Les nouveautés en cardiologie ISA 2024

ISA
INTERNATIONAL SOCIETY OF AMYLOIDOSIS

XIX International Symposium on Amyloidosis

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Hopital Henri Mondor

Centre de référence des Amyloses Cardiaques

Créteil

Amyloidosis: Lessons Learned and Towards Precision Medicine Therapies and Biomarkers

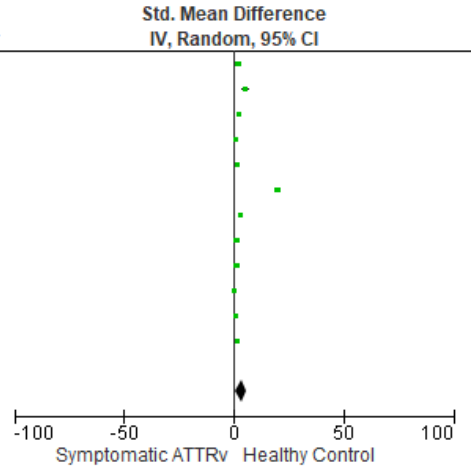
Serum neurofilament light chain levels show promise as a biomarker for early detection and diagnosis of ATTRv amyloidosis: A meta-analysis

RESULTS

- There is a significantly higher level of sNfl in symptomatic ATTRv patients than in health controls, with a relatively larger standard mean difference (SMD) of 3.36.

Study or Subgroup	Symptomatic ATTRv Mean	SD	Total	Healthy Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Maia, L.F (Cohort 1)	111.915	63.01	26	7.41	0.98	16	8.3%	2.06 [1.28, 2.83]	2020
Maia, L.F (Cohort 2)	93.29	22.19	18	7.41	0.98	16	8.1%	5.18 [3.71, 6.65]	2020
Louwsma, J	68.38	26.44	53	8.85	1.41	15	8.3%	2.51 [1.79, 3.23]	2020
Ticau, S (APOLLO_p'siran)	99.64	89.77	136	21.95	31.78	57	8.4%	1.00 [0.67, 1.32]	2021
Ticau, S (APOLLO_pbo)	87.45	54.75	53	21.95	31.78	57	8.4%	1.47 [1.04, 1.89]	2021
Loser, V	24.52	11.45	14	7.3	0.61	4532	8.3%	19.93 [19.27, 20.60]	2022
Luigetti, M	85.23	36.87	15	17.95	7.31	26	8.3%	2.89 [1.97, 3.80]	2022
Ticau, S (APOLLO_patisiran)	72	45.7	111	21.95	31.78	57	8.4%	1.20 [0.85, 1.54]	2023
Ticau, S (APOLLO_placebo)	63.2	32.2	47	21.95	31.78	57	8.4%	1.28 [0.86, 1.71]	2023
Ticau, S (P2 OLE_patisiran)	32.9	14.4	26	21.95	31.78	57	8.4%	0.39 [-0.07, 0.86]	2023
González-Moreno, J	117.33	14.07	29	96.67	32.21	30	8.4%	0.82 [0.28, 1.35]	2024
Romano, A	74	43.45	61	17.7	8.44	50	8.4%	1.71 [1.27, 2.15]	2024
Total (95% CI)			**589**			**4970**	**100.0%**	**3.36 [0.99, 5.73]**	

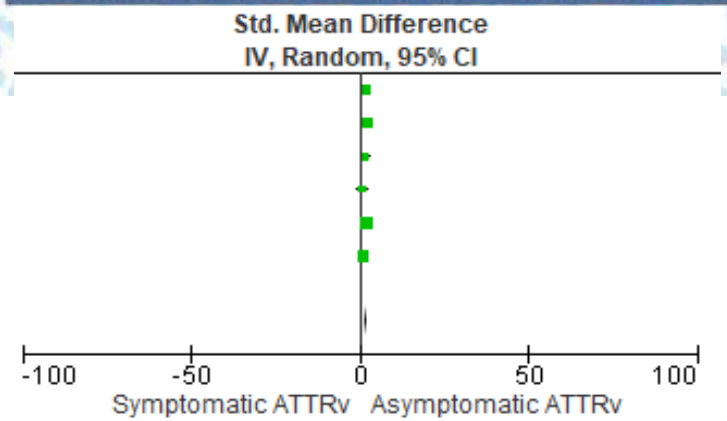
Heterogeneity: Tau² = 17.42; Chi² = 2945.80, df = 11 (P < 0.00001); I² = 100%
Test for overall effect: Z = 2.78 (P = 0.005)

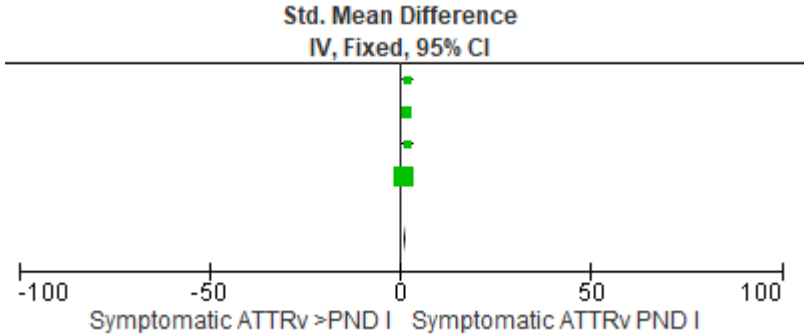


- A higher significant level of sNfl was observed in the symptomatic ATTRv patients than in the asymptomatic ATTRv patient group with an SMD value of 1.77.

- There are relatively lower but insignificant sNfl levels in the asymptomatic ATTRv group than in healthy controls, as shown in the negative SMD value of -0.18.

- A higher significant sNfl level in the greater than I Polyneuropathy Disability (PND) score category than in a corresponding PND score I in Symptomatic ATTRv Amyloidosis patients with an SMD value of 1.39.





CONCLUSION:

In conclusion, the trends of increase in the levels of sNfl in ATTRv Amyloidosis patients has shown promise as a potential biomarker for early detection and diagnosis of ATTRv Amyloidosis this condition as evidenced in the marked

Kwaku Appiah-Kubi, PhD (C. K. Tedam University of Technology and Applied Sciences)

3e CONGRÈS FRANCOPHONE MULTIDISCIPLINAIRE DE L'AMYLOSE

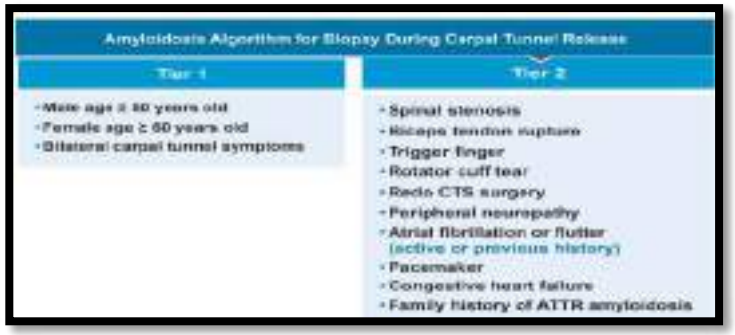
SCREENING FOR AMYLOIDOSIS AT THE TIME OF CARPAL TUNNEL RELEASE SURGERY IN REAL WORLD PRACTICE

