

Fifth Virtual Congress of Cardiology
September 1 to November 30, 2007

Predicting Death in Chagas' Heart Disease

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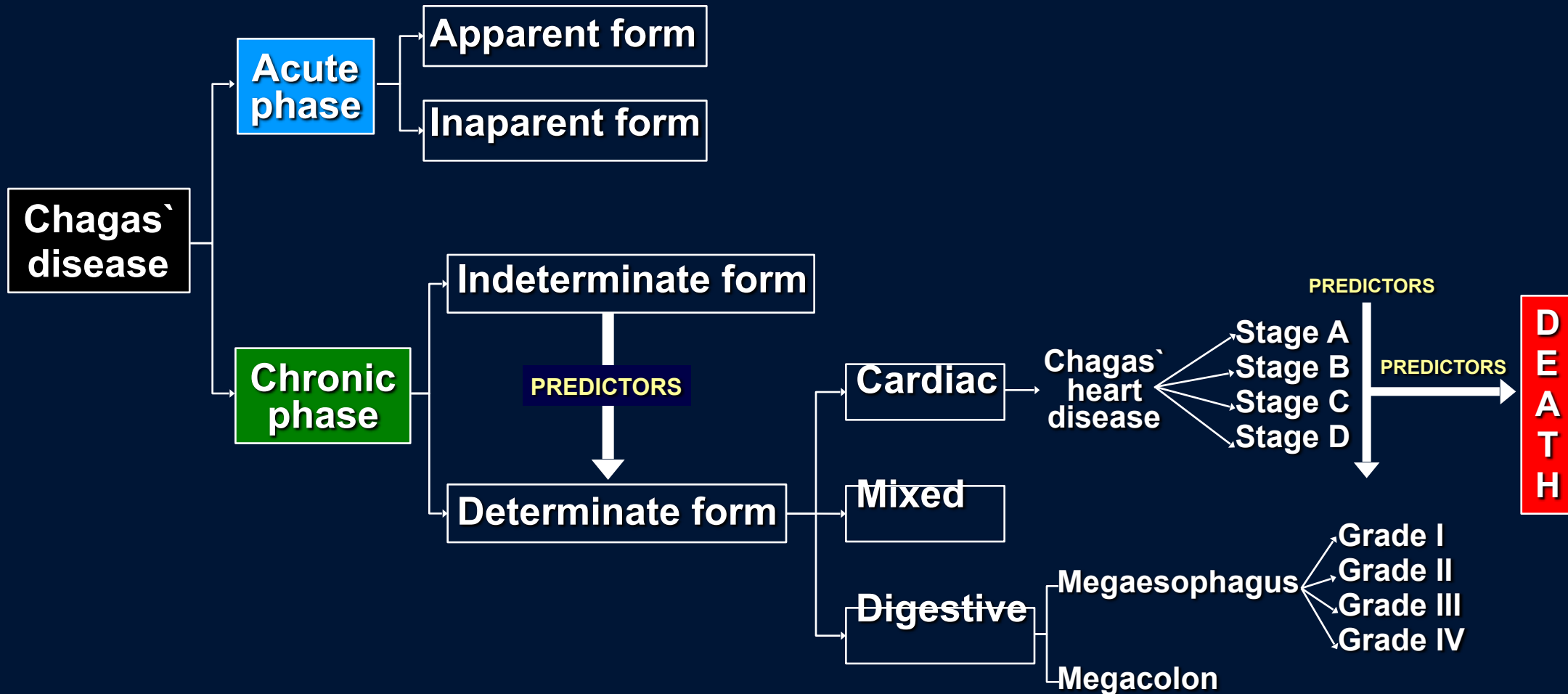
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NO COMPETING INTERESTS



ANIS RASSI HOSPITAL

Chagas` Disease: Phases, Forms, and Stages



Identification of Prognostic Factors

- 3 Notion about the disease severity
- 3 Prediction of individual survival probabilities
- 3 Aim in clinical-decision making
- 3 Guide for clinical trial design and interpretation
- 3 Allocation of healthcare resources (always limited)



Prognostic Markers in Chronic Chagas` Disease

Limitations of Longitudinal Studies of the Last Decades

- Utilization of insensitive methods such as 12-lead ECG and chest x-ray
- Inclusion of selected patients from tertiary centers
- Evaluation of small number of patients for relatively short periods
- Retrospective nature of the investigation
- Study of a heterogeneous cohort (patients with and without manifest cardiomyopathy)
- Univariate methods of statistical analysis



Development and Validation of a Risk Score for Predicting Death in Chagas' Heart Disease

Anis Rassi Jr, M.D., Anis Rassi, M.D., Sérgio X. Salles, M.D., Sérgio G. Rassi, M.D., Alexandre G. Rassi, M.D., Gustavo G. Rassi, M.D., Alejandro Hasslocher-Moreno, M.D., Andrea S. Sousa, M.D., and Maurício I. Scanavacca, M.D.

- 424 nonselected patients with Chagas' heart disease (typical ECG and/or ECHO findings)
- Examined in a single institution during an outpatient visit
- Initial work-up: clinical evaluation and performance of noninvasive tests (ECG, chest r-ray, Holter, HRV, ETT, and echocardiography)
- Mean follow-up of 7.9 ± 3.2 years (3% of losts)

- Objectives:

- 1) to identify the causes of death in outpatients with Chagas' heart disease;
- 2) to assess the prognostic value for mortality of several demographic, clinical and noninvasive laboratorial parameters;
- 3) to develop and validate a risk score model derived by the combination of independent prognostic variables with the potentiality of accurate predicting outcome.

Clinical Evaluation and Noninvasive Studies

Age and gender.....	424 (100%)
Symptoms (palpitations, near-syncope, syncope, pedal edema, dyspnea, and angina).....	424 (100%)
NYHA functional class.....	424 (100%)
12-lead ECG (isolated abnormalities).....	396 (93%)
Chest x-ray (cardiomegaly and pulmonary congestion)...	354 (83%)
Echocardiogram (visual estimation of EF and LVEDD)....	424 (100%)
24-h Holter (frequency and complexity of PVCs).....	374 (88%)
Heart rate variability (time domain).....	259 (61%)
Exercise testing (complex PVCs).....	

Follow-up, Treatment Strategies, and End Point

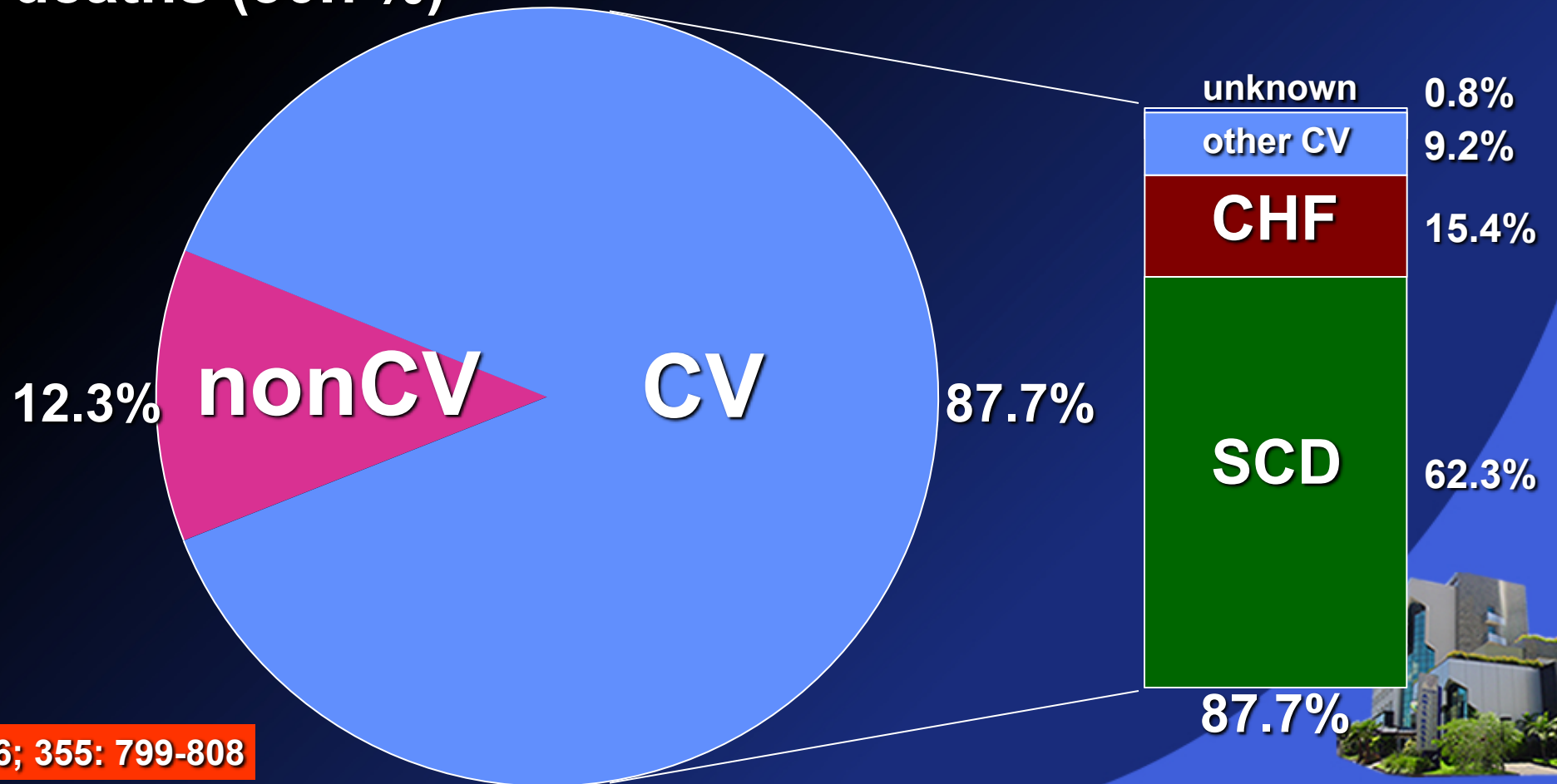
- 3 Follow-up assessment by a single investigator (yearly basis)
- 3 Digoxin, diuretics and/or ACEI for CHF; amiodarone for complex ventricular arrhythmias; aspirin or oral anticoagulants for atrial fibrillation, previous embolic episodes or apical aneurysm with thrombus; and pacemaker for severe bradyarrhythmias
- 3 Date of the last evaluation: 1997-1998 (appointments, telephone interview, active search of information)
- 3 End Point: all cause mortality
- 3 Mode of death classified as cardiovascular (SCD, CHF, stroke, other vascular) and noncardiovascular

