Clinical Burden of Classical Homocystinuria in the United States: A Retrospective Analysis of Optum Market Clarity

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Poster #B36

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RESULTS

Patient Demographics and Clinical Characteristics

- There were 601 patients who met the inclusion criteria
- Overall, a majority of the sample was White, with nearly 50% females (**Table 1**)
- More than 60% of the overall sample was 45 years or older (**Table 1**)
- Similar demographic trends were observed in the patient groups with highest tHcy levels above and below 50 µM (**Table 1**)
- In the overall cohort, 212 (35.3%) patients had a highest tHcy of 50 to <100 µM and 111 (18.5%) had a highest tHcy ≥100 µM

Table 1. Patient Demographics

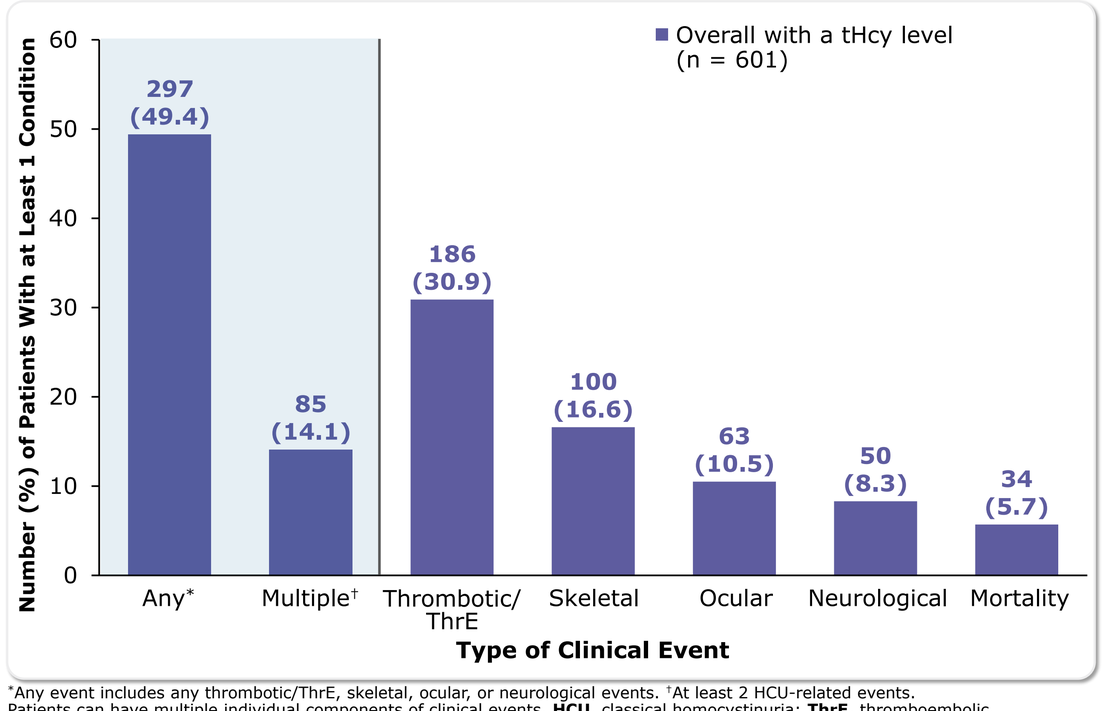
	Overall with a tHcy level (n = 601)	Highest tHcy <50 µM (n=278)	Highest tHcy ≥50 µM (n=323)
Gender, female, n (%)	277 (46.1)	122 (43.9)	155 (48.0)
Age at index (continuous), y			
Mean (SD)	49.7 (18.0)	54.0 (16.2)	46.1 (18.8)
Age at index (categorical), y, n (%)			
<18	33 (5.5)	5 (1.8)	28 (8.7)
18-44	181 (30.1)	66 (23.7)	115 (35.6)
45-64	256 (42.6)	130 (46.8)	126 (39.0)
65-74	88 (14.6)	51 (18.3)	37 (11.5)
≥75	43 (7.2)	26 (9.4)	17 (5.3)
Race, n (%)			
White	475 (79.0)	227 (81.7)	248 (76.8)
African American	75 (12.5)	27 (9.7)	48 (14.9)
Other/Unknown	42 (7.0)	22 (7.9)	20 (6.2)
Asian	9 (1.5)	2 (0.7)	7 (2.2)
Follow-up time, months,* Median (Q1, Q3)	29.2 (14.2, 45.5)	30.0 (13.0, 45.4)	28.7 (15.6, 45.6)

*Time based on activity in electronic health record database during period of interest. Because of rounding, percentages may not total 100.
Q1, 1st quartile; **Q3**, 3rd quartile; **SD**, standard deviation; **tHcy**, total homocysteine; **y**, years.

