THE HEART AND HYPERTENSION

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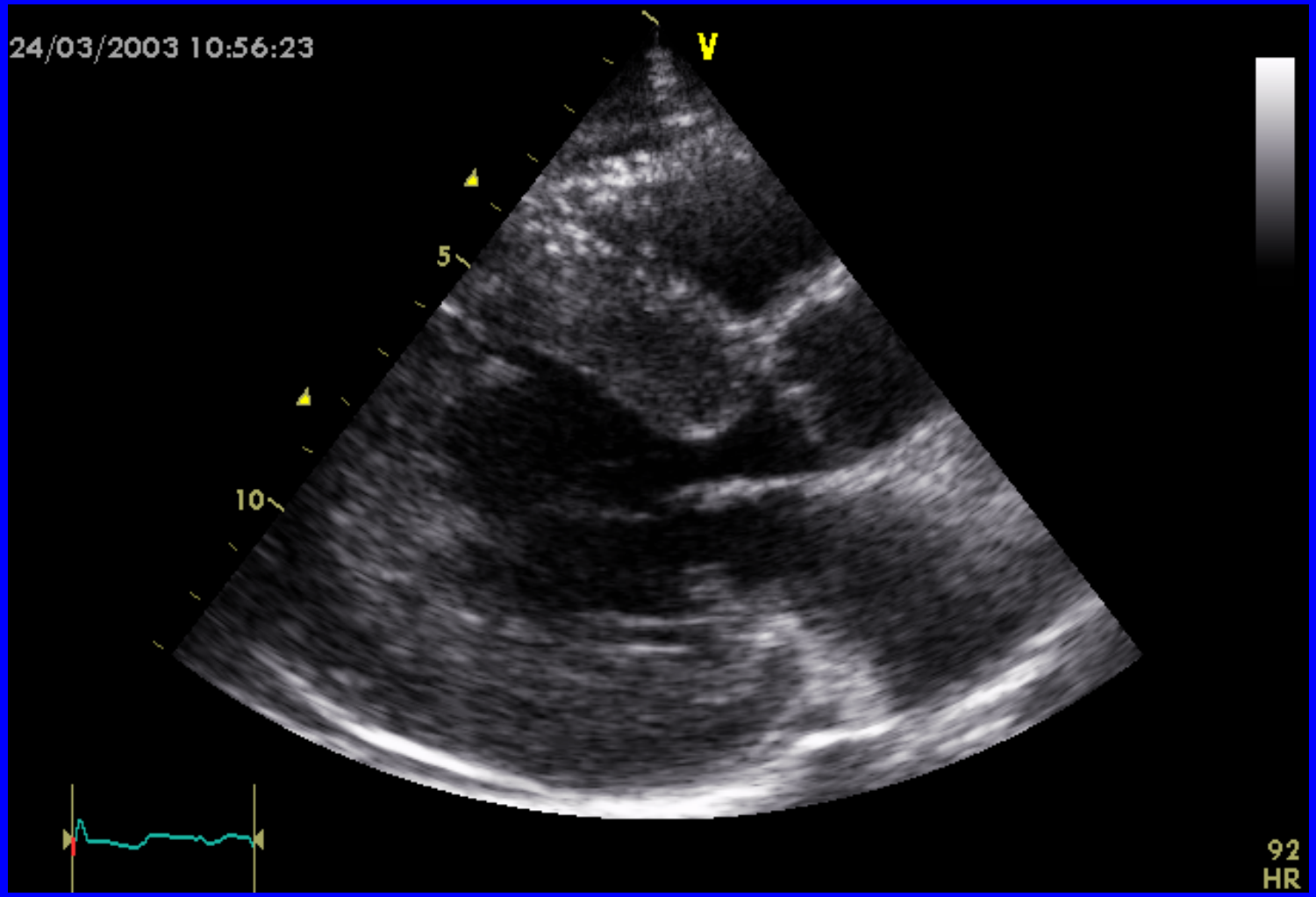
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V
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HR

INCREASED LVM

- Cardiomyocytes hypertrophy is a response to pressure overload
- This response is influenced by many factors and genes
- It has long been viewed as an adaptative process to normalize wall stress and restore heart muscle economy. But this view is now seriously challenged
- Increased LVM is not muscle only

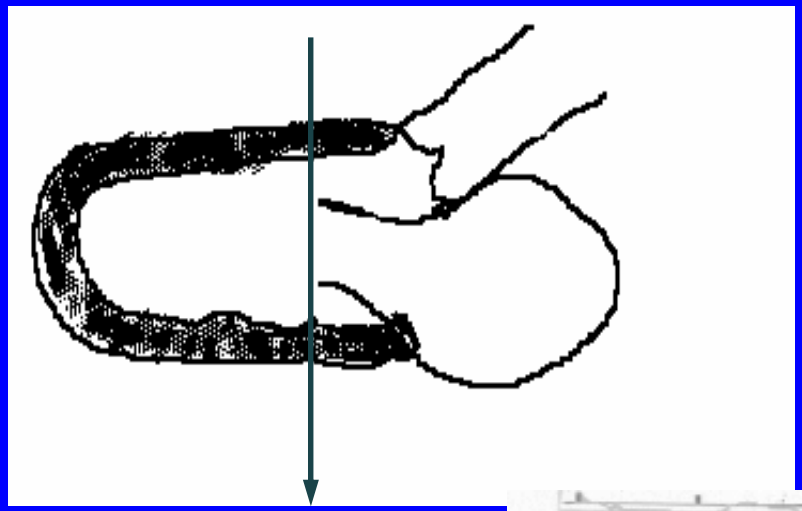
INCREASED LVM

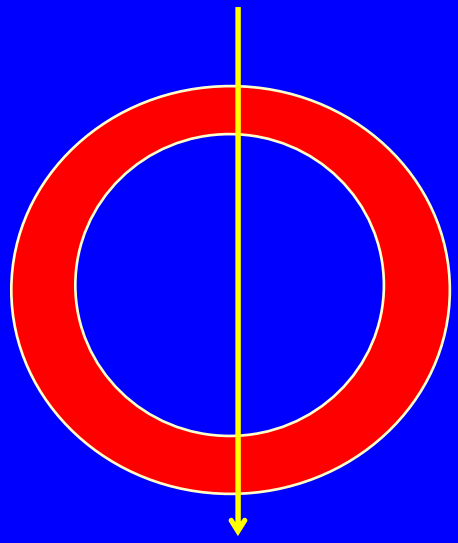
- HYPERTROPHY
  - Requires mechanical stress
  - Modulated by non mechanical factors
    - Hormones
    - Salt
    - Genes
  - May show regression within weeks
- FIBROSIS (>6%, up to 30%)
  - Independent of mechanical stress
  - Influence of
    - AII
    - Aldosterone
    - ?
  - Regression may require months

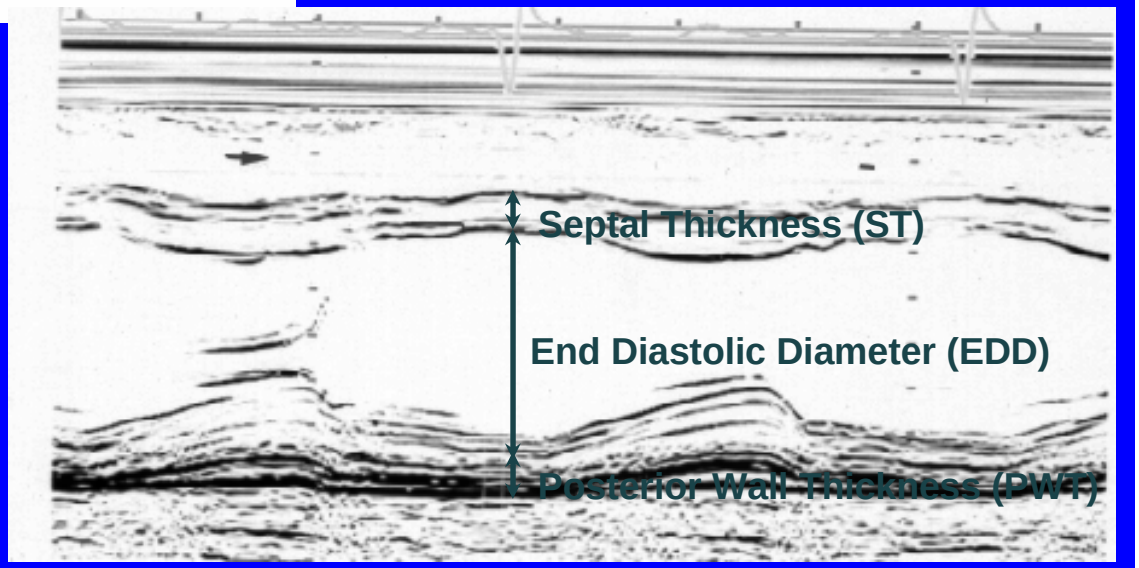
LVH DIAGNOSIS

- ECG
  - Voltage
    - Sokolow: Sv1+Rv5 or Rv6 > 35(8) mm
    - Cornell: RavL + Sv3 + 8 mm(F)> 28
  - Cornell Voltage*QRS duration >2440
  - *Repolarization abnormalities*
- ECHO
  - M mode
  - 2D, 3D
- Magnetic Resonance Imaging
- BNP?