NEJM 2006; 355: 799-808

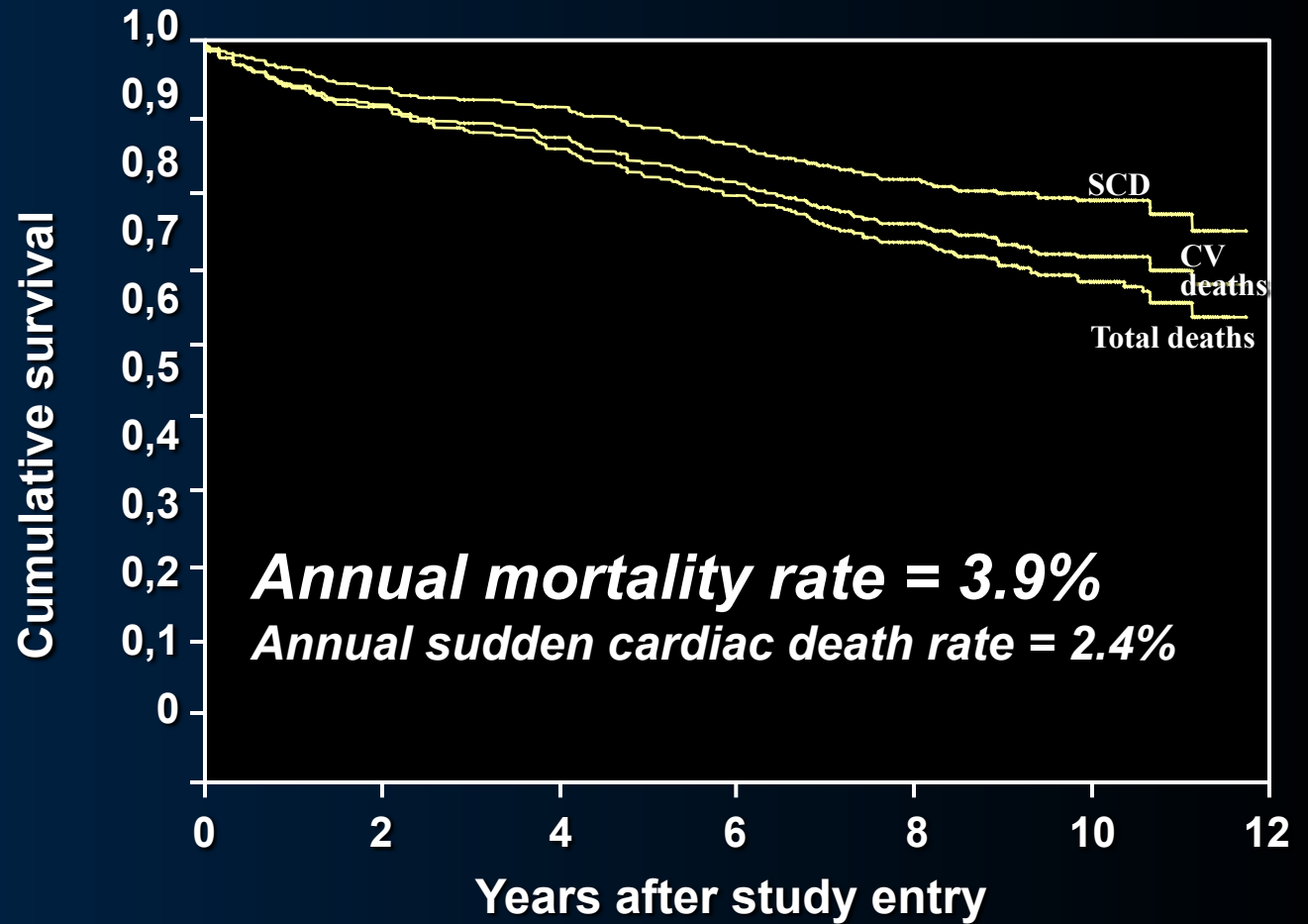


Chagas`Heart Disease: Causes of Death

- 424 nonselected outpatients
- mean follow-up: 7.9 ± 3.2 years
- 130 deaths (30.7%)

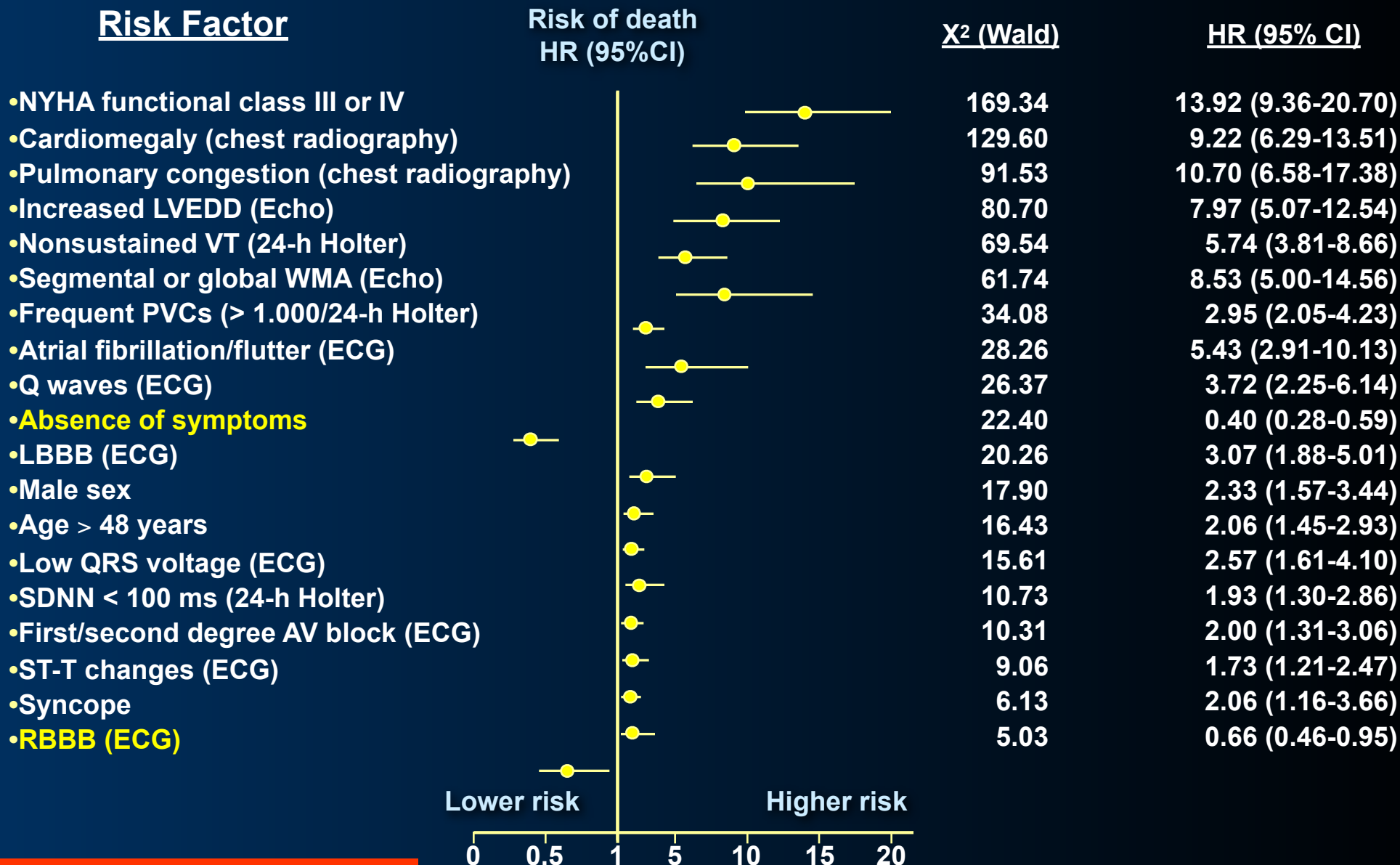


**Actuarial Survival
Curves of 424
Patients with
Chagas' Heart
Disease
(Kaplan-Meier)**



	N	424	386	358	329	269	143
<u>% survival</u>							
SCD	100	94	92	87	82	79	
CV deaths	100	92	88	82	76	72	
Total deaths	100	92	86	80	74	68	

