Supplementary Appendix: Contemporary Description of Clinical Characteristics and Outcomes in Patients with Hereditary ATTR Amyloidosis: Results from the Multicountry OverTTuRe Study

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Data sources

Optum® CDM is an administrative claims database containing de-identified information on medical and pharmacy claims from both primary and secondary care settings, patient demographics, diagnoses, procedures, and prescriptions for commercially insured and Medicare Advantage members in the United States (US). Clinical Practice Research Datalink (CPRD) is a United Kingdom (UK) primary care electronic health record database, and Hospital Episode Statistics (HES) captures administrative data on all hospital admissions in England, thus enabling analyses of longitudinal patient data that include primary care records, hospital admissions, diagnoses, procedures, and outcomes. Medical Data Vision (MDV) is a Japanese administrative claims database containing anonymized patient-level information, including diagnoses, procedures, laboratory test results, prescribed medications, and billing information from participating MDV acute care hospitals. Whilst the MDV database primarily includes information on acute and specialized care, primary care provided at an MDV hospital is also captured. CROSS-TRACKS is a population-based, open cohort capturing routinely collected administrative data on primary and secondary care, linked to national registries, from the Central Denmark Region. The CELOSIA study database comprised data extracted from several national registries for patients with chronic kidney disease, diabetes, and heart failure (includes E85 diagnosis codes for amyloidosis): National Patient Registry (includes diagnoses and procedures from hospital admissions and outpatient visits), Prescribed Drug Register (captures all medications dispensed by community pharmacies), and National Cause of Death Register.

Coding systems

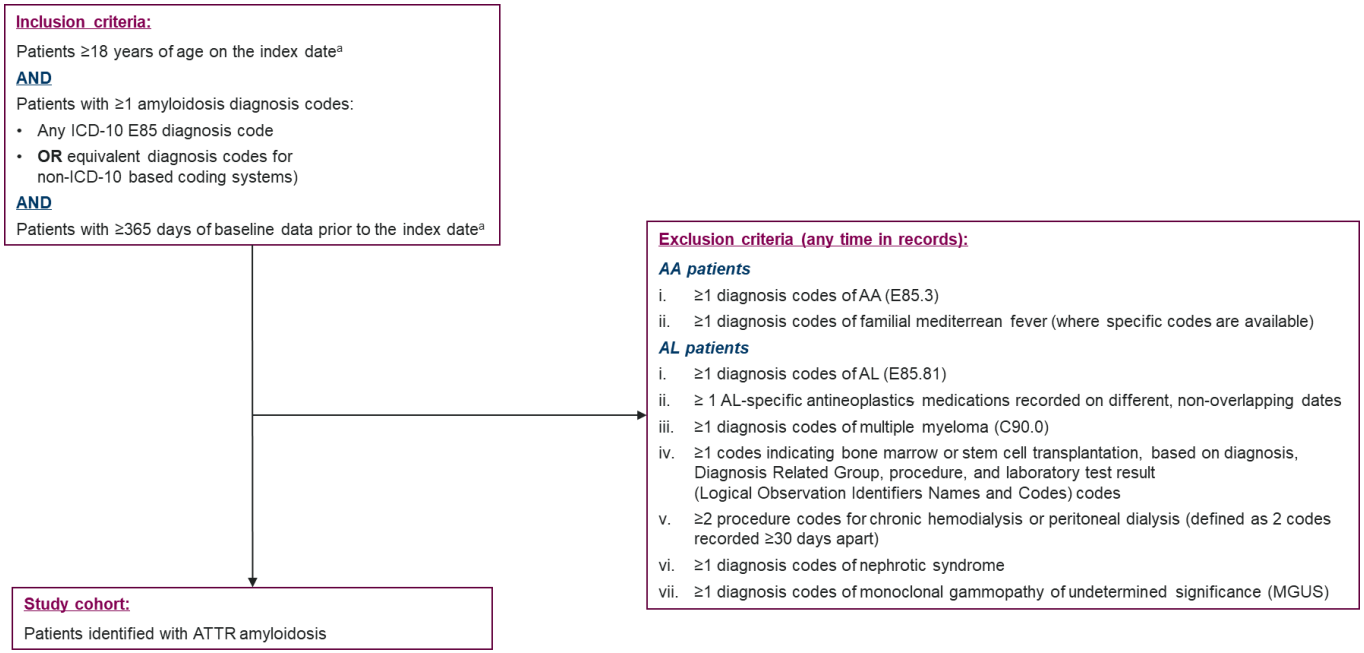
Optum® CDM uses International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) for diagnoses, Current Procedural Terminology and Healthcare Common Procedure Coding System for procedures, and National Drug Codes for medications. CPRD Aurum uses Systematized Nomenclature of Medicine-Clinical Terms codes for diagnoses, and ICD-10 and Office of Population Censuses and Surveys Classification of Interventions and Procedures codes are used for diagnoses and procedures in HES, respectively. MDV uses Japanese Disease Name Codes (based on ICD-10 codes), the Japanese K-code system for procedures, and national drug codes (YJ and HOT codes) for medications. CROSS-TRACKS uses ICD-10 codes for diagnoses, Nordic Classification of Surgical Procedures codes for procedures, and the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system for medications. The CELOSIA study uses ICD-10 codes for diagnoses, a national standardized classification system for procedures (klassifikation av vårdåtgärder codes), and WHO ATC codes for medications.