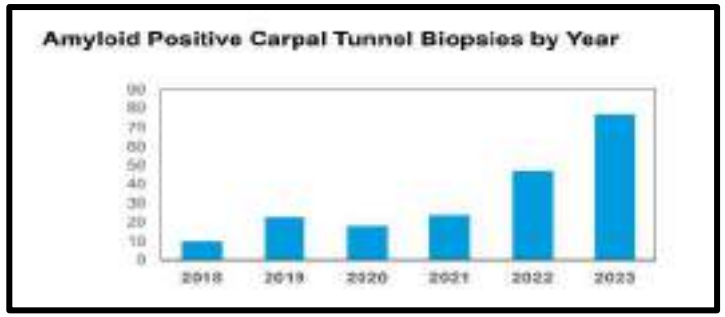
SUCCESSFUL STRATEGY AT DIAGNOSING EARLY CARDIAC AMYLOIDOSIS

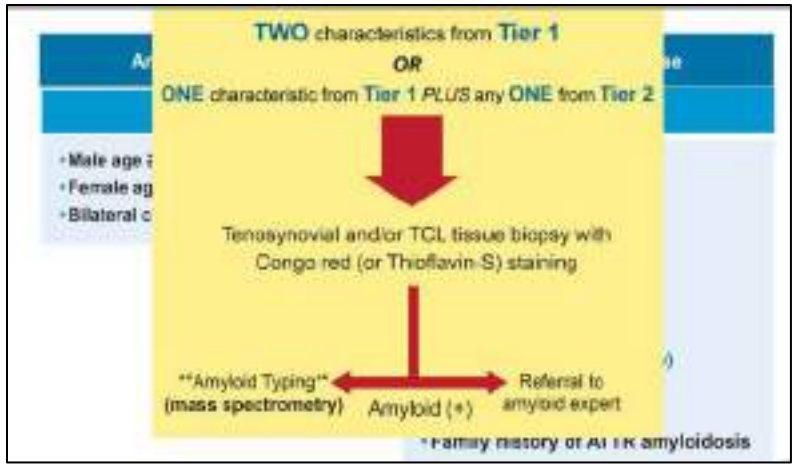
Jeudi 13 juin 2024
iermans-Lapôtre ■PARIS

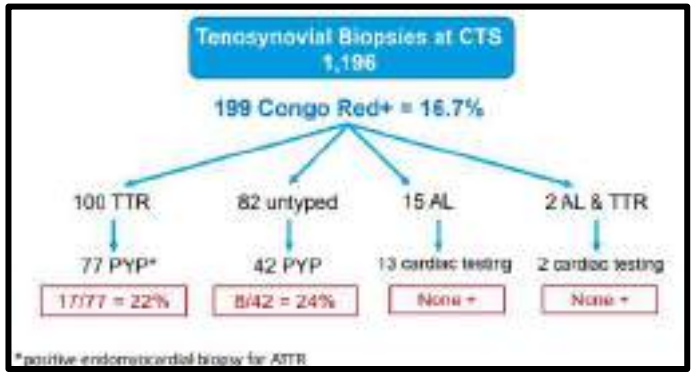
MAZEN HANNA, MD

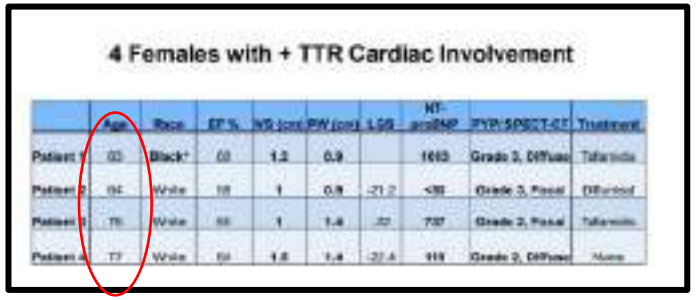
- 10 / 99 patients (10%) prevalence of + amyloid
- 2 found to have cardiac involvement at baseline
  - 1 ATTRwt
  - 1 AL
- All amyloid+ patients had bilateral CTS











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Jeudi 13 juin 2024

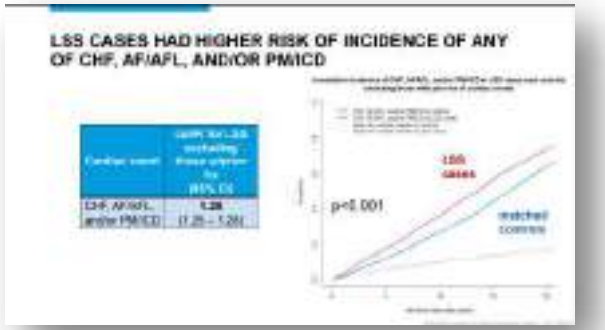
Biermans-Lapôtre ■PARIS

LUMBAR SPINAL STENOSIS (LSS) AND CARPAL TUNNEL SYNDROME (CTS) AS SURROGATES FOR WILD-TYPE TRANSTHYRETIN AMYLOID CARDIOMYOPATHY (ATTR-CM)

Laura De Michieli [1,2], Susan Geyer[1], Ellen McPhail[1], Mohamad Bydon[1], Benjamin Elder[1], Julie Rosenthal [3], MaryJurisson[1], Sanjeev Kakar[1], Alberto Cipriani[2], Omar Abou Ezzeddine[1], Surendra Dasari[1], Morie Gertz[1], Martha Grogan[1], **Angela Dispenzieri[1].**

[1] Mayo Clinic, Rochester, Minnesota, USA [2] University Of Padova, Padova, Italy [3] Mayo Clinic, Phoenix, Arizona, USA

LSS CASES HAD HIGHER RISK OF INCIDENCE OF ANY OF CHF, AF/AFL, AND/OR PM/ICD

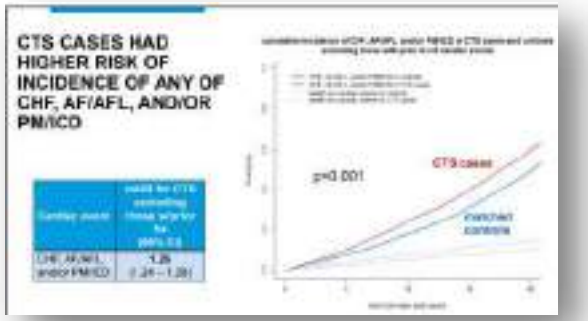


LSS COHORT HAD A HIGHER RATE OF PRIOR CE

- Initially selected 25,405 subjects from the REP database
- Analysis cohort → N = 22,453

Characteristic	Controls N = 16,342	LSS cases N = 6,111	OR	p-value
Biological sex				
Male	7,386	2,751		
Female	8,956 (55%)	3,360 (55%)		
Age at	(11.7)	68.8 (10.9)		
		857 (14.0%)	1.66	<0.0001
		(3.8%)	1.17	0.09
			1.60	<0.0001
history of PM/ICD				
for history of any of these cardiac events	3,408 (1			