Predictors of Death by Univariate Cox Proportional Analysis



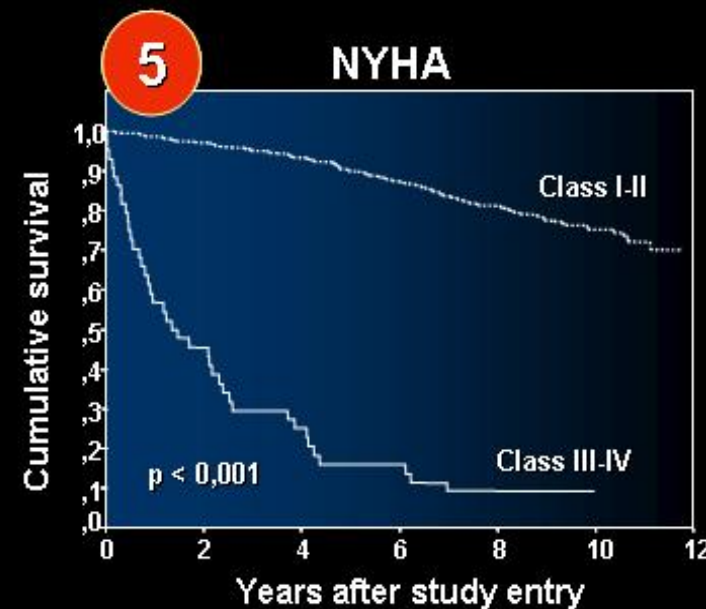
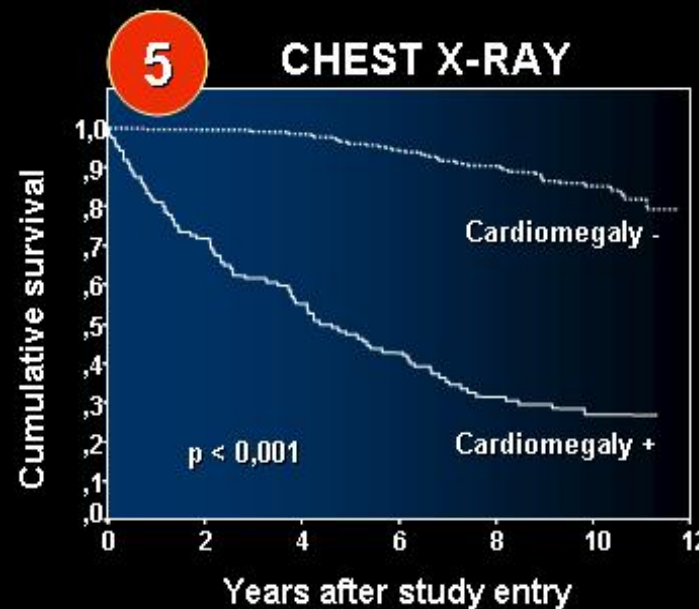
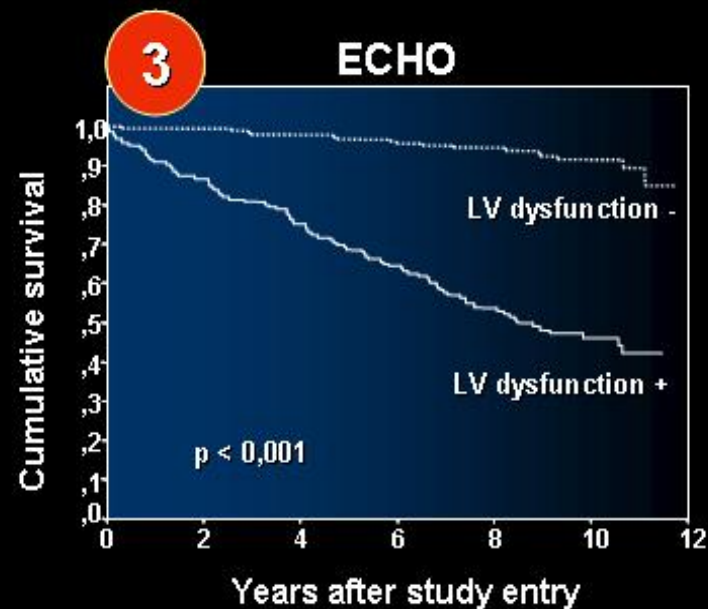
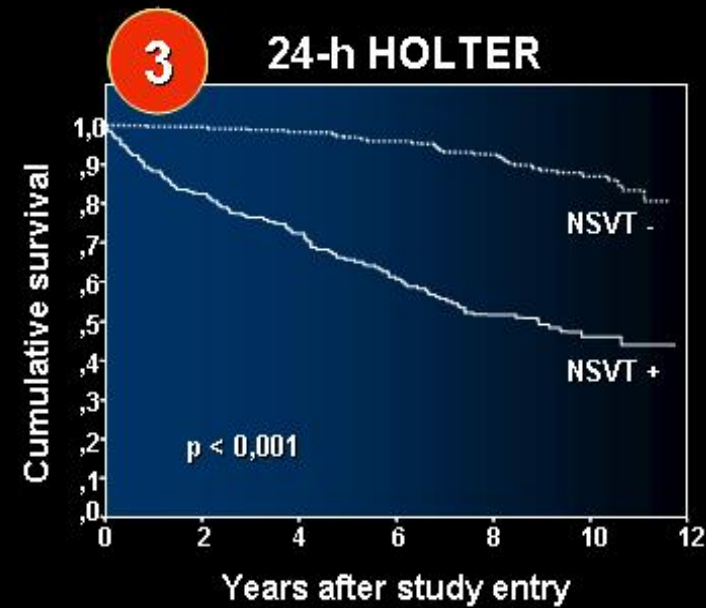
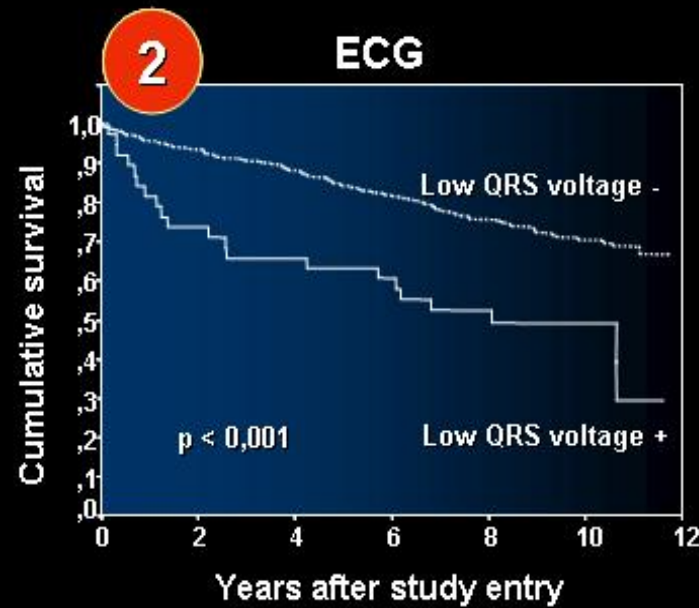
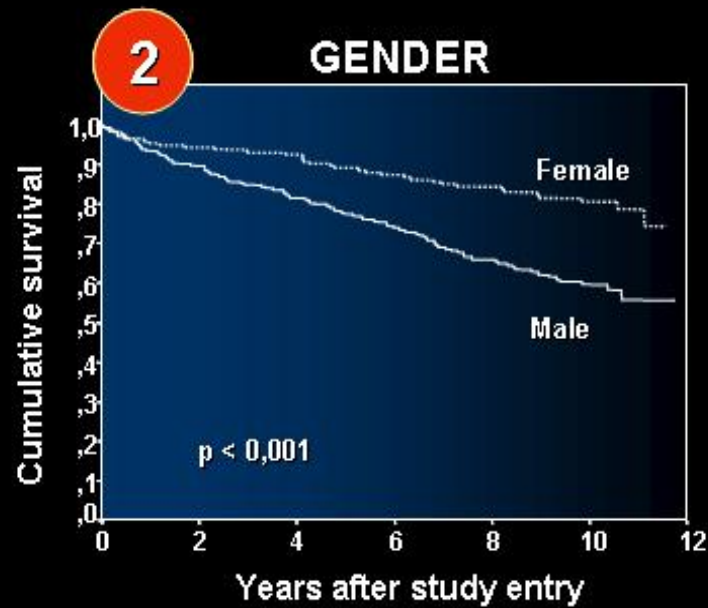
Multivariate Cox Proportional Analysis and Point Scoring System*

