

Advances in Cardiac Arrhythmias and Great Innovations in Cardiology Torino, September 27th-28th, 2013

Luccheon III

Heart and kidneys: Renal denervation as therapy for hypertension

Renal sympathetic innervations and atrial natriuretic control. Without preventing atrial electrical remodeling, will renal denervation provide effective ventricular rate control during atrial fibrillation?

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IRCCS Sesto S. Giovanni

Cardiology O. U.

S. Giuseppe Hospital Milano

CARDIOVASCULAR DEPARTMENT

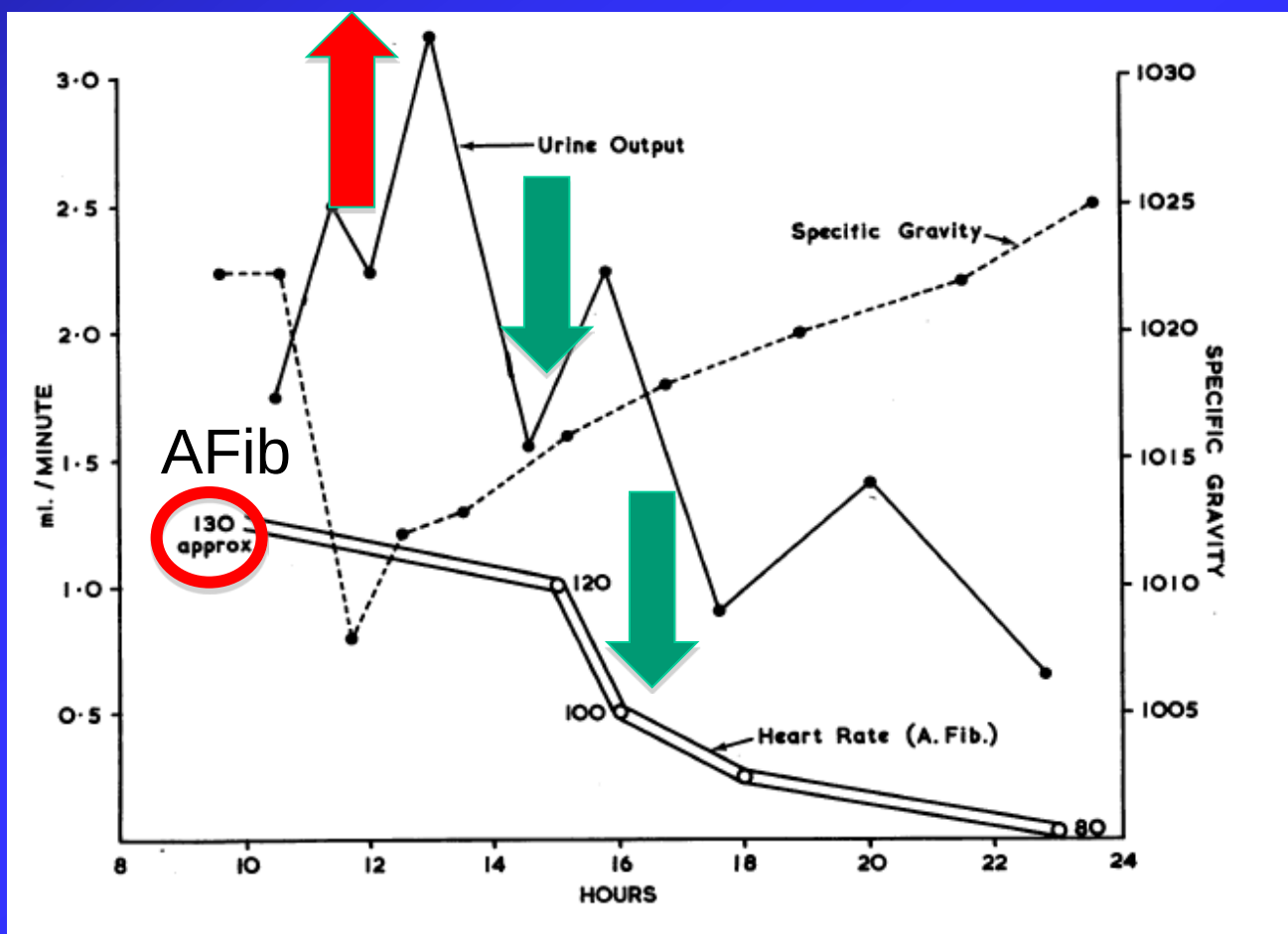
MultiMedica Group



POLYURIA IN PAROXYSMAL TACHYCARDIA AND PAROXYSMAL ATRIAL FLUTTER AND FIBRILLATION

BY

PAUL WOOD *Br Heart Soc 1961*



the mechanism of the diuresis was obscure

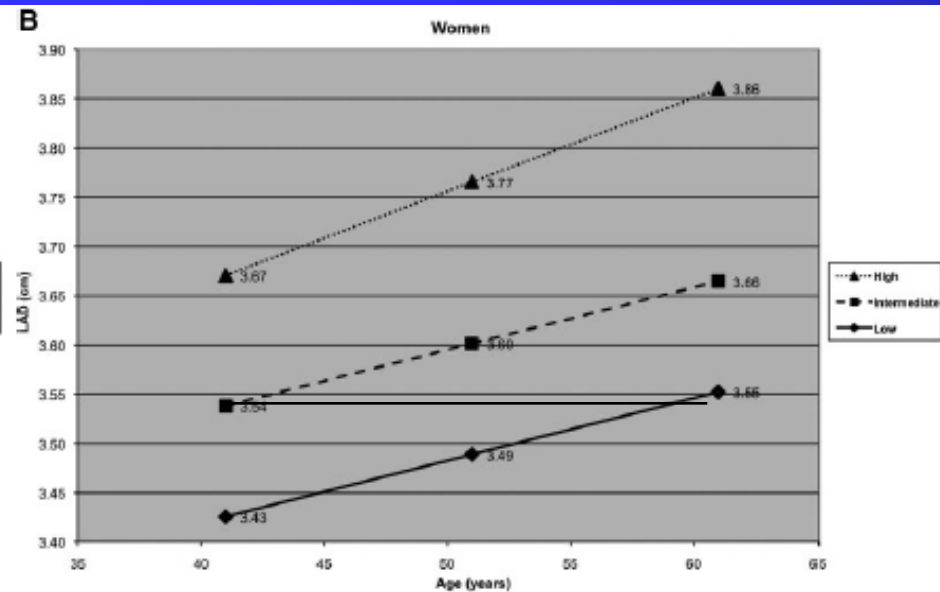
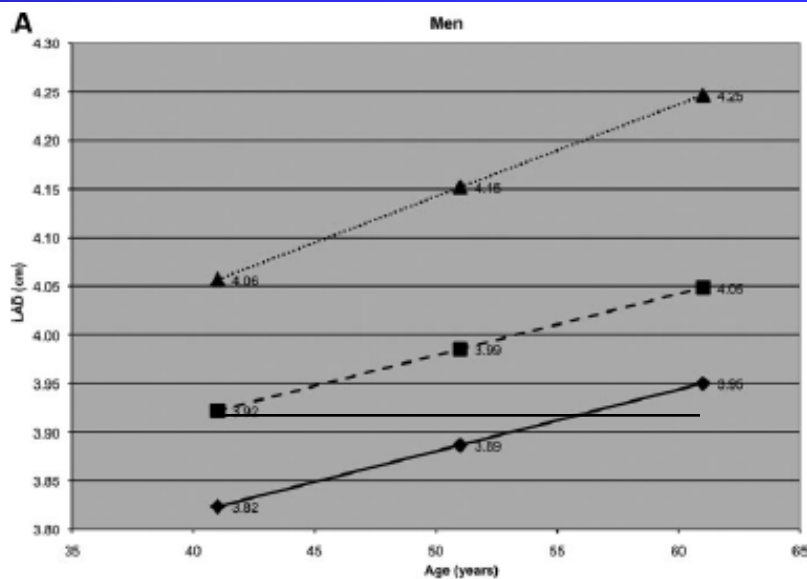
Campbell M Br H J 1962

The phenomenon seems little known. Thus Paul White (1951) says “An occasional symptom during or following paroxysmal tachycardia is increased frequency or increased amount of urination, doubtless a nervous reflex.” Friedberg in his first edition (1949) states that “there may be polyuria at the termination of the paroxysm,” but changes this in his second edition (1956) to “during or at the termination of the paroxysm.” Katz and Pick (1956) in a book devoted to the arrhythmias say “Frequency of urination is an unusual symptom in short attacks, but polyuria is often seen after the termination of long ones.” I could find no other mention of polyuria relating to paroxysmal tachycardia in any textbook of cardiology written in the English language—except in the second edition of my own book (1956) where it says “If the heart is normal, there is usually a remarkable degree of polyuria during the attack.”

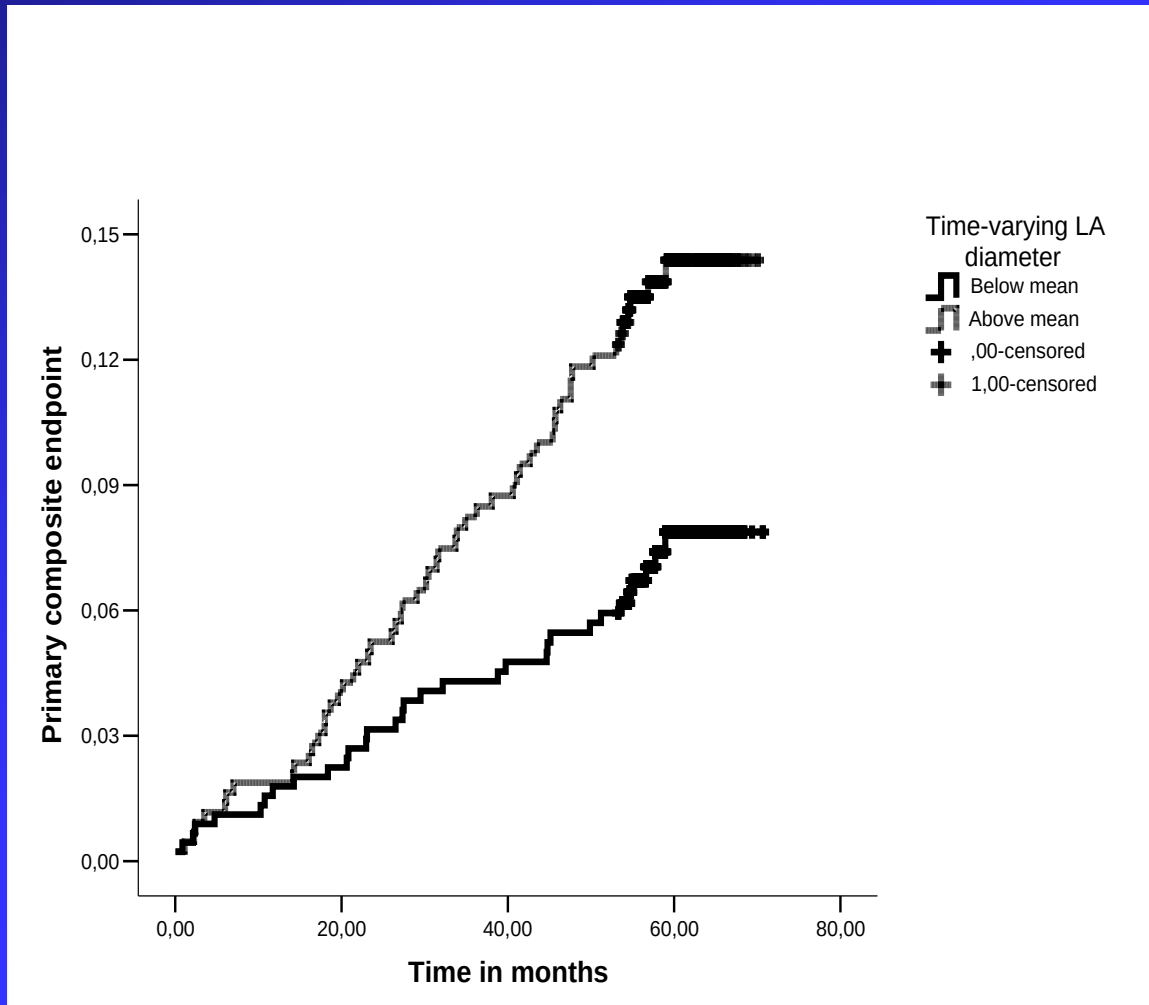
Reeves (1956) induced a large diuresis by distending a balloon in the left atrium, but not by constricting pulmonary veins; the diuresis was reduced by cold block of the vagus. Henry and Pearce

Clinical Correlates in the Community Longitudinal Tracking of Left Atrial Diameter Over the Adult Life Course

1. Low risk group : BMI of 25 kg/m² with normal BP (defined as having a median BP of 113/73)
2. Intermediate risk group: BMI of 27.5 kg/m² and pre-hypertension (defined as having a median BP of 133/86) not receiving anti-hypertensive medications
3. High risk group : BMI of 30 kg/m² and hypertension (defined as having a median BP of 146/91).



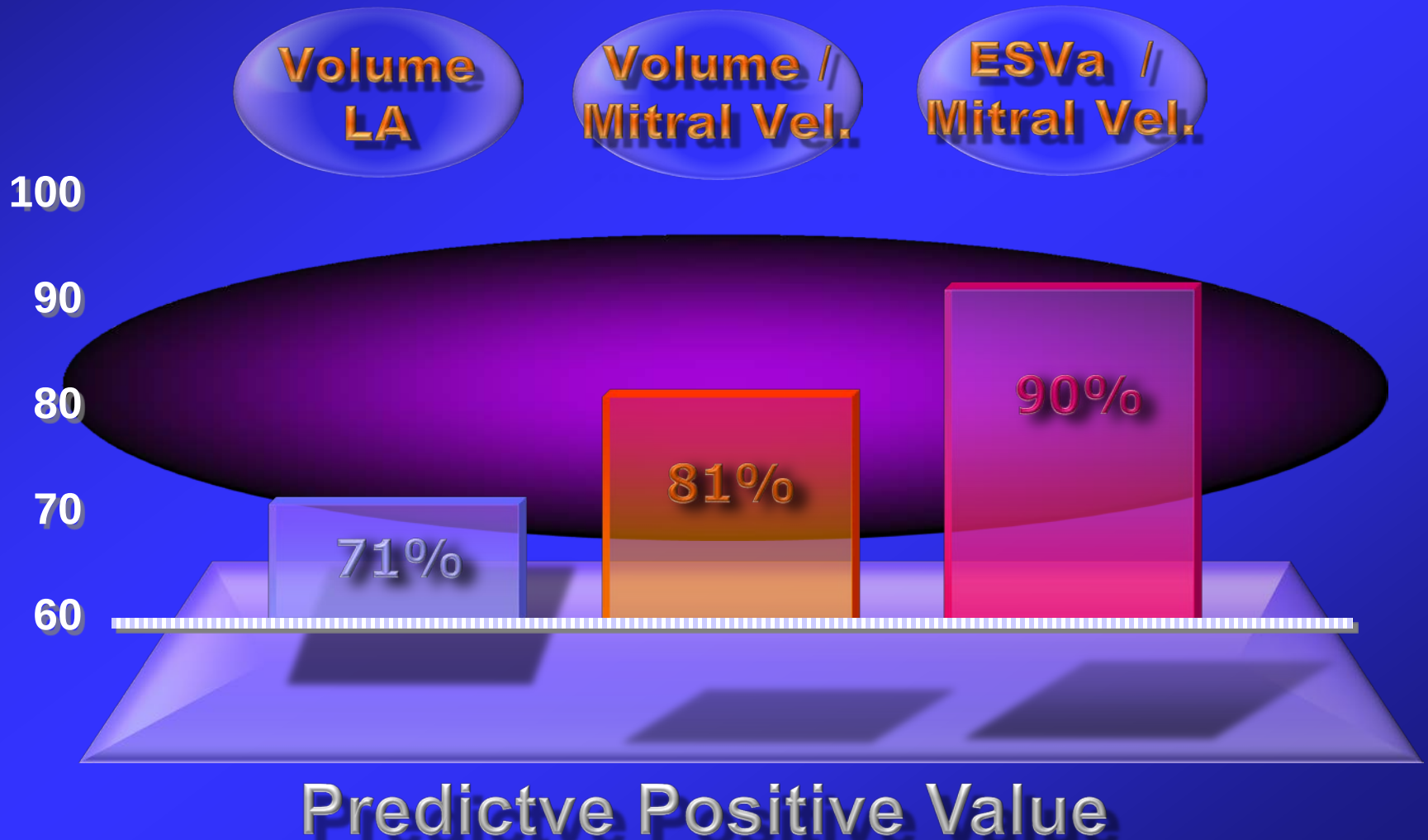
LIFE Echo: Higher Time-Varying Left Atrial Diameter Associated with More CV Events*



