American Trypanosomiasis
Chagas` Disease

1909

"European Society of Cardiology and the Brazilian Society of Cardiology

Epidemiology Transition
Clinical Forms and Evolution
Pathogenesis of Chagas' heart disease
Pathophysiology of the Cardiomyopathy
The Indeterminate Form Enigma
Clinical and Laboratory Manifestations
Risk Stratification for Death
Management of Chagas' Heart Disease
The ICD Issue
Etiologic Treatment in the Chronic Phase

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Amsterdam
September 02, 2013

No conflicts of interest to disclose

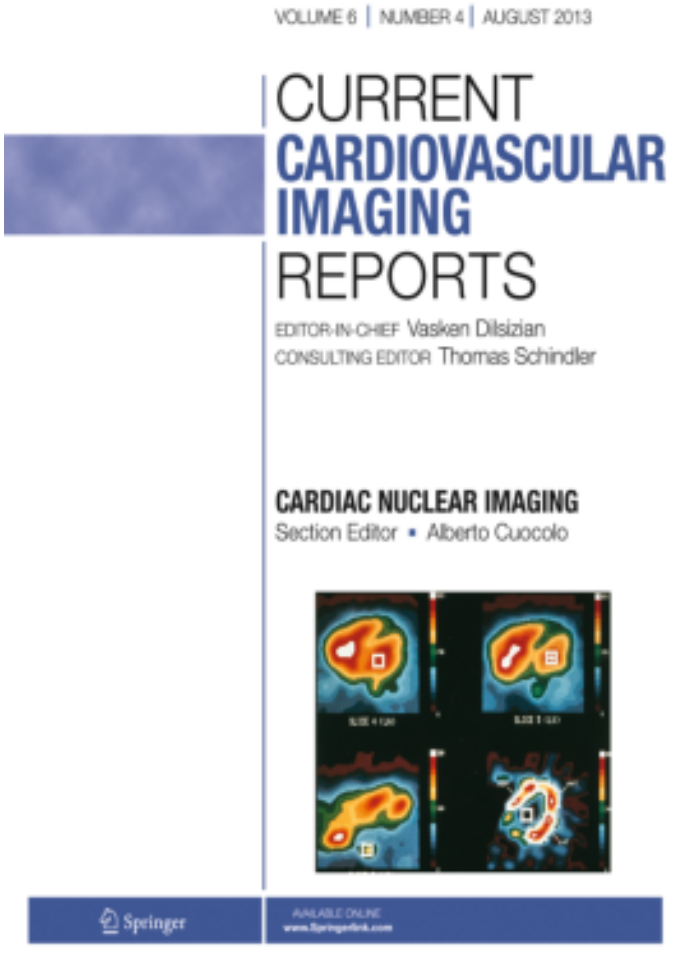
Curr Cardiovasc Imaging Rep (2015) 8: 9
DOI 10.1007/s12410-015-9324-2

SPECIFIC POPULATIONS AND EMERGING MARKETS (V DILSIZIAN AND T SCHINDLER, SECTION EDITOR)

Cardiac Imaging in Latin America: Chagas Heart Disease

J. Antônio Marin-Neto · Minna M. Dias Romano · Benedito Carlos Maciel · Marcus Vinícius Simões · André Schmidt

Published online: 27 February 2015



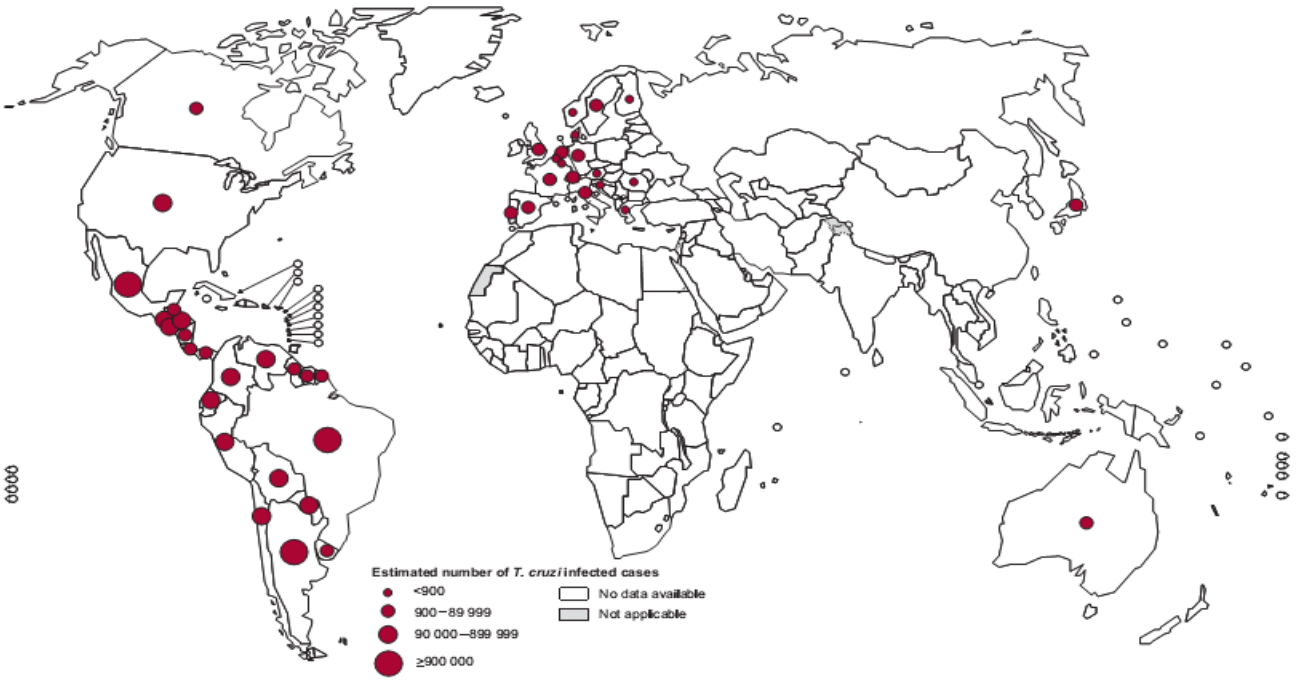
Chest X-rays
Cardiac Catheterization Coronary Angiography, Contrast Ventriculography
Echocardiography
Cardiac Nuclear Imaging
Cardiac Magnetic Resonance

