ΑΜΥΛΟΕΙΔΩΣΗ ΚΑΙ ΑΓΓΕΙΑ

ΚΙΜΩΝ ΣΤΑΜΑΤΕΛΟΠΟΥΛΟΣ

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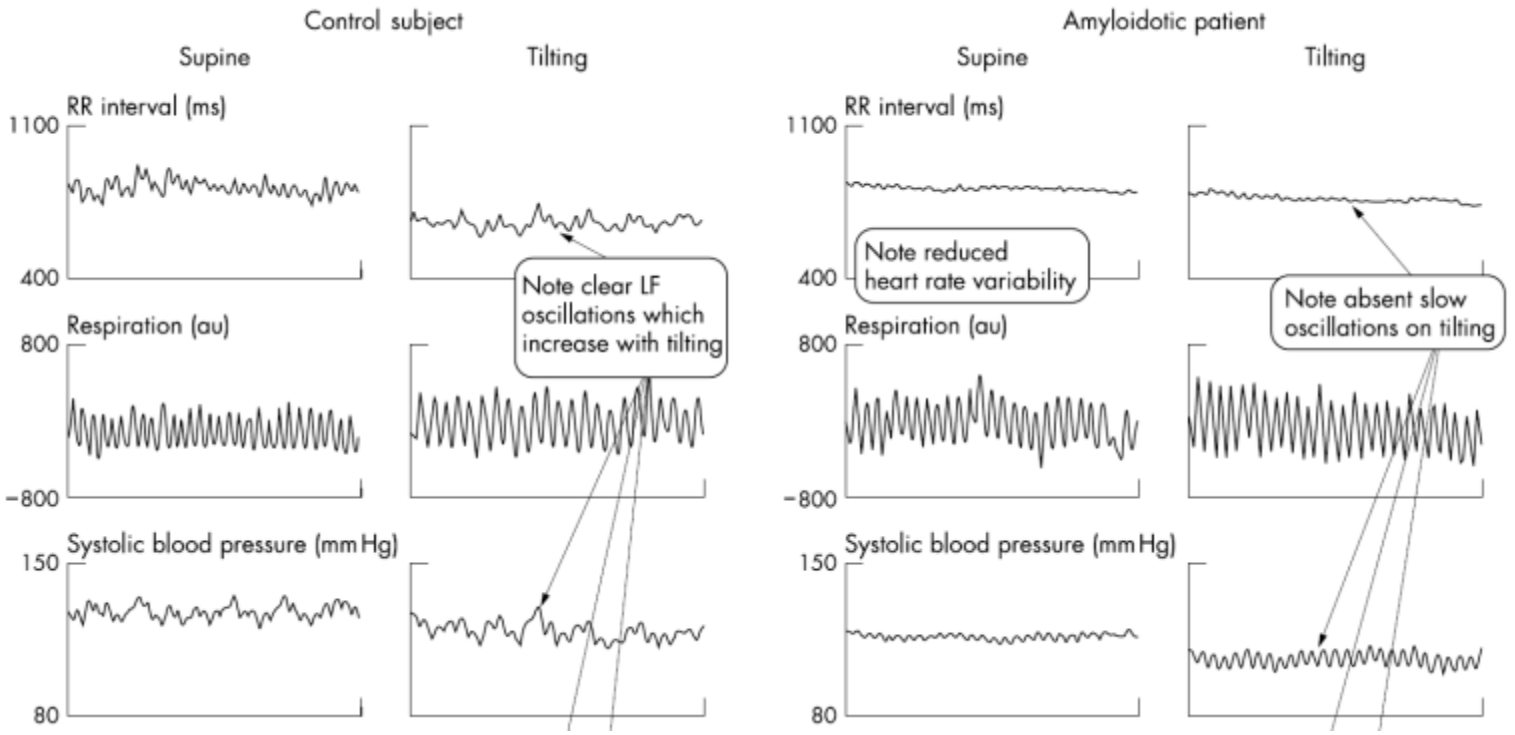
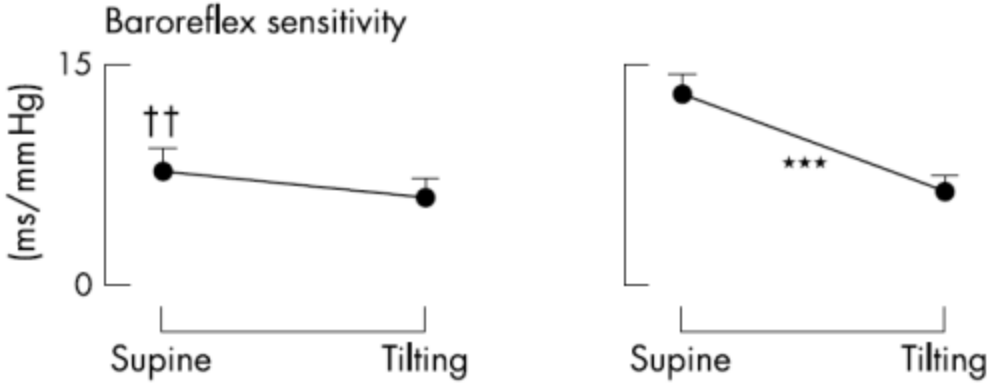
Widespread cardiovascular autonomic dysfunction in primary amyloidosis



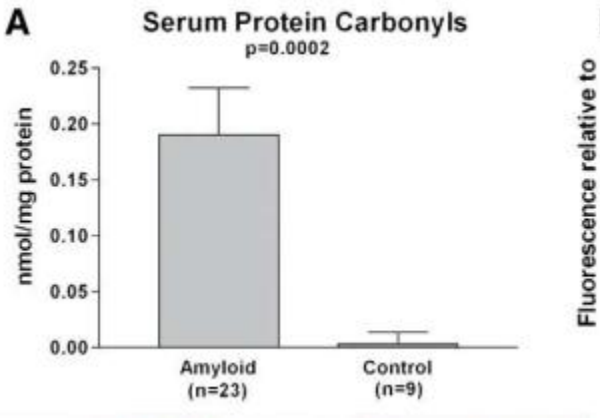


HYPOTENSION

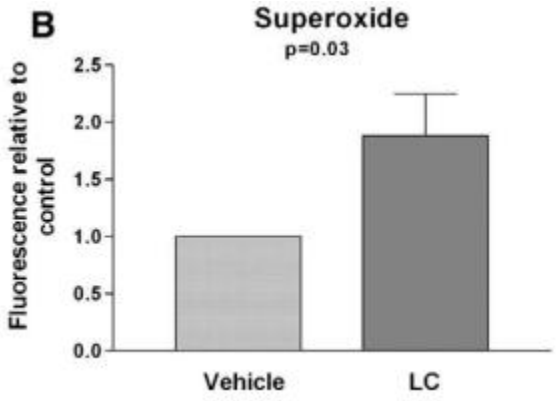
Bernardi L et al. Heart 2002

Light chain proteins (LC) induce microvascular oxidative stress

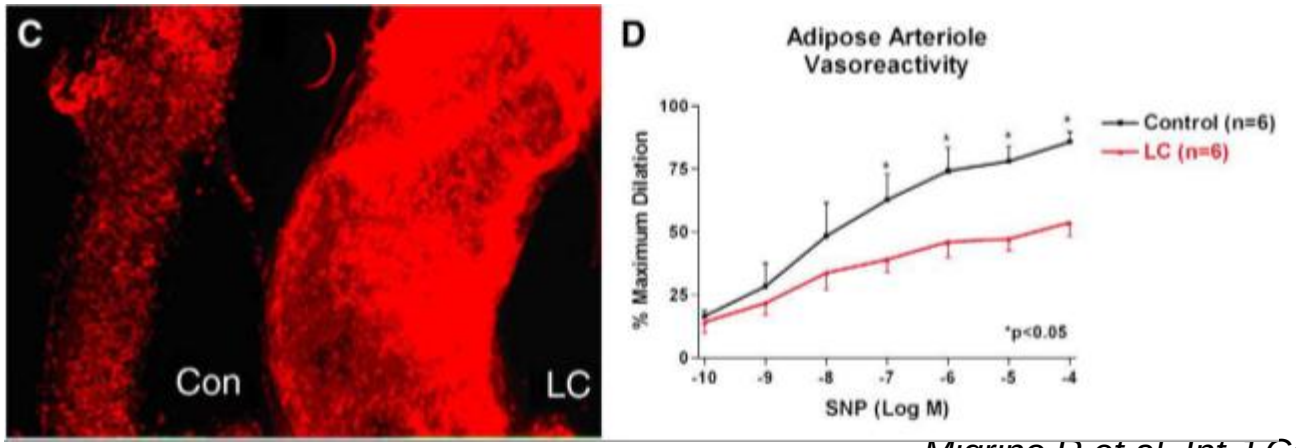
Increased systemic oxidative stress in AL amyloidosis



LC induces oxidative stress

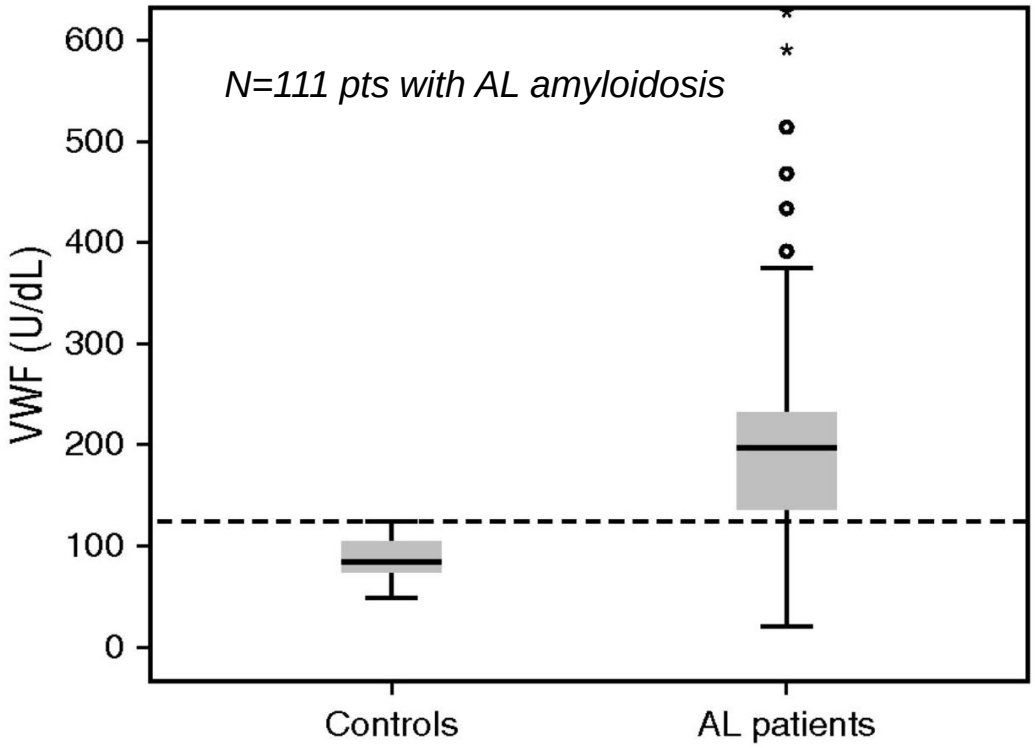


LC impairs vasodilatory capacity



Migrino R et al. Int J Cardiol 2005

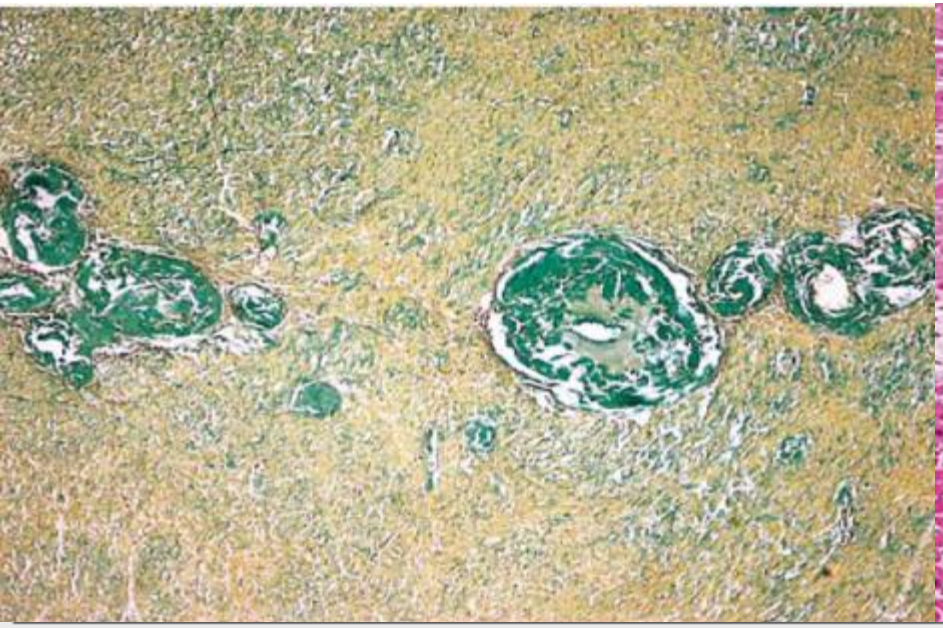
Increased systemic endothelial activation in AL amyloidosis

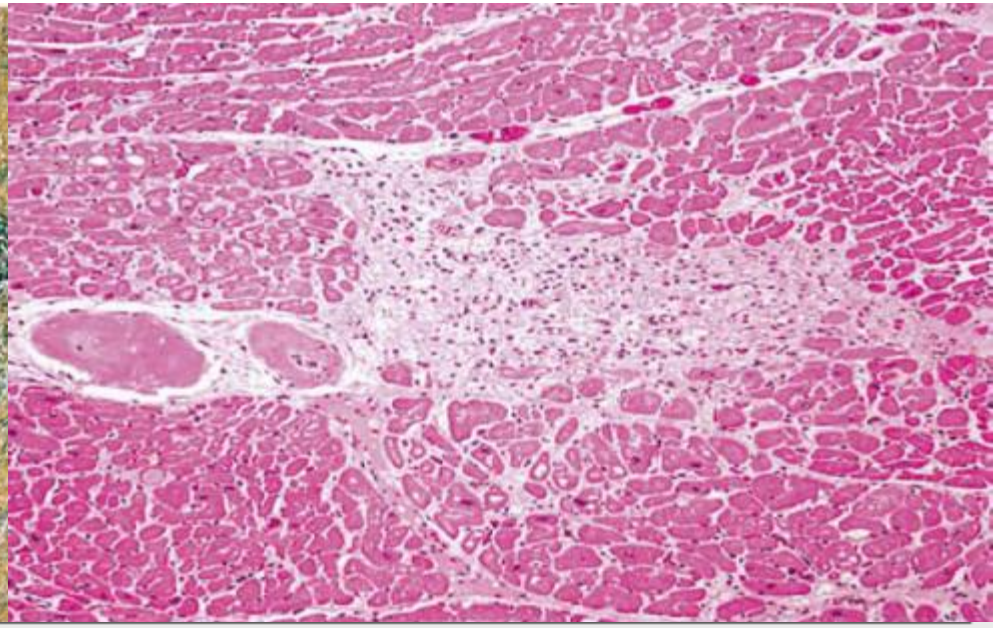


Arterial involvement in AL amyloidosis ➔ accelerated atherosclerosis?

Kastritis E. et al. Blood 2016;128:405-409

Coronary microvascular involvement and myocardial ischemia are common in primary AL amyloidosis

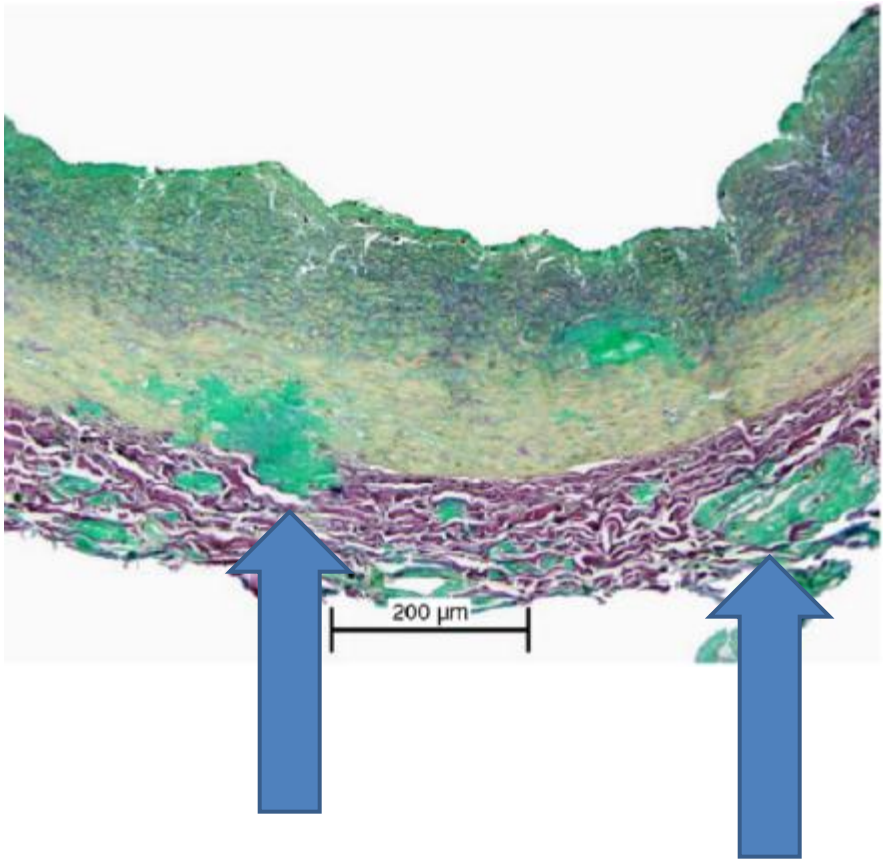




Nebben-Wittich CA t al. Am J Med 2005

	Obstructive intramural coronary amyloidosis						
	Present (n = 47)		Absent (n = 29)			Total (n = 76)	
Myocardial ischemia	No.	%	No.	%	*P* value	No.	%
Present	39	83	13	45	<.001	52	68
Chronic only	30	64	11	38	.028	41	54
Acute + chronic	9	19	1	3	.079	10	13
Acute only	0	0	1	3	. . .	1	1
Absent	8	17	16	55	. . .	24	32

Obstructive coronary epicardial involvement in primary amyloidosis is very rare



- In 56 of 58 patients (97%), amyloid was present in epicardial coronary arteries.
- Amyloid was identified in all artery layers intima, media, and adventitia), and more patients had amyloid in the adventitia.
- Widely affected vasa vasora and in many patients obstructed by amyloid.

