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Phenotypic characteristics of p.Val142Ile hereditary Amyloidosis in the HEAR Registry

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RATIONALE

Transthyretin amyloidosis (ATTR amyloidosis) is a progressive multisystemic disorder with two primary forms: wild-type (ATTRwt) and hereditary (ATTRv). The p.Val142Ile mutation is one of the most common pathogenic variants of the TTR gene and is associated with a predominantly cardiac phenotype (ATTR-CM). As novel, potent therapeutic options emerge, it becomes imperative to revisit the natural history of p.Val142Ile ATTR-CM to better understand its trajectory and optimize patient care.

The Healthcare European Amyloid Registry (HEAR), the largest ongoing global registry for ATTR amyloidosis, presents a unique opportunity to achieve this goal. By incorporating both a historic cohort and a modern-era cohort of patients receiving disease-specific treatments, HEAR facilitates comprehensive insights into the evolution of p.Val142Ile ATTR-CM and the impact of current therapeutic strategies.

Main objective:

- To describe the baseline clinical and demographic features of symptomatic patients with p.Val142Ile hereditary transthyretin cardiac amyloidosis across two cohorts: a historical cohort and a modern-era cohort.
- These characteristics will be contrasted with those of patients with wild-type transthyretin cardiac amyloidosis (ATTRwt) and patients with hereditary cardiac amyloidosis associated with other pathogenic TTR variants.

Secondary objective:

- To evaluate survival outcomes in symptomatic patients with p.Val142Ile hereditary transthyretin cardiac amyloidosis (ATTR-CM) across the historical and the modern-era cohorts.
- These outcomes will be compared to those of patients with wild-type transthyretin cardiac amyloidosis (ATTRwt) and hereditary cardiac amyloidosis caused by other pathogenic TTR variants.

Inclusion criteria:

- ATTR-CM defined either by biopsy or by Gillmore algorithm
- TTR genotype

Exclusion criteria:

- Cardiomyopathy from other causes

Study parameters – Table 1 – Clinical and demographic data at baseline in patients

	p.V142I ATTR-CM	wtATTR-CM	p-value	Other hATTR-CM	p-value
Age at diagnosis, years					
Male gender, n(%)					
African descent, n(%)					
High blood pressure					
type 2 diabetes , n(%)					
dyslipemia, n(%)					
History of heart failure, n(%)					
History of Stroke, n(%)					
History of thromboembolic event, n(%)					
History of orthopedic surgery, n(%)					
systolic blood pressure, mmHg					
diastolic blood pressure, mmHg					
Weight, kg					

Height, cm					
BMI, Kg/m^2					
History of carpal tunnel syndrome, n(%)					
History of spinal lumbar stenosis, n(%)					
History of spinal cervical stenosis, n(%)					
History of Hearing loss , n(%)					
NYHA functional class I-II, n(%)					
NYHA functional III-IV, n(%)					
Age at initiation of first specific treatment, years					
Delay in specific treatment (age at treatment initiation minus age at diagnosis) , months					
History of PaceMaker implantation					

Study parameters – Table 2 – Multimodal disease evaluation at baseline

	p.V142I	wtATTR-CM	p-value	Other hATTR-CM	p-value
Sinus Rhythm					
Atrial Fibrillation					
PR duration					
QRS duration					
IVS (interventricular septum thickness)					
PP (posterior wall thickness)					
RWT (relative wall thickness)					
LV (left ventricle dimensions)					
Stroke volume					
LVEF (left ventricular ejection fraction)					
Cardiac Index					
Global longitudinal Strain					
Myocardial Contraction Fraction					
Strain Apex to base ratio (normal vs. abnormal)					
6-minute walk distance (6MWD)					
NT-proBNP					
BNP					

Troponin					
Urea					
creatinine					
eGFR					
Sodium					
potassium					
Perugini score					

Evaluation of the secondary objective:

Kaplan-Meier plots adjusted for age will be generated for the three patient groups within both cohorts.

Additionally, the impact of therapeutic delay on survival will be assessed using Cox proportional hazards analysis.