REV USP 2017

Curr Cardiovasc Imaging Rep 2015

Epidemiology and clinical aspects of Chagas disease in endemic versus non-endemic countries

WCC 2014 : HOT TOPICS IN CHAGAS DISEASE



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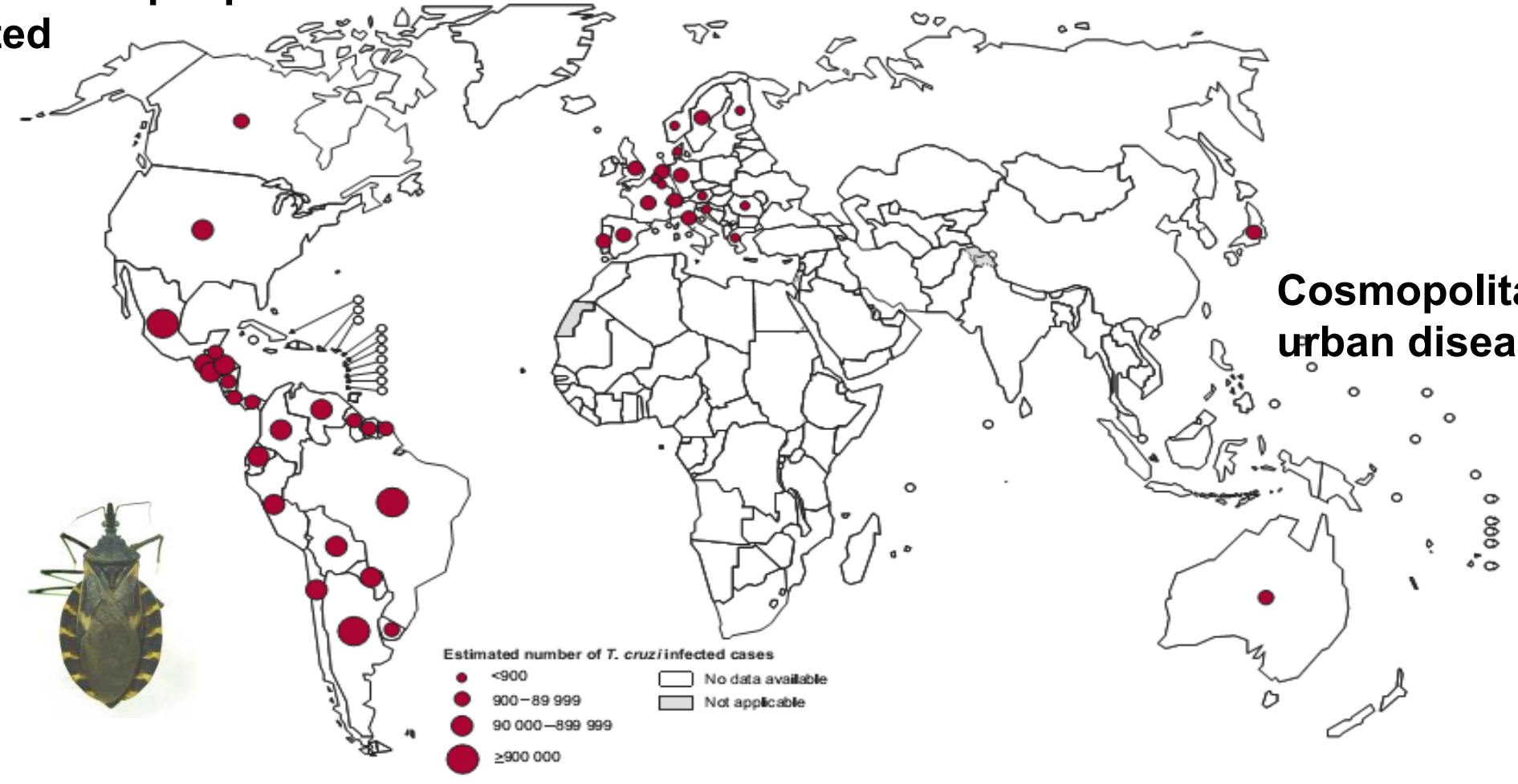
1909

Melbourne, Australia
May 06, 2014

No conflicts of interest to disclose

CHAGAS DISEASE
New Epidemiologic Scenery

7- 10 million people infected



Cosmopolitan urban disease

SECOND WHO REPORT ON NEGLECTED TROPICAL DISEASES **World Health Organization 2013**

CHAGAS' HEART DISEASE EPIDEMIOLOGIC ISSUES IN 2014

Endemic in 18 countries

~ 100 million at risk

~ 8 million infected

41 200 new cases per year

12 500 deaths per year

More than 12 million Latin American immigrants living outside endemic areas

Population mobility toward non-endemic areas : 1 – 26% of migrants are infected, depending on the country of origin

Acute Chagas Disease in non-endemic areas ?

