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## THAOS in 2017: Looking to the future

Dear THAOS Investigators,

I would first like to thank the THAOS Scientific Board for the opportunity to serve as the Chair-Elect for the THAOS Registry and for electing me to the position. It is with pleasure that I accept this role and I look forward to working with our Chair Márcia Waddington-Cruz, the rest of the board and global investigators to help expand and develop the THAOS registry in the coming years.

The THAOS Registry continues to grow with regard to the wealth of data acquired on subjects and gene carriers of TTR amyloidosis and with this, our investigators continue to be very active in disseminating important research. To this end, in 2017 we have seen three publications based on data from the registry including:

- Cruz MW, Barroso F, González-Duarte A, et al. ; on behalf of the THAOS Investigators. The demographic, genetic, and clinical characteristics of Latin American subjects enrolled in the Transthyretin Amyloidosis Outcomes Survey. *Amyloid*. 2017;24(sup1):107-108.
- Cruz MW, Foguel D, Berensztejn AC, et al. ; THAOS Investigators. The demographic, genetic, and clinical characteristics of Brazilian subjects enrolled in the

Transthyretin Amyloidosis Outcomes Survey. *Amyloid*. 2017;24(sup1):103-104.

- Kristen AV, Maurer MS, Rapezzi C, et al; THAOS investigators. Impact of genotype and phenotype on cardiac biomarkers in patients with transthyretin amyloidosis – Report from the Transthyretin Amyloidosis Outcome Survey (THAOS). *PLoS One*. 2017;12(4):e0173086.

In addition, there are a number of manuscripts in development for 2017 that we look forward to seeing published. Areas of research include evaluating renal disease, European genotypes and cardiac phenotypes, an overview of Brazilian subjects in the registry, as well as the effects of gender and myocardial contraction fraction (MCF) on cardiac outcomes in THAOS subjects. We look forward to seeing the publication of learnings from THAOS continue this year and beyond.

As of January 30<sup>th</sup> 2017, 3231 subjects from 20 countries with 96 mutations have been enrolled in THAOS. This is an impressive 27% increase since January 2015 and reflects the continued efforts of the investigator community. On behalf of the Board, I would like to thank all investigators for their continued hard work in helping to progress and

evolve the THAOS registry. The work we do ensures that the registry remains an excellent resource that can help to improve our knowledge, our clinical practice and the lives of patients with TTR amyloidosis.

October will see our group meet in Rome for the next Investigator meeting. This meeting always stimulates active discussion and debate around how we can best utilise THAOS to improve awareness of TTR amyloidosis and, ultimately, to facilitate the provision of optimal care for our patients. I look forward to seeing you all in Rome.

**Arnt Kristen,**

*Chair-Elect of the THAOS Scientific Board,*  
Department of Cardiology, University  
Clinical Centre Heidelberg, Germany



## THAOS Scientific Board

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# Spotlight

Each edition of the THAOS newsletter will feature a 5-minute interview with an investigator who will explain their rationale for being part of the registry, how it works within their clinic and their aspirations for the registry in the future.

Violaine Planté-Bordeneuve holds a position as a Professor of Neurology at the Department of Neurology, CHU Henri Mondor, Créteil, France where she set up a multidisciplinary network dedicated to amyloidosis, recently labelled reference center. Her main research interests include neurogenetics, neuromuscular disorders, particularly inflammatory neuropathies and inherited neuropathies. In the field of transthyretin familial amyloid polyneuropathy her works covered genotypic–phenotypic correlations, genetic epidemiology and therapeutic approaches.

## Q1: How is THAOS organized in your clinic?

Each week we hold a clinic for patients with ATTR and I carefully evaluate the neurologic aspects of their disease. At my centre, we are organised within a multidisciplinary network and patients will typically also receive cardiologic evaluation on the same day. The following day, a dedicated member of the team will upload all data collected at the clinic to THAOS ready for my review and signature. THAOS prompts us to upload data on a regular basis and we rely on the database for accurate follow up of our patients. We know that by using THAOS as our guide, we will achieve appropriate follow-up of all aspects of the disease for every patient.

## Q2: What do you see as the key value of THAOS for patients and physicians?

In addition to supporting accuracy of follow up for each patient we monitor, THAOS ensures that we pay attention to other manifestations of this systemic disease. As neurologists, we tend to see only the neurologic aspects of disease. THAOS is helpful in ensuring that we gather a global overview of a patient's disease. This is important for ensuring that we deliver the best care for each individual patient. Beyond this, THAOS has been important in helping us to develop new tools for disease assessment such as cardiac scintigraphy.

