# Pilot Study to Evaluate Effect of Antihypertensive Therapy on the Rates of Clinical Events in Patients with Vascular Ehlers-Danlos Syndrome

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## BACKGROUND

**Ehlers-Danlos syndromes (EDS) are a heterogeneous group of connective tissue disorders. The most serious subtype of which is the vascular Ehlers-Danlos syndrome (vEDS).**

- EDS includes many clinical subtypes with widely different phenotypes and prognoses.
- vEDS is most serious, caused by mutation in *COL3A1* gene, resulting in defective type III collagen protein.
- Defective type III collagen in the walls of arteries and hollow organs leads to tissue fragility and increased susceptibility to rupture.
- vEDS has an unpredictable course that may lead to premature death from spontaneous arterial or organ ruptures.
- The median age of death for vEDS patients is 51 years[1].
- Significant unmet medical need for improving outcomes in patients with vEDS.

**Despite the severity of vEDS relative to other subtypes of EDS, United States medical coding groups all EDS under a single code. This has limited studying vEDS outcomes and standard of care.**

- Majority of vEDS patients are diagnosed following a major complication (70%) at an average age of 28 years[1].
- The current standard of care is behavioral modification to reduce potential mechanical sheer stress on vessels[2].
- While there are no approved medications to treat vEDS, some physicians reportedly treat patients with antihypertensives, but how often these are used and whether there is any effect on the rate of clinical events in vEDS are not known.

**To distinguish vEDS patients from other subtypes of EDS, we developed an inception cohort strategy to identify patients with rupture events using real-world evidence from a large administrative claims database (Figure 1).**

- The International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10) as well as the Current Procedural Terminology (CPT) were reviewed to identify diagnosis and procedure codes pertinent to vEDS.
- vEDS is clinically suspected in patients with any of the major diagnostic criteria[3]: (1) family history of vEDS; (2) arterial rupture; (3) spontaneous sigmoid colon perforation; (4) uterine rupture during pregnancy; or (5) carotid-cavernous sinus fistula formation.
- We selected diagnosis, laboratory test, and procedure codes that indicate one of the above major diagnostic criteria.
- Using this approach, we identified a population of suspected vEDS patients and evaluated the effect of antihypertensive use on the rate of rupture events.

## METHODS

**Data**: This study used data from the Truven MarketScan® claims database, an administrative database covering over 190 million patients across the United States, of which ~90 million were actively enrolled during the study period (2014-2017). The database includes medical, laboratory, and procedural claims. Use of medical services is recorded in the database with date of service, provider-type, associated diagnoses, and performed procedures. This database is compliant with the Health Insurance Portability and Accountability Act. Because the data are commercially available and deidentified, institutional review board approval was not required. Analyses were conducted in March and April 2019.

**Study design**: Administrative claims data, including diagnosis, procedure, and laboratory tests, were evaluated over a four-year identification period from January 1, 2014 to December 31, 2017. Patients were identified as having EDS if they had at least 2 medical claims for an EDS diagnoses on different days, separated by at least 2 months; requiring 2 separate EDS diagnoses helped to minimize misdiagnoses. Patients with suspected vEDS were further identified using the inclusion criteria described below. Because hypermobility is common in many subtypes of EDS, but very uncommon in vEDS, patients with any claims for hypermobility syndrome were excluded from the vEDS group.

