

VENERDI' I MARZO

UNA NUOVA TERAPIA PER L'AMILOIDOSI: UNA MALATTIA NON PIÙ ORFANA

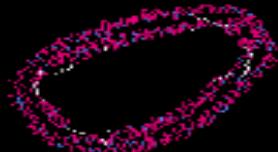
Claudio Rapezzi

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Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale
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TTR-CM: the great pretender

- Challenging
- Fascinating
- Mysterious
- Not as rare as supposed
- Relatively easy to detect (when suspected !)
- Treatable !!

Apo A



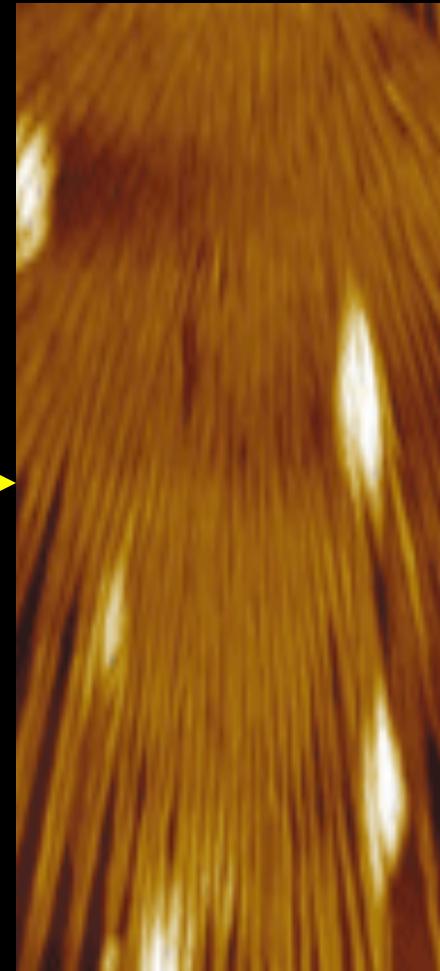
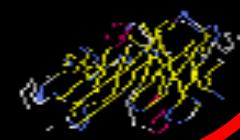
Immunoglobulin



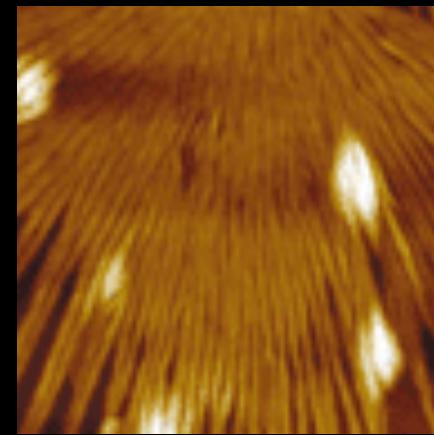
Lysozime



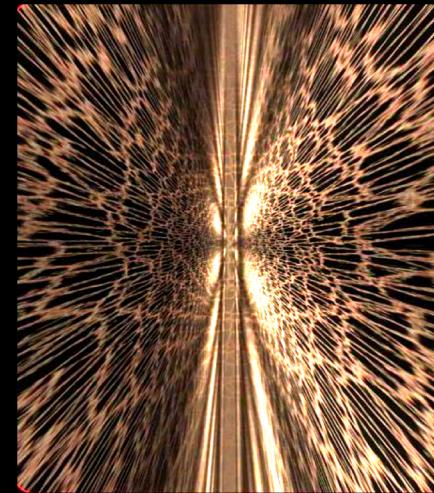
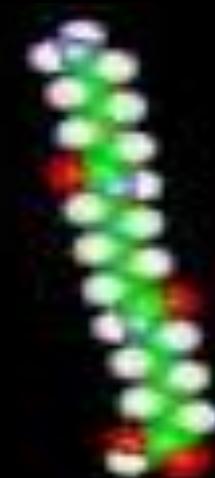
TTR



Amiloide



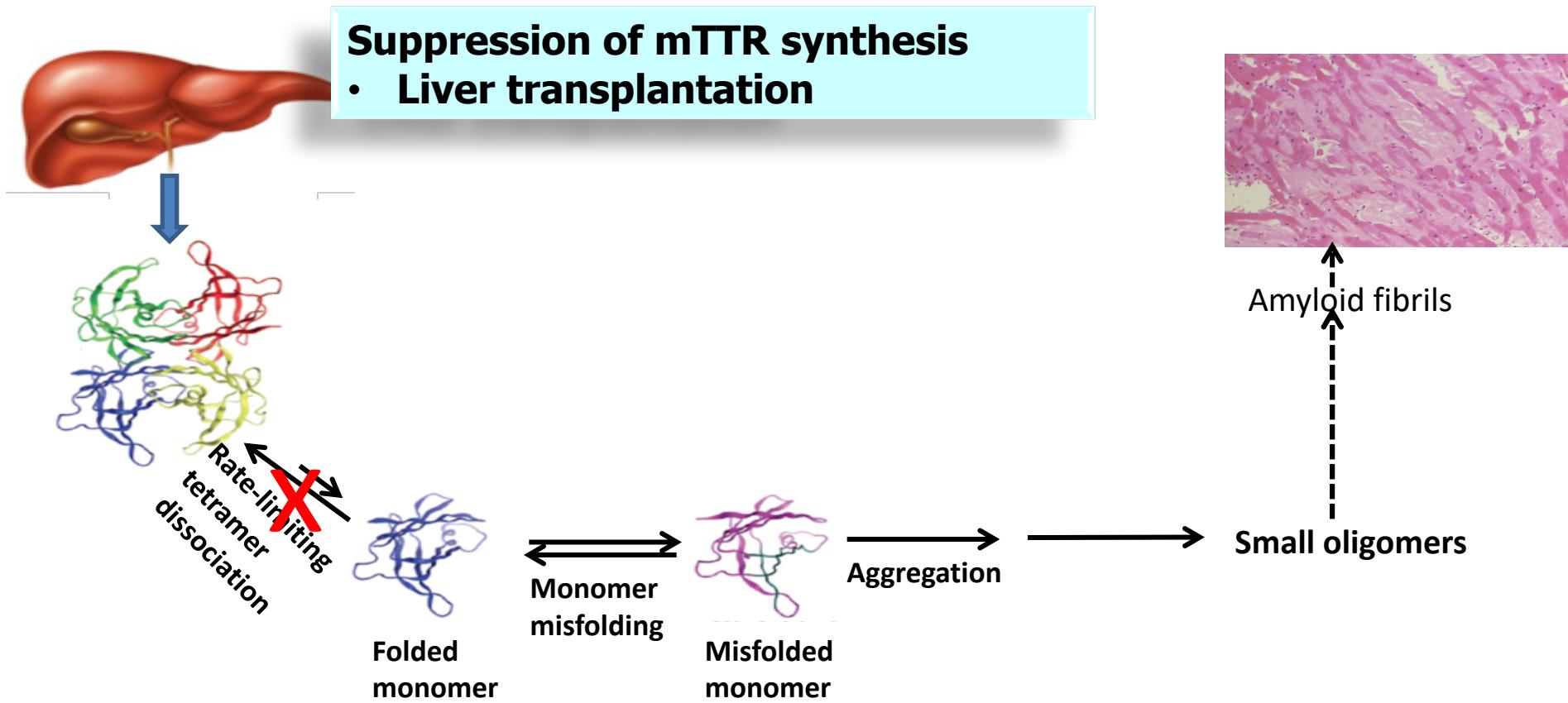
Nylon

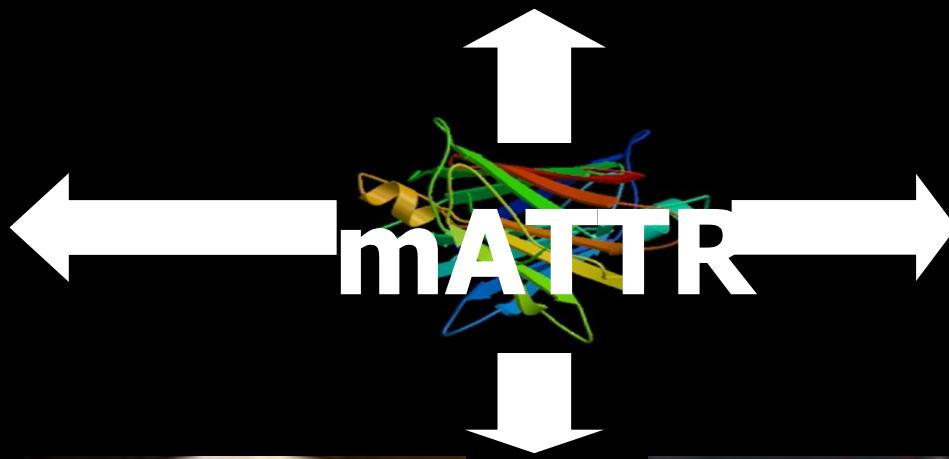


struttura

microscopio atomico

TTR Amyloidosis: Therapeutic opportunities



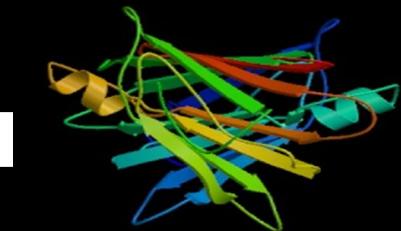


wt TTR-related Amyloidosis

“Senile Systemic Amyloidosis”