## Q3: How do you believe THAOS has shaped understanding of ATTR and clinical practice?

THAOS has offered important input into our understanding of ATTR. A wealth

of data has been collected in THAOS that helps improve understanding of the phenotype and genotype of the disease in different areas across the world. We have learned a tremendous amount about different aspects of the disease; cardiologic aspects in particular are now far better delineated. THAOS helped us to understand ATTR as a systemic disease, not just a neurologic disease as it was historically known. Beyond this, as Investigators we have also learnt a lot from each other and THAOS has facilitated this by increasing interaction between different physicians in different specialities.

## Q4: What advantages does THAOS bring to your research?

Using the THAOS database, it is easy for us to extract information on different aspects of our patient population. This can then be covered in educational presentations or used to answer questions we have in our clinical research. For example, as we know, misdiagnosis is an important challenge we face with ATTR. Through analysing the data in THAOS on subjects who have been misdiagnosed I have been able to prepare presentations that provide accurate information on patient groups in which ATTR should be considered to help avoid misdiagnosis.

## Q5: What do you hope THAOS will contribute over the next five years?

Today, we better understand the phenotype and genotypes of ATTR, and this is in large part thanks to THAOS. Moving forwards, I think that THAOS can really support us, both in improving follow up of these patients and in

understanding how different aspects of this systemic disease progress. I believe that THAOS will help us to understand how the disease course varies within different groups of patients and will help us to not only understand the natural history according to genotype and phenotype, but also the impact that treatment has on patients in the long term.

## Q6: If you could give one piece of advice to a new THAOS center, what would it be?

I would strongly recommend that physicians set up a network between neurologists, cardiologists and other specialities in their hospital to ensure that all aspects of a patient's disease are being fully assessed. We must consider this disease as truly systemic and must follow all aspects of their disease, at least every year. We must be prepared to use the information that we gather and modify treatments if necessary in order to deliver the best possible care for our patients.



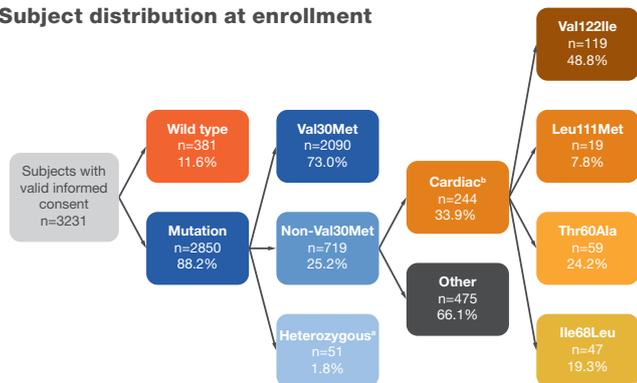
## Violaine Planté-Bordeneuve

Department of Neurology,  
CHU Henri Mondor, Créteil, France

# THAOS Today

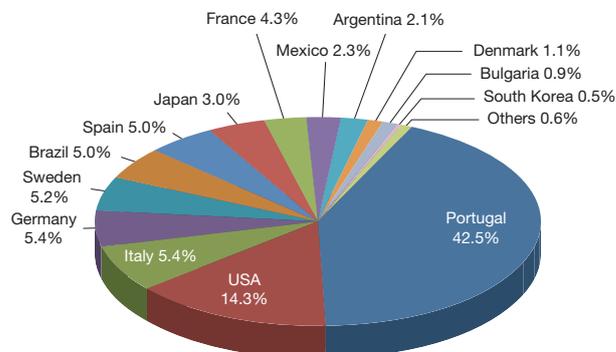
## Genotype, Phenotype and Geography

### Subject distribution at enrollment

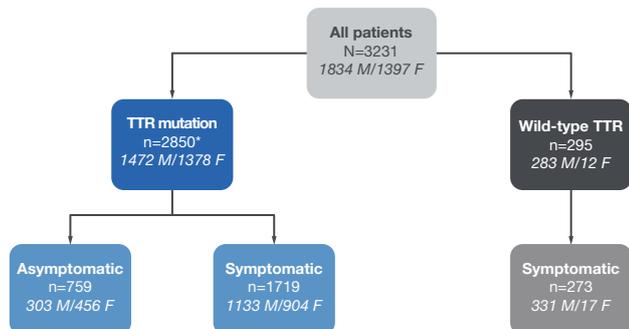


\*Reported TTR mutation but missing specific genotype details.  
 †Cardiac mutations include: Val122Ile, Leu111Met, Thr60Ala, and Ile68Leu.

### Countries and contributions to THAOS (%): 20 countries, 3231 subjects, as of January 2017



### THAOS subject disposition: 30 January 2017



F, female; M, male.  
 \* 54 subjects symptomatic status unknown.