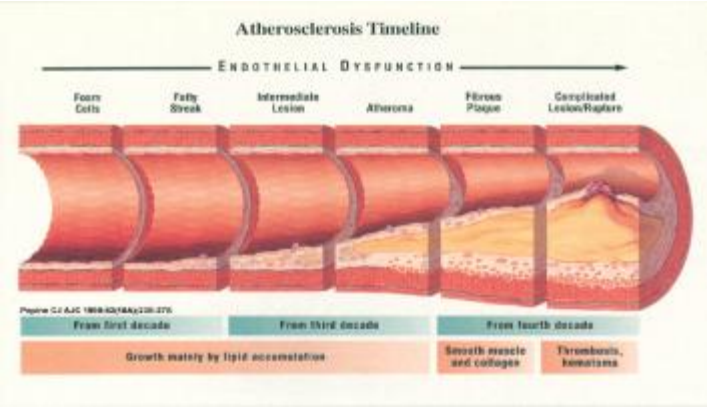
Myocardial ischemia => microvascular origin?

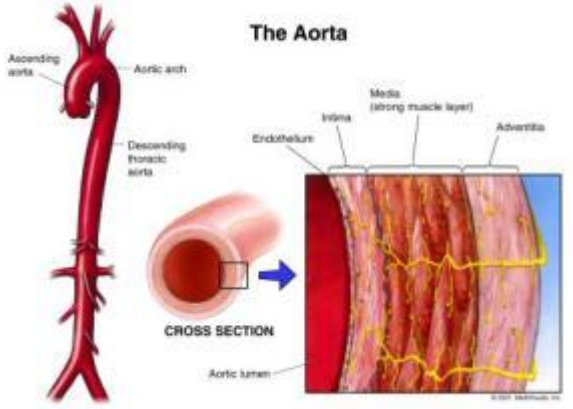
Wittich CM et al. Cardiovascular Pathology 2007

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

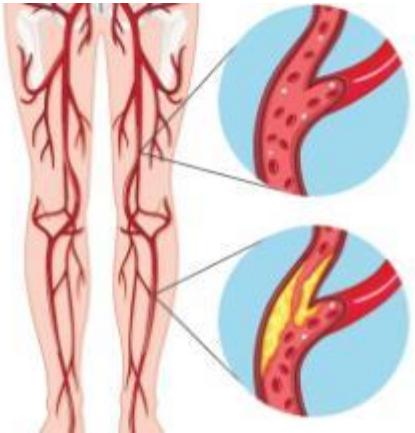
Peripheral artery disease ?

Atherosclerosis

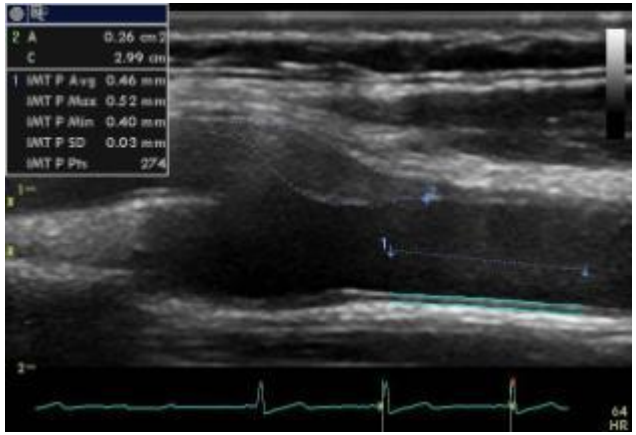




Peripheral Artery Disease

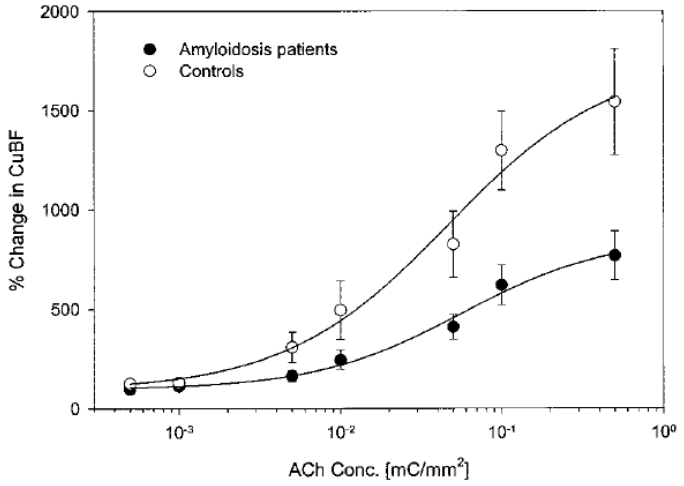


Carotid artery disease



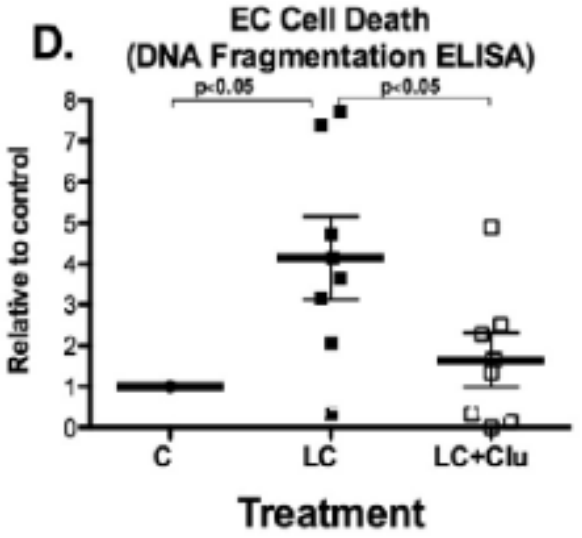
Peripheral microvascular dysfunction and LC induced aortic cell death in AL amyloidosis

Cutaneous endothelial dysfunction



Berghoff M et al. Ann Neurol 2003

Human aortic endothelial cells



Franco D et al. Atherosclerosis 2012

PERIPHERAL CONDUIT ARTERIES

Peripheral conduit arterial function and structure in AL amyloidosis

No differences in obstructive or subclinical peripheral arterial disease

Parameters	AL (n=115)	Matched controls (n=115)	P value
SBP	↓123.7±22.5	132.0±20.9	0.005
DBP	↓72.2±10.2	75.0±10.3	0.041
FMD (%)	↑4.00 (1.92-6.06)	2.32 (0.96-4.55)	0.002
PWVfemoral (m/sec)	9.8 (8.3-12.05)	10.3 (9.2-12.50)	0.179
Augmentation index(%)	↓18.5 (9.0-28)	32 (26.0-39)	<0.001
Carotid IMT (mm)	0.848 (0.752-0.962)	0.813 (0.717-0.933)	0.202
Presence of any carotid plaque, n (%)	57 (49.6%)	63 (54.8%)	0.428
Presence of femoral plaque, n (%)	45 (39.1%)	39(33.9%)	0.238
Presence of any plaque,n(%)	69 (60%)	68 (59.1%)	0.957

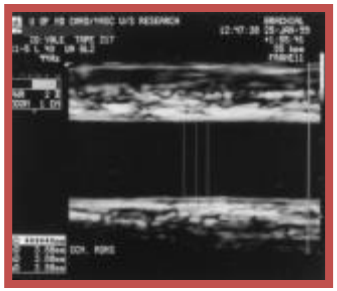
Submitted data

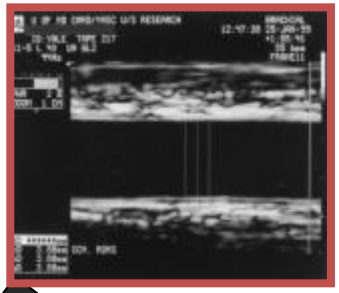
Increased FMD in AL amyloidosis is associated with cardiac involvement and severity

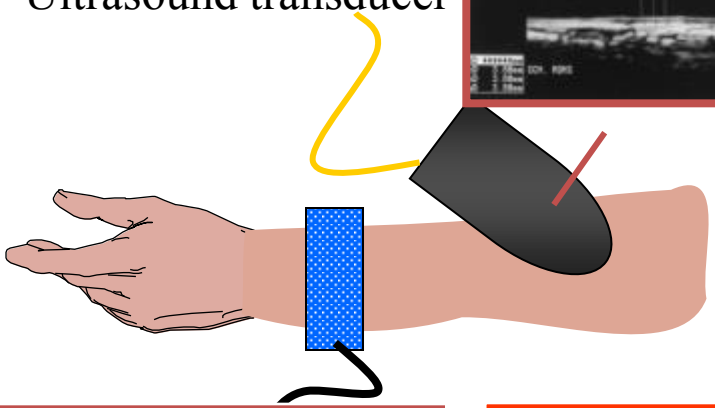
	FMD<4.5%	FMD≥4.5%	P
Heart involvement, n(%)	36 (54.5)	37 (75.5)	0.021
hsTnT, nmol/L	33 (17-57.3)	58.5 (41-94)	0.007
NTproBNP, nmole/L	1414(236-3823)	2683 (841-7600)	0.023
Mayo stage (=III), n (%)	12 (18.2)	18 (36.7)	0.033

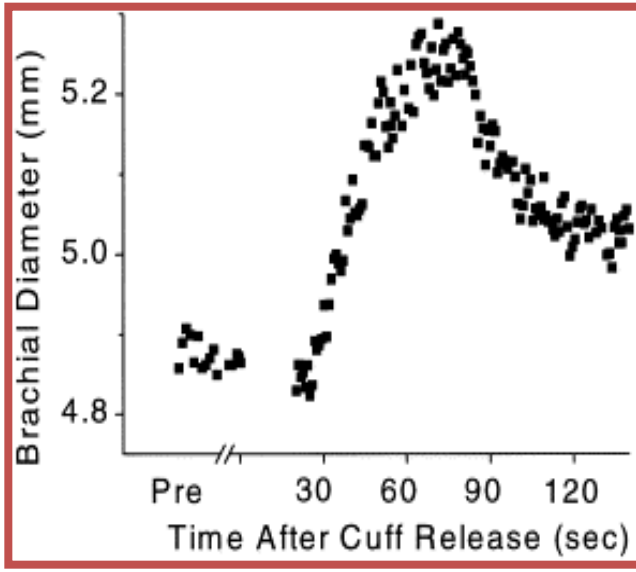
Submitted

Flow-mediated dilatation of the brachial artery (FMD)









Baseline measurements

3 to 5 min

Cuff inflation

45-120 sec after

Cuff deflation - Hyperemia

↓ **FMD**

Endothelial dysfunction

↑ **FMD**

- Increased vascular reactivity
- Orthostatic Hypotension

Corretti et al. JACC 2002

↑ ↑ Nitric oxide bioavailability and/or **↑ ↑ oxidation into peroxynitrite**

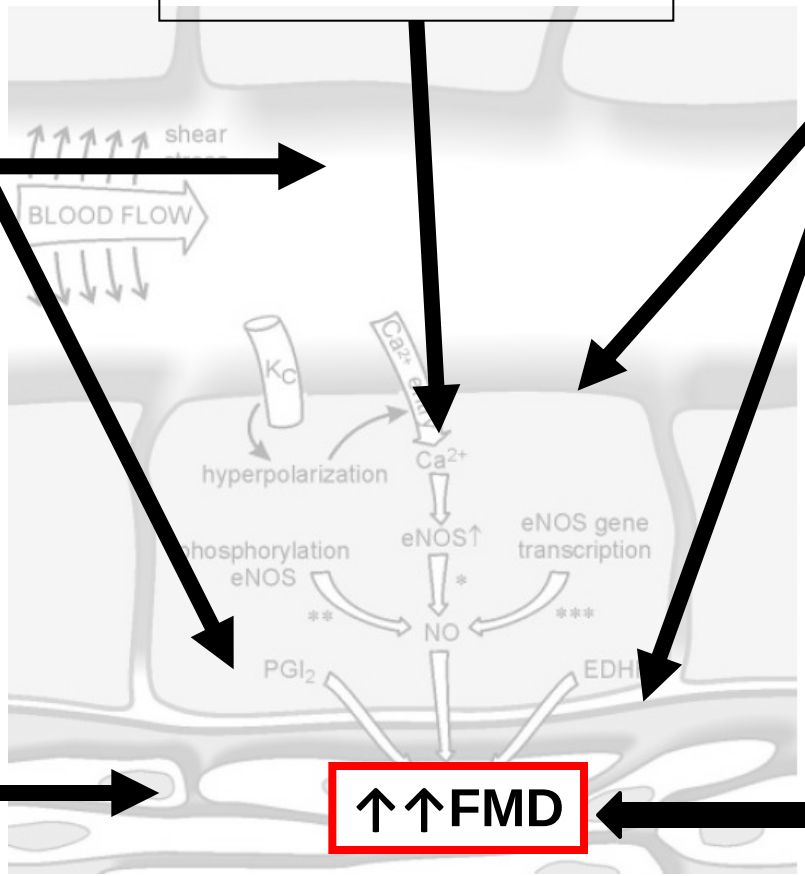
Circulation 1995
Circ Res. 2004
Shock 2010

↑ ↑ non-NO vasodilator bioavailability
- Hyperpolarizing factor
- Prostaglandins
- Other?

Circ Res 1999

Autonomic dysfunction
sympathetic denervation

Am J Physiol Heart Circ Physiol 2006
Clin Cardiol. 2000



Increased conduit arterial reactivity in AL amyloidosis

↑ reactivity of VSMC layer

JACC 2002

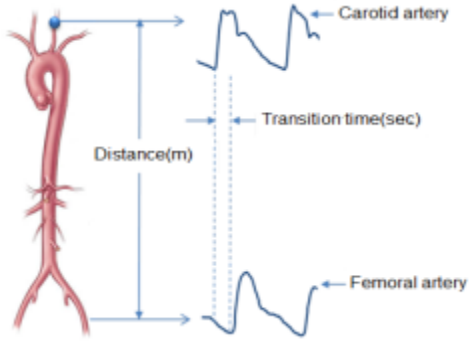
↑↑FMD

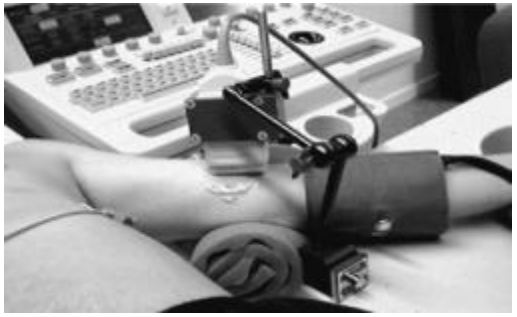
HYPOTENSION?

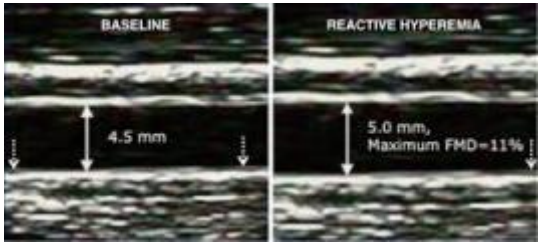
Moens A et al.Chest 200

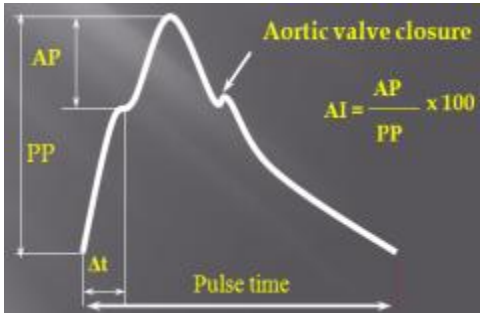
What is the prognostic clinical significance of vascular involvement in AL amyloidosis?

