



Amiloidosi da transtiretina nella stenosi aortica: implicazioni cliniche e terapeutiche

Claudio Rapezzi, *Ferrara*



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GVM Care & Research, Cotignola (Ravenna)

Disclosures:

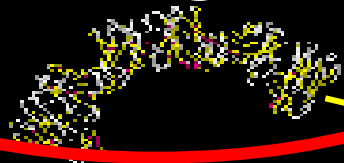
Grant istituzionali da Pfizer

Onorari da: Pfizer, Alnylam Akcea, Novartis, Sanofi

Apo A



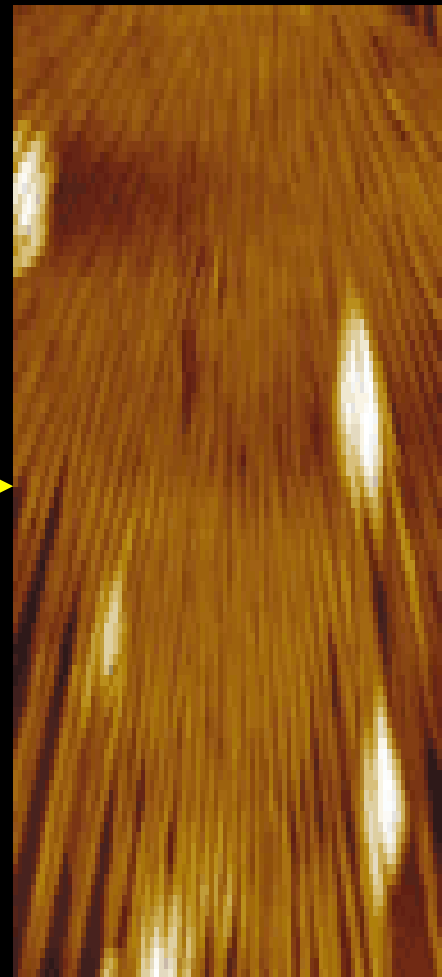
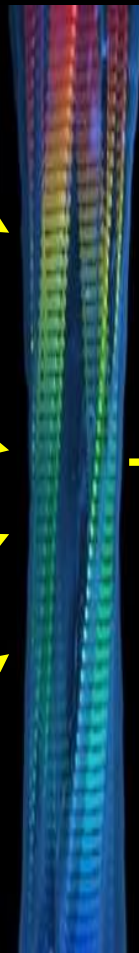
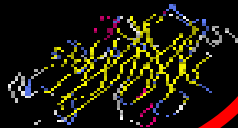
immunoglobulin