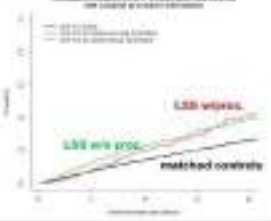
CTS CASES HAD HIGHER RISK OF INCIDENCE OF ANY OF CHF, AF/AFL, AND/OR PM/ICD



CARDIAC RISK IN LSS CASES WHO DID VS. DID NOT HAVE LSS-RELATED SURGICAL PROCEDURES REPORTED

- Of the 6,111 LSS cases, 1,014 (16.6%) had a LSS-related surgical procedure reported when identified as a case
- Those who had LSS procedures had lower risks of cardiac events overall, but most pronounced for risk of CHF

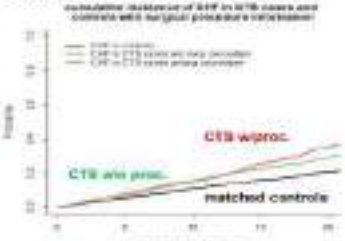
aHR for CHF in relation to matched controls	
LSS cases w/procedure	1.39
LSS cases w/o procedure	1.56



CARDIAC RISK IN CTS CASES WHO DID VS. DID NOT HAVE CTS-RELATED PROCEDURES REPORTED

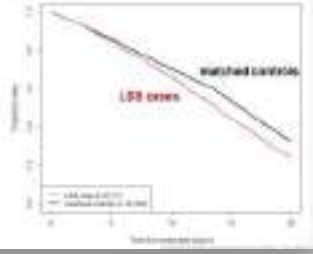
- Of the 6,956 CTS cases, 2,000 (29%) had a CTS-related procedure reported when identified as a case
- Those who had CTS procedures had lower risks of cardiac events overall, but not as pronounced as that observed for LSS cases

aHR for CHF in relation to matched controls	
CTS cases w/procedure	1.39
CTS cases w/o procedure	1.44



OVERALL SURVIVAL WAS WORSE IN LSS CASES VS. MATCHED CONTROLS

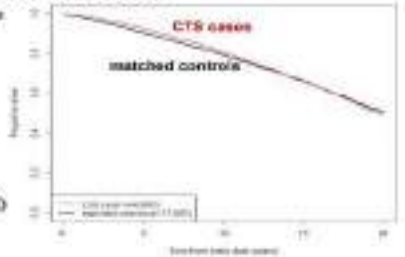
- Median f/u across cohort was 8.2 years
- 6,547 deaths reported
- LSS cases had significantly worse OS compared to their matched controls
- HR = 1.25 (95% CI: 1.18 – 1.33) p<0.001



- Historically, ATTR-CM has been underdiagnosed
- We hypothesized that if there were a true association between ATTR-CM and LSS and/or CTS, patients with these diagnoses would have higher rates of cardiac events and inferior survival compared to age-matched controls
- Patients with LSS had a 1.6x higher rate of CHF, AF/AFL, PM/ICD and a 1.3 hazard rate of death compared to controls
- Patients with CTS had a 1.3x higher rate of CHF, AF/AFL, PM/ICD but no difference in overall survival compared to controls

OVERALL SURVIVAL WAS NOT WORSE IN CTS CASES VS. MATCHED CONTROLS

- Median f/u across cohort was 9.6 years
- 5,865 deaths reported
- CTS cases did not have significantly differential OS compared to their matched controls
- HR = 0.95 (95% CI: 0.90 – 1.01) p = 0.10



TRAITEMENT

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CLINICAL IMPACT OF BETA-BLOCKER WITHDRAWAL IN TRANSTHYRETIN AMYLOID CARDIOMYOPATHY

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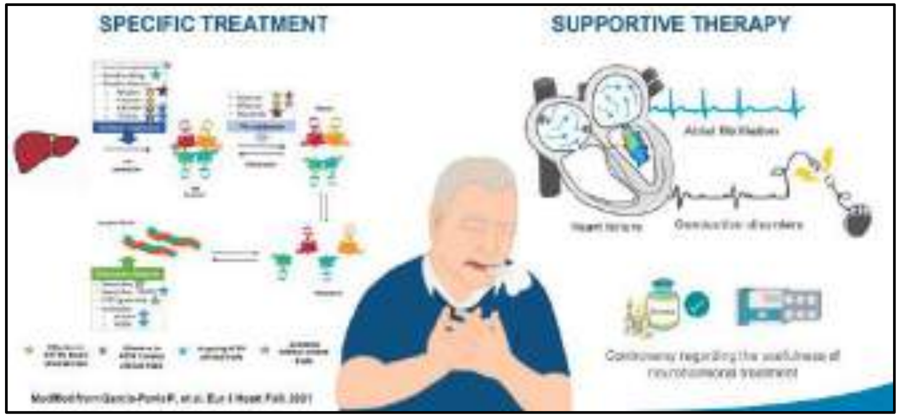
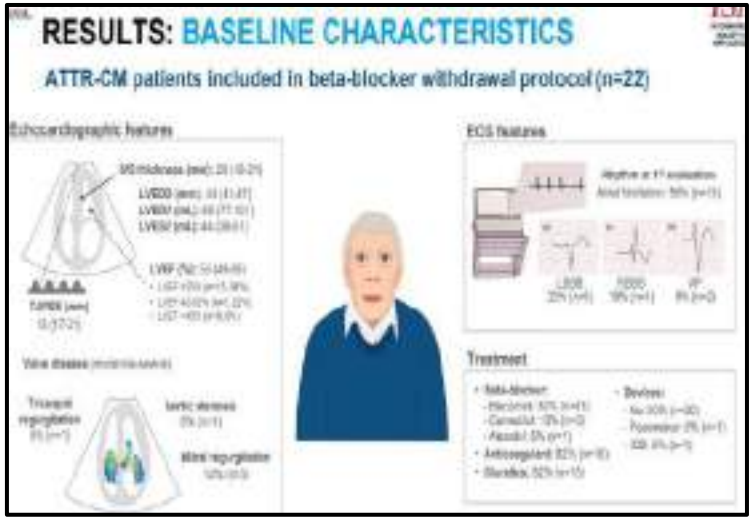
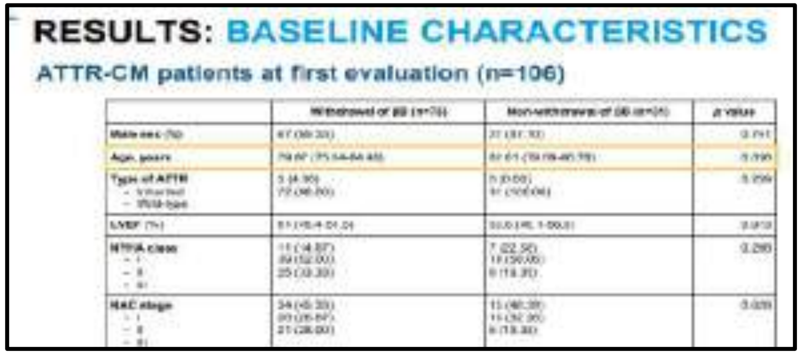
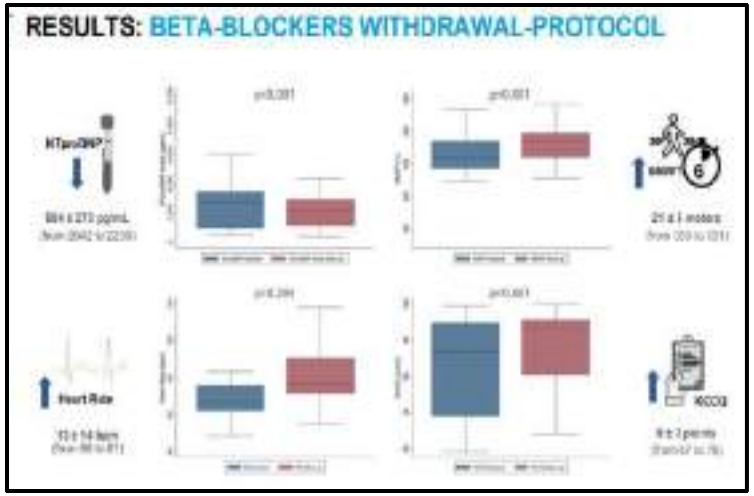






