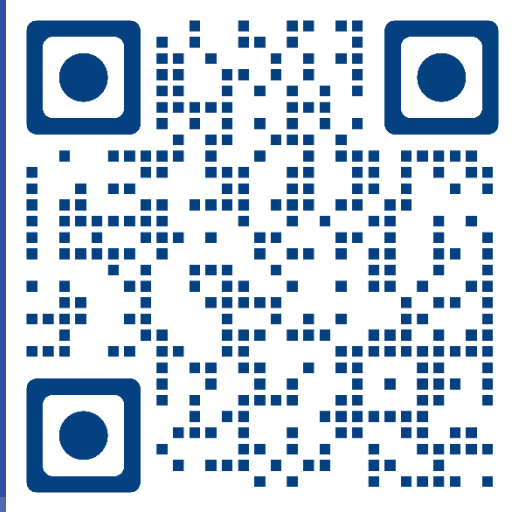


# Vutrisiran Healthcare Resource Utilization, Costs, Discontinuation, and Mortality: a Retrospective Database Analysis

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OBJECTIVE

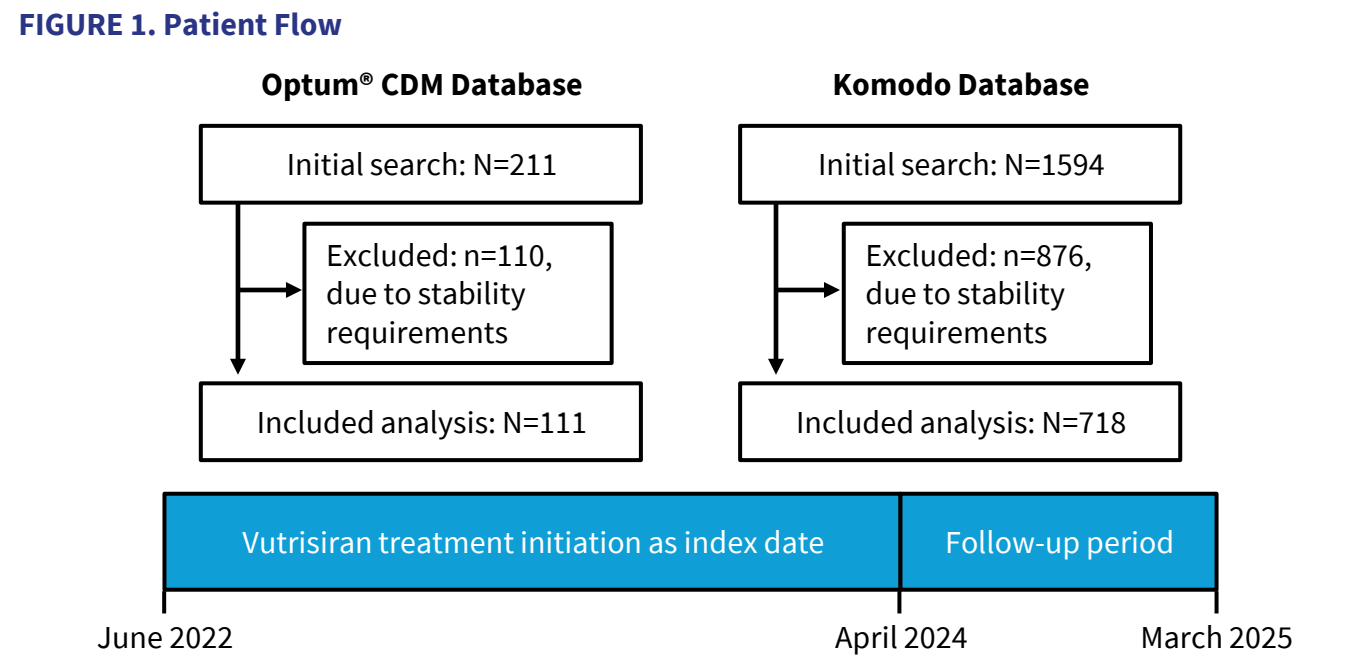
- To report real-world vutrisiran healthcare resource utilization (HCRU), costs, discontinuation, and mortality in the US, during a period when vutrisiran was approved for hereditary ATTR-PN

