Improving Risk Stratification in Asymptomatic Severe AS:

Neurohormones

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Disclosure, conflict of interest

- Nothing to disclose

Why Biomarkers in Valve Disease?

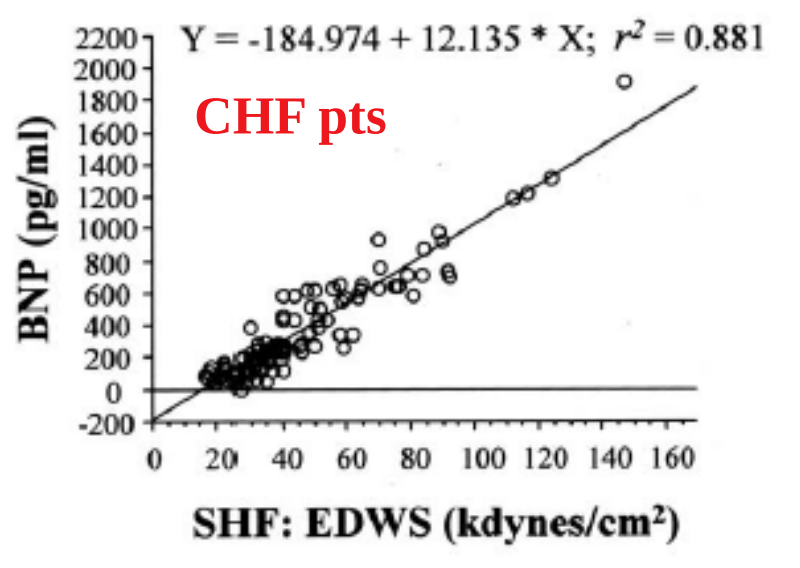
- Symptoms frequently not reported, unspecific...
- Echo not always available, expertise, imaging quality
- Biomarkers easy to assess, objective, can be serially repeated in any setting

➢ Prognostic value of natriuretic peptides established in heart failure, coronary disease...

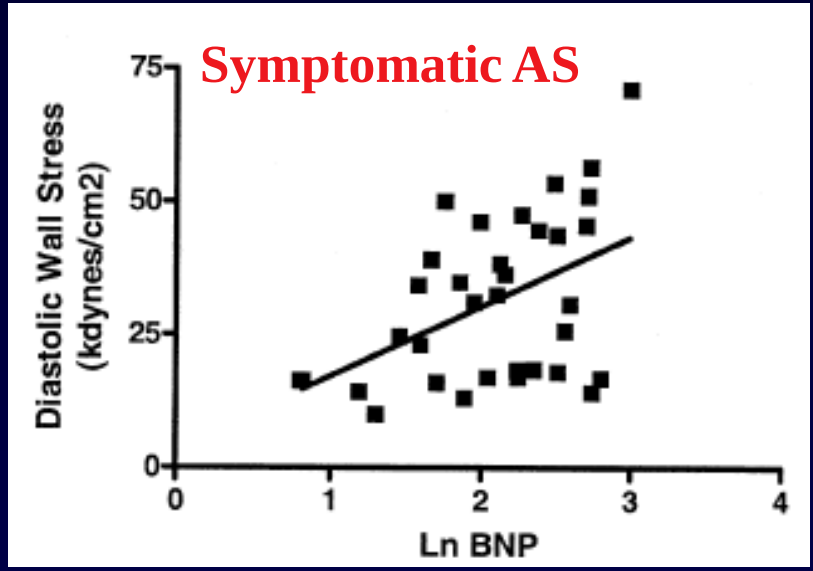
Steadman C, J AmColl Cardiol 2010;55
Bhattacharyya S , Senior R, Eur Heart J 2012

Why is BNP increased in AS?
BNP and Myocardial Wall Stress

→ Diastolic stretch induces BNP expression in myocyte
Volume overload CHF, AR,MR. Pressure overload AS

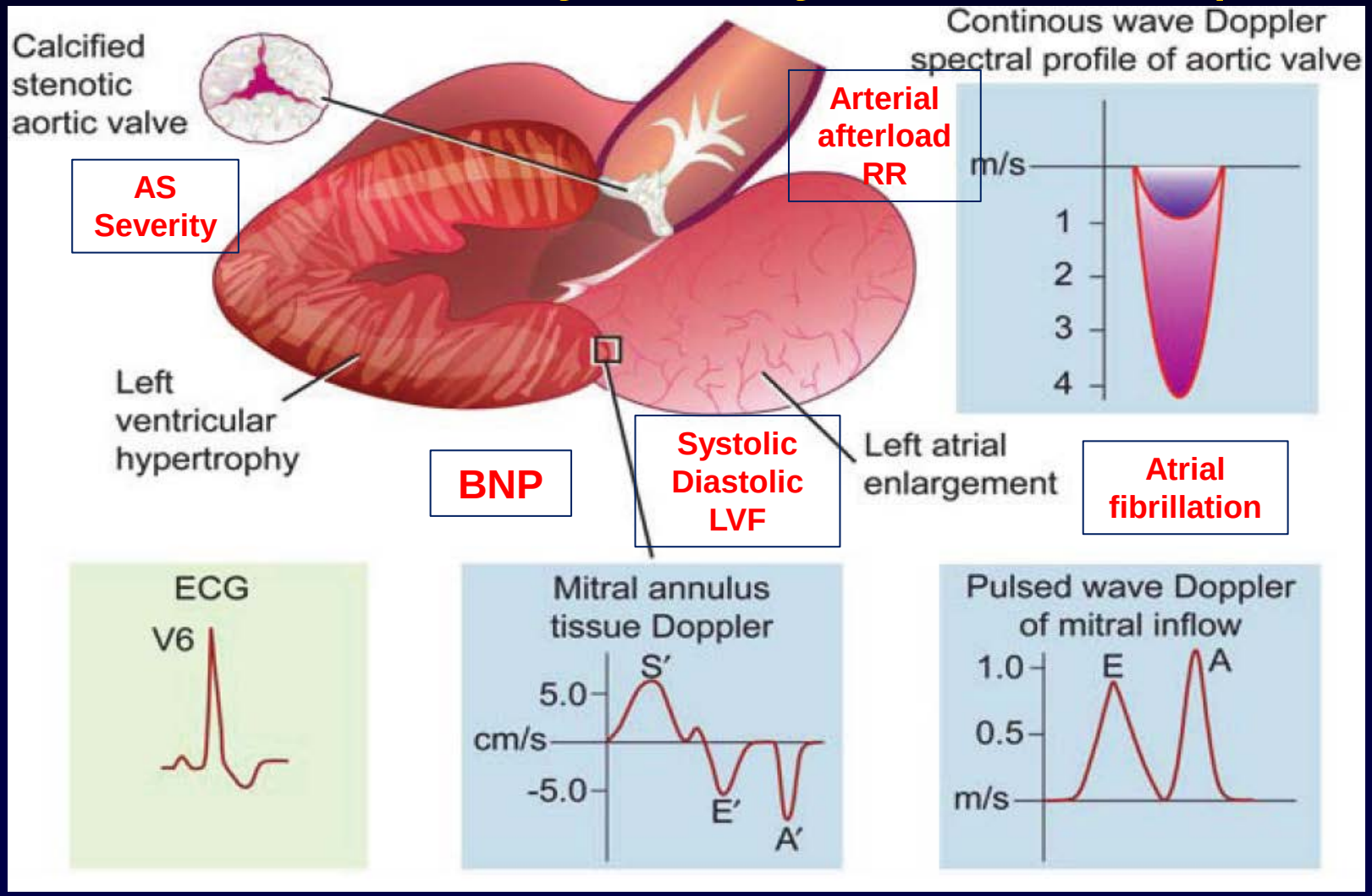


Iwanaga et al. JACC 2006; 47 (4)



Vanderheyden M; JACC 2004; 2349

Interplay of Determinants in AS Obstruction Severity vs Physiol. Consequences



Bergler-Klein, ESC 2010

Adapted from: Pellikka P. Eur Heart 2010; June 17

Natriuretic Peptides reflect Severity of AS - Pressure Overload

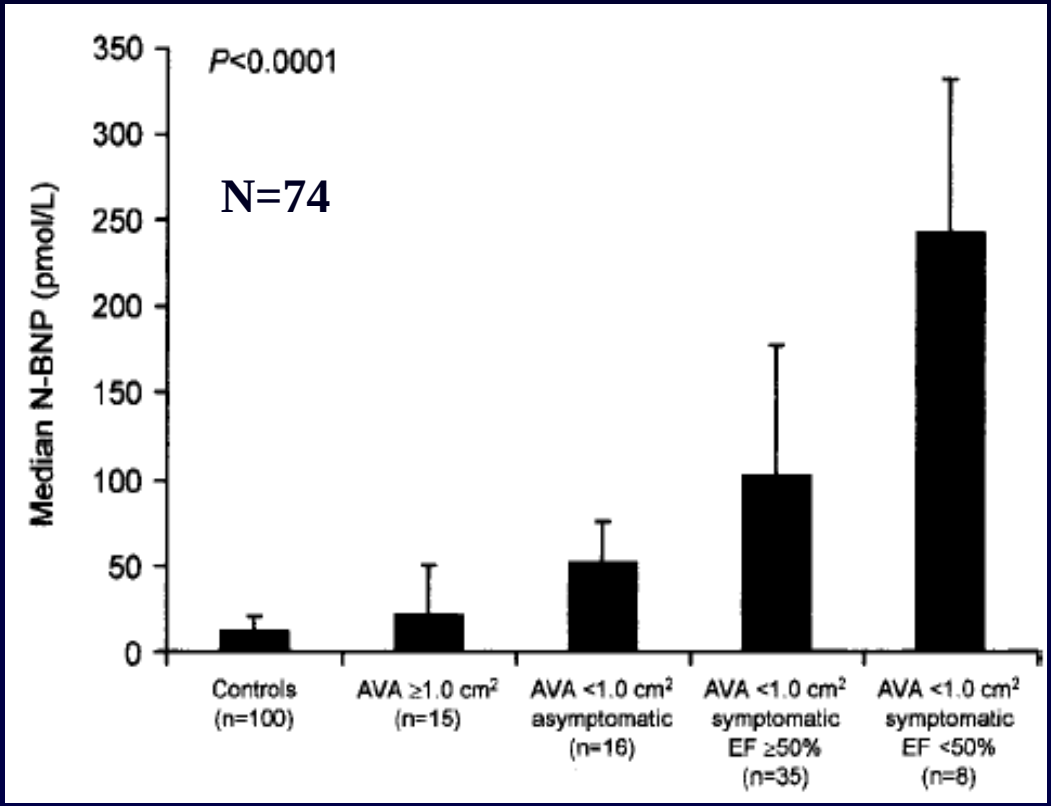
	BNP r	NT-proBNP r	NT-proANP r
AVA	-0.55	-0.57	-0.55
Peak Vel	0.33	0.35	0.38
MG	0.36	0.37	0.38
LA	0.30	0.34	0.35
LV Mass Index	0.62	0.59	0.46
LV EF	-0.48	-0.42	-0.39

Bergler-Klein, Circulation 2004 and 2007
Gerber I, Circulation 2003;
Weber M, Eur Heart J 2005
Blackshear J, Am J Cardiol 2013
Cimadevilla C, Messika Zeitoun, Heart 2013

NT-BNP reflects AS severity, Symptoms and LVF

Transition of compensated to decomp. LVF

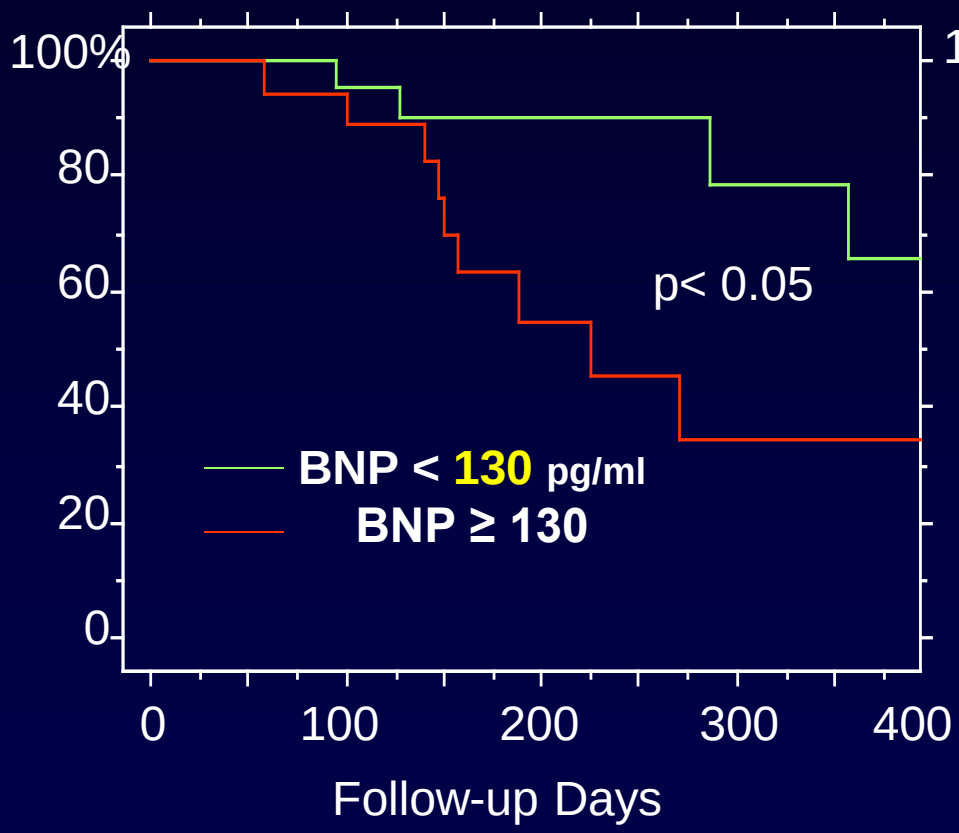
Subgroups according to AVA, symptoms and EF