SUPPORTIVE THERAPY: Beta-blockers. Prescribe it or not?



Conclusions:

- Discontinuation of beta-blockers in patients with ATTR-CM leads to clinical improvement at short term with increase in quality of life and functional capacity.
- There is an urgent need for randomized controlled clinical trials to assess the use of HF medications in ATTR-CM.

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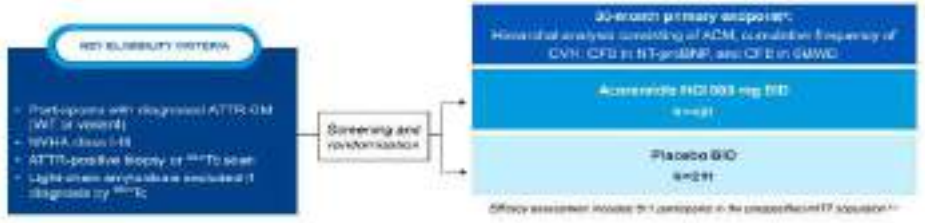
ACORAMIDIS ACHIEVES EARLY REDUCTION IN CARDIOVASCULAR-RELATED DEATH OR HOSPITALIZATION IN TRANSTHYRETIN AMYLOID CARDIOMYOPATHY (ATTR-CM): RESULTS FROM THE ATTRibute-CM CLINICAL TRIAL

Kevin M. Alexander[1], Daniel P. Judge[2], Francesco Cappelli[3], Marianna Fontana[4], Pablo Garcia-Pavia[5], Martha Grogan[6], Mazen Hanna[7], Ahmad Masri[8], Mathew S. Maurer[9], Laura Obici[10], Prem Soman[11], Xiaofan Cao[12], Jean-François Tamby[12], Suresh Siddhanti[12], Leonid Kotz[12], Jonathan C. Fox[12], Kenneth W. Mahaffey[13], Julian D. Gillmore[4]

- **Acoramidis is a next-generation, investigational, near-complete TTR stabilizer (>90%) for the treatment of patients with ATTR-CM3-5**
- **Acoramidis demonstrated a significant improvement in a 4-step primary hierarchical endpoint of mortality, morbidity, and function in the phase 3 ATTRibute-CMa study6**
- **Acoramidis also demonstrated a 50% relative risk reduction in the cumulative frequency of CVH compared with placebo over 30 months3,6**

METHODS: ATTRIBUTE-CM STUDY DESIGN

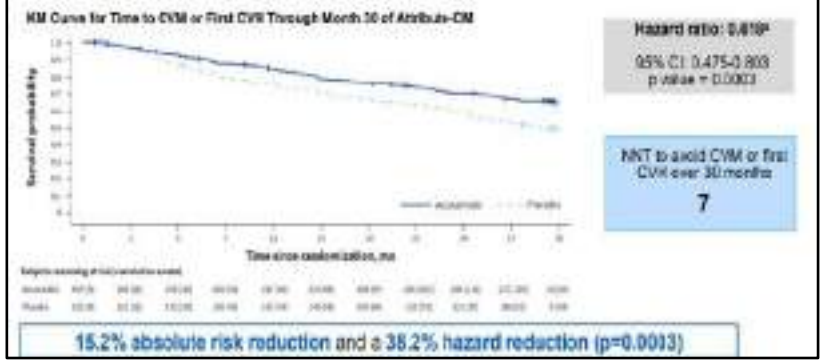


BASELINE CHARACTERISTICS WERE COMPARABLE BETWEEN TREATMENT GROUPS

	mITT Population N=611	
	Acoramidis n=409	Placebo n=202
Mean age, years (SD)	77 (6.5)	77 (6.7)
Sex, n (%)		
Male	374 (91.4)	181 (89.6)
NYHA class, n (%)		
I	51 (12.5)	17 (8.4)
II	288 (70.4)	156 (77.2)
III	70 (17.1)	29 (14.4)
eGFR, mL/min/1.73 m²		
Mean (SD)	62 (17.4)	63 (17.5)
Median (IQR)	62 (49, 74)	61 (48, 74)
NT-proBNP, pg/mL		
Mean (SD)	2865 (2149.6)	2859 (1999.5)
Median (IQR)	2073 (1515, 3872)	2276 (1128, 3880)
Genetic status[a], n (%)		
Wild-type	370 (90.5)	182 (90.1)
Variant	39 (9.5)	20 (9.9)

ACORAMIDIS SIGNIFICANTLY IMPROVED CV OUTCOMES COMPARED WITH PLACEBO

KM curves separate early, at Month 3, and steadily diverge through Month 30



15.2% absolute risk reduction and a 38.2% hazard reduction (p=0.0003)

NO SAFETY SIGNALS OF POTENTIAL CLINICAL CONCERN WERE IDENTIFIED

Participants with ≥1 event	Acoramidis n=421	Placebo n=211
Any TEAEs, n (%)	413 (98.1)	206 (97.6)
TEAE with fatal outcome	60 (14.3)	36 (17.1)
TEAE leading to hospitalization	212 (50.4)	128 (60.7)
TEAE leading to study drug discontinuation	39 (9.3)	16 (8.5)
Any TESAEs, n (%)	230 (54.6)	137 (64.9)
TESAEs leading to study drug discontinuation	21 (5.0)	15 (7.1)
Severe TEAEs, n (%)[a]	157(37.3)	96 (45.5)

Acoramidis treatment resulted in an early and significant reduction in the composite endpoint of CVM or first CVH in patients with ATTR-CM ATTR-CM, **transthyretin amyloidcardiomyopathy; CVH, cardiovascular-related** hospitalization; CVM, cardiovascular-related mortality; KM, Kaplan-Meier. early separation of KM curves at 3 months represents the most rapid clinical benefit on the composite endpoint of CVM and CVH outcomes

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TREATMENT FOR ATTR

IS THERE A ROLE FOR DUAL (TRIPLE) THERAPY?