100%



**wild-type
ATTR**



35%

55 sites from 18 countries enrolled patients

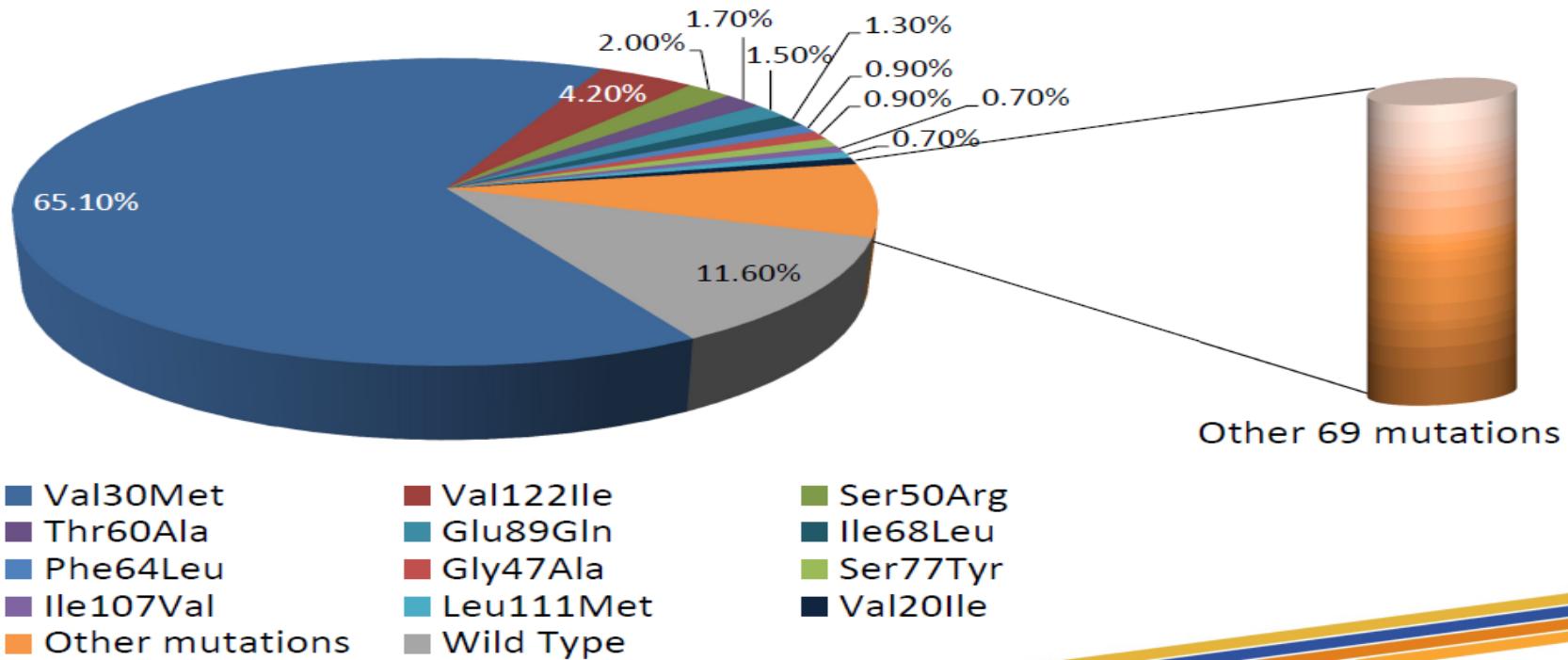
THAOS REGISTRY



2015 May THAOS Scientific Board

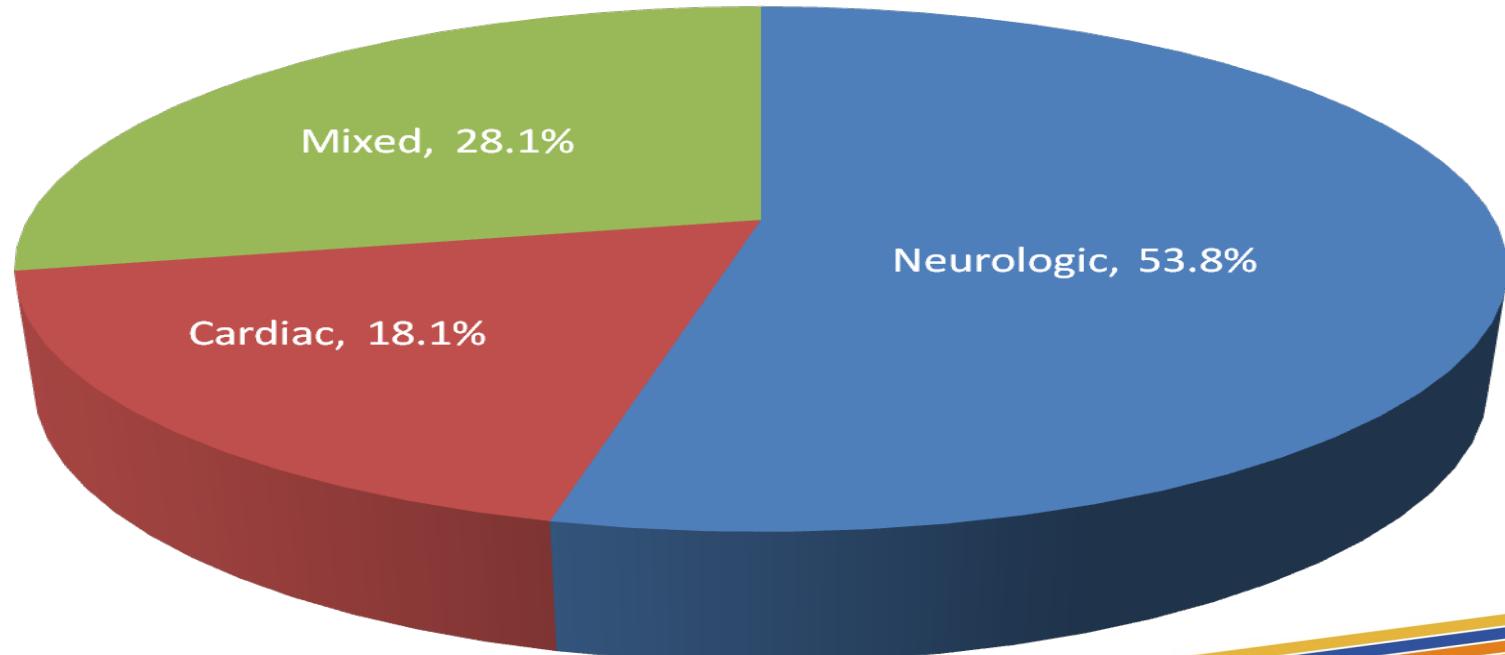
Spectrum of genotypes (%)