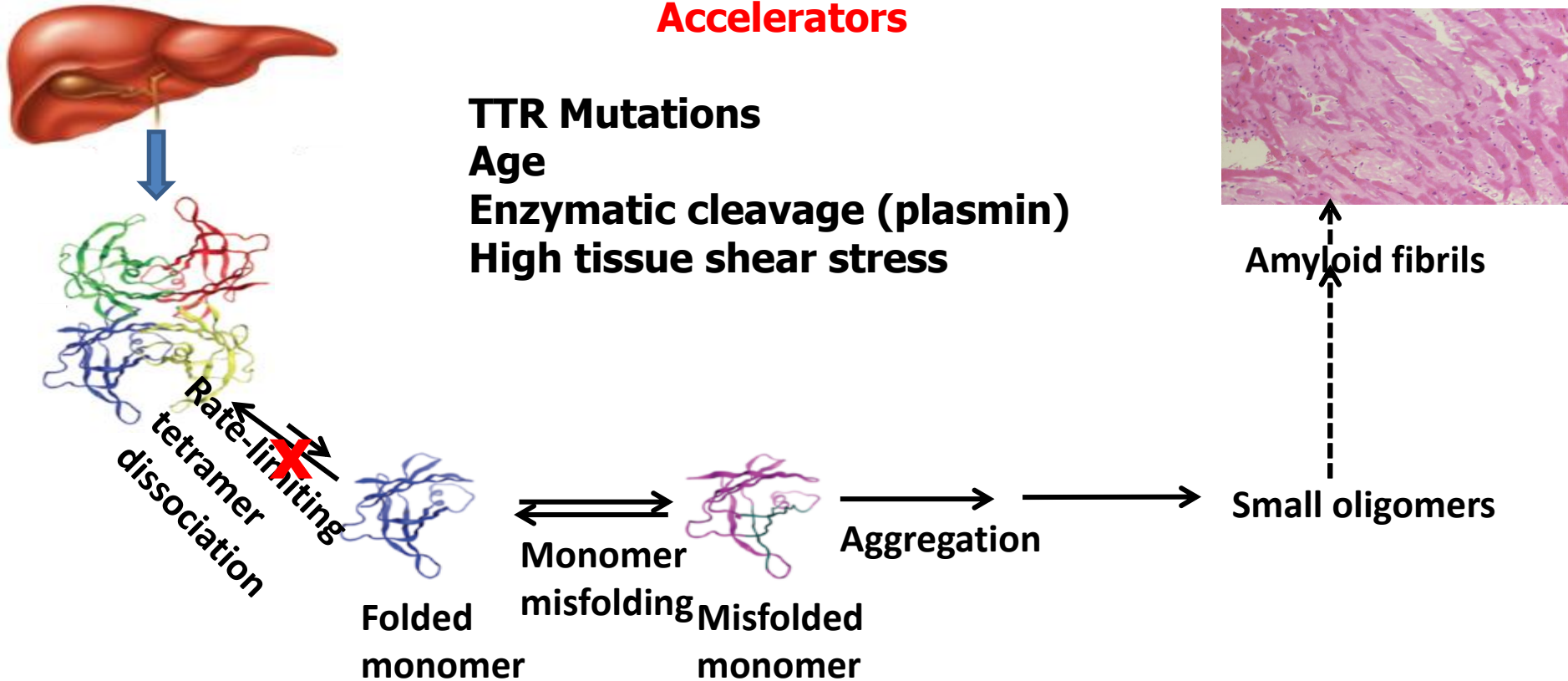
Lysozyme

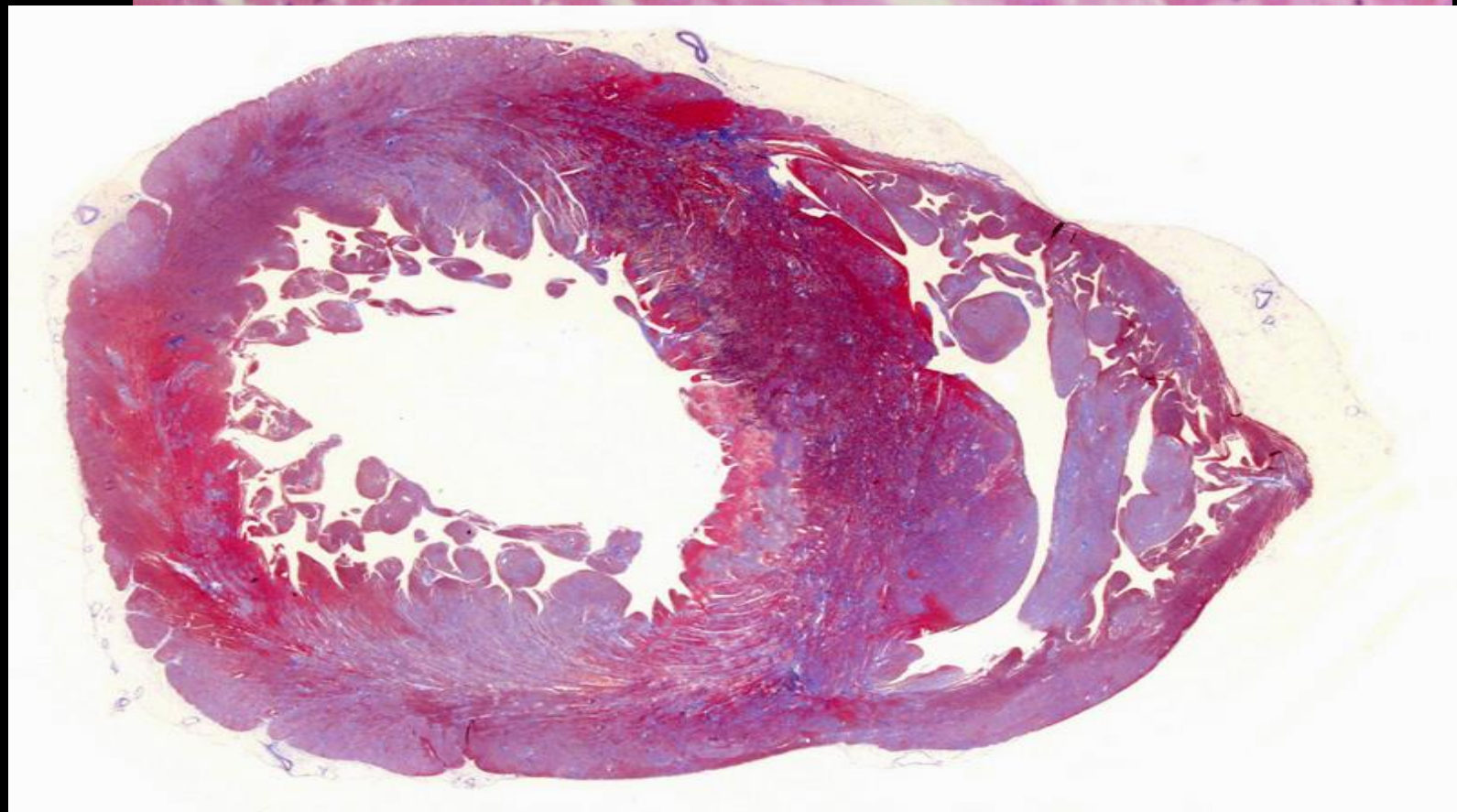


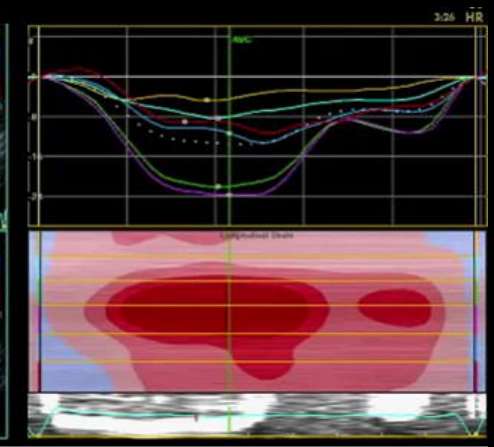
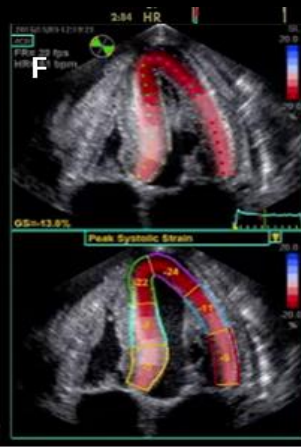
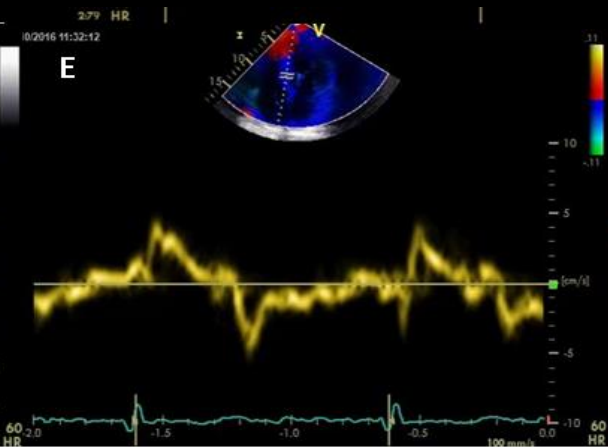
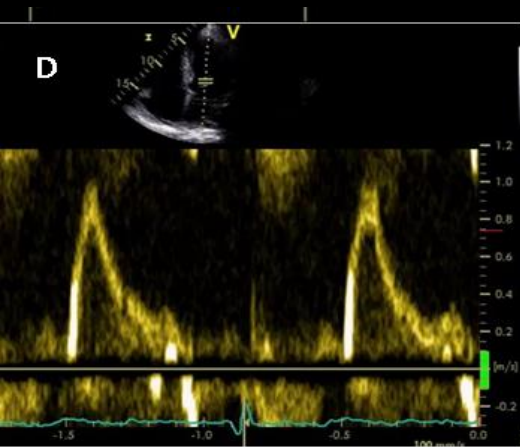
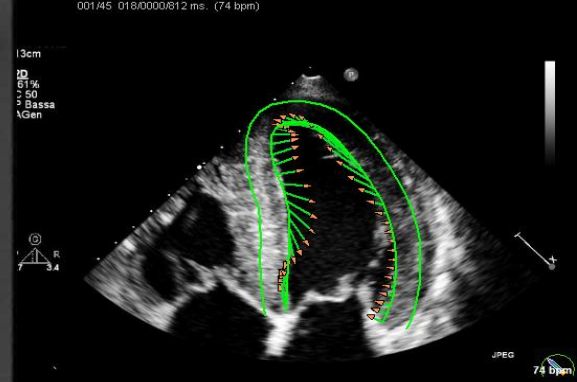
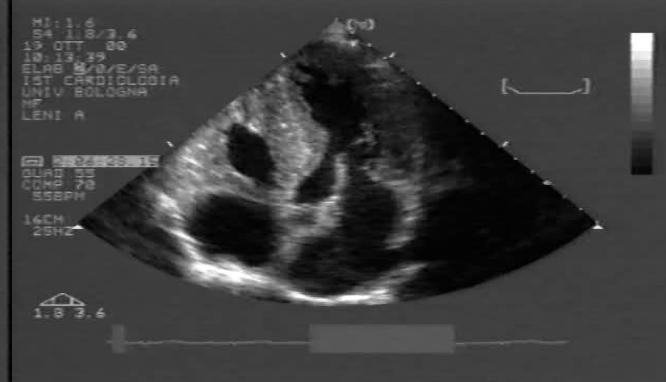
TTR