Risk Factor	Prevalence of Risk Factor	HR (95% CI)	P value	β regression coefficient	Points†
NYHA class III or IV	10.0%	4.05 (2.46-6.67)	<0.001	1.40	5
Cardiomegaly	26.9%	3.43 (2.06-5.72)	<0.001	1.23	5
Segmental or global WMA	46.8%	2.46 (1.26-4.79)	0.008	0.90	3
Nonsustained VT	48.3%	2.15 (1.28-3.62)	0.004	0.77	3
Low QRS voltage	8.5%	1.87 (1.03-3.37)	0.039	0.62	2
Male sex	60.4%	1.72 (1.06-2.81)	0.030	0.54	2

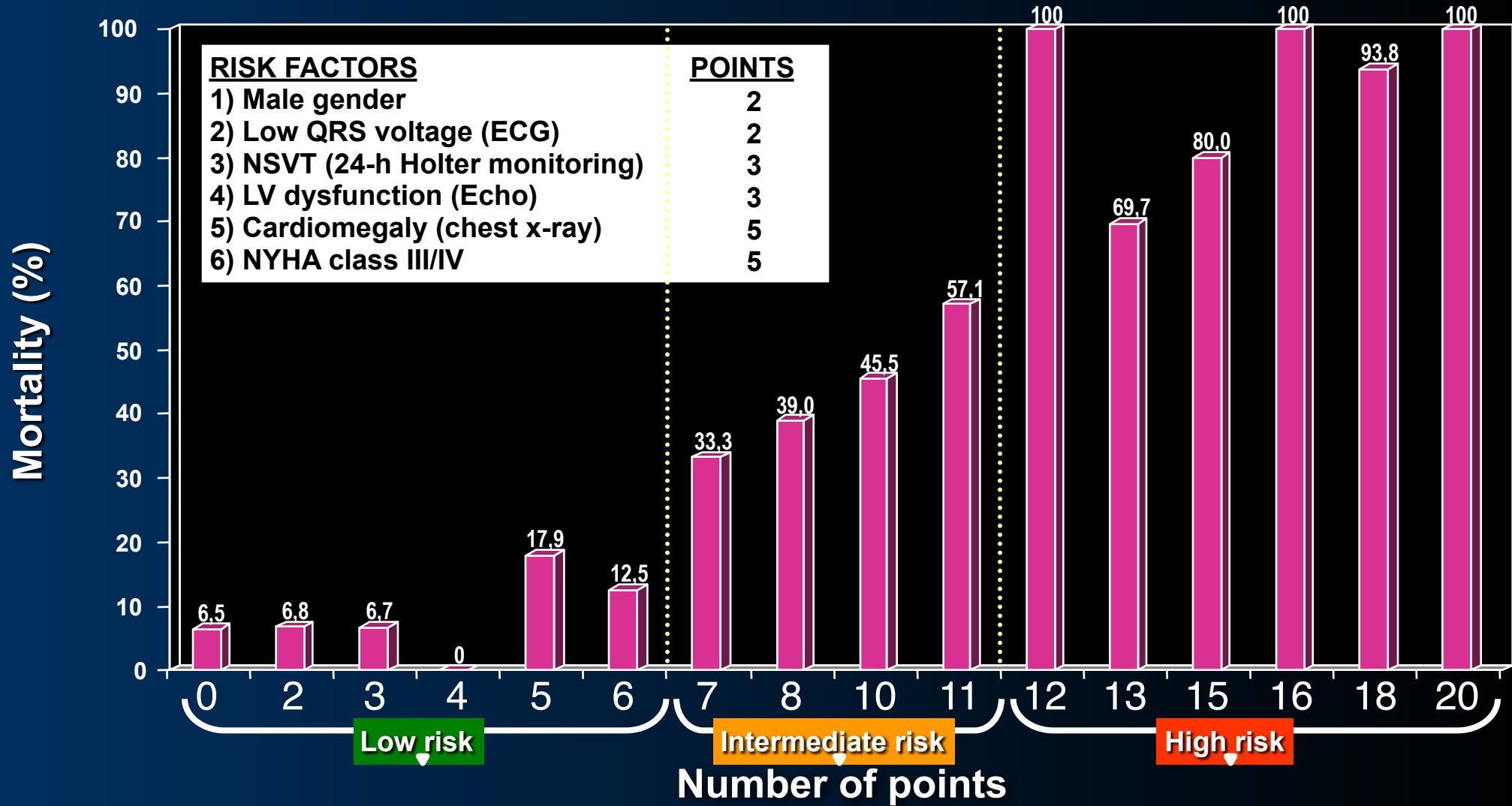
* Due to missing data on some variables the final sample used in our multivariate analysis consisted of 331 patients with 98 deaths. CI denotes confidence interval, NYHA New York Heart Association, WMA wall motion abnormality, and VT ventricular tachycardia.

† Assignment of points to risk factors was based on a linear transformation of the corresponding β regression coefficient. The coefficient of each variable was divided by 0.54 (lowest β = male sex), multiplied by a constant (2), and rounded to the nearest integer.

Probability of survival (by Kaplan Meier estimates) for 6 variables that were significantly associated with outcome in multivariate analysis



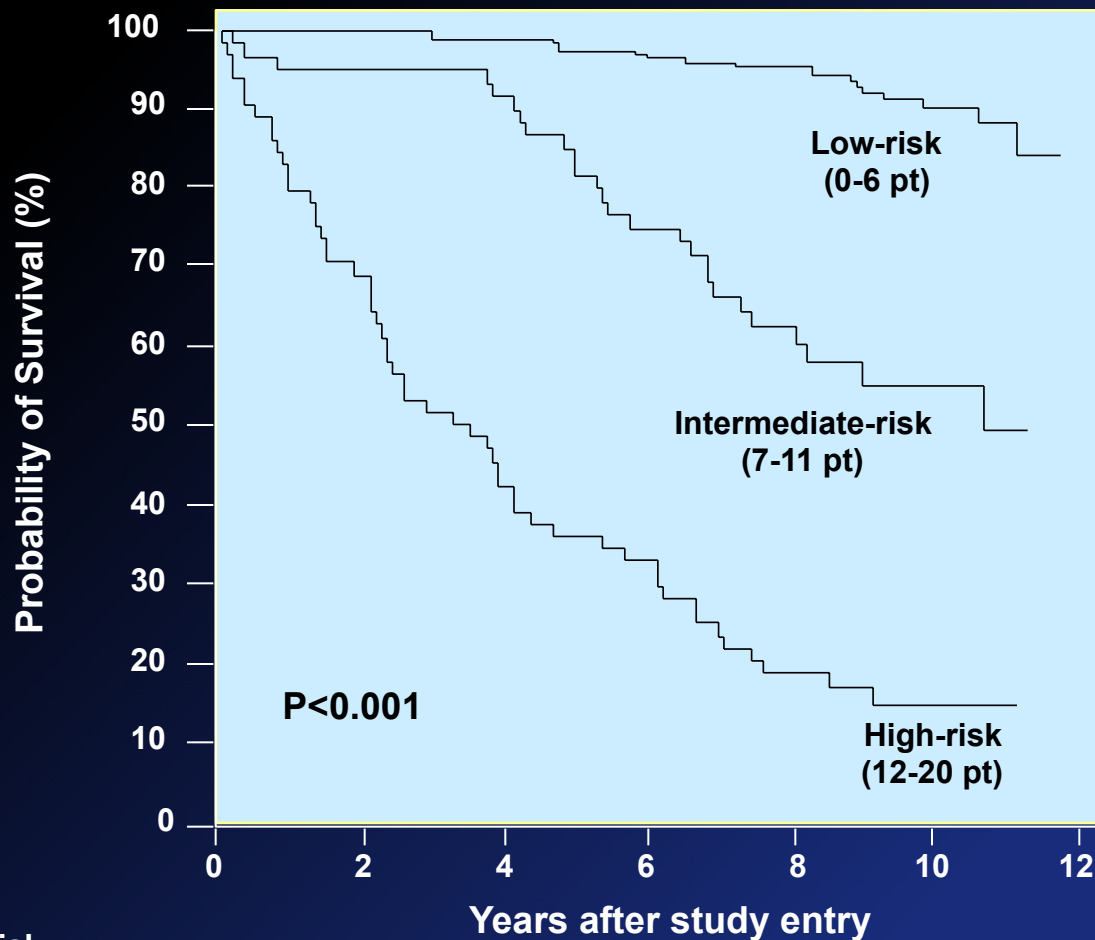
RASSI`score: number of points and mortality in Chagas`heart disease



