEDS since they are young?
- What is the optimal surgical repair strategy in vEDS?
- Does prophylactic surgical repair in vEDS improve survival?

Pragmatic Feasibility / Study Design

A reasonable trial design to help determine the importance of vEDS surveillance would be a pragmatic trial that compares the outcomes of "regular" vs. "as-needed" surveillance (CT scans / MR scans / Duplex exams) among patients with different gene mutations. An additional study design that would be a survey of vascular surgeons that evaluates their approach to vEDS surveillance and vascular repair, to help better understand current practices.

Potential Study Design Concerns

As with many rare diseases, it is challenging to conduct prospective trials that evaluate clinical practices for vEDS, as patients with vEDS are so widely dispersed across the country. It would likely not be feasible to engage vascular surgeons across the country to participate in a trial that evaluates different modalities for vEDS surveillance and repair. A potential survey of vascular surgeons would be a feasible design, however it would be important to ensure we recruited a representative sample of vascular surgeons to truly understand diversity of practice and outcomes.

Takeaways

Surveillance appears to be effective in vascular diseases and is well established in vascular practices. However it is not clear if surveillance makes a difference in vEDS patients.

Recommendations

At this time, a stand-alone trial is likely not feasible. However, there are two ways to evaluate this:

- A systematic review of all published cases and case series evaluating outcomes of repairs (elective vs. emergent). Ideally these would be presented by anatomic location:
    - Extracranial carotid and vertebral arteries, and subclavian arteries
    - Thoracic Aorta: Ascending, Arch, and Descending thoracic aorta
    - Mesenteric and renal arteries
    - Abdominal aorta/iliac arteries
    - External iliac arteries and peripheral arteries
- Secondary analysis of data collected as part of a randomized trial evaluating medical therapy where surveillance would be one way to evaluate outcomes of the therapy. The secondary analysis will focus on aneurysm growth rates, asymptomatic dissections, dissection related aneurysmal degeneration.
- A survey to understand the current practices of vascular surgeons in vEDS surveillance and repair

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FACTSHEET E

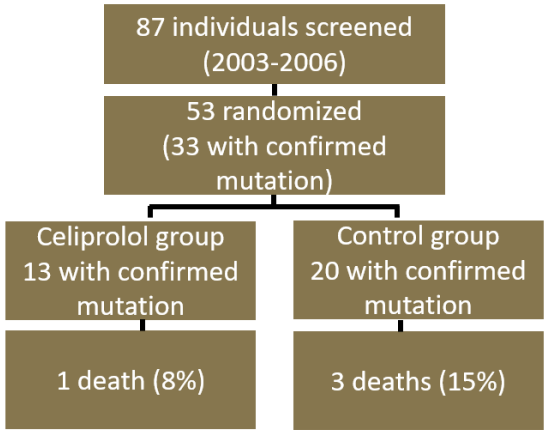
vEDS Treatment

vEDS COLLABORATIVE
Vascular Ehlers-Danlos Syndrome Research

Current State

Beta Blockers

- The major target of medical intervention in vEDS has been the maintenance of blood pressure in the normal or low normal range and prevention of surges in blood pressure with the intent to minimize the likelihood of arterial dissection or rupture.[1]
- These data are derived from early work demonstrating that anti-impulse therapy with beta blockers to reduce heart rate and blood pressure is an effective treatment in patients with dissection in the descending thoracic aorta (type B dissection).[2]
- There is one randomized trial in France, BBEST (Beta Blocker in Ehlers-Danlos Syndrome Trial), evaluating the use of Celiprolol in 33 individuals with genetically confirmed vEDS and showed a reduction of mortality (1 death in a group of 13 individuals on Celiprolol vs 3 deaths in a group of 20 individuals in the control group).[3] The study suggests that treatment extends the time to vascular complications compared to those not treated. Celiprolol is (□1-adrenoceptor antagonist [reduced sympathoadrenal activity] with a □2 adrenoceptor agonist action [vasodilation], and a weak □2adrenorecentor antagonist [increase of adrenergic, dopaminergic, and serotonergic neurotransmitters & insulin secretion. Also may exert B3-adrenoceptor agonist activity (coronary vasorelaxation and stimulation of nitric oxide release). Reduces systolic and diastolic blood pressure.



- This study had several limitations including small sample size, open label design, and lack of mandatory genetic testing at baseline thus randomization prior to confirming the genetic diagnosis (see figure).
- Long term data were recently polished (April 2019).[4] A summary of the study was compiled by the patient advocacy group FIGHT vEDS (see Appendix).

What is not known

- Mechanism of action of Celiprolol is now well understood (postulated endothelial nitric oxide synthase activation or TGF□ inhibition). If the presumably beneficial effect of celiprolol can be extrapolated to other beta blockers
- We do not know if other medications improve outcomes: Losartan, vitamin C,
- We do not know if a combination "cocktail" of medications improves outcomes

Pragmatic Feasibility / Study Design

Prior to proceeding with a trial, a survey to ascertain the willingness to randomize vs. simply enroll into an observational study while determining a-prior what category the patient will be in (celiprolol vs. beta blocker vs. no beta blocker). Additional assessment of other medications such as losartan, Vitamin C, Metformin, and doxycycline is warranted.

Potential Study Design Concerns

It is possible that the group choosing to not take any beta blockers are different at baseline from those agreeing to be placed on a beta blocker. It is also unknown if all patients will start taking Celiprolol if it is approved by the FDA (see Appendix). Additional unresolved questions include:

- What is the optimal outcome measurement?
- What is a reasonable follow up duration? Is one year from the date of enrollment adequate or is a longer time horizon of three or five years ideal?

Takeaways

At this time, the strongest data available suggest that celiprolol may be effective. These data however, are insufficient to determine that celiprolol is effective.

Recommendations

A randomized prospective trial (blinded) comparing celiprolol to another beta blocker in patients with genetically confirmed vEDS: Compared to patients who manage their vEDS symptoms with beta-blockers, do patients who take different (or no) medication have fewer adverse events?

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