- Low arterial blood pressure
- Increased FMD
- Decreased arterial wave reflections

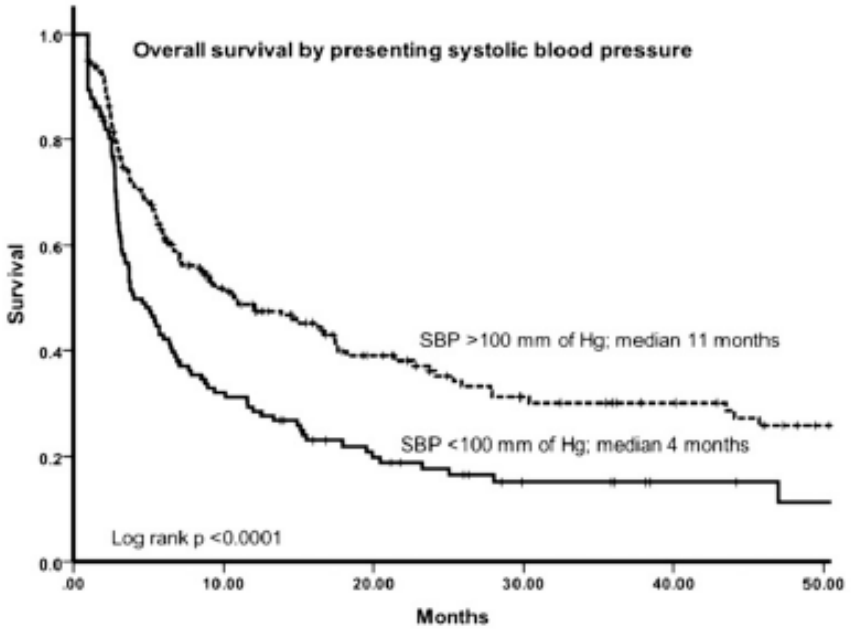


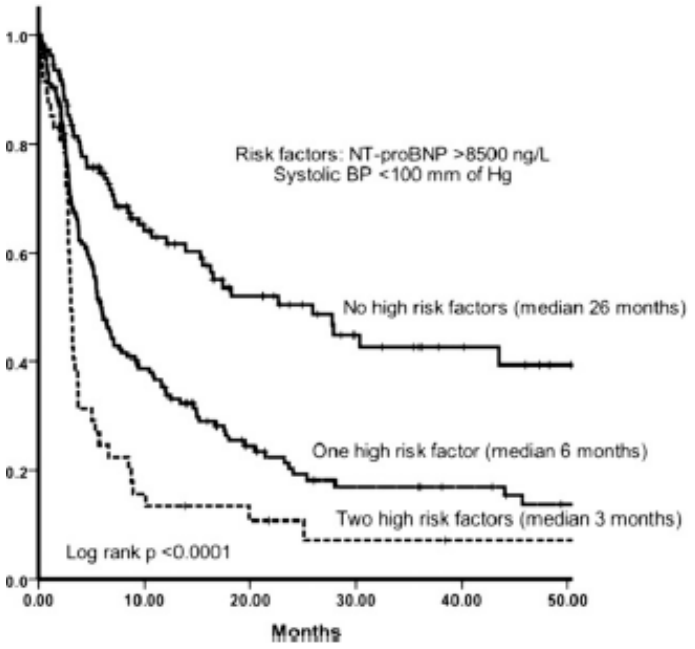






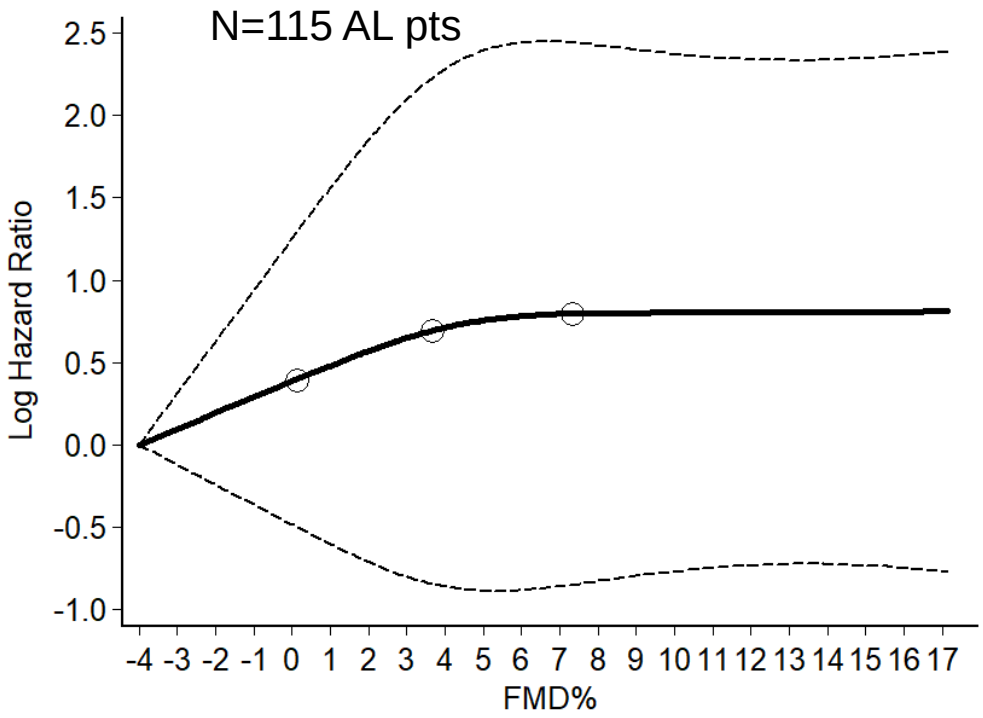
Low systolic BP is associated with high mortality in AL amyloidosis





Wechalekar A et al. Blood 2013

High FMD in AL amyloidosis: Dose-response relationship with mortality



Optimal cutoff at FMD > 4.5%

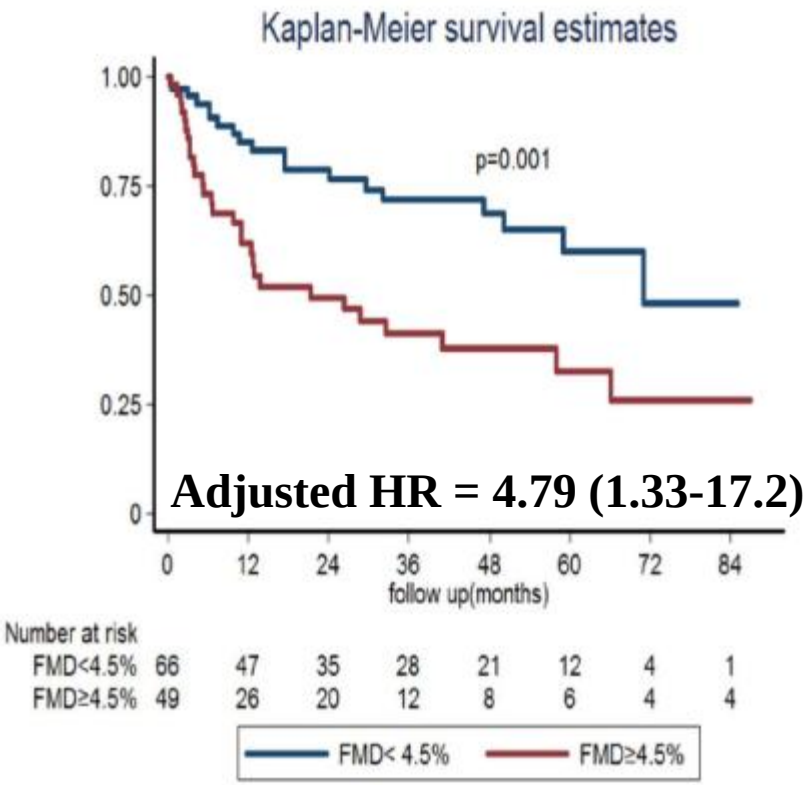
Low arterial stiffness
Low arterial wave reflections

→ No association with mortality

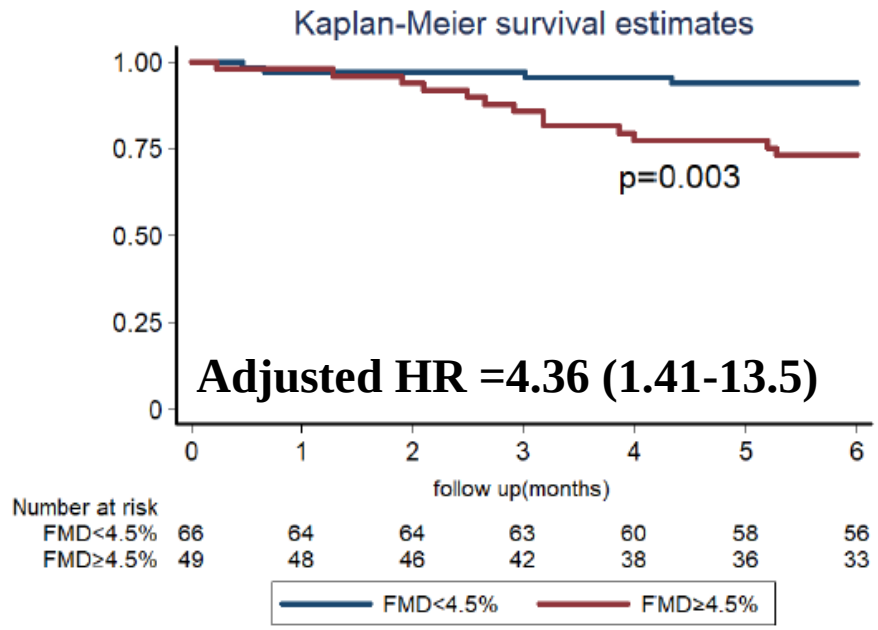
Submitted

FMD is an independent predictor of all cause mortality in AL patients

All cause mortality across the follow up period



Early all-cause mortality within the first 6 months of the follow up

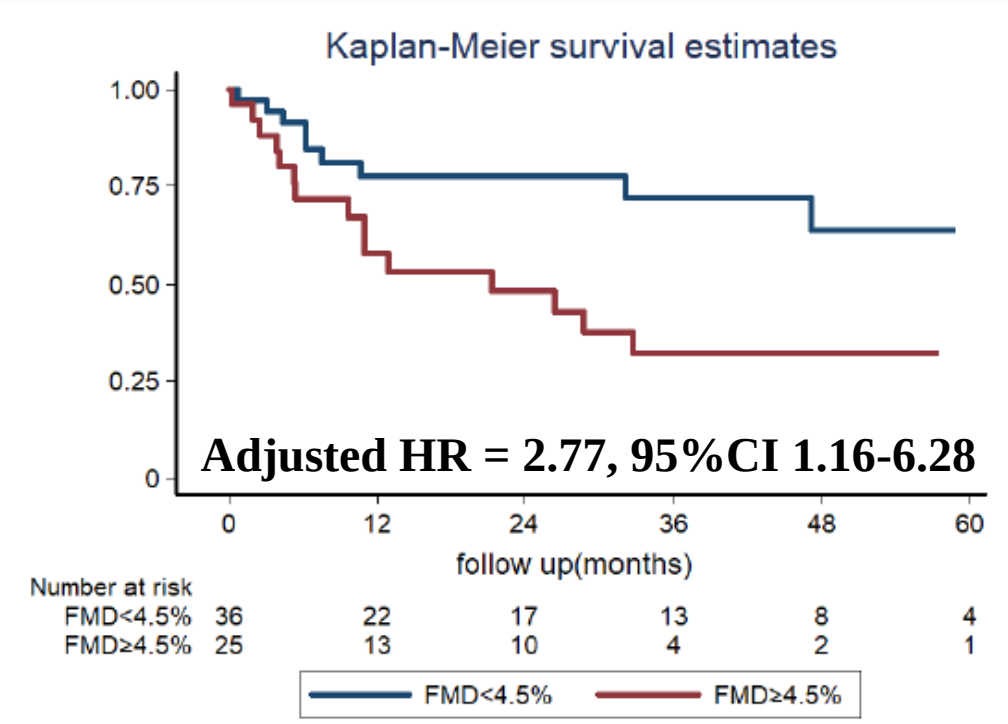


MV model: age, gender, SBP<100mmHg, vWF, Mayo stage, neurologic involvement, atherosclerosis

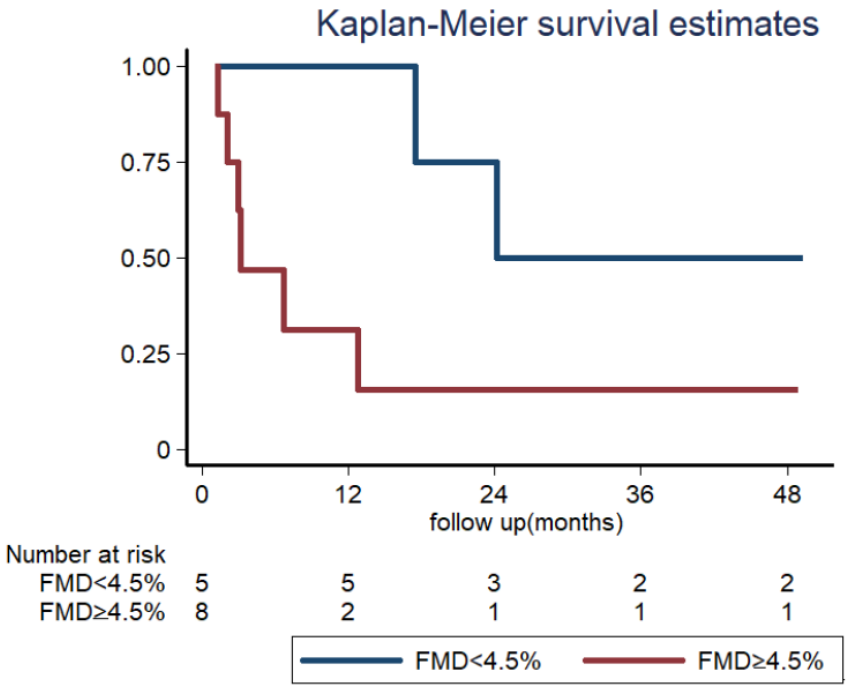
Submitted

FMD is an independent predictor of all cause mortality in AL patients with cardiac involvement

Mayo Stage II



Mayo Stage IIIB



MV model: age, gender, SBP<100mmHg

Submitted data

FMD correctly reclassifies risk in AL amyloidosis over Mayo stage, low SBP and neurological involvement

Table 2. Reclassification value of FMD over the best predictive model for early and overall all-cause mortality in 115 AL patients

	Continuous NRI					IDI	
	Subjects correctly reclassified (%)	Subjects incorrectly reclassified (%)	Net reclassification gain (%)	Overall NRI (SE)	P-value	IDI (SE)	P-value
All-cause mortality at the end of the follow-up							
Events (n=48)	29 (60.4%)	19 (39.6%)	20.8%	**61.1%** (18.9) *[23.1%-99.2%]	0.001	3.6 (1.8)	0.044
Non events (n=67)	47 (70.1%)	20 (29.8%)	40.3%				
Early mortality at 6-months							
Events (n=17)	13 (76.4%)	4 (23.5%)	52.9%	**57.9%** (29.0) *[9.5%-106%]	0.045	6.5 (3.0)	0.031
Non events (n=98)	51.5 (52.5%)	46.5 (47.5%)	5.0%				

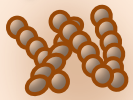
Submitted

Light chain generation

Plasma cell clone

Monoclonal light chains

Monoclonal light chains toxic oligomers, amyloid fibrils



↑↑ oxidative stress, direct cell damage, tissue deposition

AL mediated cell damage

Endothelial cells

Vascular SMCs

Autonomic dysfunction

Vascular and neuronal cell activation and dysfunction

Conduit arteries
Extreme vasodilation

?

?

Microcirculation
Obstruction-ischemia

Vasa vasora

?