### Most common TTR mutations in Jan 2017 (96 unique mutations in 3231 subjects)

Mutation	Total number of patients	% of patients with TTR mutation (N=2850)	Cumulative (%)
Val30Met	2080	73.0	73.7
Val122Ile	119	4.2	77.9
Glu89Gln	67	2.4	80.2
Ser50Arg	67	2.4	82.6
Thr60Ala	59	2.1	84.6
Ile68Leu	47	1.6	86.3
Phe64Leu	32	1.1	87.4
Ser77Tyr	28	1.0	88.4

Additional 84 different mutations reported in 15 or less subjects

## Upcoming posters

Abstracts based on research from THAOS have been accepted at the following meetings:

### PNS

Peripheral Nerve Society – 2017 Biennial Meeting,  
July 8–12, 2017, Sitges, Spain

Autonomic symptoms in transthyretin amyloidosis: an analysis of symptomatic subjects from the THAOS registry.

F. Barroso, Y. Ando, A. Gonzalez-Duarte, H. Schmidt, R. Mundayat.

### HFSA

Heart Failure Society of America – 21st Annual Scientific Meeting, September 16–19, Dallas, TX, USA

A Survival Analysis of Subjects with Transthyretin Amyloid Cardiomyopathy from the Transthyretin Amyloidosis Outcomes Survey

M. Grogan, A. Dispenzieri, M. Carlsson, M. Stewart, J. Schumacher

Description of the Health-Related Quality of Life of Transthyretin Amyloid Cardiomyopathy Subjects from the Transthyretin Amyloidosis Outcomes Survey

M. Grogan, A. Dispenzieri, M. Carlsson, J. Schumacher, M. Stewart

### WCN

World Congress of Neurology 2017,  
September 16–21 2017, Kyoto, Japan

Late-Onset Transthyretin Familial Amyloid Polyneuropathy: Characterization of Brazilian Subjects From The THAOS Registry  
M. Waddington Cruz, A. Berensztejn, M.V. Pinto, R. Mundayat

Assessing the Onset and Characteristics of Orthostatic Hypotension in Patients with Transthyretin Amyloidosis from The Transthyretin Amyloidosis Outcomes Survey (THAOS)  
A. Gonzalez-Duarte, R. Mundayat, B. Shapiro

The Demographic, Genetic, and Clinical Characteristics of Asian Subjects Enrolled in The Transthyretin Amyloidosis Outcomes Survey (THAOS)

M. Waddington Cruz, Y. Sekijima, R. Mundayat

# Recent THAOS research

## Impact of genotype and phenotype on cardiac biomarkers in patients with transthyretin amyloidosis – Report from the Transthyretin Amyloidosis Outcome Survey (THAOS)

Kristen K, Maurer M, Rapezzi C, Suhr O, Damy T, et al.; On behalf of the THAOS Investigators *PLoS One* April 2017

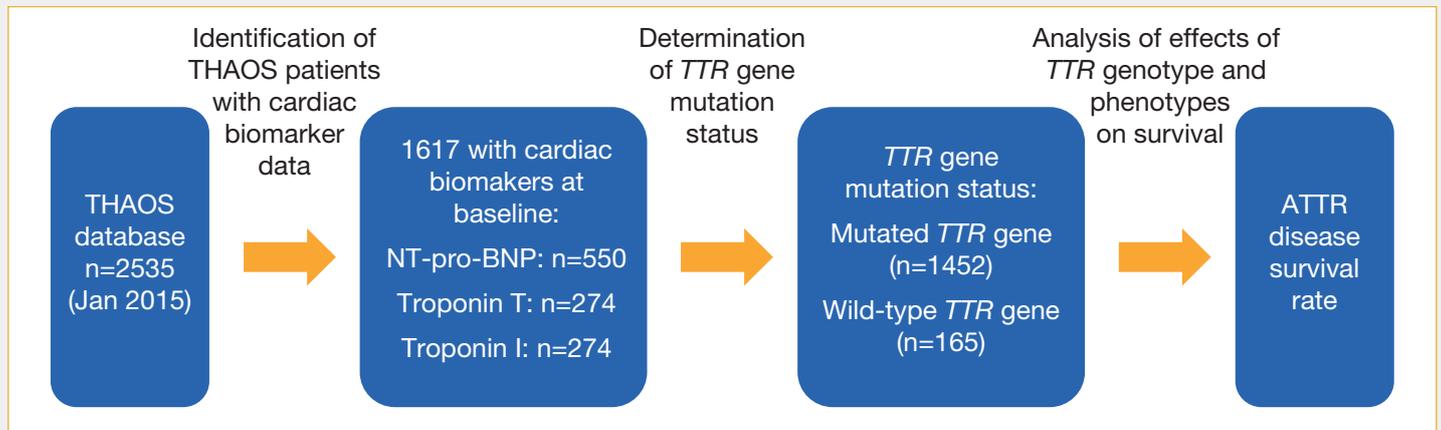


Figure 1

### Aim and study design

The cardiac biomarkers troponin I and T and the natriuretic peptides NT-proBNP and BNP were analysed for differences between genotypes and phenotypes and their association with survival in transthyretin amyloidosis (ATTR) subjects using the large and heterogeneous THAOS database cohort (Figure 1).