INTRODUCTION

- ATTR is a progressive, life-threatening condition caused by misfolded TTR protein aggregation into amyloid fibrils that deposit in various organs and tissues<sup>1</sup>
  - ATTR presents as 2 primary phenotypes: ATTR-PN with predominant peripheral nervous system manifestations and ATTR-CM with predominant cardiac involvement<sup>1</sup>
- ATTR is associated with a high cost of care
  - In patients with ATTR-PN, intravenous and subcutaneous therapy requiring hospital visits for administration (inotersen, patisiran) were more costly than oral tafamidis in a Spanish study<sup>2</sup>
  - Hospitalizations and related costs associated with ATTR-CM were found to exceed those of nonamyloid heart failure<sup>3</sup>
- Vutrisiran, a TTR-directed siRNA, was approved in the US for subcutaneous administration by a healthcare professional to treat hereditary ATTR-PN in 2022 and wild-type or hereditary ATTR-CM in 2025<sup>4</sup>
  - The cost of vutrisiran is approximately \$477,000 per year for 4 subcutaneous doses<sup>5</sup>
- There are no real-world data in the US on vutrisiran discontinuations; in the HELIOS-A randomized-controlled trial in patients with ATTR-PN, 3 (2.5%) patients receiving vutrisiran discontinued due to AEs<sup>6</sup>; however, it is typical for persistence to be higher in clinical trials compared with real-world clinical practice<sup>7</sup>
- We aimed to identify the real-world cost and persistence rates of vutrisiran

METHODS

- Data Sources and Study Design
- This was a retrospective analysis of patients initiating vutrisiran from June 22, 2022, to April 30, 2024 (before approval for ATTR-CM) from Optum’s de-identified Clinformatics® Data Mart Database (Figure 1)
    - Patients were included if they had ≥1 vutrisiran claim
    - Patients were followed from vutrisiran initiation until death, enrollment end (≥1 year of continuous enrollment after initiation required for patients who did not die), or last date of available data (March 31, 2025), whichever came first
  - Discontinuation analyses were replicated in the Komodo Healthcare Map® to serve as a comparator
    - Patients were included if they had initiated vutrisiran and had a minimum of 4 consecutive quarters of continuous medication and medical service claims activity after the index date, or until death if death occurred sooner



- Outcomes and Statistical Analyses
- HCRU (excluding COVID-19–related events) and costs associated with inpatient acute hospitalizations, ED visits not leading to inpatient hospitalizations, and outpatient visits; outpatient visits by setting were also assessed
    - Due to the high cost of vutrisiran, visits related to vutrisiran therapy were excluded
    - Outpatient visit was defined as acute care at an outpatient hospital facility with no admittance to an inpatient setting; ED visits were not included in outpatient care at a hospital facility, as they were captured separately
  - Total PPPY costs (excluding vutrisiran costs), regardless of treatment setting
  - Persistence and discontinuation of vutrisiran within 12 months of treatment initiation
    - Persistence was defined as a vutrisiran claim within 180 days from the previous claim (90-day supply + 90-day grace period)
    - Discontinuation was defined as no vutrisiran claim within 180 days of the previous claim
  - Post-discontinuation events, including restart of vutrisiran and therapy switching, and other treatment changes were also reported
  - Mortality within 12 months of treatment initiation
  - Demographic and all outcome variables were assessed descriptively