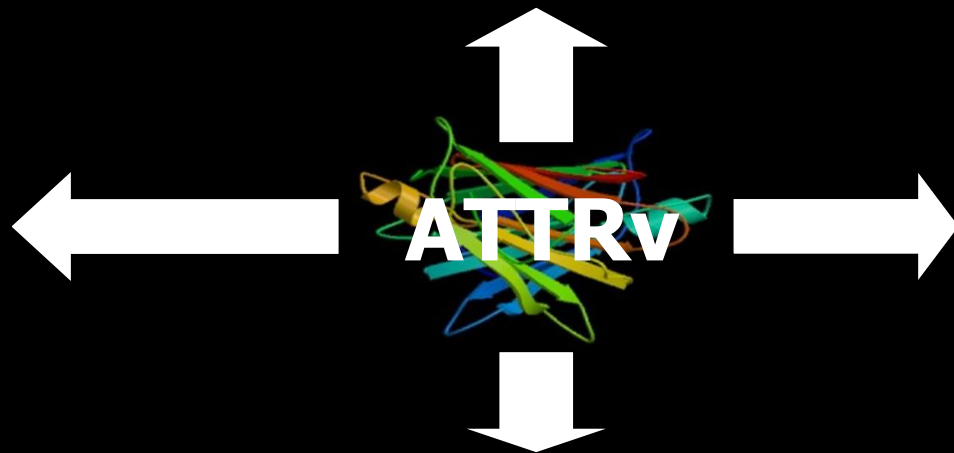


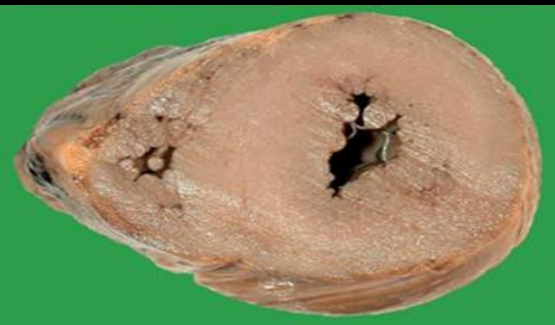
Amyloidogenesis of ATTR







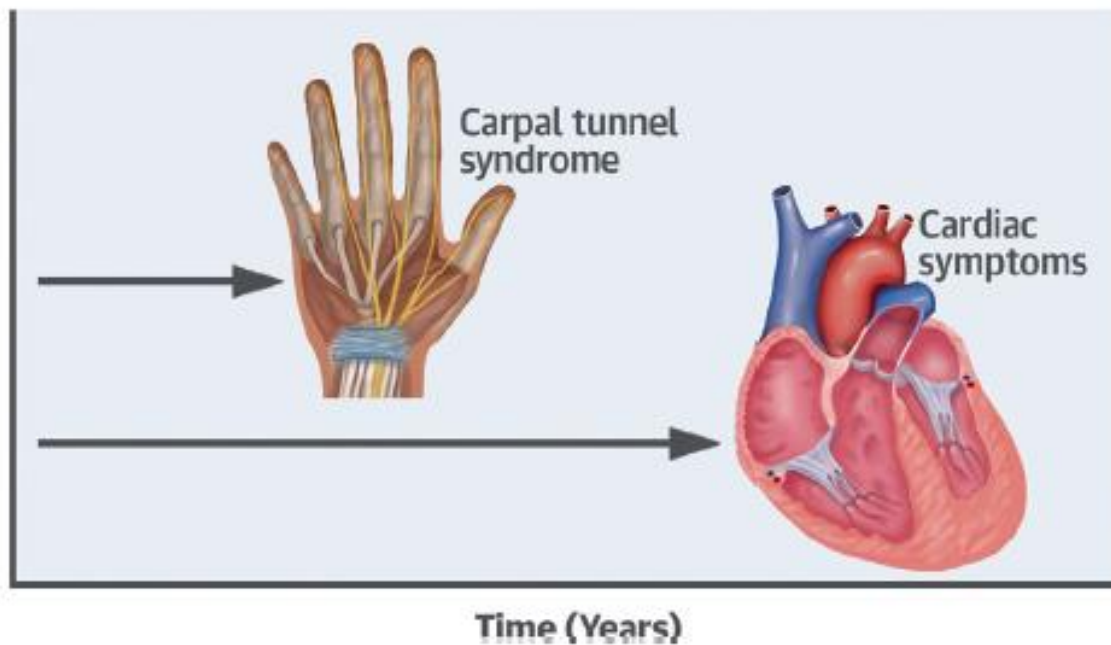




100%



35%



Sperry, B.W. et al. J Am Coll Cardiol. 2018;72(17):2040-50.

Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Diagnosis of Cardiac Amyloidosis

Invasive

(all types)

Cardiac Biopsy positive for
amyloid

or

Extracardiac Biopsy positive for
amyloid
+
Echocardiographic/CMR criteria

Non-Invasive

(only for ATTR)

Grade 2 or 3 cardiac uptake at
diphosponate Scintigraphy

+

Negative serum free light chains &
negative serum and urine
immunofixation (SPIE & UPIE)

+

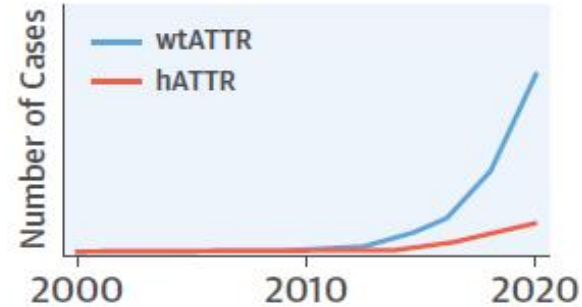
Echocardiographic/CMR criteria

Cardiac Amyloidosis: an Exciting Season

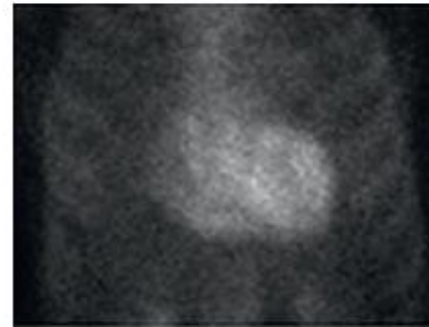
Epidemiology



Recognition of ATTR-CM



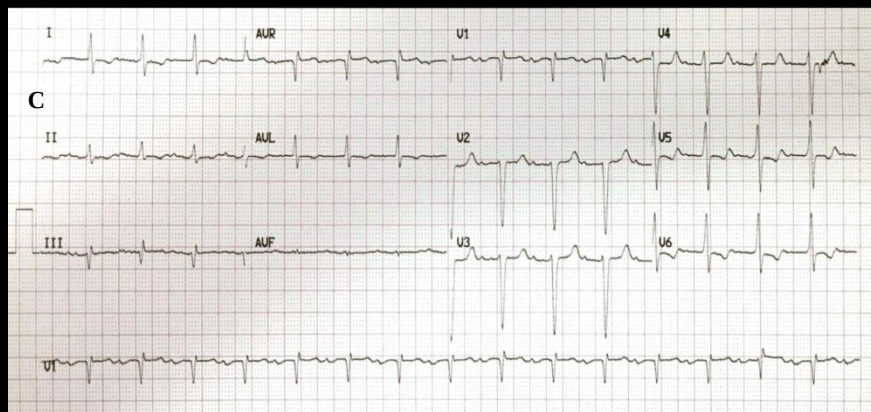
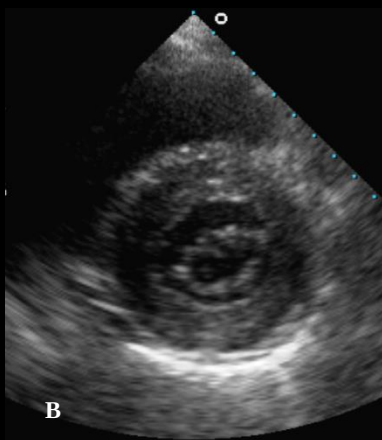
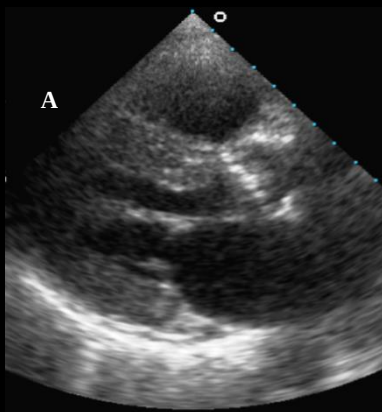
Noninvasive-Scintigraphy

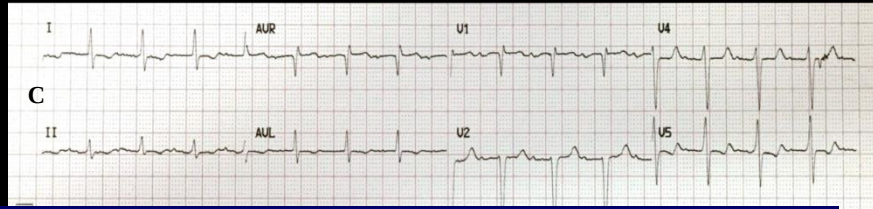
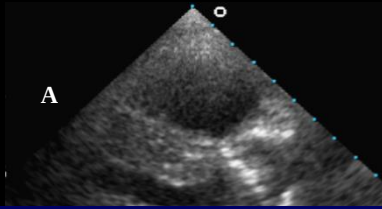


Diagnosis

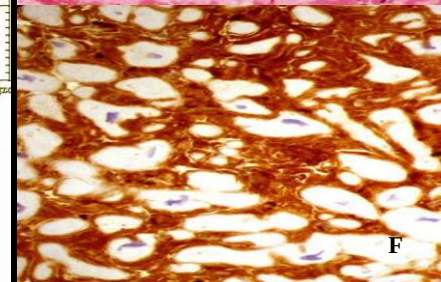
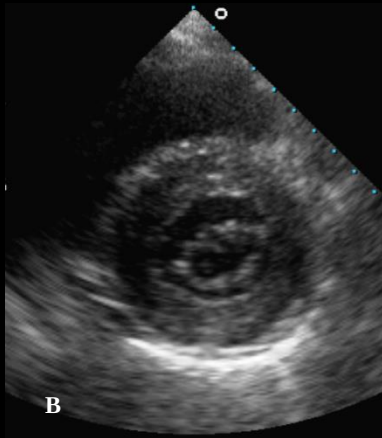