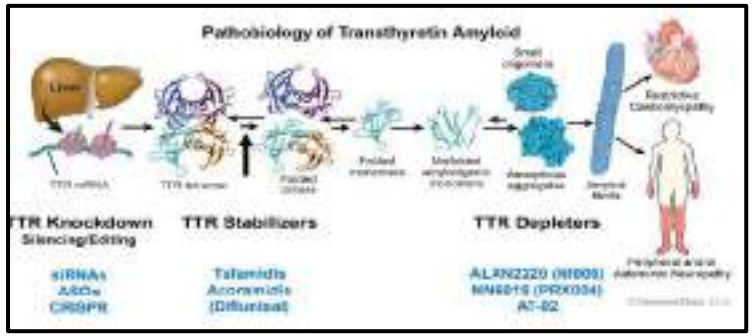
MAZEN HANNA, MD

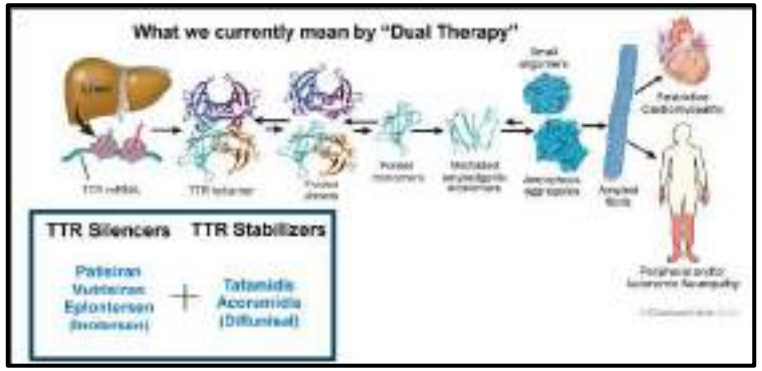
COMBINATION THERAPY APPLIES TO OTHER DISEASES

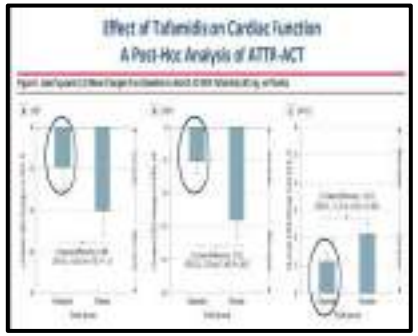
Heart Failure

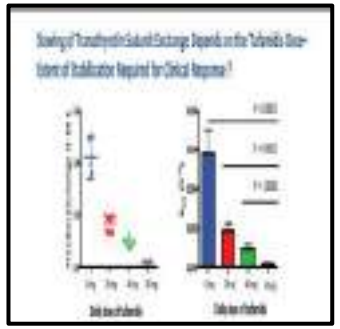
Hypertension

Will dual (triple) therapy work for Transthyretin Amyloidosis?



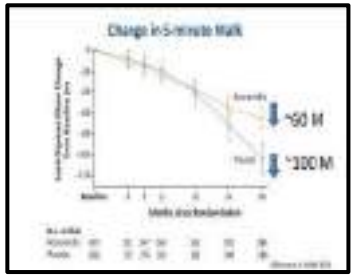


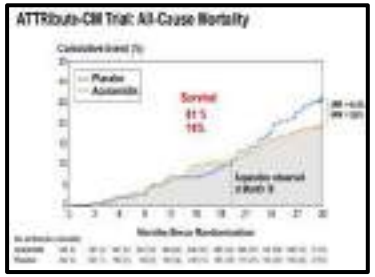


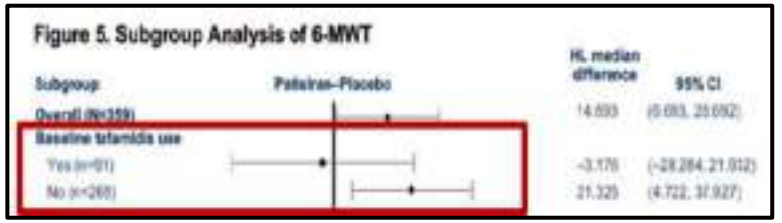


Statistically Significant ? Clinically Significant

Who determines clinical significance?
Us or the patient?







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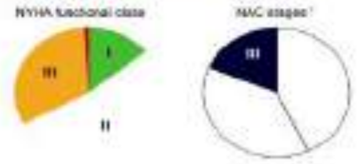
RV-PA uncoupling is a strong predictor of mortality in transthyretin amyloid cardiomyopathy

S. K. Schwarting[1,2], M. Poledniczek[2], E. Hofmann[2], N. Frey[2], S. Kaeaeb[1], U. Hegenbart[3], S. Schoenland[3], F. Aus dem Siepen[2]

Analysis on a typical ATTR-CM cohort – Baseline characteristics

Parameter	Overall (n = 418)
Age, years	79.5 [75.8-83.3]
Male	351 (81)
ATTRv, n	22 (5)
BMI, kg/m²	23.3 [20.4-23.8]
AFib/flutter, n	243 (58)
CAD	163 (39)
Heart rate, BPM	73 [64-88]
QRS, ms	111 [98-142]
CIED, n	65 (13)
eGFR, ml/min	60.5 [46.0-74.9]
NT-proBNP, pg/ml	3268 [1449-6173]



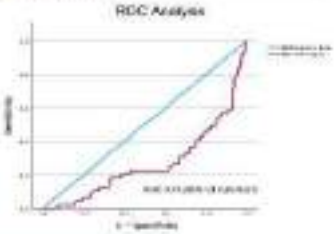
Concomitant HF medication	
ß-blockers, n	251 (60)
ACEi/ARBs/ARNI, n	269 (64)
MRA, n	167 (40)
SGLT-2i, n	97 (23)
Diuretic dose, % of maximum torasemid dose equivalent	4 [0-6]

LV echocardiographic parameters at baseline

Left ventricular parameter	Overall (n = 418)
IVSd, mm	19 [17-21]
LVEDD, mm	45 [41-49]
RWT, %	0.75 [0.62-0.87]
LVEF, %	47 [40-52]
LV GLS, (-%)	10.5 [12.9-8.3]
E/E' mean, ratio	15.0 [11.0-19.0]
MR grade ≥ 2, n	58 (14)
LA diameter, mm	46 [42-50]

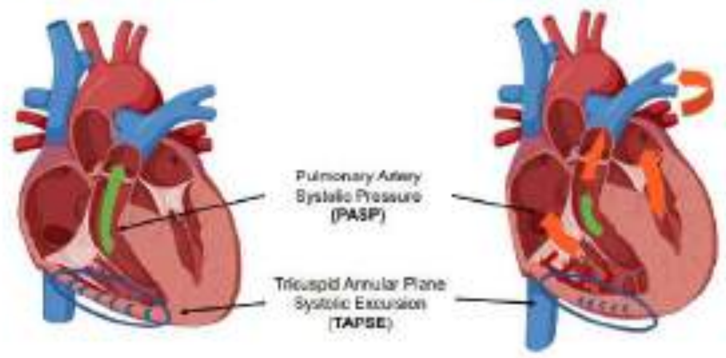
RV echocardiographic parameters at baseline