***HR = 1.98 per cm/m, independent of Framingham risk score, ethnicity, echo LVH, AF, CHF and Losartan-based therapy**

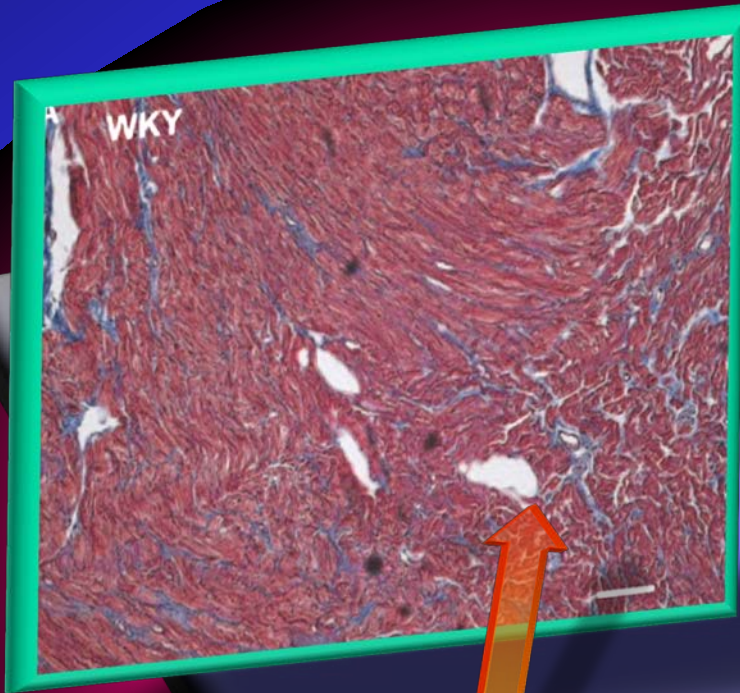
Atrial Volume and AF Risk

(Toh, Hypertension 2010)

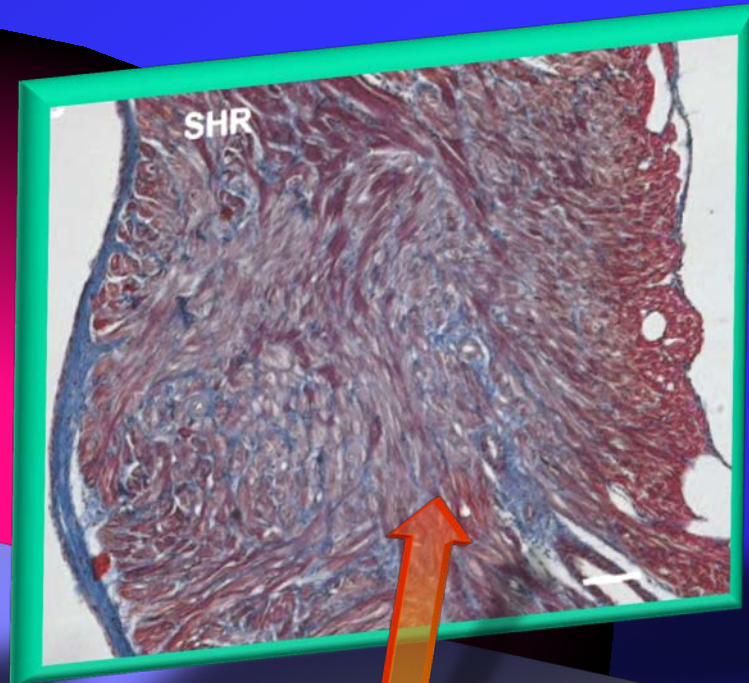


Hypertension, atrial fibrosis and tachyarrhythmia

(Choisy, Hypertension 2007)



Control



Hypertensive rat

Prevalent atrial expression of myocardial fibrosis.

The Culprit AT II

- Regional distribution of forming ATII in the Heart
 - ACE levels are highest in the atria
 - Kymase are highest in the ventricles

1. Urata H et al J Clin Invest 1993;91:1269-81

- Pressure independent effect of ATII on hypertensive myocardial fibrosis (ARB candesartan, at sub-depressor dose prevented MCP-1-mediated inflammatory process)

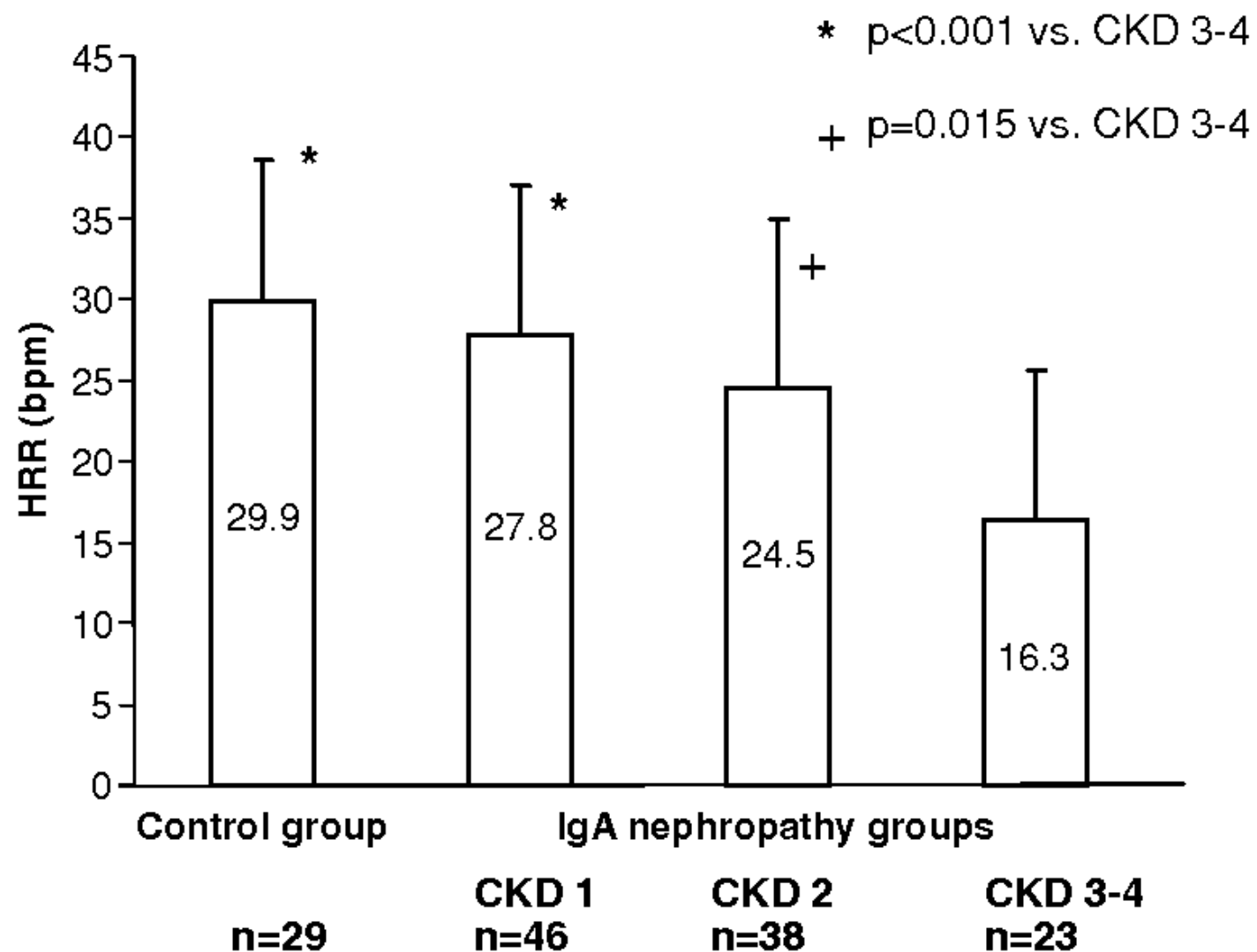
2. Tokuda K et al *Hypertension* 2004;43:499-503

- Regional differences exist in structural remodeling vulnerability with the atria more prone to fibrosis

3. Cardin S, Leung TK, Nattel S. Differences in atrial versus ventricular remodeling in dogs with ventricular tachypacing-induced congestive heart failure. *Cardiovasc. Res* 2004;63:236–44.

Heart Rate Recovery (HRR) in CKD

Kcsoi I et al. Nephrol Dial Transplant 2009



eGFR
ml/min

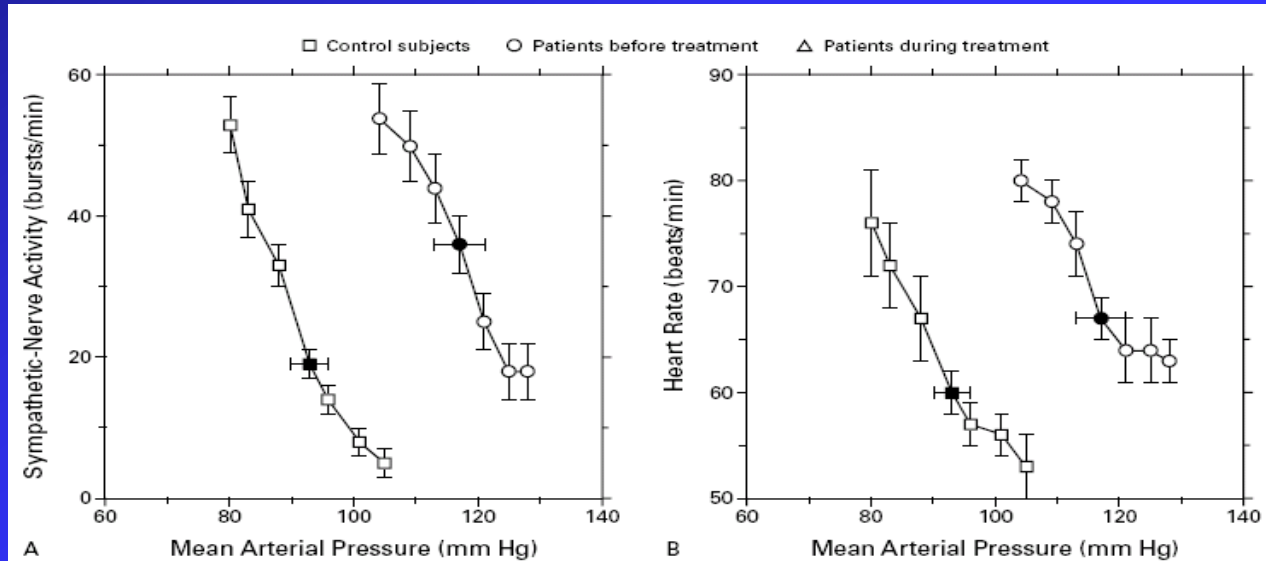
102 ± 18

116 ± 18

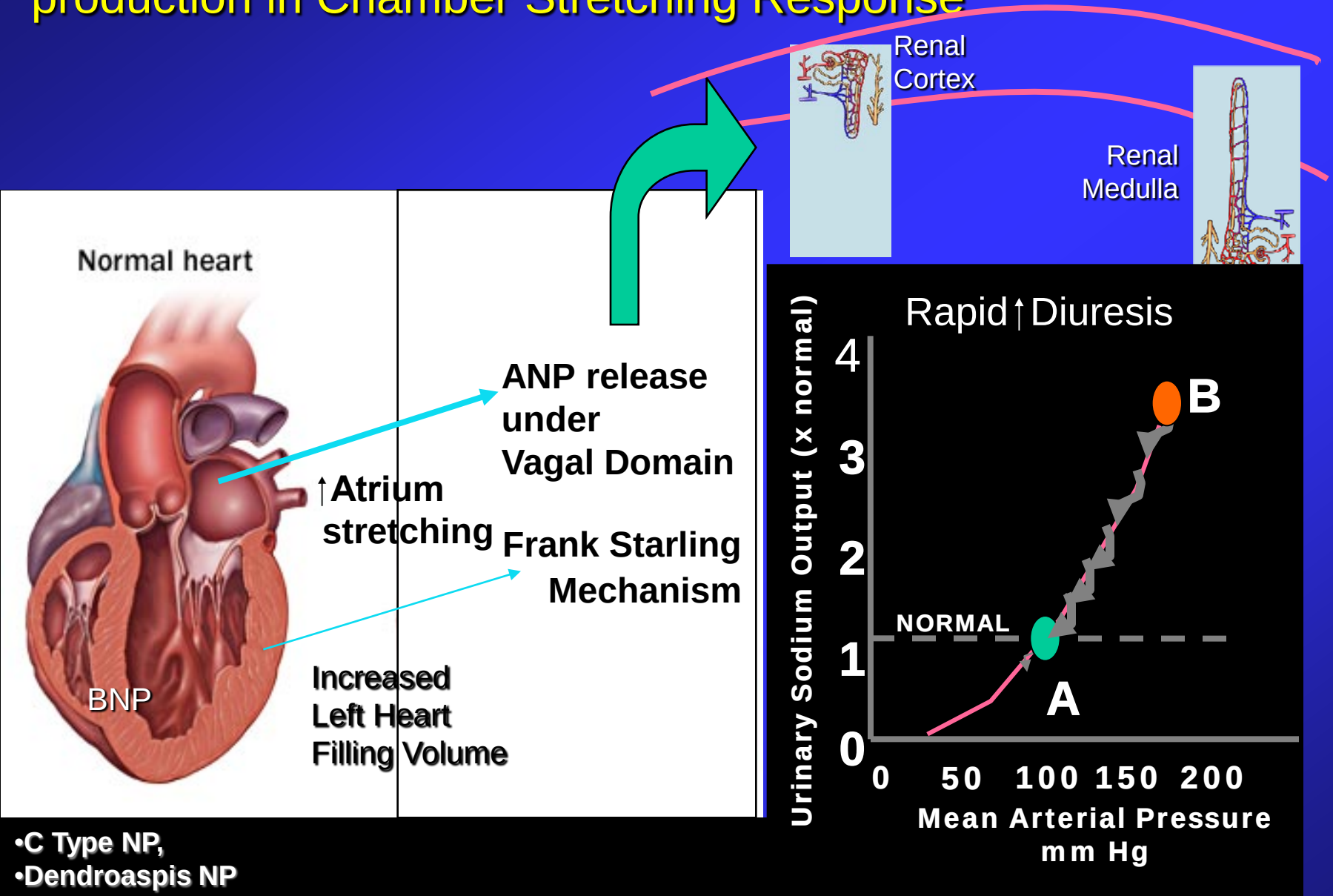
74 ± 9

34 ± 17

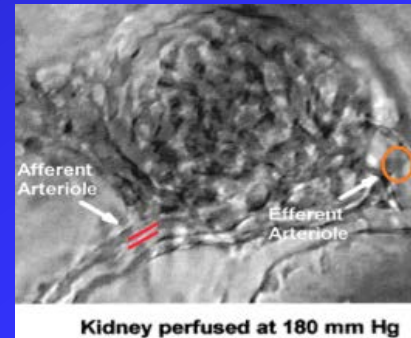
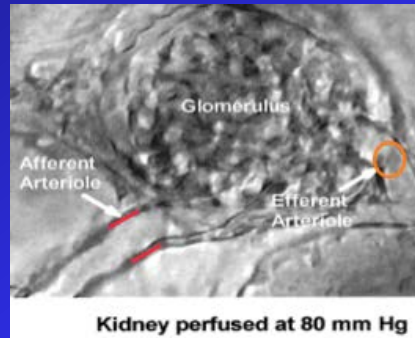
REDUCTION OF SYMPATHETIC HYPERACTIVITY BY ENALAPRIL IN PATIENTS WITH CHRONIC RENAL FAILURE



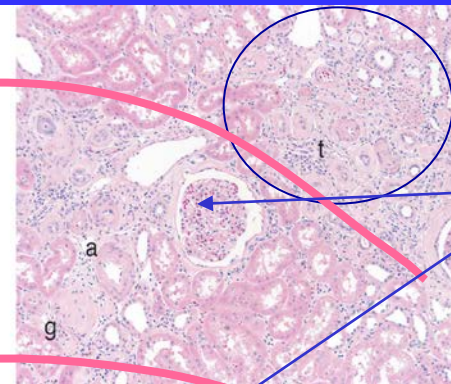
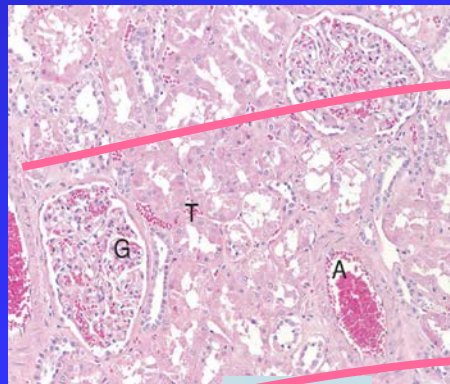
Cardiac PRESSURE/VOLUME regulation: ANP, BNP production in Chamber Stretching Response



Human Kidneys



(Loutzenisher R.
Circ Res.2002)

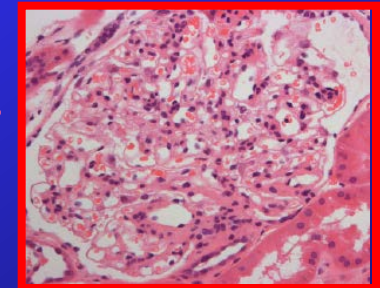
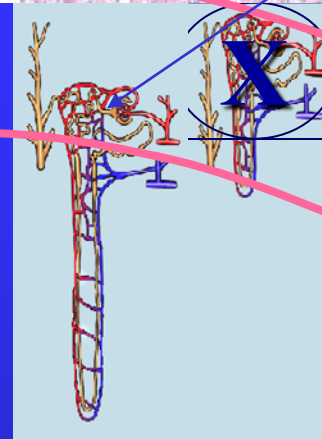
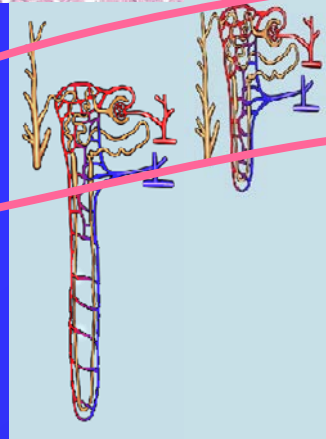