**Quanto è realmente frequente
l'associazione fra stenosi aortica
degenerativa e amiloidosi cardiaca ATTR?**





5/43 pts (12%)



AS & Cardiac Amyloidosis

Author, Journal, year	Study context	Diagnosis modality	N	Prevalence of CA (%)	Male (%)	Mean age
Nitsche C, JACC 2021 *	Referred for TAVR	Non-invasive	391	12	49	84
Rosenblum H, EJHF 2020	Referred for TAVR	Non-invasive	204	13	65	83
Scully PR , EHJ 2020	Referred for TAVR	Non-invasive	200	14	50	85
Nitsche C, EJHF 2020	Referred for TAVR	Non-invasive	191	8.4	50	82
Cavalcante JL, JACC 2018	Referred for CMR	CMR	113	16 >74yr	89	88
Castano A, EHJ 2017	Referred for TAVR	Non-invasive	151	16	68	84
Treibel TA, Circ Img 2016	Referred for AVR	Intraop. biopsy	112	4 >65yr	58	75
Longhi S, JACC Img 2016	Referred for AVR	Non-invasive	43	12	80	84
Nietlispach F, JACC Int 2012	Autopsy after TAVR	Histology	17	29	33	85

*The study population is partially composed by patients enrolled in other studies showed in this table.

Chi sono i pazienti con Sao associata ad amiloidosi cardiaca e come identificarli ?

Identikit del paziente con SAo e CA ATTR

Maschio o femmina

Età >80 anni

Nell'anamnesi: tunnel carpale bilaterale

Sao severa low flow –low gradient paradoxical (un terzo dei casi)

FEVSn 50-55%

SV <35 cc

VS_n non dilatato

Ridotta funzione longitudinale VS_n

Profilo restrittivo transmitralico (un terzo dei casi)

SIV 15 mm

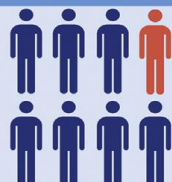
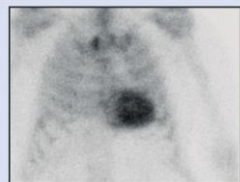
BBDx (un quarto dei casi)

IVNSn ECG lieve o assente

NT proBNP >3000

Diagnosed by DPD
Bone Scintigraphy

1:8 Patients Referred
for TAVR



Clinical Score for Screening AS-CA

Carpal Tunnel
Syndrome



Wall
Thickness



Age



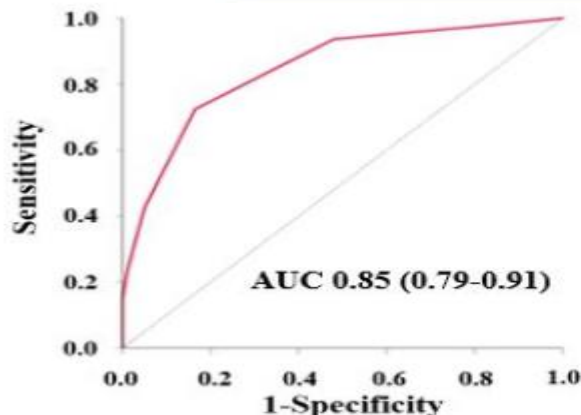
E/A Ratio



RBBB/Low
Voltage



Troponin



Parameter	Points
CTS	3
RBBB	2
Age $\geq$ 85y	1
Hs-TnT $>$ 20ng/L	1
IVS $\geq$ 18mm	1
If in SR*: E/A ratio $>$ 1.4	1
If no BBB or PM: Sokolow index $<$ 1.9mV	1

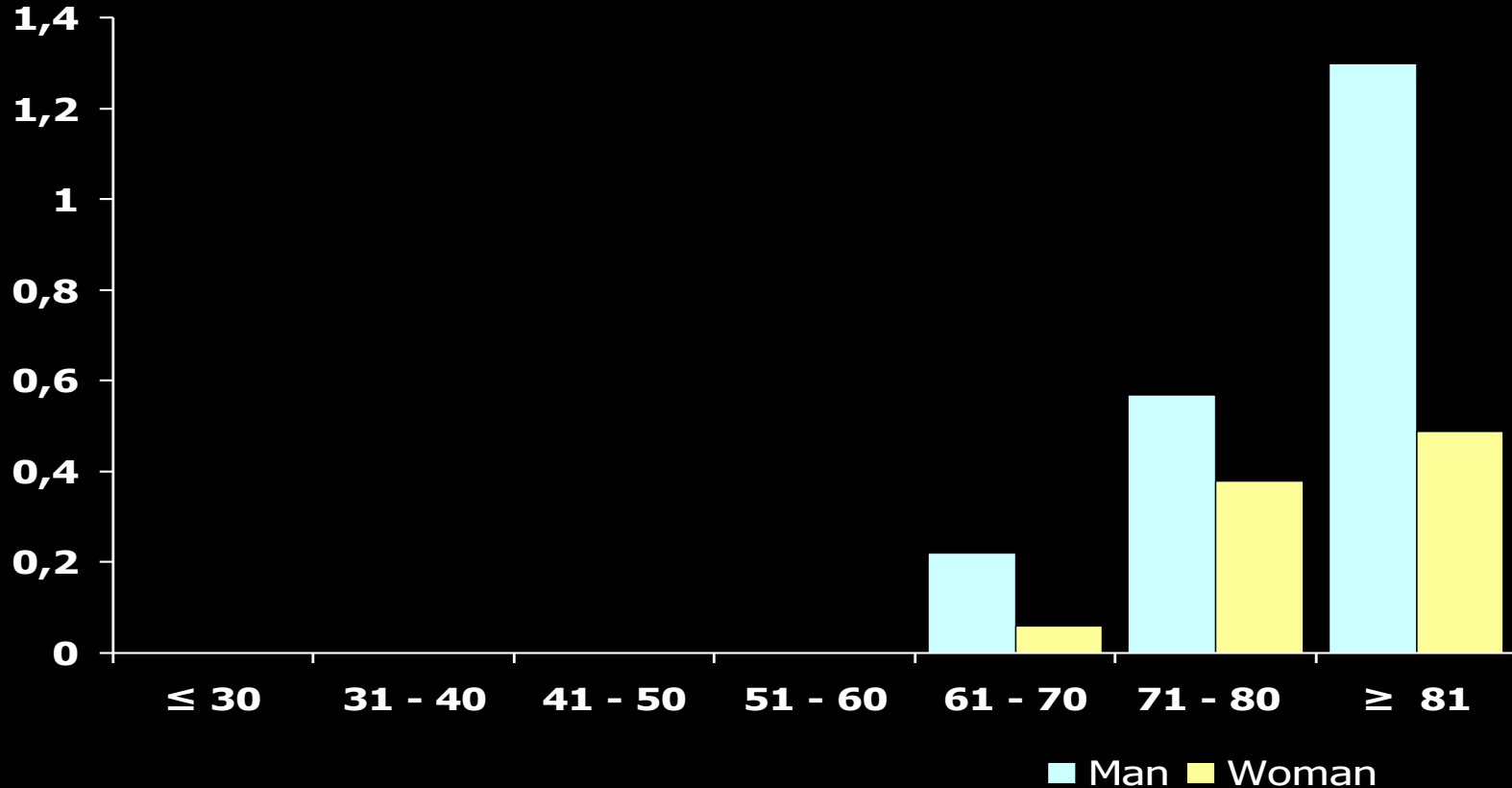
*) AUC for AFib sub-cohort: 0.83

Score	Specificity	Sensitivity
$\geq$ 6 points	100%	14.9%
$\geq$ 5 points	98.9%	23.4%
$\geq$ 4 points	95.0%	42.6%
$\geq$ 3 points	83.6%	72.3%
$\geq$ 2 points	52.1%	93.6%
$\geq$ 1 point	16.7%	97.9%

Qual' è il meccanismo alla base della associazione fra le due patologie ?