Clinical Implications

Subclinical Vascular Dysfunction

Arterio-ventricular coupling

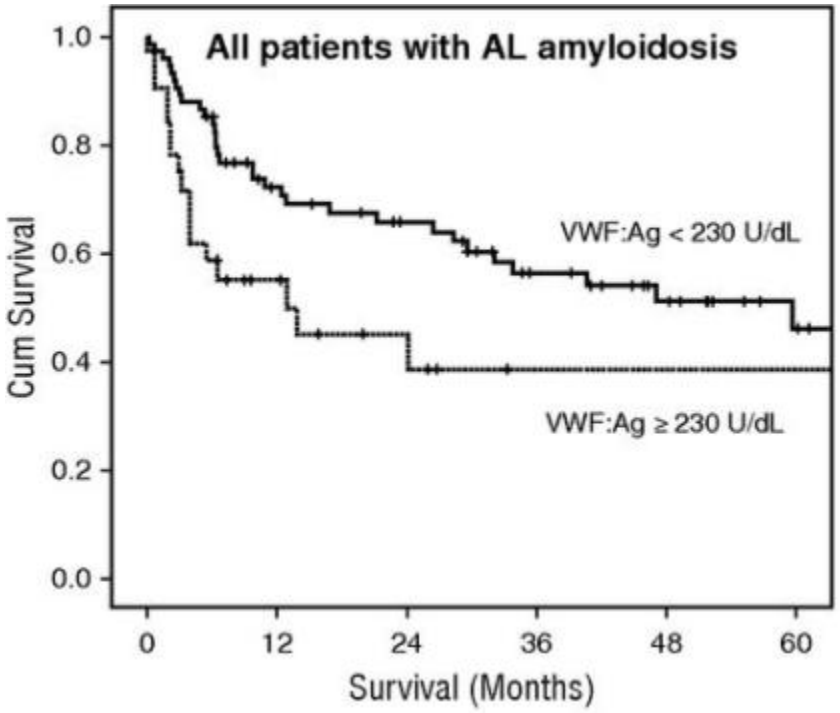
Clinical Events

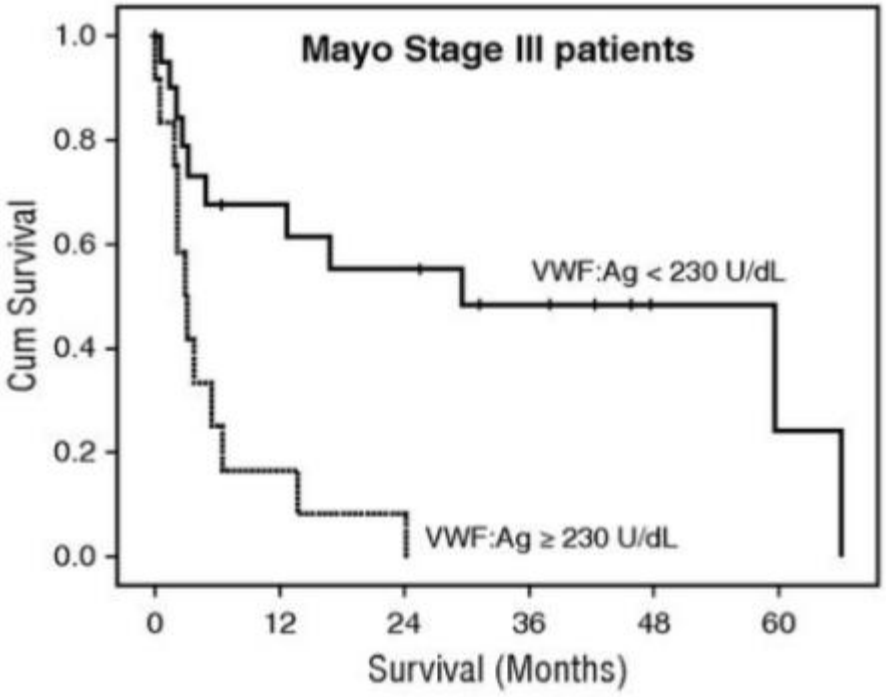
AL amyloidosis is associated with vascular over-reactivity (↑ FMD, ↓Blood pressure, ↓ arterial wave reflections)

↑ FMD in AL amyloidosis is associated with More frequent Heart involvement ↑NYHA, ↑ Mayo stage ↑ NTproBNP, ↑ Troponin

↑ FMD in AL amyloidosis is associated with All cause and cardiac mortality & Reclassifies Patients into Correct Risk Categories

High VWF levels predict mortality in AL patients with cardiac involvement and Mayo stage IIIB



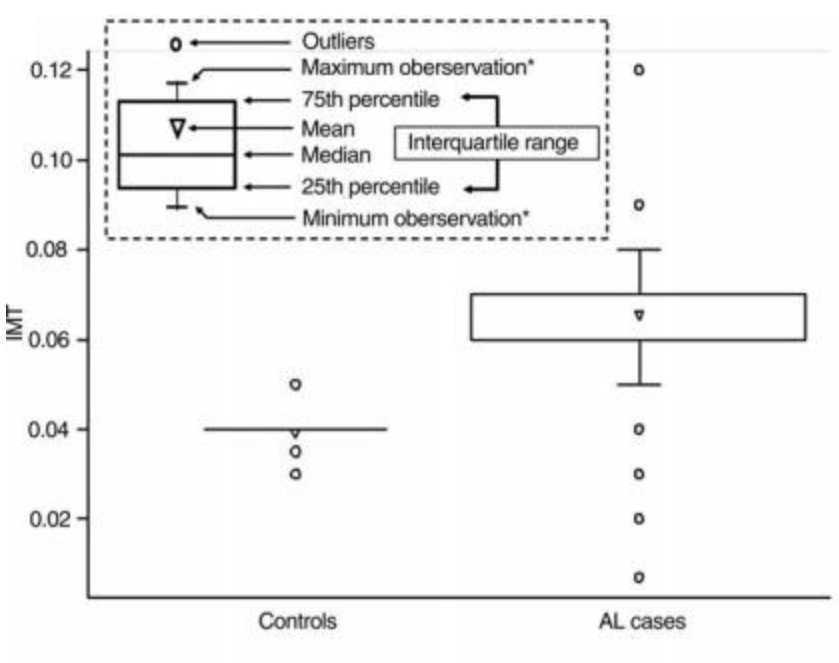


Kastritis E et al. Blood 2016;128:405-409

Subclinical atherosclerosis in AL amyloidosis

No adjustment for traditional risk factors and GFR

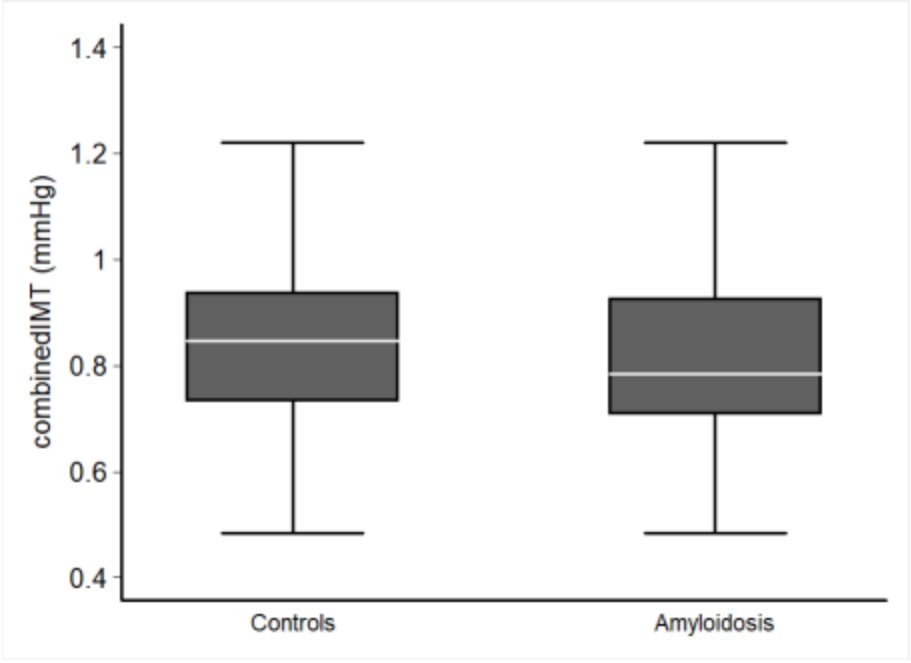
N=59 AL amyloidosis pts



Modesto KM et al. Eur Heart J 2007

Adjustment for traditional risk factors and GFR

N=115 AL amyloidosis pts

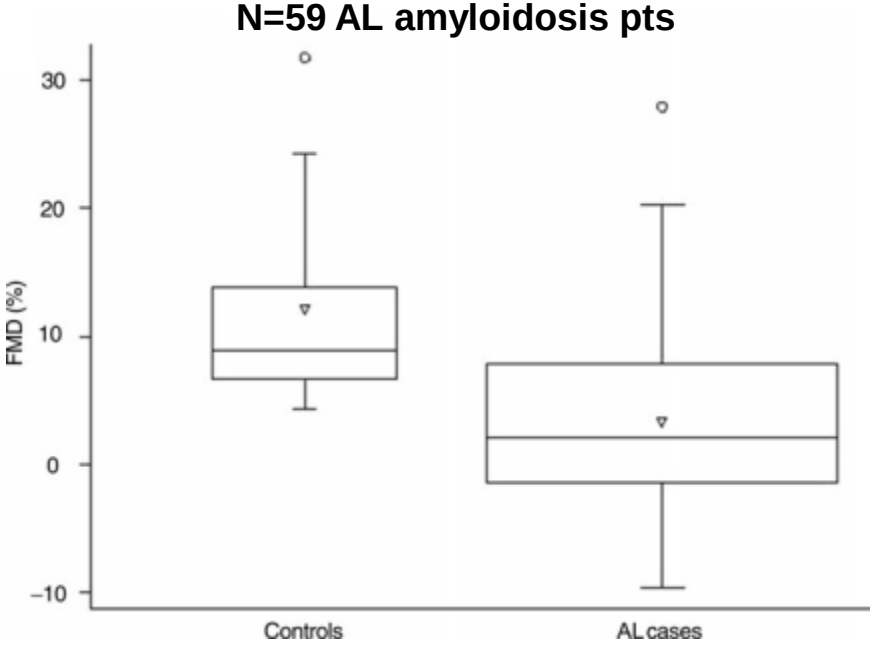


Submitted

Increased vascular reactivity in AL amyloidosis

No adjustment for traditional risk factors and GFR

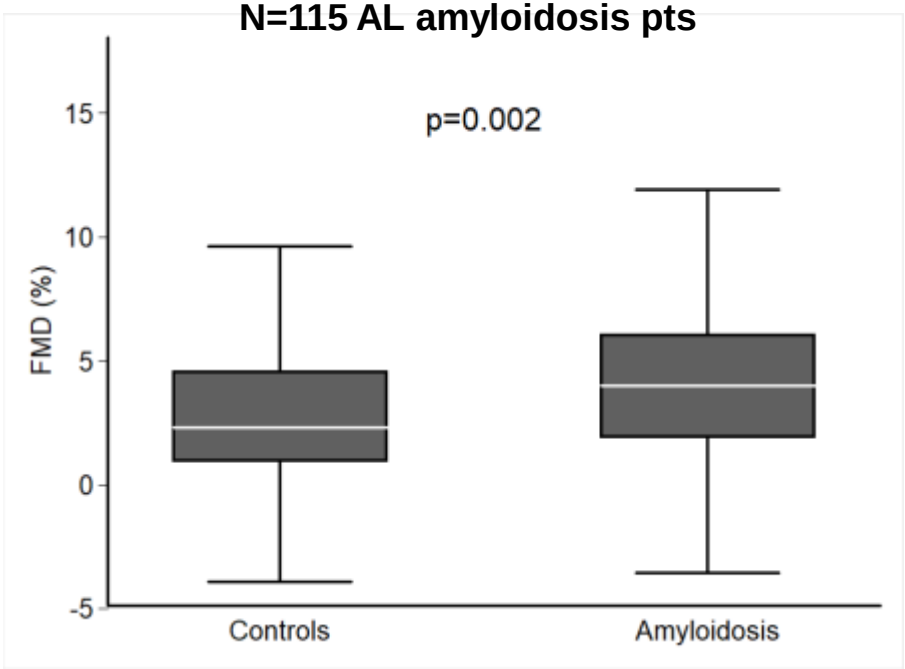
N=59 AL amyloidosis pts



Modesto KM et al. Eur Heart J 2007

Adjustment for traditional risk factors and GFR

N=115 AL amyloidosis pts

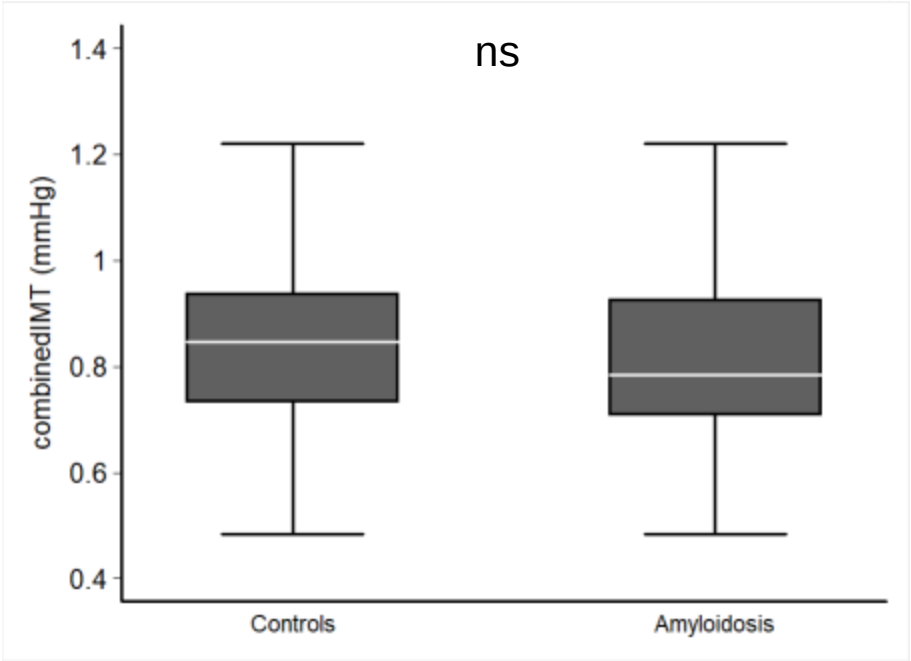


Submitted data

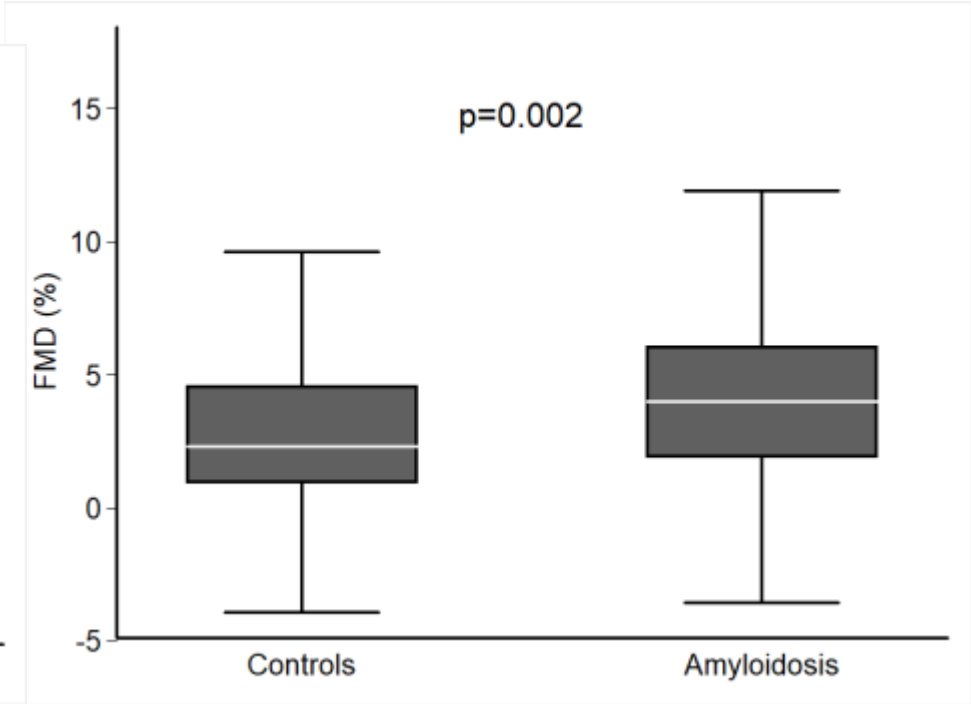
Increased vascular reactivity in AL amyloidosis