Additional exclusion criteria

Patients were excluded if they died before the index date, or had diagnosis, medication, and/or procedure codes for any of the following recorded at any time in their medical history: amyloid serum A protein amyloidosis, familial mediterranean fever, immunoglobulin light chain (AL) amyloidosis, multiple myeloma, AL-specific antineoplastic medications, bone marrow or stem cell transplantation, chronic hemodialysis, monoclonal gammopathy of undetermined significance, or a type of amyloidosis other than ATTR amyloidosis or those listed above. Patients were also

excluded if they had amyloidosis codes recorded on the index date that indicated both hereditary and wildtype disease.

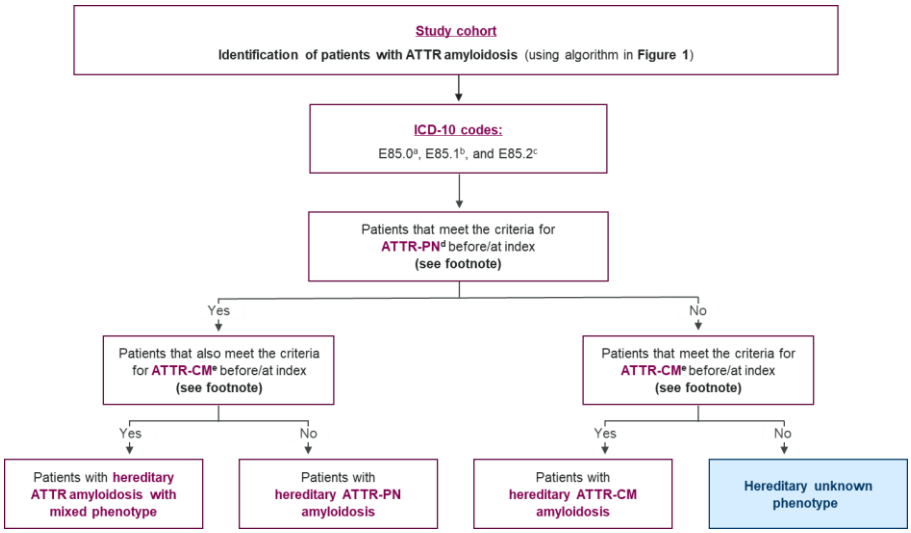
Fig. S1 OverTTuRe algorithm identifying patients with ATTR amyloidosis from claims and electronic medical record databases.