- 1) Associazione puramente epidemiologica**
- 2) Amiloidosi come causa di entrambe, cardiomiopatia e valvulopatia**
- 3) Cardiomiopatia come conseguenza della SAo**

Prevalence of incidental myocardial uptake of $^{99}\text{Tc-DPD}$ (n=12.300)



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**2) Amiloidosi come causa di entrambe,
cardiomiopatia e valvulopatia**

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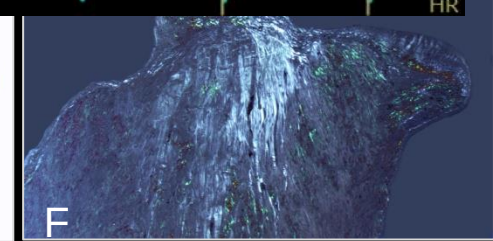
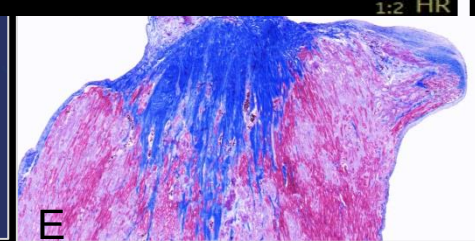
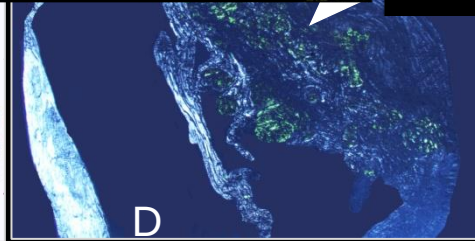
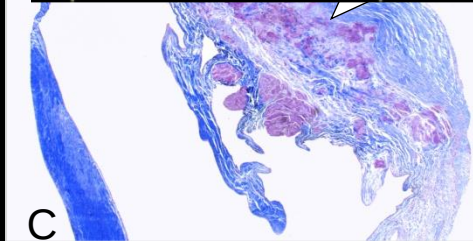
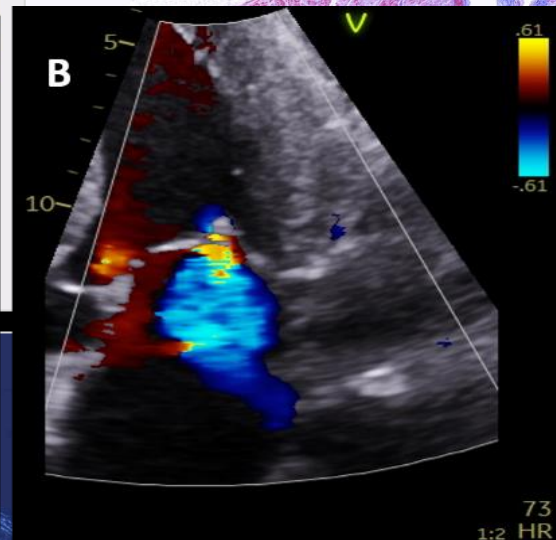
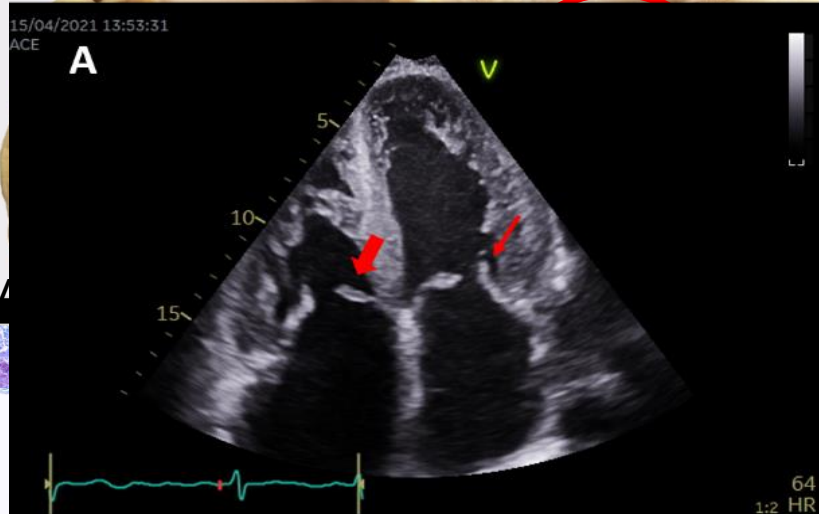
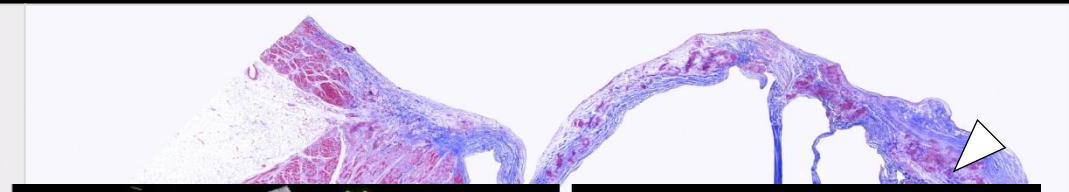
H1: 1.6
S4 1.8/3.6
19 OTT 80
10:13:39
ELAB 8/0/E/SA
1ST CARDIOLOGIA
UNIV BOLOGNA
MF
LENI A

002628-15
GARD 55
COMP 70
55BPH

16CH
25HZ

1.8 3.6





High prevalence of amyloid in 150 surgically removed heart valves—a comparison of histological and clinical data reveals a correlation to atheroinflammatory conditions

Arnt V. Kristen^{a,*}, Philipp A. Schnabel^b, Bettina Winter^a, Burkhard M. Helmke^b, Thomas Longerich^b, Stefan Hardt^a, Achim Koch^c, Falk-Udo Sack^c, Hugo A. Katus^a, Reinhold P. Linke^{d,1}, Thomas J. Dengler^{a,1}

Cardiovascular Pathology 19 (2010) 228–235

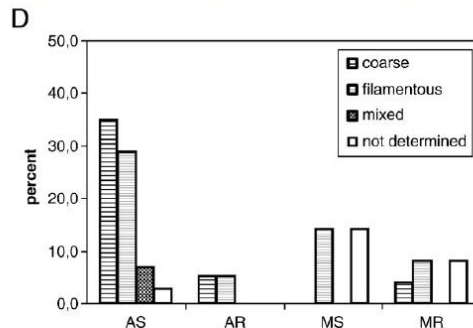
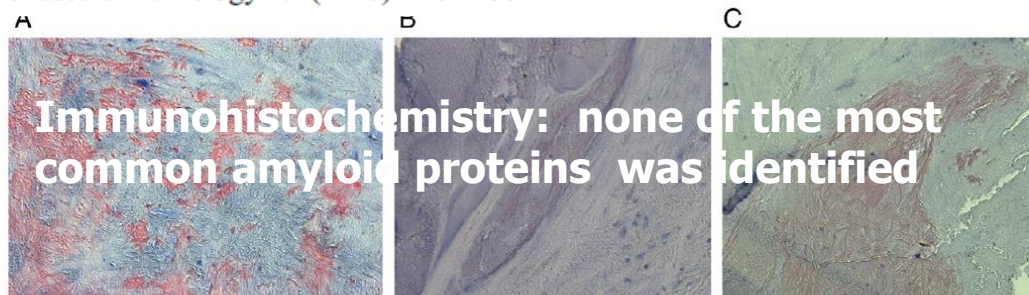


Fig. 3. Representative images of (A) coarse polymorphic deposits with jagged edges and (B) filamentous (“cloudy”) amyloid distribution patterns in degenerative valve diseases. (C) A mixture of coarse and filamentous amyloid deposition pattern. (D) Quantitative analysis of amyloid deposition patterns according to the valvular diagnosis. AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation.