N=2538



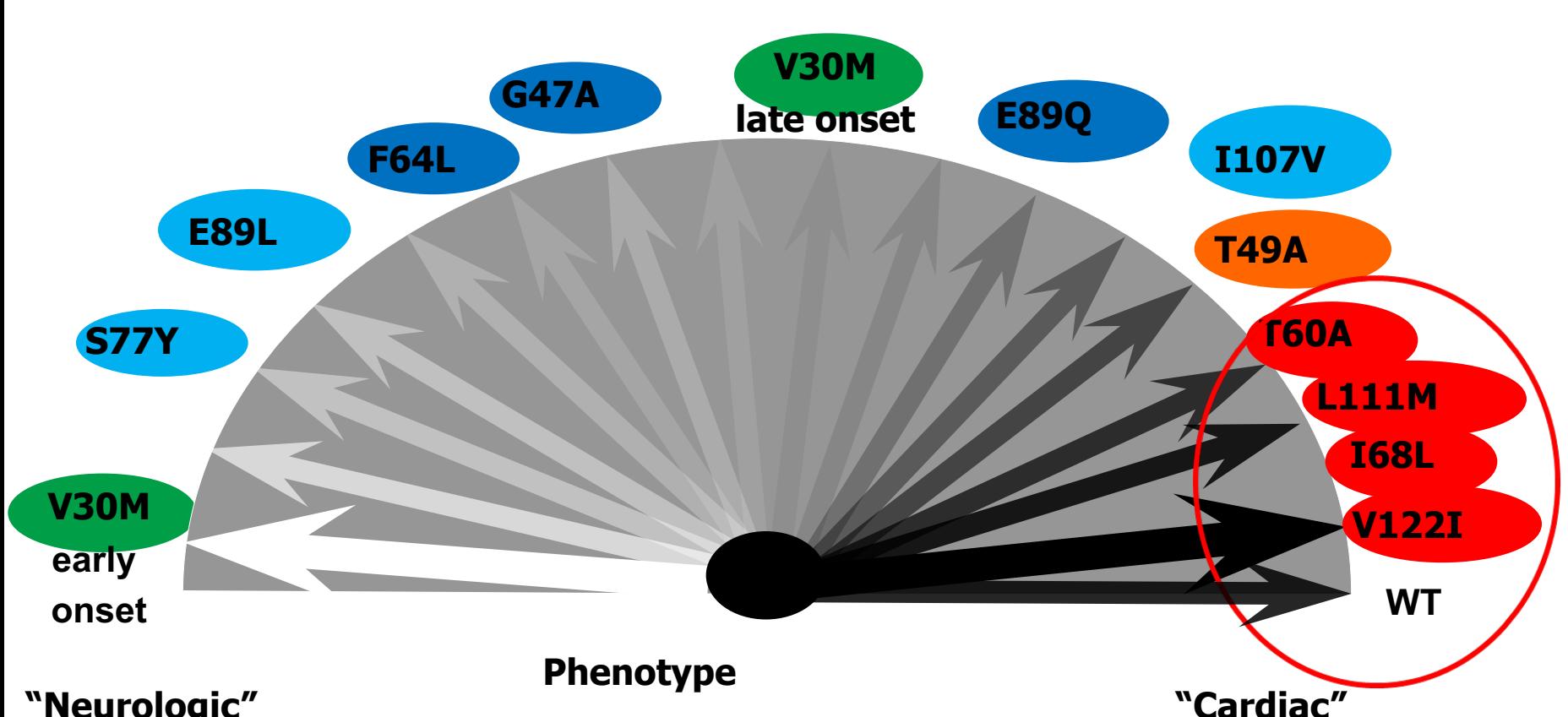
Data as of 06 January 2015

Frequency of main of phenotypes at presentations N=2064

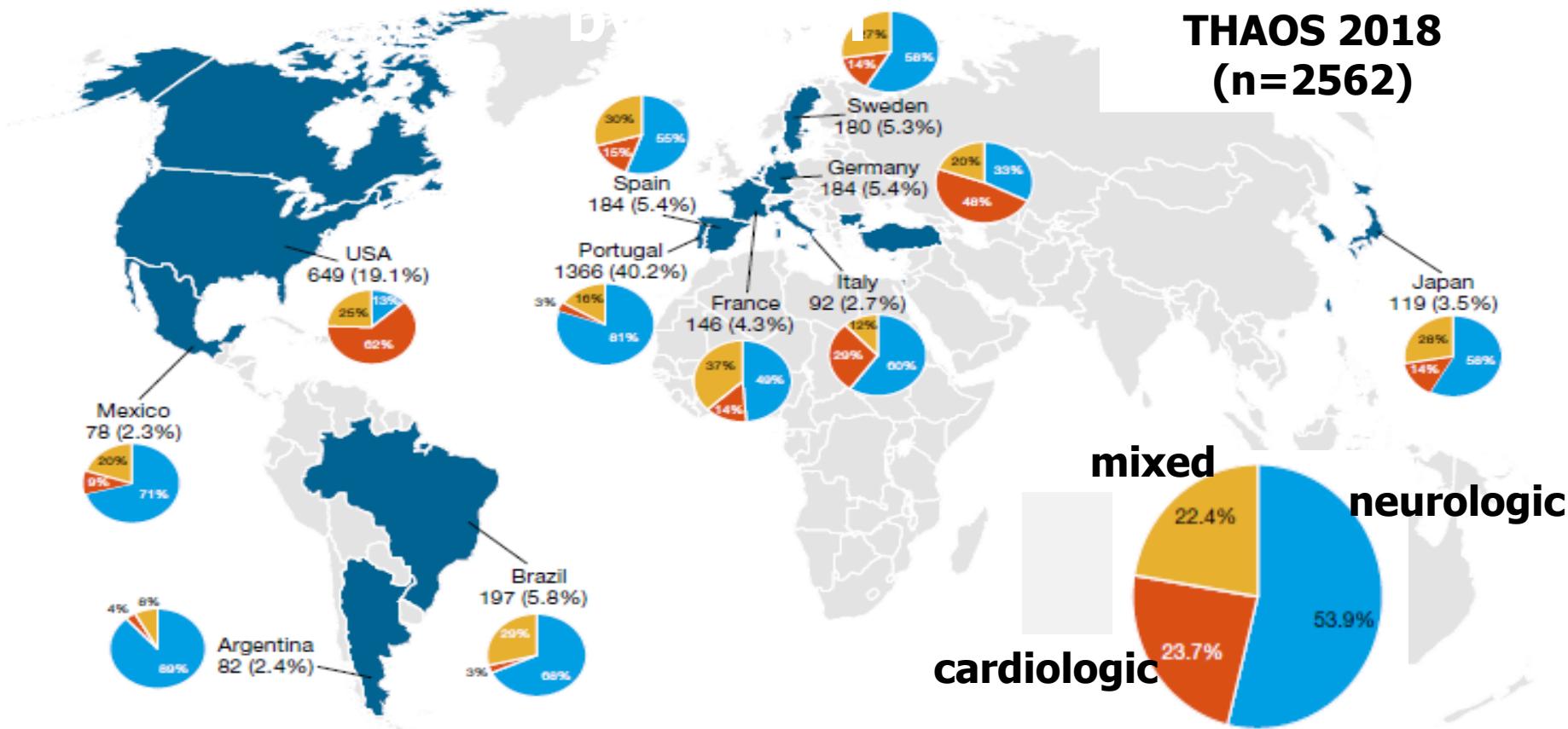


Data as of 06 January 2015

Genotypic-Phenotypic Correlation in ATTR



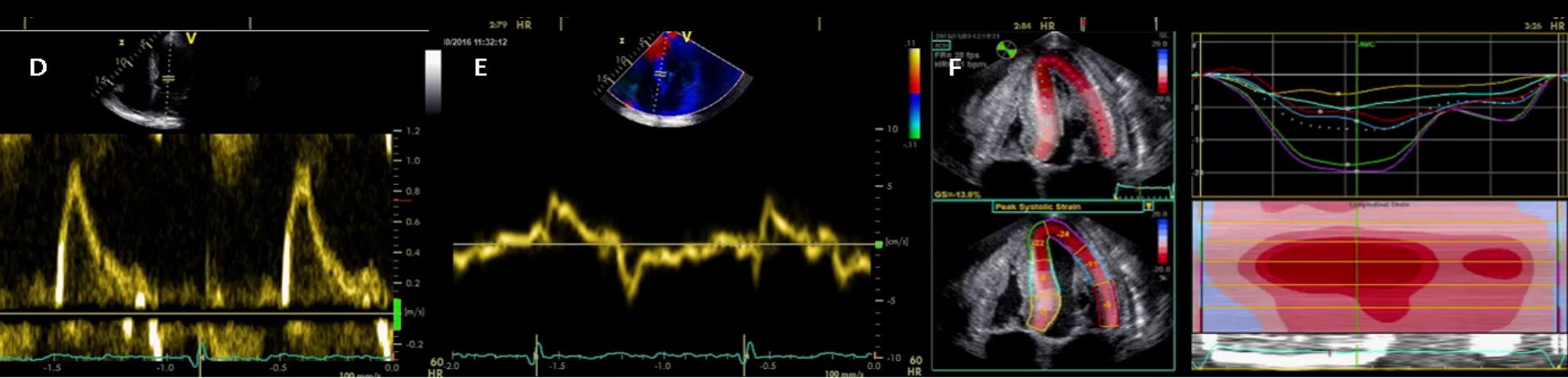
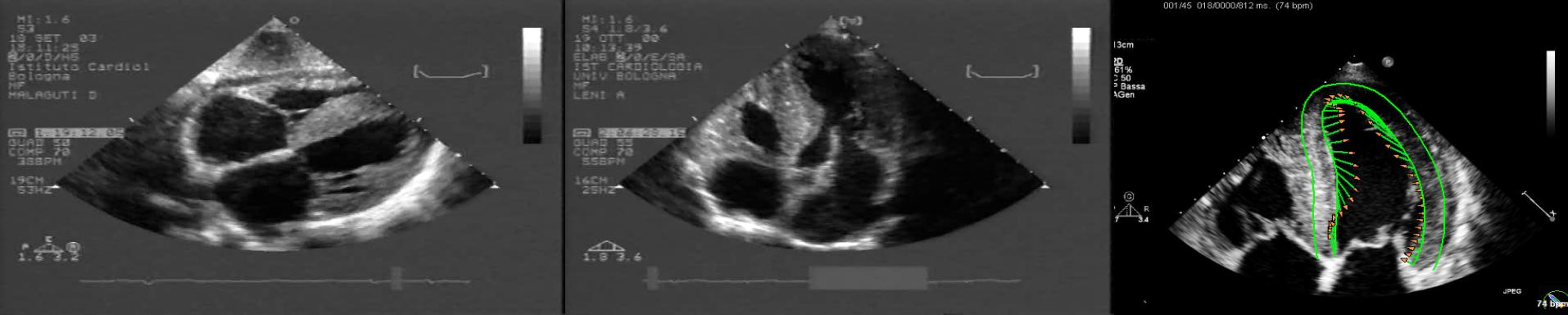
THAOS REGISTRY: Distribution of phenotypes



Data at each country name are presented as n (%). *Countries contributing <2.3% enrollment: Belgium, Bulgaria, Canada, Cyprus, Denmark, Israel, the Netherlands, South Korea, Taiwan, Turkey.

General Profile of TTR-CM patients with Exclusively Cardiac Phenotype

- **Male gender**
- **Average age ~ 72 yrs**
- **No apparent family history of ATTR**
- **Heart failure symptoms**
- **Frequent history of CTS**
- **Symmetric “LV hypertrophy”**
- **Absent or mild LV dilatation**
- **Normal or mildly reduced LVEF**
- **Normal or near normal QRS voltages but reduced QRS voltage / LV thickness**