CONCLUSIONS

- One-third to one-half of patients had a hospitalization or cardiovascular visit, highlighting continued disease burden and progression despite therapy during the period when vutrisiran was approved for ATTR-PN
- Vutrisiran treatment was associated with a high cost of care (mean PPPY cost, \$64,400, irrespective of treatment setting), which excluded the cost of treatment itself; outpatient care at a hospital facility and office visits were the main cost drivers
- Within 12 months of starting vutrisiran, 12%-20% of patients discontinued therapy, with many switching to other ATTR treatments; an additional 3%-12% of patients died across the 2 databases
- These findings suggest that vutrisiran-treated patients continue to experience significant HCRU and costs related to disease progression despite treatment; there remains a need for new therapies to further reduce burden and costs

RESULTS

- Patients
- A total of 111 patients in the Optum® CDM database and 718 patients in the Komodo database were identified and included in the analysis (Table 1)
    - In the Optum® CDM population, mean age was 70.9 years, 62.2% were male, 27.0% were White, and 41.4% were Black
    - In the Komodo population, mean age was 71.0 years, 61.4% were male, 38.9% were White, and 42.5% were Black
  - Tafamidis use in the 12 months following index was 40.0% and 35.2% in the Optum® CDM and Komodo databases, respectively; the use of loop diuretics, SGLT2 inhibitors, and drugs to treat heart failure were generally similar between the two populations
  - Greater proportions of patients in the Optum® CDM database had CV comorbidities in the 12 months following index compared with those in the Komodo database

TABLE 1. Baseline Demographics and Patient Characteristics

| Characteristic                                                                     | Optum® CDM database (N=111) | Komodo database (N=718) |
|------------------------------------------------------------------------------------|-----------------------------|-------------------------|
| Mean (SD) age, years                                                               | 70.9 (9.9)                  | 71.0 (11.0)             |
| Age distribution, n (%), years                                                     |                             |                         |
| 19-44                                                                              | <5 (2.7)                    | 20 (2.8)                |
| 45-64                                                                              | 19 (17.1)                   | 134 (18.7)              |
| 65-80                                                                              | 76 (68.5)                   | 429 (59.7)              |
| ≥80                                                                                | 13 (11.7)                   | 131 (18.2)              |
| Unknown                                                                            | —                           | 4 (0.6)                 |
| Sex, n (%)                                                                         |                             |                         |
| Male                                                                               | 69 (62.2)                   | 441 (61.4)              |
| Female                                                                             | 42 (37.8)                   | 264 (36.8)              |
| Unknown                                                                            | —                           | 13 (1.8)                |
| Race, n (%)                                                                        |                             |                         |
| Black                                                                              | 46 (41.4)                   | 305 (42.5)              |
| White                                                                              | 30 (27.0)                   | 279 (38.9)              |
| Asian                                                                              | <5 (1.8)                    | 17 (2.4)                |
| Unknown                                                                            | 33 (29.7)                   | 117 (16.3)              |
| Ethnicity, n (%)                                                                   |                             |                         |
| Hispanic                                                                           | 7 (6.3)                     | 50 (7.0)                |
| Non-Hispanic                                                                       | 59 (53.2)                   | 601 (83.7)              |
| Unknown                                                                            | 45 (40.5)                   | 67 (9.3)                |
| Medication use in the 12 months following index, n (%) <sup>a</sup>                |                             |                         |
| Tafamidis                                                                          | 34 (40.0)                   | 229 (35.2)              |
| Loop diuretics                                                                     | 48 (56.5)                   | 353 (54.3)              |
| SGLT2 inhibitors                                                                   | 20 (23.5)                   | 172 (26.5)              |
| Beta blockers                                                                      | 37 (43.5)                   | 254 (39.1)              |
| Mineralocorticoid receptor antagonists                                             | 28 (32.9)                   | 189 (29.1)              |
| CV comorbidities (≥25% in either database) in the 12 months following index, n (%) |                             |                         |
| Heart failure                                                                      | 78 (70.3)                   | 351 (48.9)              |
| Essential primary hypertension                                                     | 74 (66.7)                   | 332 (46.2)              |
| Cardiomyopathy disease classified elsewhere                                        | 69 (62.2)                   | 198 (27.6)              |
| Atrial fibrillation and flutter                                                    | 45 (40.5)                   | 190 (26.5)              |
| Hypertensive heart disease                                                         | 43 (38.7)                   | 92 (12.8)               |
| Cardiomyopathy                                                                     | 43 (38.7)                   | 150 (20.9)              |
| Chronic ischemic heart disease                                                     | 39 (35.1)                   | 132 (18.4)              |
| Hypertensive heart disease and chronic kidney disease                              | 37 (33.3)                   | 73 (10.2)               |
| Complications and ill-defined descriptions of heart disease                        | 35 (31.5)                   | 99 (13.8)               |
| Other pulmonary heart diseases                                                     | 28 (25.2)                   | 28 (3.9)                |
| Hypertensive chronic kidney disease                                                | 28 (25.2)                   | 57 (7.9)                |