Right ventricular parameter	Overall (n = 418)
RVEDD, mm	38 [34-41]
RV free wall thickness, mm	10 [8-12]
TAPSE, mm	16 [13-20]
TR ≥ 2, n	10 (2)
PASP, mmHg	36 [34-40]
TAPSE/PASP, mm/mmHg	0.457 [0.315-0.719]



Youden's Index: Best discriminating cut-off value: 0.382mm/mmHg

RV-PAc – mechanism to uncoupling



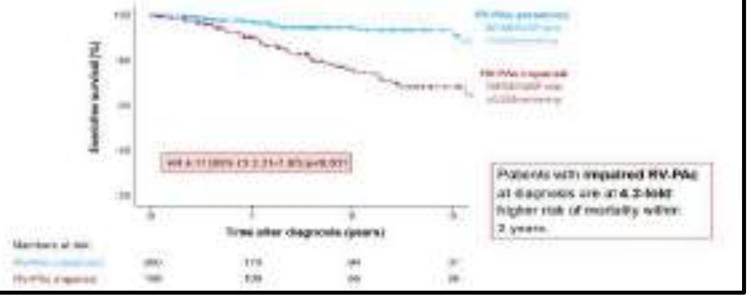
Conclusion & Clinical Perspective

RV-PA uncoupling in ATTR-CM

- is a **common feature** of advanced disease stage.
- is **related** to reduced **left ventricular function**.
- is associated with **increased risk of all-cause mortality** (cut-off ≤ 0.382mm/mmHg)
- is an **independent predictor of all-cause mortality within 3 years** after initial diagnosis.

Assessment of **right ventricular adaptation to pulmonary circulatory hemodynamics** should be included into comprehensive echocardiographic study upon diagnosis for **risk assessment** in ATTR-CM patients.

RV-PA uncoupling is associated with worse outcome in ATTR-CM



Characteristics of ATTR-CM patients with impaired RV-PAc

Parameter	Overall (n = 418)	RV-PAc preserved	RV-PAc impaired (n = 158)	p-value
Age, years	[illegible]	[illegible]	[illegible]	[illegible]
Male, n	381 (91)	213 (90)	168 (91)	0.727
ATTRv, n	[illegible]	[illegible]	[illegible]	[illegible]
BMI, kg/m²	[illegible]	[illegible]	[illegible]	[illegible]
AFib/flutter, n	[illegible]	[illegible]	[illegible]	[illegible]
Heart rate, BPM	[illegible]	[illegible]	[illegible]	[illegible]
QRS, ms	[illegible]	[illegible]	[illegible]	[illegible]
CAD, n	[illegible]	[illegible]	[illegible]	[illegible]
CIED, n	[illegible]	[illegible]	[illegible]	[illegible]
eGFR, ml/min	[illegible]	[illegible]	[illegible]	[illegible]
NT-proBNP, pg/ml	[illegible]	[illegible]	[illegible]	[illegible]
NYHA functional class ≥ 3, n	[illegible]	[illegible]	[illegible]	[illegible]

Patients with impaired RV-PA coupling are characterized by **advanced disease stage at diagnosis, higher occurrence of atrial fibrillation and prolonged QRS duration**

Multivariate analysis on echocardiographic predictors of 3-years all-cause mortality

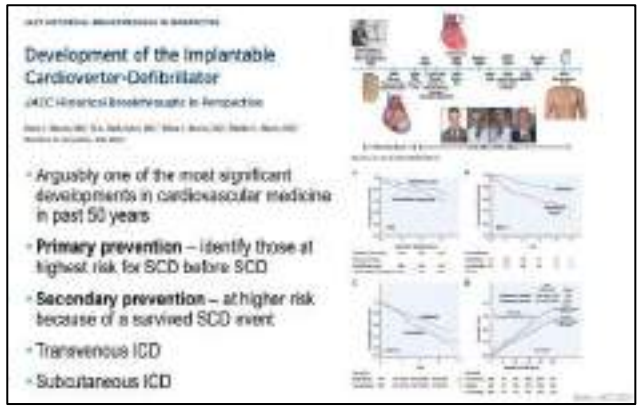
	univariate			multivariate		
	hazard ratio	confidence interval	p-value	hazard ratio	confidence interval	p-value
RWT, per %	1.04	0.46-5.00	0.404			
LVEF, per %	0.94	0.92-0.96	<0.001	0.95	0.93-0.99	0.015
LV GLS, per -%	1.21	1.10-1.33	<0.001	1.09	0.96-1.23	0.176
LA diameter, per mm	1.05	1.01-1.10	0.013	1.00	0.95-1.05	0.930
MR ≥ 2	1.83	1.00-3.28	0.048			
RVEDD ≥ 40mm	2.06	1.16-3.67	0.011	1.43	0.79-2.61	0.240
RV-PAc ≤ 0.382mm/mmHg	4.28	2.39-7.66	<0.001	3.3	1.17-6.30	<0.001

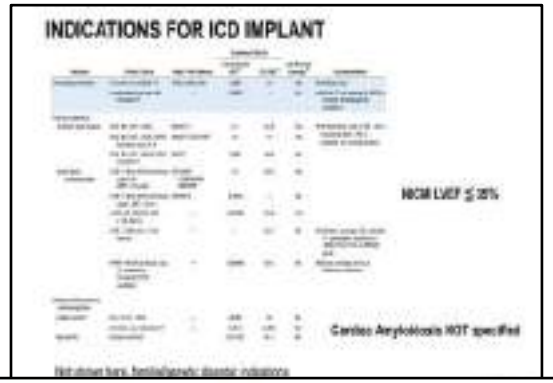
RV-PAc ≤ 0.382mm/mmHg and LVEF were **independent echocardiographic predictors** of all-cause mortality in our cohort