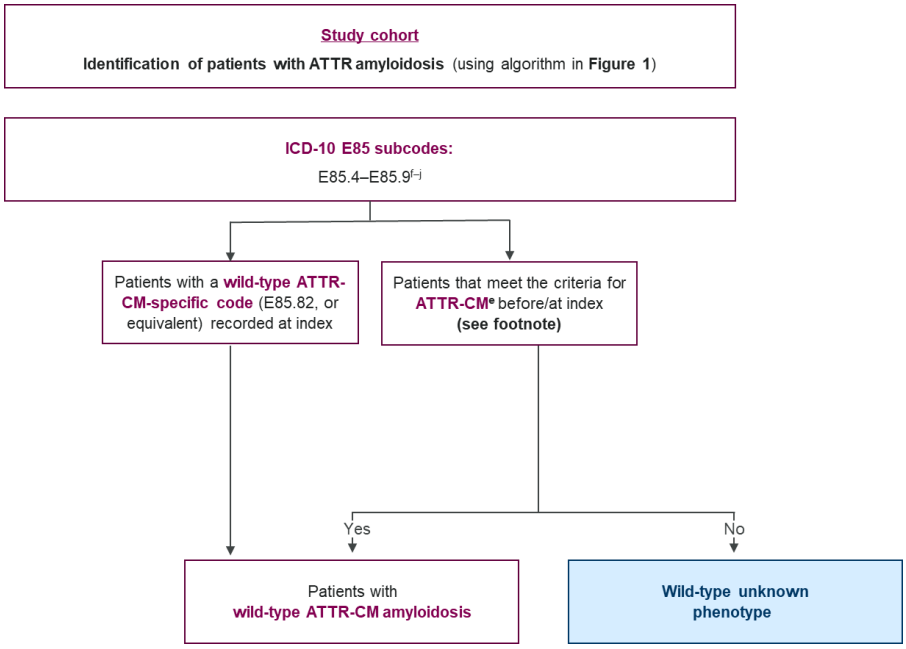
[a] The index date is the date of the earliest recorded amyloidosis diagnosis code. *AA* amyloid A, *AL* amyloid light chain, *ATTR* amyloid transthyretin, *ICD-10* International Classification of Disease, Tenth Revision

Fig. S2 Categorization of OverTTuRe **a** hereditary and **b** wild-type ATTR amyloidosis study groups

a



b



[a] E85.0: Non-neuropathic heredofamilial amyloidosis. [b] E85.1: Neuropathic heredofamilial amyloidosis. [c] E85.2: Heredofamilial amyloidosis, unspecified. [d] ATTR-PN is defined as the presence of a recorded E85.1 code (or equivalent), or diagnosis codes for any of the following conditions: neuropathy (including mono- and polyneuropathy) or autonomic dysfunction (see code list). [e] ATTR-CM is defined as diagnosis codes for any of

the following conditions: heart failure, cardiomyopathy, sinoatrial dysfunction, AV block, atrial fibrillation or flutter, aortic valve stenosis (see code list).[f] E85.4: Organ-limited amyloidosis. [g] E85.8: Other amyloidosis. [h] E85.82: Wild-type transthyretin-related (ATTR) amyloidosis. [i] E85.89: Other amyloidosis. [j] 85.9: Amyloidosis, unspecified

ATTR amyloid transthyretin, *ATTR-CM* ATTR amyloidosis with cardiomyopathy, *ATTR-PN* ATTR amyloidosis with polyneuropathy, *AV* atrioventricular, ICD-*10* International Classification of Diseases Tenth Revision

Table S1 Approval or reimbursement dates for ATTRv-PN therapies available during or prior to the study period by country

	United States	United Kingdom	Japan	Denmark	Sweden
***TTR* gene silencers**					
Vutrisiran	June 2022	Not reimbursed during the study period	September 2022	Not approved and/or reimbursed during the study period	November 2023[a]
Patisiran	August 2018	August 2019[a]	June 2019	November 2020	December 2018[b]
Inotersen	October 2018	May 2019[a]	Not approved during the study period	Not approved and/or reimbursed during the study period	May 2019[b]
TTR protein stabilizers					
Diflunisal	January 1996	January 1996	Not approved during the study period	Not approved and/or reimbursed during the study period	January 1996
Tafamidis	Not approved during the study period	Not reimbursed during the study period	September 2013[c]	March 2020[a,c]	November 2011[b,c]