Adjustment for traditional risk factors and GFR

Subclinical carotid atherosclerosis



Flow mediated vasodilatation



N=115 AL amyloidosis pts

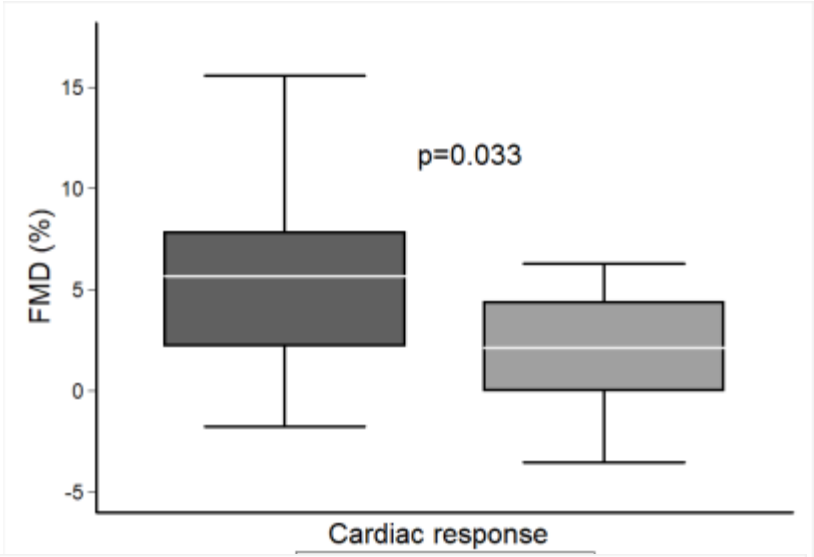
Submitted data

Increased VWF levels are independently associated with a higher risk of death

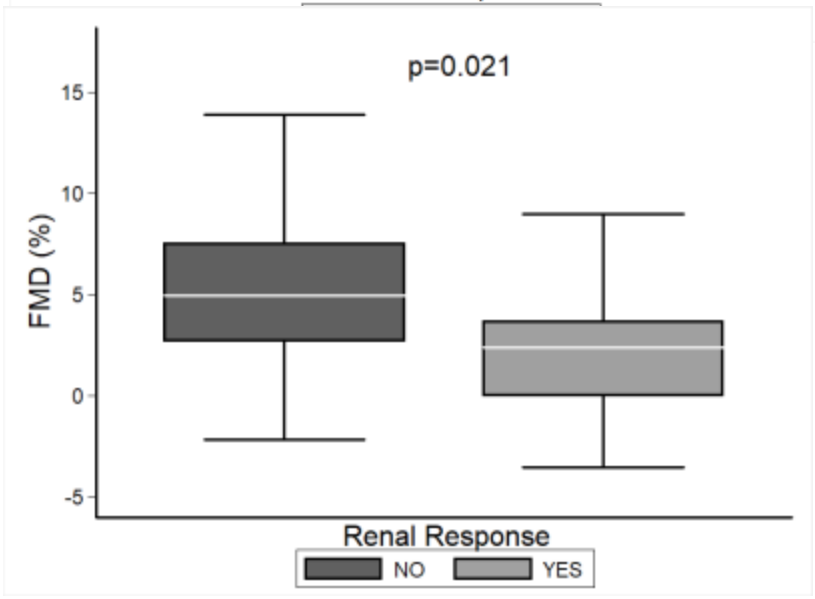
Table 2. Multivariate analysis for survival in 111 patients with AL amyloidosis

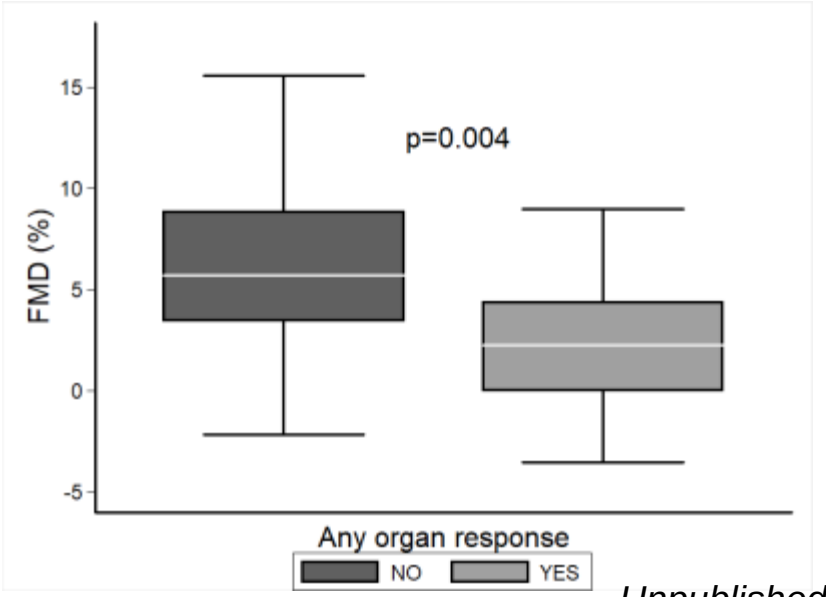
			95% CI for HR	
	P value	HR	Lower	Upper
VWF ≥230.0 U/dL	.011	2.173	1.193	3.957
SBP <100 mm Hg	.009	2.278	1.227	4.232
Mayo stage I		1		
Mayo stage II	.001	7.833	2.259	27.166
Mayo stage III	<.001	15.078	4.247	53.533

Efstathios Kastritis et al. Blood 2016;128:405-409



Lower FMD is associated with better organ response





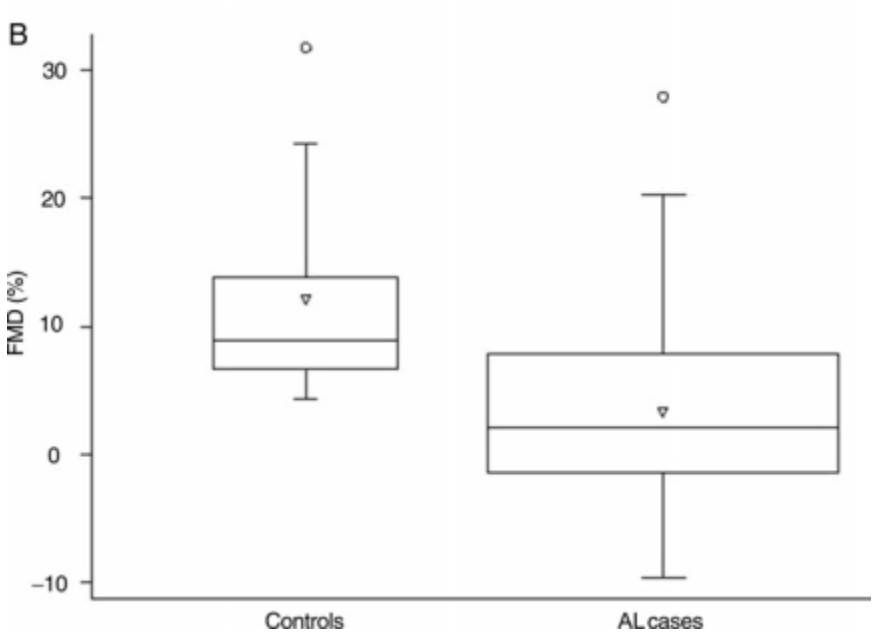
Unpublished data

Table 1. Descriptive characteristics of the overall amyloidosis population and the matched amyloidosis and control groups.

Parameters	Amyloidosis overall population (n=125)	Amyloidosis (n=93)	Controls (n=93)	P value
Age (years)	64.7±10.0	64.73±9.56	63.4±9.73	0.145
Gender (male)	69 (55.2%)	53 (57%)	53 (57%)	0.999
Diabetes n(%)	16 (12.8%)	14 (15.1%)	20 (21.5%)	0.146
Hyperlipidemia n(%)	53 (42.4%)	43(46.2%)	52(55.9%)	0.078
Smoke n(%)	20 (16.0%)	12(13.2%)	8(8.8%)	0.344
Hypertension n(%)	52 (41.6%)	38(40.9%)	51(54.8%)	0.002
GFR stage				
Stage <2	68 (54.4%)	58 (62.4%)	58 (62.4%)	0.999
Stage 3A	19 (15.2%)	10 (10.8%)	10 (10.8%)	0.999
Stage 3B	14 (11.2%)	10(10.8%)	10(10.8%)	0.999
Stage 4	8 (6.4%)	6 (6.5%)	6 (6.5%)	0.999
Stage 5	16 (12.8%)	9 (9.7%)	9 (9.7%)	0.999
Coronary artery disease n(%)	15 (12.0%)	11 (11.8%)	14 (15.1%)	0.508

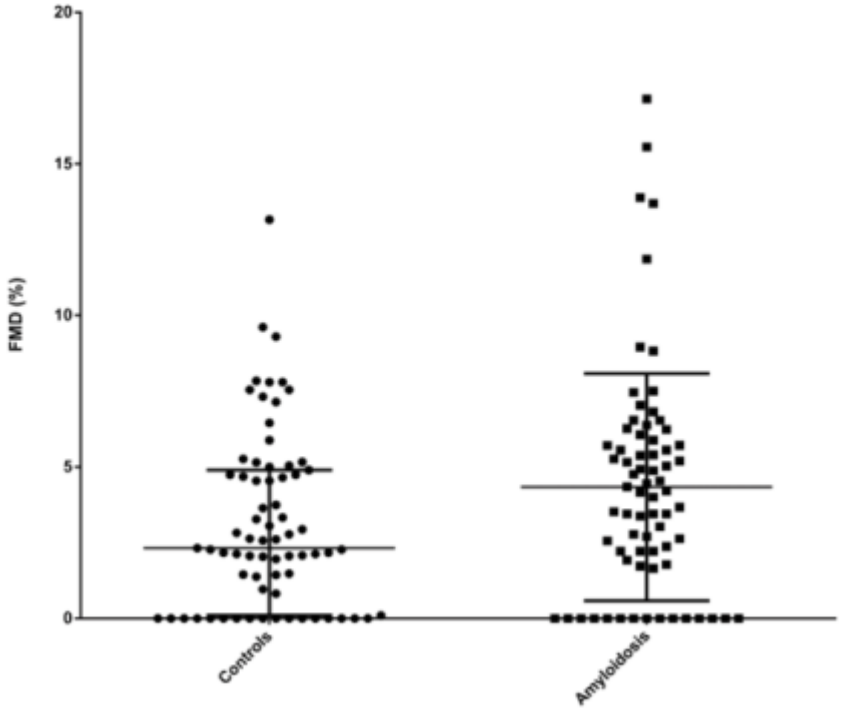
Vascular reactivity in AL amyloidosis

No adjustment for traditional risk factors and GFR



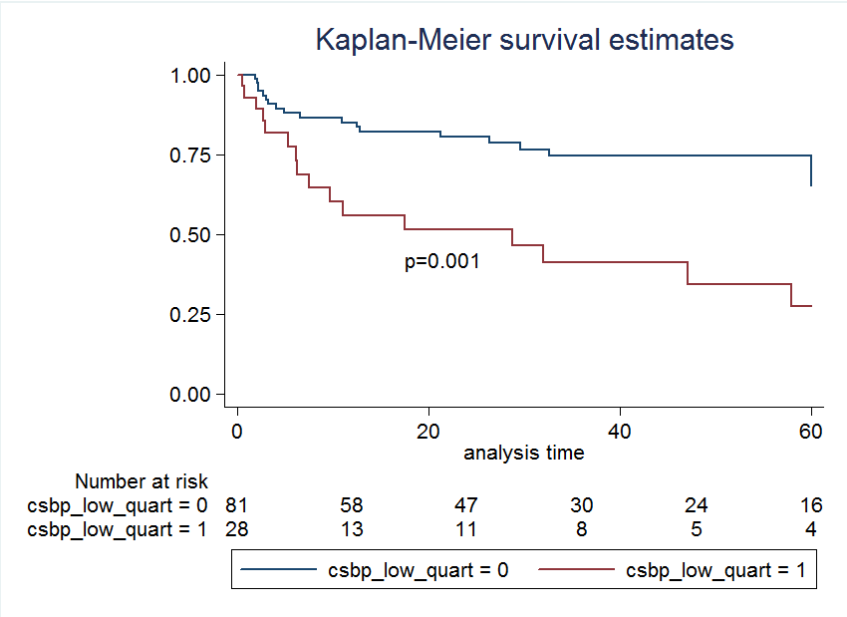
Modesto KM et al. Eur Heart J 2007

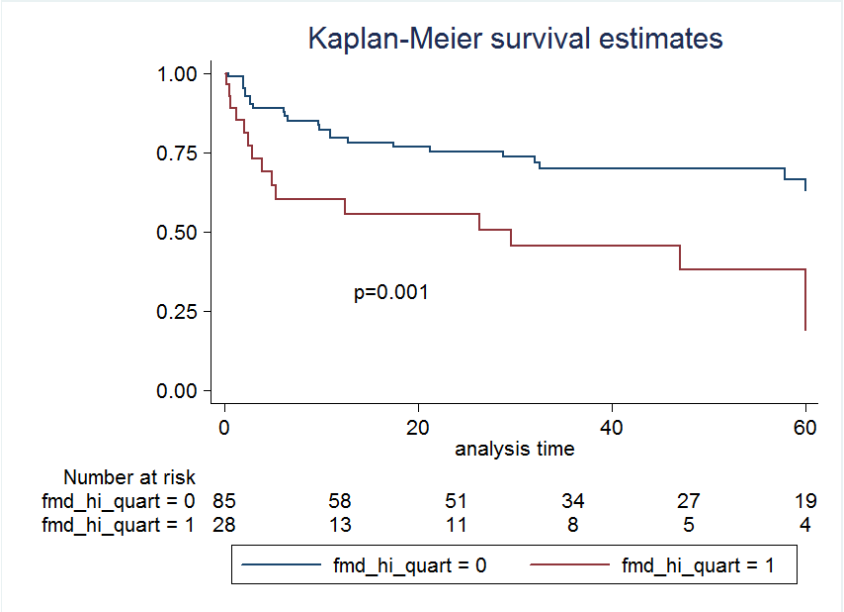
Adjustment for traditional risk factors and GFR



Stamatelopoulos et al.

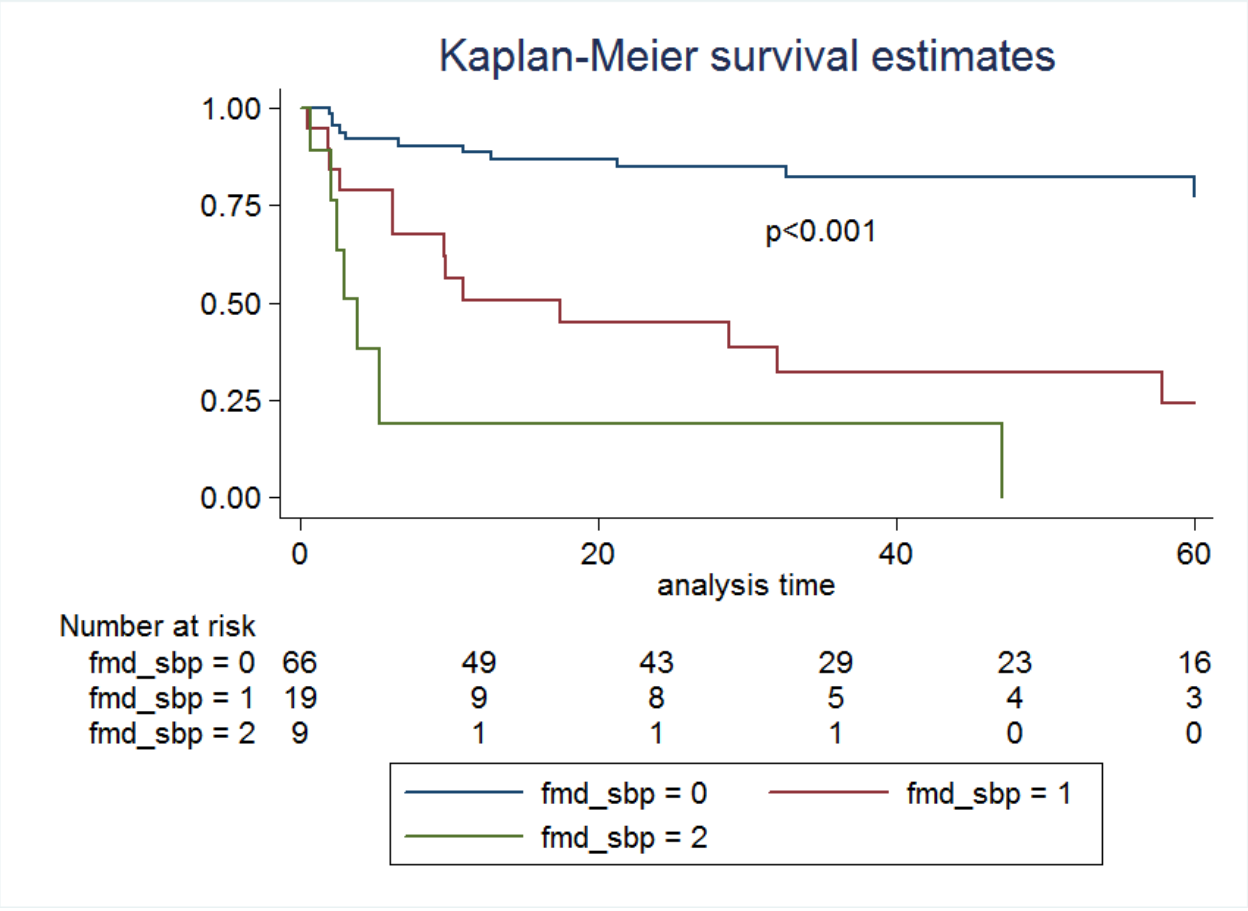
FMD is an independent predictor of mortality in AL amyloidosis





	B	SE	Wald	df	Sig.	Exp(B)	95,0% CI for Exp(B)	
							Lower	Upper
Mayo_Stage			4,184	2	,123			
Mayo_Stage(1)	1,600	,782	4,182	1	,041	4,954	1,069	22,960
Mayo_Stage(2)	1,389	,815	2,904	1	,088	4,010	,812	19,808
sbp_2	-,031	,012	6,707	1	,010	,970	,948	,993
fmd_4.5	,999	,454	4,828	1	,028	2,715	1,114	6,615
vWF	,002	,002	,946	1	,331	1,002	,998	1,005

Very high early mortality in Pts with BOTH increased FMD and low SBP



Incremental value of FMD as a prognostic factor in patients with AL amyloidosis

	Regression parameters		Discrimination Parameters		Reclassification parameters				
					Continuous NRI				IDI
	HR (95%CI)	p-value	Harrell's C	p-value	Among Event Subjects	Among Non-Event Subjects	Overall (SE)	P-value	Coefficient (SE)
Primary Endpoint (All cause mortality, events n=48)									
FMD	2.57 (1.44-4.6)	0.001	0.657 (0.578-0.737)						
Model1+ FMD	2.1 (1.14-3.87)	0.018	0.694 (0.612-0.776)	0.046	20.84%	30.3%	61.13% (18.91)	0.001	*4.6 (2)
Secondary Endpoint (Cardiac mortality, events n=38)									
FMD	2.32(1.22-4.43)	0.011	0.715 (0.635-0.795)						
Model1+ FMD	1.71(0.858-3.42)	0.127	0.731 (0.648- 0.814)	0.270	15.78%	26.32%	42.11% (19.87)	0.034	0.64(0.94)

Η αυξημένη αγγειοδραστικότητα αντικατοπτρίζει στοιχεία αγγειοπάρεσης;

FMD is increased in cirrhotic patients

Abstract

Send to:

Liver Int. 2008 Dec;28(10):1396-401. doi: 10.1111/j.1478-3231.2008.01847.x. Epub 2008 Jul 29.