2D guided M Mode recording of LV parasternal view

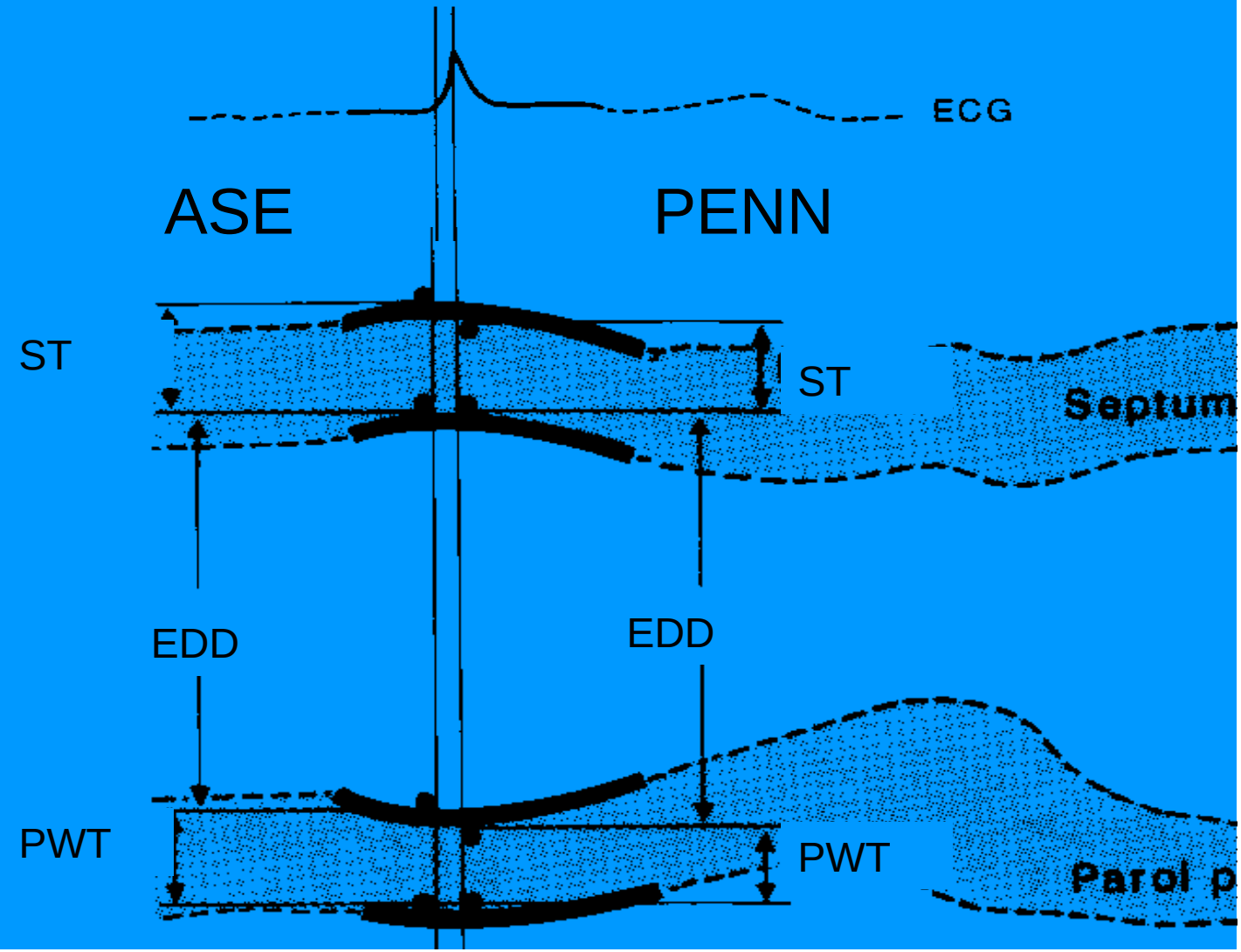






AVOID:
Oblique recording
Recording of «non wall structures»

HOW TO READ M MODE RECORDINGS?



LIMITS LINKED TO GEOMETRY HYPOTHESIS

$$\mathbf{LVM=1.04((EDD+ST+PWT)^3-EDD^3)-13.6}$$

- WALL MOTION ABNORMALITIES
- ASYMETRIC HYPERTROPHY
- LV DILATATION
  - do not calculate if EDD>60mm

REPRODUCIBILITY

AUTHOR	POPULATION	Mean DIFF.	SDD	CV
GOSSE	Misc	30g	40g	15.6%
1983	20			
DEVEREUX	Normal	26g	29g	
1984	89			
GOTTDIENER	HT	27g	27g	8.3%
1995	96			
GOSSE	HT	27g	32g	14.6%
1995	47			

LVH CUT OFF

- **INDEXATION FOR LVM**
  - **BSA**
  - **Height**
  - **Height$^{2.7}$**
- **Gender influence**
- **Influence of physical training?**
- **Cut off, usually based on 95th percentile in normal subjects**
  - **M:125-130 g/m^2, F:110g/m^2**
  - **M: 50 g/m$^{2.7}$, F:47 g/m$^{2.7}$**

CUTOFF For prediction of CVE

	CVE	cut off	Sens	Spé	AUC
BX cohort					
M+F (637)	95	52g/m$^{2.7}$	78%	51%	0.69
M (395)	70	55g/m$^{2.7}$	71%	53%	0.66
F (242)	25	47g/m$^{2.7}$	88%	51%	0.72
ARIC Black (57%HT) *Nunez, Hypertension 2005*					
M (570)+F (1046)	192	51g/m$^{2.7}$	53%	62%	

LVH PREVALENCE

Bordeaux cohort of never treated hypertensives

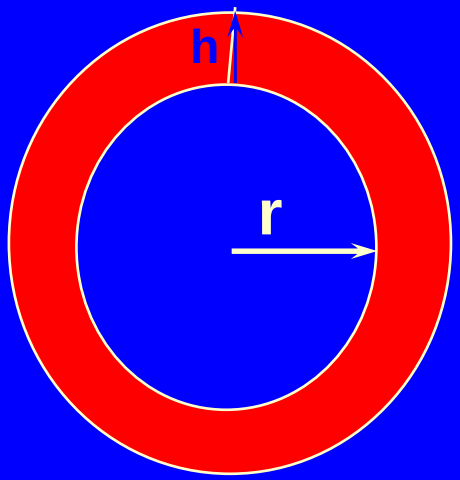
(n=500)

- **ECG**
  - SOKOLOW > 35 mm : 6 %, > 38mm : 3 %
  - CORNELL product > 2440 : 10 %
  - ECG LIFE : 12 %
- M mode **ECHO**
  - g/m^2 : M 134, F 110 : 36 %
  - $g/m^{2.7}$: M 53, F 47 : 51 %

LV REMODELING

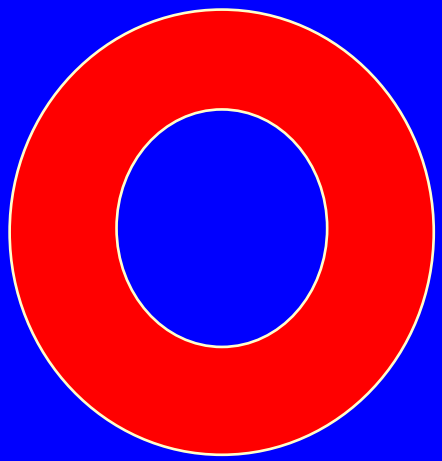
NORMAL

h=10 mm
r=25 mm
RWT=0.4
LVM=213 g



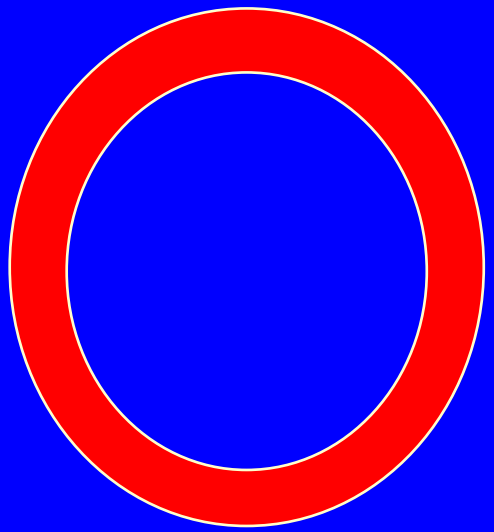
CONCENTRIC

h=14 mm
r=22.5 mm
RWT=0.62
LVM=296 g



ECCENTRIC

h=10 mm
r=30 mm
RWT=0.33
LVM=294 g



REMODELAGE VG ET HTA

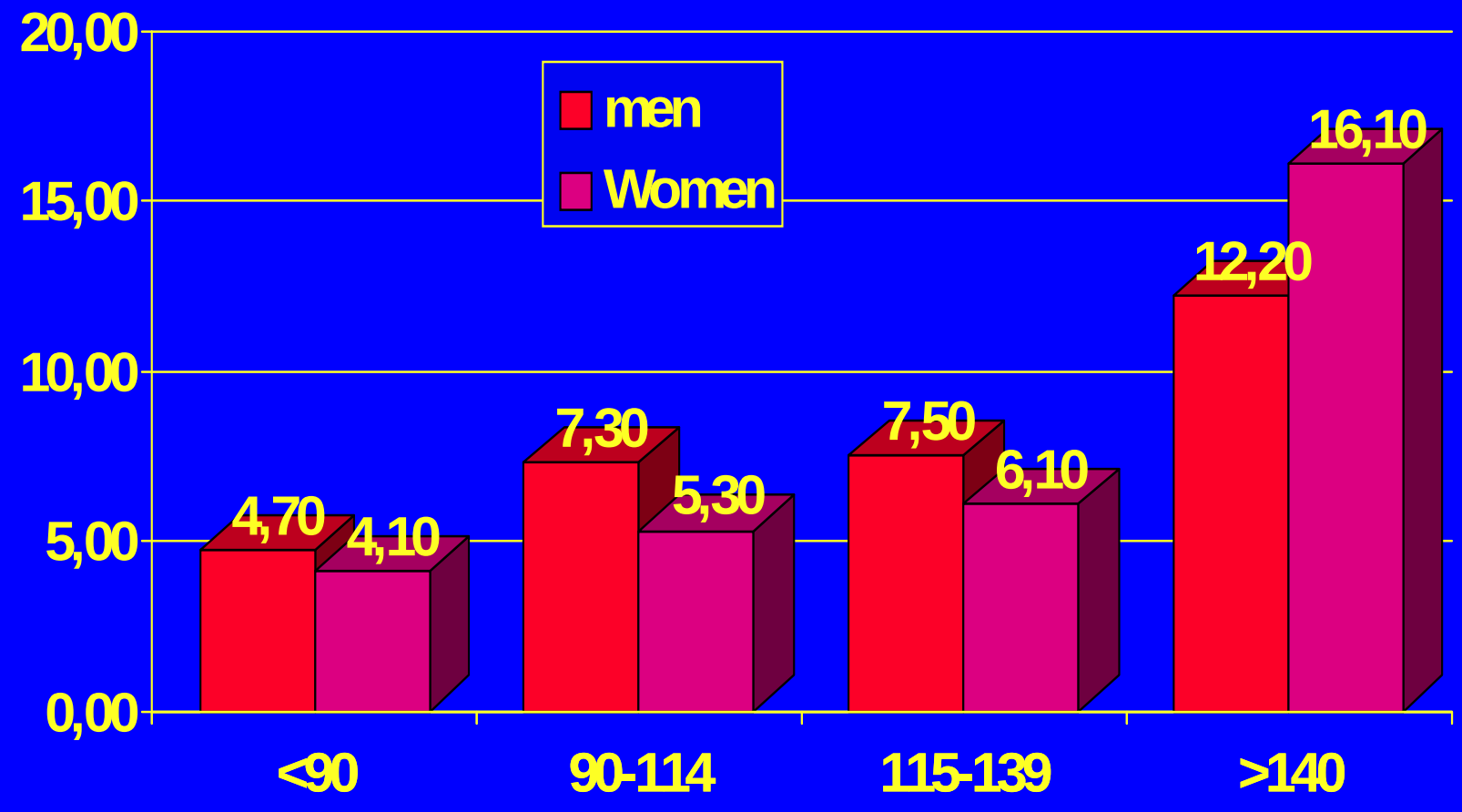
- HVG CONCENTRIQUE ↑MVG, ↑H/R: 8%
- HVG EXCENTRIQUE: ↑MVG, H/R=: 27%
- REMODELAGE CONCENTRIQUE ↑H/R, MVG Nale: 13%
- VG NORMAL: 52%