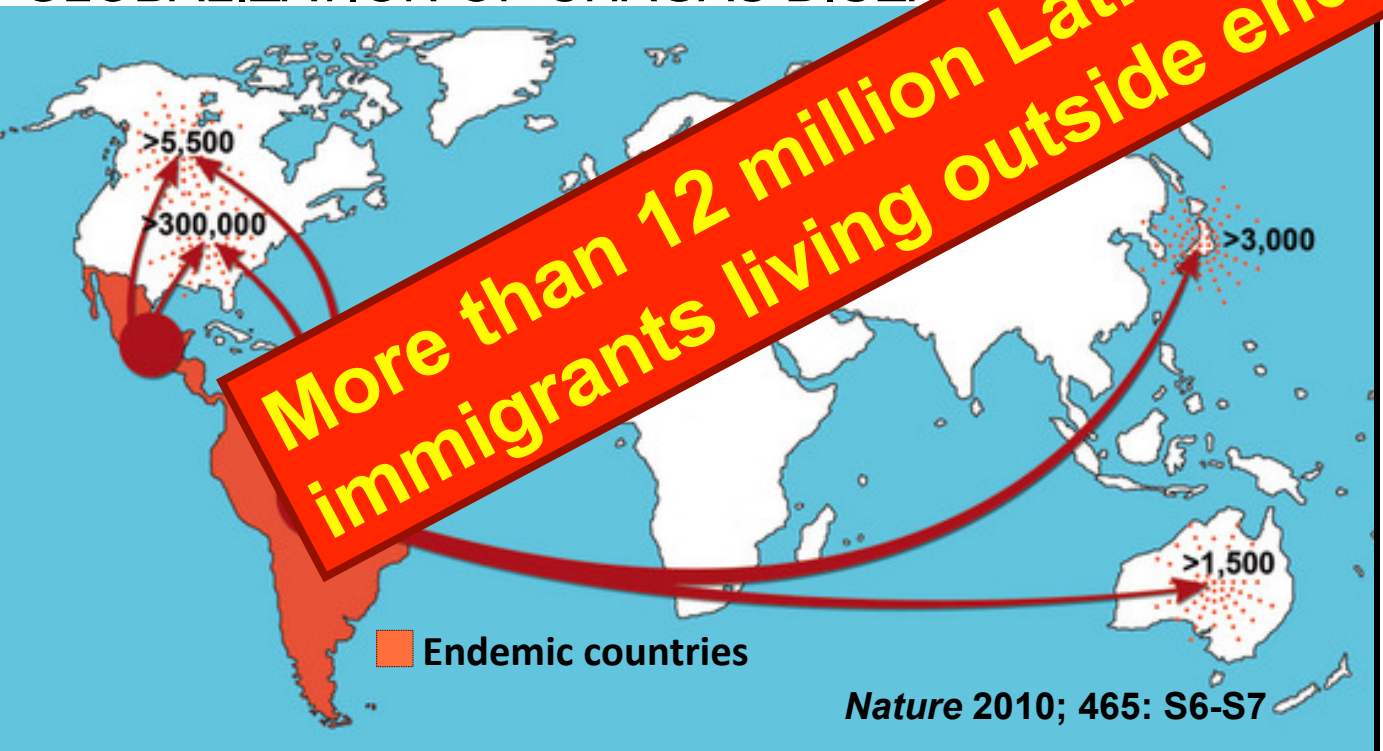
Reactivation in chronically infected people

Vertical transmission

Immune-compromised recipients of infected organs or blood

(WHO 2013)

GLOBALIZATION OF CHAGAS DISEASE



Nature 2010; 465: S6-S7

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Editorial

An Unfolding Tragedy of Chagas Disease in North America

Peter J. Hotez[1,2*], Eric Dumonteil[3], Miguel Betancourt Cravioto[4], Maria Elena Bottazzi[1], Roberto Tapia-Conyer[4], Sheba Meymandi[5], Unni Karunakara[6], Isabela Ribeiro[7], Rachel M. Cohen[7], Bernard Pecoul[7]

PLoS Negl Trop Dis 2013 Oct 31;7(10):e2300

Figure 1. Estimated number of Chagas disease cases in North America.

Chagas disease: a new worldwide challenge

Endemic Chagas disease began as a neglected disease of poor, rural and forgotten populations. Its spread from Latin America to non-endemic countries is a new worldwide challenge, say **José Rodrigues Coura** and **Pedro Albajar Viñas**.

Nature 2010 Jun 24;465(7301):S6-7

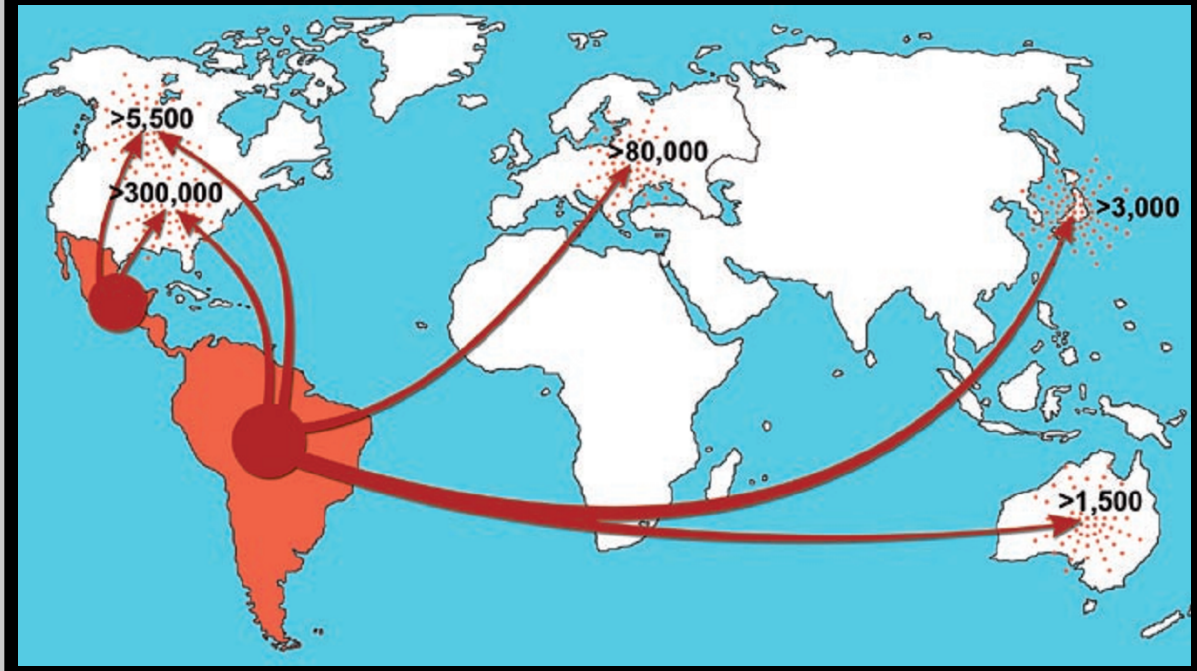
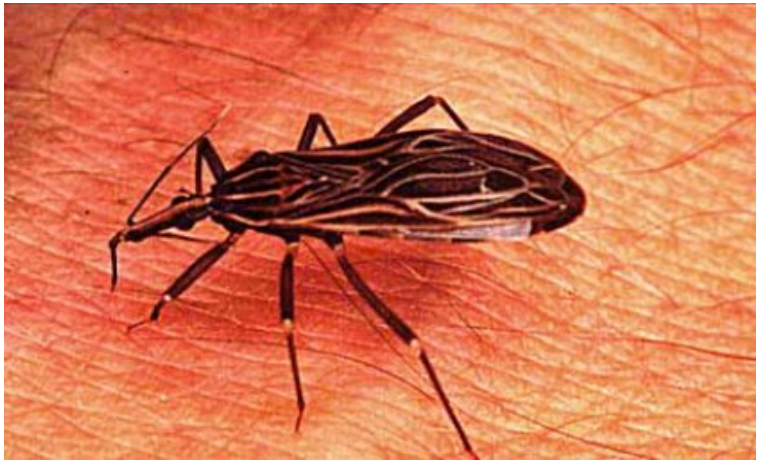
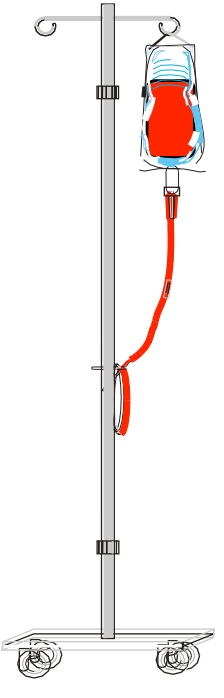