<u>N of patients</u>	62	59	30	5	39	8	3	41	11	7	1	33	5	5	16	6
%	19	18	9	1,5	12	2,5	1,0	12	3,3	2,1	0,3	10	1,5	1,5	4,8	1,8
Mean fu (yrs)	9,7	9,2	9,1	10	9,2	8,3	7,2	7,7	7,8	6,2	2,6	6,0	4,2	2,3	2,6	0,6

Kaplan-Meier Survival Curves According to Our Three Group Prognostic Classification

NEJM 2006; 355: 799-808



No. at risk

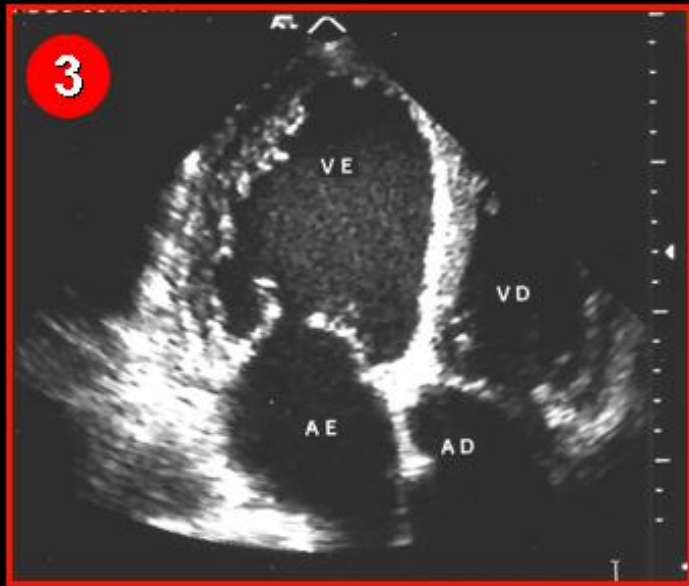
Low-risk

Interm-risk

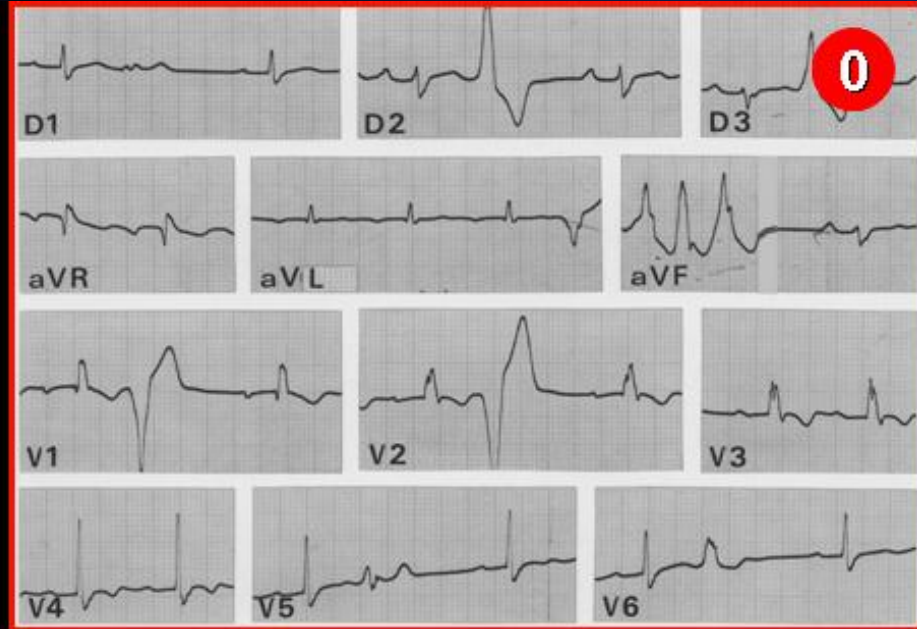
High-risk

203	203	200	194	172	79
62	59	56	45	29	15
66	45	28	22	13	4

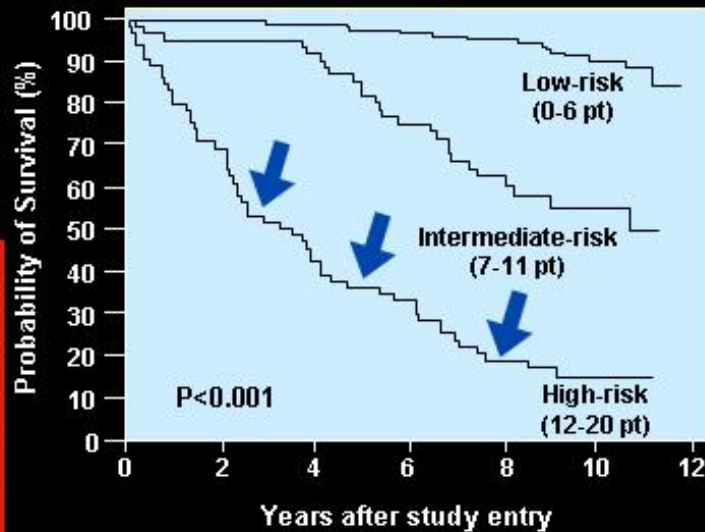
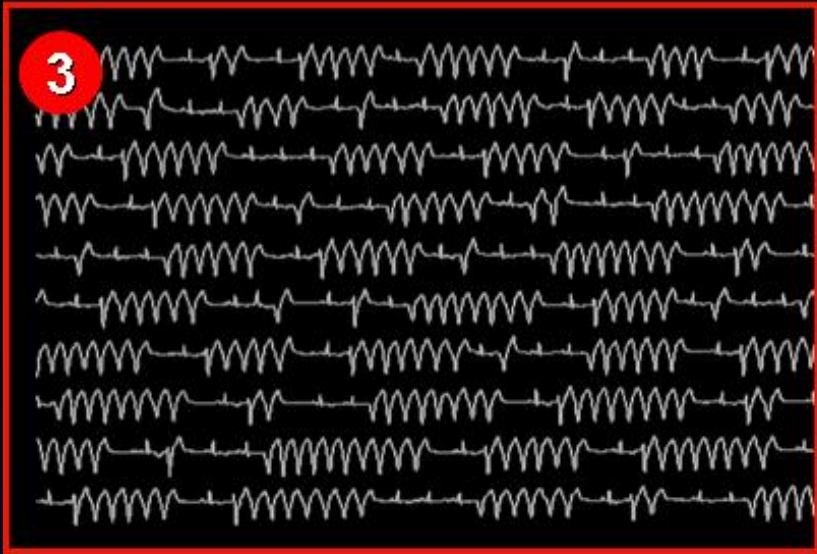