GANAU, JACC 1992, 19:1550-1558

THE CASE AGAINST THE VALIDITY OF WALL-STRESS HYPOTHESIS

- LVH IS A STRONG AND INDEPENDENT RISK FACTOR WITH A CONTINUOUS RELATIONSHIP BETWEEN LVM AND RISK
- SYSTOLIC FUNCTION IS OFTEN IMPAIRED DESPITE NORMAL REST EJECTION FRACTION
  - MIDWALL FRACTIONNAL SHORTENING
  - TISSUE DOPPLER IMAGING
- LEFT VENTRICULAR FILLING IS IMPAIRED
  - RELAXATION
  - COMPLIANCE
- CORONARY PERFUSION IS OFTEN IMPAIRED IN HYPERTENSION
- EXPERIMENTAL DATA SHOW THAT CARDIAC HYPERTROPHY IS NOT AN ADAPTATIVE RESPONSE

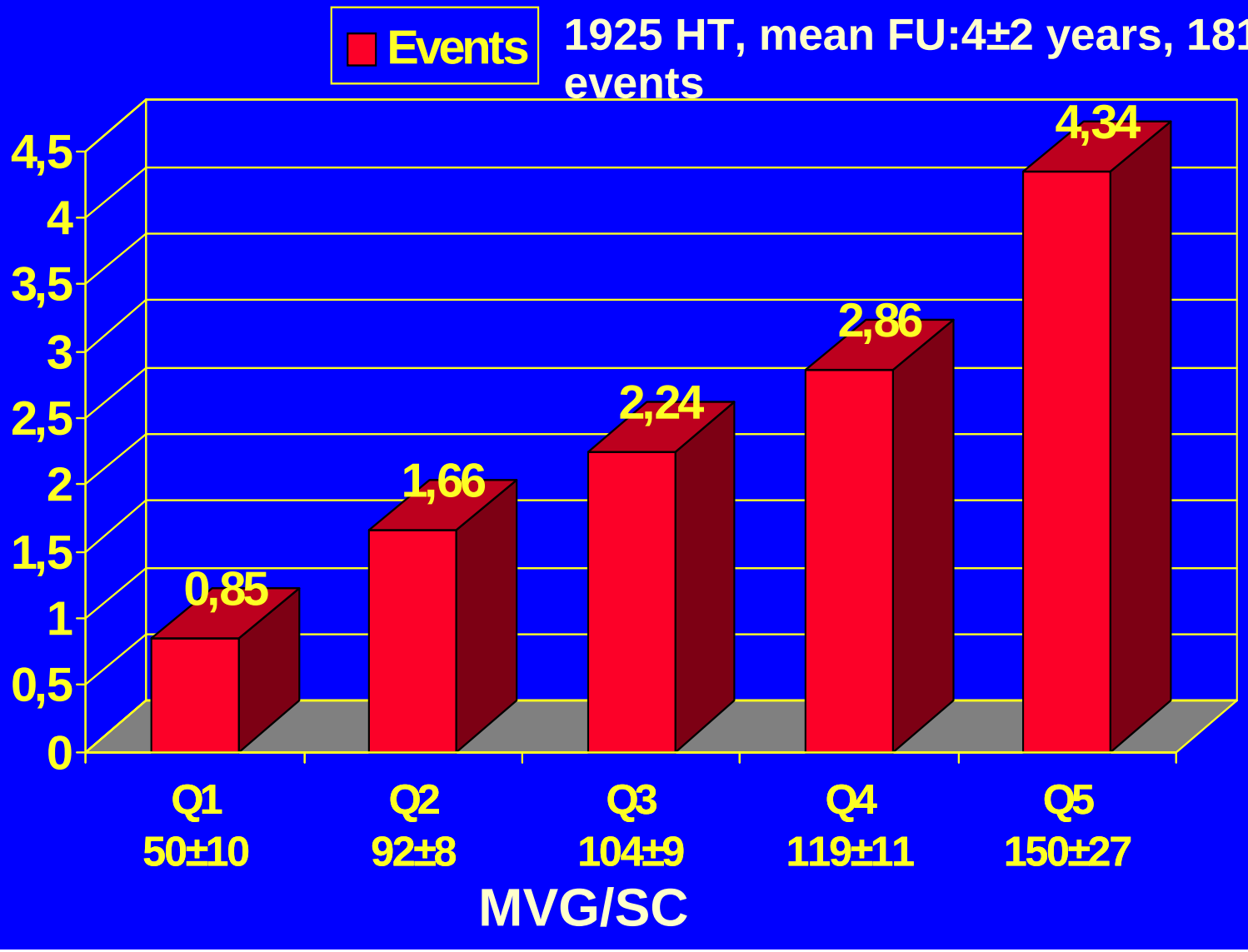
4 year age-adjusted incidence (/100 pts) of cardiovascular disease according to LVM/h (Framingham)



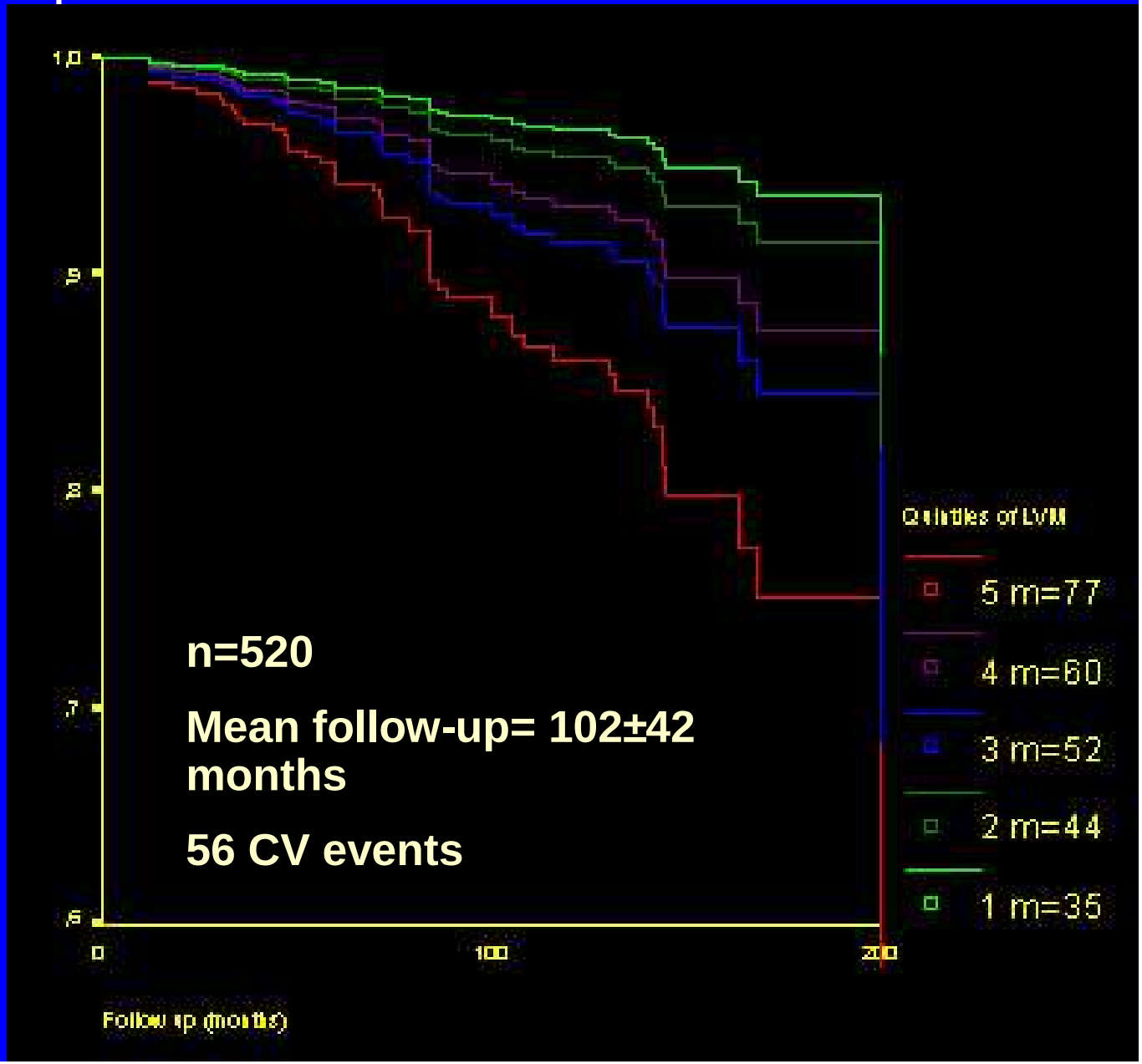
Levy, NEJM 1990, 322:1561-1566

PIUMA STUDY

Schillaci, Hypertension 2000,35:580-586



Age, sex and BP adjusted event free survivals curves for LVM/$h^{2.7}$ quintiles in Bordeaux cohort