Glomerular
Hyperfiltration

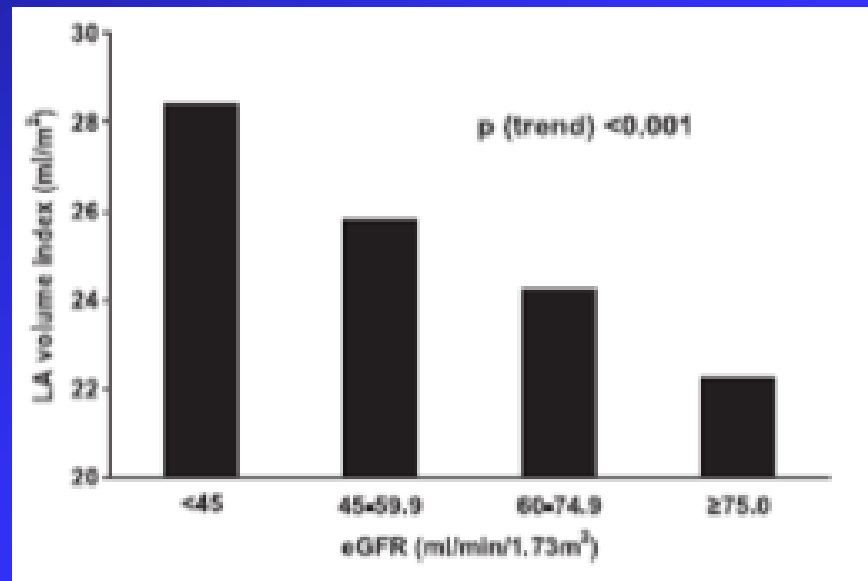
Hypertrophic
Glomerulus,
Compensating
for Obsolete
Ones

CORTEX

MEDULLA

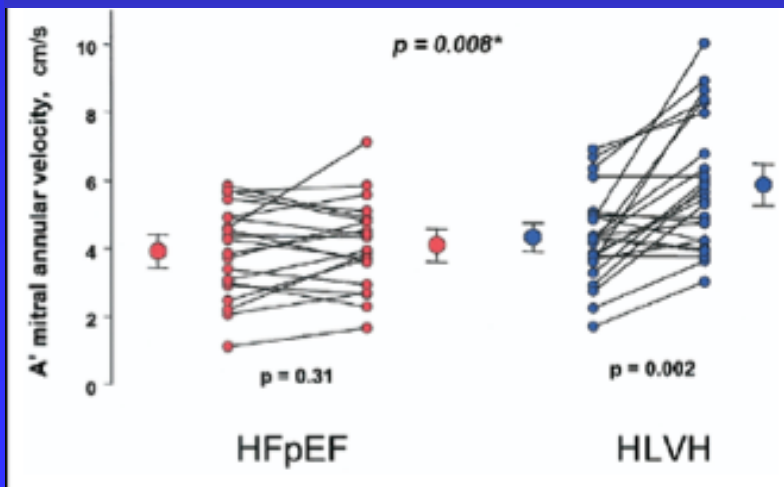


Relation between left atrium dilation and chronic kidney disease



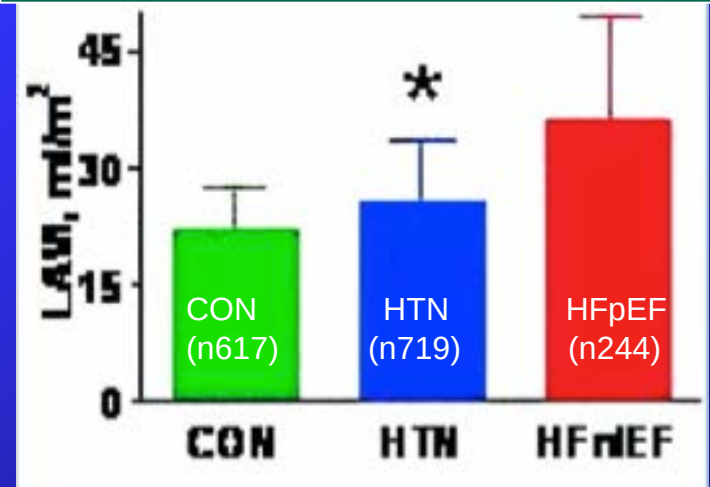
Verma et al. JACC, 2007;50:1238–45

Gender ♀%	84	78	p 0.28
Age yrs	65 ± 10	67 ± 10	p 0.61
Creat (mg/dl)	1.4 ± 0.7	1.0 ± 0.3	p < 0.01



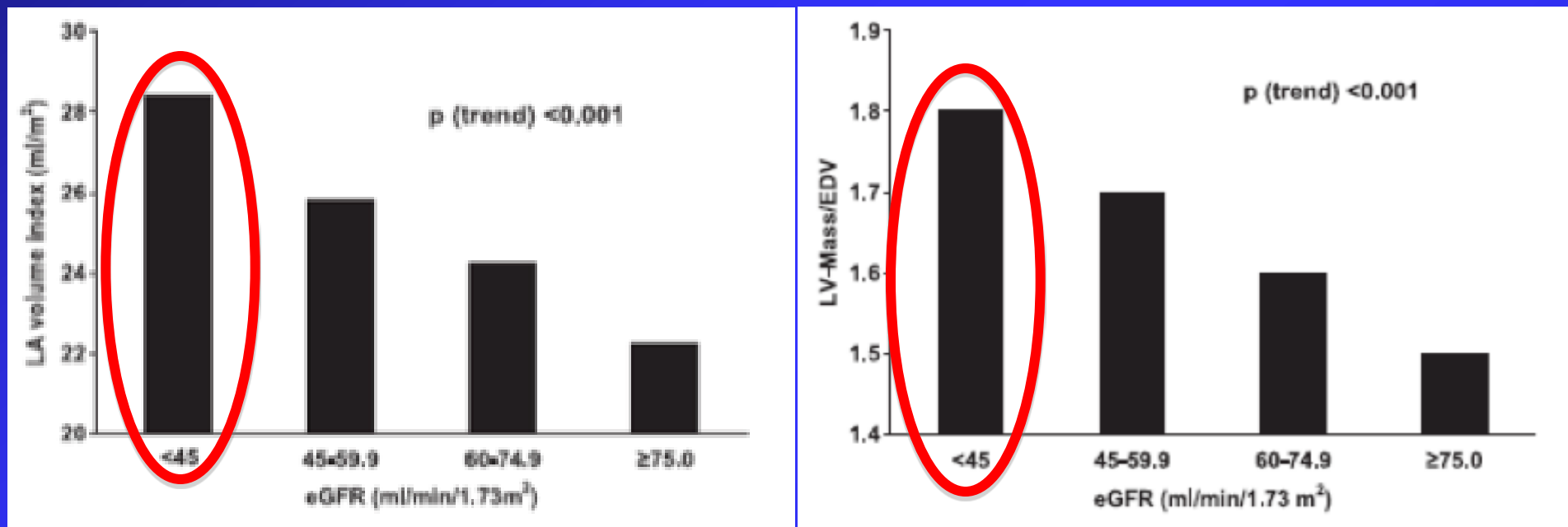
Melenovsky V. et al. JACC 2007;49:198–207

eGFR	74.4 ± 14.1	74.7 ± 37.0	64.32 ± 8.1*†
(ml/min/1.73 m²)			



Lan CSP et al. Circulation. 2007;115:1982-1990

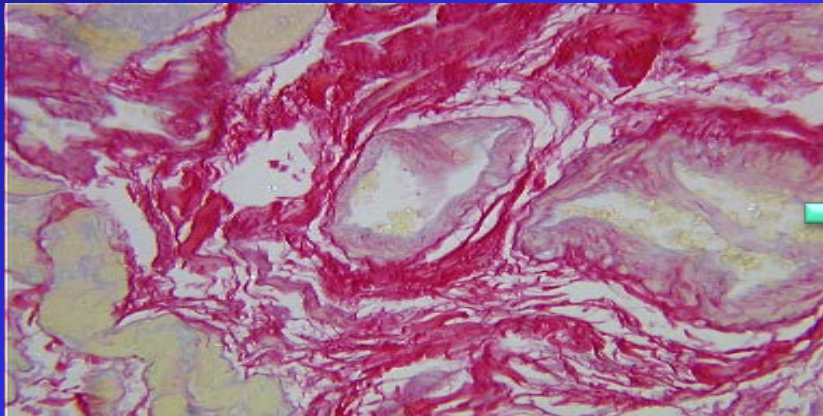
Relation between heart damage and chronic kidney disease



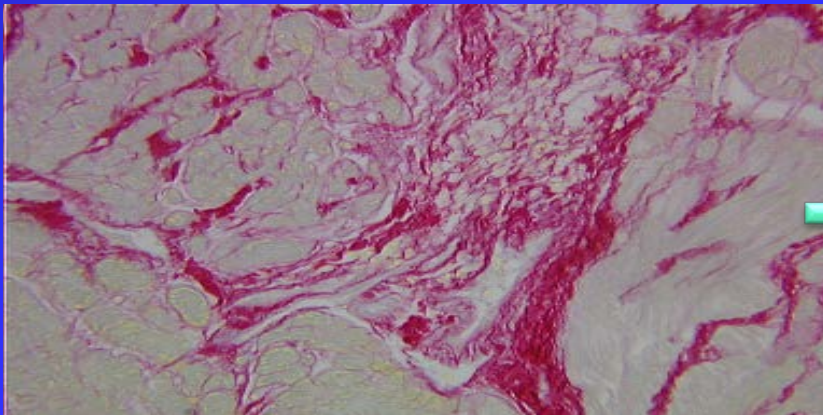
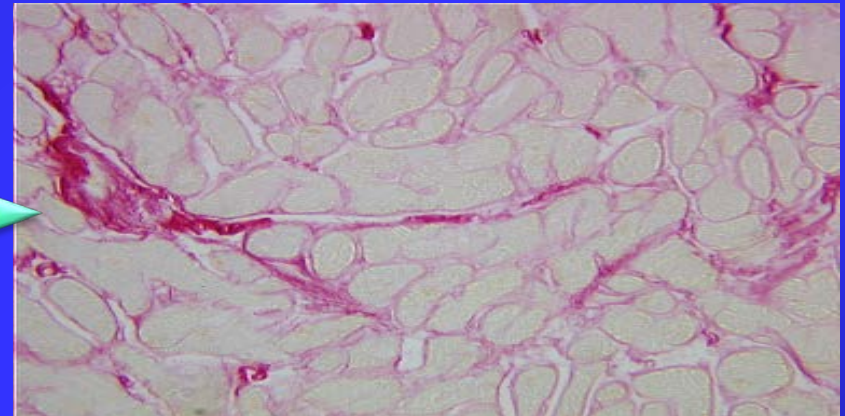
Verma et al. JACC, 2007;50:1238–45

Losartan: myocardial fibrosis in hypertensive patients

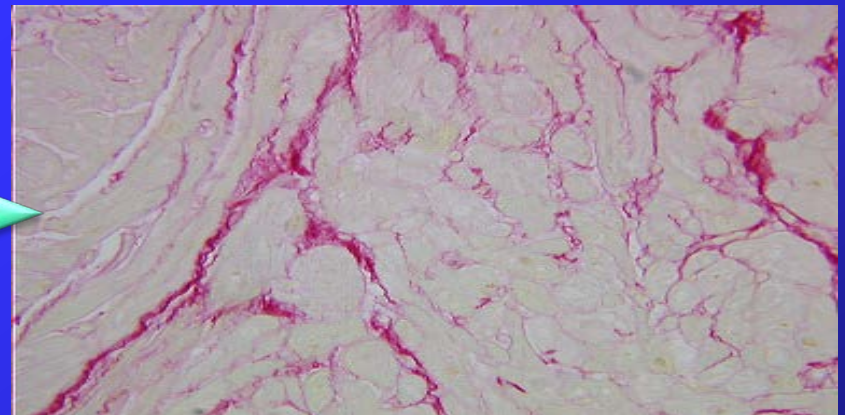
Before (CVF = 8.65 %)



After (CVF = 3.52 %)



Before (CVF = 8.05 %)



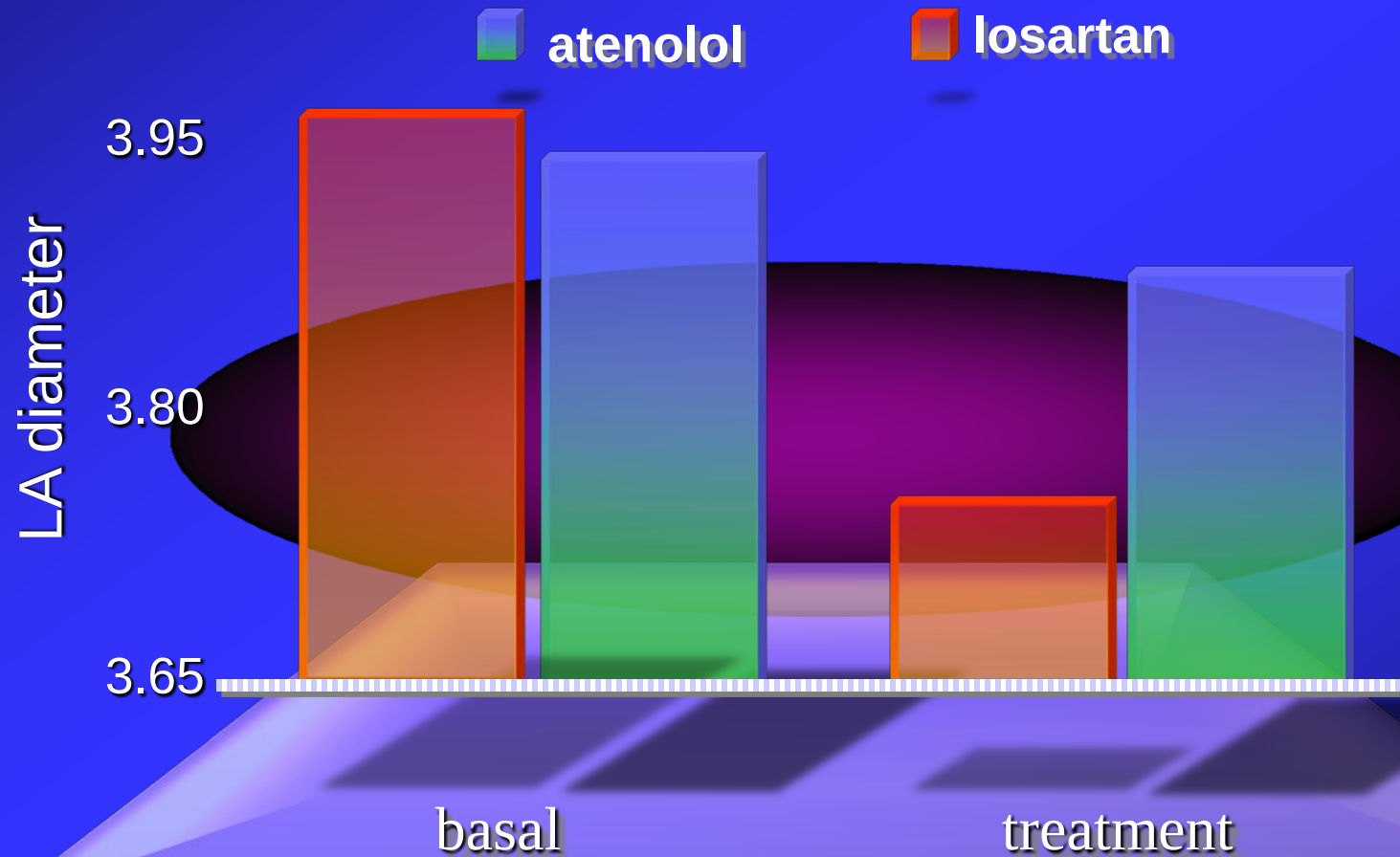
After (CVF = 3.29 %)



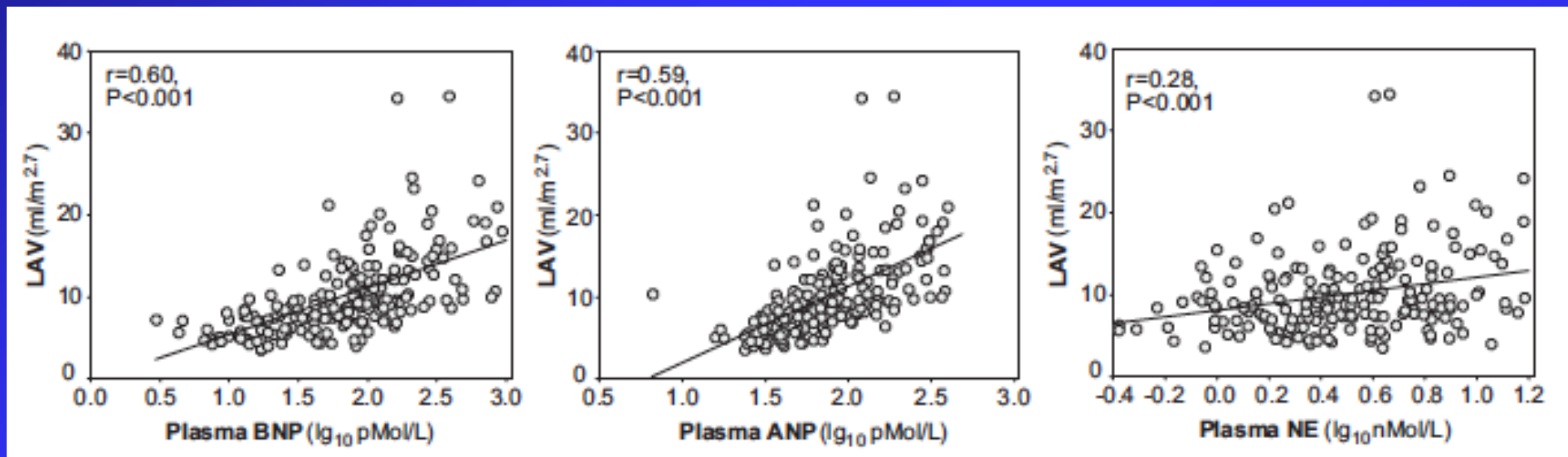
CVF= % of Collagen Volume Fraction

LIFE: left atrial diameter

(Wachtell, JACC 2005)