January 1996 simply indicates that this drug was available for the whole study period and is not necessarily the exact approval date for indications of this drug (i.e. not specific to ATTR amyloidosis)

[a] Reimbursement date

[b] The CELOSIA study database does not capture data on patisiran and inotersen use, and data on tafamidis 20mg prescription may not be fully captured as this treatment was dispensed from hospital outpatient clinics

[c] Reflects approval or reimbursement dates, as otherwise indicated, for tafamidis 20mg dose

ATTR amyloid transthyretin, *ATTRv-PN* hereditary ATTR amyloidosis with polyneuropathy, *TTR* transthyretin

Table S2 Patient population by country

	United States		United Kingdom		Japan		Denmark		Sweden	
	Patients included, *n*	**Patients excluded, *n***	**Patients included, *n***	**Patients excluded, *n***	**Patients included, *n***	**Patients excluded, *n***	**Patients included, *n***	**Patients excluded, *n***	**Patients included, *n***	**Patients excluded, *n***
Patients with ≥ 1 E85 diagnosis code any time in their records (set the first record as the index date)	57,290	NA	14,240	NA	28,952	NA	776[a]	NA	9831	NA
Exclude patients who died before the index date or who were not aged ≥ 18 years on the index date	55,066	2224	8410	5830[b]	28,302	650	NA	NR	7734	2097
Exclude patients with ≥ 1 diagnosis code of AA any time in their record	53,720	1346	7517	893	19,942	8360	747	29	7354	380
Exclude patients with ≥ 1 diagnosis code for FMF any time in their record	53,720	0	7420	97	19,942	0	606	141	NA	NA
Exclude patients with ≥ 1 diagnosis code of AL any time in their record	49,051	4669	7180	240	17,660	2282	523	83	6488	866
Exclude patients who had multiple myeloma any time in their record or who had bone	43,628	5423	6523	657	13,667	3993	493[c]	30	6145	343

marrow or stem cell transplantation any time in their record										
Exclude patients who had ≥ 1 AL-specific antineoplastics medication/injection records any time in their record	43,063	565	6494	29	13,574	93	NA	NR	6065	80
Exclude patients who had ≥ 2 procedure or diagnosis codes for chronic hemodialysis or peritoneal dialysis (≥ 30 days apart), any time in their record	41,573	1490	6218	276	12,665	909	480	13	5871	194
Exclude patients who had ≥ 1 diagnosis code for nephrotic syndrome any time in their record	41,125	448	6041	177	12,233	432	472	8	5813	58
Exclude patients who had ≥ 1 diagnosis code for MGUS any time in their record	39,171	1954	5856	185	12,126	107	442	30	5580	233
Exclude patients with ≥ 1 diagnosis code of other amyloidosis (not AL/AA/ATTR) any	39,171	0	3929	1927	7693	4433	NA	NA	NA	NA

time in their record (applicable to non–ICD-10-based coding systems only)										
Exclude patients who had ≥ 1 diagnosis code for cerebral amyloid angiopathy (I68.0) any time in their record	NA	NA	NA	NA	NA	NA	NA	NA	4296	1284
Exclude patients who did not have their first E85 diagnosis code at any of the accepted care unit types	NA	NA	NA	NA	NA	NA	NA	NA	2237[d]	2059
Exclude patients with both hereditary and wild-type amyloidosis diagnosis codes on the index date	39,097	74	3921	8	7609	84	NA	NA	2237[d]	0
Exclude patients with unknown sex	39,087	10	NA	NA	NA	NA	NA	NA	NA	NA
Patients with earliest diagnosis (index date) between January 1, 2014, and December 31, 2023, and had been enrolled	20,240	18,847	2201	1720	3100	4509	371	71	1676	561