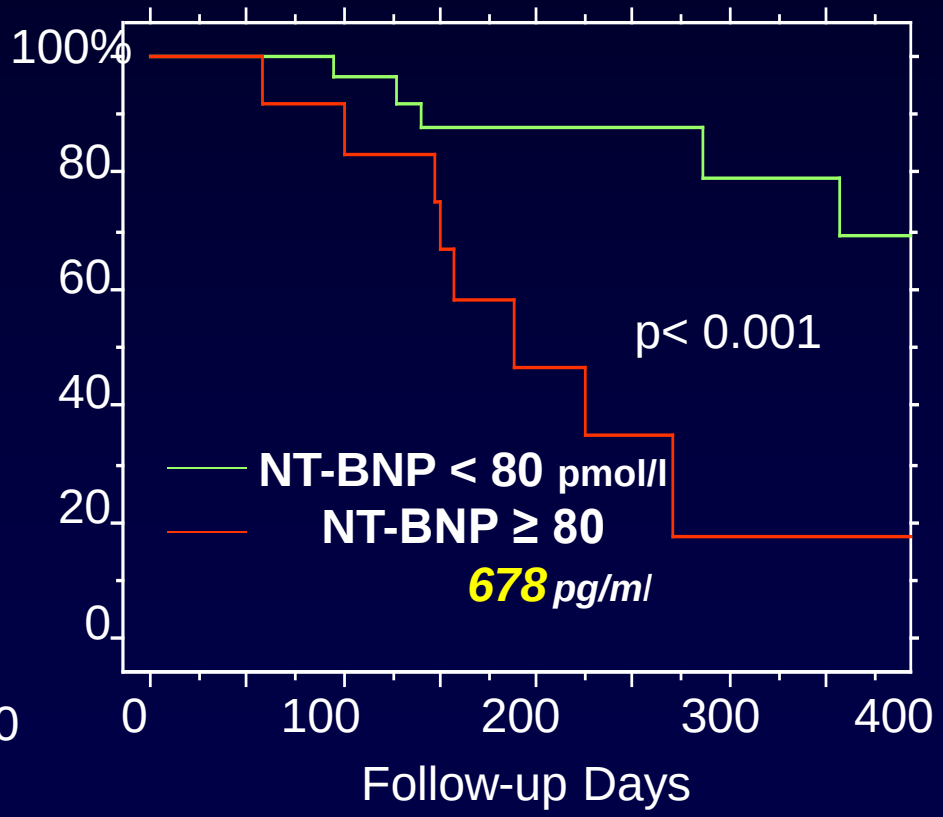


Gerber I et al, Circulation 2003; 107

Symptom-Free Survival in Asymptomatic Severe AS

BNP and NT-proBNP



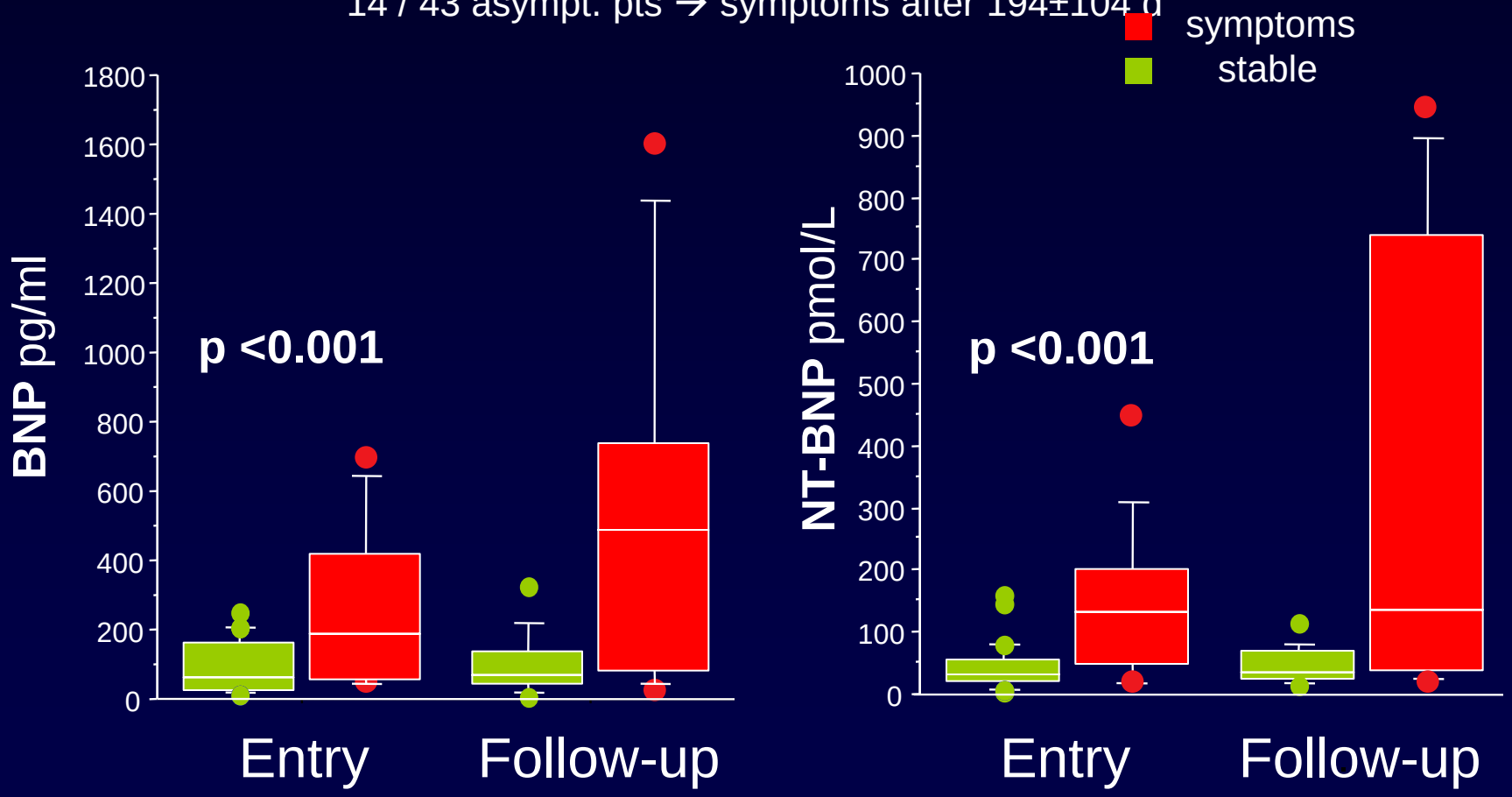


Bergler-Klein J, Rosenhek R, Baumgartner H, Circulation 2004; 109

Serial BNP and Symptom Development in Severe AS

Pts developing symptoms had higher BNP at entry and follow up

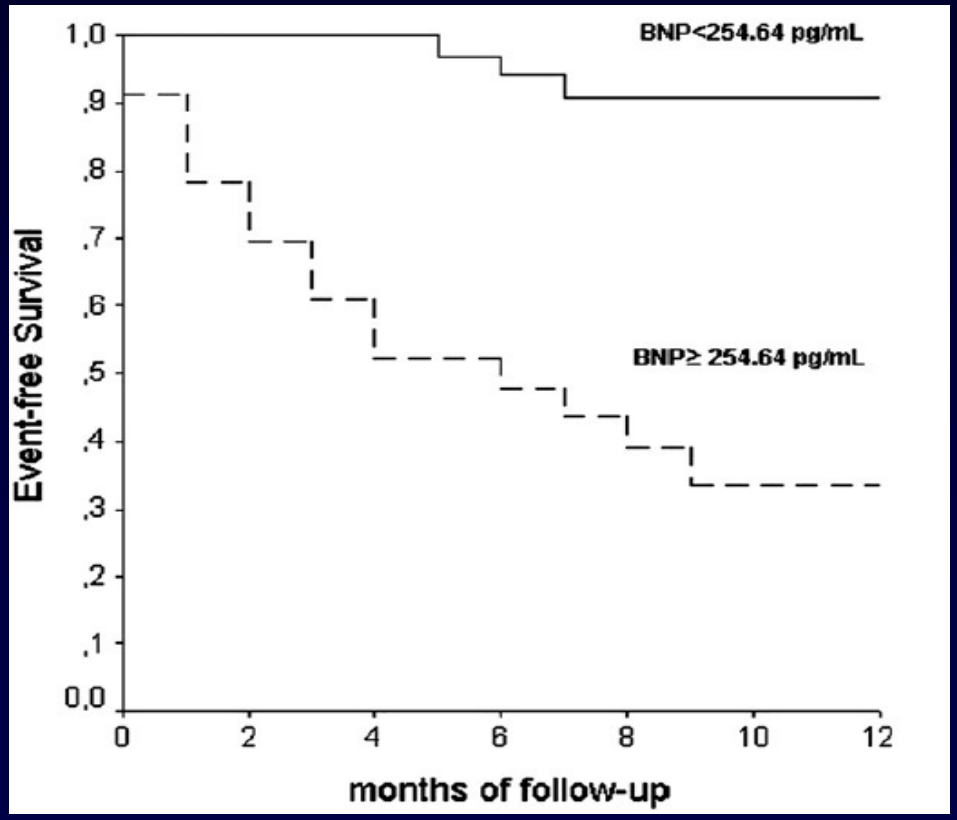
14 / 43 asympt. pts → symptoms after 194±104 d



Bergler-Klein , Circulation 2004

Mortality or Events in Severe AS

- Combined cardiac death, urgent AVR, HF hospitalization
- BNP >254, BNP increase with NYHA



64 pts, asympt. + sympt. AS
Age 76±9 y

7 deaths
2 urgent AVR
9 hospitalized CHF
Reduced EF in 24 pts

Antonini-Canterin, Popescu et al. Int J Cardiol 2008;128

Pitfalls of BNP? Confounders / Overlap

- Age, Gender
- Renal function
- Volume changes, exercise variations
- Hypertension
- Atrial fibrillation
- Diastolic dysfunction
- Coronary or other cardiac comorbiditities
- ***.....***

Seferovics, JACC 2014
Cimadevilla, Messika-Zeitoun, Heart 2013
Bergler-Klein, Can J Cardiol 2014

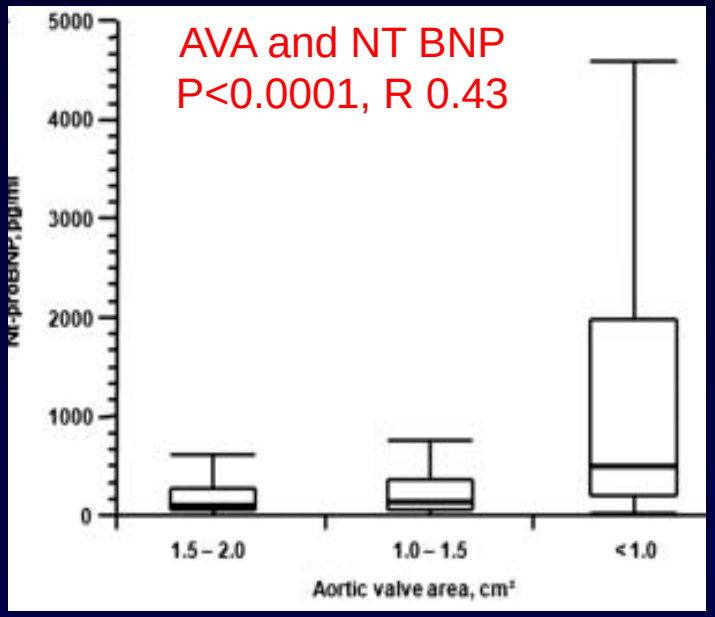
BNP or NT-ProBNP?

- No direct comparisons of „numbers“
- Pg/ml or pmol/l
- Renal function more influence on „Pro“BNP

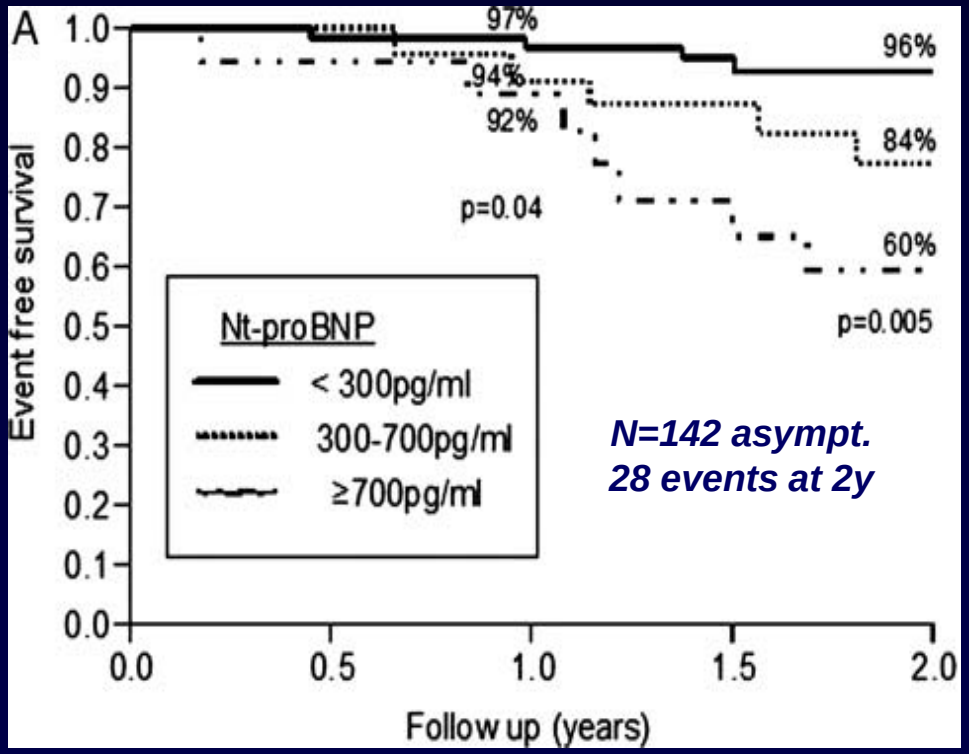
→role in elderly pts?