TcDPD Scintigraphy

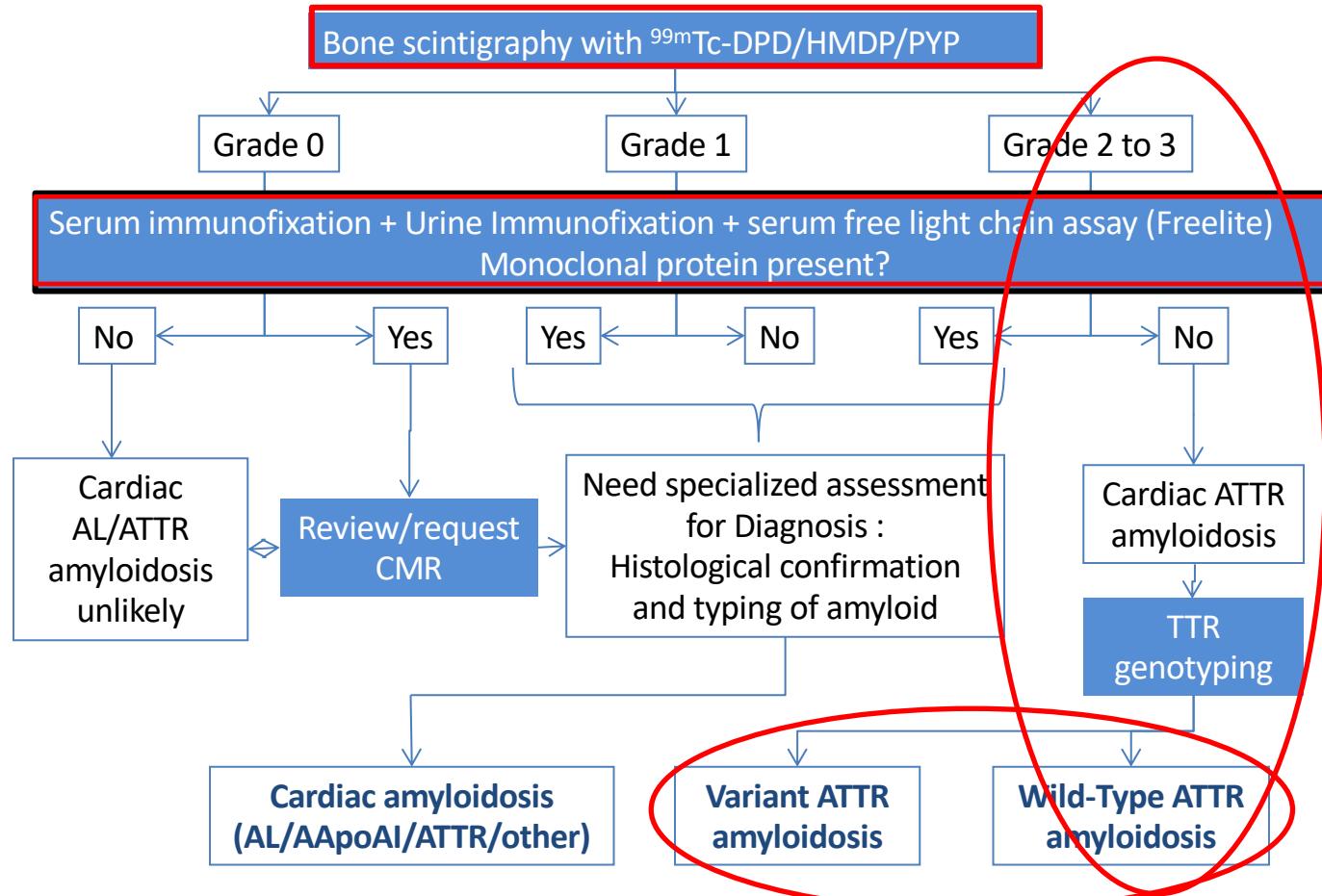


Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis

Julian D. Gillmore, MD, PhD; Mathew S. Maurer, MD; Rodney H. Falk, MD;
Giampaolo Merlini, MD; Thibaud Damy, MD; Angela Dispenzieri, MD;
Ashutosh D. Wechalekar, MD, DM; John L. Berk, MD; Candida C. Quarta, MD, PhD;
Martha Grogan, MD; Helen J. Lachmann, MD; Sabahat Bokhari, MD; Adam Castano, MD;
Sharmila Dorbala, MD, MPH; Geoff B. Johnson, MD, PhD;
Andor W.J.M. Glaudemans, MD, PhD; Tamer Rezk, BSc; Marianna Fontana, MD;
Giovanni Palladini, MD, PhD; Paolo Milani, MD; Pierluigi L. Guidalotti, MD;
Katarina Flatman; Thirusha Lane, MSc; Frederick W. Vonberg, MBBS; Carol J. Whelan, MD;
James C. Moon, MD; Frederick L. Ruberg, MD; Edward J. Miller, MD, PhD;
David F. Hutt, BApSc; Bouke P. Hazenberg, MD, PhD; Claudio Rapezzi, MD;
Philip N. Hawkins, PhD, FMedSci

Circulation. 2016;133:2404-2412.

Heart failure, syncope, or bradyarrhythmia, with echocardiogram and/or cardiac magnetic resonance imaging (CMR) suggesting/indicating cardiac amyloid



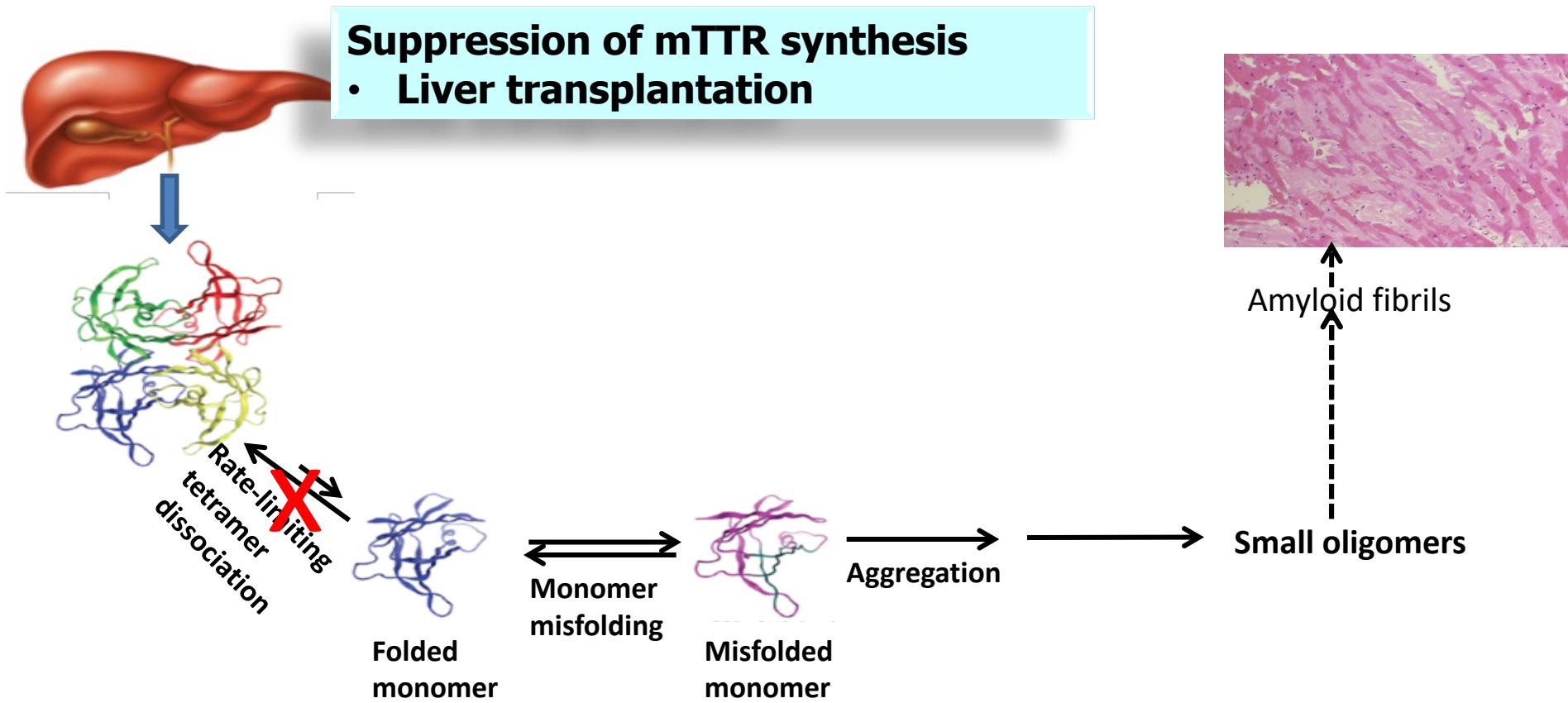
Modern epidemiology of ATTR

Frequency of cardiac ATTR in different settings

Amyloid deposits in autopsied subjects (mean age 69 yrs) without HF	8%
Unexpected bone tracer myocardial uptake in pts >75yr undergoing scintigraphy for non cardiac reasons²	2 %
Unexpected TTR mutations in pts with supposed sarcomeric HCM³	5%
Hospitalized pts with HFpEF⁴	13%
Amyloid deposits in autopsied elderly pts (mean age 76 yrs) with HFpEF¹	17%
Elderly pts with severe degenerative Ao Stenosis⁵	16%

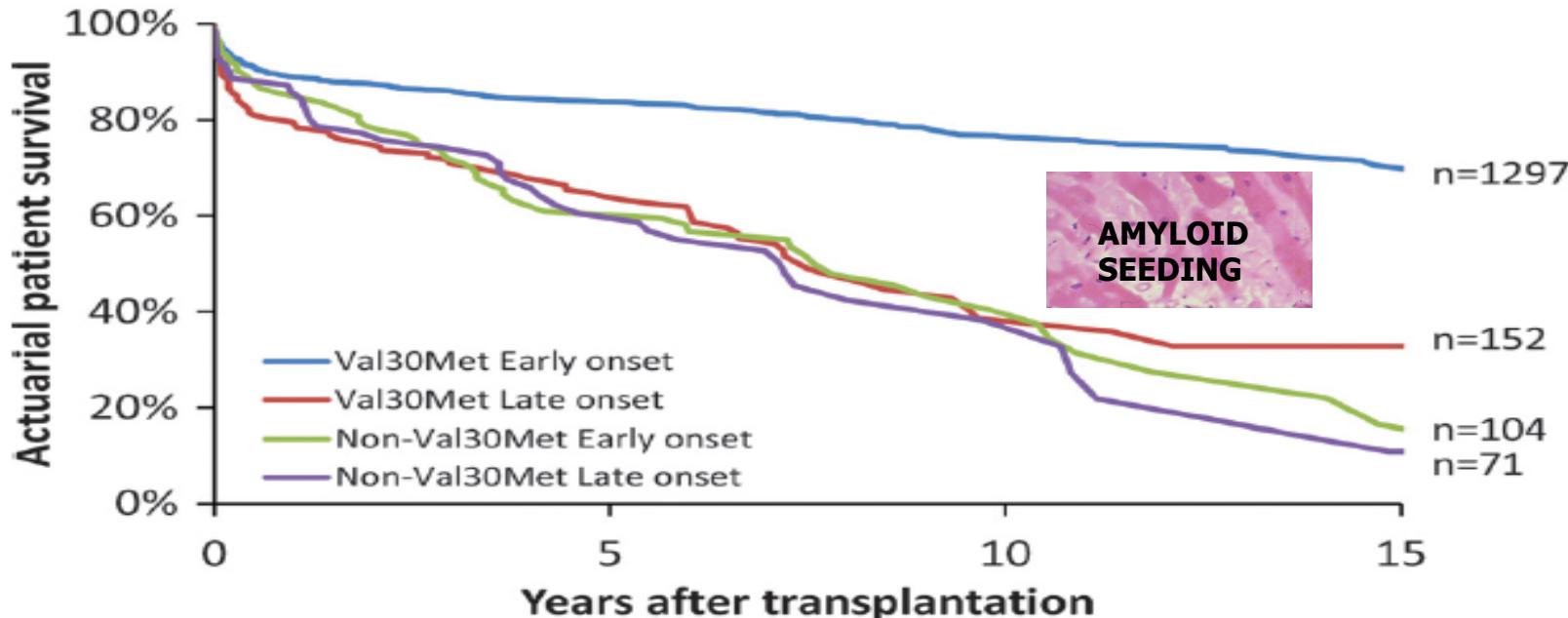
¹Mohammed SF et al JACC Heart Fail. 2014;2:113-22. ²Longhi et al JACC Cardiovasc Imaging 2014;7:531-2. ³Damy T et al. Eur Heart J 2016;37:1826-34. ⁴Gonzalez-Lopez E et al. Eur Heart J 2015;36:2585-94. ⁵Castano A et al. Eur Heart J 2017;38:2879-87. ⁵Grogan M et al. J Am Coll Cardiol 2016;68:1014-20