Fig. 2 | Migration routes from Latin America and estimation of the total number of infected individuals in non-endemic countries.

Transmission of Chagas disease in Endemic Countries
Infection caused by *Trypanosoma cruzi*

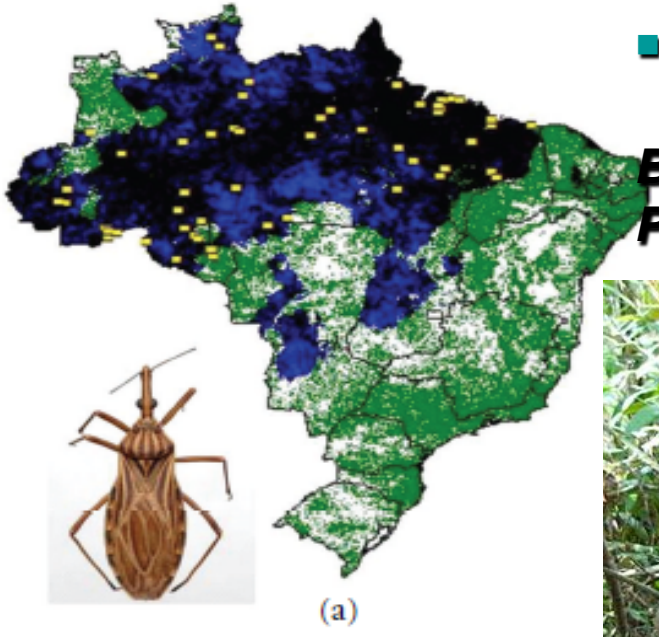
- Contact with faeces from the vectors, including ingestion of contaminated food
- Transfusion of infected blood
- Organ transplantation
- Congenital infection
- Laboratory accidents





Acute Chagas Disease in the Amazon
Current Vectorial Transmission

- *R. robustus, R. pictipes, P. Geniculatus* in the Amazon



(a)

- Emerging problem in other ecosystems (Amazon)

Briceño-León R - Cad Saud Publ 23 suppl 1 (RJ) 2007

Not domiciliated sylvatic vectors

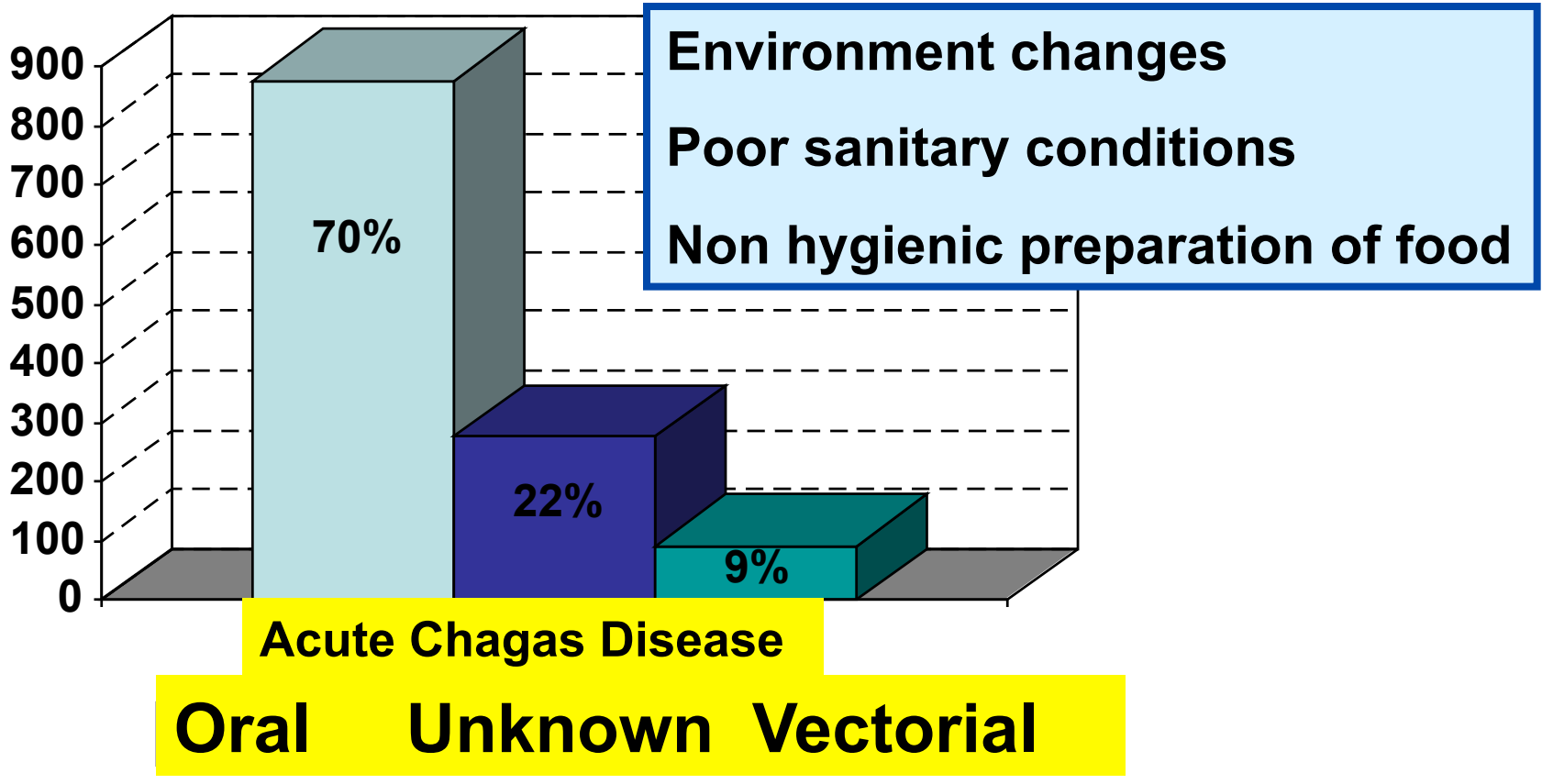
"The expansion of Chagas disease is thus a perverse effect of the deforestation process in the Amazon".