NT-BNP and Events in Elderly AS

- AVA severity related to NtBNP
- Higher baseline NtBNP p=0.001 in 28 events of 142 pts at 2y
  but not signif. adjusted for age, AVA
- Poor survival in NT-BNP >700 - but high overlap



361 AS mild/ mod to severe
79±6 years, 230 severe



Cimadevilla C, Messika-Zeitoun D, Heart 2013;99

New concepts for BNP?

- Exercise BNP
- BNP clinical activation, ratio
- Serial BNP, individualized value

Usefulness of Serial B-type Natriuretic Peptide Assessment in Asymptomatic Aortic Stenosis

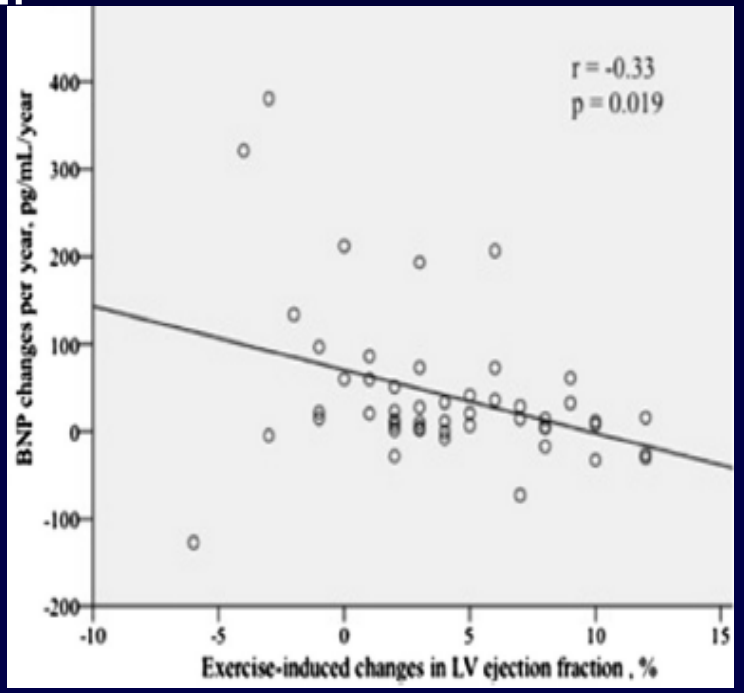
Am J Cardiol 2014;114:441–448

Christine Henri, MD[a,b], Julien Magne, PhD[a], Raluca Dulgheru, MD[a], Laurent Davin, MD[a], Saloua Laaraibi, MD[a], Damien Voilliot, MD[a], Seisyou Kou, MD[a], Alain Nchimi, MD[a], Cécile Oury, Luc A. Pierard, MD, PhD[a], and Patrizio Lancellotti, MD, PhD[a,*]

Bicycle Exercise *echo, 61 Asympt. AS >moderate, mean MG 37, preserved EF*

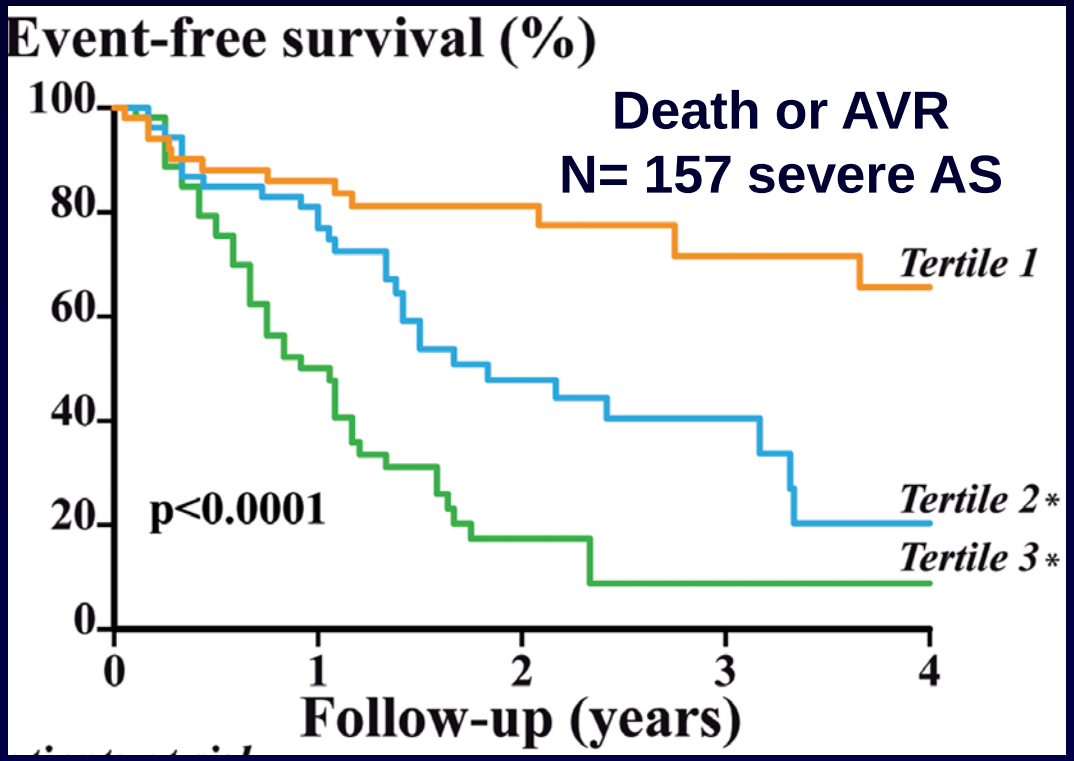
- Higher serial BNP – subclin LV dysf
  - less contractile reserve - exercise EF
  - more diastolic burden - LA size
- BNP changes determined by
  - LA area indexed
  - Diastolic E/e´
  - Exercise EF increase,

    adj. for age, MG, basal BNP.
- High variation during FU



Exercise BNP: Prognostic value

- Higher event risk in asympt. severe AS with marked increase in peak exercise BNP
- Superior to resting BNP, incremental to Echo



211 asympt AS
preserved LVEF
2 centers
Bicycle test

Tertile 3
95- 956 pg/mL

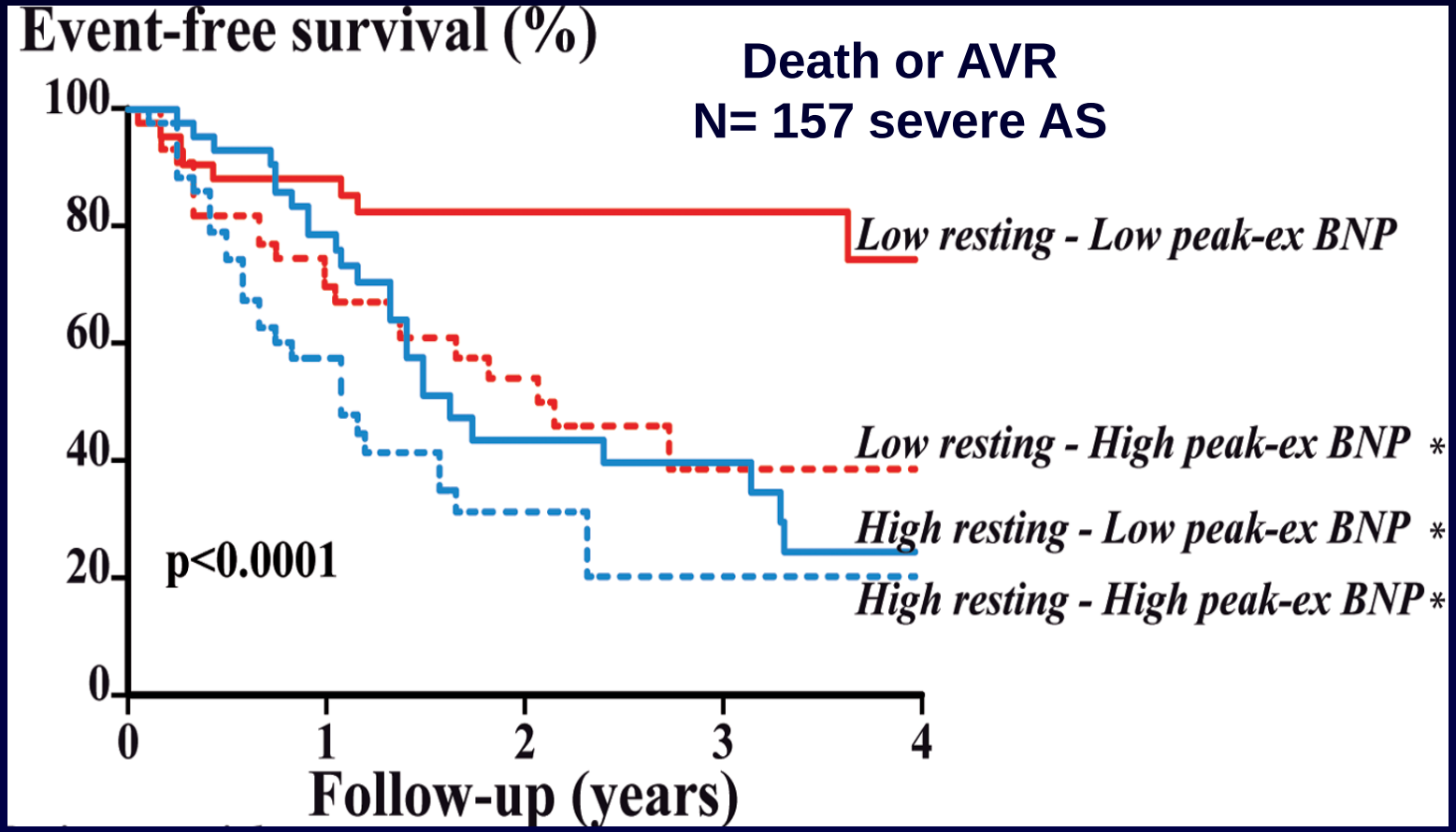
Delta tertile 3
+ 20- 337 pg/ml

Capoulade R, Magne J....Lancellotti, Pibarot P. Heart 2014, July

Exercise / Resting BNP

Exercise BNP reflects transition of LV compensation

Subsets low / high resting / exercise BNP



Capoulade R, Magne J.... Pibarot P. Heart 2014

Exercise BNP- new risk parameter?

- Ex BNP easy to perform, can be added in treadmill or bicycle test +- stress echo

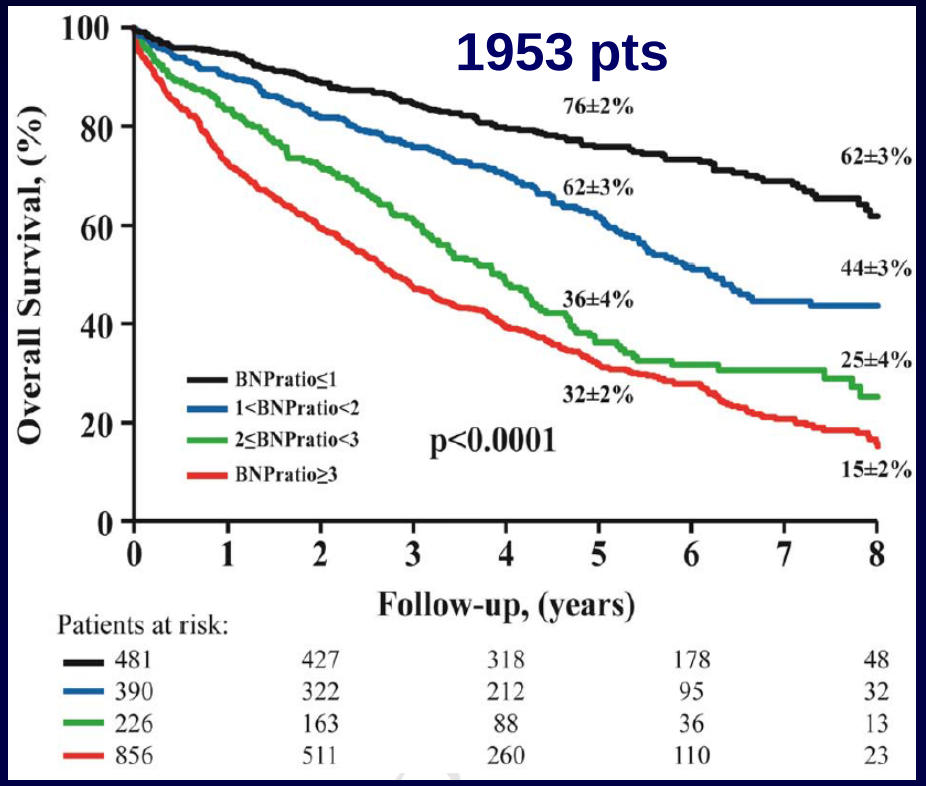
- Ex BNP not specific to AS severity alone, reflects total cardiac burden: arterial+ global load.

BNP Clinical Activation
Survival in AS

- **BNP Ratio >1**: Measured BNP / Max normal BNP specific to age and gender → individualized value

→ excess mortality in all AS subgroups, asympt.+ symptom

→ Incremental, independent of all baseline charact.