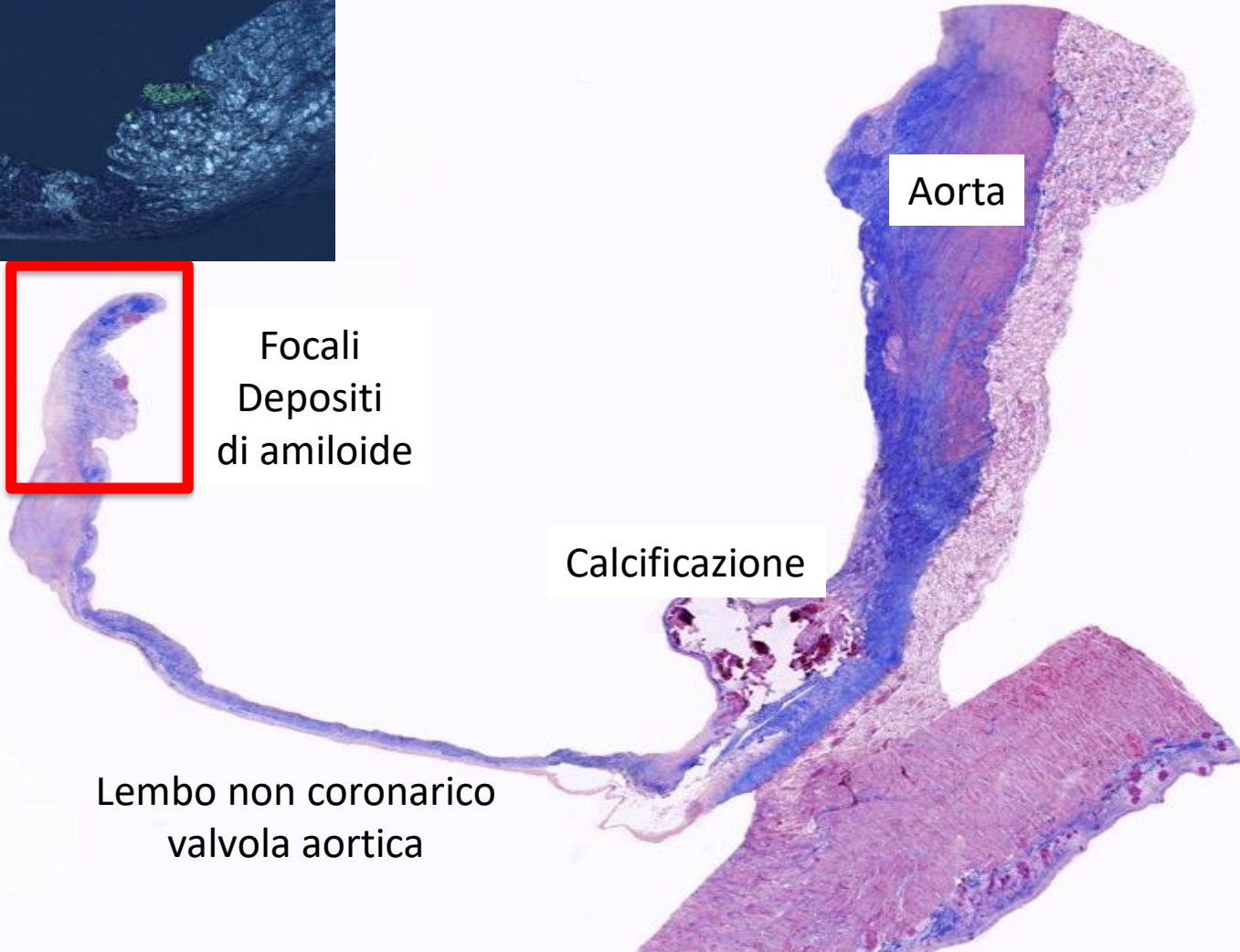


Focali
Depositi
di amiloide

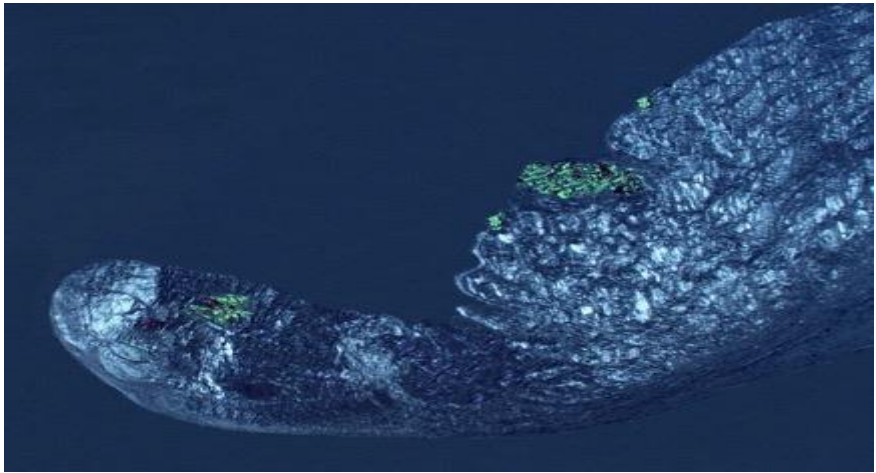
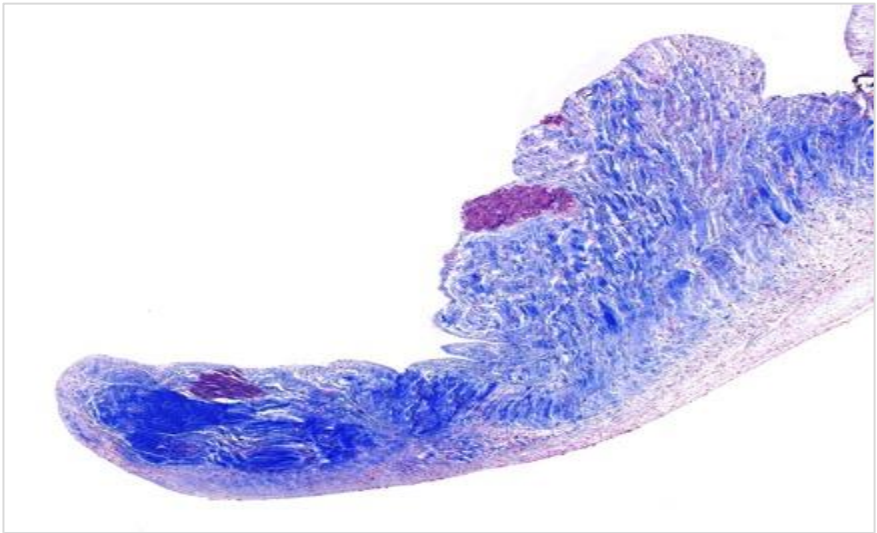
Lembo non coronarico
valvola aortica