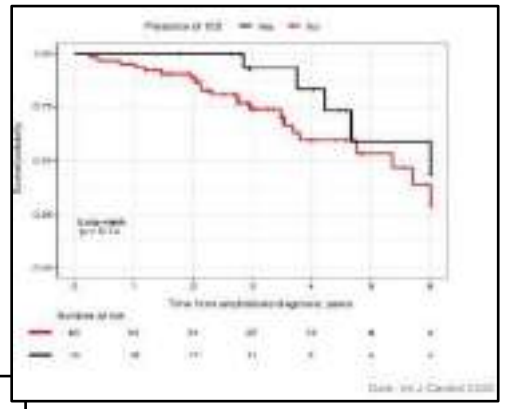
ICD IN CARDIAC AMYLOIDOSIS

THURSDAY, MAY 30, 2024

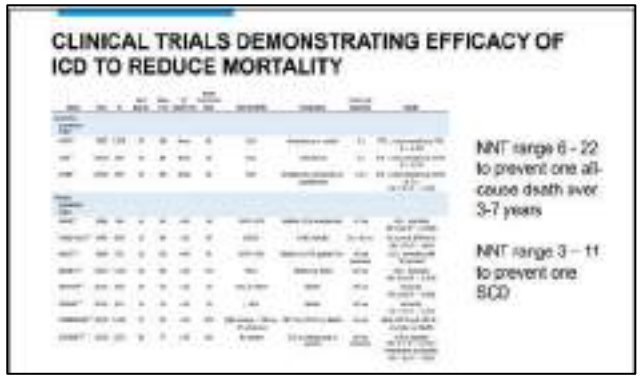
FREDERICK L. RUBERG, MD

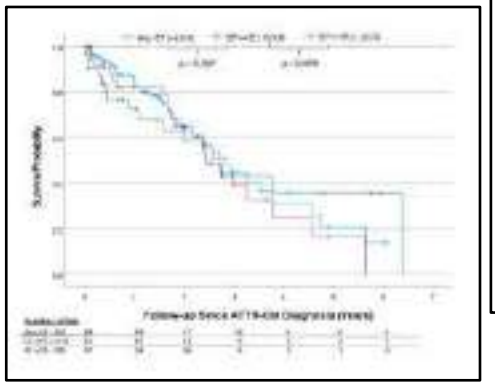






- Retrospective study of 84 ATTR-CA (67 ATTRwt) patients of who 19 had ICD (18 primary prevention)
- No mortality benefit





CONCLUSIONS

- Ventricular fibrillation and ventricular tachycardia are the cause of sudden cardiac death (SCD) treatable by defibrillation
- ICDs are implanted in patients deemed high risk for SCD, but implant carries short term and long term risks that need to be balanced against potential benefits
- ICD implants occur in context of primary and secondary prevention
- Evidence does suggest that ICD may terminate VT/VF in some instances, but ICDs do not improve mortality in cardiac amyloidosis
- There are no accepted risk markers for SCD in cardiac amyloidosis, including LVEF, and non-sustained VT is common
- ICD implant requires an individuated, shared decision process
  - Secondary prevention if survival expected to be > 1 year
  - Primary prevention if LVEF < 35% and / a pacing indication is present
  - Can be considered in certain special scenarios including listing for heart transplant, "high-risk" AL patients undergoing chemotherapy

ATTR patients

AL

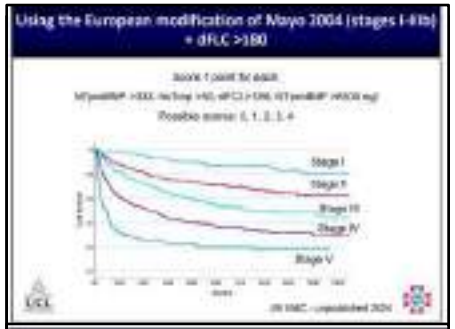
Limitations of current staging systems in AL amyloidosis

Ashutosh Wechalekar

Professor of Medicine and Haematology

20-year anniversary of AL staging

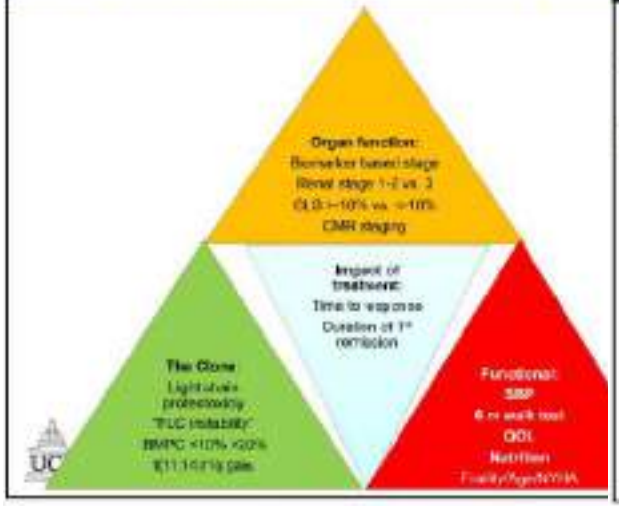
Using the European modification of Mayo 2004 (stages I-IIIb) + dFLC >180



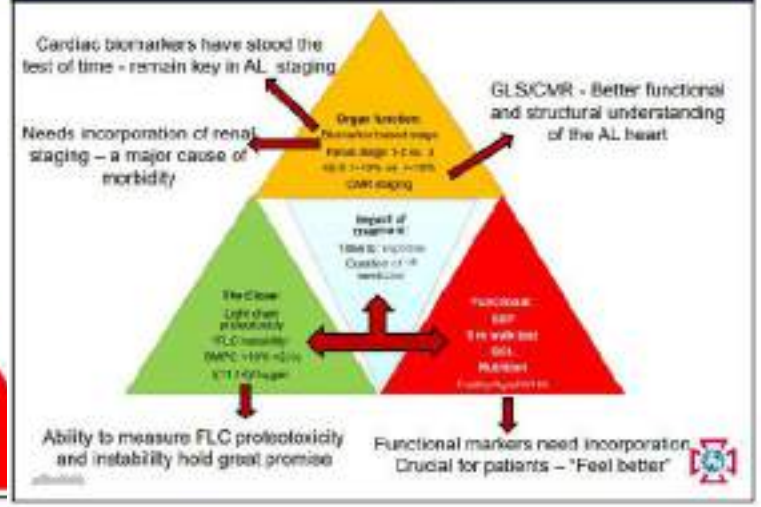
Renal stage : important but often forgotten/ignored

Nutritional status directly impacts survival

The wider view of factors impacting out



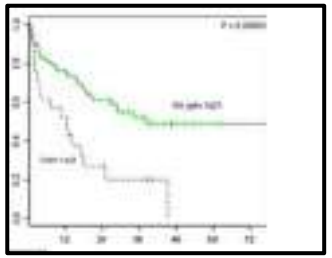
Conclusion



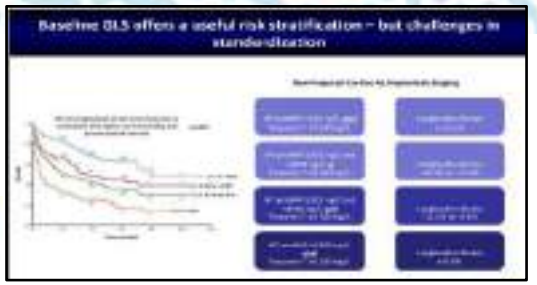
Worsening prognosis with increasing plasmacytosis

Clonal cytogenetics and outcomes

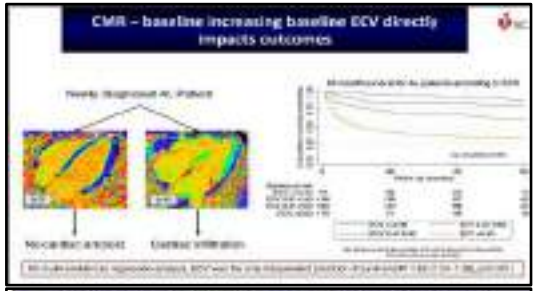
Shorter duration of response = poorer outcomes