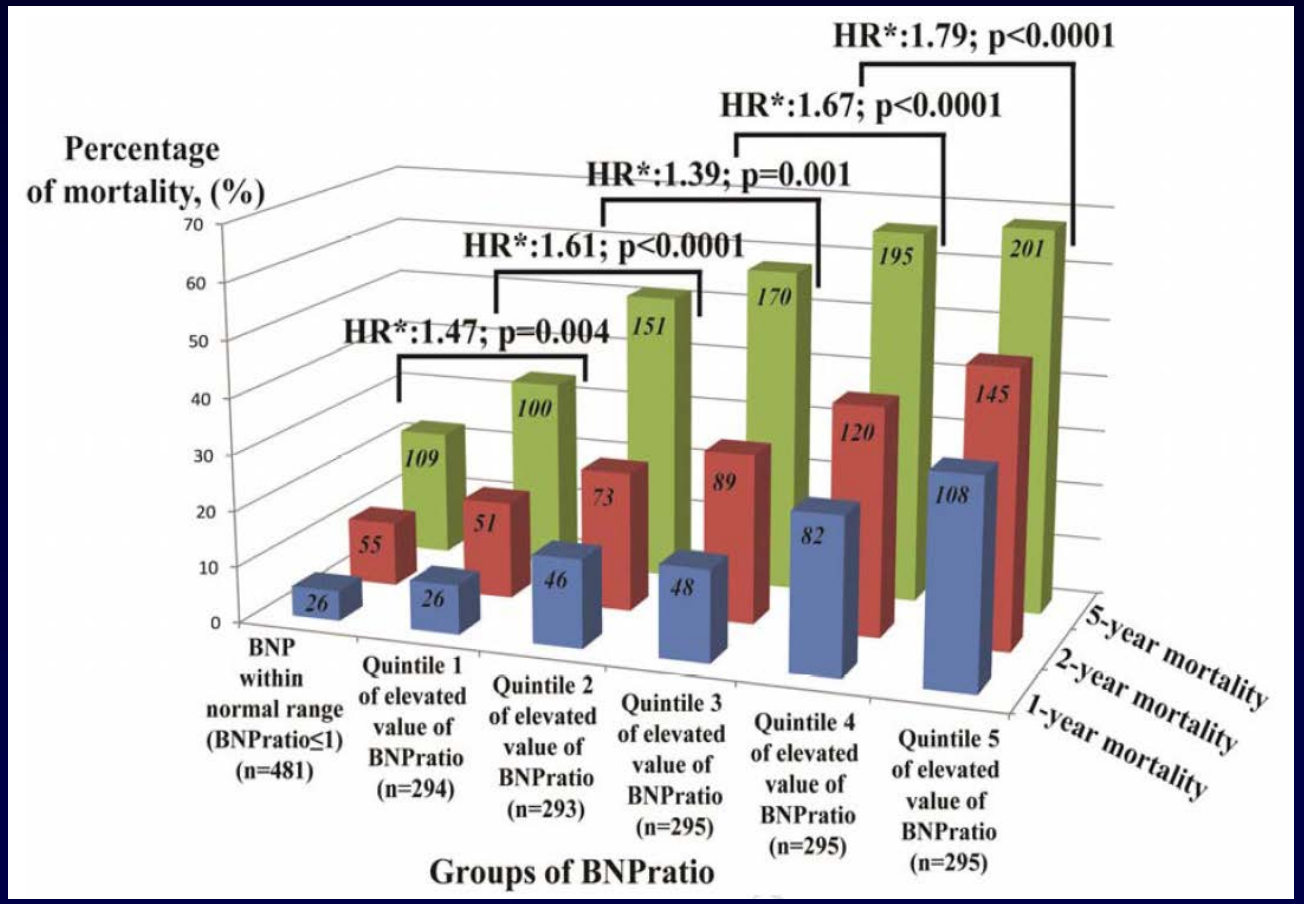
1953 pts > moderate AS
76 ±12 y, Sympt 60%
BNP 252 IQR 98-592

Clavel MA, Malouf J, Michelena H,... Enriquez-Sarano et al. JACC 2014; March

BNP Ratio linked to AS Mortality

Quantitative increase of BNP Ratio linked to increased mortality

1953 pts

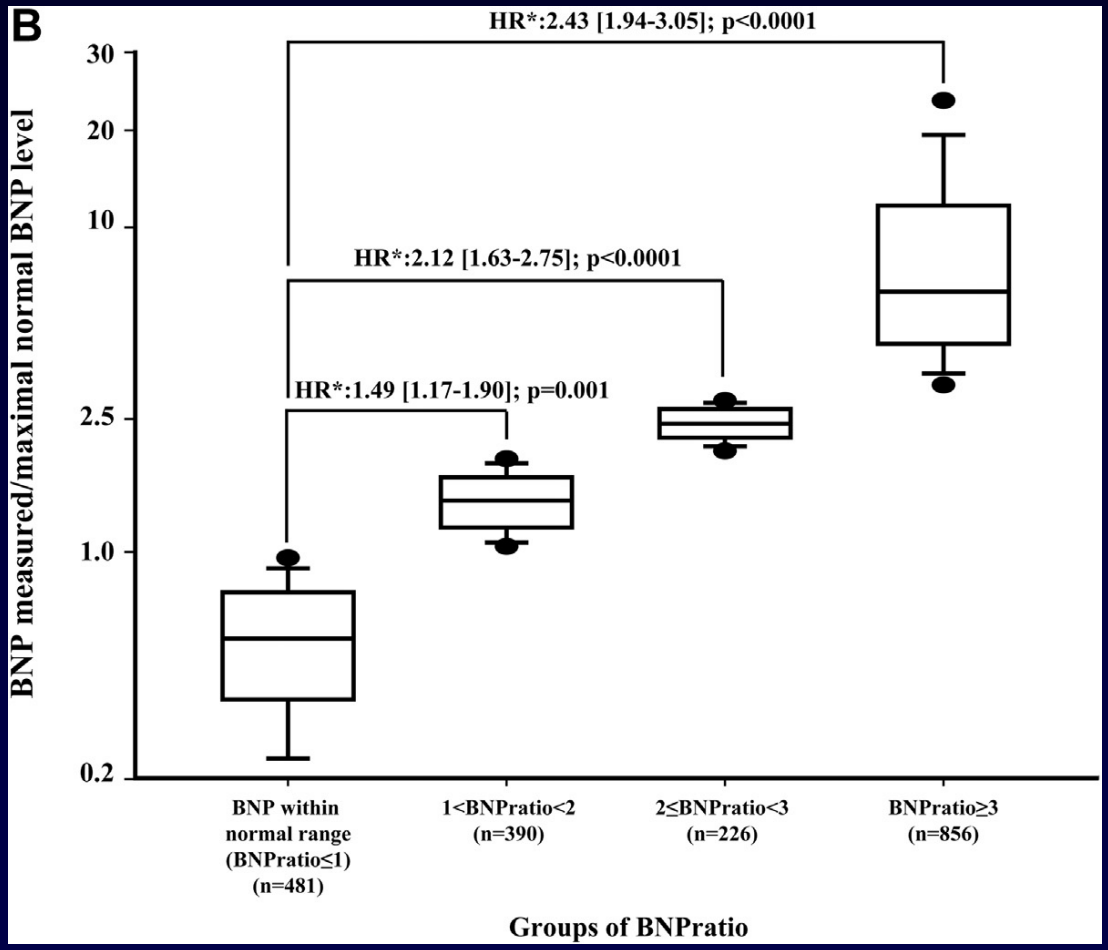


Clavel MA, Malouf J, Michelena H,... Enriquez-Sarano et al. JACC 2014; March

BNP and Mortality Risk in AS

elevated BNP ratio <2 → 49% increased mortality risk
BNP ratio 2-3: 112%
BNP ratio >3: 143%

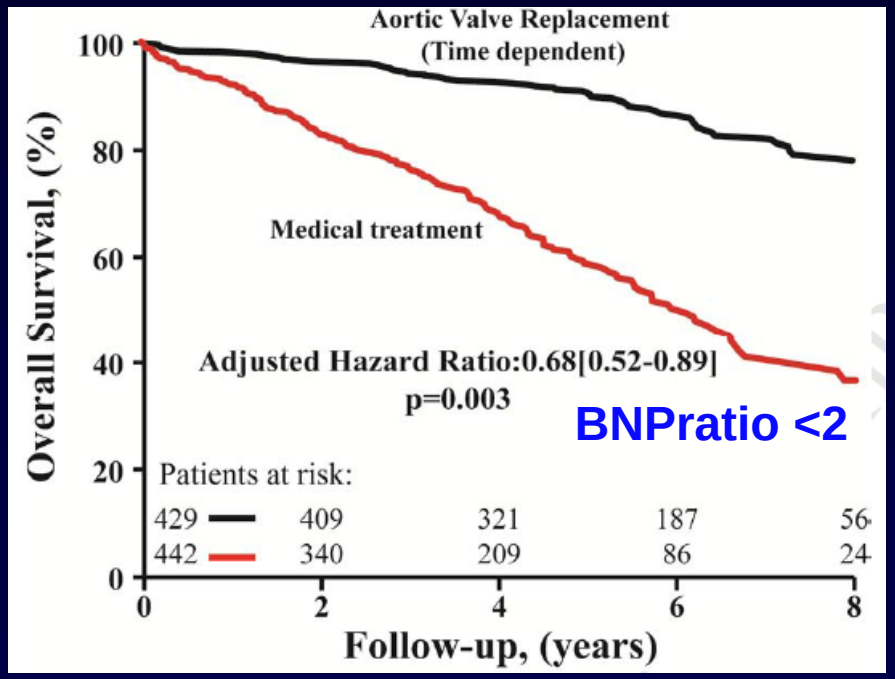
adjusted HR
for baseline characterist.

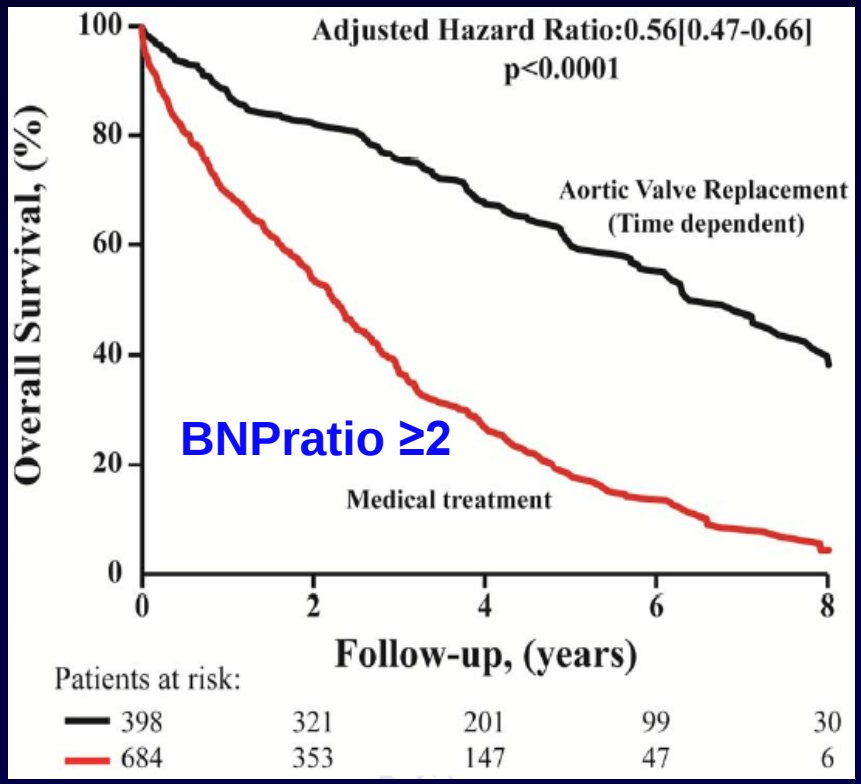


Clavel MA, o et al. JACC 2014; March

Increased BNP and AVR

Higher risk in higher BNP ratio group.
→ but AVR improves survival in both groups: BNP is AS related.





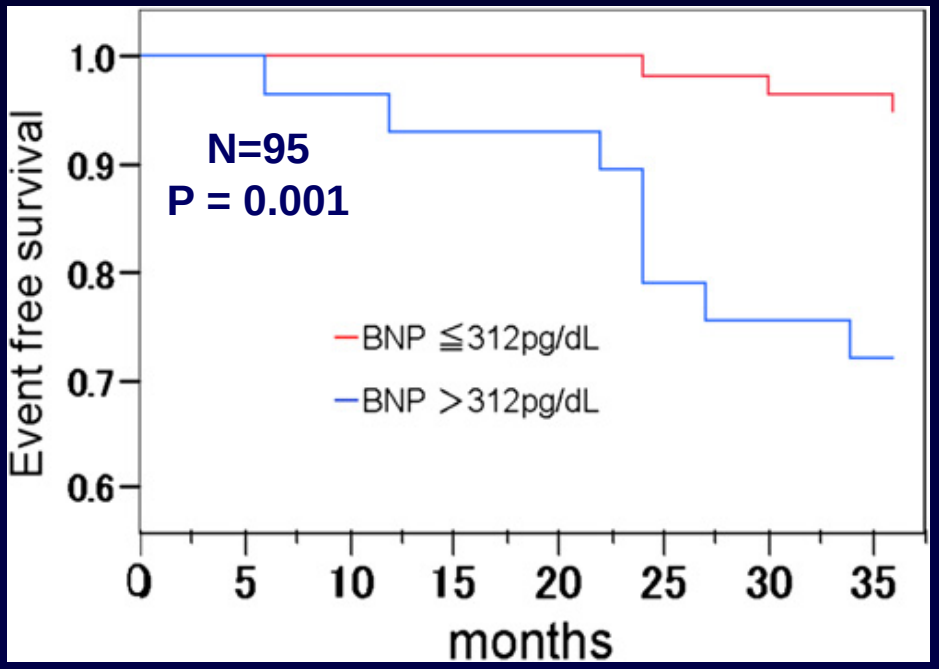
Clavel MA, Malouf J, Michelena H,... Enriquez-Sarano et al. JACC 2014; March

Survival after AVR

High preop BNP >312 strongest predictor of MACE, rehospital, heart fail, periop. complications, arrhythmias.