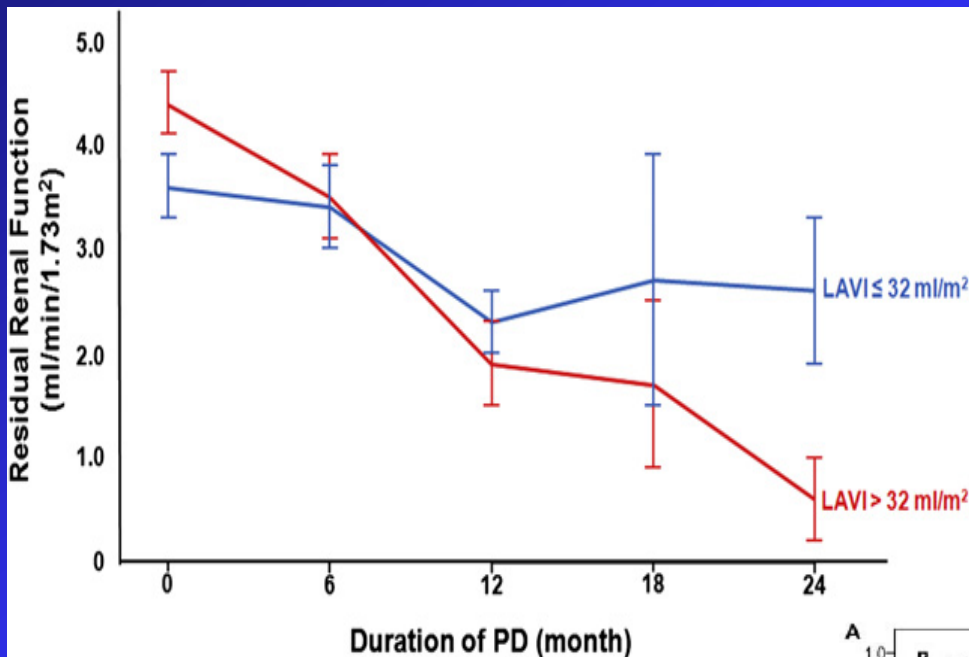


Biomarkers of left atrial volume in ESRD



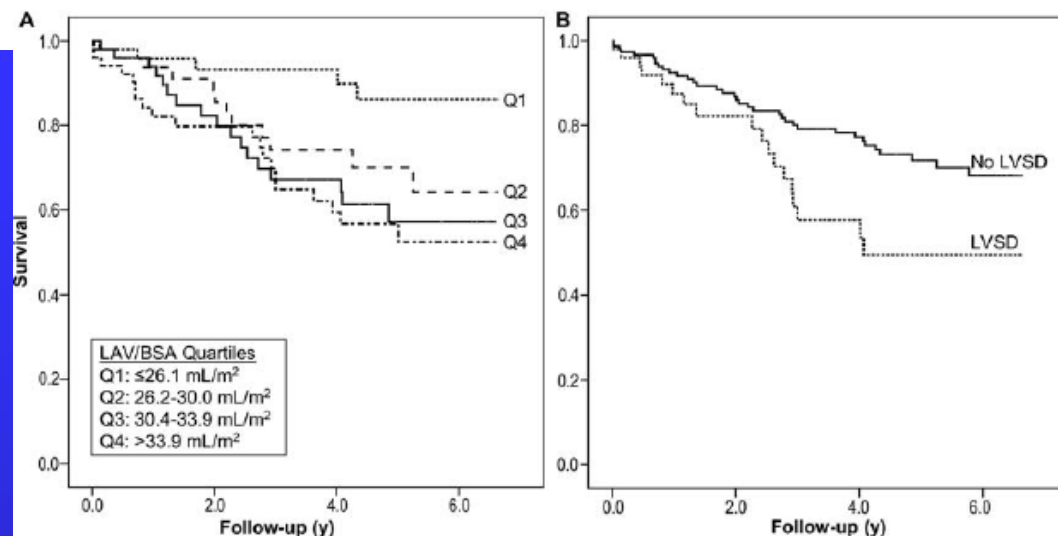
Tripepi G et al Hypertension 2009;54:818-24

Relation between left atrial dilation and CKD



Patel RK et al Am J Kidney Dis 2012

Kim SJ Am Soc Echocardiogr 2012;25:421-7



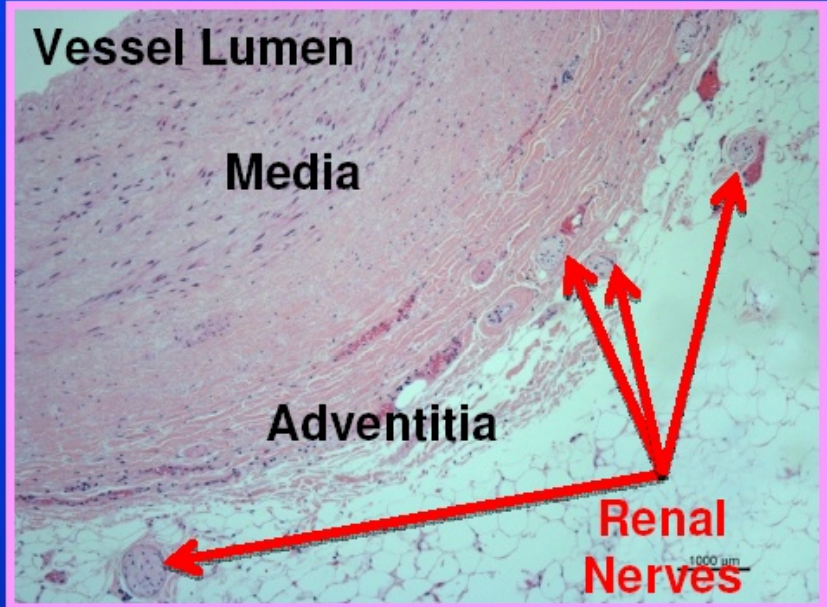
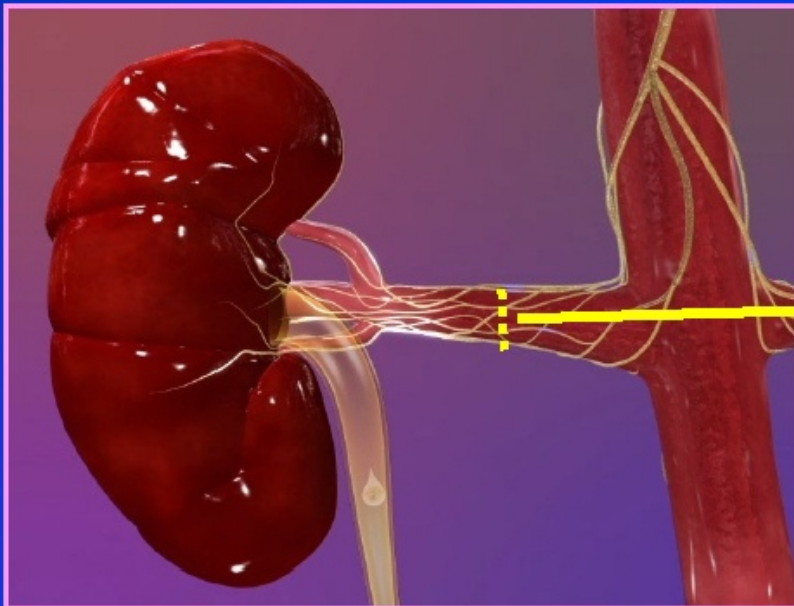
Innovations in Cardiovascular Interventions ICI 2009,
Tel Aviv, Israel, Dec 6-8, 2009

Radiofrequency Ablation of the Renal Arteries for Treatment of Severe Hypertension: A New treatment Concept

Sievert H, Id D, Wunderlich N, Krum H, Schlaich M, Whitbourn
R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A,
Thambar S, Abraham WT, Esler M
CardioVascular Center Frankfurt
Frankfurt, Germany

The Renal Nerves

- Arise from T10- L1
- Follow the renal artery to the kidney
- Primarily lie within the adventitia



Therapeutic renal denervation of native kidney in ESRD

Baseline

MSNA: 46 burst/min
BP: 155/95 mmHg



3 Month Follow-up

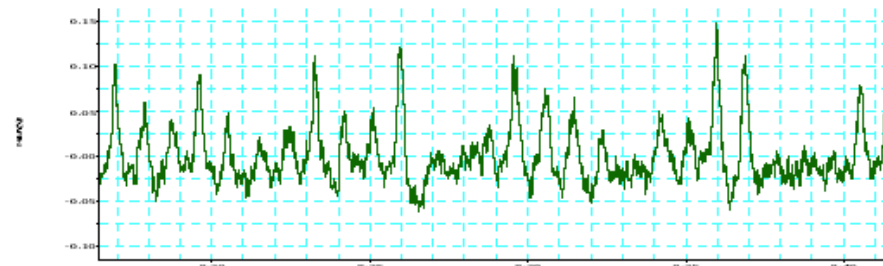
MSNA: 33 burst/min (↓~30%)
BP: 133/78 mmHg (↓22/17 mmHg)



12 Month Follow-up

MSNA: 21 burst/min (↓~54%)
BP: 132/75 mmHg (↓23/20 mmHg)

baseline MSNA: 46 burst/min



3 Months FU MSNA: 33 burst/min

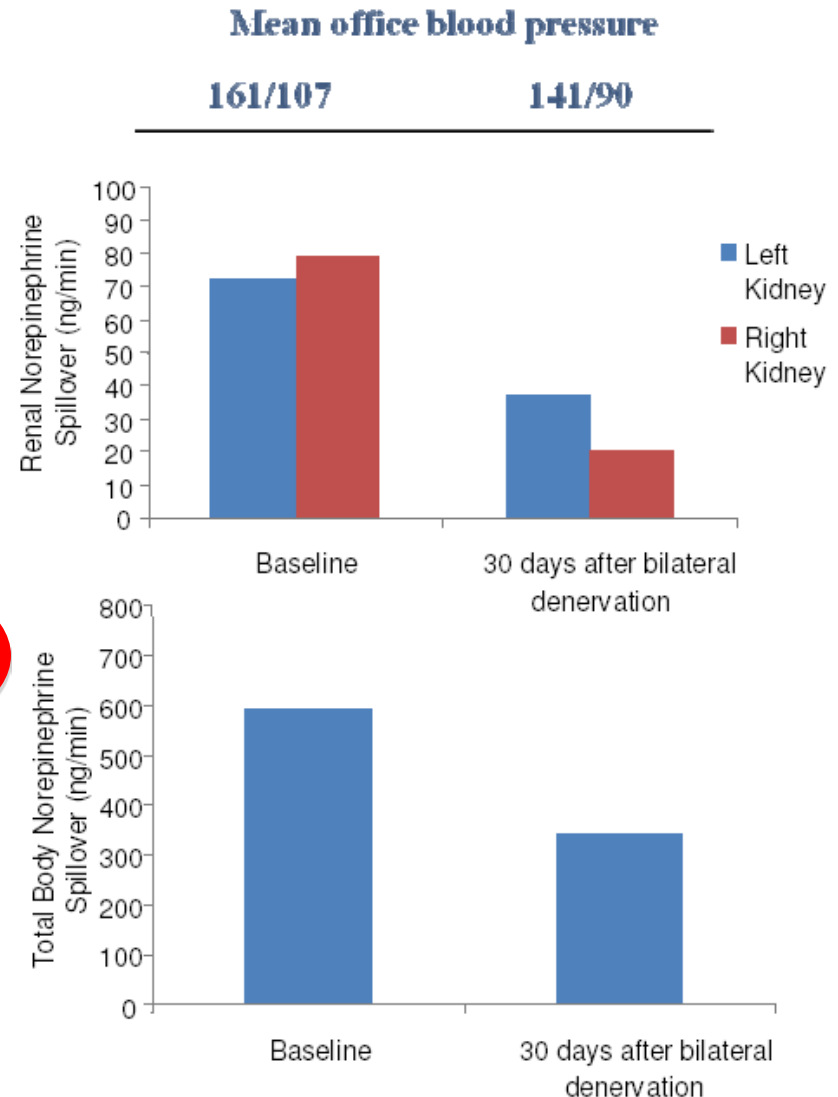


12 Months FU MSNA: 21 burst/min



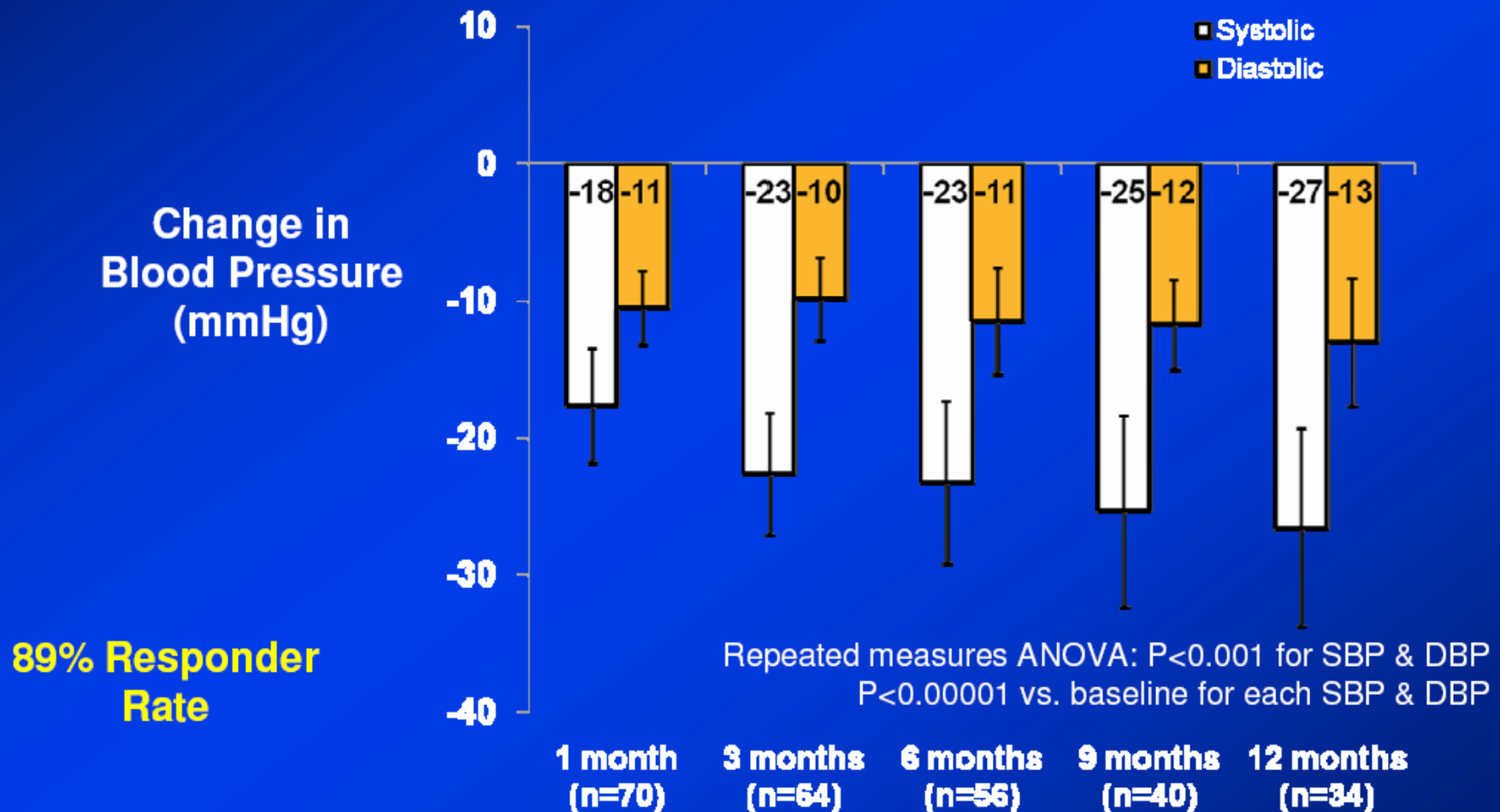
Renal Sympathetic Nerve Ablation for Uncontrolled Hypertension: NEJM Case

- Reduction of Plasma Renin Activity
 - 0.3mcg/l/hr to 0.15 mcg/l/hr
- Increase in Total Renal Plasma Flow
 - 719 ml/min to 1126 ml/min
- Reduction of Renal Norepinephrine Spillover
 - 48% left kidney, 75% right kidney
- Reduction of Total Body Norepinephrine Spillover
 - 42%
- Reduction of Left Ventricular Mass by MRI at 12 months
 - 184g to 169g (78.8g/m² to 73.1g/m²)
- Sustained Reduction in Blood Pressure
 - 161/107 mmHg at baseline
 - 141/90 mmHg at 1 mo
 - 127/81 mmHg at 12 mo (with 2 anti-hypertensive medications removed)



Blood Pressure Response

Full Experience



Symplicity HTN-1: Late Results

Changes in Blood Pressure After Renal Denervation

	2 Years (n =114)	3 Years (n = 34)
Δ Systolic (mm Hg)	- 32.7 ± 18.4	- 33.1 ± 13.3

Patients with office-based SBP ≥ 160 mm Hg despite ≥ 3 antihypertensive drugs (including 1 diuretic) or ≥ 150 mm Hg and type 2 diabetes (34%)

Of patients with < 10 mm Hg drop in SBP at 1 month 64%, 82%, and 100% responded with SBP drop > 10 mm Hg at 1, 2, and 3 years, respectively.