≥ 365 days before the index date[e]										
Patients identified as having a diagnosis of ATTRv amyloidosis and categorized as ATTRv-PN or ATTRv mixed phenotype status	978	19,262	110	2091	80	3020	6[f]	365	328	1348
Patients with ≥ 1826 days (5 years) enrollment before the index date (applicable to early clinical manifestations and HCRU pre-diagnosis analyses only)	392	586	87	23	41	39	6[f]	0	328	0

[a] Includes patients who died before the index date, or who were not aged ≥ 18 years on the index date ($n < 5$); these excluded patients are captured here to protect patient confidentiality

[b] Patients who died or were transferred out before practice up-to-standard or registration start date were also excluded

[c] Or who had at least one AL-specific antineoplastics medication/injection any time in their record ($n < 5$); these excluded patients are captured here to protect patient confidentiality

[d] Accepted care unit types for first E85 diagnosis in Sweden: Internal Medicine Care, Gastroenterology Care, Neurology Care, Cardiology Care

[e] Patients in the US cohort were diagnosed with ATTR amyloidosis between January 1, 2017, and December 31, 2023, and patients in the UK cohort between January 1, 2014, and December 31, 2022

[f] Number is approximate; includes 6 ATTR-PN patients. ATTRv mixed count was <5 so suppressed to protect patient confidentiality

AA amyloid A, *AL* amyloid light-chain, *ATTR* amyloid transthyretin, *ATTRv mixed* hereditary ATTR amyloidosis with mixed phenotype, *ATTRv-PN* hereditary ATTR amyloidosis with polyneuropathy, *FMF* familial Mediterranean fever, *HCRU* healthcare resource utilization, *ICD-10* International Classification of Diseases, Tenth Revision, *MGUS* monoclonal gammopathy of undetermined significance, *NA* not available, *NR* not reportable

Table S3 Additional cardiac manifestation data in patients with ATTRv mixed, by country

	United states	United Kingdom	Japan	Denmark	Sweden
Patients, *n*	208	42	22	< 5	119
Any cardiac manifestations, *n* (%)	163 (78.4)	37 (88.1)	20 (90.9)	NR	118 (99.2)
Median (IQR) time from manifestation to diagnosis, years	1.6 (0.4–3.4)	0.4 (0.0–2.5)	1.6 (0.1–2.8)	NR	0.9 (0.0–3.1)
Aortic valve stenosis, *n* (%)	45 (21.6)	7 (16.7)	< 5	NR	12 (10.1)
Median (IQR) time from manifestation to diagnosis, years	1.6 (1.1–4.1)	1.9 (0.6–3.4)	NR	NR	3.5 (2.5–4.0),
AF or AFL, *n* (%)	56 (26.9)	20 (47.6)	6 (27.3)	NR	55 (46.2)
Median (IQR) time from manifestation to diagnosis, years	2.2 (0.6–3.6)	0.4 (0.0–2.6)	0.4 (0.0–1.6)	NR	2.0 (0.5–3.7)
AV block, *n* (%)	42 (20.2)	6 (14.3)	< 5	NR	17 (14.3)
Median (IQR) time from manifestation to diagnosis, years	1.2 (0.5–2.7)	2.0 (0.5–3.2)	NR	NR	1.1 (0.4–1.9)

Cardiomyopathy, *n* (%)	31 (14.9)	< 5	< 5	NR	57 (47.9)
Median (IQR) time from manifestation to diagnosis, years	2.4 (1.0–3.9)	NR	NR	NR	0.0 (0.0–0.3)
Heart failure, *n* (%)	84 (40.4)	19 (45.2)	15 (68.2)	NR	51 (42.9)
Median (IQR) time from manifestation to diagnosis, years	1.3 (0.3–3.1)	0.6 (0.0–3.2)	1.9 (0.8–3.2)	NR	0.5 (0.1–1.4)
Patients with ≥2 cardiac manifestations, *n* (%)	61 (29.3)	13 (31.0)	6 (27.3)	NR	56 (47.1)