→BNP reflects Myocardial structure, related to LV mass + EF

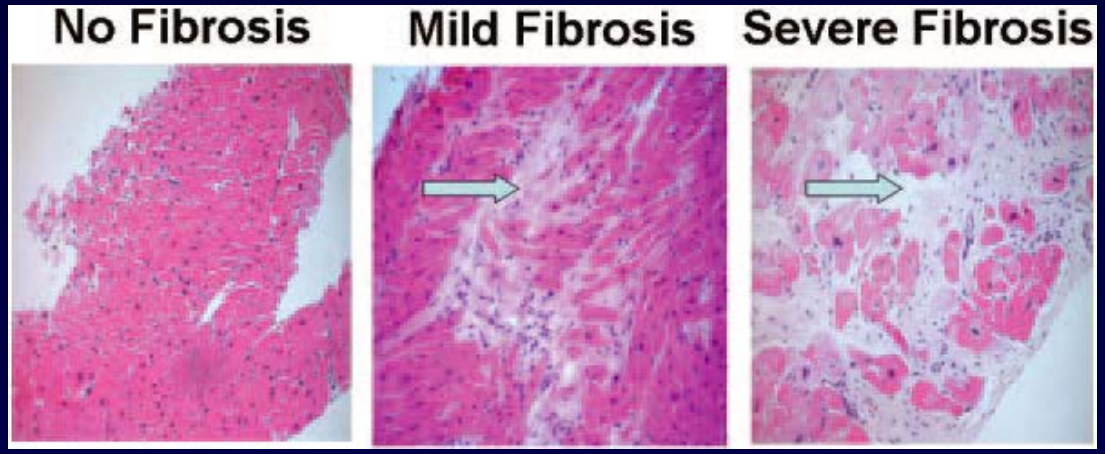
Postop survival



Iwahashi N et al. JASE 2011; 24:984

Fibrosis and BNP in AS

- Myocardial fibrosis related to longitud. strain desp. normal EF
  - MRI pos. late enhancement: replacement fibrosis
  - Higher NT-BNP 2043 vs 377 no fibrosis
  - Fibrosis related to worse outcome, LVF after AVR
  - Paradox. low-flow AS: more subendocard. fibrosis in MRI



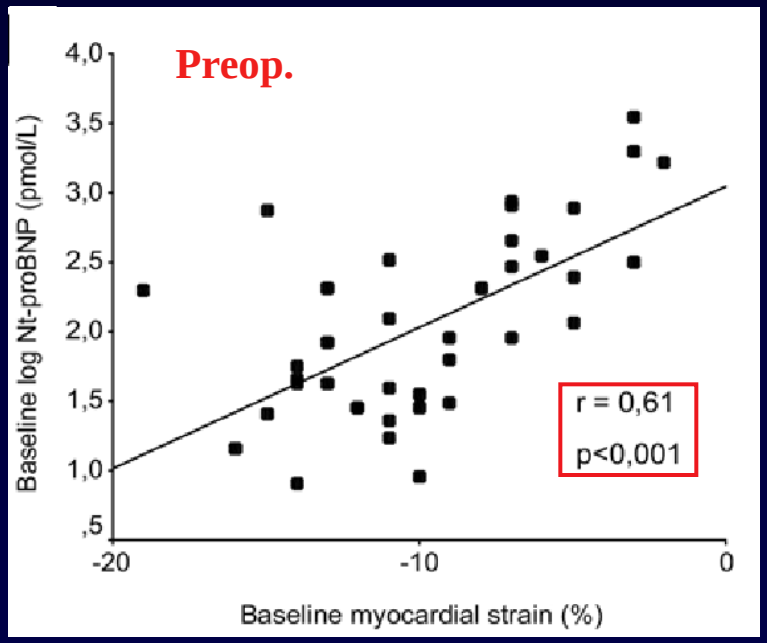
N=58
symptom. severe AS
MRI fibrosis + biopsies

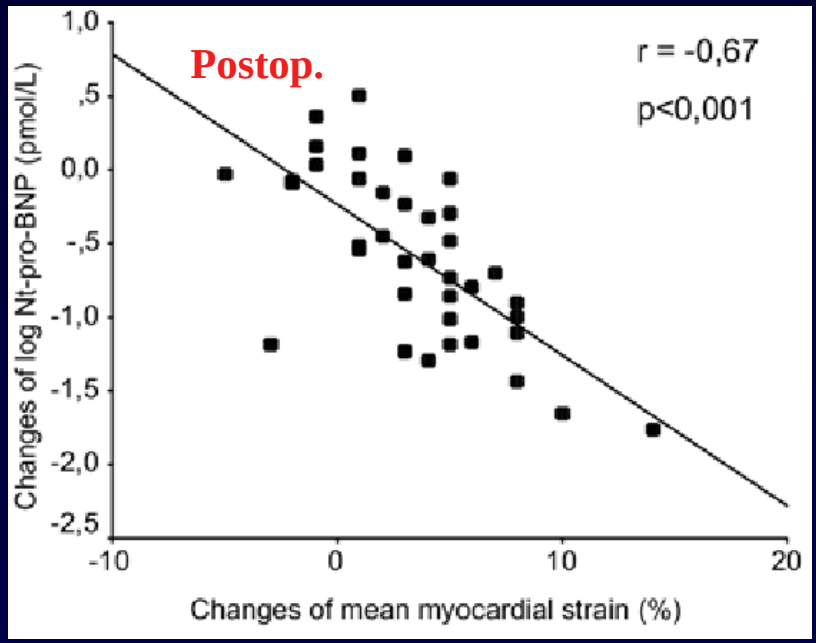
Weidemann F, Circulation 2009
Herrmann S, Weidemann F, J Am Coll Cardiol 2011

Longit. Strain and NT-BNP: Recovery after AVR

Strain TDI related to NT-BNP in AS, reflects LV deterioration despite preserved EF. Postop. recovery of BNP and strain.

45 pts, no CAD



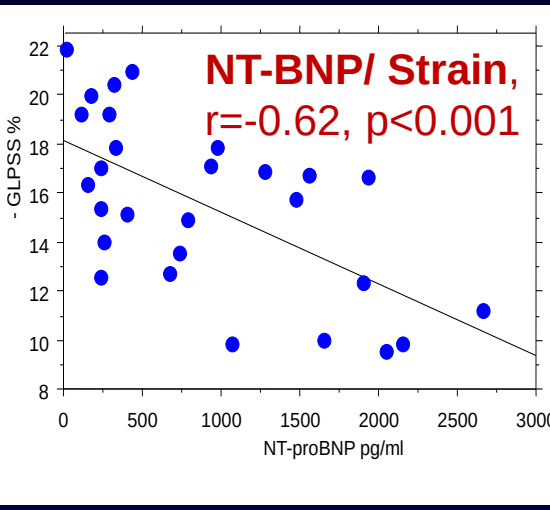


Poulsen S, Sogaard P et al. J Am Soc Echocardiogr 2007;20

NT-BNP and 2D Strain Outcome in Severe Asympt. AS

Need for AVR, 6-12mo: NT-BNP previous visit >800, longit strain <13%
NT-BNP related to impaired strain in 2D speckle tracking

	Remained Asympt. (157)	Recommended AVR (31)	P
Age	61 ±19	67 ±14	n.s./0.07
AVA	0.69 ±0.14	0.59 ±0.18	0.002
MG	62 ±17	79 ±26	<0.0001
EF 50-55/<50	3	4 / 2	<0.0001
NT-proBNP	**248** (128-543)	**940** (530-1846)	**<0.0001**



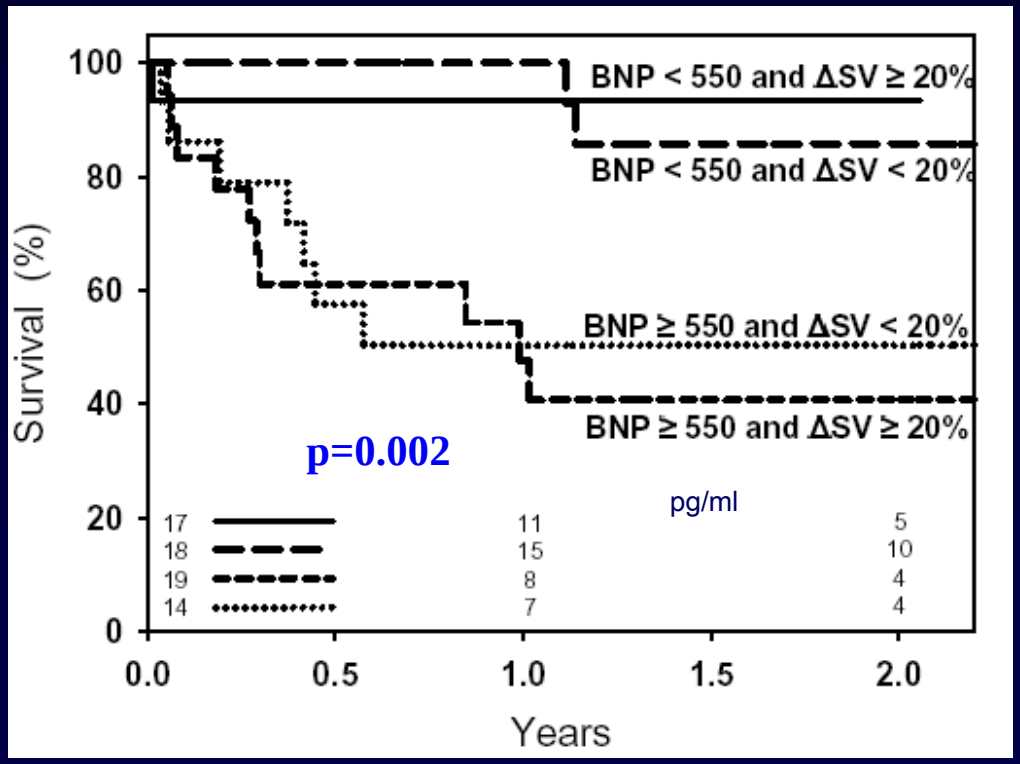
NT-BNP p<0.0001, MG p=0.03, independent predictors

Bergler-Klein et al. ACC 2010. Can J Cardiol 2014

BNP for Risk Stratification in Low Flow Low Gradient Low EF AS

Survival poor in high BNP ≥550

Independent of Contractile Reserve →even without CR and low BNP better outcome →AVR, no CR and high BNP →TAVI?



Multicenter **TOPAS**

True or Pseudosevere AS Study

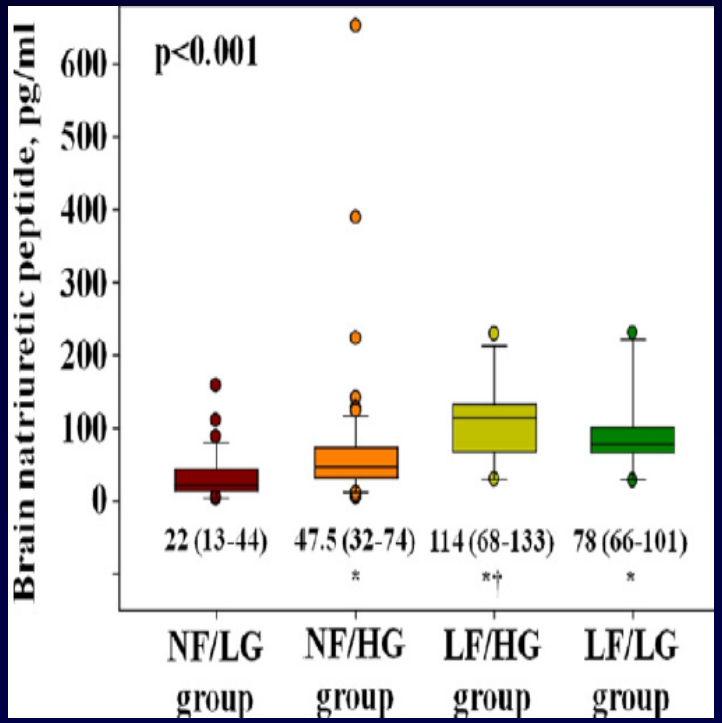
Quebec, Vienna, Ottawa, Muenster

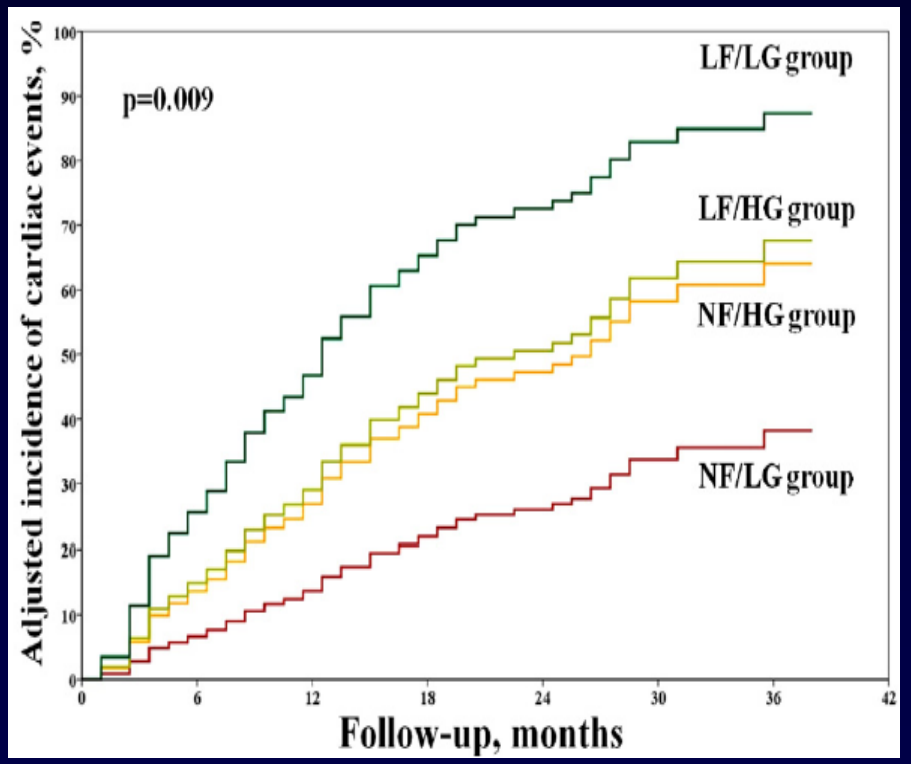
Bergler-Klein, Pibarot P, Dumesnil J, Circulation 2007