<sup>a</sup>n=85 for the Optum® CDM database; n=650 for the Komodo database.

- HCRU and Costs
- Mean (SD) follow-up was 1.5 years (0.6) (Table 2)
  - During the follow-up period, 41 (36.9%) patients experienced acute inpatient hospitalization (90 total interactions; 2.2 per patient) with a median length of stay per hospitalization of 6 days and a median of 9.3 days hospitalized annually
    - Total inpatient hospitalization costs for all patients were \$3,814,891
  - ED visits not requiring hospitalization occurred in 55 (49.5%) patients with 132 total interactions (2.4 per patient) and a median of 1.3 days of ED visit stays annually
    - Total ED costs for all patients were \$455,831
  - All patients had outpatient visits with a total of 9111 interactions over the follow-up period (mean visits per patient: 82.1; mean visits PPPY: 58.2; median visits PPPY: 42.6)
    - Total outpatient visit costs for all patients were \$18,682,508
  - Mean PPPY cost was \$64,400, irrespective of treatment setting and excluding vutrisiran claims

Table 2. HCRU and Costs by Care setting in the Optum® CDM Database

| Metric                                              | Inpatient acute hospitalization (±ED visit) | ED visits not leading to hospitalization | Outpatient visits (excluding vutrisiran claims) |
|-----------------------------------------------------|---------------------------------------------|------------------------------------------|-------------------------------------------------|
| Patients with events, n (%)                         | 41 (36.9)                                   | 55 (49.5)                                | 111 (100)                                       |
| Mean (SD) follow-up, years                          | 1.45 (0.57)                                 | 1.50 (0.55)                              | 1.52 (0.52)                                     |
| Total interactions, n                               | 90                                          | 132                                      | 9111                                            |
| Mean interactions per patient                       | 2.2                                         | 2.4                                      | 82.1                                            |
| Median (range) length of hospital/ED visit, days    | 6 (1-24)                                    | 1 (1-1)                                  | NA                                              |
| Median (range) annual days hospitalized per patient | 9.3 (0.4-106.9)                             | 1.3 (0.4-9.4)                            | NA                                              |
| Total cost of all interactions in care setting, USD | \$3,814,891                                 | \$455,831                                | \$18,682,508                                    |
| Total cost per interaction, USD                     |                                             |                                          |                                                 |
| Median (range)                                      | \$35,885 (\$5670-\$138,516)                 | \$2968 (\$16-\$14,669)                   | \$206 (\$0.01-\$282,880)                        |
| Mean (SD)                                           | \$42,388 (\$27,767)                         | \$3453 (\$2594)                          | \$610 (\$3826)                                  |
| Total cost PPPY, USD                                |                                             |                                          |                                                 |
| Median (range)                                      | \$51,644 (\$6730-\$396,532)                 | \$3913 (\$339-\$41,154)                  | \$18,346 (\$363-\$312,556)                      |
| Mean (SD)                                           | \$80,536 (\$83,907)                         | \$6339 (\$7484)                          | \$32,724 (\$50,875)                             |