Any cardiac manifestation includes heart failure, cardiomyopathy, atrial fibrillation or flutter, AV block, and aortic valve stenosis. Includes only patients with 5 years of available lookback data. Cardiac manifestations reported in patients with ATTRv mixed only. Groups with cardiac manifestations that were reported in < 5 patients have been excluded

AF atrial fibrillation, *AFL* atrial flutter, *ATTR* amyloid transthyretin, *ATTRv mixed* hereditary ATTR amyloidosis with mixed phenotype, *AV* atrioventricular, *IQR* interquartile range, *NA* not available, *NR* not reportable

Table S4 Additional noncardiac manifestation data, by country and phenotype

	United States		United Kingdom		Japan		Denmark		Sweden	
	ATTRv-PN	**ATTRv mixed**	**ATTRv-PN**	**ATTRv mixed**	**ATTRv-PN**	**ATTRv mixed**	**ATTRv-PN**	**ATTRv mixed**	**ATTRv-PN**	**ATTRv mixed**
Patients, *n*	184	208	45	42	19	22	6	< 5	209	119
Any noncardiac manifestation, *n* (%)	135 (73.4)	136 (65.4)	19 (42.2)	23 (54.8)	18 (94.7)	19 (86.4)	5 (83.3)	NR	101 (48.3)	60 (50.4)
Median (IQR) time from manifestation to diagnosis, years	2.9 (1.0–4.0)	2.4 (0.8–3.7)	0.3 (0.0–3.0)	1.0 (0.5–2.7)	0.0 (0.0–0.3)	0.7 (0.0–3.2)	2.8 (2.6–3.3)	NR	0.5 (0.2–2.1)	1.2 (0.4–3.1)
CTS, *n* (%)	15 (8.2)	15 (7.2)	< 5	0 (0.0)	0 (0.0)	0 (0.0)	< 5	NR	15 (7.2)	14 (11.8)
Median (IQR) time from manifestation to diagnosis, years	2.1 (0.6–3.6)	2.3 (1.1–3.6)	NR	NA	NA	NA	NR	NR	2.2 (1.2–2.9)	3.0 (1.6–3.9)
CTS surgery, *n* (%)	< 5	< 5	0 (0.0)	< 5	0 (0.0)	0 (0.0)	< 5	NR	< 5	< 5
Median (IQR) time from manifestation to diagnosis, years	NR	NR	NA	NR	NA	NA	NR	NR	NR	NR
Erectile dysfunction, *n* (%)	< 5	< 5	< 5	< 5	0 (0.0)	0 (0.0)	< 5	NR	< 5	< 5
Median (IQR) time from manifestation to diagnosis, years	NR	NR	NR	NR	NA	NA	NR	NR	NR	NR

GI dysfunction, *n* (%)	77 (41.8)	72 (34.6)	13 (28.9)	19 (45.2)	6 (31.6)	9 (40.9)	< 5	NR	23 (11.0)	15 (12.6)
Median (IQR) time from manifestation to diagnosis, years	3.0 (1.6–4.1)	2.7 (1.0–4.2)	0.6 (0.0–3.0)	1.0 (0.5–2.7)	1.7 (0.0–3.1)	2.3 (1.0–3.5)	NR	NR	0.9 (0.4–3.8)	1.4 (0.6–3.3)
Neuropathy, *n* (%)[a]	54 (29.3)	64 (30.8)	7 (15.6)	< 5	17 (89.5)	14 (63.6)	< 5	NR	76 (36.4)	42 (35.3)
Median (IQR) time from manifestation to diagnosis, years	1.8 (0.2–3.4)	1.6 (0.4–3.0)	0.3 (0.0–3.7)	NR	0.0 (0.0–0.2)	0.0 (0.0–1.5)	NR	NR	0.3 (0.2–0.9)	0.4 (0.2–0.7)
Spinal stenosis, *n* (%)	32 (17.4)	36 (17.3)	< 5	0 (0.0)	0 (0.0)	6 (27.3)	< 5	NR	9 (4.3)	6 (5.0)
Median (IQR) time from manifestation to diagnosis, years	2.5 (1.1–3.7)	2.8 (1.2–3.6)	NR	NA	NA	1.6 (0.7–2.0)	NR	NR	2.0 (0.6–2.3)	3.0 (0.9–4.4)
Patients with ≥2 noncardiac manifestations, *n* (%)	37 (20.1)	43 (20.7)	< 5	< 5	5 (26.3)	9 (40.9)	< 5	NR	19 (9.1)	17 (14.3)