BNP and Low Flow AS

Preserved EF >55%, Asymptom. AVA <1, Low Flow <35 ml/m²

Low Flow pattern: higher BNP, impaired longit. LVF, poor survival





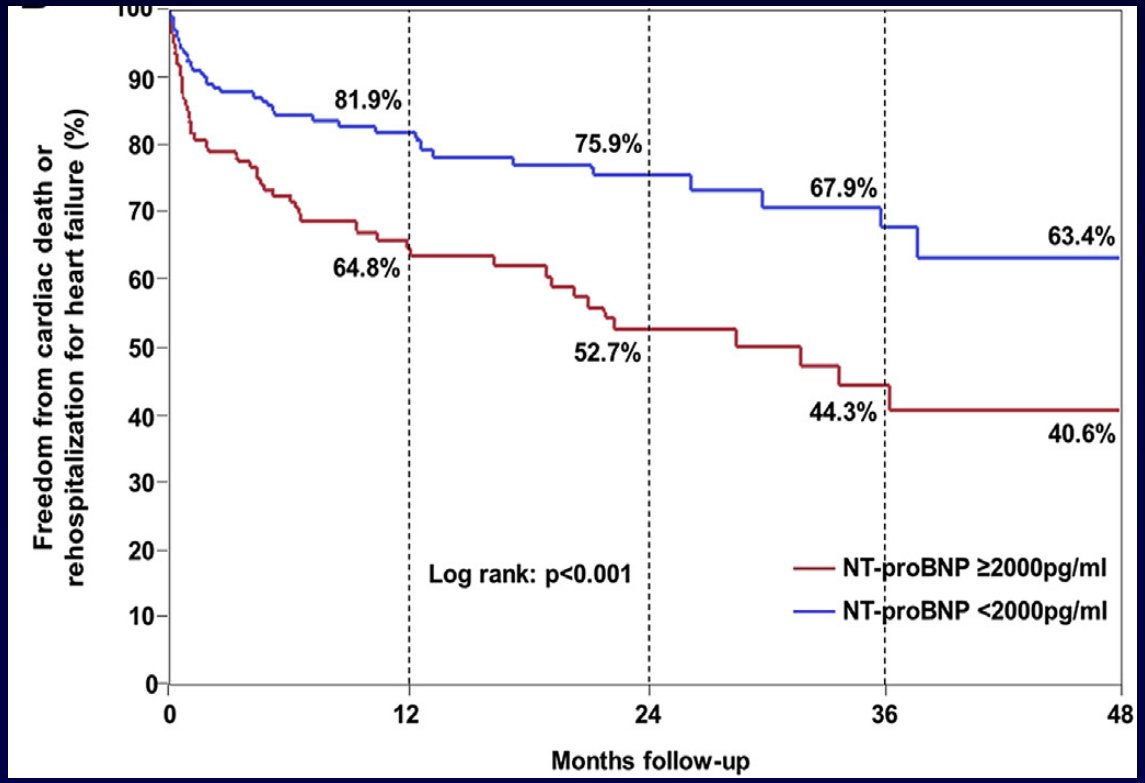
Lancellotti P, J Am Coll Cardiol 2012.

NT-BNP and TAVI

- Higher baseline NT-/ BNP →higher event rate and death after TAVI
- Lack of BNP improvement after TAVI predicts poor outcome

333 pts

>2000 NT-BNP
Worse survival



Ribeiro H, Pibarot, Rodes Cabau, Am J Cardiol 2014

NT-proBNP Predictor for outcome after transfemoral TAVI?

MEDICAL UNIVERSITY OF VIENNA

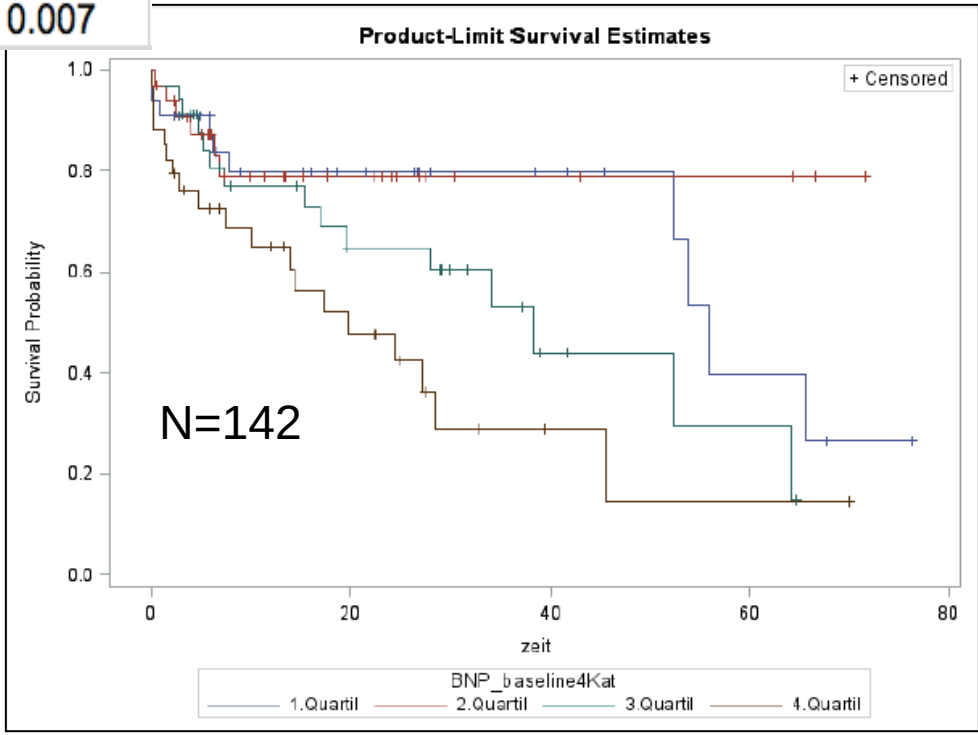
	Median NT-proBNP pg/ml	IQR pg/ml	p
Baseline	1912	1040-4750	-
30 d FUP	1715	858-3455	0.055
6 m FUP	1214	632-2806	0.003
1 y FUP	1271	654-2395	0.007

Decrease of NT- BNP after TAVI

Survival rate 1 yr **75.6% CI 0.67-0.82**
Reduction of **NYHA class p=0.0001**

Baseline NT-BNP impact on survival:
HR 1.339; p=0.0116 ➔ increased mortality in upper quartiles

Course of sequential NT-proBNP on survival: **HR 1.58; p=0.0002**



Scherzer S, ... Bergler-Klein J, EACVI 2015

BNP clinically useful in AS

	NT- BNP	
Symptom. severe AS	+	Surgery indicated. BNP for risk evaluation, AVR outcome
Asymptom. severe AS	+	High or serial BNP (exercise, Ratio) to predict symptoms + EF deterioration
Unclear symptoms in severe AS	+	Symptoms differentiation: e.g. dyspnea - pulmonary
Moderate AS	+	Rising serial BNP may point to progression of severity
Timing of AVR, FU	+	High or increasing serial BNP (>130) NT-proBNP (>700)
Low Flow AS, low EF	+	Risk stratification, prognosis
Paradox. Low flow AS	+	Reflects LV afterload, fibrosis
TAVI	+	High BNP pre+ post TAVI → mortality

Bergler-Klein, Can J Cardiol 2014

Conclusion

- NT-pro / BNP easy to determine, reflects the overall LV burden in AS.
- New concepts of exercise BNP and BNP ratio for age and gender.
- Baseline individual BNP and serial increase *together* with echo + clinics are useful in FU of AS.

➢ High BNP translates into higher risk

- ***Thank you***

BNP Risk Score for Asymptom. AS

Independent Predictors of Outcome, validated by 2nd cohort

N=107	Odds ratio	95% confidence interval	p
Baseline BNP	**3.9**	**1.8 - 8.1**	**0.0001**
Baseline Peak Velocity	**6.2**	**2.1 - 17.9**	**0.001**
Female gender	**5.2**	**1.5 - 18.6**	**0.012**

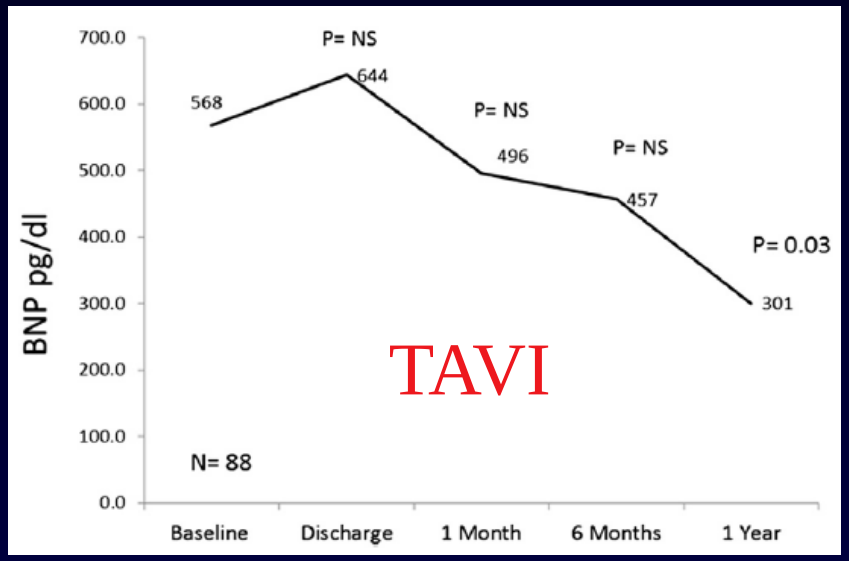
→ **Interplay of valve obstruction and LV function**

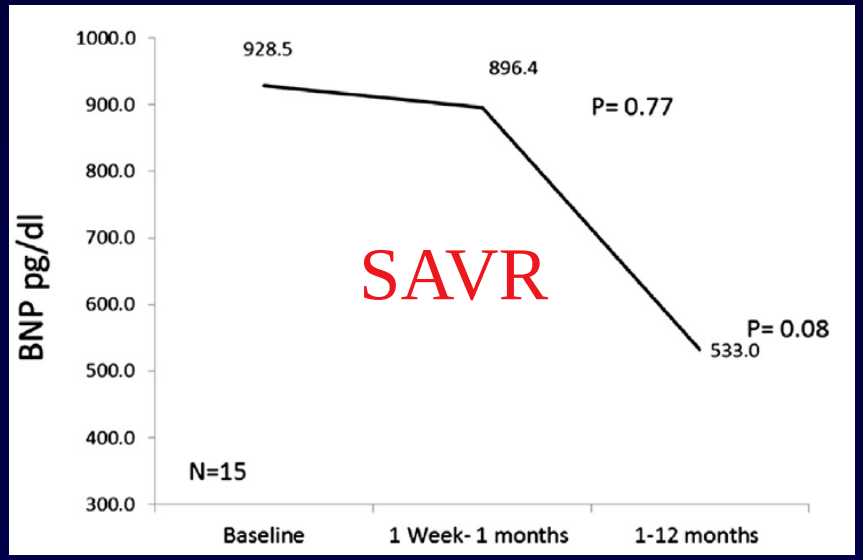
RISK SCORE:

[**Peak velocity (m/s) x 2**] + [**natural Log BNP x 1.5**] **+1.5** (female)

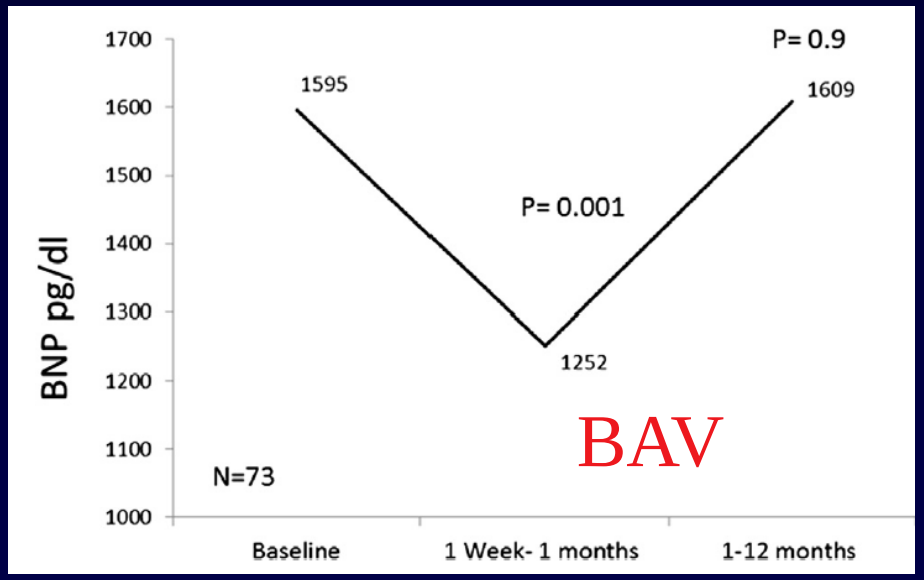
Monin JL, Lancellotti P et al. Circulation 2009; 120:69-75

Serial BNP in TAVI, SAVR, BAV





TAVI or SAVR pts had lower BNP than BAV pts in worse status, rise long term associated with mortal. More likely to tolerate procedure and benefit long term in low BNP.