1 progression of a pre-existing renal artery stenosis

RDN HF Prevention - Management

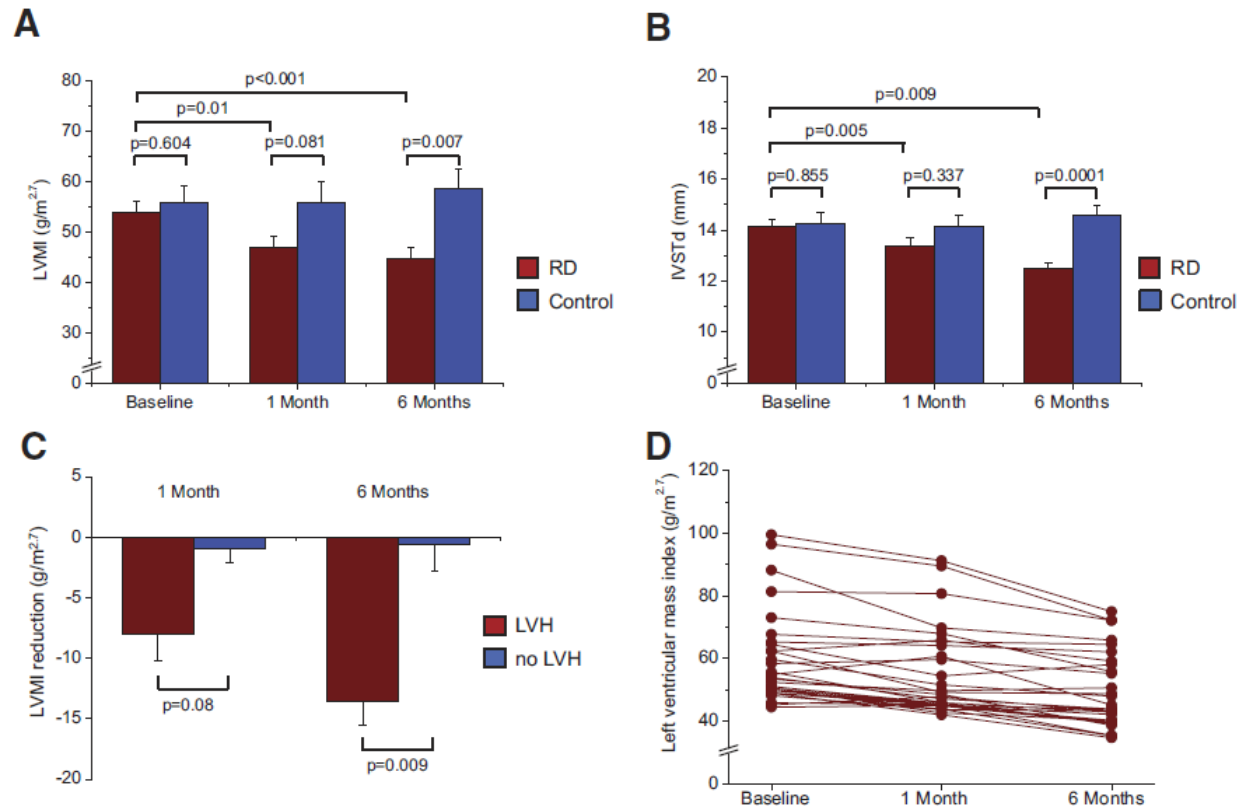


Figure 2 Impact of RDN on LV Mass

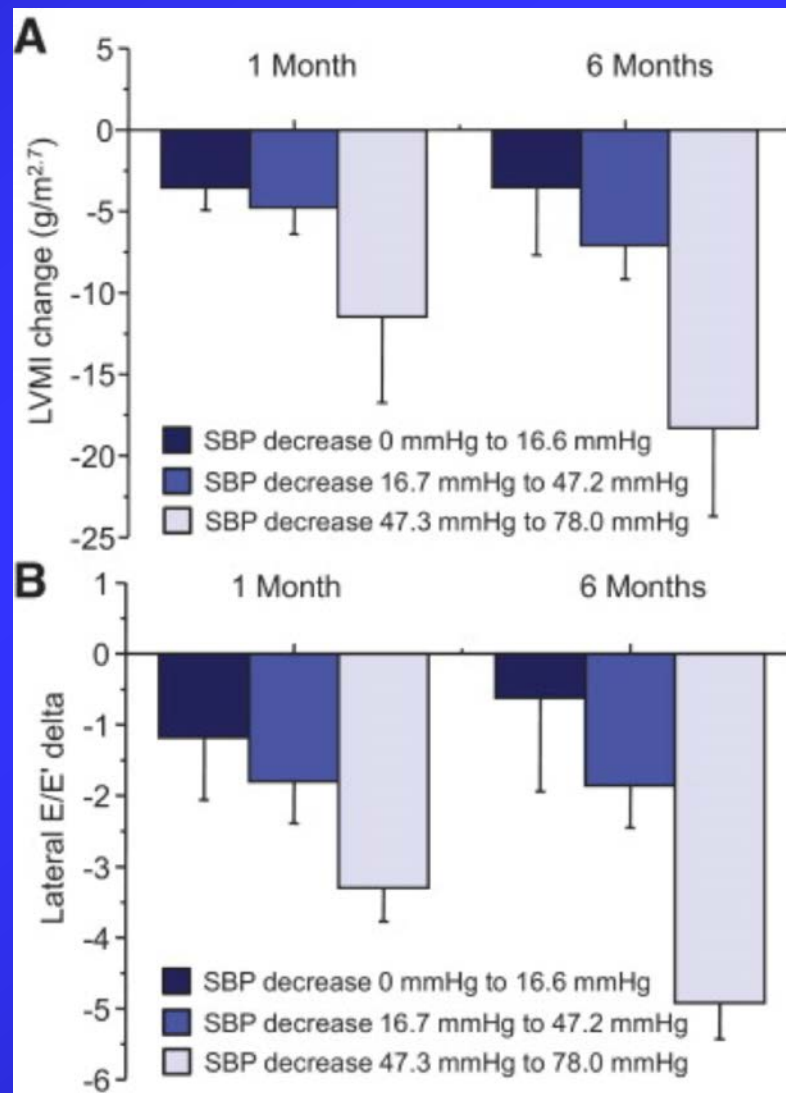
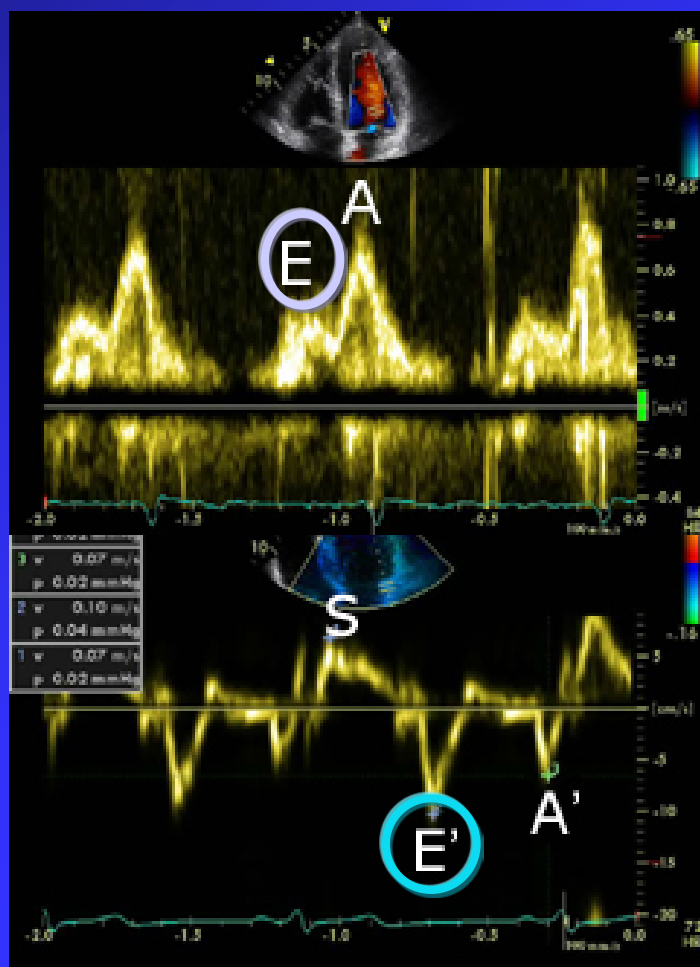
(A) Left ventricular (LV) mass/height^{2.7} and (B) end-diastolic interventricular septum thickness (IVSTd) measured in renal sympathetic denervation (RD) and control patients at baseline, 1 month, and 6 months. While there was a steady decrease in the average left ventricular (LV) mass and IVSTd after RD, these parameters slightly increased in control patients. In the treatment group, p for statistical trend was p = 0.004 for LV mass/height^{2.7} (A), p = 0.007 for IVSTd (B). (C) Differential effect of RD on LV mass regression depends on the degree of left ventricular hypertrophy (LVH) at baseline. LV mass/height^{2.7} regression by RD was significantly greater in those patients with LVH at baseline. Values are presented as mean ± standard error. (D) Regression of LV mass after RD in individual patients with a LVH at baseline (n = 29). LVMI = left ventricular mass index.

RDN, IMPACT on DIASTOLE

E/E'

E, peak early diastolic filling velocity

E' , lateral mitral annulus velocity

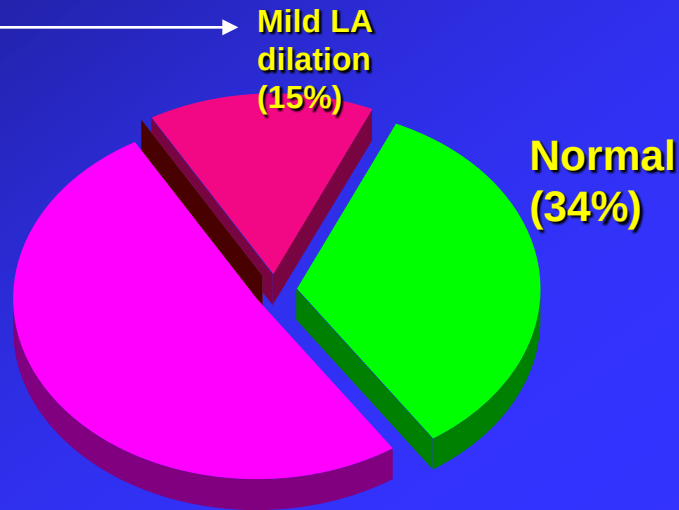


HFpEF

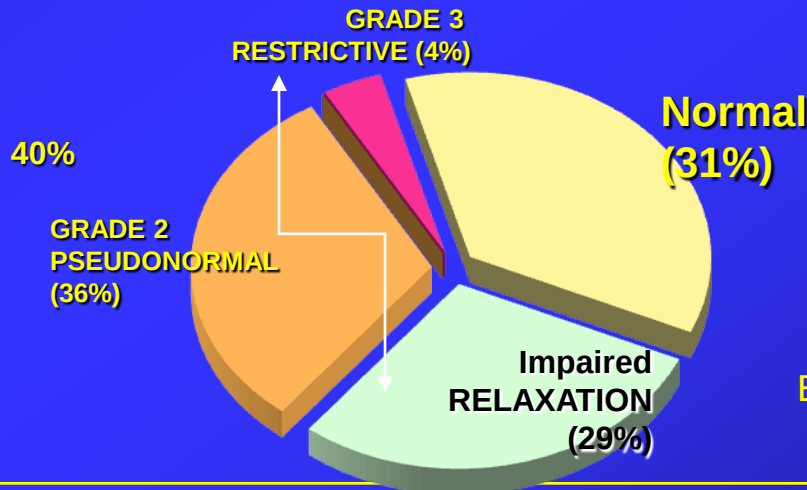
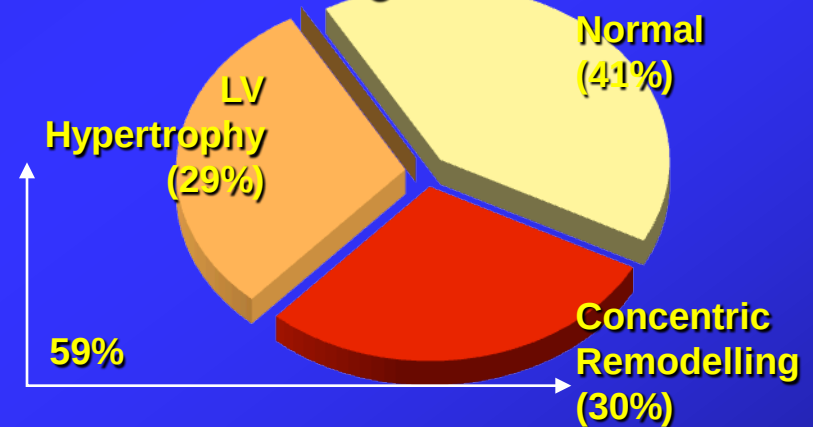
Functional and Structural Changes

(I-PRESERVE Study - ECHO assessment # 745 pts)

Left Atrial Size

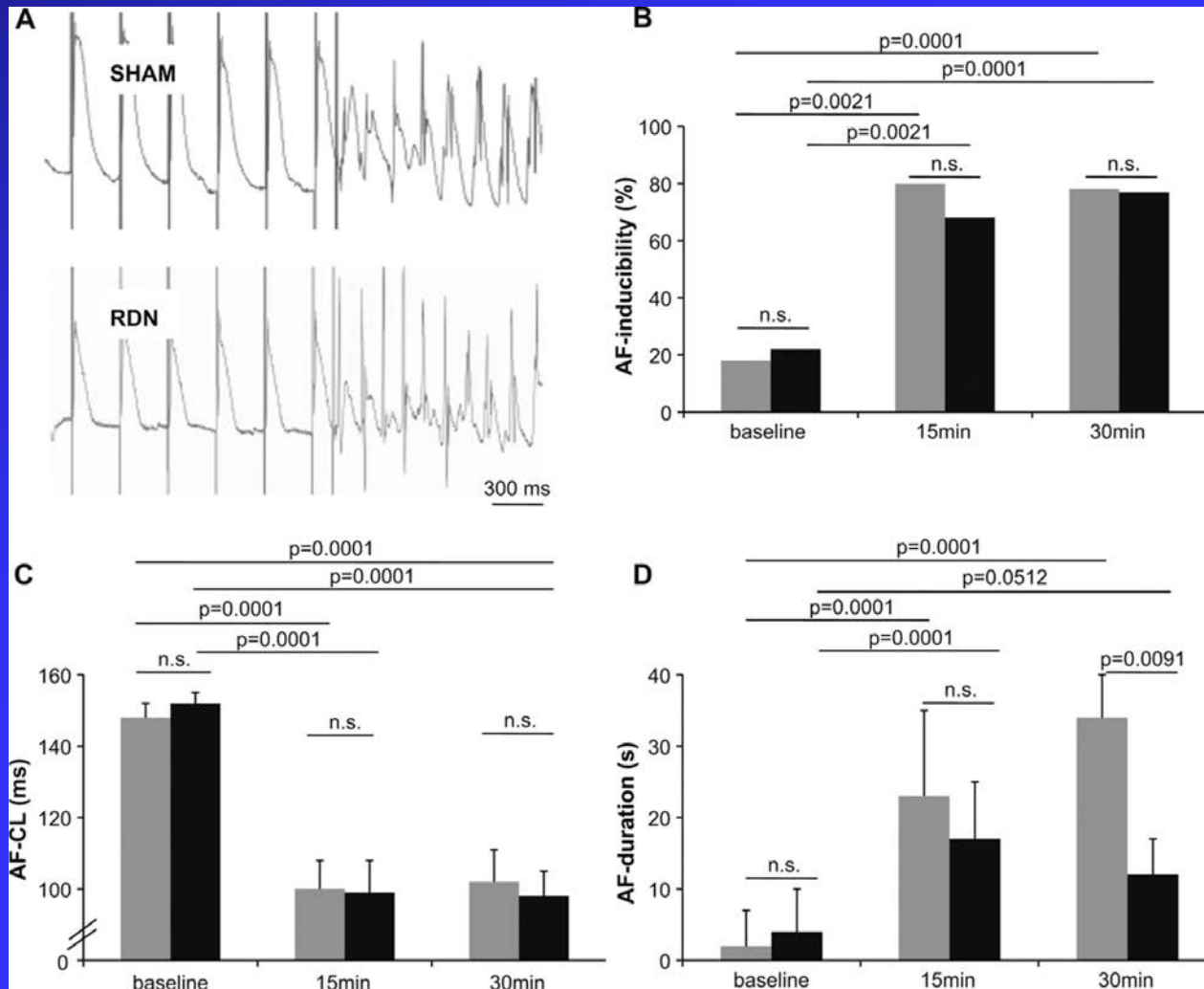


L&V Concentric Remodeling



HFpEF Cohort - Normal range
E/E' lateral $10,0 \pm 4,2$ 4,5-11,5

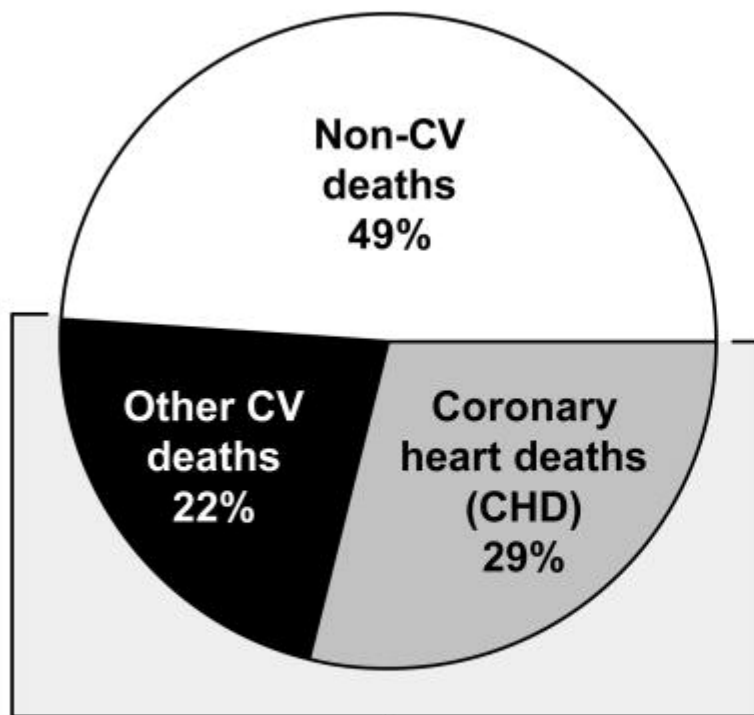
Electrophysiological effects of renal denervation (RDN) on atrial fibrillation (AF).