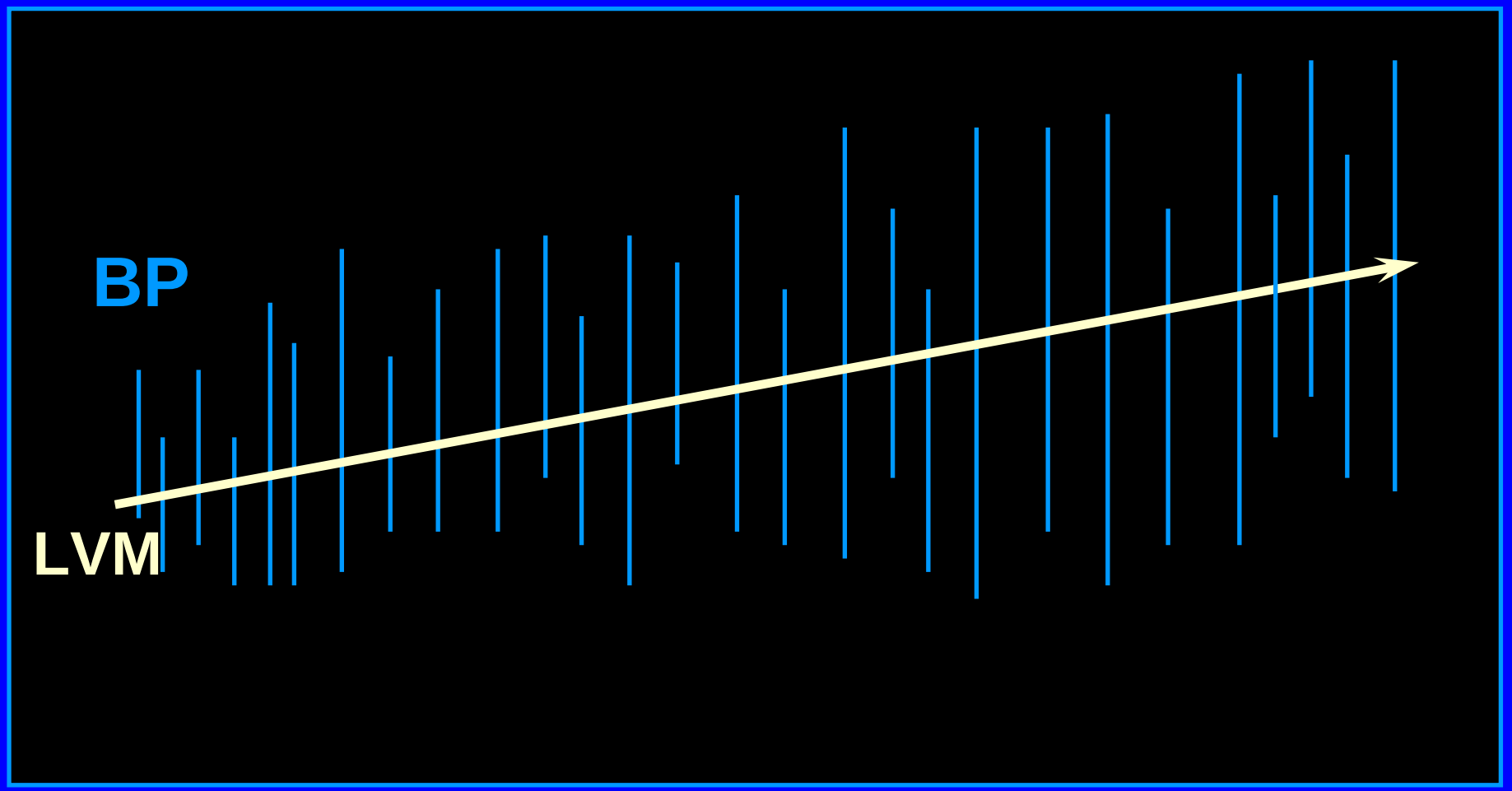


LVH: MARKER OF RISK

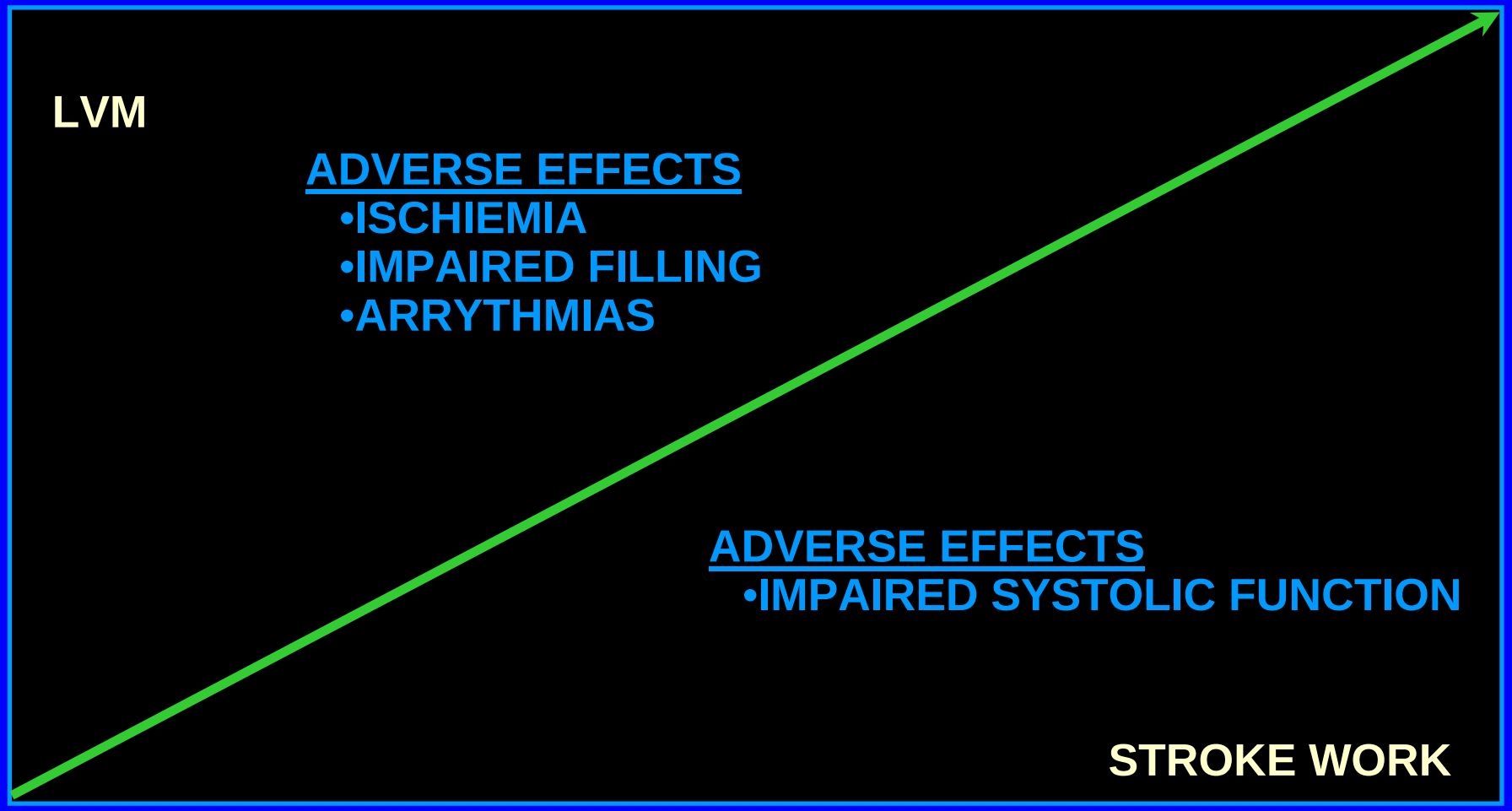
⇒INFLUENCED BY SEVERAL RISK FACTORS: Age, gender, BP(central), Blood viscosity, overweight, alcool, salt, cholesterol?....

⇒INTEGRATES THEIR VARIATIONS WITH TIME

LVM as a witness of BP over time



Inappropriate LVH



Prognostic impact of inappropriate LVM in hypertension: the MAVI study

de Simone, Hypertension 2002, 40:470

CV event free survival curves at mean of covariates (age, sex, BMI, SBP...) according to LVM