- Costs of outpatient care at hospital facilities (cumulative total, \$2,852,541) were the biggest driver of outpatient total costs, followed by office visits (cumulative total, \$1,102,085) (excluding cost of vutrisiran) (Table 3)
  - Mean PPPY costs for outpatient care at hospital facilities and office visits were \$19,026 and \$6075, respectively
- HCRU from end-stage renal disease treatment facilities accounted for a small proportion of visits (9.5%) but the highest overall cost (mean, \$64,849 PPPY), followed by ambulance needs (3.5%; mean, \$22,142 PPPY) and outpatient care at hospital facilities (25.0%; mean, \$19,026 PPPY)

Table 3. Outpatient Costs Excluding Vutrisiran Claims by Place of Service in Descending Order of Total Cost

| Place of service                                 | Patients, n (n=111) | Visits, n (%) (n=9111) | Total cost (all visits), USD | Mean cost per patient (all visits), USD | Mean cost per visit, USD | Mean cost PPPY, USD | Mean cost per visit PPPY, USD |
|--------------------------------------------------|---------------------|------------------------|------------------------------|-----------------------------------------|--------------------------|---------------------|-------------------------------|
| Outpatient hospital facility <sup>a</sup>        | 100                 | 2278 (25.0)            | \$2,852,541                  | \$28,525                                | \$1252                   | \$19,026            | \$15                          |
| Office                                           | 108                 | 2836 (31.1)            | \$1,102,085                  | \$10,204                                | \$389                    | \$6075              | \$17                          |
| Home                                             | 64                  | 1720 (18.9)            | \$622,683                    | \$9729                                  | \$362                    | \$7232              | \$25                          |
| End-stage renal disease treatment facility       | <5                  | 865 (9.5)              | \$424,119                    | \$106,030                               | \$490                    | \$64,849            | \$141                         |
| Ambulance                                        | <5                  | 316 (3.5)              | \$188,571                    | \$47,143                                | \$597                    | \$22,142            | \$37                          |
| Ambulatory surgical center                       | 20                  | 61 (0.7)               | \$157,284                    | \$7864                                  | \$2578                   | \$5076              | \$2                           |
| Independent laboratory                           | 91                  | 628 (6.9)              | \$113,746                    | \$1250                                  | \$181                    | \$981               | \$5                           |
| Off campus – outpatient hospital facility        | 20                  | 111 (1.2)              | \$19,065                     | \$953                                   | \$172                    | \$568               | \$3                           |
| Skilled nursing facility                         | <5                  | 92 (1.0)               | \$13,937                     | \$3484                                  | \$151                    | \$4364              | \$29                          |
| In-home telehealth                               | 27                  | 78 (0.9)               | \$12,305                     | \$456                                   | \$158                    | \$288               | \$2                           |
| Comprehensive outpatient rehabilitation facility | <5                  | 52 (0.6)               | \$12,099                     | \$12,099                                | \$233                    | \$8509              | \$37                          |
| Other unlisted facility                          | 15                  | 70 (0.8)               | \$8684                       | \$579                                   | \$124                    | \$374               | \$3                           |
| Independent clinic                               | <5                  | 28 (0.3)               | \$7214                       | \$3607                                  | \$258                    | \$1604              | \$6                           |
| Out-of-home telehealth                           | 20                  | 48 (0.5)               | \$6962                       | \$348                                   | \$145                    | \$257               | \$2                           |
| Urgent care facility                             | 15                  | 22 (0.2)               | \$6359                       | \$424                                   | \$289                    | \$290               | \$1                           |
| Nursing facility                                 | <5                  | 17 (0.2)               | \$3850                       | \$1925                                  | \$226                    | \$2620              | \$12                          |
| Residential substance abuse treatment facility   | 6                   | 25 (0.3)               | \$3111                       | \$519                                   | \$124                    | \$308               | \$3                           |
| Mass immunization center                         | 6                   | 7 (<0.1)               | \$1374                       | \$229                                   | \$196                    | \$163               | \$1                           |
| Mobile unit                                      | <5                  | 3 (<0.1)               | \$766                        | \$383                                   | \$255                    | \$288               | \$1                           |
| Federally qualified health center                | <5                  | 2 (<0.1)               | \$195                        | \$195                                   | \$97                     | \$170               | \$2                           |

<sup>a</sup>Excludes ED and inpatient hospital visits.