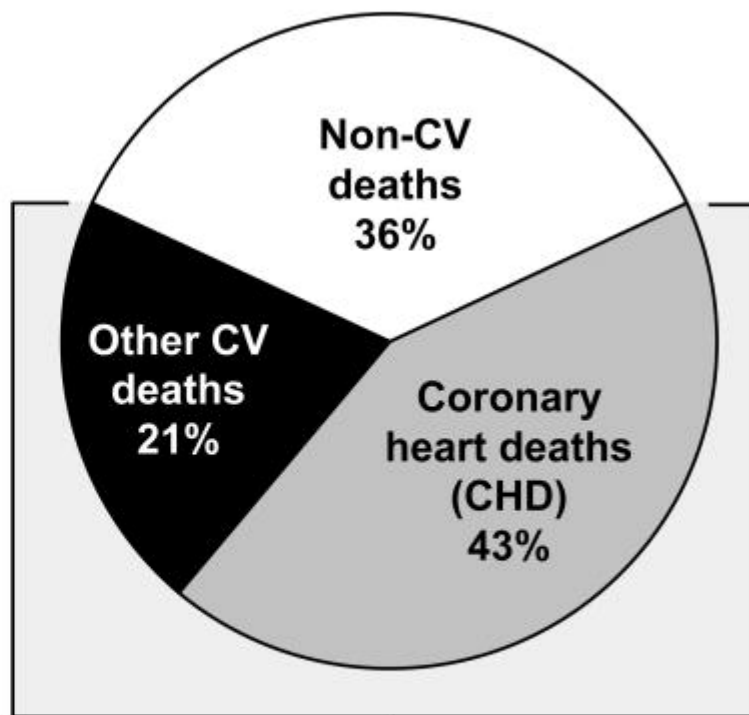
Linz D et al. Hypertension 2013;61:225-231

Cause of death in HF population

Preserved Ejection Fraction



Reduced Ejection Fraction



Cardiovascular deaths

I PRESERVE (#4128 pts) - Baseline Characteristics of Patients Who Died of Non CV Versus CV Causes and Sudden Death Versus HF Mortality (I)

	Non-CV (n268)	CV (n532)	P	SD (n231)	HF (n125)	P
Mean age y	75±8	74±7	0.036	74±7	76±7	0.028
Anemia, n (%)	66 (26)	96 (18)	0.019	48 (21)	24 (20)	0.89
Diastolic Pressure mmHg	77±10	78±9	0.106	78±8	75±9	0.008
NT-proBNP, pg/mL Median	787	986	0.016	924	1244	0.071

I PRESERVE (#4128 pts) - Baseline Characteristics of Patients Who Died of Non CV Versus CV Causes and Sudden Death Versus HF Mortality (II)

	Non-CV (n268)	CV (n532)	P	SD (n231)	HF (n125)	P
History of A Fib (%) 	105 (39)	221 (42)	0.543	86 (37)	63 (50)	0.018
A Fib/FI (%) 	63 (24)	131 (25)	0.793	48 (21)	44 (35)	0.004
eGFR <60 mL min 1.73 m2 	63±23 129 (50)	67±23 214 (41)	0.033 0.018	70±24 81 (35)	62±22 67 (55)	0.002 0.001

Ziles M et al Circulation 2010;121:1393-1405

Conclusion

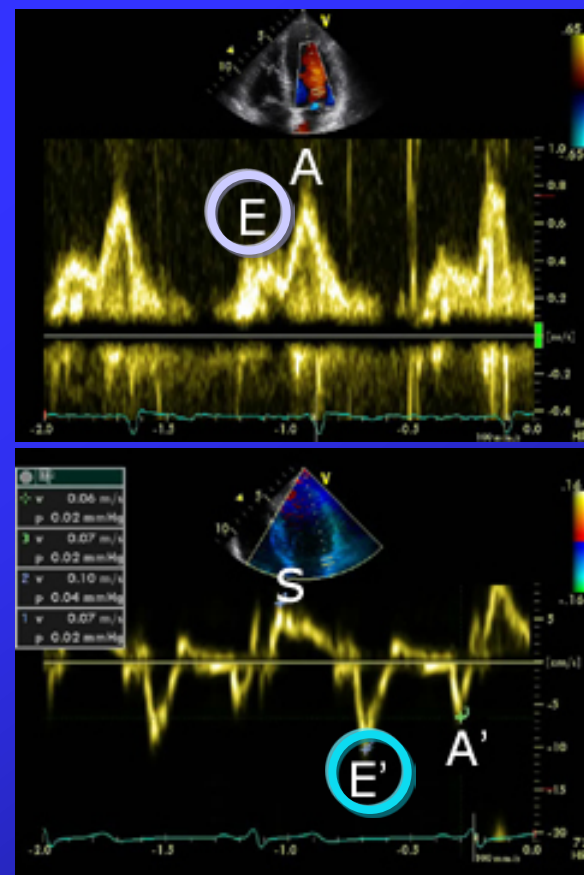
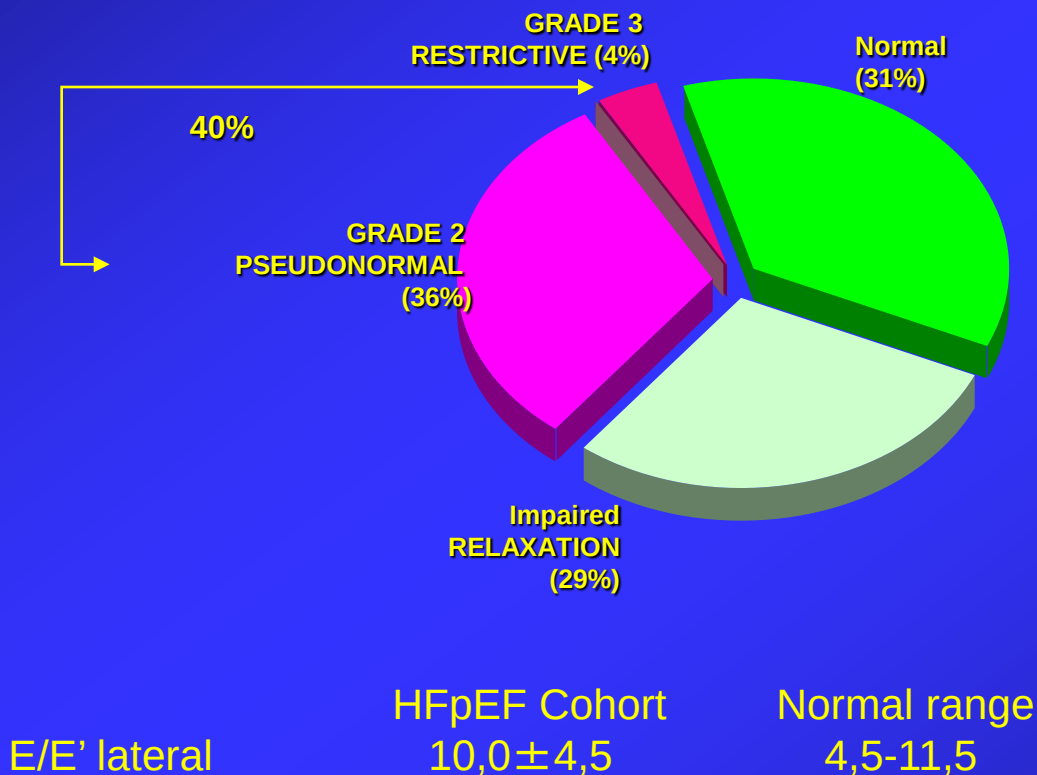
- By reviewed data it's possible to argue that :
 - 1.Atrial function is physiologically related to heart rythm and performace, as well as to circulatory volume control via neural (sympathetic and vagal) and neuro-hormonal (ANP) connections with kidney.
 - 2.Kidney is a source and a target of neural activation mediated by atrial connection.
 - 3.Atrial size and kidney function are tightly related to cardiovascular prognosis.
 - 4.By tapering cardiovascular sympathetic tone, renal denervation can effectively decrease atrial propensity to arrhythmia reducing myocardium damage and heart rate when atrial fibrillation occurs.
 - 5.This mechanistic effect may translate in clinical benefit for long term prognosis.

Prevalenza e Significato delle Alterazioni Strutturali e Funzionali Presenti nel Cuore dei Soggetti con HFpEF

(valutazione ecocardiografica in 745 paz. dello studio I-PRESERVE)

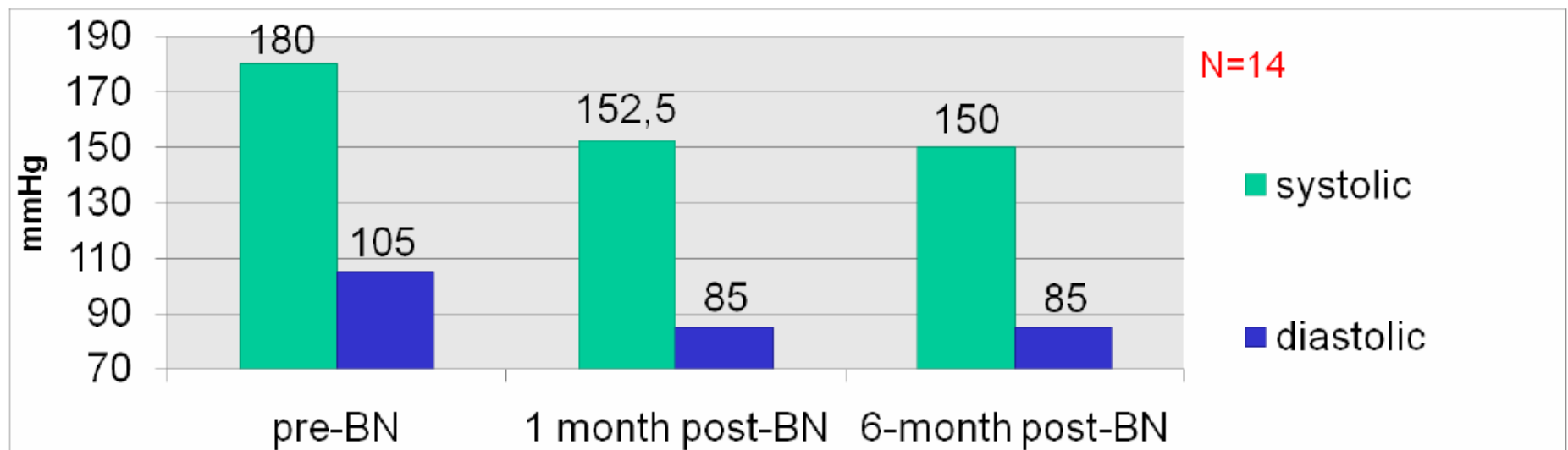
Diastolic Function

E/E'
 E , peak early diastolic filling velocity
 E' , lateral mitral annulus velocity



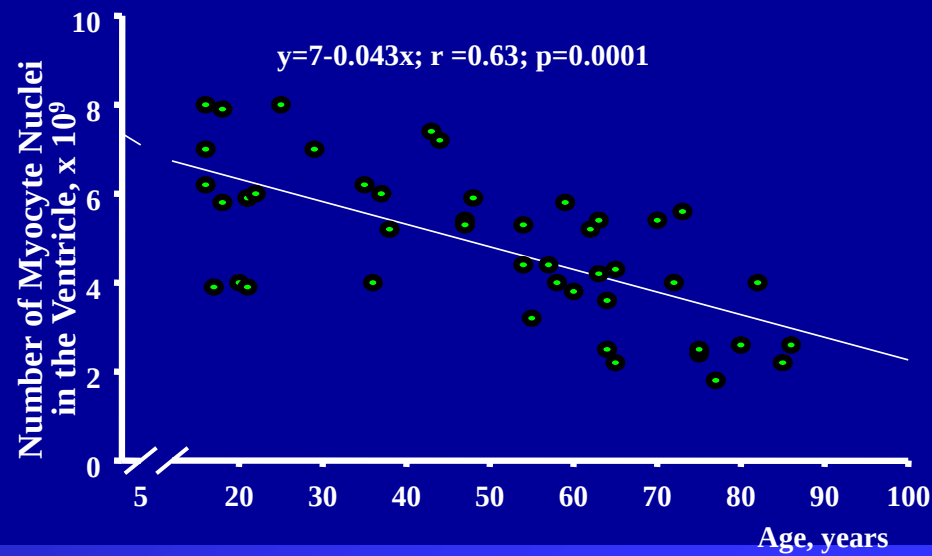
Bilateral nephrectomy for the treatment of hypertension after renal transplantation

- 14 patients underwent laparoscopic bilateral nephrectomy (BN)
- All patients showed well controlled blood pressure on an decreased antihypertensive drug regime
- Results indicates that bilateral nephrectomy can be an effective alternative method for a selected group of patients with hypertension



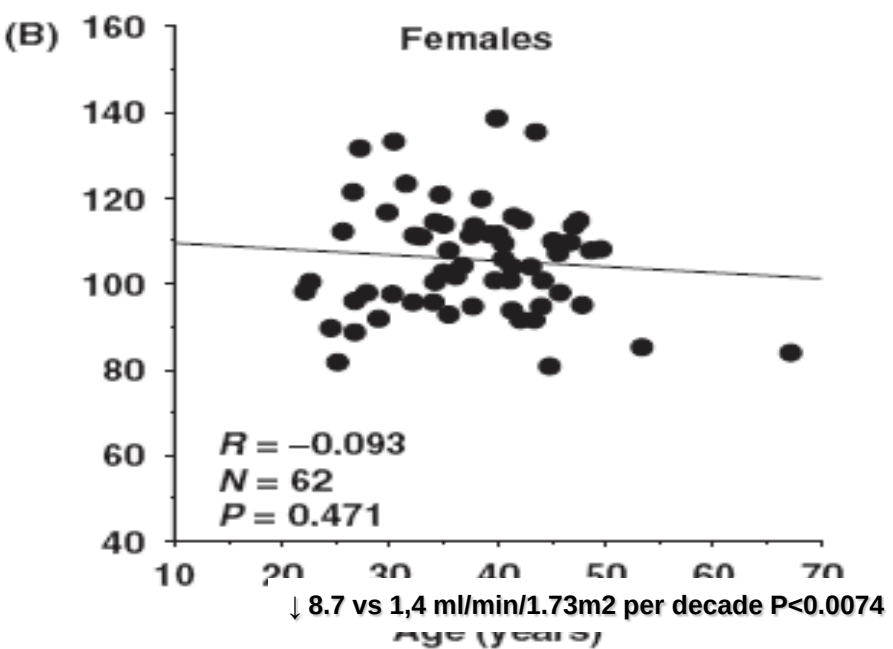
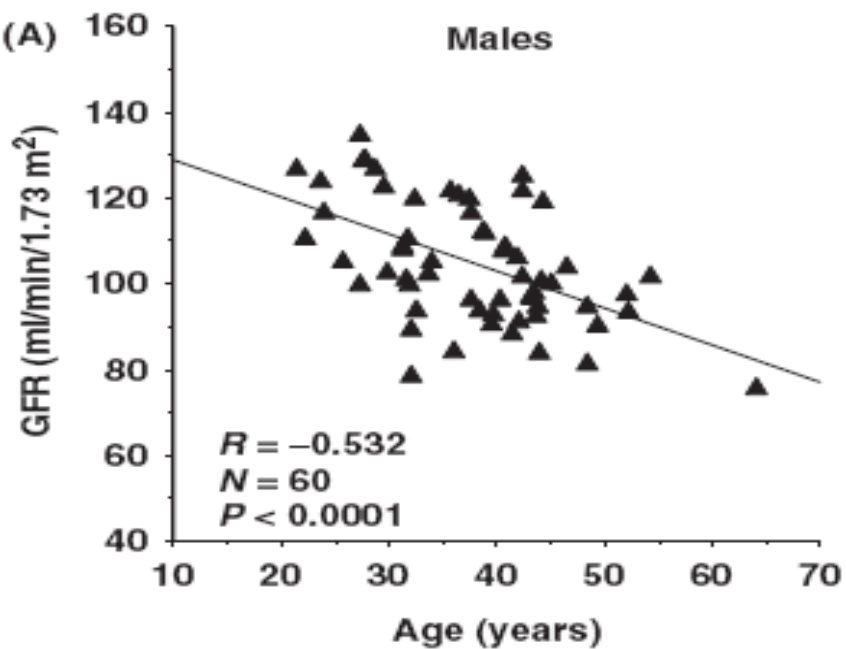
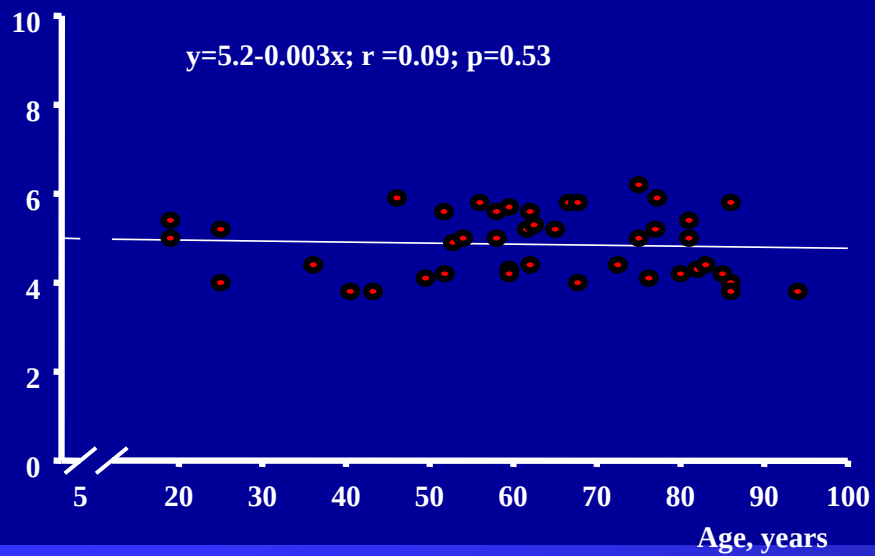
Effect of Age on the **Number** of Left Ventricular Myocytes . **JACC 1995; 26: 1073**