Includes only patients with 5 years of available lookback data. For patients with ATTRv mixed from Denmark, data were not presented due to small patient numbers. Groups with noncardiac manifestations that were reported in < 5 patients have been excluded

[a] Includes mono-, poly- and other neuropathy, and autonomic neuropathy

ATTR amyloid transthyretin, *ATTRv mixed* hereditary ATTR amyloidosis with mixed phenotype, *ATTRv-PN* hereditary ATTR amyloidosis with polyneuropathy, *CTS* carpal tunnel syndrome, *GI* gastrointestinal, *IQR* interquartile range, *NA* not available, *NR* not reportable

Table S5 Treatment patterns after diagnosis of ATTR amyloidosis

	United States		United Kingdom		Japan		Sweden	
	ATTRv-PN	**ATTRv mixed**	**ATTRv-PN**	**ATTRv mixed**	**ATTRv-PN**	**ATTRv mixed**	**ATTRv-PN**	**ATTRv mixed**
Post-treatment approval cohort, *n*	529	449	60	50	41	39	209	119
Patients treated with any ATTR amyloidosis treatment, *n* (%)	15 (2.8)	< 5	< 5	0 (0.0)	< 5	14 (35.9)	108 (51.7)	70 (58.8)
TTR protein stabilizers								
Post-treatment approval cohort, *n*	529	449	60	50	41	39	209	119
Patients treated with TTR protein stabilizers, *n* (%)	6 (1.1)	< 5	< 5	0 (0.0)	< 5	12 (30.8)	108 (51.7)[a]	70 (58.8)[a]
***TTR* gene silencers**								
Post-treatment approval cohort, *n*	405	374	17	18	25	23	< 5	5
Patients treated with TTR gene silencers, *n* (%)	11 (2.7)	< 5	0 (0.0)	0 (0.0)	< 5	5 (21.7)	NR	0 (0.0)

Analysis cohort represents patients identified as being diagnosed with ATTR amyloidosis following the earliest approval within TTR protein stabilizer or *TTR* gene silencer treatment classes. These analyses take account of when treatments were approved for different phenotype indications in the respective countries. Treatment approval or reimbursement dates by country are presented in **Supplementary Material Table S1**. For the United States, stabilizer treatment includes diflunisal and tafamidis, and silencer treatment includes inotersen, patisiran, and vutrisiran. For the United Kingdom, stabilizer treatment includes diflunisal, and silencer treatment includes inotersen and patisiran. For Japan, stabilizer treatment includes tafamidis, and silencer treatment includes patisiran and vutrisiran. For Sweden, stabilizer treatment includes diflunisal and tafamidis, and silencer treatment includes vutrisiran. For Denmark, stabilizer treatment includes tafamidis, and silencer treatment includes patisiran (data were not reportable due to a small patient sample)

[a] Data on tafamidis 20mg prescription may not be fully captured in the CELOSIA study database as this treatment was dispensed from hospital outpatient clinics

ATTR amyloid transthyretin, *ATTRv mixed* hereditary ATTR amyloidosis with mixed phenotype, *ATTRv-PN* hereditary ATTR amyloidosis with polyneuropathy, *NR* not reportable, *TTR* transthyretin