Predicted LVM=

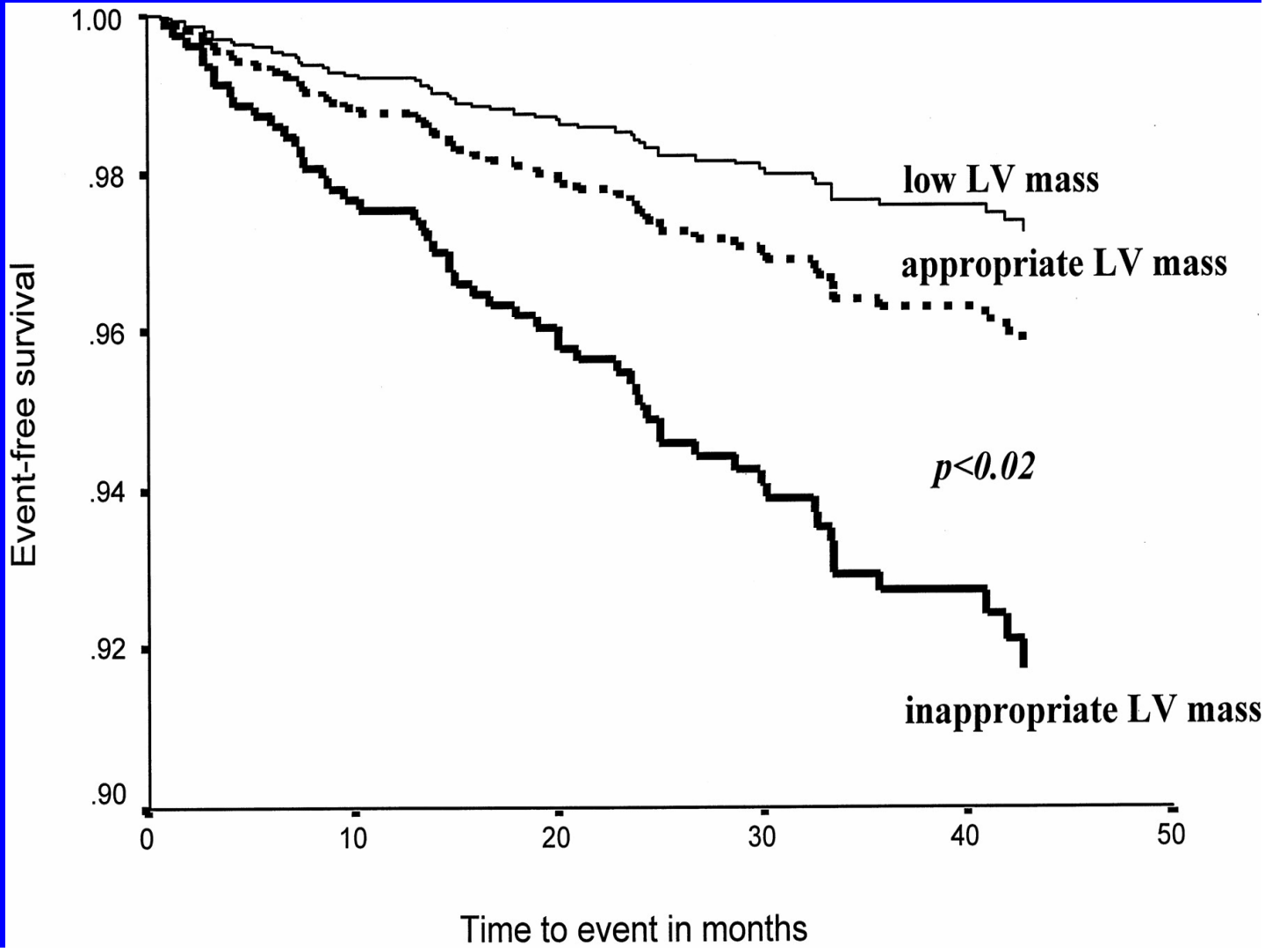
55.37

+6.64height$^{2.7}$

+0.64SW

-18.07gender

SW=SBP*Stroke volume



HYPERTENSION = PATHOLOGIC LVH

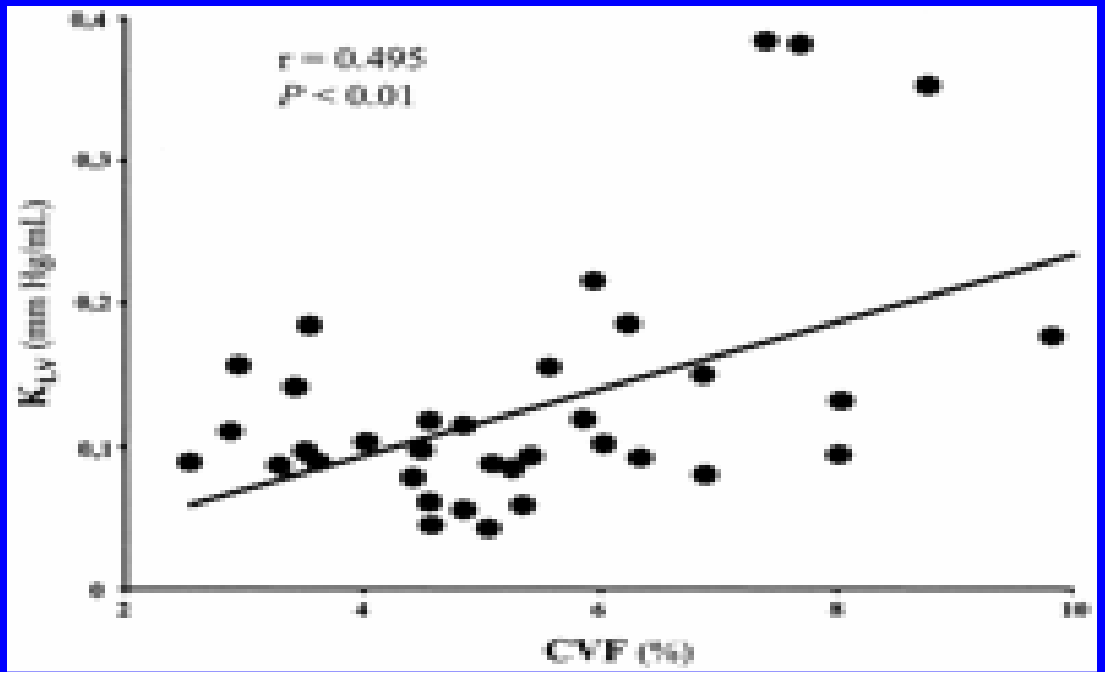
- IMPAIRED CORONARY RESERVE
  - WHY?
    - vascular remodeling
    - Impaired endothelial function
    - Capillaries rarefaction
    - Increase aortic stiffness and reduced perfusion pressure
  - CONSEQUENCES
    - Unbalanced offer and demand
    - Ischemic heart disease
      - Impaired relaxation and LV filling
      - Impaired systolic function

HYPERTENSION = PATHOLOGIC LVH

- IMPORTANCE OF FIBROSIS

Diez (*circulation 2002:2512-2517*)

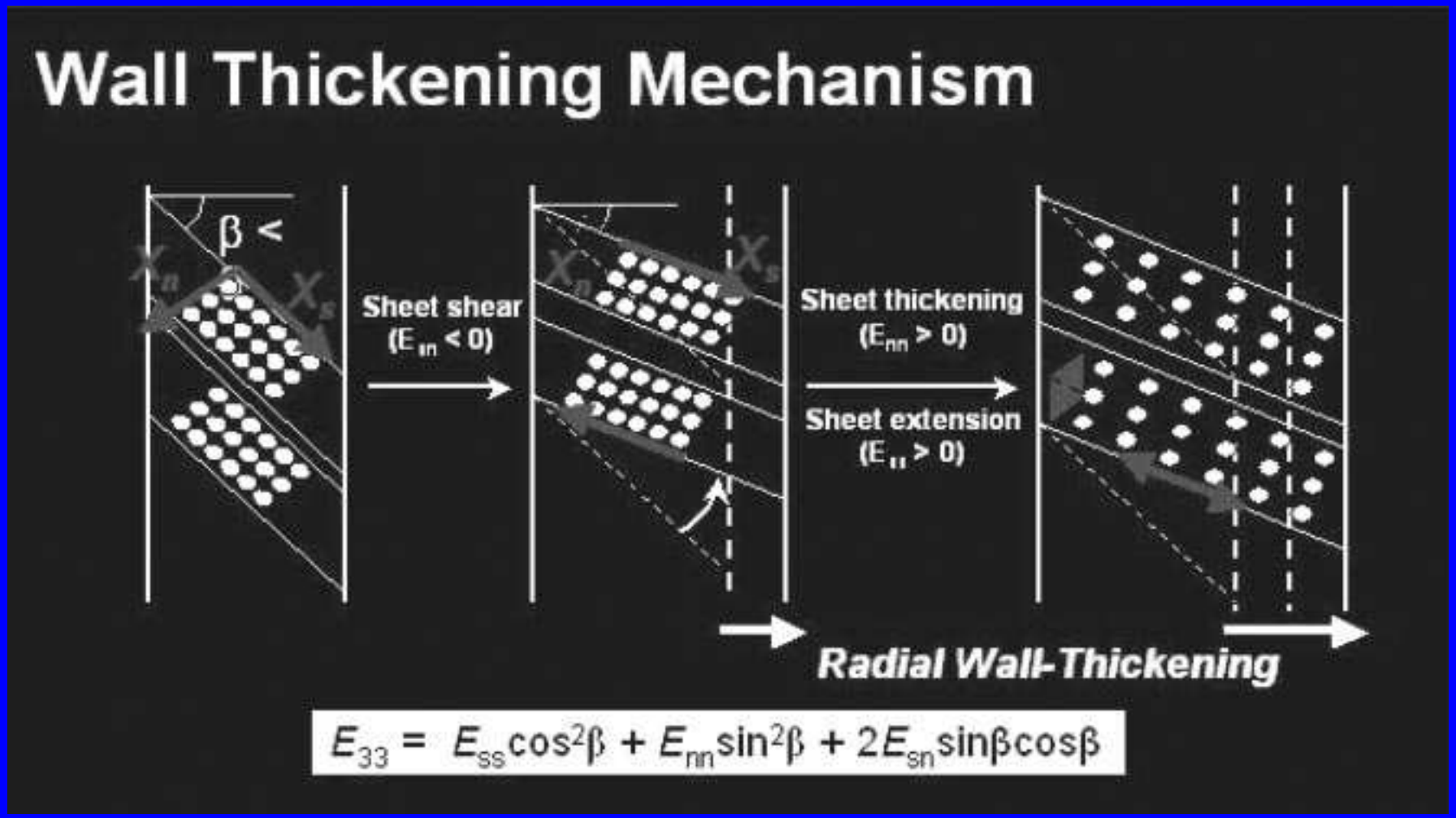
- 34 HT with LVH, transvenous endomyocardial biopsies for assessment of Collagen Volume Fraction and pulsed doppler mitral flow
- Correlation between CVF and reduced deceleration time of early mitral filling wave