2 Male gender



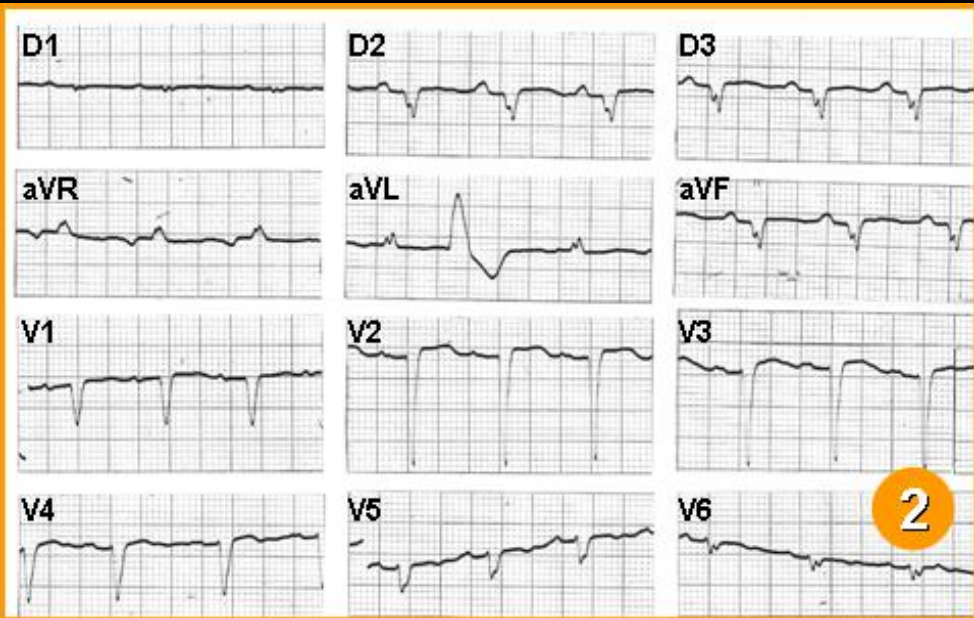
18 points



NYHA Class III

5



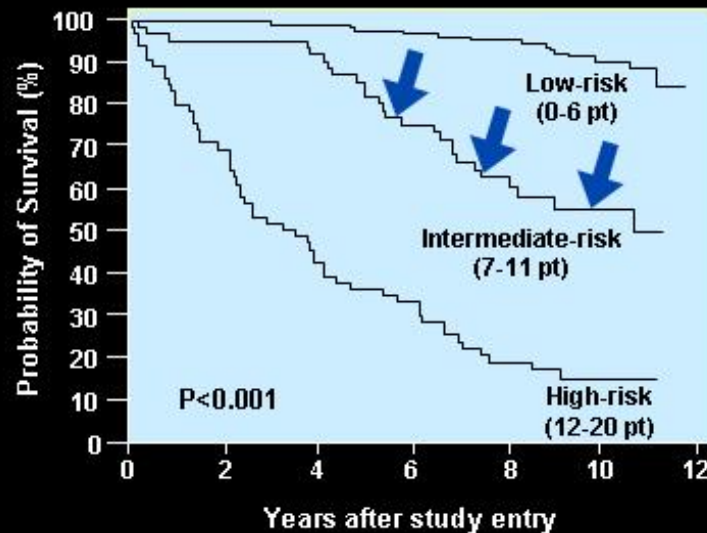


NYHA Class II

0

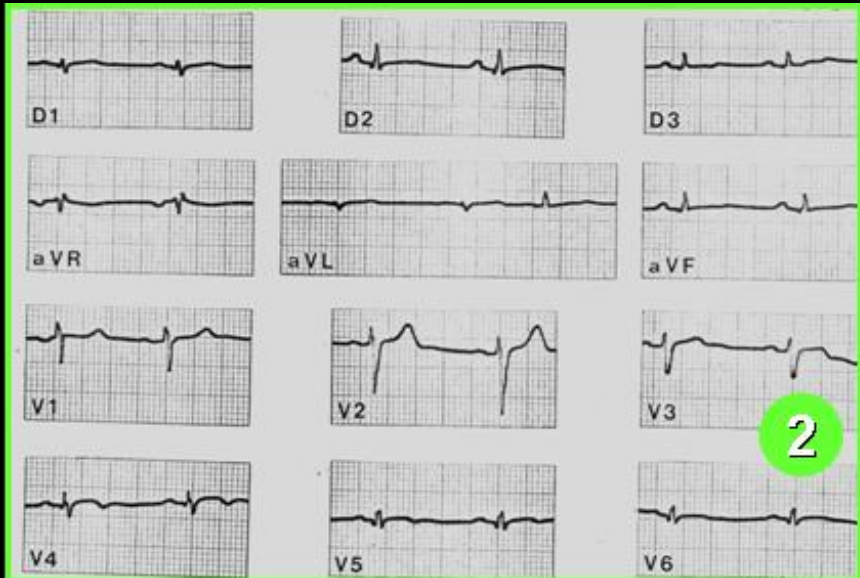
Female gender

0



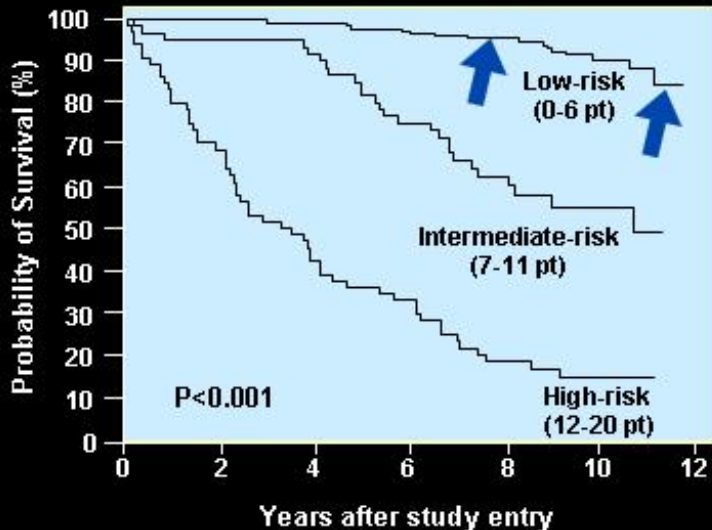
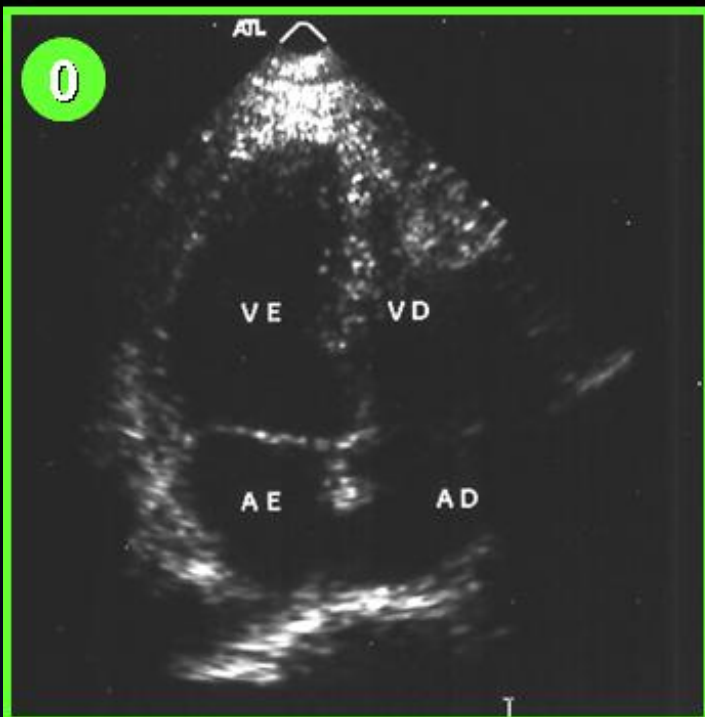
10 points

0 **24-h HOLTER (NSVT-)**



NYHA Class I 0

Female gender 0



2 points



Development Sample

Validation Sample

	Goiânia (outpatients)	Rio de Janeiro (outpatients)
•Centre		
•Selection period	1986-1991	1990-2001
•N° patients	331	153
•Mean age	47 years	48 years
•Male gender	58%*	37%
•NYHA class I/II	90%	85%
•Cardiomegaly (chest X-ray)	30%	29%
•LV dysfunction (Echo)	47%	40%
•NSVT (Holter)	46,5%*	29%
•Mean FU ± SD	7,9 ± 3,2 years	7,7 ± 4,0 years
•Mortality	31%	23%
•Sudden deaths	63,3%	57,1%