Calcificazione

Aorta

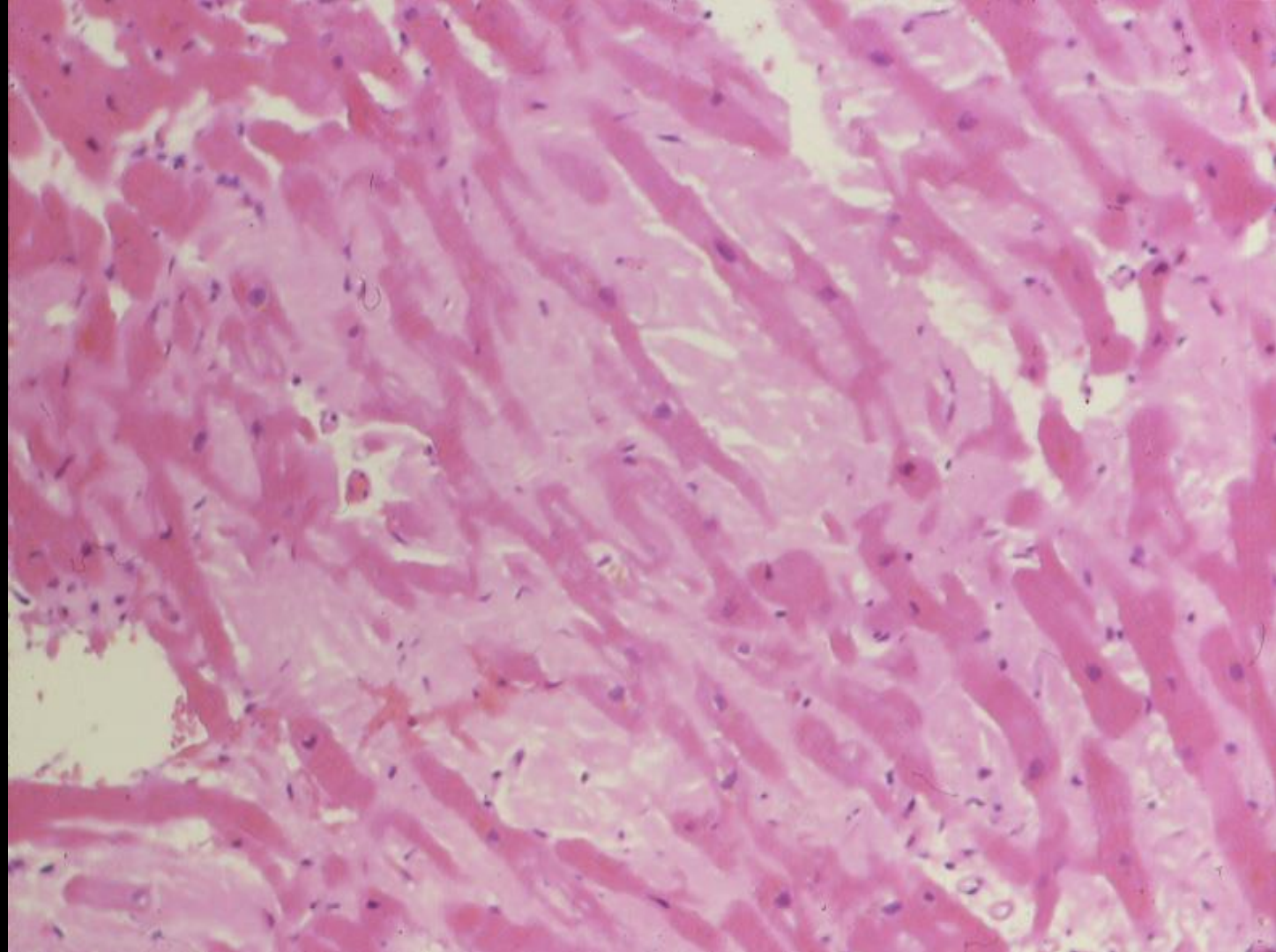


ATTR



Qual' è il meccanismo alla base della associazione fra le due patologie ?

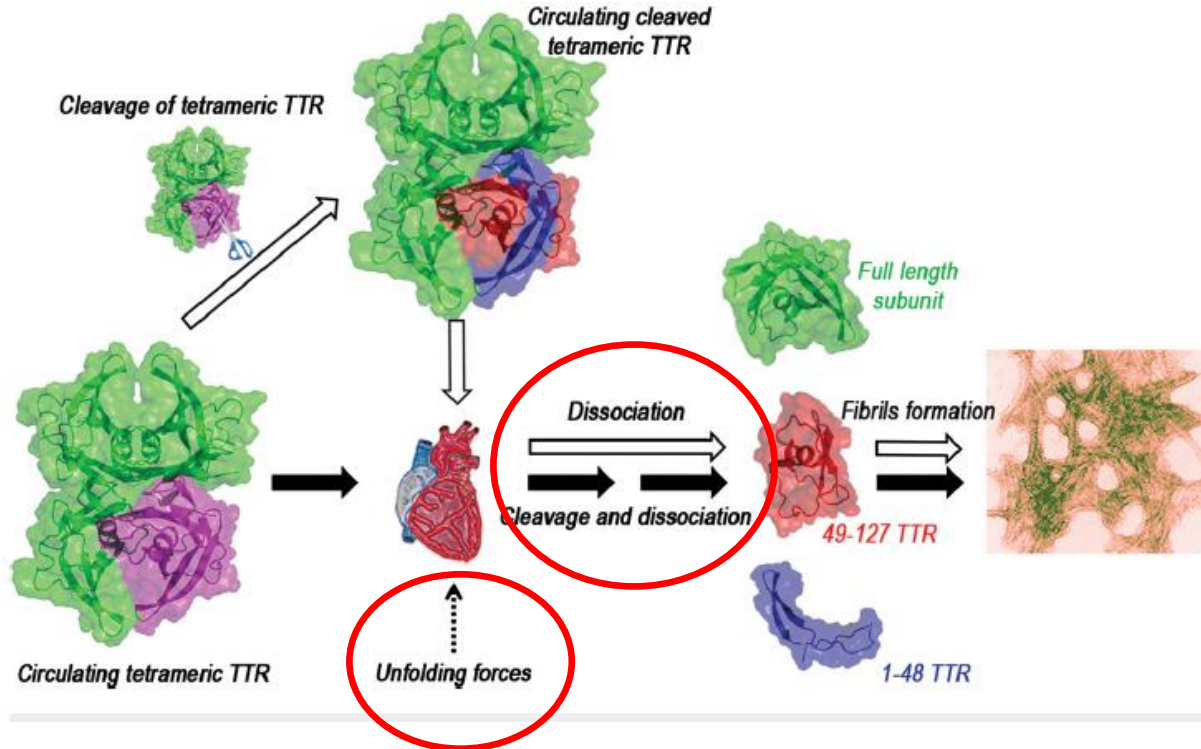
- 1) Associazione puramente epidemiologica**
- 2) Amiloidosi come causa di entrambe, cardiomiopatia e valvulopatia**
- 3) Cardiomiopatia come conseguenza della SAo**



A novel mechano-enzymatic cleavage mechanism underlies transthyretin amyloidogenesis

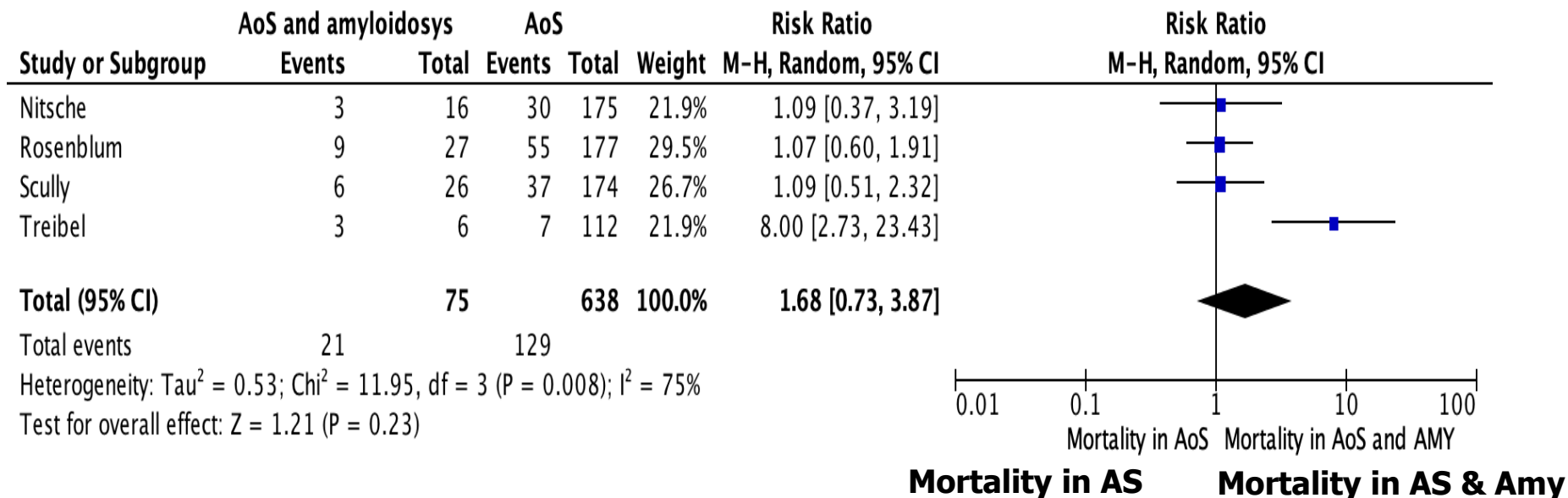
Julien Marcoux^{1,2,†,‡}, P Patrizia Mangione^{3,4,‡}, Riccardo Porcari³, Matteo T Degiacomi¹,
Guglielmo Verona^{3,4}, Graham W Taylor³, Sofia Giorgetti⁴, Sara Raimondi⁴, Sarah Sanglier-Cianfèrani²,
Justin LP Benesch¹, Ciro Cecconi^{5,6}, Mohsin M Naqvi⁶, Julian D Gillmore³, Philip N Hawkins³,
Monica Stoppini⁴, Carol V Robinson¹, Mark B Pepys³ & Vittorio Bellotti^{3,4,*}