THE LEVER EFFECT OF MYOCARDIAL FIBERS ORGANISATION

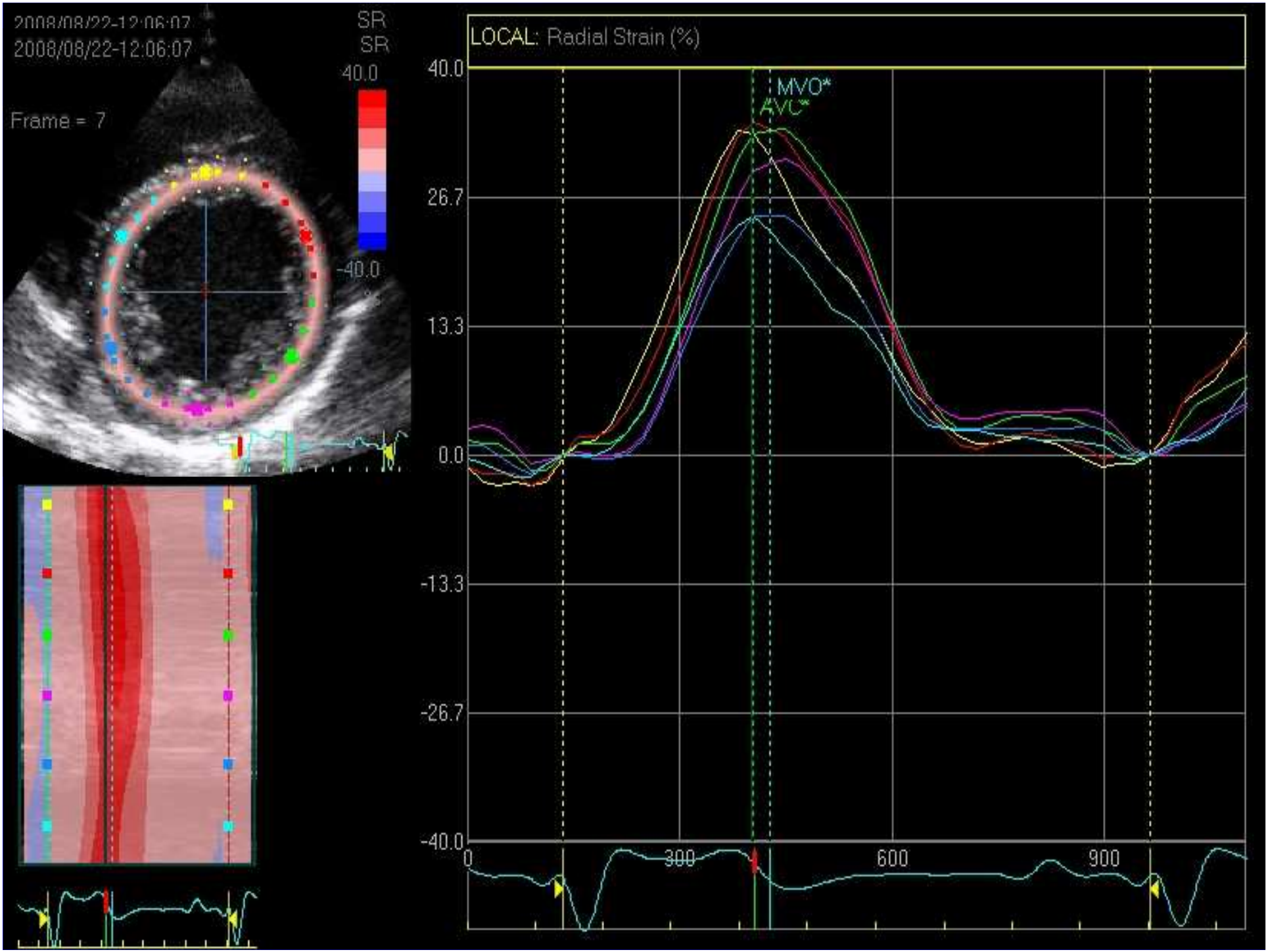
- 15% fiber shortening along the long axis leads to only an 8% increase in myocyte diameter. Yet, 40% radial LV wall thickening and 60% ejection fraction are typically observed.
- Myocardial fibers are grouped into lamina (sheets) 3*4 cells thick interconnected by extracellular matrix
- Radial and longitudinal shear of these sheets play a role of lever to increase wall thickening

Cheng, Circulation 2008, 118:713-21



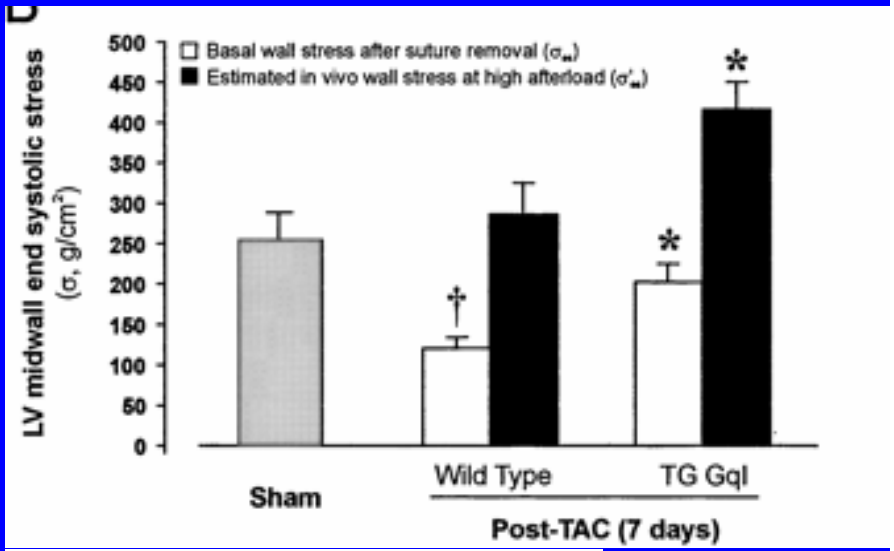
Fibrosis and systolic function?

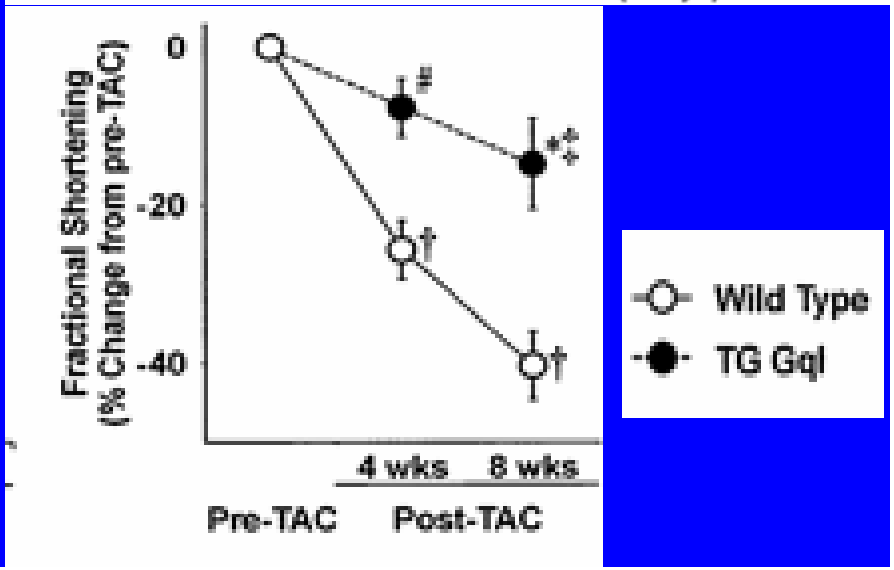
- Even small changes in the initial sheet angle may have large effects on wall thickening
- pathological changes in macrostructure of the ventricular wall may influence sheet motion and, therefore, wall thickening and synchronicity


2008/08/22-12:06:07
SR
SR
40.0
-40.0
Frame = 7
LOCAL: Radial Strain (%)
40.0
26.7
13.3
0.0
-13.3
-26.7
-40.0
MVO*
AVC*
0
300
600
900

Genetic alterations that inhibit in vivo pressure overload hypertrophy prevent cardiac dysfunction despite increased wall stress. *Esposito, Circulation 2002, 105:85-92*

- Genetically altered mice unable to develop LVH
- Transverse aortic constriction to increase afterload
- Despite high parietal stress these mice showed significantly less deterioration in cardiac function than the wild type banded mice developing LVH





ANTIHYPERTENSIVE TREATMENT REDUCES LVH

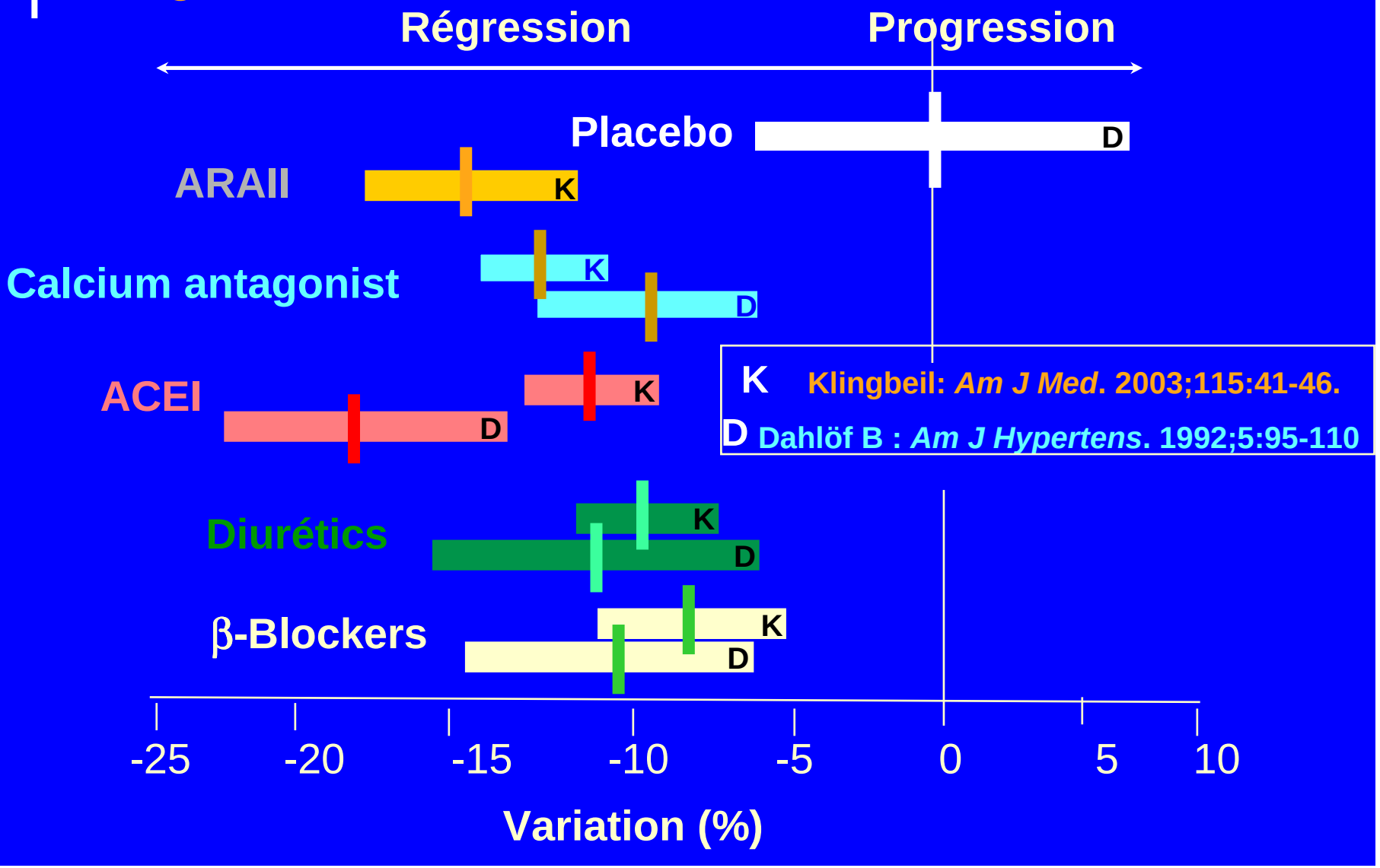
- MANY STUDIES BUT OFTEN WITH FEW PATIENTS, SHORT DURATION
- ALL DRUGS ARE EFFICIENT WITH THE EXCEPTION OF MINOXIDIL AND HYDRALAZINE
- POOR CORRELATIONS BETWEEN BP AND LVM REDUCTIONS: IS THERE A SPECIFIC DRUG ACTION??