TTR Amyloidosis: Therapeutic opportunities

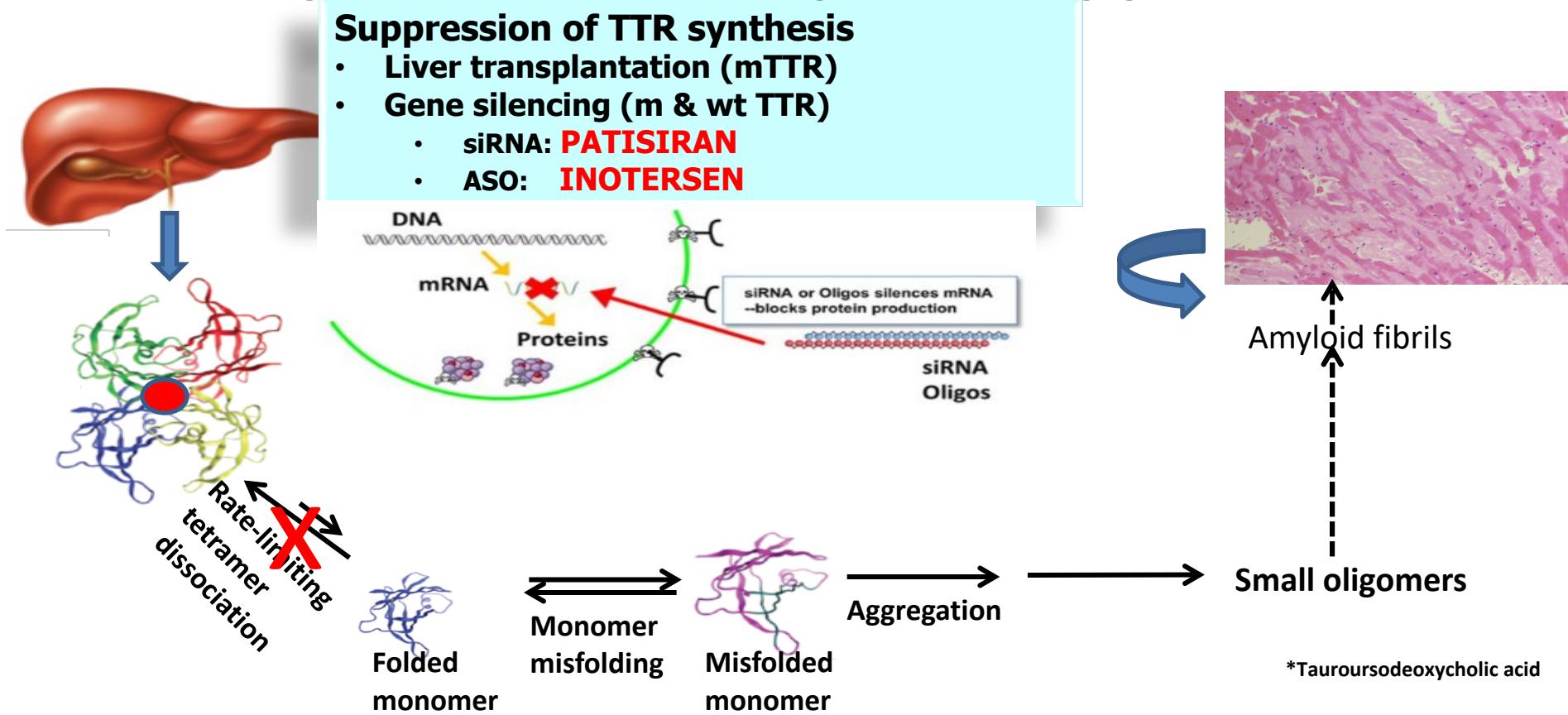


Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative?

Bo-Göran Ericzon,¹ Henryk E. Wilczek,¹ Marie Larsson,¹ Priyantha Wijayatunga,² Arie Stangou,³ João Rodrigues Pena,⁴ Emanuel Furtado,⁵ Eduardo Barroso,⁴ Jorge Daniel,⁶ Didier Samuel,⁷ Rene Adam,⁷ Vincent Karam,⁷ John Poterucha,⁸ David Lewis,⁹ Ben-Hur Ferraz-Neto,¹⁰ Márcia Waddington Cruz,¹¹ Miguel Munar-Ques,¹² Juan Fabregat,¹³ Shu-ichi Ikeda,¹⁴ Yukio Ando,¹⁵ Nigel Heaton,¹⁶ Gerd Otto,¹⁷ and Ole Suhr¹⁸



TTR Amyloidosis: Therapeutic opportunities



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Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

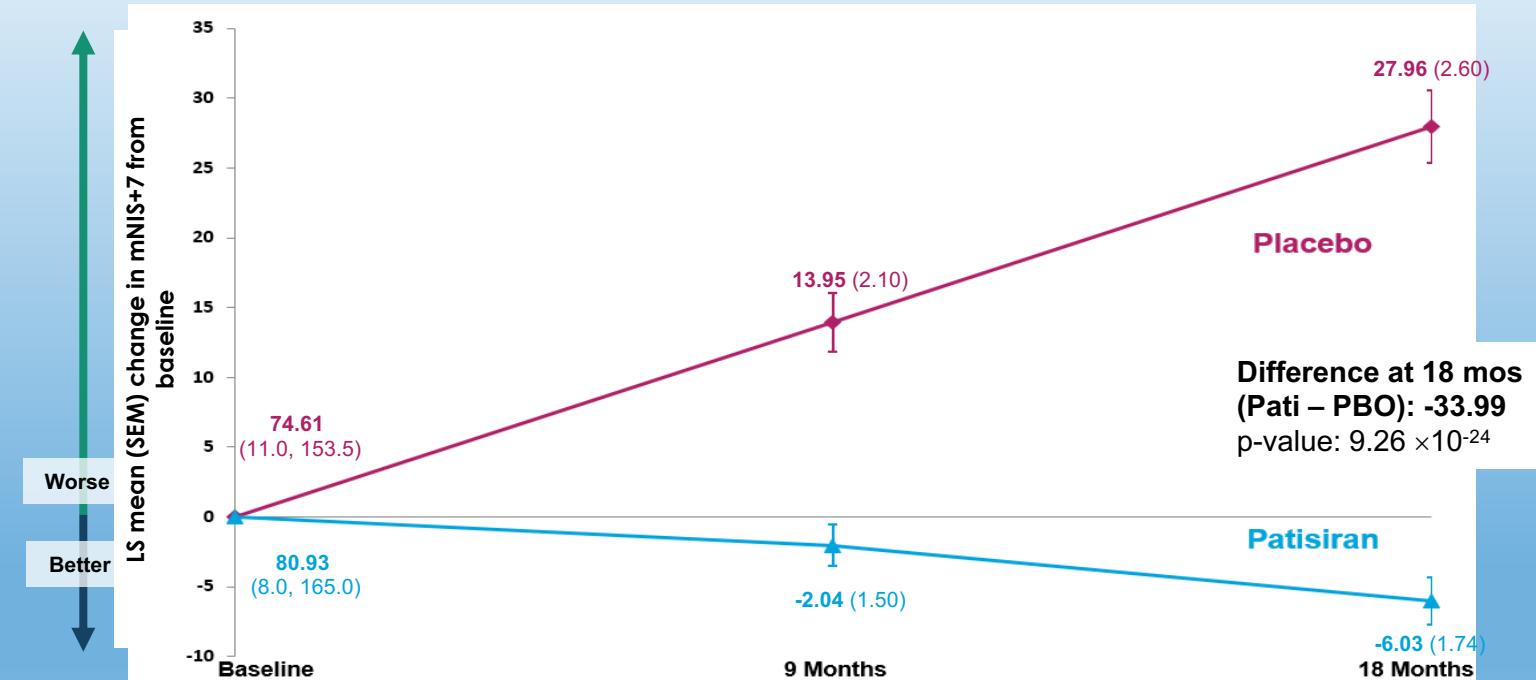
D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnav, J.A. Gollob, and O.B. Suhr