Increased flow-mediated vasodilation in cirrhotic patients with ascites: relationship with renal resistive index.

Cazzaniga M[1], Salerno F, Visentin S, Cirello I, Donarini C, Cugno M.

Author information

Abstract

BACKGROUND:

Peripheral vasodilation is the key factor in the development of hyperdynamic circulation, sodium retention and functional renal failure in patients with cirrhosis. Brachial artery flow-mediated dilation (FMD) after transient vascular occlusion is a non-invasive method to assess the shear stress-induced arterial vasodilation.

AIMS:

To evaluate FMD in cirrhotic patients with and without ascites and to assess the relationship between FMD and intrarenal resistances.

METHODS:

Flow-mediated dilation was determined in 32 cirrhotic patients (22 with ascites) and 12 healthy controls and correlated with the intrarenal resistive index (RI) assessed by Doppler exploration.

RESULTS:

Basal diameter of the brachial artery was similar in healthy controls and in cirrhotic patients, whereas FMD was significantly higher in patients with cirrhosis and ascites [29.5% (range 10.3-50%)] than in pre-ascitic patients [17.3% (range 2.4-48.5%)] and healthy control subjects [11.6% (range 5.1-17.8%)] ($P<0.001$). Intrarenal RI was significantly higher in patients with cirrhosis than in healthy subjects, and a direct relationship existed between FMD and intrarenal RI ($r=0.66$; $P<0.00001$).

CONCLUSIONS:

These findings in vivo demonstrate that cirrhotic patients with ascites have an enhanced shear stress-induced peripheral vasodilation, which is closely related to intrarenal vasoconstriction.

ΑΜΥΛΟΕΙΔΩΣΗ ΕΛΑΦΡΩΝ ΑΛΥΣΩΝ

- Η αμυλοείδωση είναι μια συστηματική νόσος οφειλόμενη στην εναπόθεση αδιάλυτων πρωτεϊνικών ινιδίων αμυλοειδούς.

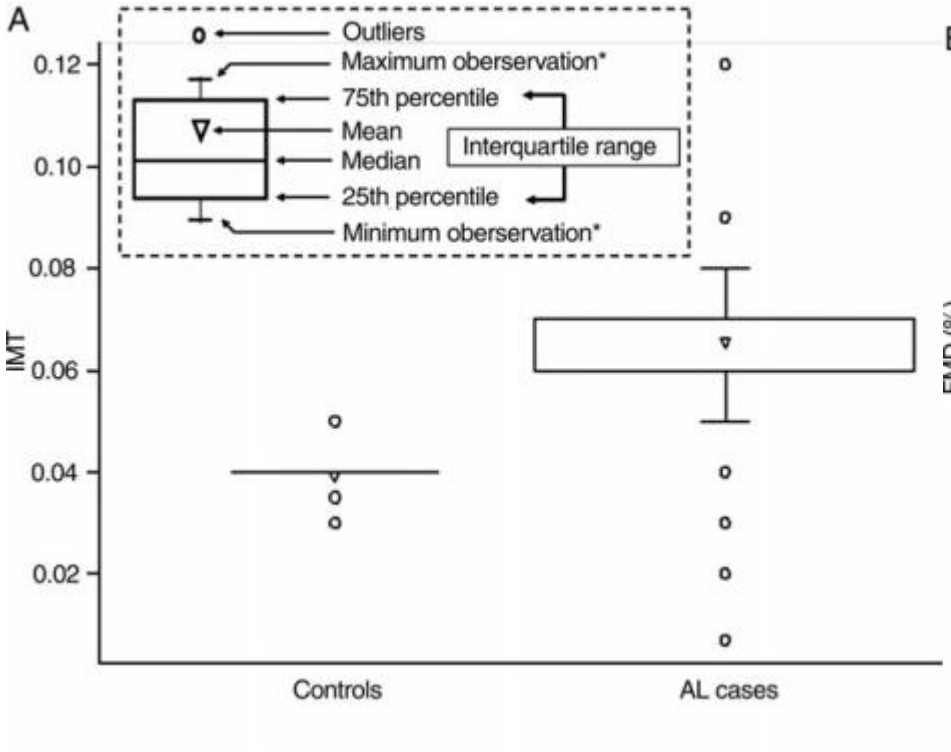
- Τα ινίδια του αμυλοειδούς εναποτίθενται σε ποικίλα όργανα συμπεριλαμβανομένου και του αγγειακού τοιχώματος με συνέπεια πιθανόν τη διαταραχή της αγγειακής λειτουργίας.

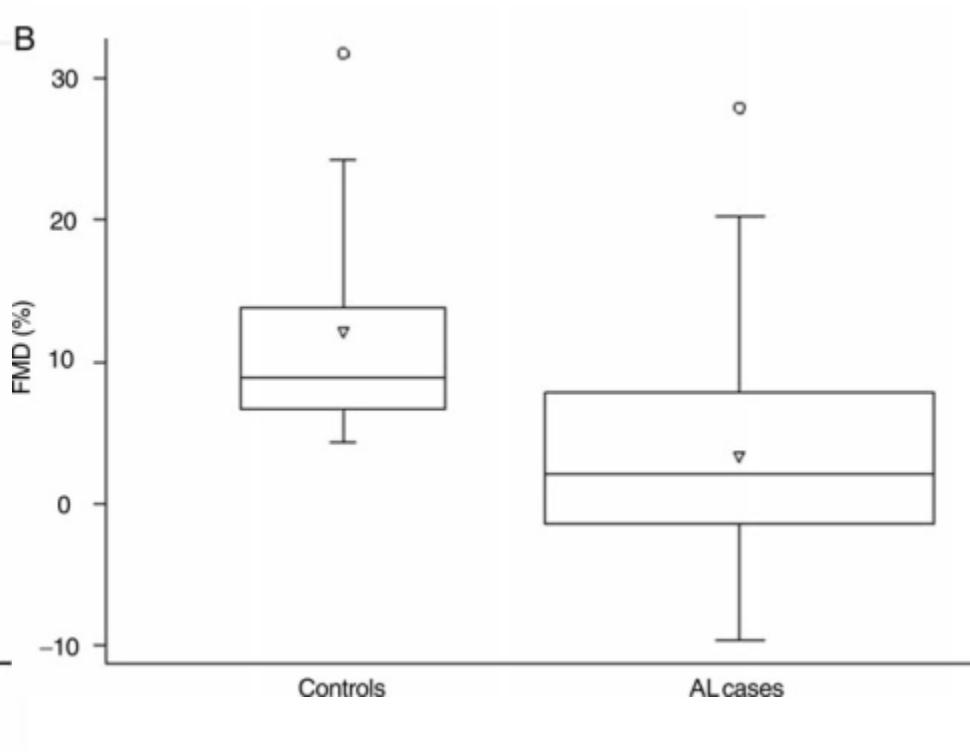
Merlini et al New England Journal of Medicine 2003

Subclinical atherosclerosis in AL amyloidosis

Increased carotid IMT

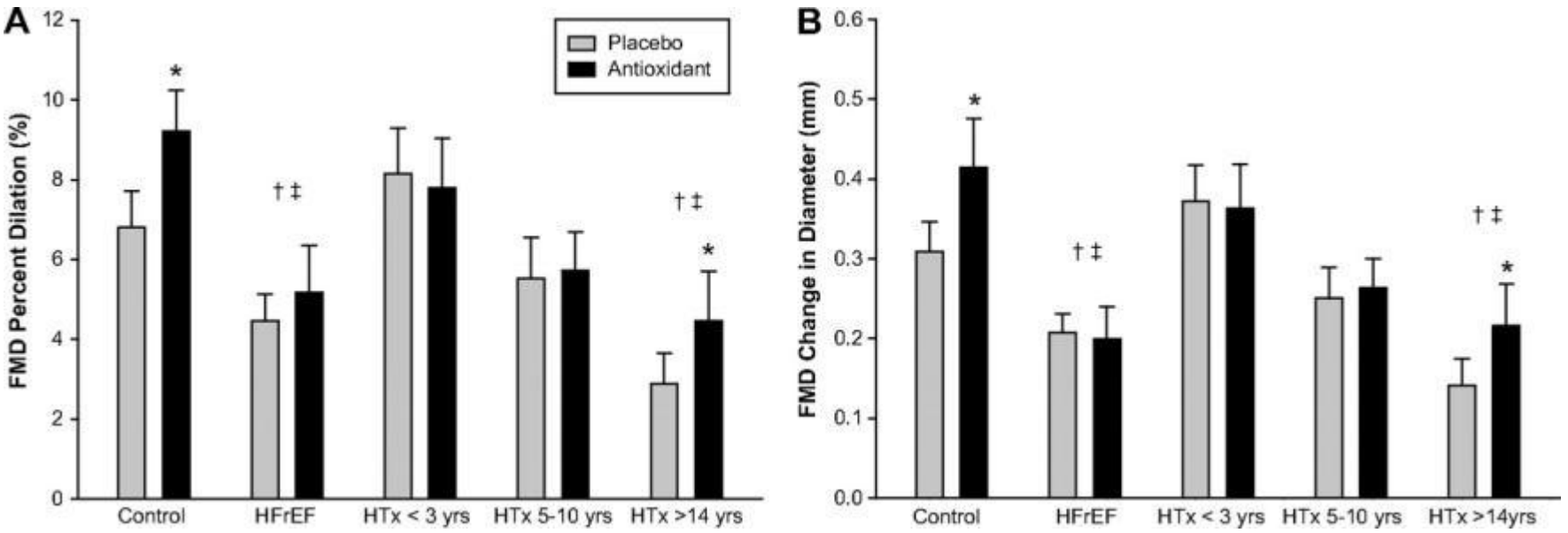
Reduced brachial FMD





Modesto KM et al. Eur Heart J 2007

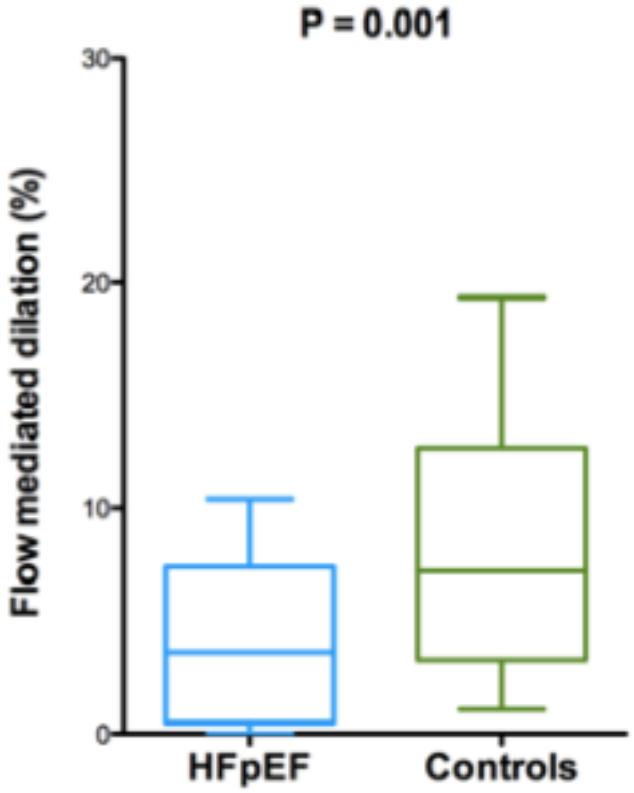
FMD is decreased in patients with heart failure with reduced ejection fraction



Melissa A.H. Witman et al. Hypertension. 2012;60:659-668

American Heart Association.

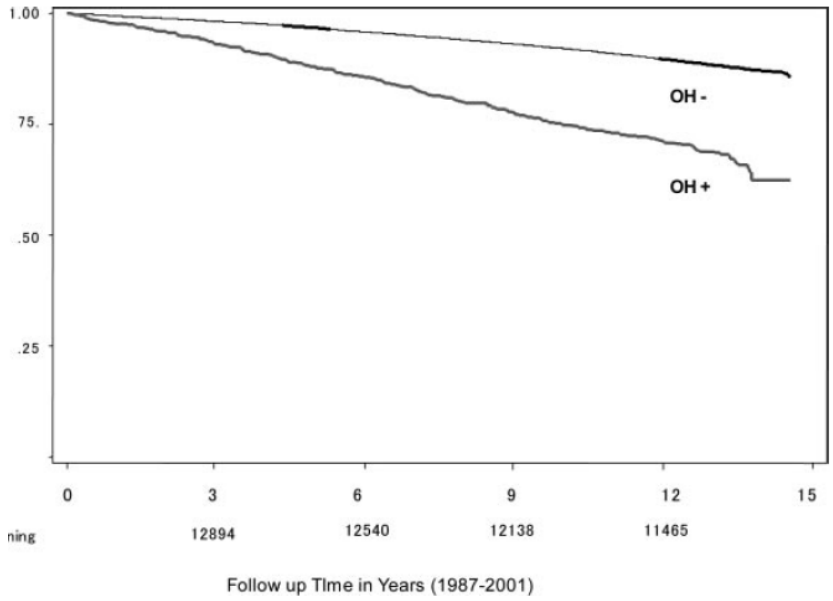
FMD is decreased in patients with heart failure with preserved ejection fraction

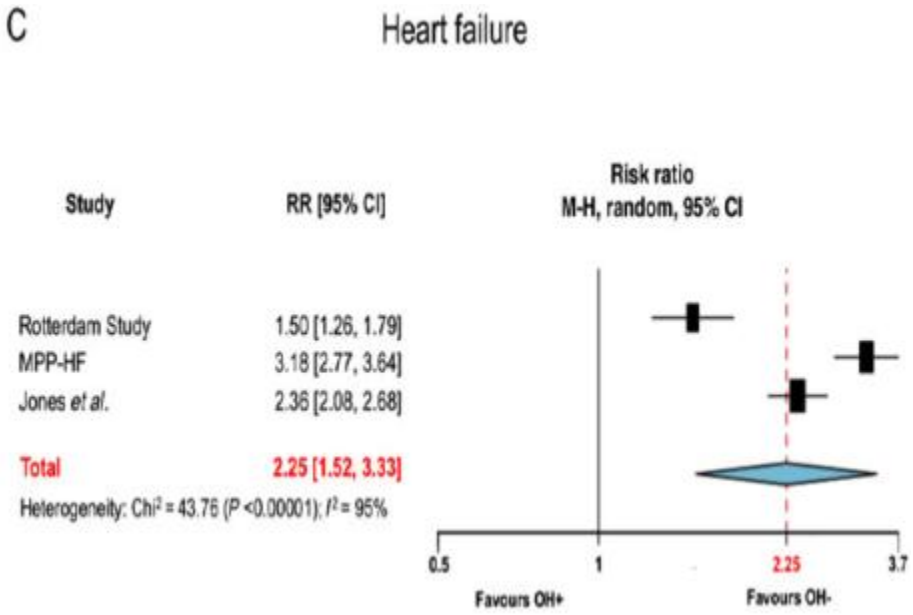


45 HFpEF patients
VS
45 hypertensives and no history or evidence of heart failure

Marechaux S et al. J Card Fail. 2015

Orthostatic hypotension is associated with increased mortality in middle aged general population ARIC study