*p<0,05 vs validation

NEJM 2006; 355: 799-808

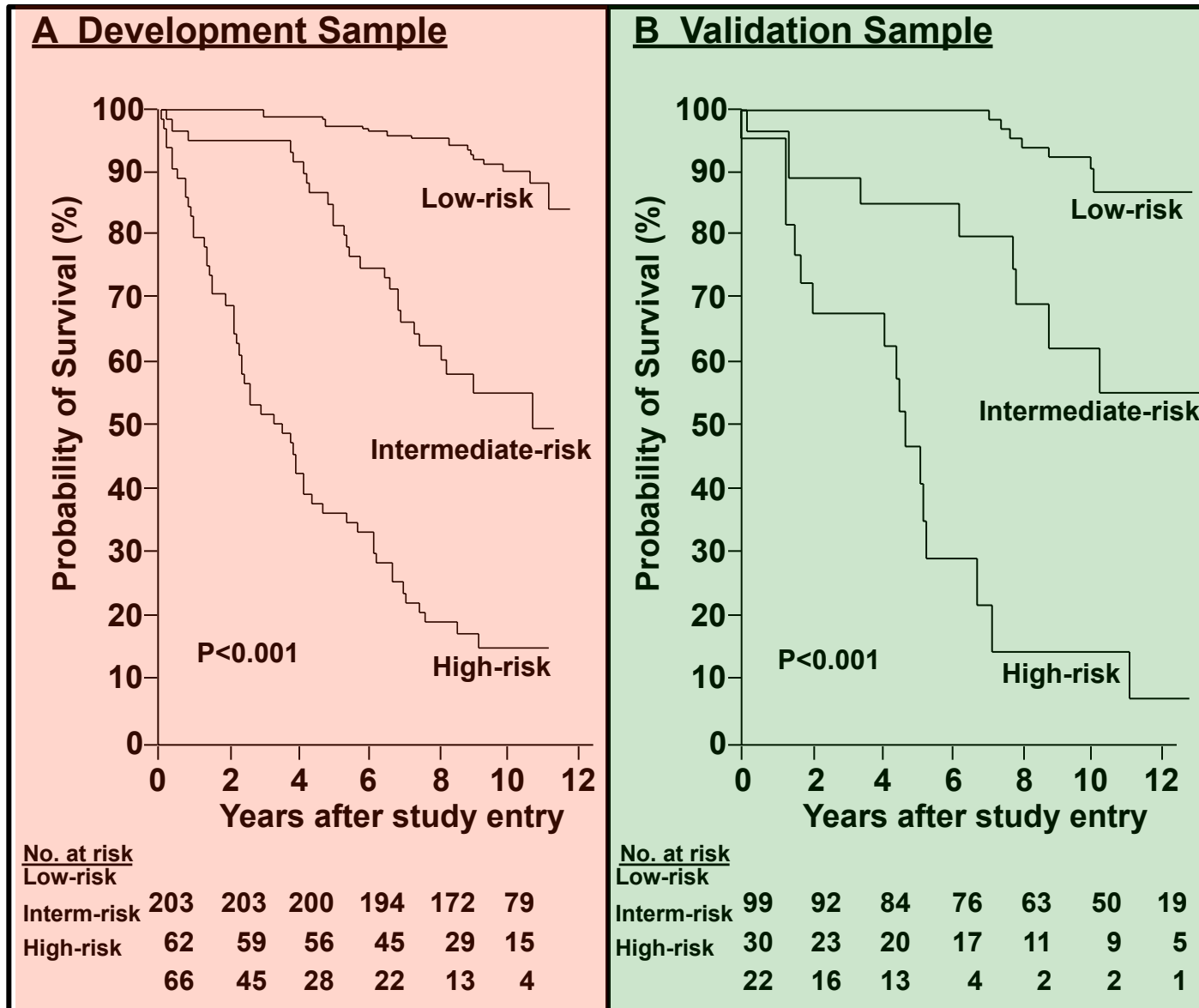
Death at 5-years and at 10-years by Risk Category in the Development and Validation Samples

Risk Category	Points	Development Sample (N=331)			Validation Sample (N=153)		
		n(%)	Death at 5-years (%)	Death at 10-years (%)	n(%)	Death at 5-years (%)	Death at 10-years (%)
Low	0-6	203 (61.3%)	2	10	100 (65.4%)	0	9
Intermediate	7-11	62 (18.7%)	18	44	30 (19.6%)	15	37
High	≥12	66 (19.9%)	63	84	23 (15.0%)	53	85
		PSEP	0.61	0.74	PSEP	0.53	0.76
C statistic (95% CI)		0.84 (0.79-0.89)			0.81 (0.72-0.90)		

NEJM 2006; 355: 799-808



Kaplan-Meier Survival Curves According to Our Three Group Prognostic Classification in the Development (Panel A) and Validation Sample (Panel B)



External Validation: UFMG Cohort

Risk Category	Rassi's Cohort (N = 331)		UFMG Cohort (N = 158)	
	No. (%)	Death at 5 years % (95% CI)	No. %	Death at 5 years % (95% CI)
Low	203 (61.3)	2 (0-5)	110 (69.6)	3 (1-7)
Intermediate	62 (18.7)	18 (8-28)	42 (26.6)	10 (4-22)
High	66 (19.9)	63 (51-75)	6 (3.8)	67 (30-90)
	<u>Difference in probability of death</u>		<u>Difference in probability of death</u>	
	0.61		0.64	
	<u>C statistic (95% CI)</u>		<u>C statistic (95% CI)</u>	
	0.84 (0.79 – 0.89)		0.84 (0.72 – 0.96)	

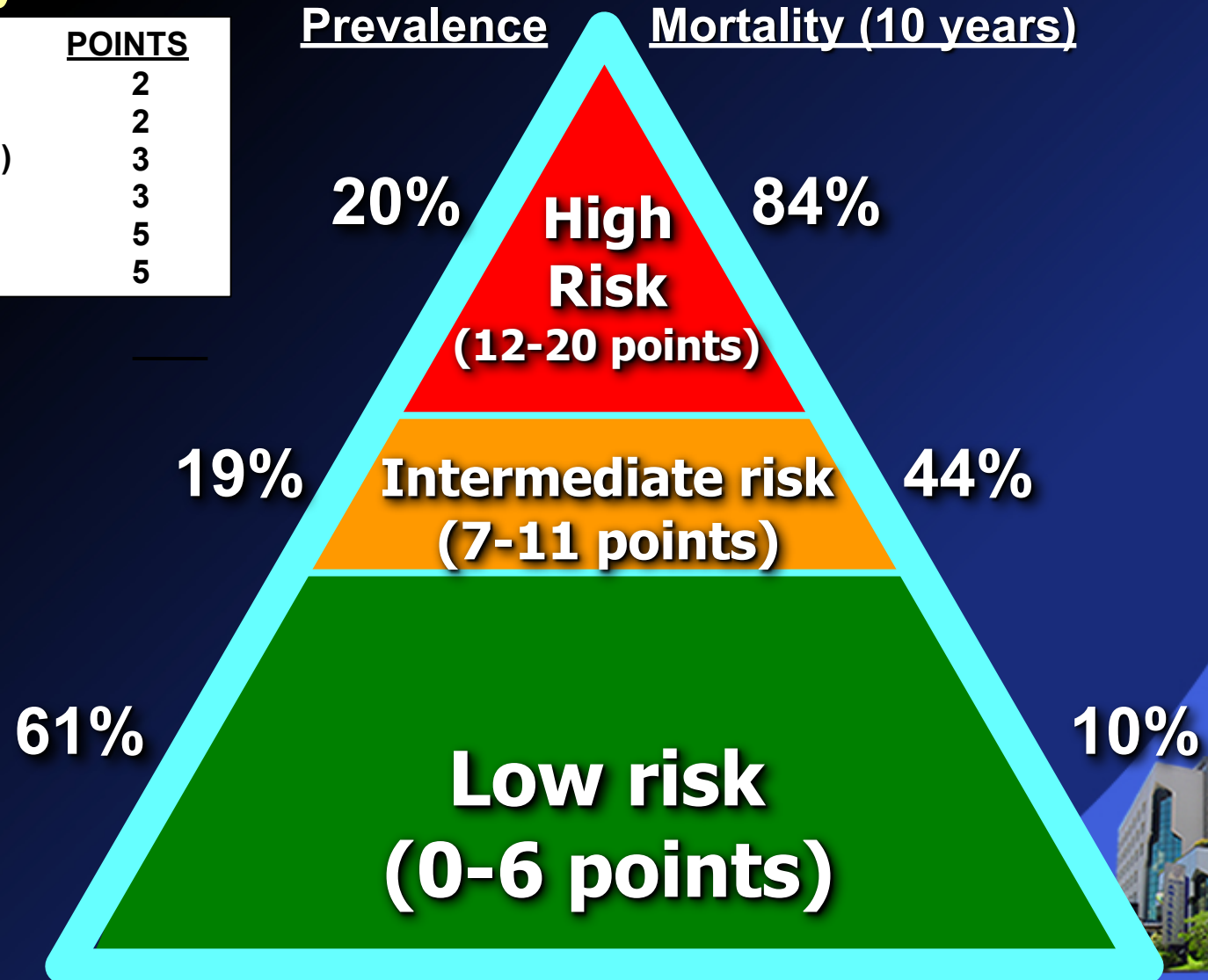
Rocha, MOC & Ribeiro AL. N Engl J Med 2006; 355:2488-2491 [Letter to Editor]



Chagas Heart Disease: Risk of Death

Multivariate analysis

<u>RISK FACTORS</u>	<u>POINTS</u>
1) Male gender	2
2) Low QRS voltage (ECG)	2
3) NSVT (24-h Holter monitoring)	3
4) LV dysfunction (Echo)	3
5) Cardiomegaly (chest x-ray)	5
6) NYHA class III/IV	5



NEJM 2006; 355: 799-808

Predictors of Mortality in Chronic Chagas Disease

A Systematic Review of Observational Studies

Anis Rassi, Jr, MD, PhD; Anis Rassi, MD; Sérgio G. Rassi, MD

Chagas AND (incidence[MeSH] OR mortality[MeSH] OR follow up studies[MeSH] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word])

Inclusion criteria:

- (1) original articles or abstracts published between January 1985 and February 2006
- (2) inclusion of patients in the chronic phase of Chagas` disease
- (3) performance of multivariable regression models of prognosis**
- (4) analysis of clearly defined outcome: all-cause mortality, sudden cardiac deaths and/or cardiovascular deaths



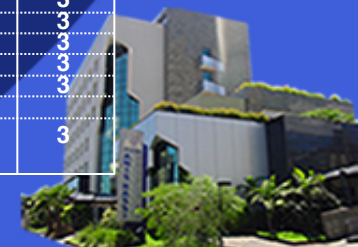
Characteristics of Multivariable Studies of Prognostic Factors for Mortality in Chagas` Disease