EMBO Mol Med (2015) 7: 1337–1349



**La coesistenza di Saa e amiloidosi cardiaca
ATTR ha conseguenze sui risultati della
sostituzione valvolare o della TAVI ?**

Forest plot for all-cause mortality in patients with Aortic Stenosis with or without amyloidosis



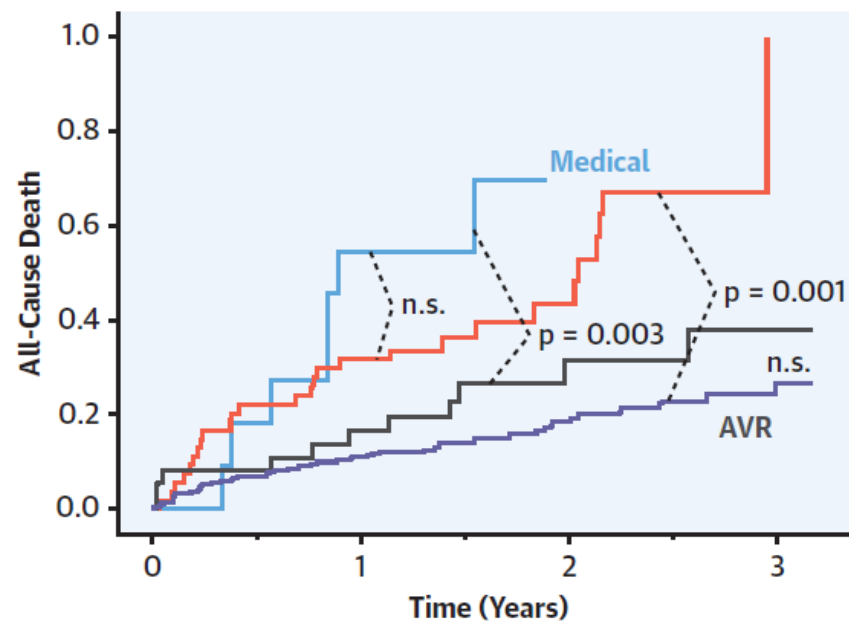
Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis



Christian Nitsche, MD,^a Paul R. Scully, PhD,^{b,c} Kush P. Patel, MBBS,^{b,d} Andreas A. Kammerlander, MD, PhD,^a Matthias Koschutnik, MD,^a Carolina Dona, MD,^a Tim Wollenweber, MD,^e Nida Ahmed, MBBS,^{b,d} George D. Thornton, MBBS,^{b,d} Andrew D. Kelion, MD,^f Nikant Sabharwal, MD,^f James D. Newton, MD,^f Muhiddin Ozkor, MD,^d Simon Kennon, MD,^d Michael Mullen, MD,^d Guy Lloyd, MD,^{b,d,g} Marianna Fontana, PhD,^h Philip N. Hawkins, FMedSci,^h Francesca Pugliese, MD,^{b,g} Leon J. Menezes, MD,^{d,i} James C. Moon, MD,^{b,d} Julia Mascherbauer, MD,^a Thomas A. Treibel, PhD^{b,d}

(J Am Coll Cardiol 2021;77:128-39)

FIGURE 4 All-Cause Mortality in Lone AS Versus AS-CA Following Aortic Valve Replacement or With Medical Therapy



No. at risk:

AS-CA - Medical	11	4	0	
Lone AS - Medical	54	35	13	0
AS-CA - AVR	37	29	13	6
Lone AS - AVR	305	249	85	30

Aortic valve replacement (AVR) improved outcomes for both lone AS and dual pathology AS-CA. Post-AVR survival of AS-CA was comparable to lone AS. Abbreviations as in [Figure 2](#).

Unveiling outcomes in coexisting severe aortic stenosis and transthyretin cardiac amyloidosis

Hannah Rosenblum^{1†}, Ahmad Masri^{2†}, David L. Narotsky¹, Jeff Goldsmith³, Nadira Hamid⁴, Rebecca T. Hahn⁴, Susheel Kodali⁴, Torsten Vahl⁴, Tamim Nazif⁴, Omar K. Khalique⁴, Sabahat Bokhari⁵, Prem Soman⁶, João L. Cavalcante⁷, Mathew S. Maurer^{1*}, and Adam Castaño^{1,3}

Table 3 Primary and secondary outcomes after transcatheter aortic valve replacement, stratified by the presence of transthyretin cardiac amyloidosis

	Overall (n = 204)	No ATTR-CA (n = 177)	ATTR-CA (n = 27)	P-value
Primary outcome				
Death, n (%)	63 (31)	54 (31)	9 (33)	0.9423
Secondary outcomes				
First HF hospitalization, n (%)	39 (19)	32 (18)	7 (26)	0.482
Recurrent HF hospitalizations				
1-year HF hospitalization rate, n/person-years	0.149	0.114	0.372	0.004
3-year HF hospitalization rate, n/person-years	0.123	0.199	0.111	0.087

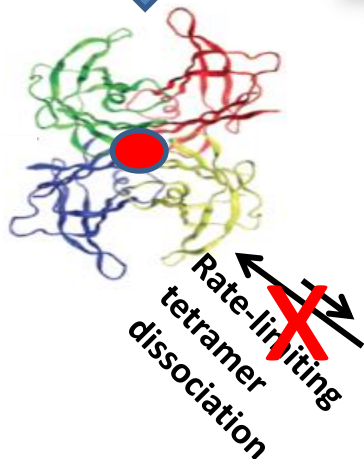
TTR Amyloidosis: therapeutic opportunities

Suppression of TTR synthesis

- Liver transplantation (mTTR)
- Gene silencing (m & wt TTR)
 - siRNA: **PATISIRAN**, VUTISIRAN (HELIOS A and B trials ongoing)
 - ASO: **INOTERSEN**, AKCEA-TTR-LRx (CARDIO TTRtransform trial ongoing)
 - CRISP Cas-9 gene editing

TTR stabilizers

- Non-selective: **DIFLUNISAL**
- Selective:
 - **TAFAMIDIS**
 - **AG10** (ATTRIBUTE-CM trial ongoing)



Folded monomer

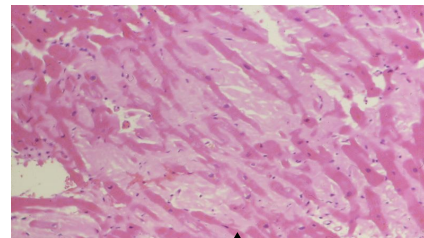
Monomer misfolding

Misfolded monomer

Aggregation

Small oligomers

Amyloid fibrils



*Tauroursodeoxycholic acid

**IN CONCLUSIONE, QUALI SONO LE
IMPLICAZIONI CLINICHE DELLA
COESISTENZA DI AMILOIDOSI CARDIACA E
STENOSI AORTICA?**

Amiloidosi cardiaca ATTR nei pazienti anziani con Sao degenerativa

- **Presente in un paziente su 8**
- **Sia maschi sia femmine**
- **Facilmente sospettabile applicando score non invasivi**
- **Diagnosticabile con scintigrafia ossea**
- **Non controindica la TAVI se clinicamente indicata (pochissimi dati per la AVR)**
- **Condiziona un aumentato rischio residuo post TAVI di scompenso cardiaco**
- **Da verificare l'efficacia di un trattamento con Tafamidis post TAVI**