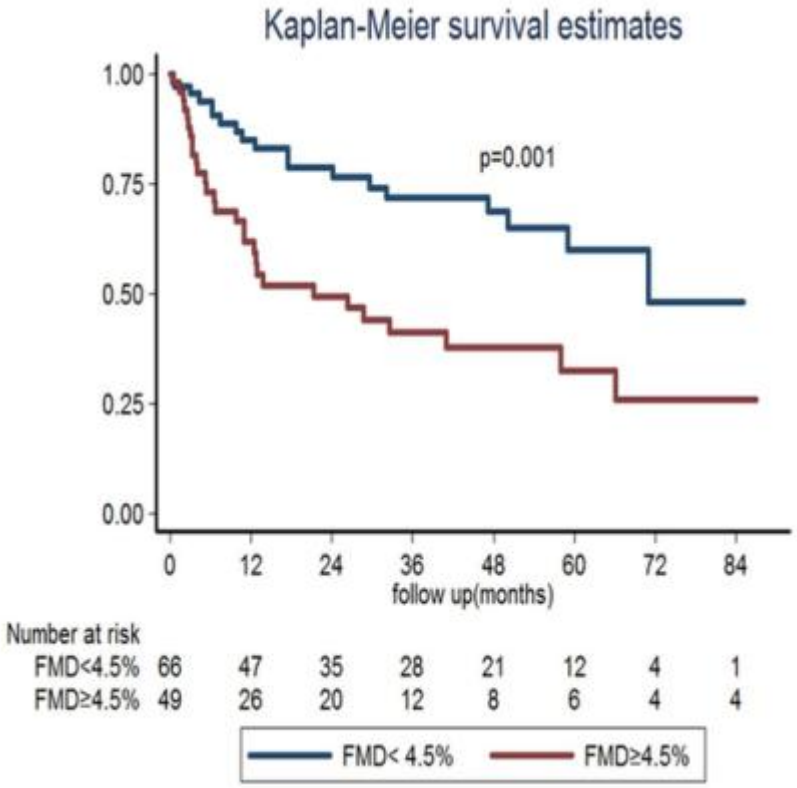




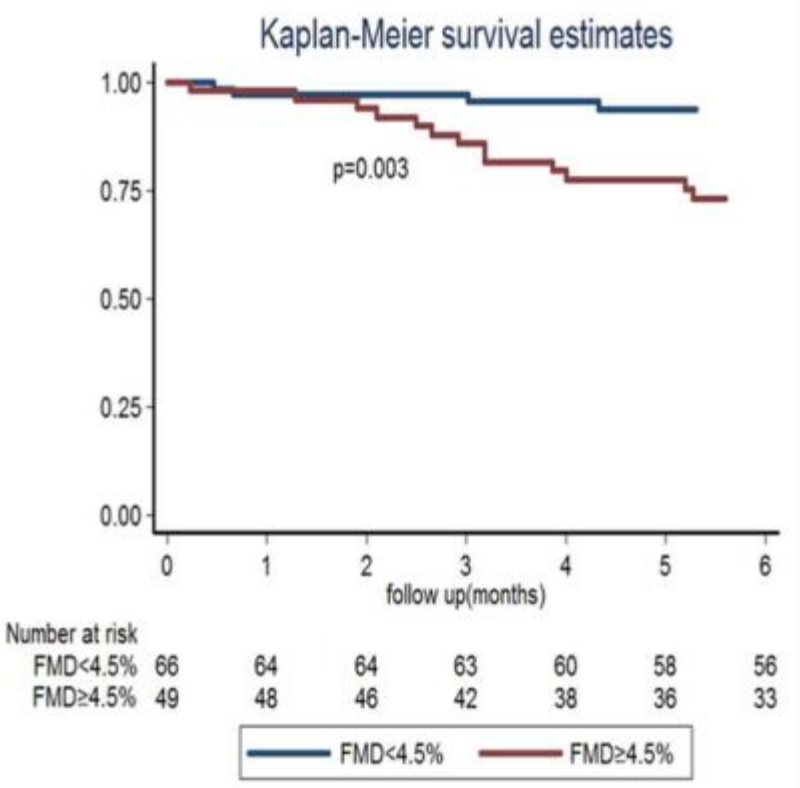
Circulation 2006

Higher mortality in patients with increased FMD as compared to those with lower levels

All cause mortality across the follow up period

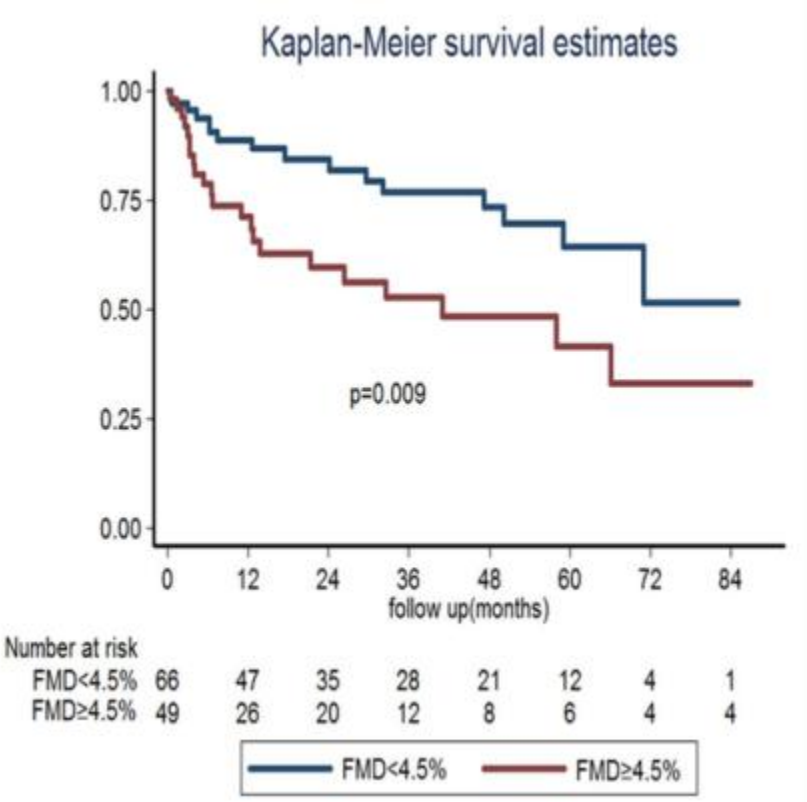


Early all-cause mortality within the first 6 months of the follow up

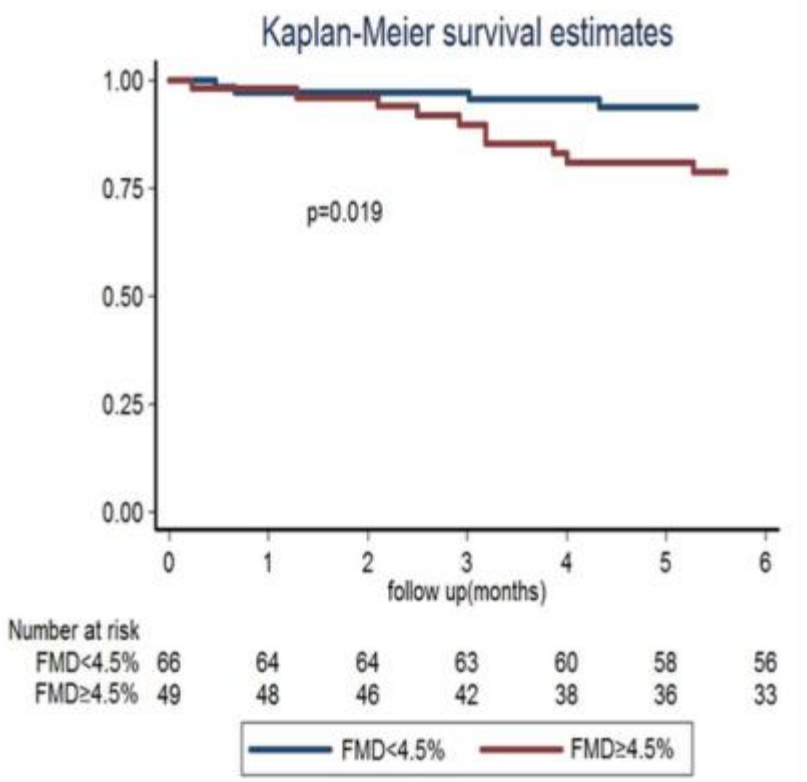


Unpublished data

Cardiac mortality across the follow up period



Early cardiac mortality within the first 6 months of the follow up



Unpublished data

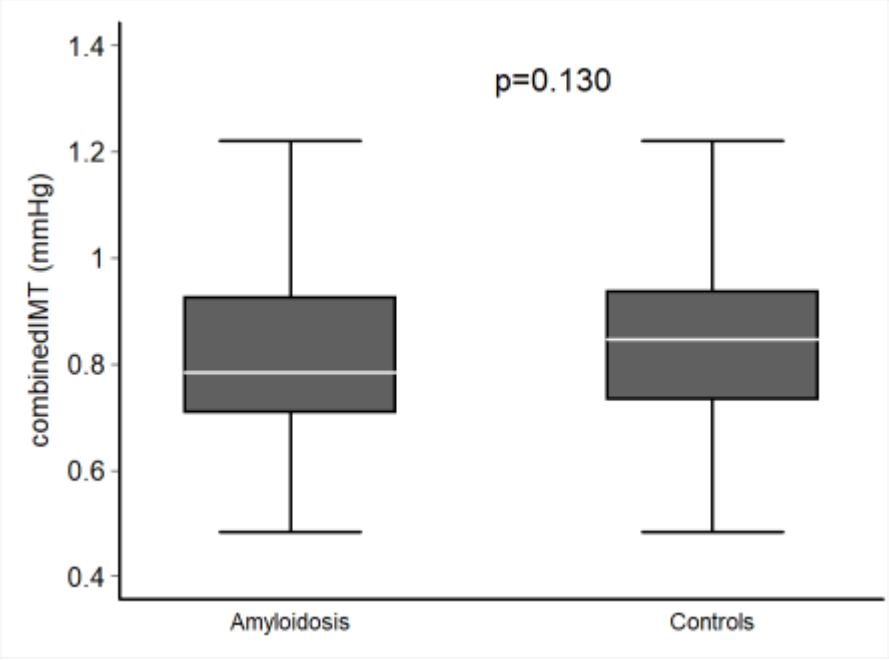
FMD reclassifies risk in amyloidosis over Mayo stage + ROC ?

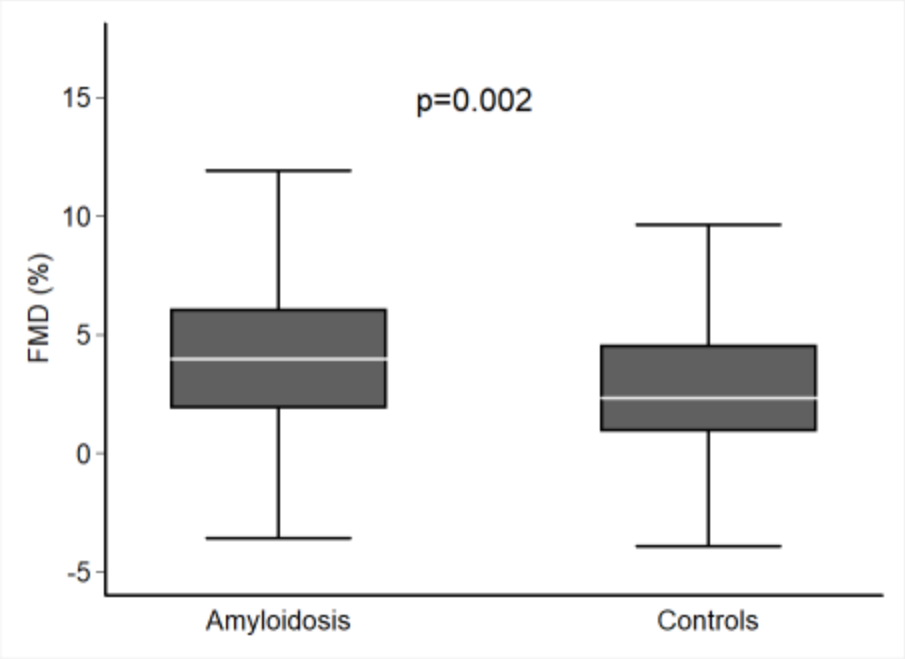
Improvement in model calibration and reclassification of vascular markers over the best predictive model for Study Main Endpoint.

	Regression parameters		Calibration parameters		Reclassification parameters					
				LR test	Continuous NRI					IDI
	HR (95%CIs)	p-value	AIC	LR chi2 (p-value)	Among Event Subjects	Among Non-Event Subjects	Overall (SE)	P-value	†NRI (SE)	Coeffic ient (SE)
Primary Endpoint (All cause mortality, n=46)										
FMD	2.39(1.2-4.74)	0.013	273	39.8 (<0.001)	-20%	67.2%	47.2% (20.9)	0.024	*21% (10.5)	*4.7 (2.35)
Model1 +FMD	2.11(1.02-4.4)	0.045	238							
C_SBP	0.982(0.965-0.99)	0.045	221	13.8 (0.001)	21.22%	10.14%	31.4% (21.2)	0.139	*22.4% (11.3)	*5.7 (2.4)
±Model2+ C_SBP	0.968(0.947-0.99)	0.005	214							
FMD_SB P	3.39(2.07-5.57)	<0.001	235	39.9	43.76%	47.52%	91.3% (21.8)	<0.001	20.1% (9.3)	**19.2 (4.5)
Model2+ FMD_SB P	3.95(2.22-7.01)	<0.001	200	<0.001						

LR test: likelihood-ratio test, LR chi2: twice the difference in log-likelihoods between nested models under chi2 distribution with one degree of freedom
* indicates level of statistical significance<0.05; ** indicates level of statistical significance<0.001
† Category based NRI:
low risk <35%, high risk >35%
NRI: Net Reclassification Index; SE: Standard Error; IDI: integrated discrimination index
Model 1: age, gender, systolic blood pressure, Mayo Stage
NC: not performed due to empty cells per category of risk
± Model 2: age, gender, Mayo Stage
FMD: flow mediated dilatation; C_SBP: aortic systolic blood pressure;
FMD_SBP: a combined ordinal variable encoded as 0: when FMD is distributed in lower quartiles and SBP in highest quartile, 1: when either FMD is distributed in highest quartile or SBP in lowest quartile and 2: when FMD is distributed in highest quartile and SBP in lowest quartile

Higher FMD in AL patients as compared to non-AL controls





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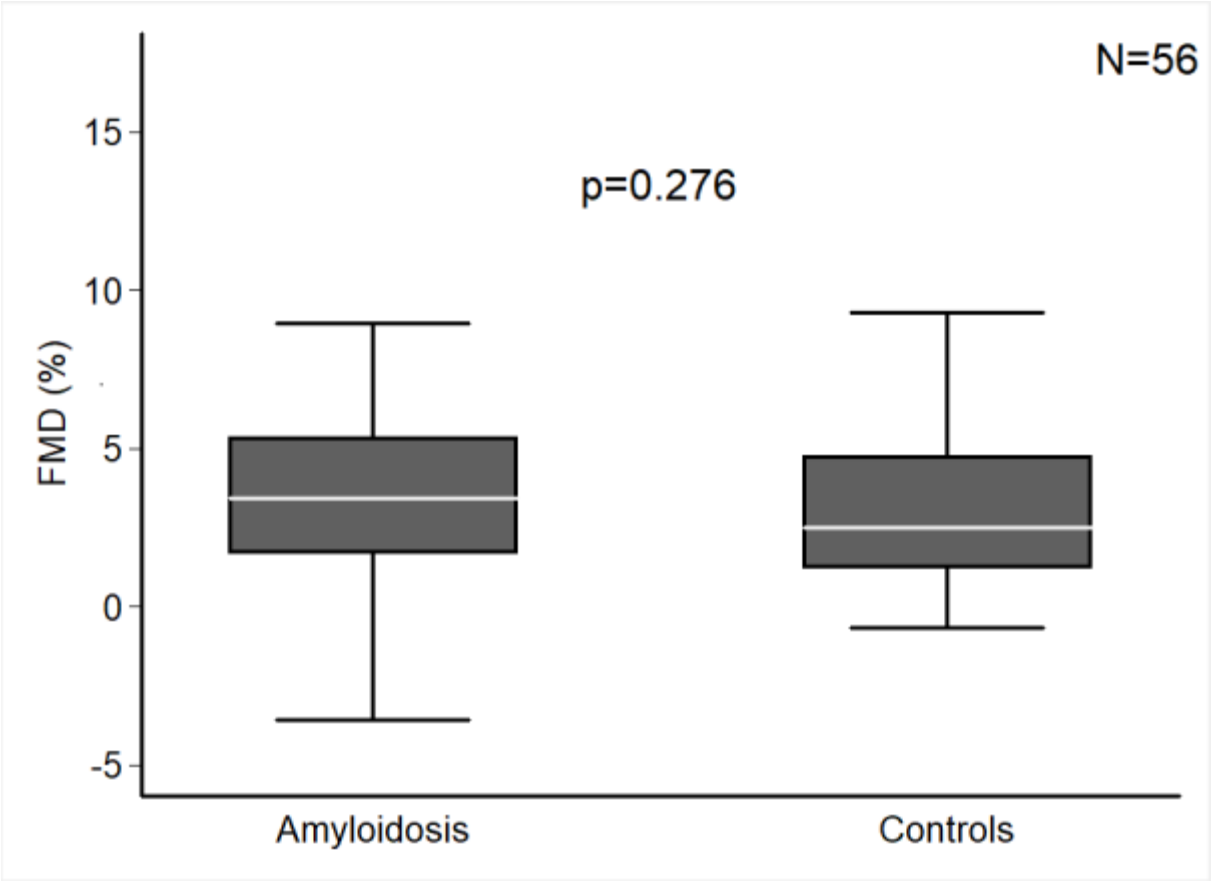


Unpublished data

Study design

- Study population
- ✓ n=115 consecutive, newly diagnosed, treatment naïve patients with biopsy-confirmed systemic AL amyloidosis
- ✓ Matched with the AL patients for age and gender and GFR control subjects