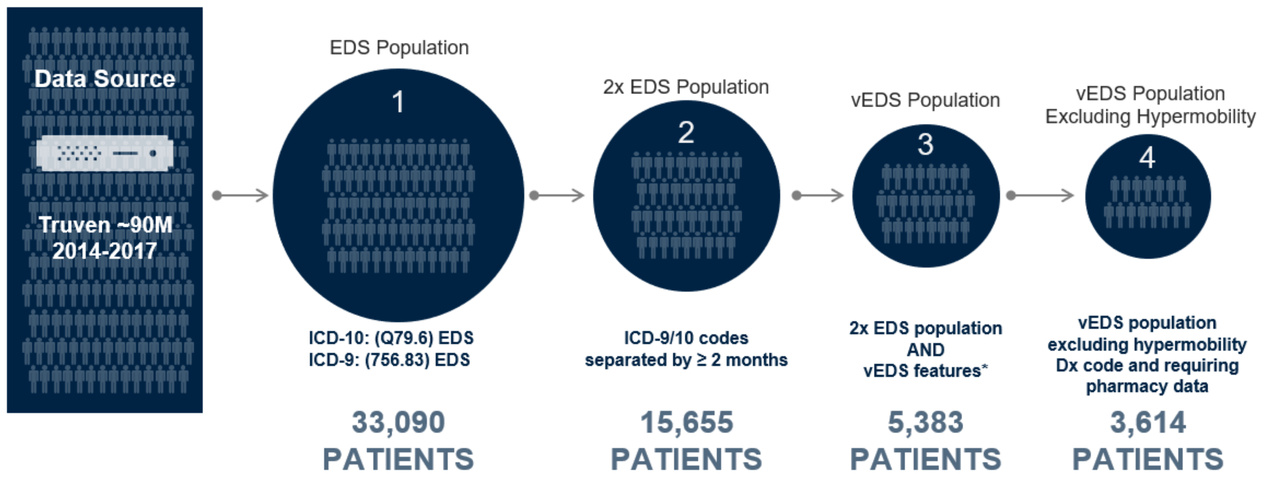
**Inclusion criteria for suspected vEDS**: Patients were suspected of having vEDS if they met the following criteria in their administrative claims history:

- ≥2 claims for a diagnosis of EDS (ICD-9: 756.83, ICD-10: Q79.6) separated by ≥2 months.
- ≥1 code of a diagnosis, laboratory test, or procedure indicating the presence of one of the vEDS major criteria for diagnosis (**Table 1**).
- No claims for hypermobility syndrome (ICD-9: 728.5, ICD-10: 728.5).

**Rate of clinical events**: To determine the rate of rupture events in the suspected vEDS patient population, we evaluated diagnosis and procedure claims related to organ rupture or related clinical events over the same four-year period. We limited evaluation to a subgroup of suspected vEDS patients with ≥1 year of claims history preceding the first EDS diagnosis. By ensuring at least 1 year of prior claims history, we could confirm that each claim for a clinical event indicated the initial claim for the event and did not reflect claims for follow up encounters for remote clinical events. Claims were grouped into one of seven different categories of clinical events, based on literature reports of the most common events in vEDS populations (**Table 2**). Total patient counts for each rupture category were reported. Counts were limited to one rupture event per category for each patient per year to prevent duplicate counting for follow up encounters.

**Comparison of clinical event rates with or without antihypertensive therapy**: To determine the effect of antihypertensive therapy on vEDS clinical event rates, we searched claims data of our vEDS population for national drug code (NDC) claims. Patients were defined as being on antihypertensive therapy if they had three or more NDC claims over the four-year study period. All other patients were defined as being on no antihypertensive therapy. Classes of antihypertensive drugs included in this analysis were beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers. We then compared the rate of clinical events between vEDS patients on each class, any, and no antihypertensive therapies. Statistical analyses were carried out with two proportion *Z*-tests. *P*-values <0.05 were considered statistically significant. All statistical tests were two-sided.

### Figure 1. Study Design and Inclusion Criteria for Suspected vEDS Patients




### Table 1. Claims Used to Identify vEDS Patients

| Claim Type | Diagnosis, Test, or Procedure |
|---|---|
| Diagnosis Codes | Aneurysm and/or dissection: |
| | Carotid artery |
| | Cerebral artery |
| | Iliac artery |
| | Splenic artery |
| | Thoracic aorta |
| | Vertebral artery |
| | Carotid-cavernous fistula |
| | Hemorrhagic stroke (age <40 y) |
| | Intestinal rupture |
| | Uterine rupture |
| Laboratory Tests | *COL3A1* genetic testing |
| Procedure Codes | Surgical or endovascular repair: |
| | Carotid artery |
| | Carotid-cavernous fistula |
| | Iliac artery |
| | Splenic artery |
| | Thoracic aorta |
| | Vertebral artery |
| | Angiography |
| | Blood transfusion |