Rassi Jr A et al Circulation 2007;115:1101-1108

Espinosa, 1991
Hagar, 1991
Carrasco, 1994
Bestetti, 1994
Mady, 1994
Bestetti, 1996
Rodriguez-Salas, 1998
Garzon, 1998
Leite, 2003
Salles, 2003
Viotti, 2004
Rassi Jr., 2006

Study details:	Venezuela 1973-1985	U.S.A 1974-1990	Venezuela 1973-1988	Brazil 1990-1992	Brazil NR	Brazil 1990-1993	Venezuela 1981-1992	Brazil 1971-1986	Brazil NR	Brazil 1989-1999	Argentina NR	Brazil 1986-1991
Country	Venezuela	U.S.A	Venezuela	Brazil	Brazil	Brazil	Venezuela	Brazil	Brazil	Brazil	Argentina	Brazil
Period of enrollment, y	1973-1985	1974-1990	1973-1988	1990-1992	NR	1990-1993	1981-1992	1971-1986	NR	1989-1999	NR	1986-1991
Type of population												
- clinic-derived	3	3	3	3	3	3	3	3	3	3	3	3
- hospital-derived												
Sample size, n	66		556	3	3	74	283	987	115	738	849	
Cases included in multivariable analysis, n	43	25	172	56	104	NR	215	NR	NR	NR	NR	424
Age, y	47	25	50	NR	104	54±14	50±14	45	52±10	46	43±11	331
Male sex, %	64	53±14	64	59±17	40±9	55	60	62	60	46	39	47±11
Chagas` disease population												
- with cardiac involvement												
- with and without cardiac involvement	3	3		3	3	3	3	3	3	3	3	3
Study design and analysis			3									
- retrospective												
- clinical database or prospective	3	3		3		3		3				3
Inclusion and exclusion criteria defined	3	3	3	3		3	3	3	3	3	3	3
No. of excluded patients specified			3			3	3			3		3
Inclusion of consecutive patients			3			3	3			3		3
Relevant baseline data shown	3	3	3	3	3	3	3		3	3	3	3
Statistical analysis:												
- Multivariable model												
- Cox regression	3	3	3		3		3	3	3	3		3
- logistic regression				3		3					3	
- Type of variables												
- continuous				3	3	3				3	3	
- dichotomized	3	3	3	3	3	3	3	3	3	3	3	3
- Reporting												
- p value	3	3	3	3	3	3	3	3	3	3	3	3
- exact p value	3	3	3	3	3	3	3	3	3	3	3	3
- hazard ratio or odds ratio	3	3	3	3	3	3	3	3	3	3	3	3
- 95% confidence interval									3	3		3
- β- regression and/or SE									3	3		3
- survival curves	3			3	3	3					3	3
- % of survival at n years		3	3	3	3		3		3	3		3
- Development of a risk score and external validation		3	3		3		3					3

Plus-minus values are means±SD. Blank spaces indicates NO or data not available. NR, not reported.

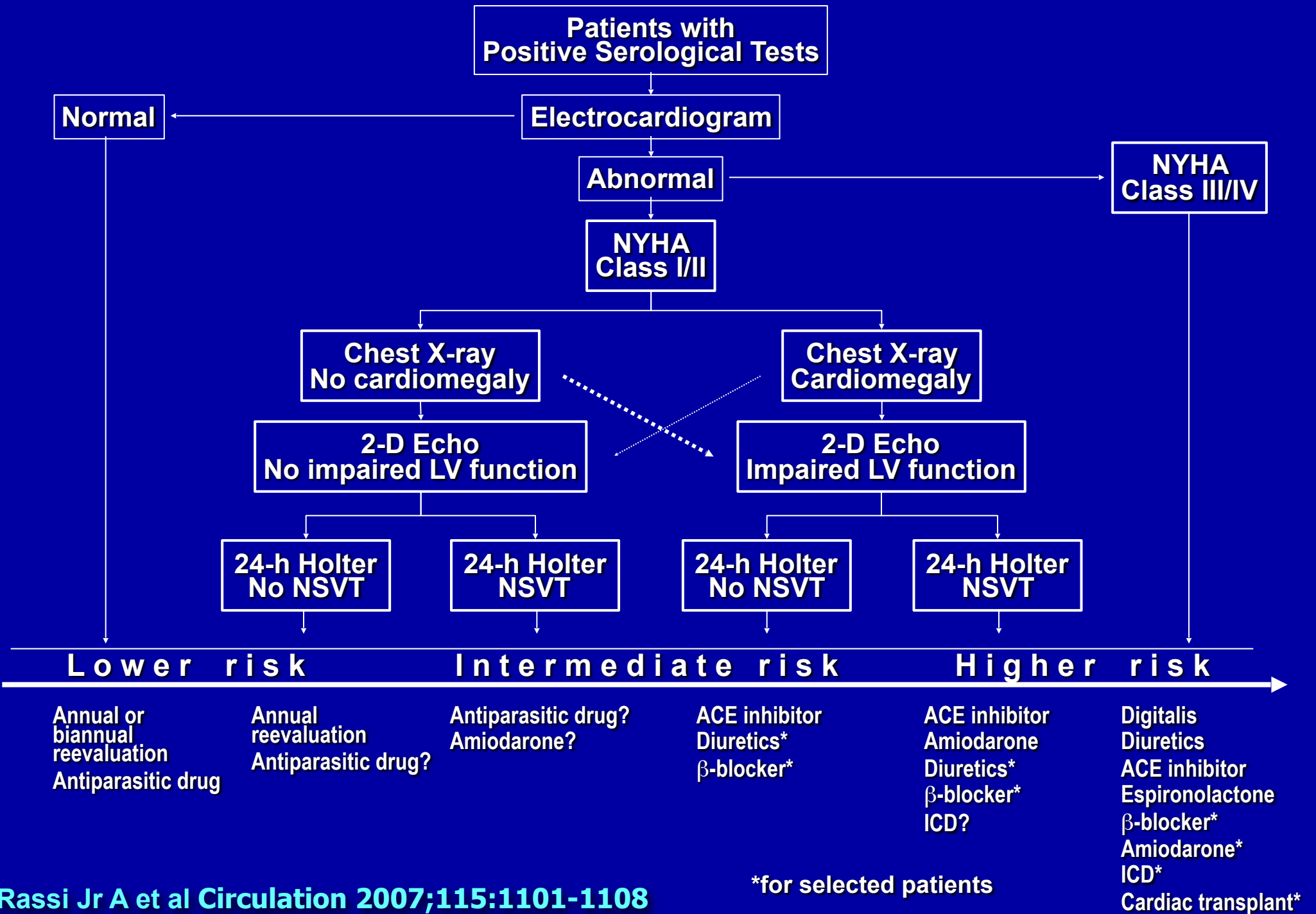


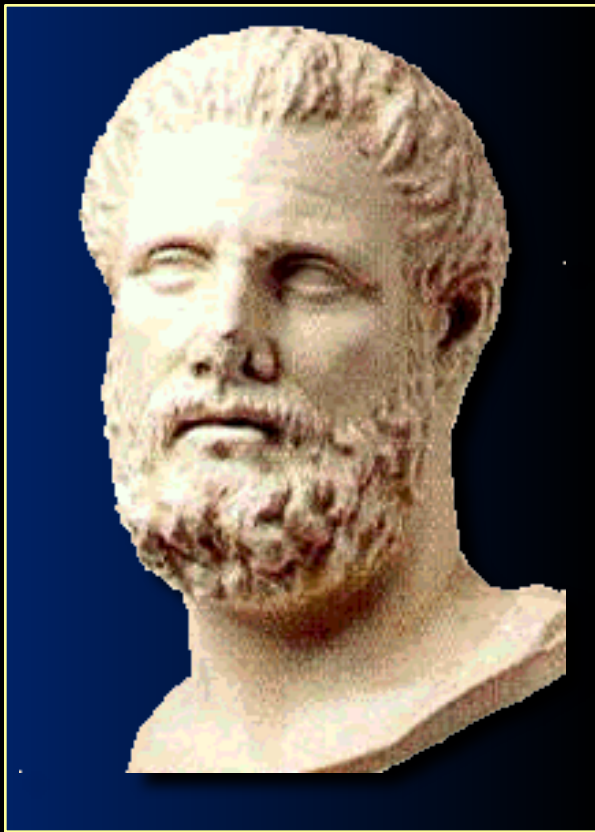
Chagas` Heart Disease

Independent Predictors of Mortality

- NYHA functional class III/IV
- Cardiomegaly (chest X-ray)
- Impaired LV function (echo)
- NSVT (Holter)







The physician`s objectives...

“Declare the past,
diagnose the present,
foretell the future”

Hippocrates [460-375 BC]

Epidemics, Bk. I, Sect. XI



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