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

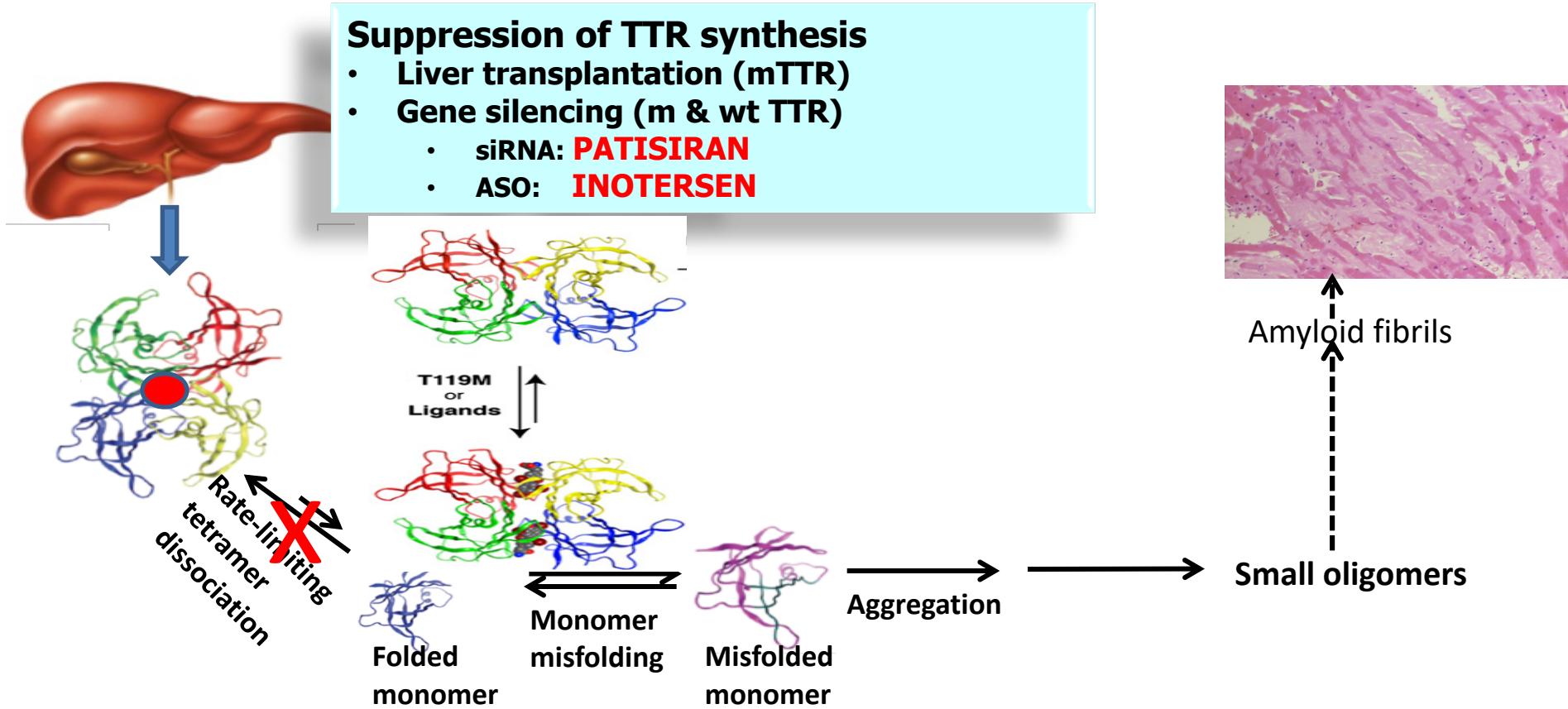
M.D. Benson, M. Waddington-Cruz, J.L. Berk, M. Polydefkis, P.J. Dyck, A.K. Wang, V. Planté-Bordeneuve, F.A. Barroso, G. Merlini, L. Obici, M. Scheinberg, T.H. Brannagan III, W.J. Litchy, C. Whelan, B.M. Drachman, D. Adams, S.B. Heitner, I. Conceição, H.H. Schmidt, G. Vita, J.M. Campistol, J. Gamez, P.D. Gorevic, E. Gane, A.M. Shah, S.D. Solomon, B.P. Monia, S.G. Hughes, T.J. Kwok, B.W. McEvoy, S.W. Jung, B.F. Baker, E.J. Ackermann, M.A. Gertz, and T. Coelho

Patisiran Phase 3 APOLLO Study Results

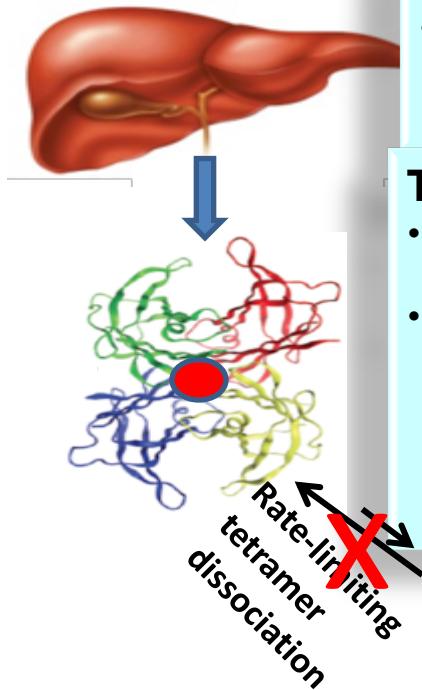
• mNIS+7: Change from Baseline



TTR Amyloidosis: Therapeutic opportunities



TTR Amyloidosis: Therapeutic opportunities



Suppression of TTR synthesis

- Liver transplantation (mTTR)
- Gene silencing (m & wt TTR)
 - siRNA: **PATISIRAN**
 - ASO: **INOTERSEN**

TTR stabilizers

- Non-selective:
DIFLUNISAL
- Selective:
 - **TAFAMIDIS**
 - **TOLCAPONE**
 - **AG10**
 - (curcumin)
 - green tea (EGCG)

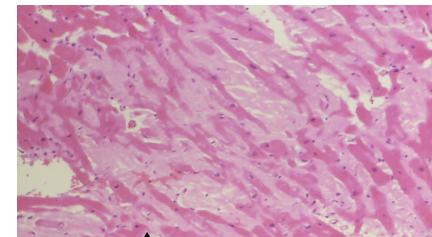


Monomer
misfolding



Aggregation

Small oligomers



Amyloid fibrils



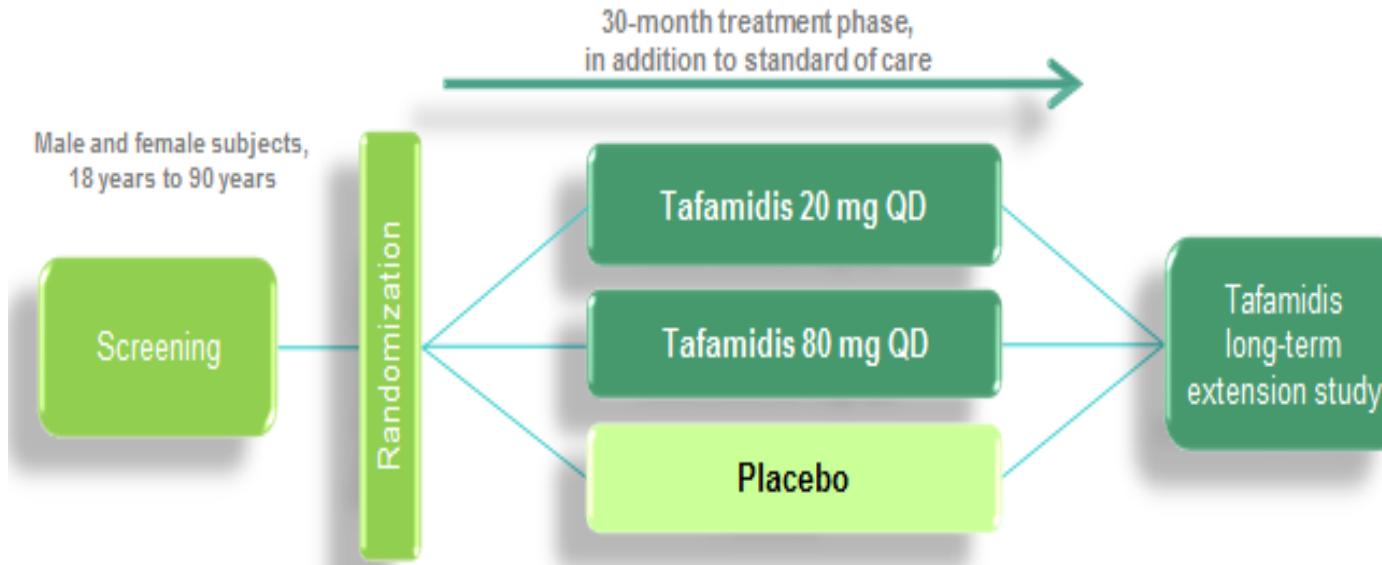
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ORIGINAL ARTICLE

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

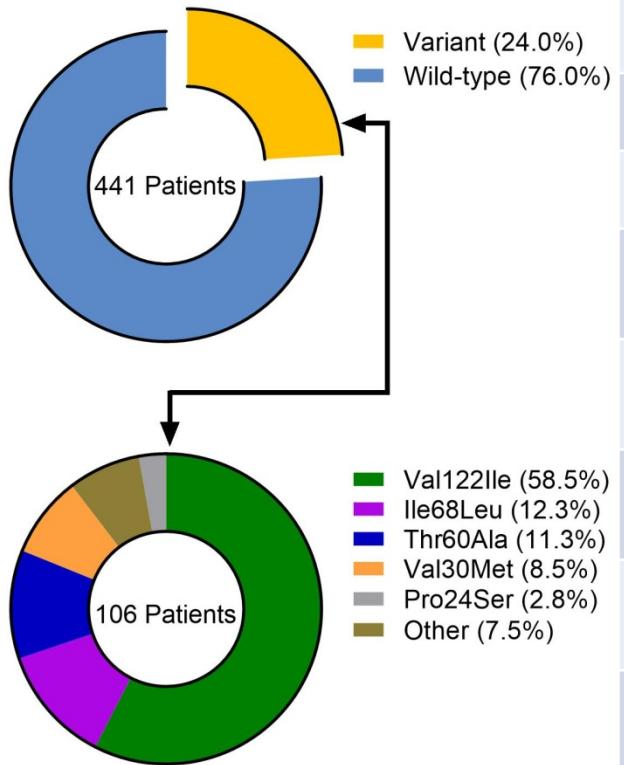
Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D.,
Balarama Gundapaneni, M.S., Perry M. Elliott, M.D.,
Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D.,
Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D.,
Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D.,
Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D.,
Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D.,
Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D.,
Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT
Study Investigators*