- Exclusion criteria: Control subjects with autoimmune or chronic inflammatory diseases, cancer, active infection, acute renal failure, acute coronary syndrome, acute stroke and any condition limiting survival to less than 1 year

- Flow-mediated dilatation and carotid and femoral ultrasound

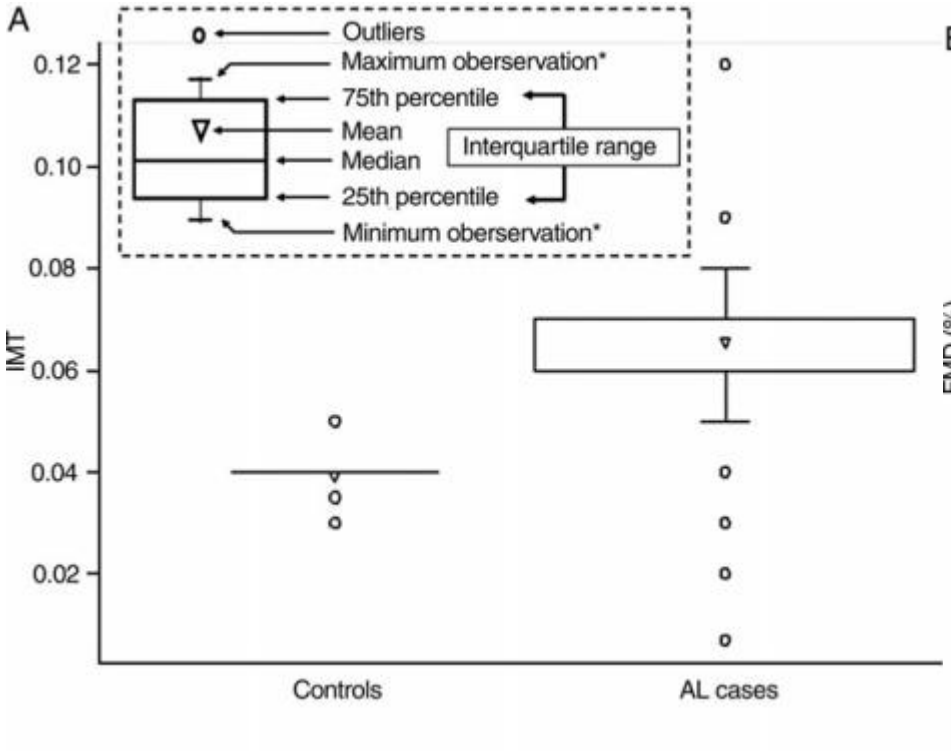
Conduit arteries

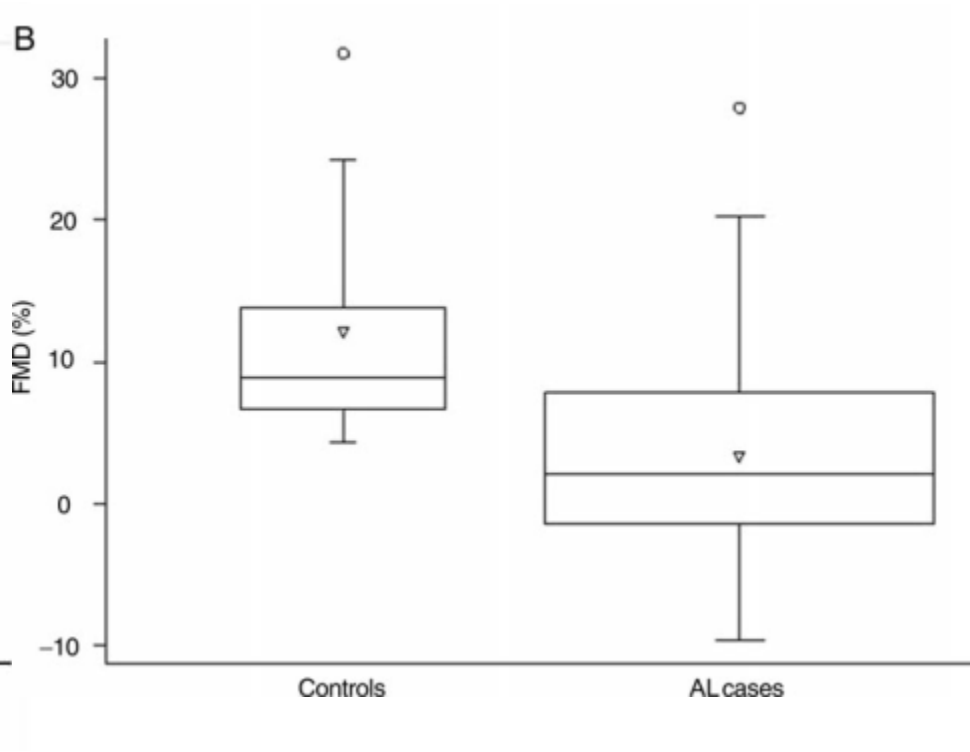
Subclinical human arterial involvement in AL amyloidosis

Increased carotid IMT

Reduced brachial FMD

N=59 AL amyloidosis pts





Modesto KM et al. Eur Heart J 2007

High rate of co-morbidities in AL amyloidosis

Table 1 Population characteristics

	Controls ($n = 17$)	NCAL ($n = 19$)	CAL ($n = 40$)	All AL ($n = 59$)	Pure AL ($n = 37$)
Clinical characteristics					
Age (years)	61.1 ± 7.4	58.2 ± 9.5	57.7 ± 9.4	57.9 ± 9.4	59.3 ± 9.4
Male (%)*	5 (29)	9 (47)	24 (60)	33 (56)	20 (54)
Body surface area (kg/m^2)	1.89 ± 0.19	1.85 ± 0.22	1.87 ± 0.25	1.86 ± 0.24	1.84 ± 0.25
Heart rate (b.p.m.)	69 ± 8	67 ± 12	79 ± 15	75 ± 15	75 ± 15
SBP (mmHg)*	126 ± 9	117 ± 18	112 ± 18	113 ± 18	115 ± 17
DBP (mmHg)*	78 ± 5	70 ± 14	69 ± 11	69 ± 12	69 ± 12
Hypertension	–	0 (0%)	5 (13%)	5 (8%)	–
Coronary artery disease	–	0 (0%)	5 (13%)	5 (9%)	–
Diabetes mellitus	–	1 (5%)	2 (5%)	3 (5%)	–
Renal failure	–	4 (21%)	9 (23%)	13 (22%)	–
ACE inhibitor/ARB II	–	4 (21%)	5 (13%)	9 (15%)	6 (16%)
Calcium channel blockers		1 (5%)	2 (5%)	3 (5%)	2 (5%)
β-blockers					3 (8%)
Diuretics*					20 (54%)
Statins					7 (19%)
Nitroglycerin					1 (3%)
Laboratory values					
Aspartate amino transferase (mg/dL)	24 ± 3	27 ± 11	35 ± 25	33 ± 22	33 ± 23
Serum creatinine (mg/dL)	1.04 ± 0.23	1.31 ± 0.64	1.69 ± 1.51	1.57 ± 1.30	1.29 ± 0.65

40 % Cr >1.6 mg/dl, 70% renal involvement vs, none in the control group

Modesto KM et al. Eur Heart J 2007

FMD is severely decreased in renal failure

Table 1. Brachial artery characteristics

Variable	Controls (1) $n = 22$	ESRD-CVD$^-$ (2) $n = 18$	ESRD-CVD$^+$(3) $n = 17$	*P*-ANOVA
Age (years)	50.1 ± 15.6	48.2 ± 10.5	63.5 ± 10.6	<0.01[a]
Gender (male/female)	13/9	11/7	11/6	0.44
Body mass index (kg/m^2)	24.5 ± 2.9	24.6 ± 4.4	25.9 ± 3.6	0.22
Systolic blood pressure (mmHg)	126 ± 17.5	136 ± 19.5	155 ± 23.8	<0.001[a]
Diastolic blood pressure (mmHg)	77 ± 11.1	75.5 ± 12.6	74 ± 9.2	0.78
Mean blood pressure (mmHg)	93 ± 11.2	96 ± 14.2	101 ± 11.4	0.21
Pulse pressure (mmHg)	49 ± 17	61 ± 12.3	80 ± 23	<0.001[a]
BA intima-media thickness (μm)	427 ± 60	450 ± 55	479 ± 50	<0.05[e]
Baseline BA diameter (mm)	4.10 ± 0.65	4.40 ± 0.70	4.90 ± 0.95	<0.01[d]
Baseline BA Einc (kPa x 10^3)	3.06 ± 1.15	3.95 ± 2.1	6.28 ± 3.15	<0.001[a]
Baseline BA blood velocity (cm/s)	4.15 ± 1.9	3.95 ± 1.85	2.35 ± 1.9	<0.01[a]
Baseline BA blood flow (ml/s)	35.0 ± 23	36.0 ± 20.1	22.8 ± 17	<0.05[a]
Baseline BA shear rate (s^{-1})	49 ± 11.4	45.5 ± 21.1	35.4 ± 20.1	<0.01[a]
Whole blood viscosity (cPoise)	3.58 ± 0.36	2.70 ± 0.35[b]	2.78 ± 0.34	<0.001[b;c]
Baseline BA shear stress (dynes/cm^2)	17.6 ± 4.7	12.6 ± 5.8	8.3 ± 6.2	<0.001[a]
ΔBA diameter (% from baseline at 44°C)	7.5 ± 3.62	4.7 ± 2.72[f]	1.5 ± 1.65	<0.001[a;f]
Δ Shear stress (% from baseline at 44°C)	234 ± 125	289 ± 169	395 ± 295	<0.05
FMD (ΔBA diameter/Δshear stress)	3.6 ± 1.7	1.85 ± 1.2[b]	1.05 ± 0.85	<0.001[a;b]
GTN-induced dilation (GTN %)	20.7 ± 5.65	19.0 ± 4.3	11.20 ± 4.6	<0.001[a]
GTN/FMD (ratio)	3.50 ± 2.9	5.7 ± 2.8	8.1 ± 4.1	<0.05[c]

Clin J Am Soc Nephrol 6: 2009–2015

Characteristics of the AL amyloidosis population and of the age and gender-matched population and similar GFR

Parameters	AL (n=115)	Matched (n=115)	P value
Age (years)	64.4±10.2	64.3±10.1	0.938
Gender (male), n (%)	62 (53.9%)	62 (53.9%)	0.999
Diabetes n (%)	14 (12.2%)	21 (18.3%)	0.189
Hyperlipidemia n (%)	50 (43.5%)	69 (60.0%)	0.009
Smoking n (%)	18 (15.7%)	23 (20.0%)	0.371
Hypertension, n (%)[a]	45 (39.1%)	68 (59.1%)	0.002
GFR stage			0.288
Stage 1	36 (31.3%)	26 (22.6%)	
Stage 2	27 (23.5%)	33 (28.7%)	
Stage 3A	18 (15.7%)	15 (13.0%)	
Stage 3B	13 (11.3%)	5 (4.35%)	
Stage 4	8 (6.96%)	6 (5.22%)	
Stage 5	13 (11.3%)	6 (5.22%)	
History of Coronary artery disease n (%)	12 (10.4%)	14 (12.2%)	0.659

Submitted data

Increased vascular reactivity in AL amyloidosis

Autonomic dysfunction
sympathetic denervation

Am J Physiol Heart Circ Physiol 2006
Clin Cardiol. 2000

↑ ↑ Nitric oxide bioavailability and/or
↑ ↑ oxidation into peroxynitrite

Circulation 1995
Circ Res. 2004
Shock 2010

↑FMD

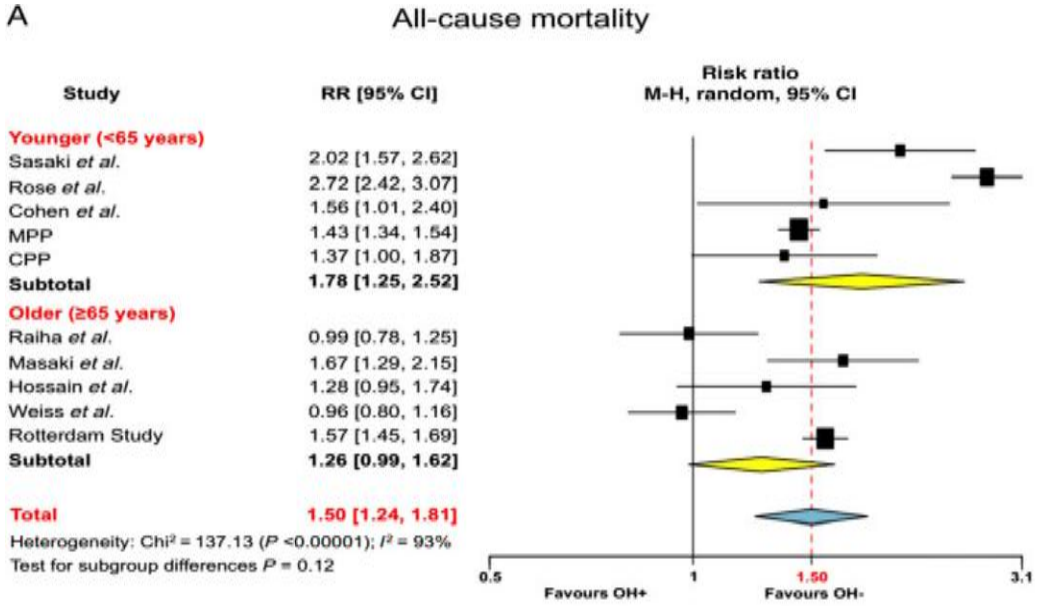
↑ ↑ non-NO vasodilator bioavailability
- Hyperpolarizing factor
- Prostaglandins
- Other

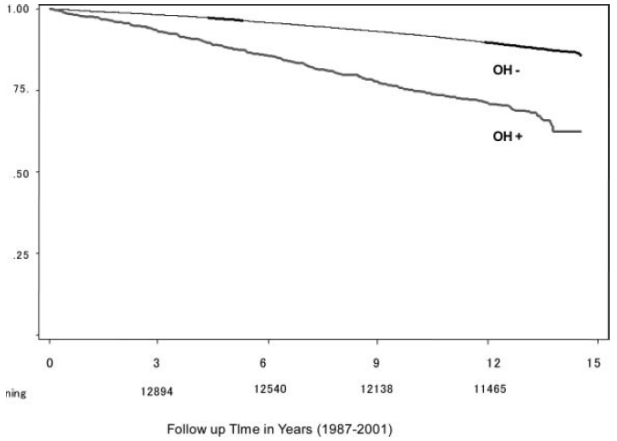
Circ Res 1999

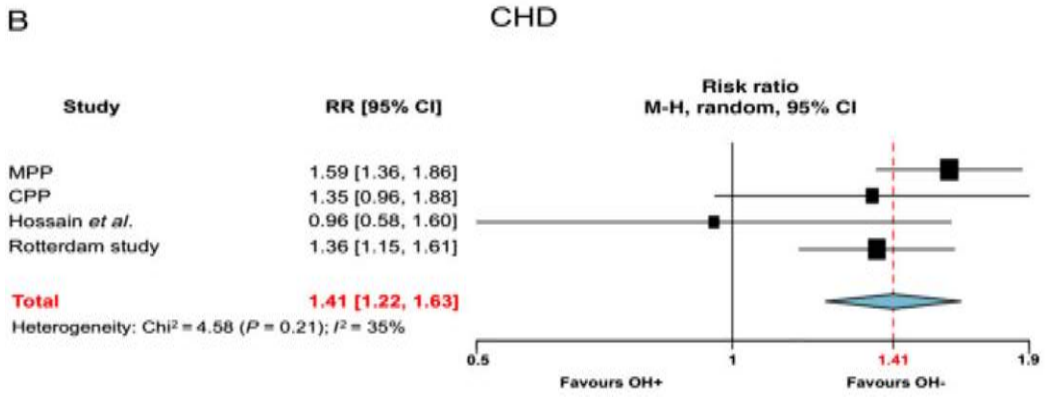
↑ reactivity of VSMC layer

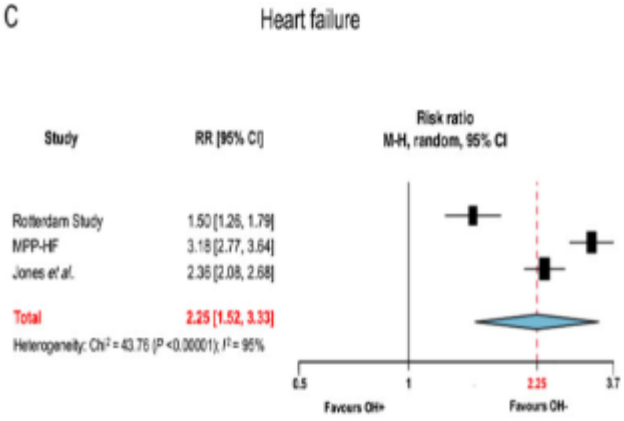
JACC 2002

Orthostatic hypotension is associated with increased mortality in middle aged general population ARIC study









Circulation 2006
Eur Heart J 2015