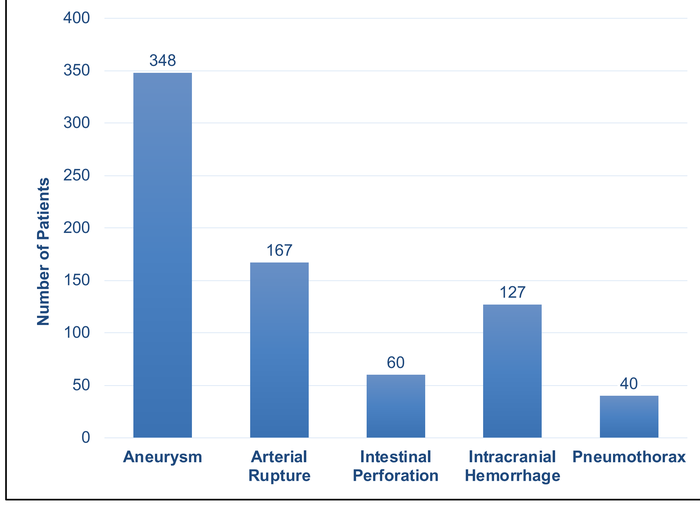
### Table 2. Claims Used to Identify vEDS Clinical Events

| Event Category | Included Diagnoses | Excluded Diagnoses |
|---|---|---|
| Aneurysm | Aneurysms of large- or medium-sized arteries | Abdominal aorta |
| Arterial rupture | Rupture/dissection of large- or medium-sized arteries | Abdominal aorta |
| | Heart wall rupture | Coronary artery |
| | Chordae tendineae rupture | |
| | Mitral valve prolapse | |
| | Carotid-cavernous sinus fistula | |
| Intracranial hemorrhage | Intraparenchymal hemorrhage | Ischemic stroke |
| | Subdural hemorrhage | Embolic stroke |
| | Subarachnoid hemorrhage | |
| | Stroke (age <45 years) | |
| Intestinal perforation | Bowel wall rupture | Gastrointestinal hemorrhage |
| | | Perforated ulcers |
| Pneumothorax | Pneumothorax | Pulmonary hemorrhage |
| Eye | Globe rupture | Microvascular disease |
| Other organ rupture | Bladder wall rupture | |
| | Spleen rupture | |
| | Kidney rupture | |

### Table 3. Patient Characteristics and Antihypertensive Usage

| | No. (%) | |
|---|---|---|
| **Variable** | **Sample Size** | **vEDS Patients** |
| Total patients | 89,078,064 | 3,614 |
| Male | 42,288,940 (47.5%) | 749 (20.7%) |
| Female | 46,789,124 (52.5%) | 2,865 (79.3%) |
| Age category | | |
| <18 | 22,976,388 (25.8%) | 582 (16.1%) |
| 18-34 | 23,903,365 (26.8%) | 1,301 (36.0%) |
| 35-44 | 11,915,550 (13.4%) | 716 (19.8%) |
| 45-54 | 12,073,794 (13.6%) | 508 (14.1%) |
| 55-64 | 11,803,168 (13.3%) | 369 (10.2%) |
| ≥65 | 6,405,799 (7.2%) | 138 (3.8%) |
| No antihypertension therapy | 77,788,244 (87.3%) | 2,371 (65.6%) |
| Any antihypertension therapy | 11,289,820 (12.7%) | 1,243 (34.4%) |
| Beta blocker | 5,102,460 (5.7%) | 895 (24.8%) |
| ACE inhibitor | 5,118,656 (5.7%) | 231 (6.4%) |
| Angiotensin receptor blocker | 3,206,762 (3.6%) | 228 (6.3%) |
| Calcium channel blocker | 3,774,296 (4.2%) | 254 (7.0%) |

### Figure 2. Rate of vEDS Clinical Events




### Table 4. Rate of Clinical Events in vEDS Patients on Antihypertensive Therapy

| vEDS Patient Group | No. Patients (%) | Rate of Clinical Events | *P*-value (vs. No Antihypertensive) |
|---|---|---|---|
| No antihypertension therapy | 2,371 (65.6%) | 371 (15.6%) | - |
| Any antihypertension therapy | 1,243 (34.4%) | 205 (16.5%) | 0.51 |
| Beta blocker | 895 (24.8%) | 146 (16.3%) | 0.64 |
| ACE inhibitor | 231 (6.4%) | 38 (16.5%) | 0.75 |
| Angiotensin receptor blocker | 228 (6.3%) | 55 (24.1%) | 0.999 |
| Calcium channel blocker | 254 (7.0%) | 33 (13.0%) | 0.27 |