Revista da Sociedade Brasileira de Medicina Tropical 41(6):602-614, nov-dez, 2008

Journal of Tropical Medicine
Volume 2012, Article ID 705326, 15 pages

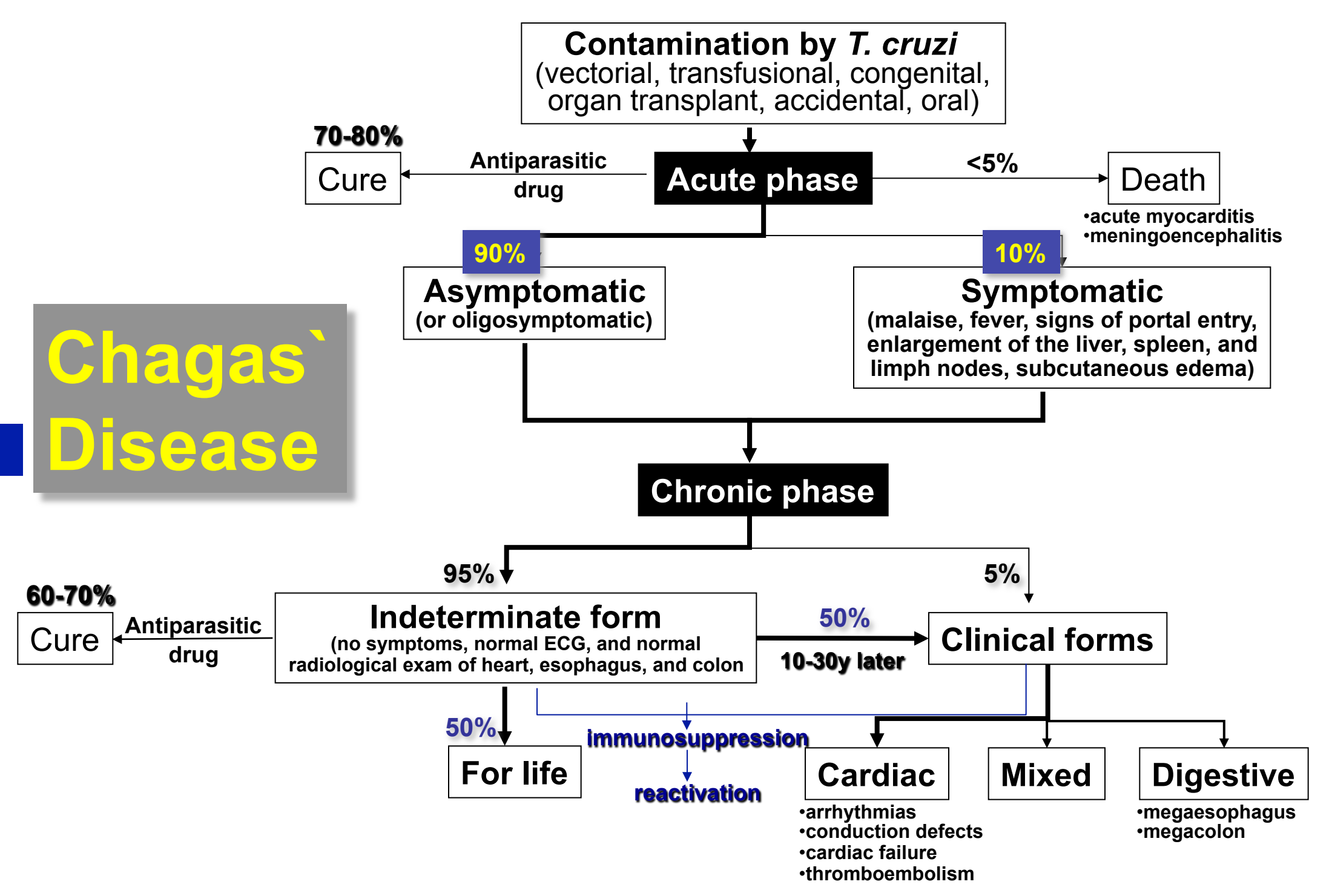
Acute Chagas Disease

- **138 outbreaks, 1.252 cases in Brazil (2000-2011)**
- **7-8 outbreaks, 112 cases in the Amazon (1965-2000)**