IS THERE A SPECIFIC DRUG ACTION ON LVH??

- COMPARATIVE STUDIES EXIST BUT FEW SHOW SUFFICIENT POWER
- META-ANALYSIS SHOW GREATER EFFICACY OF ARAII and ACE INHIBITORS VERSUS β BLOCKERS AND DIURETICS BUT
  - Many studies of poor quality
  - Diuretics often added to ACE inhibitors and ARAII
  - Publication bias
- WE NEED WELL DESIGNED AND POWERFULL COMPARATIVE STUDIES

LVH Régression Meta-analysis

Klingbeil : 80 studies / Dahlöf : 109 studies



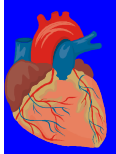
K Klingbeil: *Am J Med*. 2003;115:41-46.

D Dahlöf B : *Am J Hypertens*. 1992;5:95-110

OPTIMAL TRIAL DESIGN FEATURES

Devereux, Dahlof: J Human Hypertens 1994, 8:735-9

- ADEQUATE GENDER, AGE AND ETHNIC MIX
- DOUBLE BLIND, RANDOMISED COMPARATIVE TRIAL
- ADEQUATE SAMPLE SIZE (150-200/Gp with echo)
- ADEQUATE DURATION: >= 1 YEAR
- CENTRAL BLIND MEASUREMENTOF LVM BY TRAINED ECHOCARDIOGRAPHISTS



RECOMMANDATIONS FOR MULTICENTRIC LVH REGRESSION TRIALS

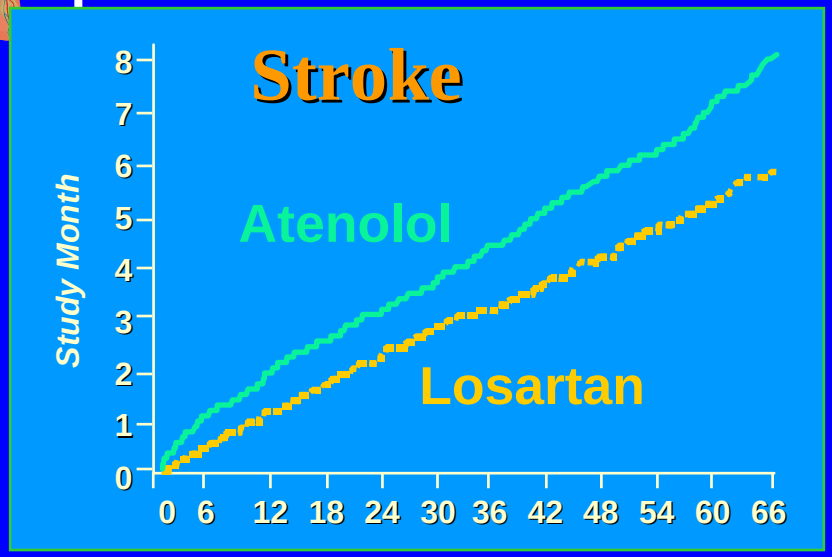
Gosse J;Hypertens 2003, 21:217-221

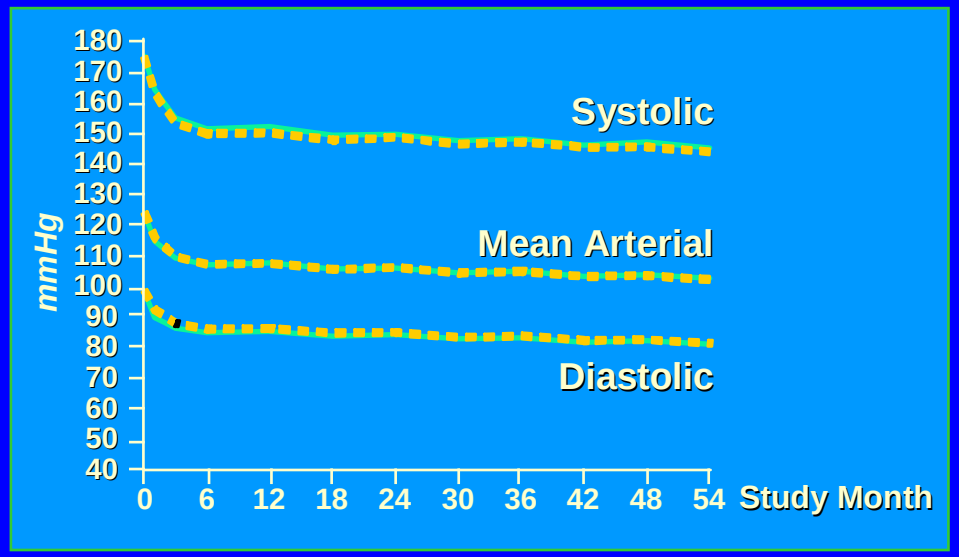
- CENTRALIZED CONTROL OF INCLUSION CRITERIA
- CENTRALIZED CONTROL OF QUALITY FOR ALL RECORDINGS
- FINAL CENTRALIZED READING
  - BLIND TO TREATMENT AND temporal SEQUENCE
  - ALL TRACINGS OF THE SAME Pt READ BY THE SAME READER
  - ALL TRACINGS MIXED TOGETHER
- 2 INITIAL ECHO separated by a 2-4 weeks placebo run-in
  - SDD as an OVERALL QUALITY INDICE
  - QUANTIFICATION OF REGRESSION TO THE MEAN

MAIN ECHO STUDIES ON LVH REGRESSION

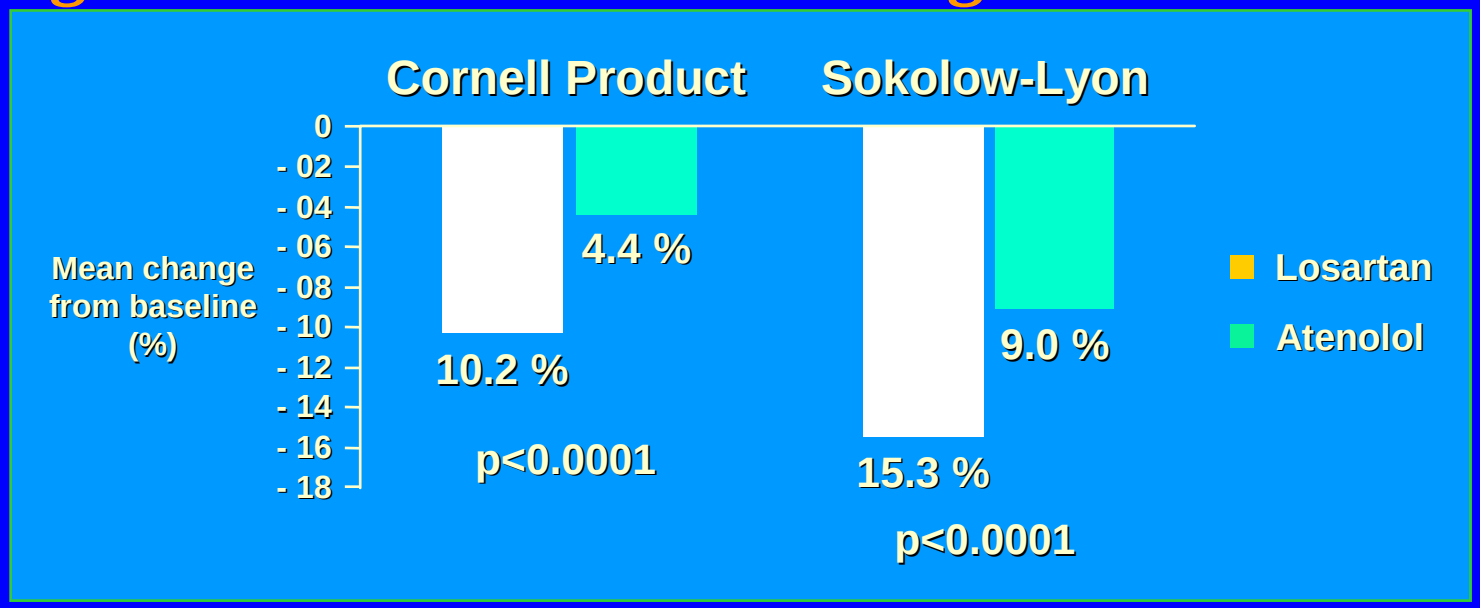
	n	Drugs	LVMI g/m2	BP mmHg	Duration (weeks)
LIFE	825	Los Vs Aten	-22±22	-30/-16	240
		(+Htz in 90%)	-18±20*	-29/-16	
PICXEL	679	Per/ind Vs Ena	-14±24	-22/-10	52
			-4±24*	-18/-8*	
LIVE	411	Ind Vs Ena	-8±30	-25/-13	48
		(+prazosin in 20%)	-2±28*	-25/-12	
CATCH	196	Cande Vs Ena	-15±23	-27/-16	48
		(+Htz in 47-54%)	-13±23	-26/-16	
PRESERVE	235	Ena Vs Nife	-15±21	-22/12	48
		(+Htz in 34-59%)	-17±18	-21/13	
REGAAL	219	Los Vs Aten	-7±20	-24/-11	36
		(+Htz in 86-78%)	-4±21	-24/-14	