Clinical Events in Patients With HCU in the Overall Cohort

- Almost half (49.4%) of patients had any thrombotic/ThrE, skeletal, ocular, or neurological event (**Figure 2**)
- Thrombotic/ThrE events were the most common type of events, followed by skeletal, ocular, and neurological events (**Figure 2**)
  - Among patients who had a thrombotic/ThrE event, stroke/TIA was the most common (46.8%), followed by deep vein thrombosis (31.2%) and pulmonary embolism (24.7%)
  - Among patients who had a skeletal event, fracture (66.0%) and osteoporosis (20.0%) were the most common
  - Among patients who had an ocular event, glaucoma (41.3%), myopia (30.2%), and lens dislocation (20.6%) were the most common
  - Among patients who had a neurological event, epilepsy (62.0%) and hemiplegia/hemiparesis (24.0%) were the most common

Figure 2. Clinical Event Categories in Patients With HCU in the Overall Cohort

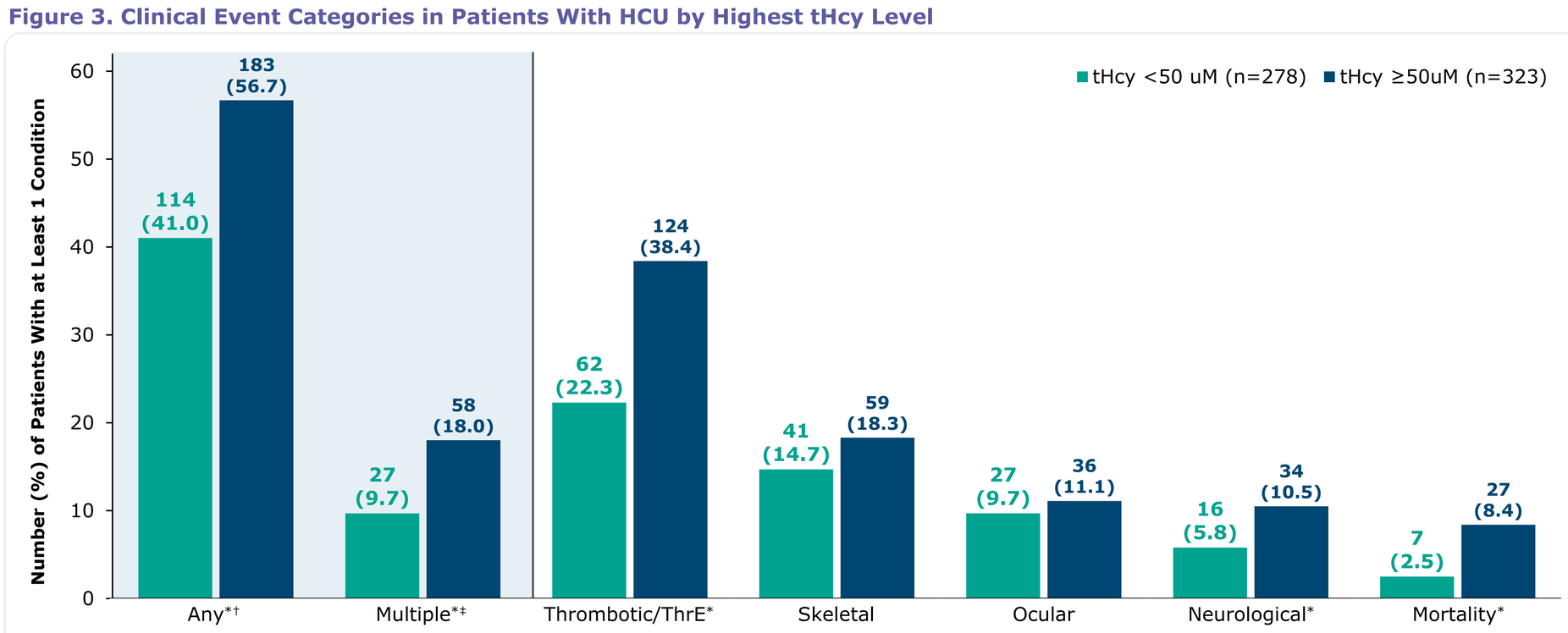


*Any event includes any thrombotic/ThrE, skeletal, ocular, or neurological events. †At least 2 HCU-related events.
Patients can have multiple individual components of clinical events. **HCU**, classical homocystinuria; **ThrE**, thromboembolic.