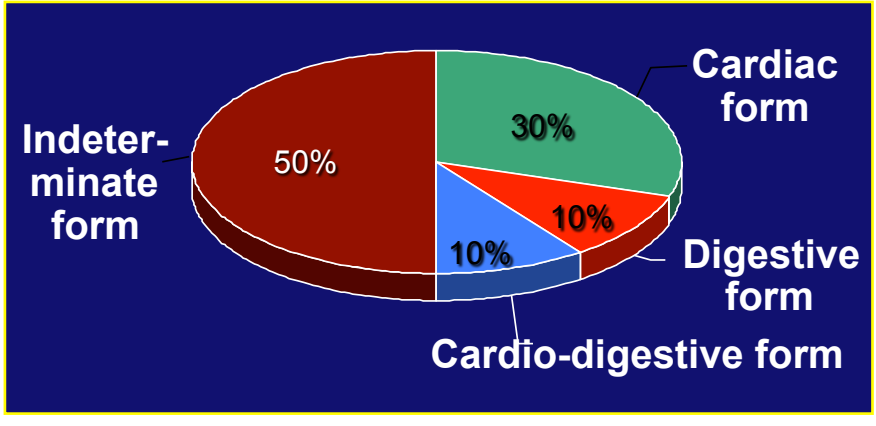


Apud A. S. Sousa, 2013

Secretaria de Vigilância Sanitária/MS - 2012


Contamination by *T. cruzi*
(vectorial, transfusional, congenital, organ transplant, accidental, oral)
70-80%
Cure
Antiparasitic drug
Acute phase
<5%
Death
•acute myocarditis
•meningoencephalitis
90%
Asymptomatic
(or oligosymptomatic)
10%
Symptomatic
(malaise, fever, signs of portal entry, enlargement of the liver, spleen, and limph nodes, subcutaneous edema)
Chagas` Disease
Chronic phase
95%
5%
60-70%
Cure
Antiparasitic drug
Indeterminate form
(no symptoms, normal ECG, and normal radiological exam of heart, esophagus, and colon
50%
10-30y later
Clinical forms
50%
For life
immunosuppression
reactivation
Cardiac
Mixed
Digestive
•arrhythmias
•conduction defects
•cardiac failure
•thromboembolism
•megaesophagus
•megacolon

Chagas` Disease: Phases, Forms, and Stages (Groups)