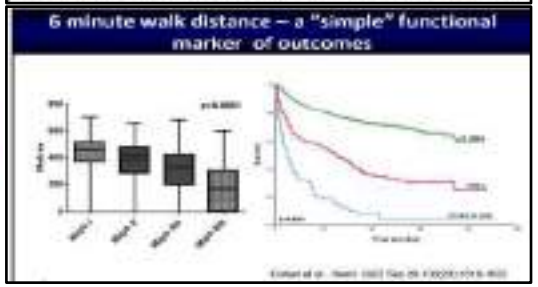
Baseline GLS offers a useful risk stratification – but challenges in standardisation



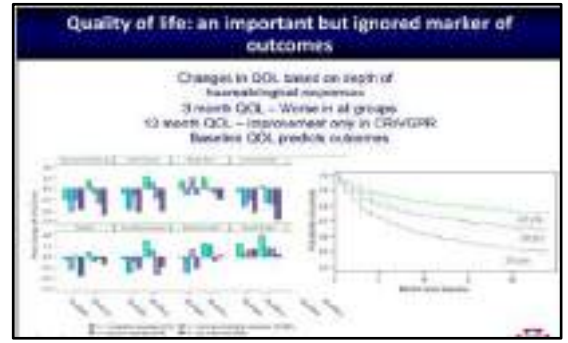
CMR – baseline increasing baseline ECV directly impacts outcomes



6 minute walk distance – a "simple" functional marker of outcomes



Quality of life: an important but ignored marker of outcomes



UNMET NEEDS IN THE TREATMENT OF AL AMYLOIDOSIS

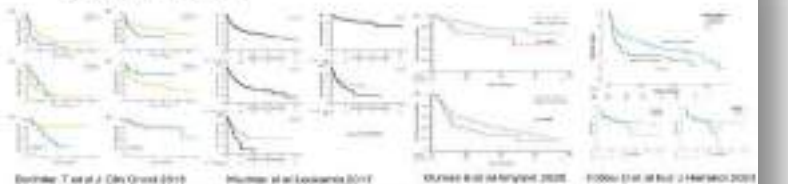
EFSTATHIOS KASTRITIS

AMYLOIDOSIS REFERRAL CENTER, PLASMA CELL DYSCRASIA UNIT, DEPARTMENT OF CLINICAL THERAPEUTICS, NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS GREECE

BIOMARKERS DIFFERENCES AMONG SUBJECTS OF DIFFERENT RACES

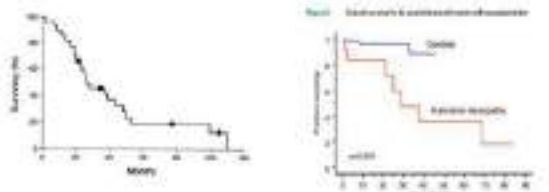
Associations of black race with biomarker concentrations among women and men

PROGNOSTIC IMPACT OF T(11;14) IN AL AMYLOIDOSIS



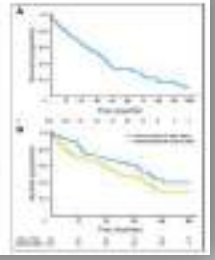
~40-50% of patients with AL amyloidosis have t(11;14)

PROGNOSTIC IMPACT OF PN IN AL AMYLOIDOSIS

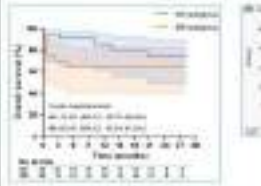


WHAT IS THE COURSE OF THE DISEASE AFTER ESRD?

- UK study included patients with renal AL between 1987 and 2006 (NAC)
- 221 patients started dialysis but 127 only after their first visit to NAC
- Median survival time from start of dialysis was 33 months
- Patients who started dialysis after 2002 survived longer than did patients starting dialysis before 2002 (43.6 v 29.8 months, P = 0.05)

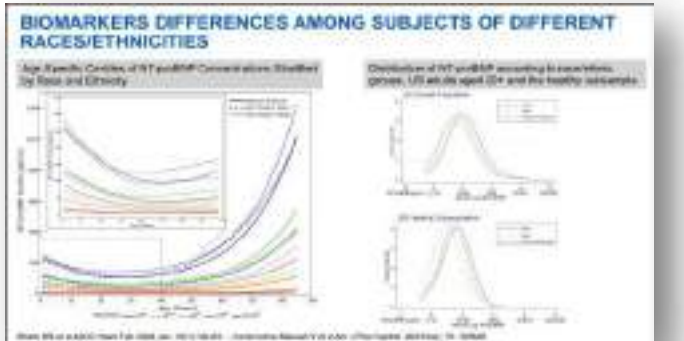


STAGE 3B: CAN WE IMPROVE?



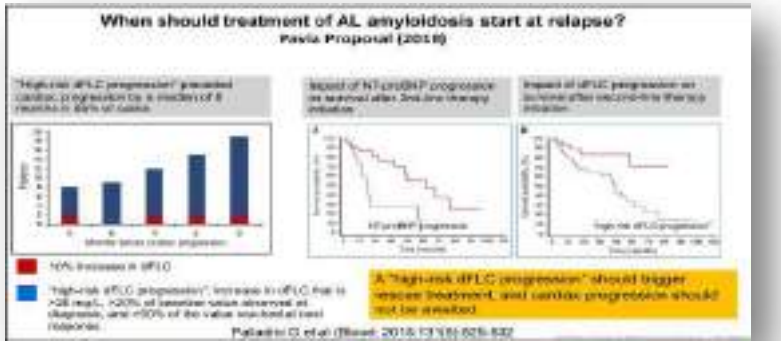
12-month mortality of 30-40% with daratumumab-based regimens: is this the best we can do?

BIOMARKERS DIFFERENCES AMONG SUBJECTS OF DIFFERENT RACES/ETHNICITIES



When should treatment of AL amyloidosis start at relapse?

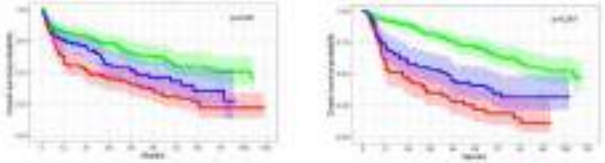
Pavia Proposal (2018)



HOW DEEP AND HOW FAST DO WE NEED CLONAL RESPONSE?

Survival differences are evident even after 1 month of therapy

At 3 months <VGPR is already associated with substantially worse outcome



>25% of patients will improve their response from <VGPR to at least VGPR from month 1 to month 3 if they continue with the same therapy

CONCLUSIONS

- Prise de conscience de la complexité de l'amylose cardiaque
- Nécessité de trouver de nouveaux moyens de diagnostic précoces
- Biomarqueurs, imagerie, intelligence artificielle , combinaison de plusieurs paramètres
- Importance de la qualité de vie du patient et du vécu des amyloses AL
- Prise en charge et évaluation globale
- Evolution de la protéomique compréhension et de la l'hétérogenité de la réponse au traitement
- Pour les AL : évolution thérapeutique , obtention de réponse hématologique rapide et profonde , importance de l'évaluation de la réponse organe