Clinical Events in Patients With HCU by Highest tHcy Level

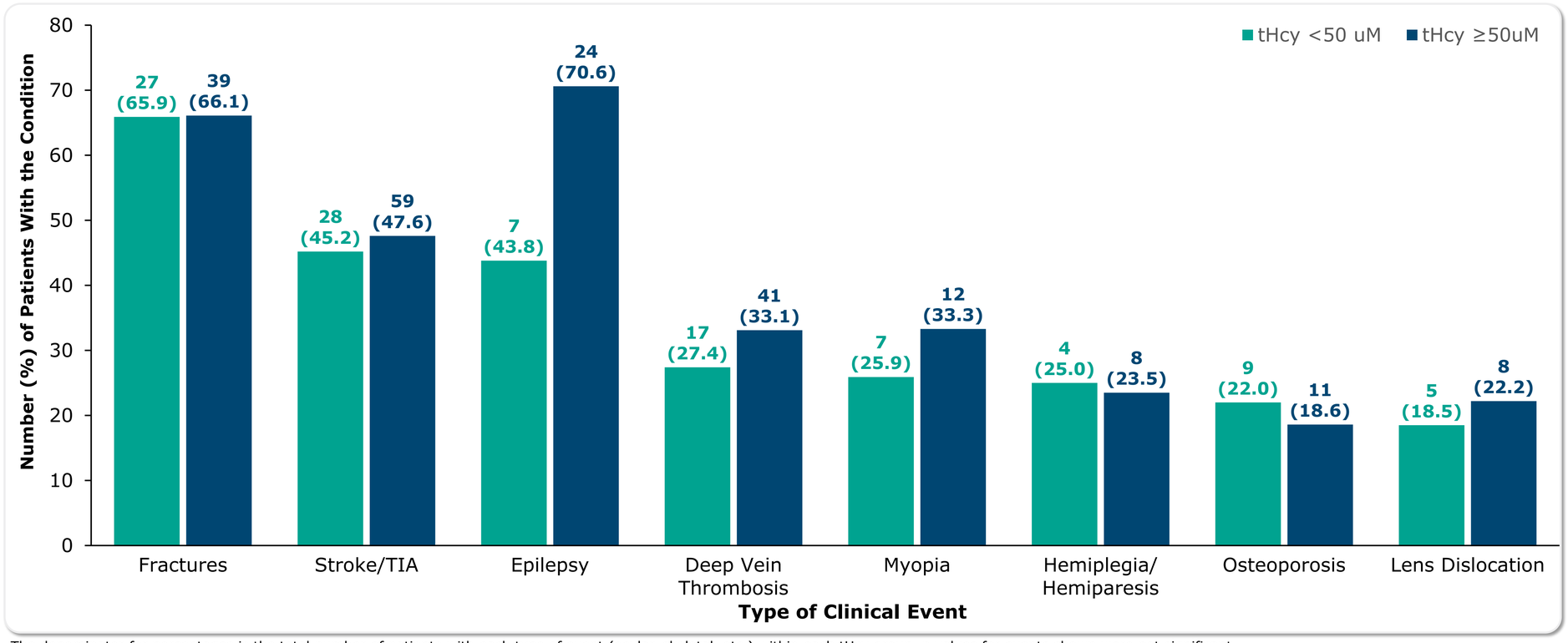
- A higher proportion of patients with tHcy levels ≥50 µM had at least one or more clinical events and showed a higher mortality rate (**Figure 3**)
- A higher proportion of patients with tHcy levels ≥50 µM had thrombotic/ThrE events, especially deep vein thrombosis (**Figures 3 and 4**)
- A higher proportion of patients with tHcy ≥50 µM were found to have epilepsy, myopia, and lens dislocation (**Figure 4**)

Figure 3. Clinical Event Categories in Patients With HCU by Highest tHcy Level



*p<0.05. †Any event includes any thrombotic/ThrE, skeletal, ocular, or neurological events. ‡At least 2 HCU-related events.
HCU, classical homocystinuria; **tHcy**, total homocysteine; **ThrE**, thromboembolic.

Figure 4. Clinical Events in Patients With HCU by Highest tHcy Level



The denominator for percentages is the total number of patients with each type of event (ocular, skeletal, etc.) within each tHcy group. p values for events shown were not significant.
HCU, classical homocystinuria; **tHcy**, total homocysteine; **TIA**, transient ischemic attack.

CONCLUSIONS

- The clinical burden of HCU is substantial with thrombotic/ThrE and skeletal events being more common than others
- The clinical burden of HCU is substantially higher in patients with tHcy levels at or above 50 µM
- These data suggest that treatments focused on lowering Hcy levels are needed to meaningfully reduce significant clinical events for patients with HCU

DISCLOSURES

MJ: has received consultancy fees from Travere Therapeutics, Inc. **LP and MS:** are employees and stockholders of Travere Therapeutics, Inc. **KMT:** has a consulting contract with Travere Therapeutics, Inc. and does not have any equity interest in Travere Therapeutics, Inc. **AR, CNM, DTA:** are employees of Genesis Research and received compensation from Travere Therapeutics, Inc. for conducting this study and providing medical writing support.