- Vutrisiran Persistence and Discontinuation
- Persistence at 1 year was ~77% in the Optum® CDM database; similar rates of persistence were observed in the Komodo database (Table 4)
  - In the Optum® CDM database, 13 (11.7%) patients discontinued vutrisiran within the first year compared with 142 (19.7%) patients in the Komodo database (Table 4, Figure 2)
    - Among patients who discontinued vutrisiran, therapy switching to tafamidis monotherapy occurred in 61.5% (8/13) of patients in the Optum® CDM database compared with 14.8% (21/142) of patients in the Komodo database (Table 4, Figure 2)
  - Within the first year of treatment, 13 (11.7%) patients in the Optum® CDM database and 22 (3.1%) patients in the Komodo database died (Table 4, Figure 2)

RESULTS

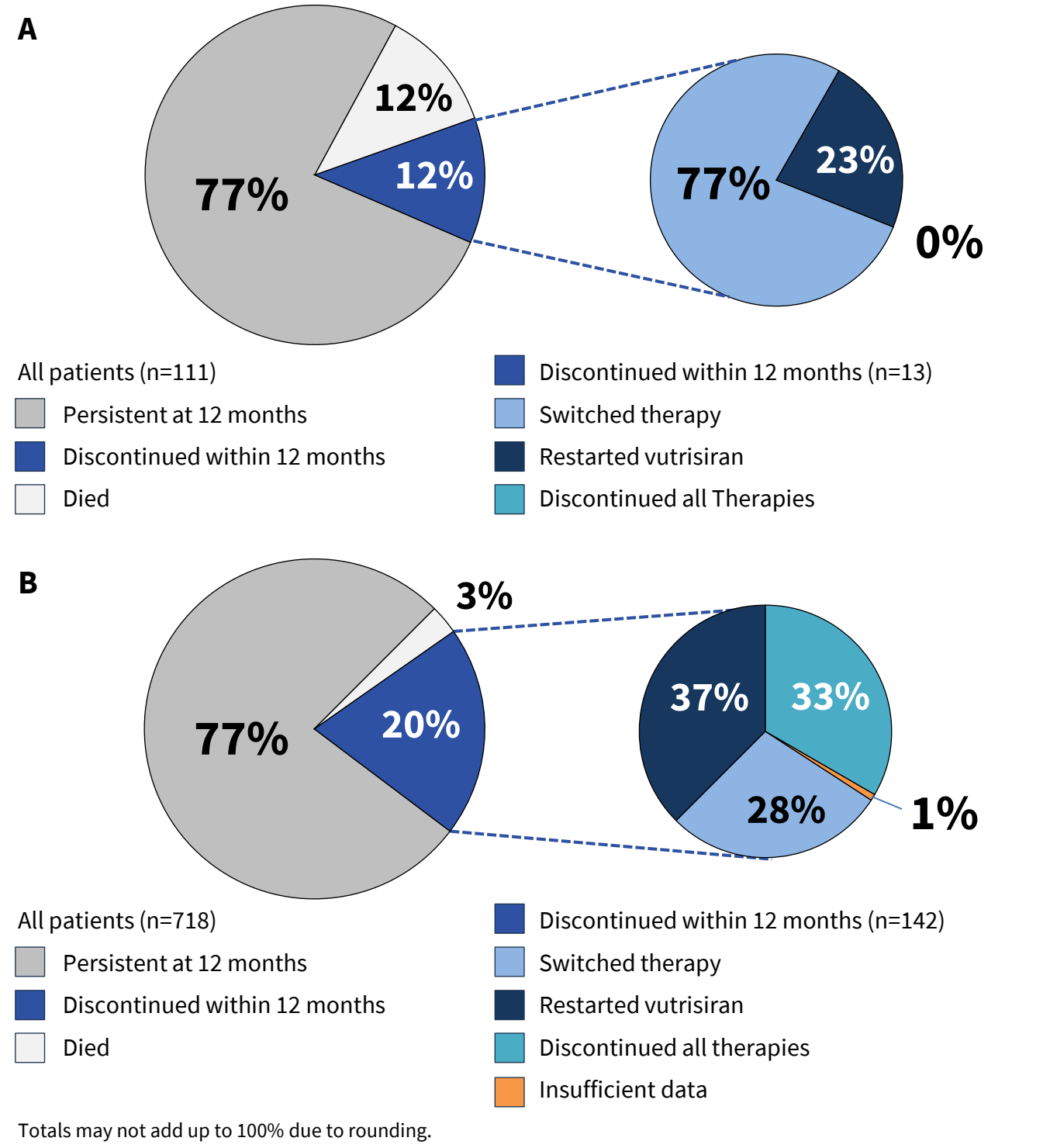
Table 4. Vutrisiran Persistence, Mortality, Discontinuation, and Post-discontinuation Treatment Patterns in the Optum® CDM and Komodo Databases