## RESULTS

**Demographic and antihypertensive usage analysis**: Summarized in **Table 3**. The base sample population consisted of approximately 89,078,064 million patients with roughly equal numbers of male and female patients. There were 3,614 suspected cases of vEDS. Compared to the base sample population, vEDS patients were younger with a mean age of 35 years and 36% of the patients between the ages of 18 and 34 years. There were more female cases in both the EDS and vEDS patient populations. The vEDS population was 79% female and 21% male. The numbers of base sample and vEDS patients on any antihypertensive therapy were 11,289,820 (12.7%) and 1,243 (34.4%), respectively. Beta blockers were the most common class of antihypertensives used by vEDS patients with 895 (24.8%) of patients taking these medications.

**Rate of clinical events**: Over the four-year period being evaluated, 15.9% of vEDS patients had at least one clinical event at an average rate of 1.19 events per year. 31.8% of patients had multiple clinical events and several of the events affected more than one arterial site or organ system. **Figure 2** illustrates the distribution of patients who had more than one clinical event in different years of the study. Of the total 745 clinical events, 348 (46.7%) involved an arterial aneurysm, 167 (22.4%) arterial rupture, 60 (8.1%) intestinal perforation, 127 (17.0%) intracranial hemorrhage, and 40 (5.4%) pneumothorax (**Figure 3**).

**Effect of antihypertensive usage of rate of clinical events**: Of the 3,614 vEDS patients identified, 2,371 (65.6%) were on no antihypertensive therapy and 1,243 (34.4%) were on antihypertensive therapy. In comparison, 12.7% of the entire database sample population were on antihypertensive therapy. The number of patients on each medication and the rate of clinical events for each group is shown in **Table 3** and **Table 4**, respectively. There was no statistically significant difference between rate of clinical events in patients in any of the medication groups compared to patients on no antihypertensive medication.

## LIMITATIONS

- Reliance on administrative claims data to diagnosis vEDS, without confirmatory biochemical or genetic testing, limits the certainty of vEDS diagnosis in our study population.
- Medical codes lack the granularity to capture unique characteristics of a rare disease such as vEDS, lowering the sensitivity and specificity of our approach.
- Although we employed a broad range of ICD and CPT codes to capture clinical events, it is possible that capture was sub-optimal and not all clinical events were captured accurately.
- The Truven database sample population may have different demographic characteristics than the Unites States population as a whole, limiting generalizability of our approach.

## CONCLUSIONS

- This study assessed the effect of antihypertensive therapy on the rate of clinical events in patients with vEDS in the United States.
- Using big data claims analyses and vEDS-associated event criteria, we identified a presumed vEDS population based on phenotypic presentation.
- The prevalence of vEDS in our population is slightly higher than expected based on reported prevalence for genotypically-confirmed cases of *COL3A1* mutation carriers. Therefore, we may be capturing some additional phenotypically similar subtypes of EDS or those due to mutations other than *COL3A1*.
- Demographics of our population were similar to prior reports.
- The rate of clinical events, including arterial ruptures and intestinal perforations, reflects a high clinical burden for these patients.
- Patients on antihypertensive therapy, regardless of agent class, had no significant reduction in clinical event rates compared to patients on no antihypertensive therapy.
- Coupled with previously published estimates that 25% of vEDS patients experience a major complication by age 20 years and 80% by 40 years, it is imperative that comprehensive efforts are geared towards improved therapies to reduce risk of clinical events in vEDS patients.
- Future studies using electronic medical/health records, genetic analysis, and specialty lab data should be leveraged to confirm and advance these findings.

## REFERENCES

1. Pepin MG, *et al.* Genet Med, 16, 881-888, (2014).
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## DISCLOSURES

TG, MB, BK, and TF are employed by HVH Precision Analytics, which received funding for this research from Acer Therapeutics Inc. ST and WA are employees of Acer Therapeutics Inc.