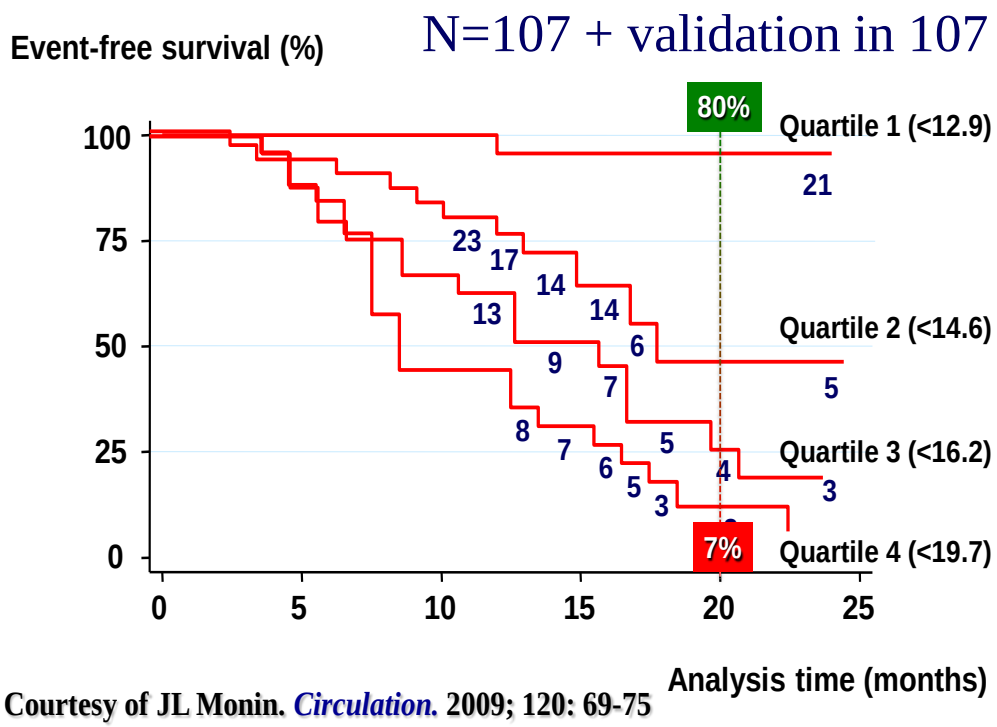
Ben-Dor I, Am J Cardiol 2013

Risk Score for Asymptom. AS

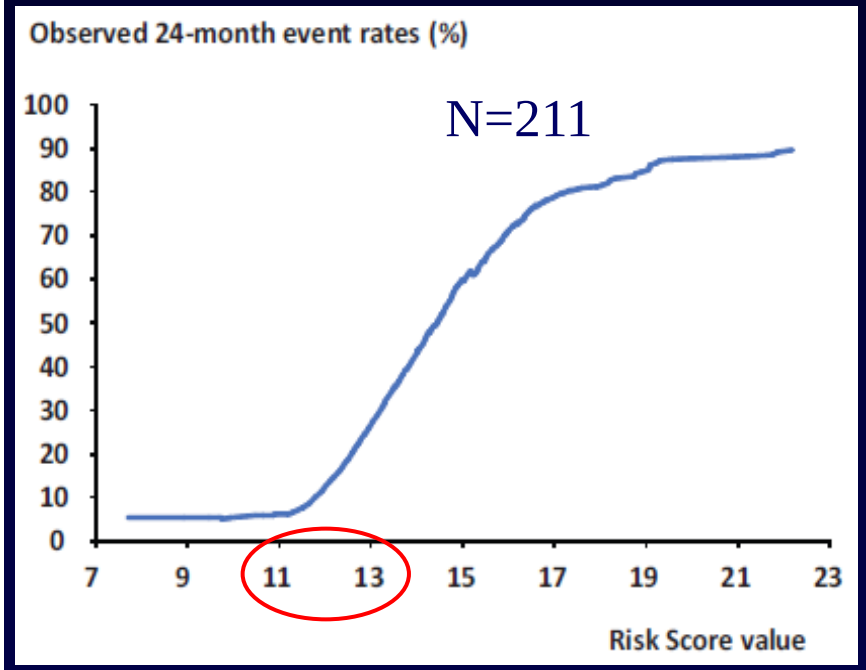
BNP incremental prognostic signif. over AV Velocity
at multivariable analysis.

Increase of events in Score >11-13 (symptoms, death) at 24 months

Outcome according to Score quartiles (Development cohort: Créteil, FR)



Courtesy of JL Monin. *Circulation.* 2009; 120: 69-75



Monin JL, Lancellotti P et al. Circulation 2009; 120

Elevated BNP in Asympt. AS

- Follow patient closely: echo, clinical FU

  → Increased risk of symptom development, clinical deterioration, acute heart failure, in AVR postop complications
- Consider atrial fib, CAD, renal failure
- Low Flow pattern despite preserved EF, impaired longitudinal strain

→ High BNP translates into higher risk

Comparison of main AS entities: Typical findings

	Severe AS		
	Normal-Flow, High-Gradient	Preserved LVEF (Paradoxical), Low-Flow, Low-Gradient	Reduced LVEF, Low-Flow, Low-Gradient
Aortic valve area, cm^2	≤1.0	≤1.0	≤1.0
Indexed aortic valve area, cm^2/m^2	<0.6	<0.6	<0.6
Mean gradient, mm Hg	>40	<40	<40
Z_{va}, mm Hg·ml^{-1}·m^2	>4.5	>4.5	>4.5
LV end-diastolic diameter, mm	45–55	<47	>50
Relative wall thickness	>0.43	>0.50	0.35–0.55
LVEF, %	>50	>50	<50
Mitral ring displacement, mm	5–15	<8	<8
Global longitudinal strain, %	14–20	<14	<14
Stroke volume index, ml/m^2	>35	<35	<35
Mean flow rate, ml/s	>200	<200	<200
Myocardial fibrosis	+	++	+++
CT valve calcium score, AU	>1,650	>1,650	>1,650
Plasma NT-proBNP, pg/ml	<1,500	>1,500	>1,500

Pibarot, Dumesnil. J Am Coll Cardiol 2011;58:402–12

Herrmann S, Weidemann F et al. J Am Coll Cardiol 2011;58:402–12

Treadmill Exercise in Asympt. AS
BNP Predicts Symptoms + Cardiac Index

- Strongest resting predictor of revealed symptoms and of peak cardiac index was BNP, p<0.001, r=-0.71
- N=65, AVA<1.5, asymptom. Pts, age ± 63, preserved EF

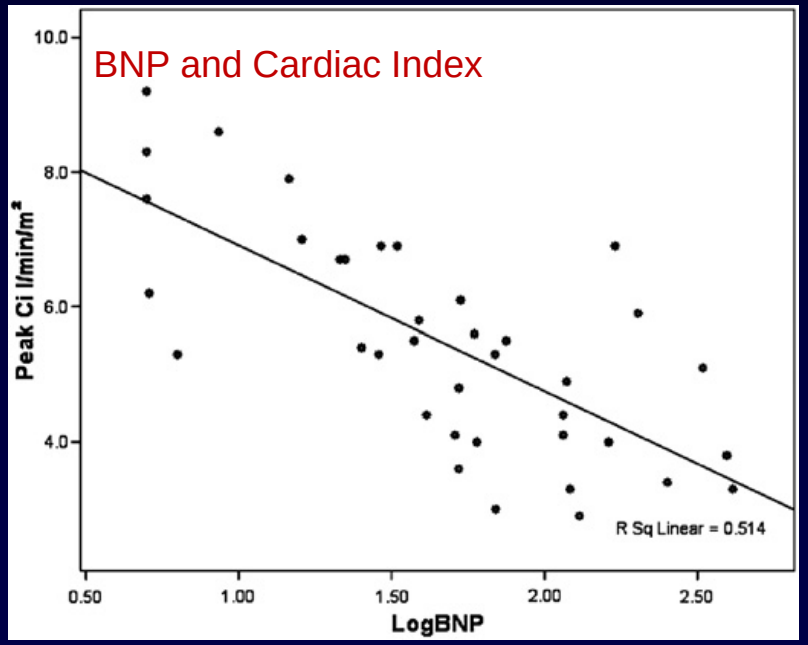


Table 4 Echocardiographic variables and BNP in patients with or without symptoms on exercise

	Asymptomatic N=28	Symptomatic N=10	p Value
Valve function			
EOA (cm^2)	1.04±0.28	0.86±0.26	0.09
EOA index (cm^2/m^2)	0.53±0.13	0.43±0.12	0.03
ΔP peak* (mm Hg)	55±24	60±23	0.53
ΔP mean† (mm Hg)	33±13	36±17	0.49
SWL (%)	18±6	19±7	0.7
Left ventricular function			
Fractional shortening (%)	39±8	38±10	0.93
Doppler tissue S (cm/s)	6.7±1.3	6.2±1.2	0.31
E/Ea	13.1±5.1	15.6±5.8	0.21
BNP (pg/ml)	55±55	186±146	0.02
Log BNP	1.5±0.5	2.13±0.37	<0.001

Rajani R, Rimington H, Chambers J. Heart 2010; 96:689-95

Impact of Global Afterload and Low Flow on Strain and BNP in Asympt. AS

Intrinsic LV dysf: Highest BNP in low flow + high afterload severe AS

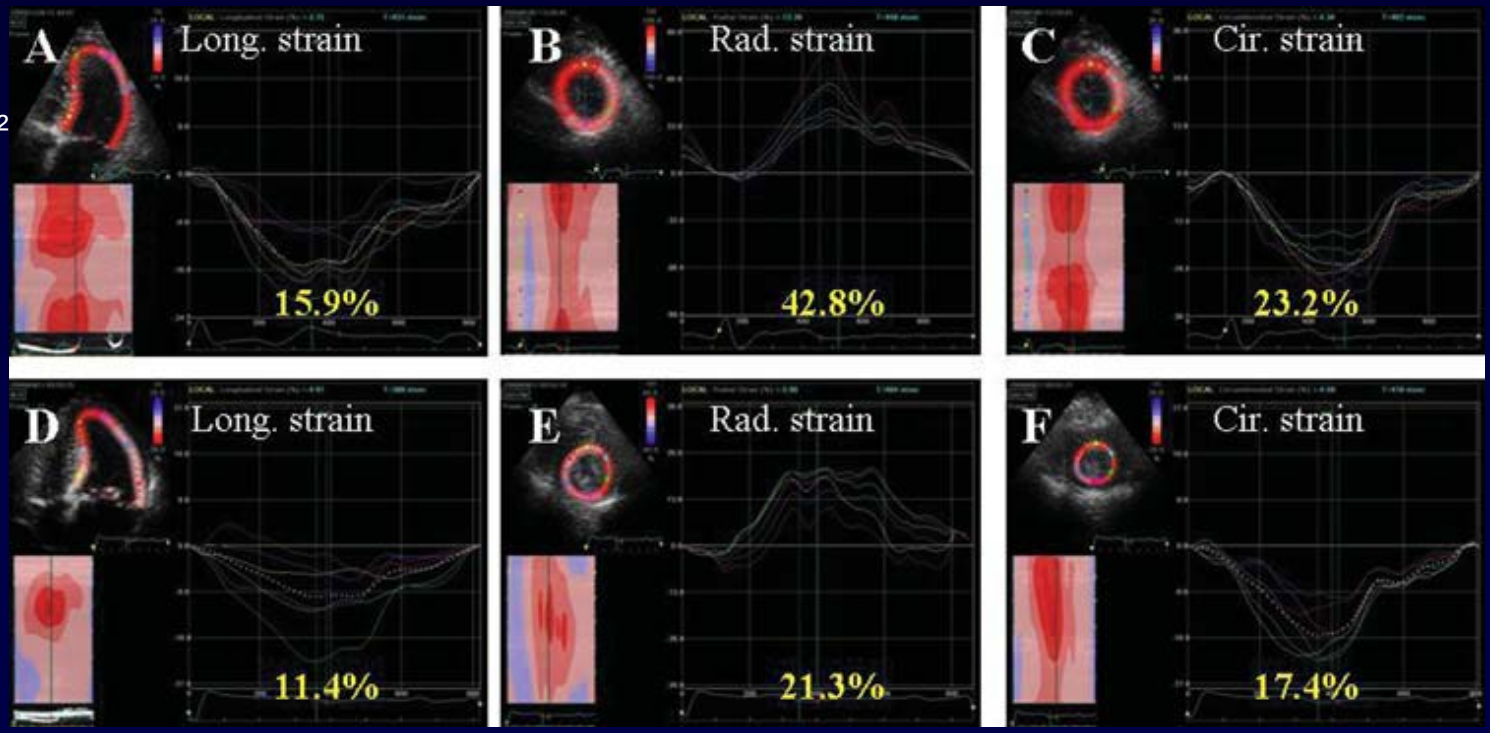
209 ±318 vs 68 ±83 pg/ml in normal flow, p<0.001