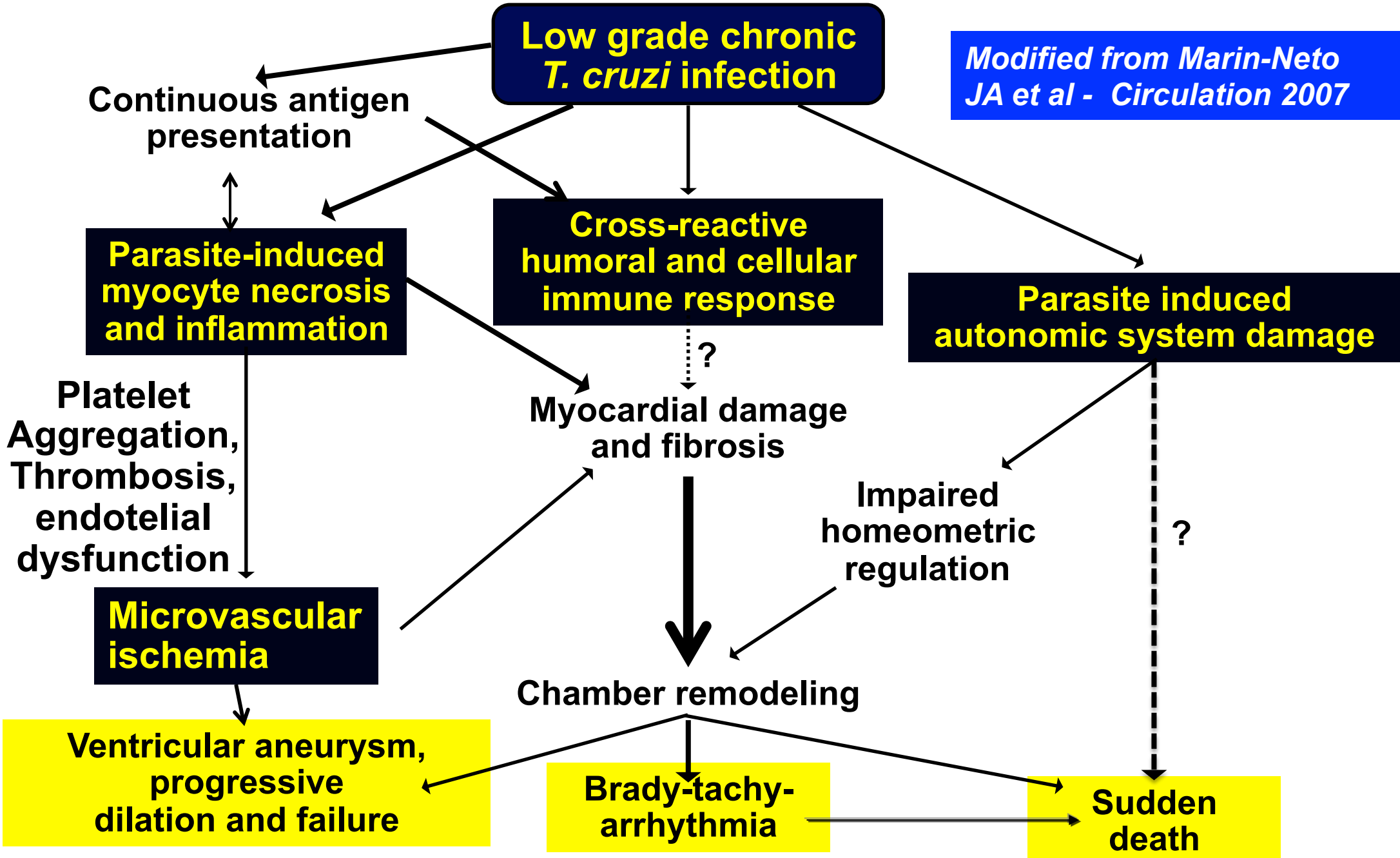


Chagas` disease

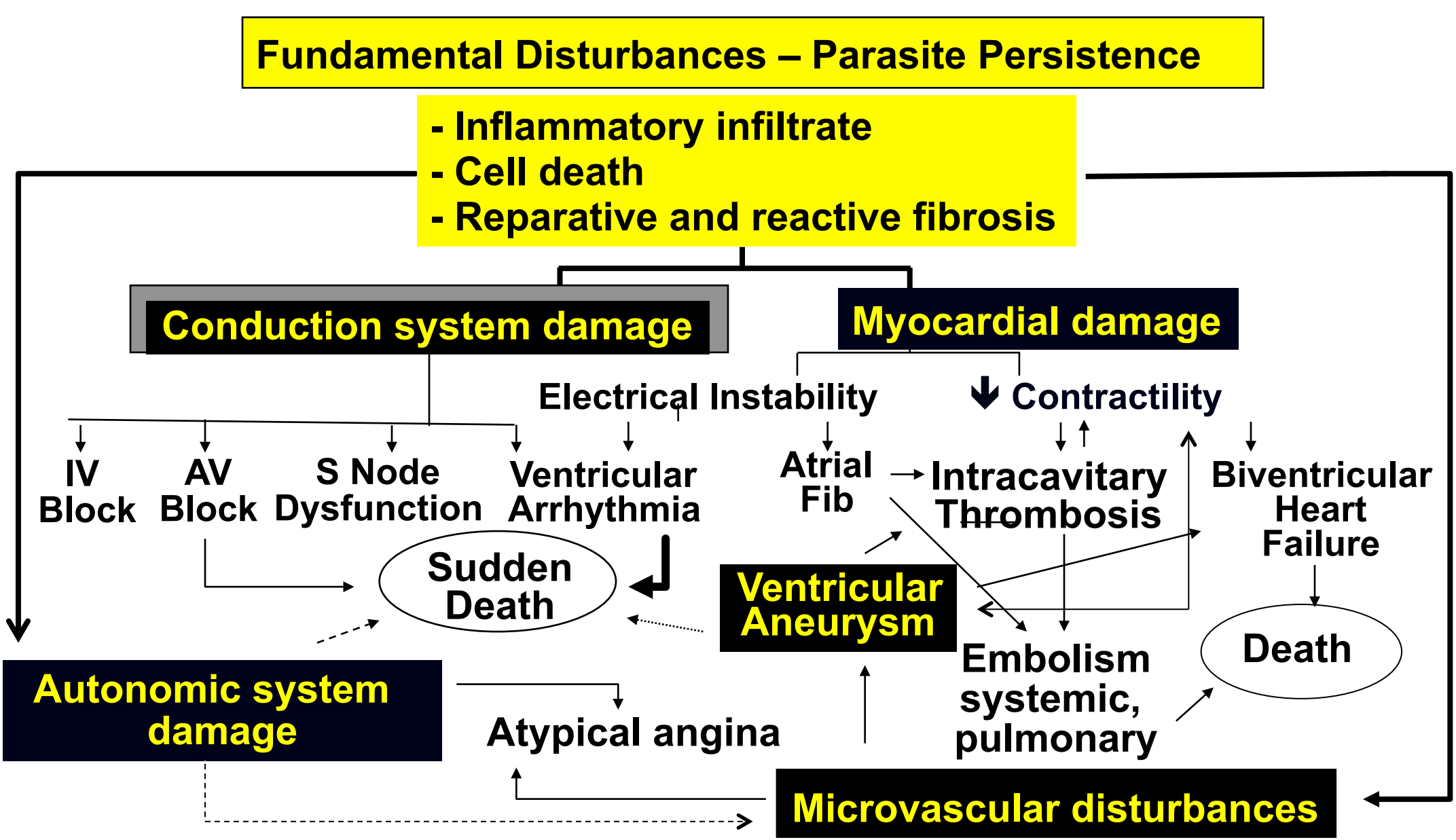
- Acute phase
  - Apparent form
  - Inaparent form
- Chronic phase
  - Indeterminate form
  - PREDICTORS?
  - Determinate form
    - Cardiac → Chagas` heart disease → Stage A / Stage B / Stage C / Stage D
      - PREDICTORS
      - PREDICTORS → DEATH
    - Mixed
    - Digestive
      - Megaesophagus → Group I / Group II / Group III / Group IV
      - Megacolon

Adapted from Marin-Neto JA, Rassi Jr A, Maciel BC et al. Chapter 51: Chagas Heart Disease. In: Yusuf S, Cairns J (eds). Evidence Based Cardiology 3rd edition, 2010

Pathogenesis of Chronic Chagas Cardiomyopathy

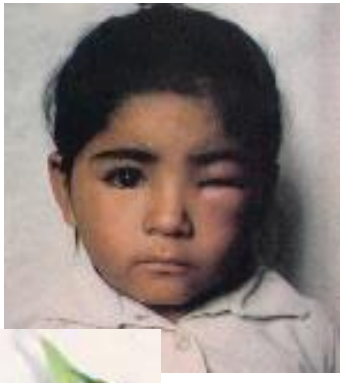


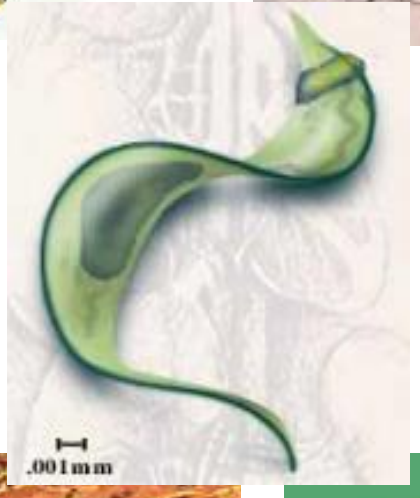
Pathophysiology of Chronic Chagas' Cardiomyopathy

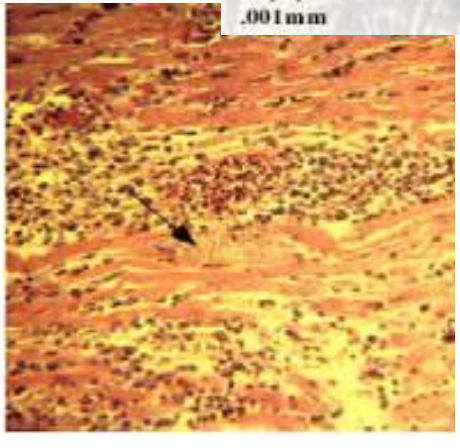


Adapted from Rassi Jr A, Rassi A, Marin-Neto JA – Mem Inst Oswaldo Cruz 2009.