LIFE

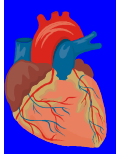


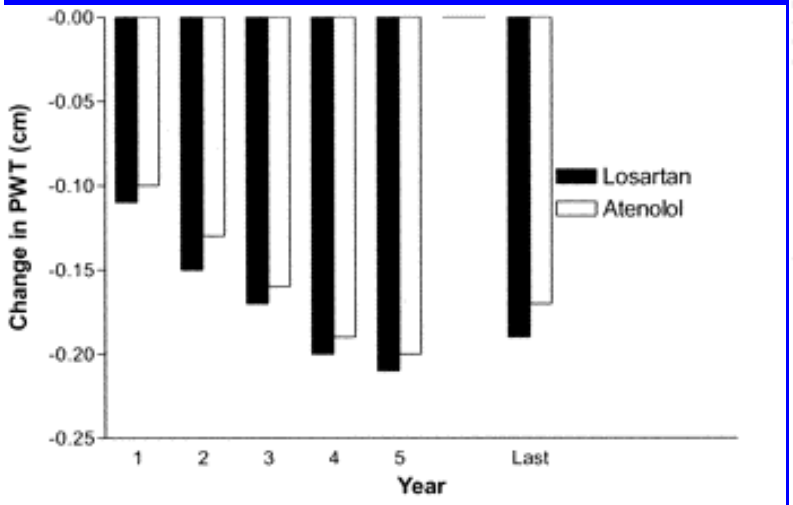


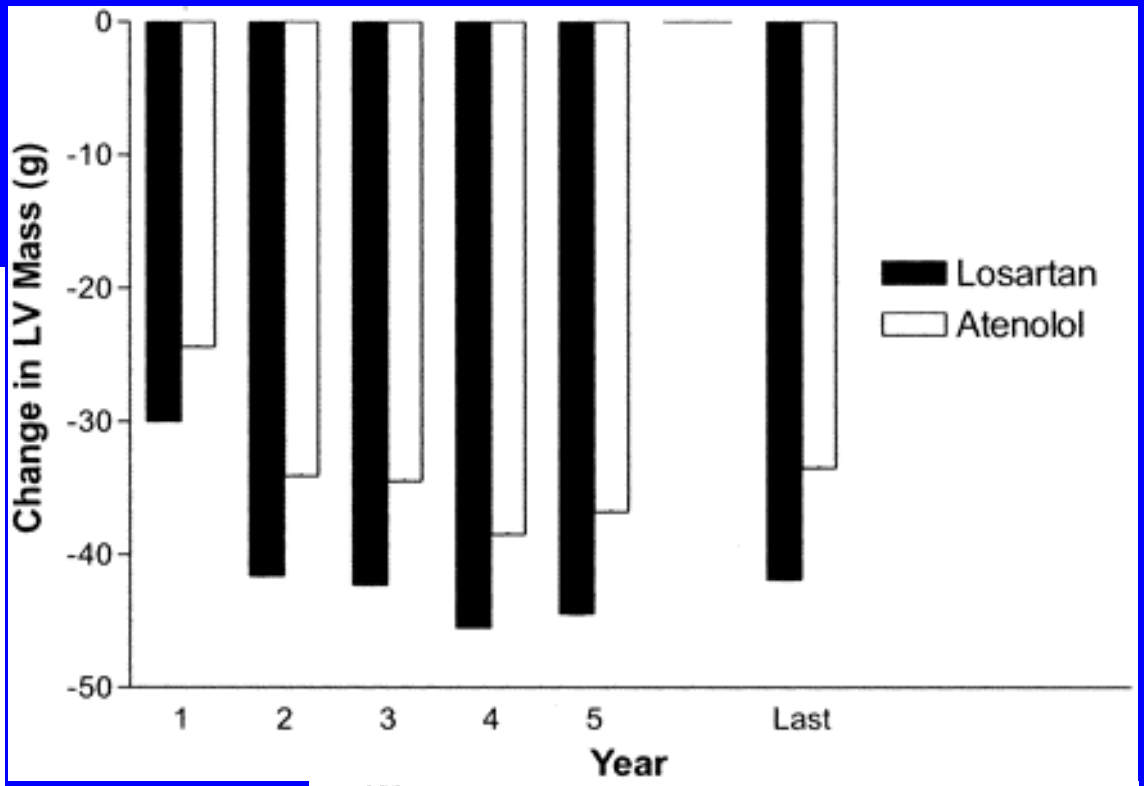
Change from Baseline in LVH Regression

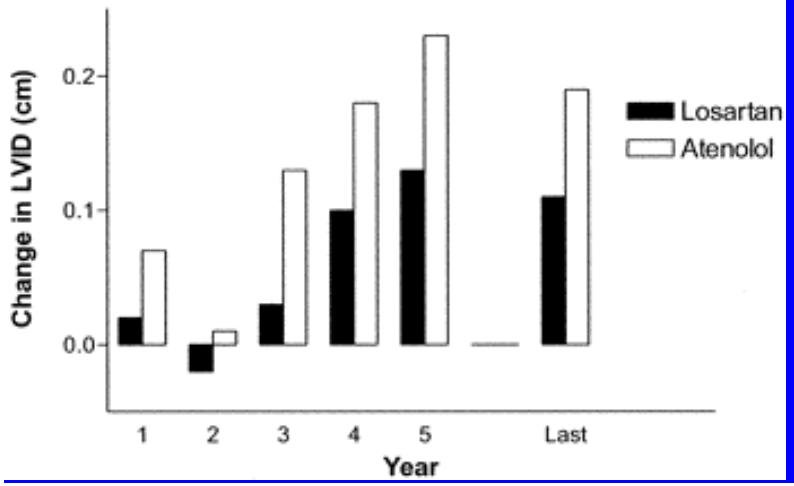


LIFE: ECHO RESULTS









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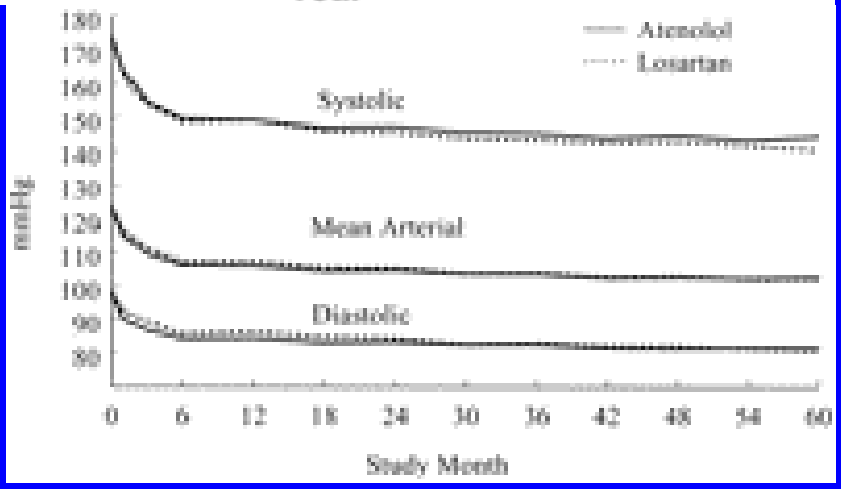
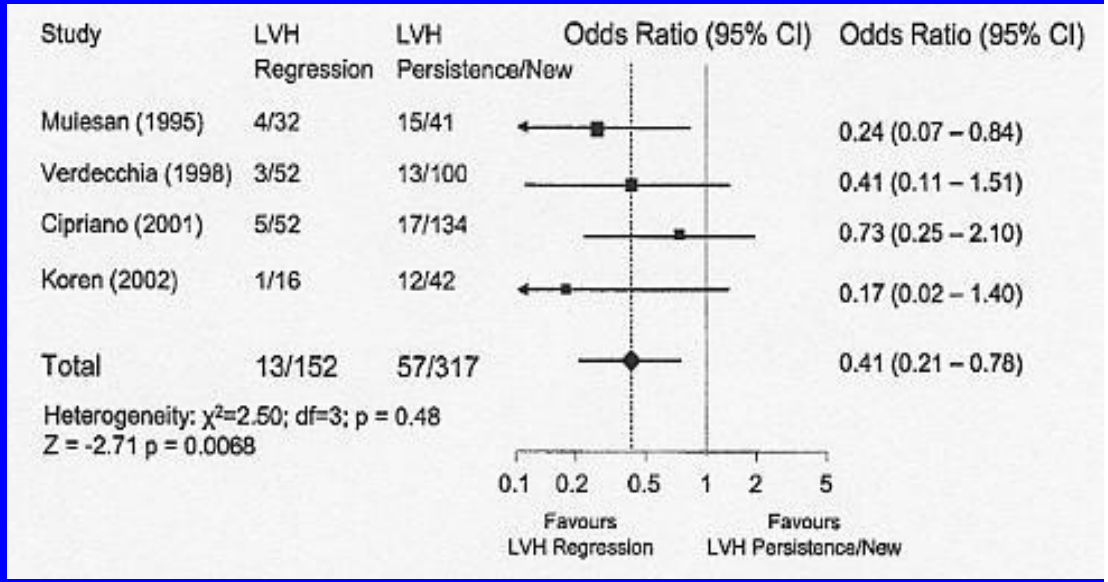


LVH REGRESSION IMPROVES OUTCOME

(Verdecchia AJH, 2003:16:895-899)

- Meta analysis of small cohorts
  (Verdecchia AJH, 2003:16:895-899)
- LIFE STUDY *(Devereux, JAMA 2004,292:2350-6)*



LVM seems to be a good surrogate end point

LVM assessment in hypertensive patient. When?

- LVM seems to be a good surrogate end point
- But
  - ECG is not sensitive enough
  - echo assessment of LVM shows insufficient reproducibility
  - MRI cannot be proposed for routine evaluation
  - No study demonstrates the cost effectiveness of systematic LVM assessment

ECG

NORMAL
Dont eliminate LVH

LVH

LOW RISK

HIGH RISK
ECHO USELESS IF ASYMPTOMATIC

Normal REPOLARISATION
High RISK
ECHO To assess LV function??

Abnormal REPOLARISATION
VERY HIGH RISK

ECHO ?
Better assessment of risk but cost/effectiveness unknown

Look for ischemic heart disease
ECHO