Valvulo-art.impedance Zva = Systol BP +Mean Grad./ StrokeVol ind

N=173, EF ≥55. 22% with SVi <35 ml/m² ,

Zva < 5
mmHg ml/m²

Zva > 5

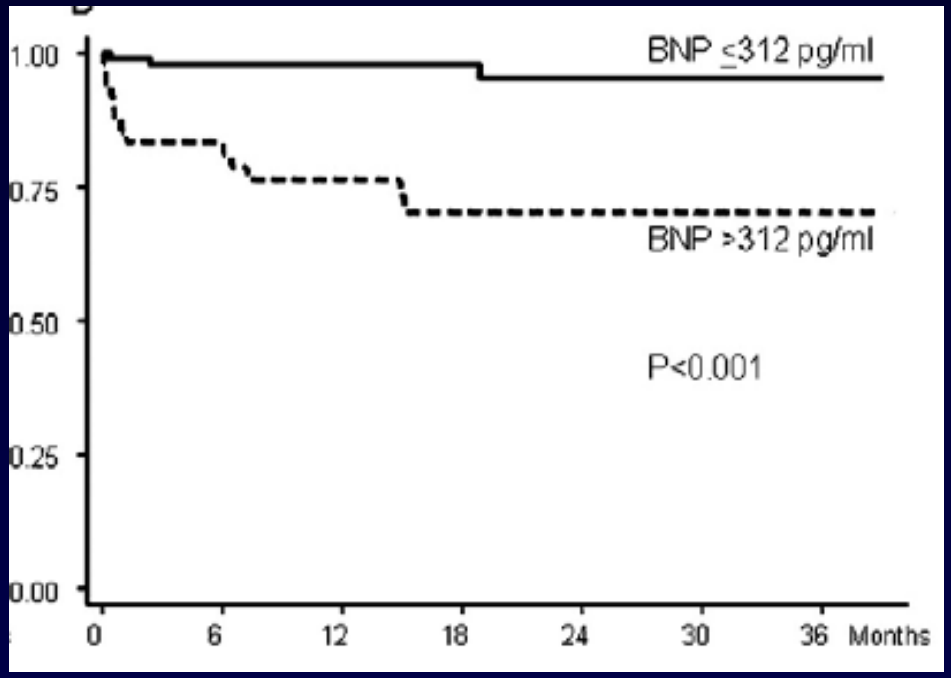


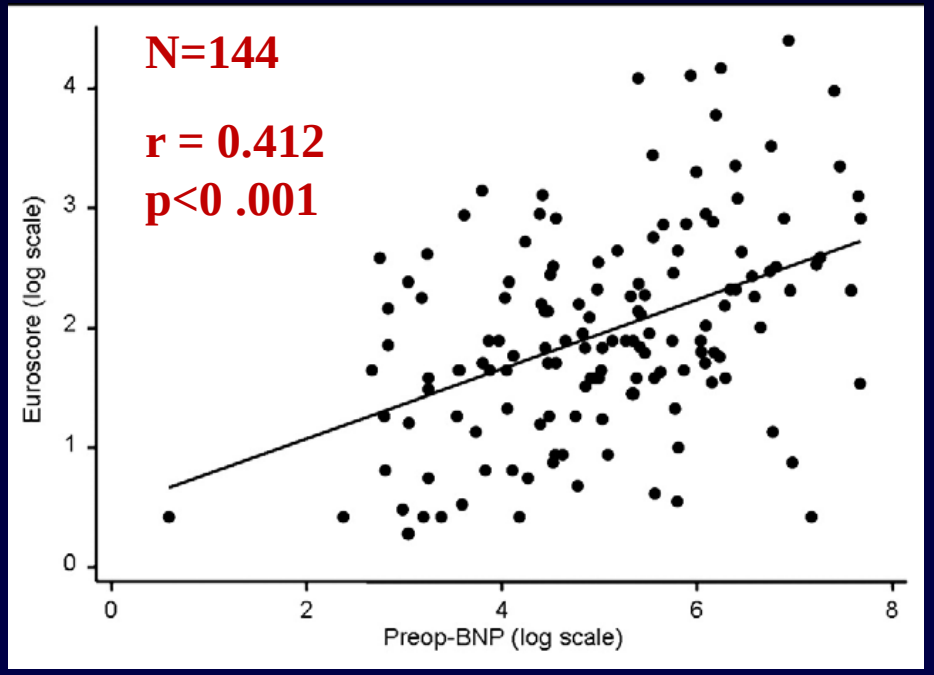
Lancellotti P, Donal E, Magne J , Eur J Echo 2010

Surgery: BNP and Euroscore in AS

Preop BNP and logistic ES signif. related in sympt. AS.

Preop BNP >312 superior in predicting postop outcome.

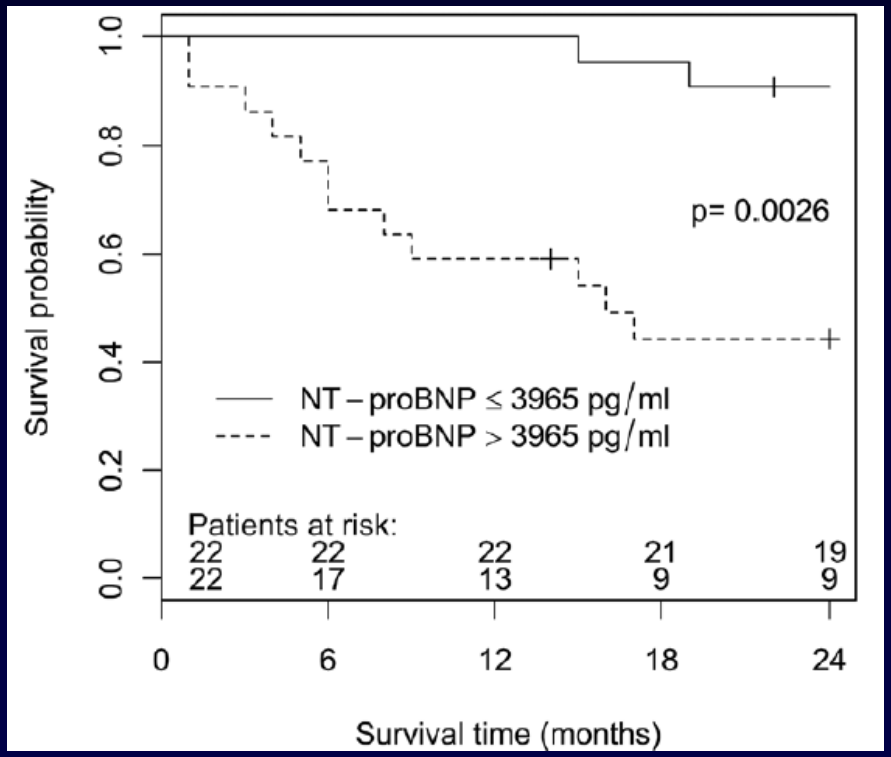


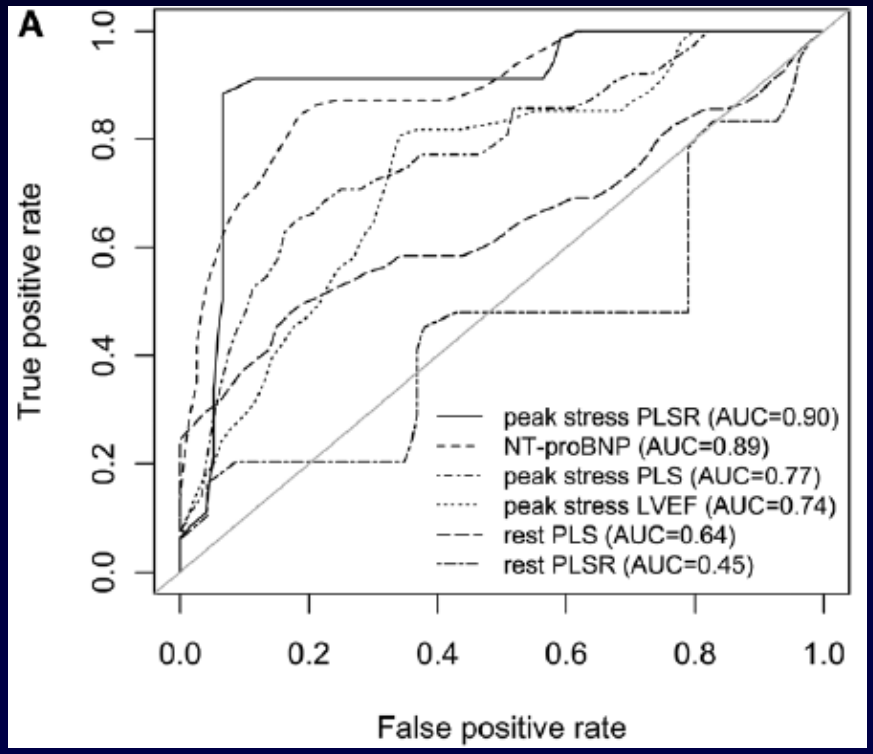


Pedrazzini G et al. Am J Cardiol 2008; 102

NT-proBNP in Low Flow Low Gradient Low EF AS:

- Stress echo: added value of peak strain, rate

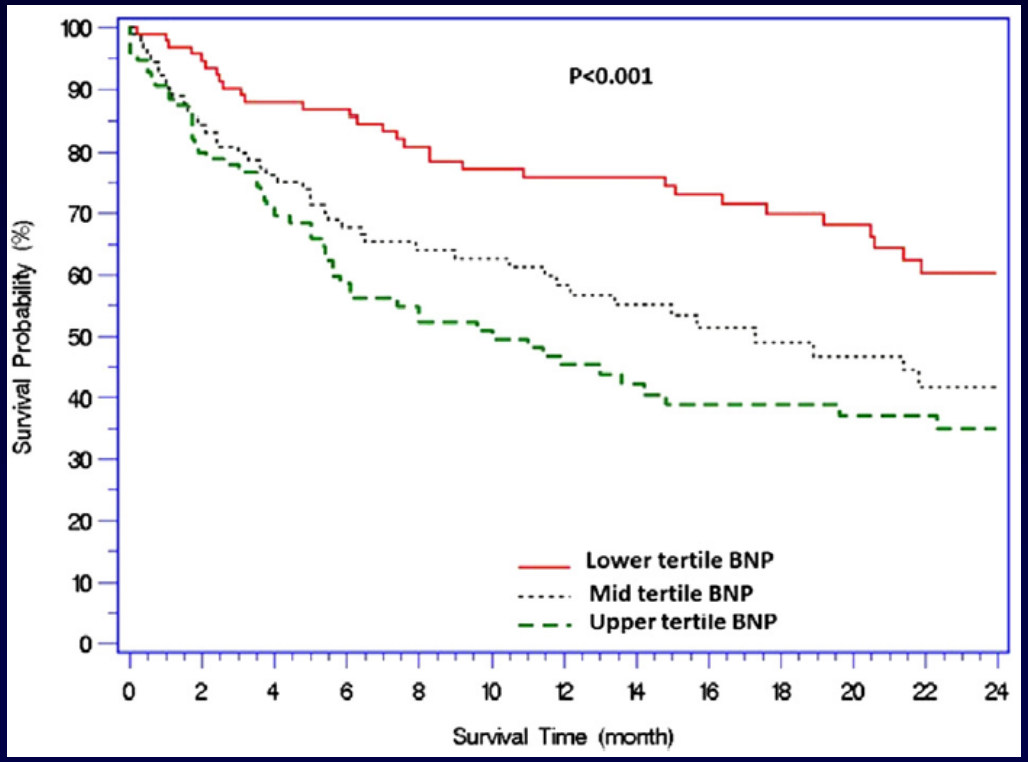




Bartko PE, Pibarot, Circ Cardiovasc Imag 2013

Role of BNP in TAVI?
Predictor of Survival

Better in lower baseline BNP, related to EF, PAPs



BNP marker of deterioration in myocardial performance. Fibrosis, Irrevers.diastol dysfunction

289 high risk severe AS pts referred for TAVI

Ben-Dor I, Waksman R, Am J Cardiol 2013

ESC Valvular Guidelines: BNP

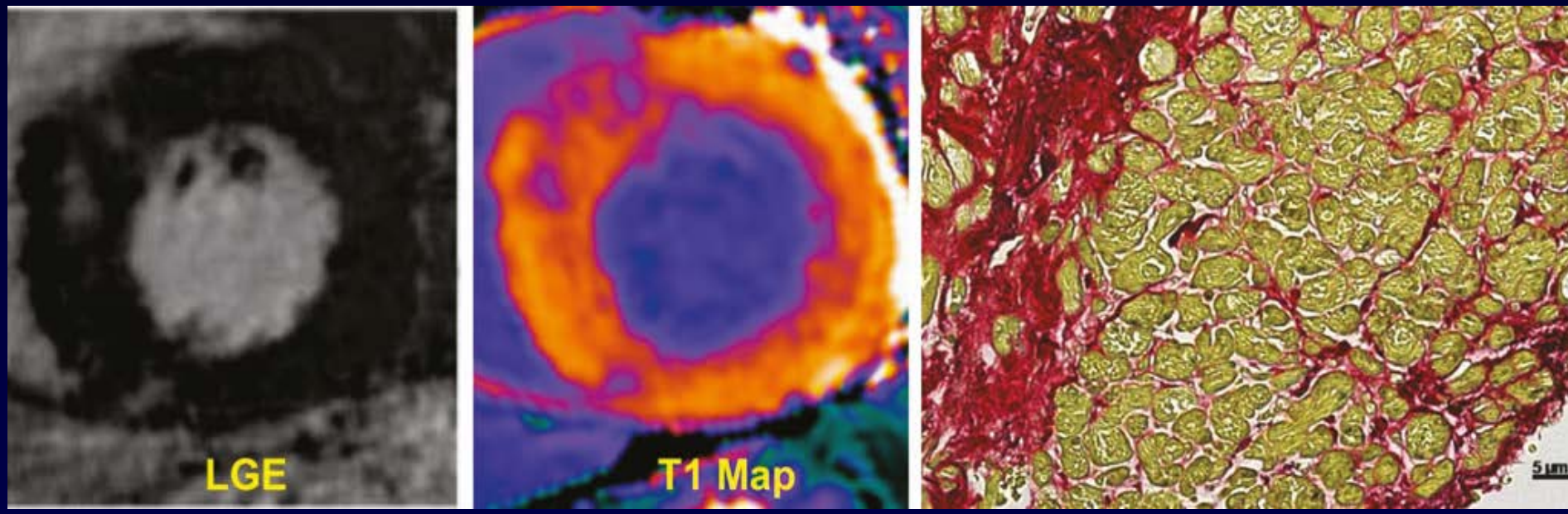
- Natriuretic pept. shown to predict symptom free survival and outcome in severe + low flow AS, may be useful asympt AS
- Elevated natriuretic pept. predictors of symptoms although precise values not well defined
- Surgery may be considered in markedly elevated natriuretic peptide levels confirmed by repeated measurements IIbC

AVR may be considered in asymptomatic patients with severe AS, normal EF and none of the above mentioned exercise test abnormalities, if surgical risk is low, and one or more of the following findings is present: • Markedly elevated natriuretic peptide levels confirmed by repeated measurements and without other explanations • Increase of mean pressure gradient with exercise by >20 mmHg • Excessive LV hypertrophy in the absence of hypertension.	IIb

Vahanian A, Valvular guidelines, Eur Heart J 2012; 33,

Troponin I in AS

Midwall fibrosis and more hypertrophy in ++ Troponine.
Trop was superior to BNP for prognosis: ongoing necrosis



Severe AS, AV Vel 4.8

Chin, Dweck M. Eur Heart 2014; 35