### Results

Following analysis of the data, NT-proBNP and BNP serum concentrations were found to be higher in ATTR subjects with wild-type compared to subjects with a variant *TTR* gene. Within the group of subjects with a variant *TTR* gene:

- Non-Val30Met mutation patients had higher BNP, NT-proBNP and troponin T levels than Val30Met mutation patients
- Late-onset Val30Met ATTR disease (first symptoms at age >50 years) was associated with higher levels of troponin I and troponin T levels compared with early-onset ATTR (first symptoms at age <30 years)

Of note, the mortality rate was seen to increase with increasing BNP and NT-proBNP serum levels.

Age, modified body mass index, *TTR* mutation type (Val30Met vs. non-Val30Met) and BNP and NT-proBNP levels were independent predictors of survival in patients with *TTR* gene mutation-type ATTR.

### Conclusions

The study revealed that the levels of cardiac biomarkers troponin I and T and the natriuretic peptides NT-proBNP and BNP were abnormal in a substantial percentage of subjects with ATTR, irrespective of *TTR* genotype.

Age, mBMI, and *TTR* mutation type (Val30Met vs. Non-Val30Met) and cardiac biomarkers were associated with ATTR disease severity and BNP and NT-proBNP were identified as independent predictors of survival in ATTR.

Further research is needed to evaluate whether increased levels of BNP and NT-proBNP represent biomarkers of unidentified cardiac involvement in ATTR.

**2017 Investigator Meeting**  
**– Rome, Italy, 7–8 October 2017**  
**– Please HOLD THE DATE**

This year, the THAOS Investigator meeting will be held in Rome on the 7<sup>th</sup> and 8<sup>th</sup> of October. More information on this event will be shared with you shortly; in the meantime, please mark this date in your calendars.

# Optimizing information capture

## Efforts to Optimize Information Capture – Cardiac assessments

As the science of TTR amyloidosis develops, we are learning that the disease does not consist of only two distinct phenotypes – neurologic and cardiac, but presents as a spectrum of systemic symptoms. Given this, the goal for all patients in the THAOS registry should be a balanced documentation of all relevant signs and symptoms of the disease as it manifests systemically.

In the past, our data focus has been largely on documenting the neurologic presentation of TTR amyloidosis with less emphasis on the cardiac symptoms. In agreement with the Scientific Board, we are updating the Minimum Dataset (MDS) to ensure inclusion of critically important cardiac endpoints that will help us accumulate the data to understand how the disease presents more broadly.

While the ultimate goal for all subjects in the registry would be data for both the neurologic and cardiac endpoints, we realize that presently that may not be possible. The changes being implemented will now also allow reimbursement for sites that care for patients with predominantly cardiac manifestations, where neurologic assessments may not be performed as part of their standard of care.

The provision of either cardiac assessment data or neurologic assessment data for a visit will therefore qualify for payment.

This update has been applied retroactively to the 1<sup>st</sup> of January 2014 onwards and we encourage all sites to enter and sign data on an ongoing basis throughout the year.

## Site payments

The next site payments for patient visits will be completed in **July 2017**. Please be sure to input and have all visit data signed by 30<sup>th</sup> of June to be eligible for the July payment cycle. If you require assistance with your username or password, please contact THAOS Support at [www.thaos-support@pcpal.eu](mailto:www.thaos-support@pcpal.eu).

## PCPal Upgrades to speed

A new PcPal release is scheduled for Q2 and includes a number of changes and improvements. More detailed information will be distributed as we near the release date.

## Cardiac assessments include:

### LABORATORY DATA

- Creatinine or not available
- BNP or NT-BNP or not available
- Troponin-T or Troponin-I or not available
- Serum Protein Electrophoresis Albumin OR not available

### ASSESSMENTS

#### Cardiovascular – electrocardiogram

- Overall interpretation of ECG
- Abnormalities in rhythm (if yes capture specifics)
- Was Pacemaker implanted?
- Implantable cardiac defibrillator inserted?
- Intervals
  - PR
  - QRS
  - QT
  - QTc
- Amplitudes
  - Low voltage
  - R-1 (mm)
  - R-III (mm)
  - R-aVL (mm)
- Abnormalities in conduction (if yes capture specifics)

#### Cardiovascular – echocardiogram

- (Only one echocardiogram is required per year)
- LV Septum thickness acquisition mode & mm
  - LV posterior wall acquisition mode & mm
  - LV diastolic diameter acquisition mode & mm
  - LV systolic diameter acquisition mode & mm
  - LV ejection fraction acquisition mode and %
  - Quantitative LV end systolic volumes
  - Quantitative end diastolic volumes
  - Valve abnormalities (yes or no)
  - Echogenicity – Sparkling (yes or no)