ATTR-ACT Study Design



- Patients randomized 2:1:2 to tafamidis 80 mg, tafamidis 20 mg, and placebo
- Stratification for genotype (wild-type or variant) and disease severity (NYHA class)
- A sample size of 400 pts was estimated to give 90% power to detect either a 30% reduction in mortality, or a reduction in the frequency of CV-related hospitalizations from 2.5 to 1.5, or both

Baseline Characteristics by Genotype



Characteristic	ATTRwt	ATTRm
Age, mean (SD)	75.2 (6.4)	71.5 (8.0)
NYHA Class I, n (%)	30 (9.0)	7 (6.6)
NYHA Class II, n (%)	212 (63.3)	51 (48.1)
NYHA Class III, n (%)	93 (27.8)	48 (45.3)
6MWT distance, mean (SD)	367.1 (117.8)	302.8 (127.0)
KCCQ-OS score, mean (SD)	67.7 (20.8)	63.5 (23.3)
Interventricular wall thickness, mean (SD)	16.5 (3.6)	16.3 (4.0)
LV Ejection Fraction, mean (SD)	49.1 (9.5)	46.4 (11.2)
NT-proBNP, mean (SD)	3714.5 (2861.0)	4516.5 (4102.1)

Efficacy Outcomes

- Primary efficacy analysis: hierarchical combination of all-cause mortality and frequency of cardiovascular-related hospitalizations comparing **pooled tafamidis data** with placebo using the **Finkelstein–Schoenfeld (F-S) method¹**
- Key secondary endpoints were change from Baseline to Month 30 in 6-minute walk test (6MWT) and Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score, analyzed using a mixed model repeated measures ANCOVA (MMRM)



Primary Analysis using Finkelstein-Schoenfeld (F-S) Method

	Pooled Tafamidis n=264	Placebo n=177
P-value from F-S method		0.0006
Patients alive ^a at Month 30, n (%)	186 (70.5)	101 (57.1)
Average cardiovascular-related hospitalizations during 30 mo (per pt per yr) among those alive at Month 30	0.297	0.455
Win-Ratio ^b (95% CI)		1.695 (1.255, 2.289)

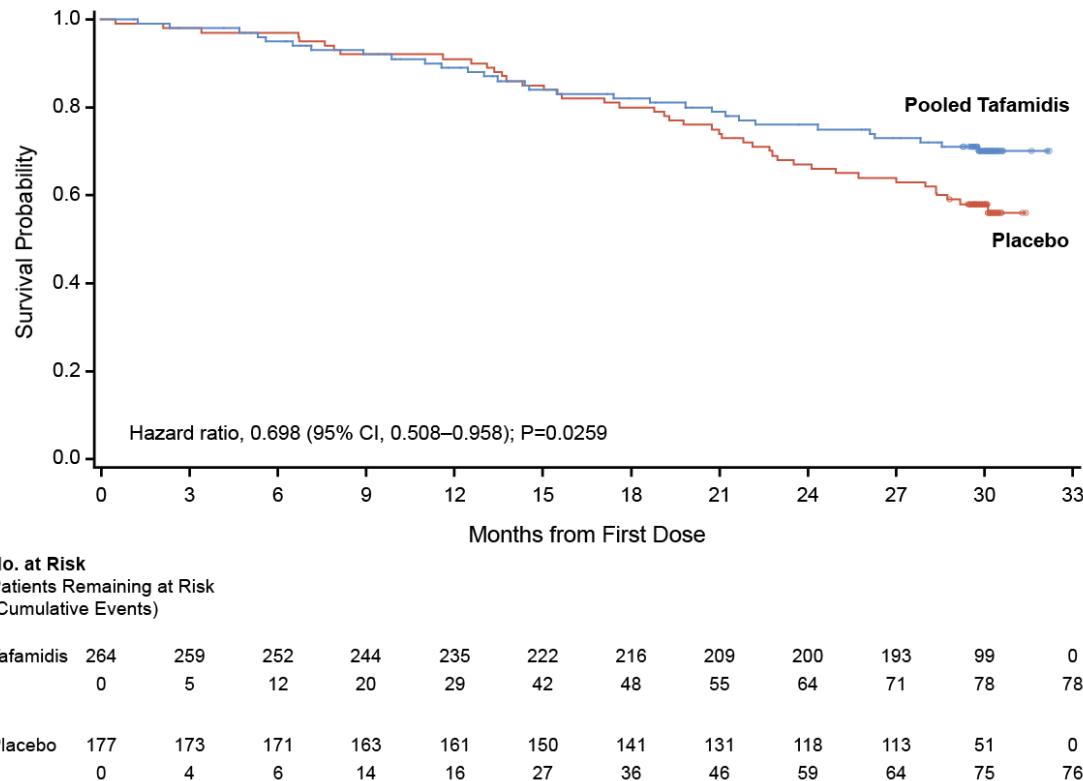
^aHeart transplant and implantation of a cardiac mechanical assist device were treated as death for this analysis

^bNumber of pairs of tafamidis-treated patient wins divided by number of pairs of placebo patient wins

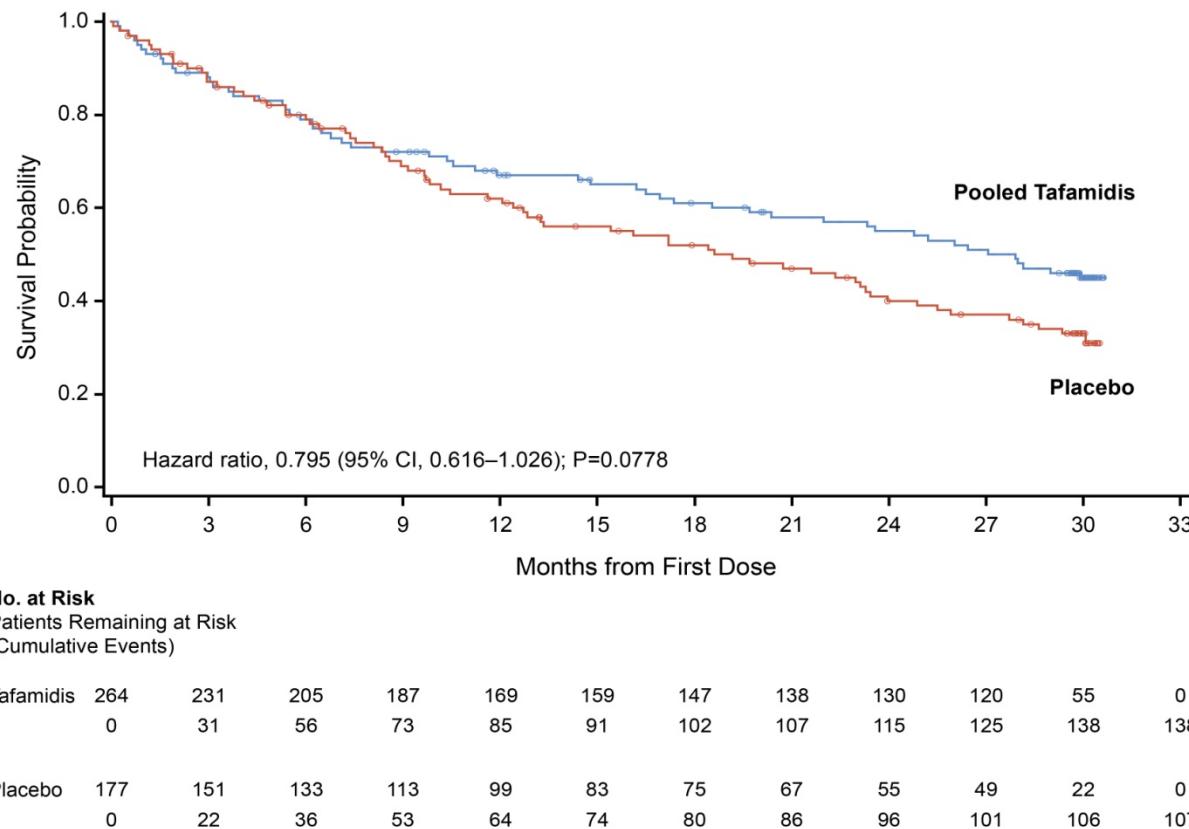
All-cause Mortality-Cox Proportional Hazard Model

30% reduction in the risk of all-cause mortality with tafamidis compared with placebo