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ABBREVIATIONS

CBS, cystathionine beta-synthase; **CKD**, chronic kidney disease; **ESKD**, end-stage kidney disease; **HCU**, classical homocystinuria; **Hcy,** homocysteine; **ICD-10**, International Classification of Diseases, Tenth Revision; **MI,** myocardial infarction; **mo,** month; **NLP**, Natural Language Processing; **Q1**, 1st quartile; **Q3**, 3rd quartile; **SD**, standard deviation; **SDS**, signs, disease, and symptoms; **tHcy**, total homocysteine; **ThrE**, thromboembolic; **TIA,** transient ischemic attack; **US**, United States; **y,** years.

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INTRODUCTION

- Classical homocystinuria (HCU) is a rare genetic metabolic disorder characterized by elevated total homocysteine (tHcy) levels and a heterogenous clinical presentation[1]
- HCU is caused by pathogenic variants in the cystathionine beta-synthase (*CBS)* gene, leading to deficient activity of the CBS enzyme[2]
- HCU is associated with risk of complications including thrombotic/thromboembolic (ThrE) events, cognitive impairment, developmental delays, ectopia lentis, myopia, and elongated arms and legs (marfanoid habitus)[1,3]
- There is limited research on the association between tHcy levels and clinical events in the HCU population

Objectives

- To describe the overall clinical burden of patients with HCU in the United States (US)
- To stratify key clinical events by tHcy levels in patients with HCU in the US

METHODS

- This was a retrospective analysis using Optum's de-identified Market Clarity Data (2007-2021) and proprietary Natural Language Processing (NLP) Data
- Study period: January 01, 2016, through September 30, 2021
- Patients were included if they had ≥1 ICD-10 diagnosis code for homocystinuria (E72.11) or homocystinuria-related terms in the NLP dataset
- tHcy levels were defined using the highest tHcy value at any time during the study period
- In patients with highest tHcy <50 µM, those with secondary causes of elevated tHcy were excluded unless they had other clinical presentations indicative of HCU (**Figure 1**)
- HCU-related events assessed included thrombotic/ThrE, skeletal, ocular, and neurological disease*
- Major clinical events were defined as ≥1 condition-related emergency department or outpatient visit, or inpatient admission

*Thrombotic/ThrE events included deep vein thrombosis, stroke/transient ischemic attack (TIA), and related conditions. Skeletal events included osteoporosis, pectus excavatum, pectus carinatum, fractures, and related conditions. Ocular events included retinal detachment, lens dislocation, myopia, and related conditions. Neurological events included seizure disorder/epilepsy, hemiplegia/hemiparesis, and related conditions.

Figure 1. HCU Patient Identification Algorithm

***Secondary causes; At any time:** Megaloblastic anemia, disorder of cobalamin metabolism, folate deficiency, CKD, ESKD, renal transplant, diabetes, hypothyroidism; **Within 12 mo:** MI. †**Phenotypic expressions:** 1. Ectopia lentis AND (cerebrovascular thrombotic/ThrE event OR neurologic feature) **exclude**: Marfanoid habitus, sulfite oxidase deficiency (E72.19); 2. Pectus excavatum AND (cerebrovascular thrombotic/ThrE event OR [any thrombotic/ThrE event AND neurologic feature]) **exclude**: Marfanoid habitus, sulfite oxidase deficiency (E72.19); 3. Marfanoid habitus AND cerebrovascular thrombotic/ThrE event AND neurologic feature AND (ectopia lentis OR pectus excavatum) **exclude**: Sulfite oxidase deficiency (E72.19). ‡Patients with outlier (≥3,000 µM) tHcy levels only (no other tHcy level) were considered as having no tHcy level for the stratifications and were thus excluded from assessment of the tHcy subgroups. **CKD**, chronic kidney disease; **ESKD**, end-stage kidney disease; **HCU**, classical homocystinuria; **MI**, myocardial infarction; **mo**, month; **SDS**, signs, disease, and symptoms; **tHcy**, total homocysteine; **ThrE**, thromboembolic.

DISCUSSION

- Approximately 50% of patients experienced at least one major HCU-related clinical event and ~14% more than 1 event, over a follow-up period of approximately 30 months
- Thrombotic/ThrE events were more common than skeletal, ocular, or neurological events in our patient population
- HCU-related clinical event rates were generally higher in patients with tHcy ≥50 µM compared with tHcy of <50 µM

Limitations

- These findings are mainly generalizable to a commercially insured population residing mostly in the Midwest US
- Missing data or errors in patient records may introduce bias into the analyses
- The higher age of our patient population could be contributing to the higher event rates in diseases such as cardiovascular disease, where age is known to be a risk factor

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