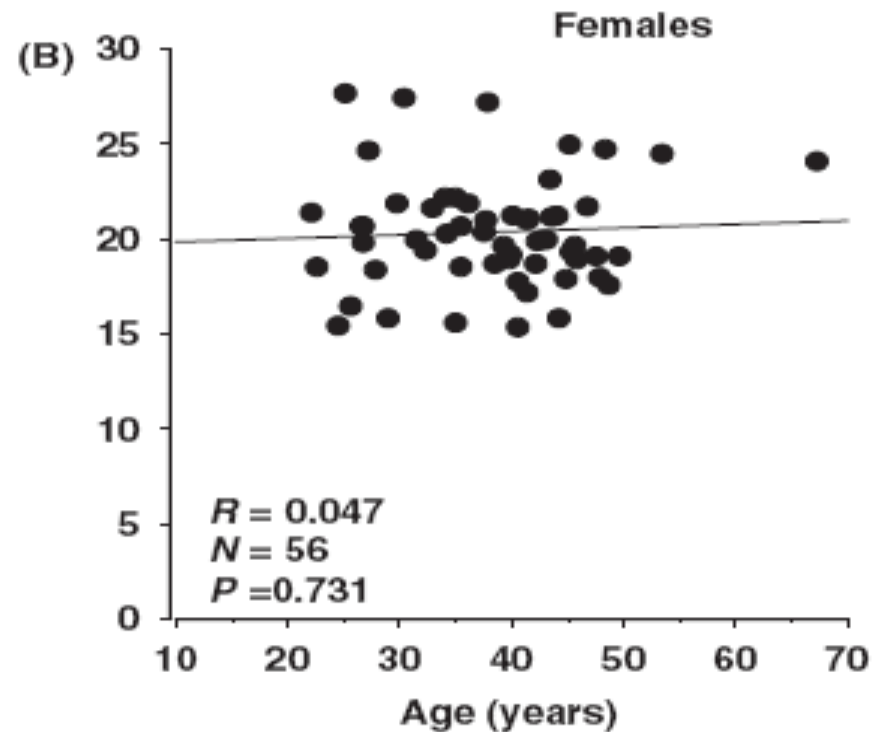
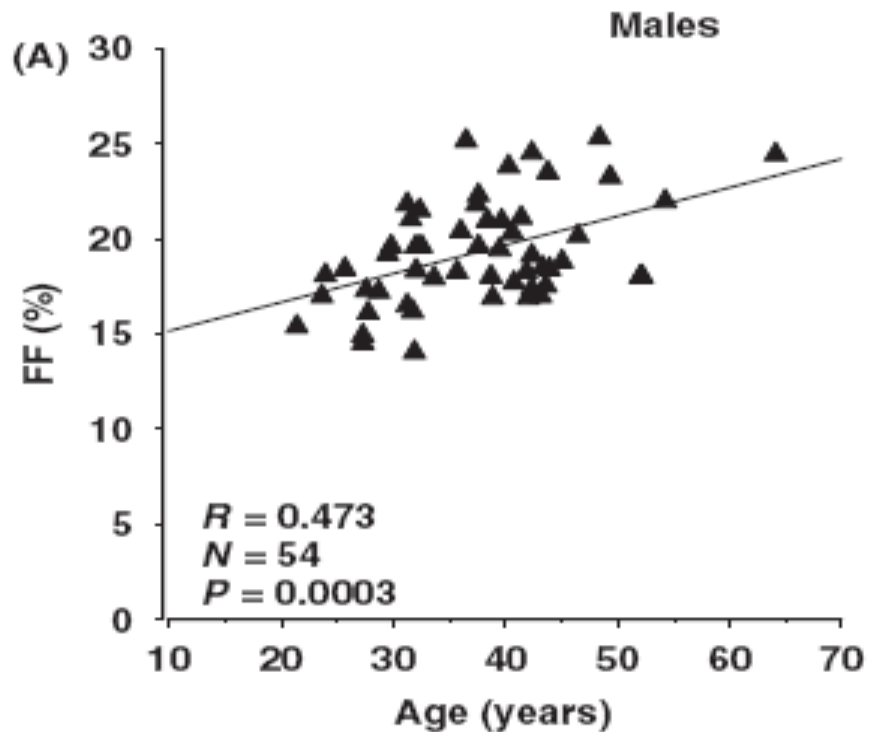
Men



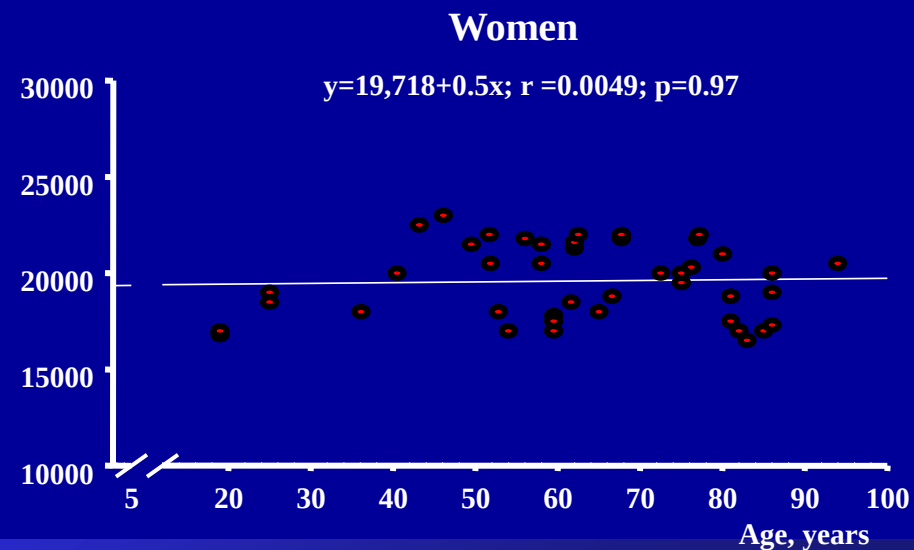
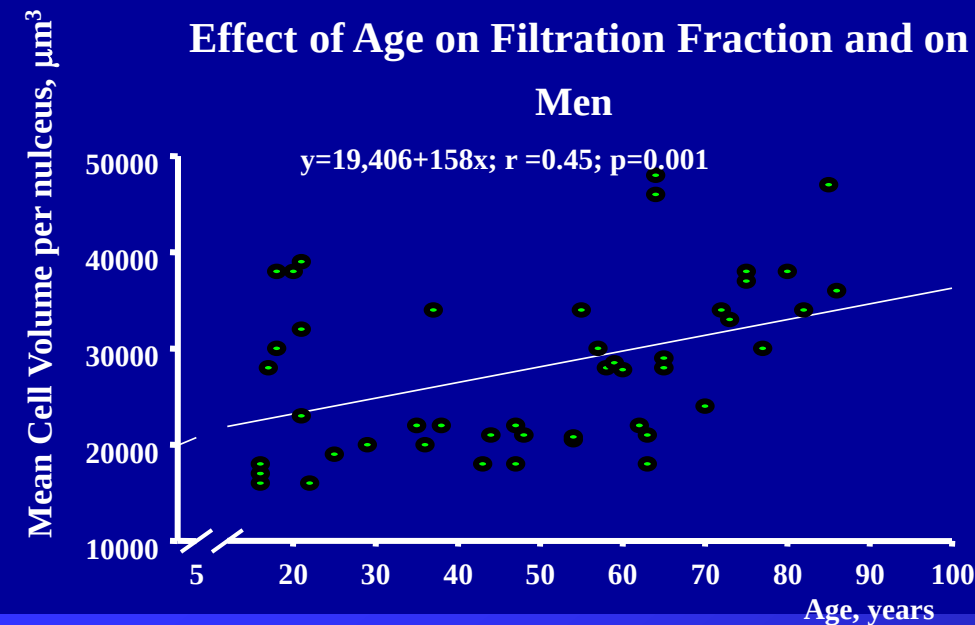
Decline in GFR with age in genders Nephrol Dial Transplant (2006) 21: 2577-2582)

Women

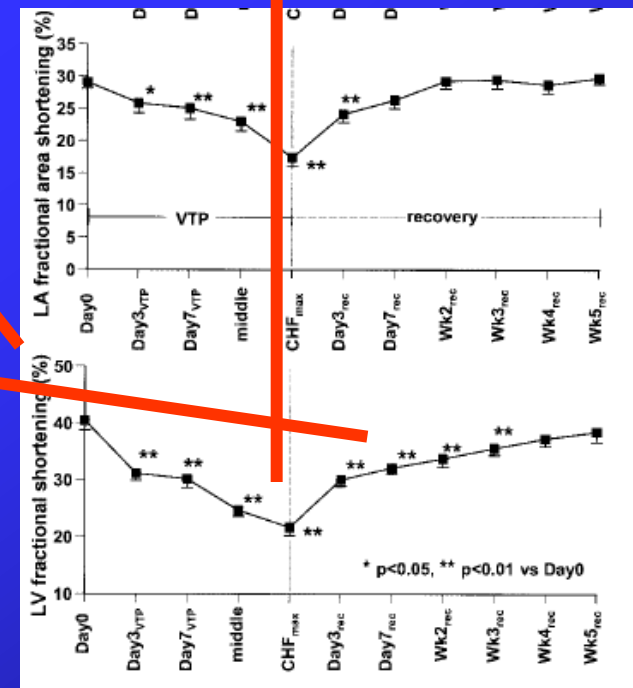
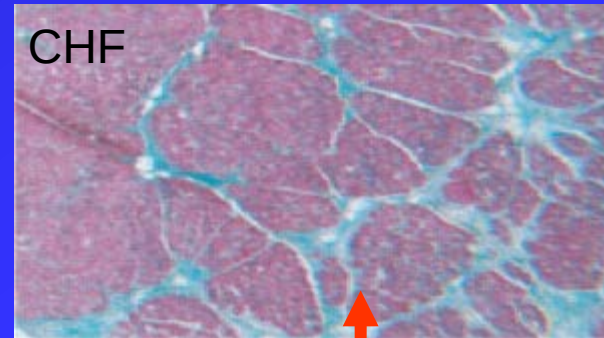




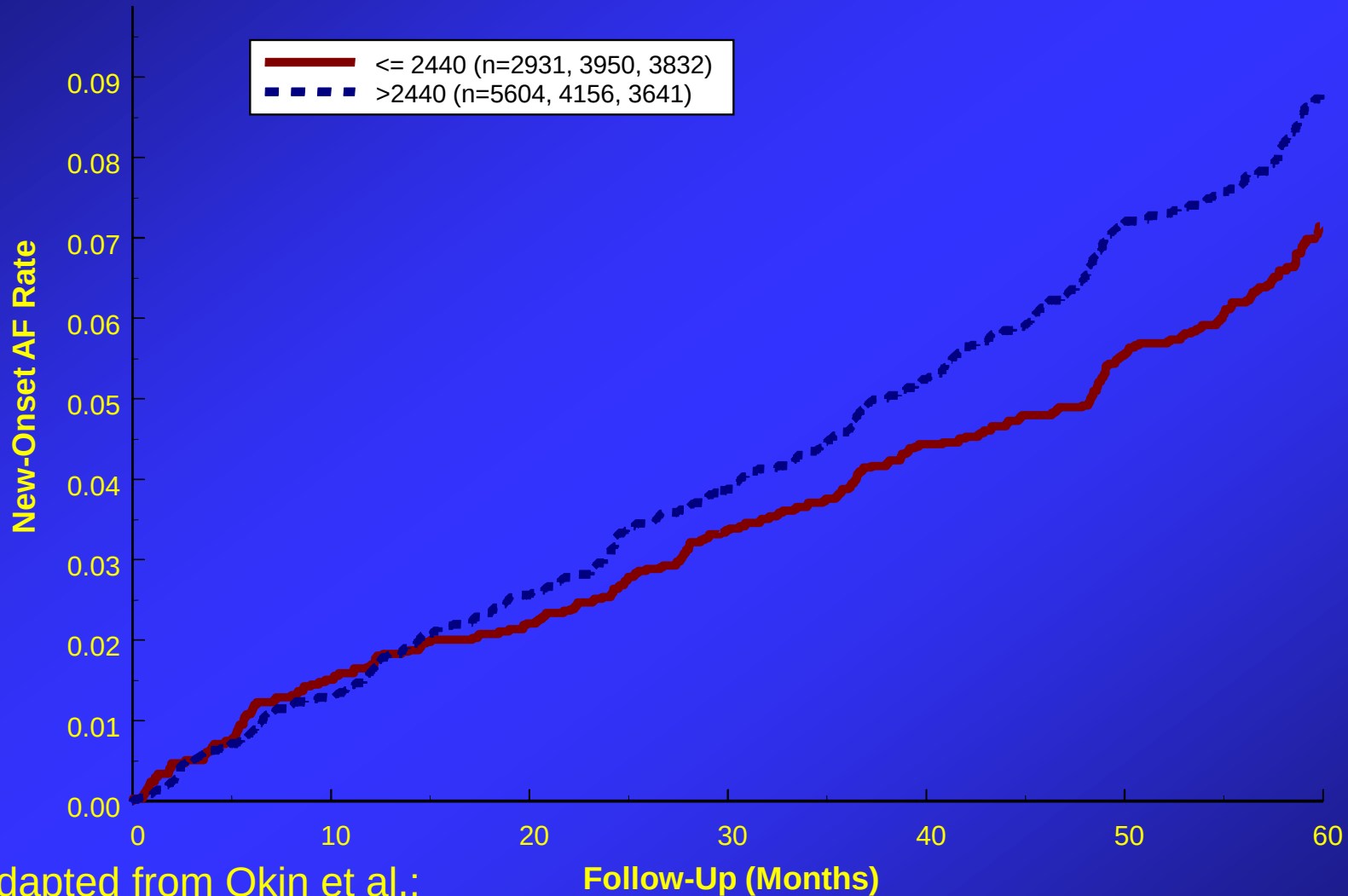
Effect of Age on Filtration Fraction and on Left Ventricular Myocyte Volume



ATRIAL HISTOLOGY IN HF + AF



New Onset of AF According to the Presence or Absence of ECG LVH by Time-Varying Cornell Voltage-Duration Product

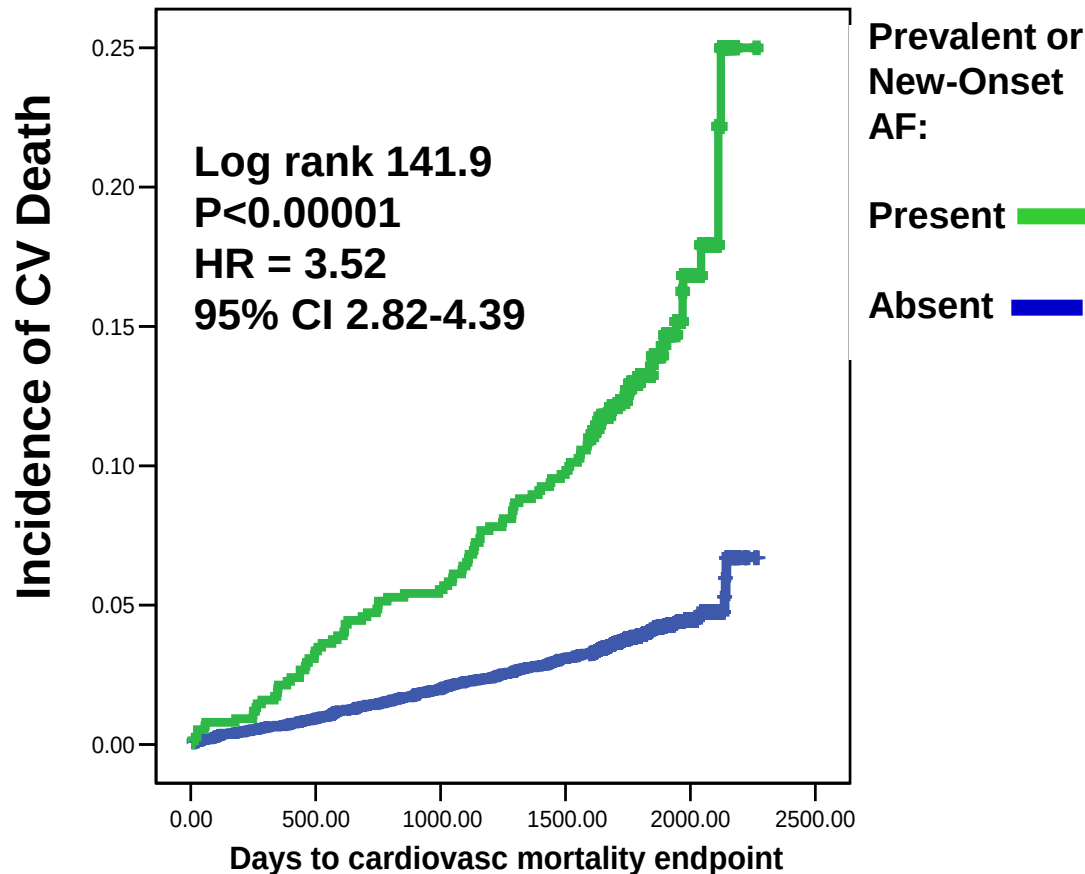


Adapted from Okin et al.:
JAMA 2006;296:1242-1248.