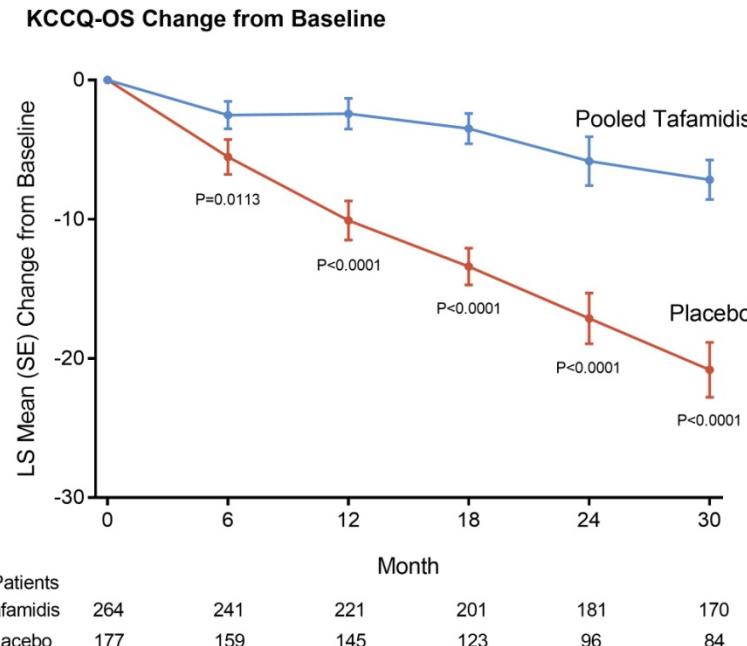
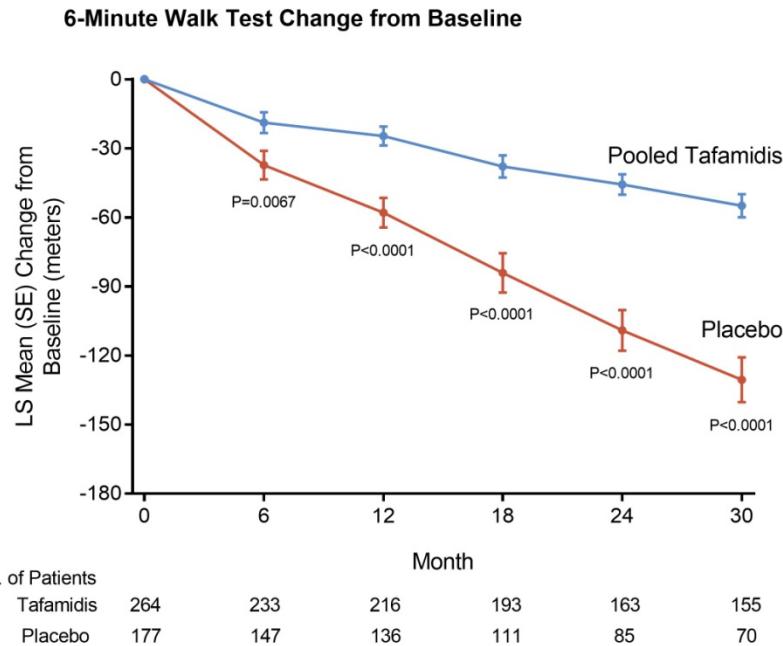
Heart transplant and implantation of a cardiac mechanical assist device were treated as death for this analysis



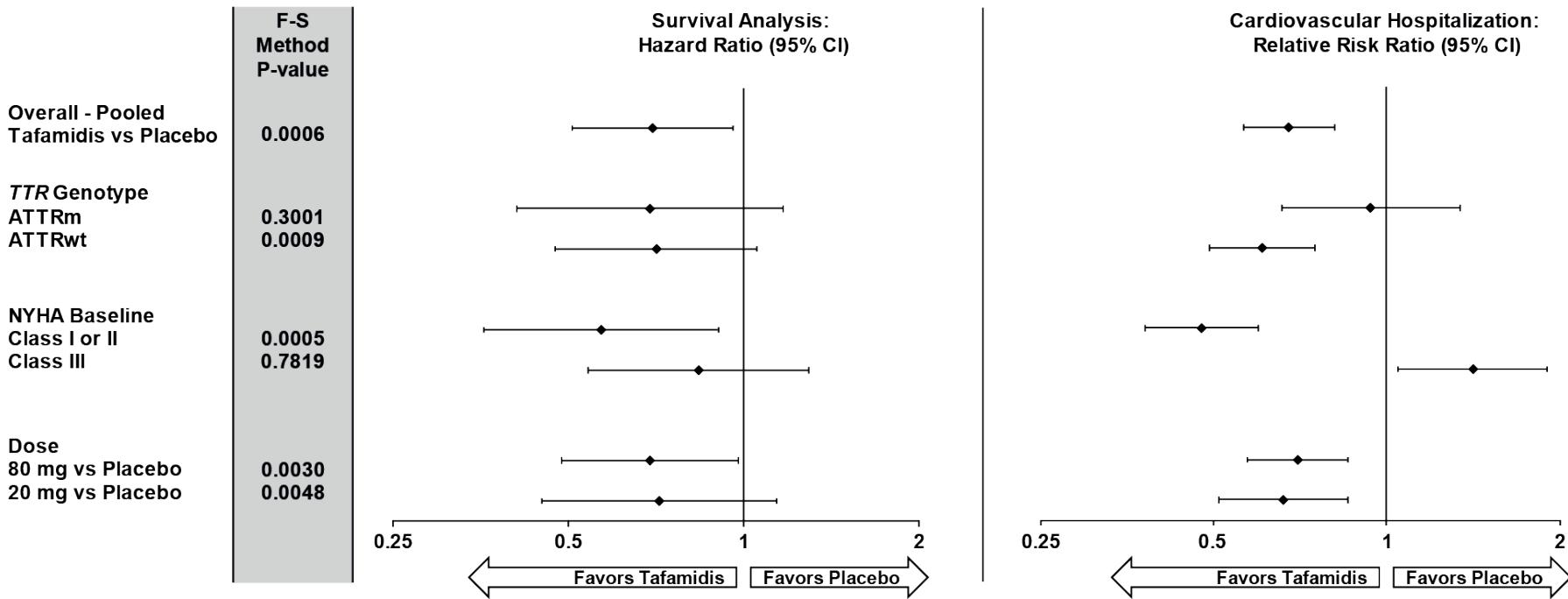
Time to First Cardiovascular Hospitalization



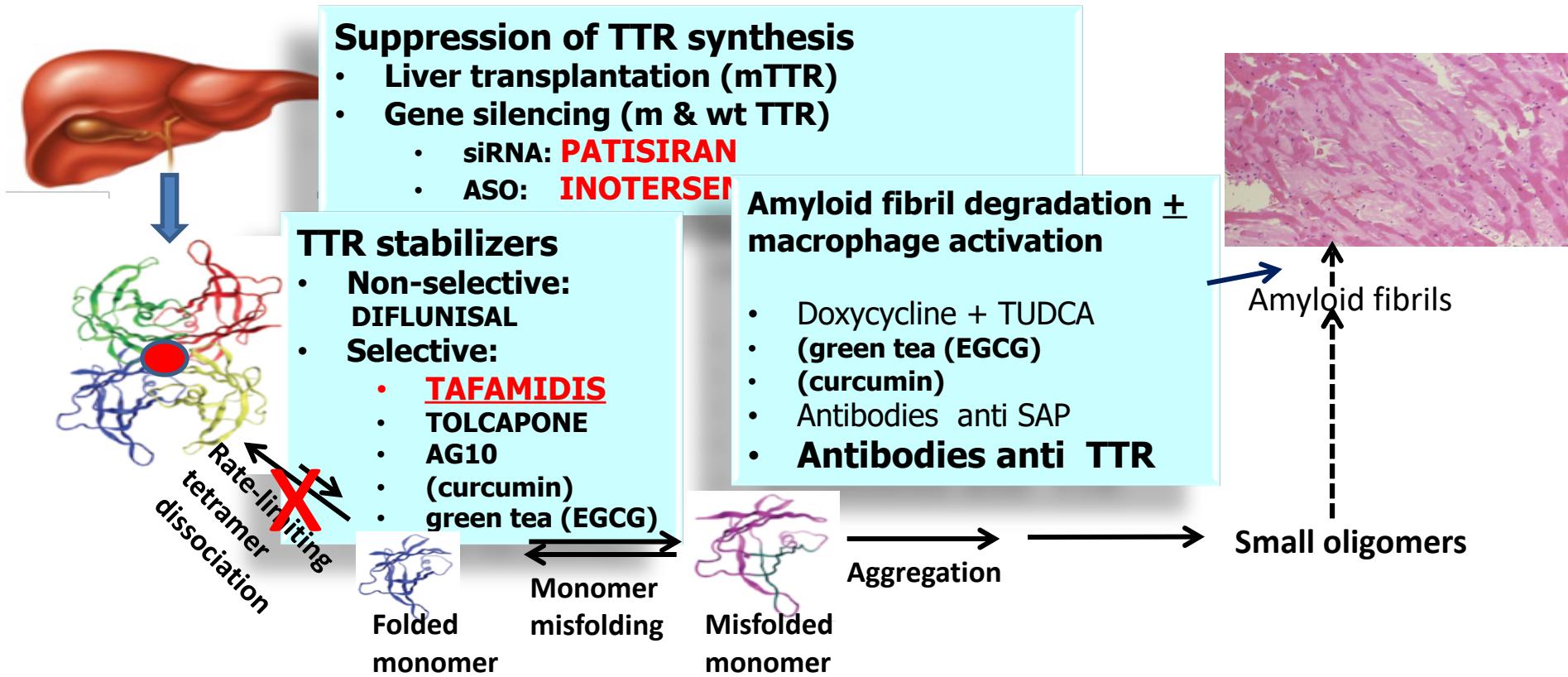
Key Secondary Endpoints: 6-minute Walk Test and KCCQ-OS



Pre-specified Subgroup Results: All-cause Mortality, and CV-related Hospitalization



TTR Amyloidosis: Therapeutic opportunities



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- Challenging
- Fascinating
- Mysterious
- Not as rare as supposed
- Relatively easy to detect (when suspected !)
- Treatable

Tafamidis : quattro “prime volte”

- **Terapia efficace della CM ATTR**
- **Medicina di precisione in Cardiologia**
- **Terapia efficace nell' HFpEF**
- **Efficace terapia “centrale” (non neurormonale) nell' HF**