| Patient category                                     | Optum® CDM            | Komodo               |
|------------------------------------------------------|-----------------------|----------------------|
| Death within the first year of vutrisiran, n (%)     | 13 (11.7)             | 22 (3.1)             |
| Vutrisiran persistence by quarter over 1 year, n (%) | n=111                 | n=718                |
| Q1                                                   | 111 (100)             | 718 (100)            |
| Q2                                                   | 98 (88.3)             | 633 (88.2)           |
| Q3                                                   | 93 (83.7)             | 614 (85.5)           |
| Q4                                                   | 85 (76.6)             | 554 (77.2)           |
| Vutrisiran discontinuation by disposition, n (%)     | n=13                  | n=142                |
| Restarted vutrisiran                                 | <5 (23.1)             | 53 (37.3)            |
| Restarted vutrisiran monotherapy                     | <5 (15.4)             | 32 (22.5)            |
| Restarted vutrisiran as a combination therapy        | <5 (7.7)              | 21 (14.8)            |
| Vutrisiran + tafamidis                               | 0                     | 20 (14.1)            |
| Vutrisiran + other                                   | <5 (7.7) <sup>a</sup> | 1 (0.7) <sup>b</sup> |
| Switched therapies                                   | 10 (76.9)             | 40 (28.2)            |
| Switched or dropped to tafamidis monotherapy         | 8 (61.5)              | 21 (14.8)            |
| Switched to tafamidis combination therapy            | <5 (7.7)              | 5 (3.5)              |
| Switched to other monotherapy or combination therapy | <5 (7.7)              | 14 (3.5)             |
| Diffusional                                          | 0                     | 5 (3.5)              |
| Eplontersen                                          | 0                     | 3 (2.1)              |
| Patisiran                                            | <5 (7.7)              | 5 (3.5)              |
| Diffusional + patisiran                              | 0                     | 1 (0.7)              |
| Discontinued all treatment                           | 0                     | 47 (33.1)            |
| Insufficient data                                    | 0                     | 2 (1.4)              |

<sup>a</sup>Vutrisiran + eplontersen.

<sup>b</sup>Vutrisiran + eplontersen + patisiran.

Figure 2. Vutrisiran Persistence, Discontinuation, and Post-discontinuation Treatment Patterns in the (A) Optum® CDM and (B) Komodo Databases



LIMITATIONS

- While Optum® CDM is a closed database well suited to assess system costs, the Komodo database only has imputed cost data; thus, we were unable to replicate the cost analyses
- It was hard to differentiate between patients with pure polynuropathy, pure cardiomyopathy, and mixed phenotype in this dataset, as ICD-10-CM coding was not used for patient identification
- The data for vutrisiran was only available during a time when it was approved for ATTR-PN; follow-up analyses will need to be conducted in the ATTR-CM population