* n= number of patients in each group at baseline, 2 and 4 years of LIFE

LIFE Atrial Fibrillation: Prevalent or New Onset AF Associated with 3.5-fold higher CV Death

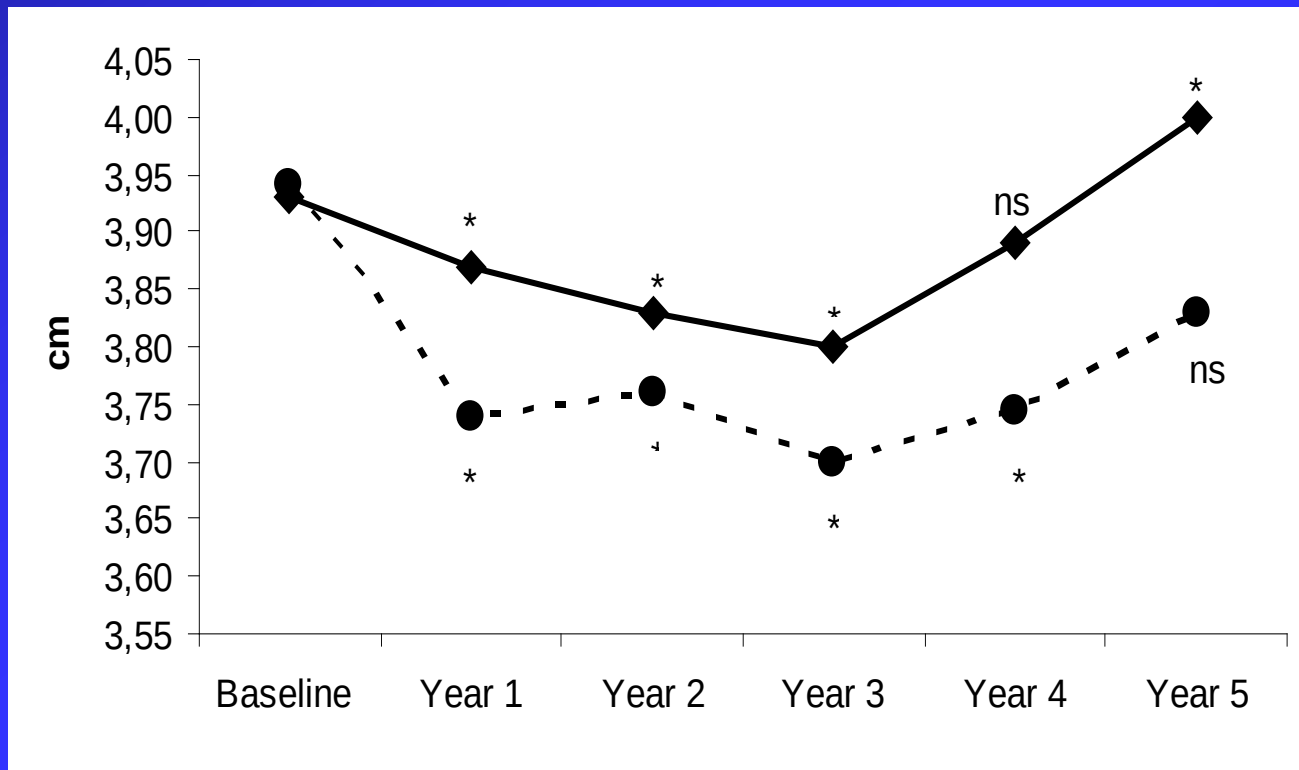
Devereux
et al. 2006



LIFE **Echo**: Losartan-Based Treatment Reduces Left Atrial Size Independently of Covariates

P<0.001, independent of baseline LA diameter, ethnicity, and time-varying LV mass, LV ejection fraction, systolic blood pressure and heart rate, and new-onset atrial fibrillation and mitral regurgitation.

Left Atrial Diameter (cm)



Years in LIFE

Sympathetic Overactivity in Chronic Renal Failure

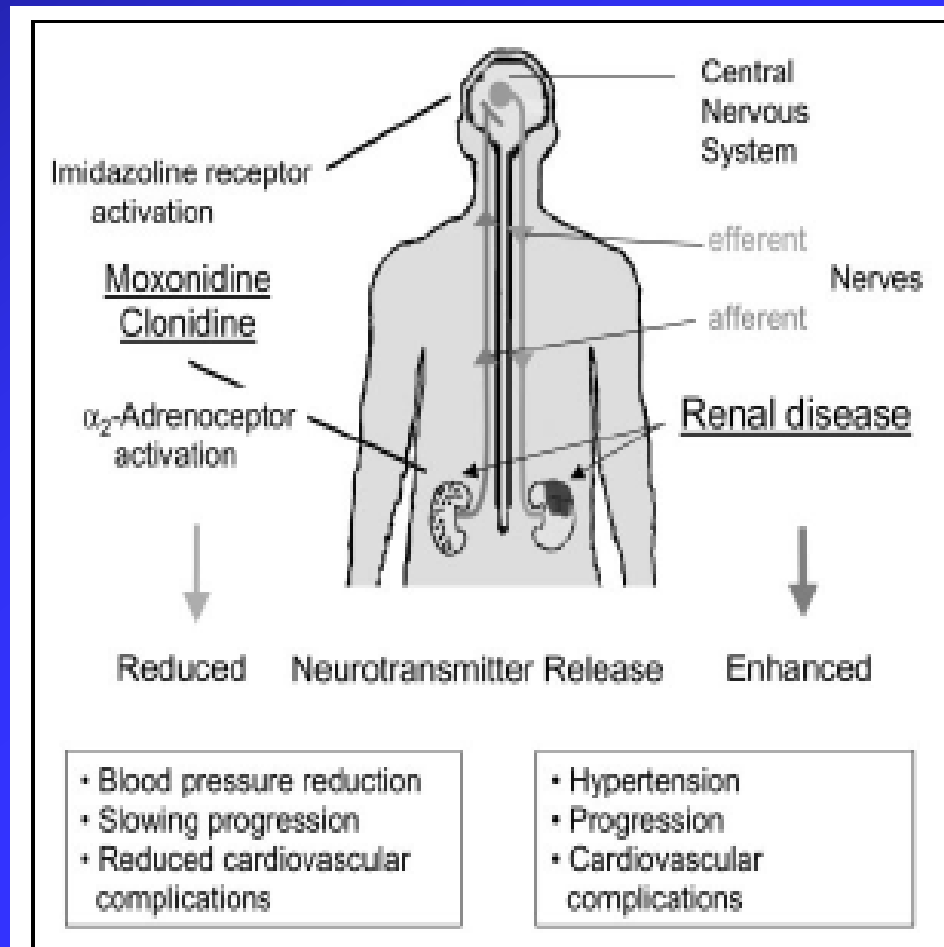
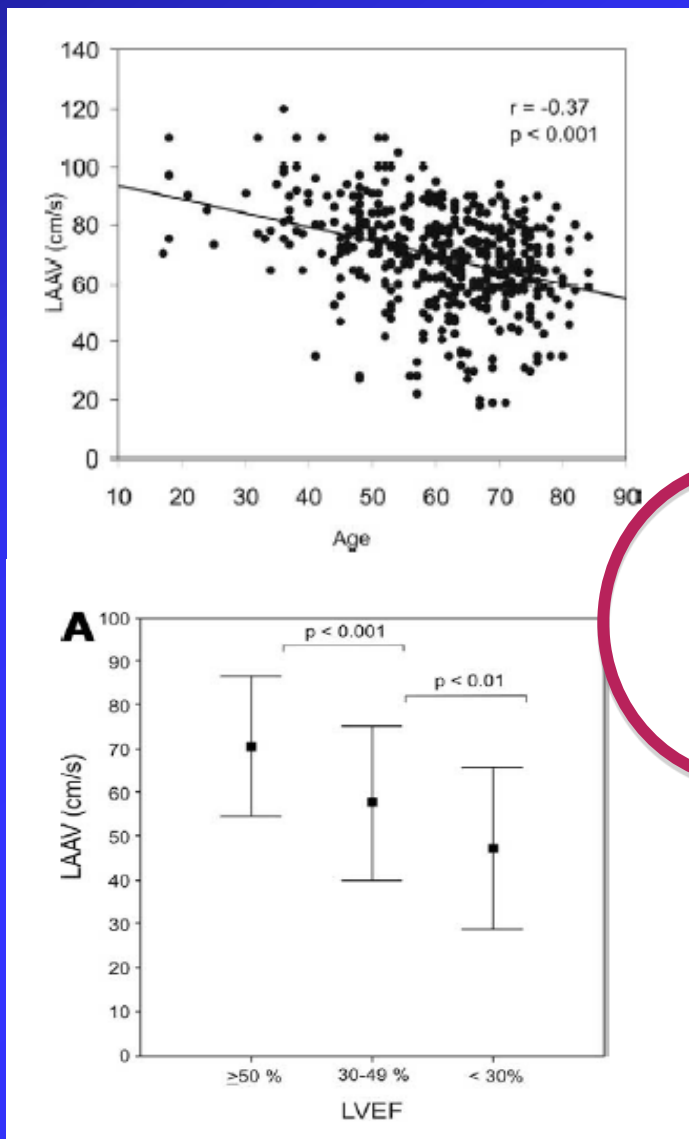
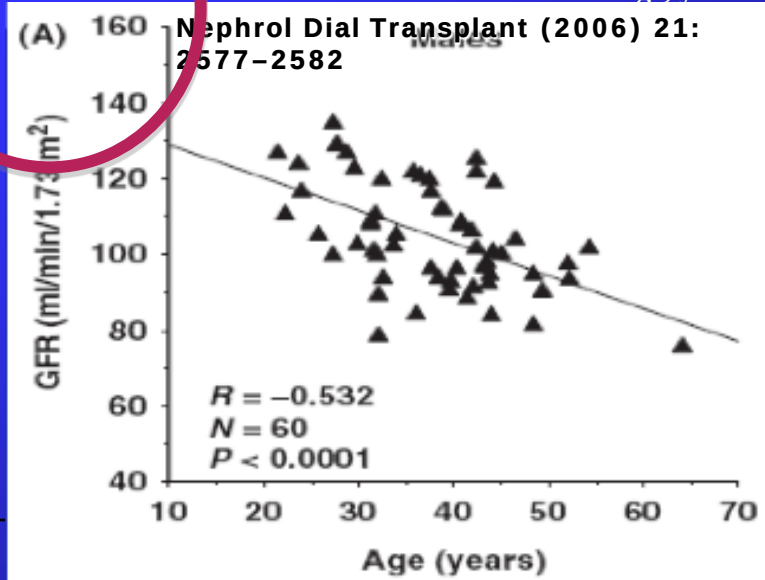
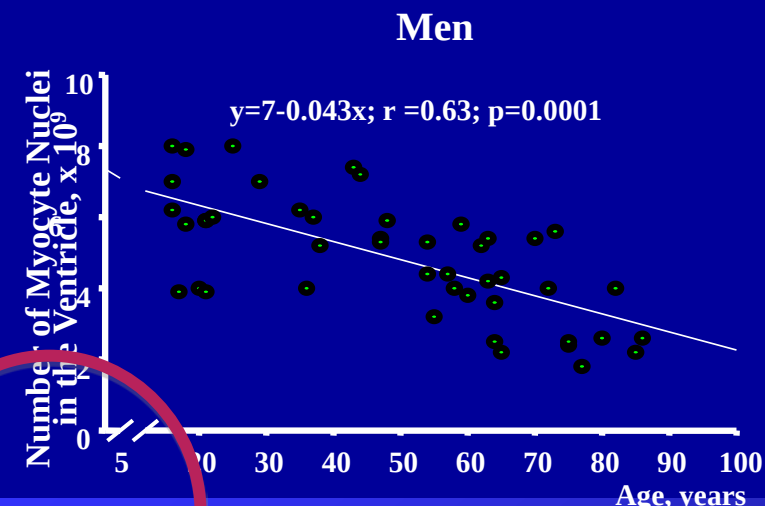


Figure 2. Synopsis of sympathetic activation in chronic renal disease and its inhibition by sympatholytic drugs

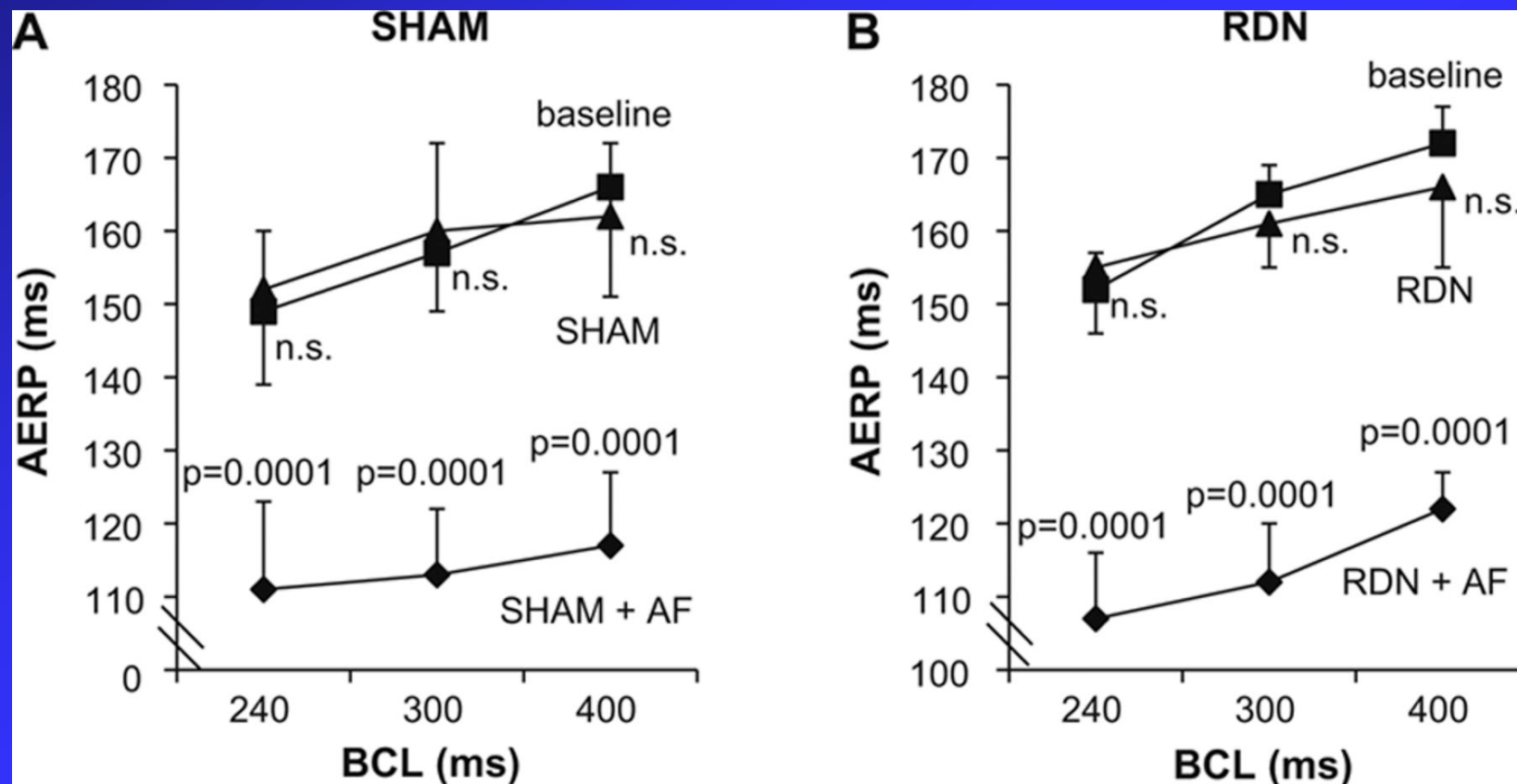
Left Atrial Appendage Flow Velocity as a Quantitative Surrogate Parameter for Thromboembolic Risk (# 500 pts with stroke)



JACC 1995; 26: 1073



Effect of renal denervation (RDN) and sham operation on atrial refractoriness and on atrial tachypacing-induced atrial effective refractory period (AERP) shortening.



Linz D et al. Hypertension 2013;61:225-231