ACUTE PHASE

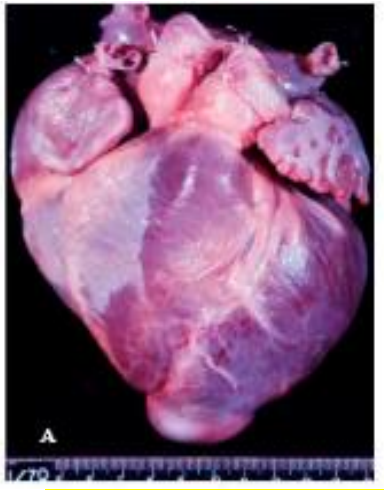






3-4 decades

CHRONIC CARDIOMIOPATHY



30 -50% of infected people

- ***Anginal symptoms***
- ***ECG alterations***
- ***Ventricular aneurysms***
- ***Biventricular failure***
- ***Thromboembolism***
- ***Arrhythmias***
- ***Sudden death***

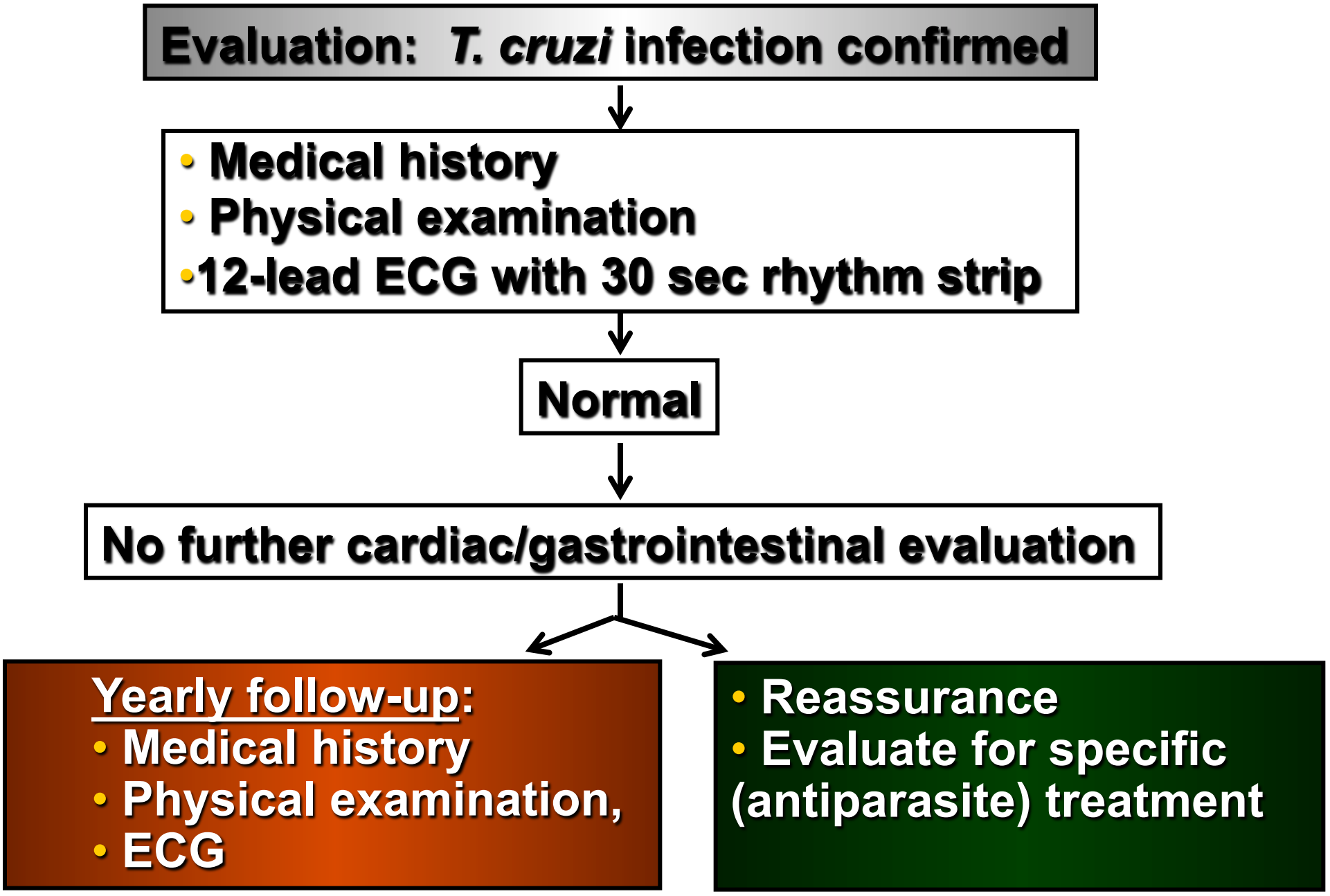
Chagas Disease

INDETERMINATE FORM

(latent, sub-clinical or non-apparent)

- **Positive serological tests**
- **No symptoms**
- **Normal ECG**
- **Normal chest x-ray**
- **Normal esophagus x-ray (barium swallow)**
- **Normal colon x-ray (barium enema)**

Enquanto o ECG fôr normal, mortalidade igual à de indivíduos não infectados, pareados por idade e gênero.



Bern C, Rassi A Jr, Marin-Neto JA et al JAMA 2007;298:2171-81
Rassi Jr A, Rassi A, Marin-Neto JA Lancet 2010;375:1388-402

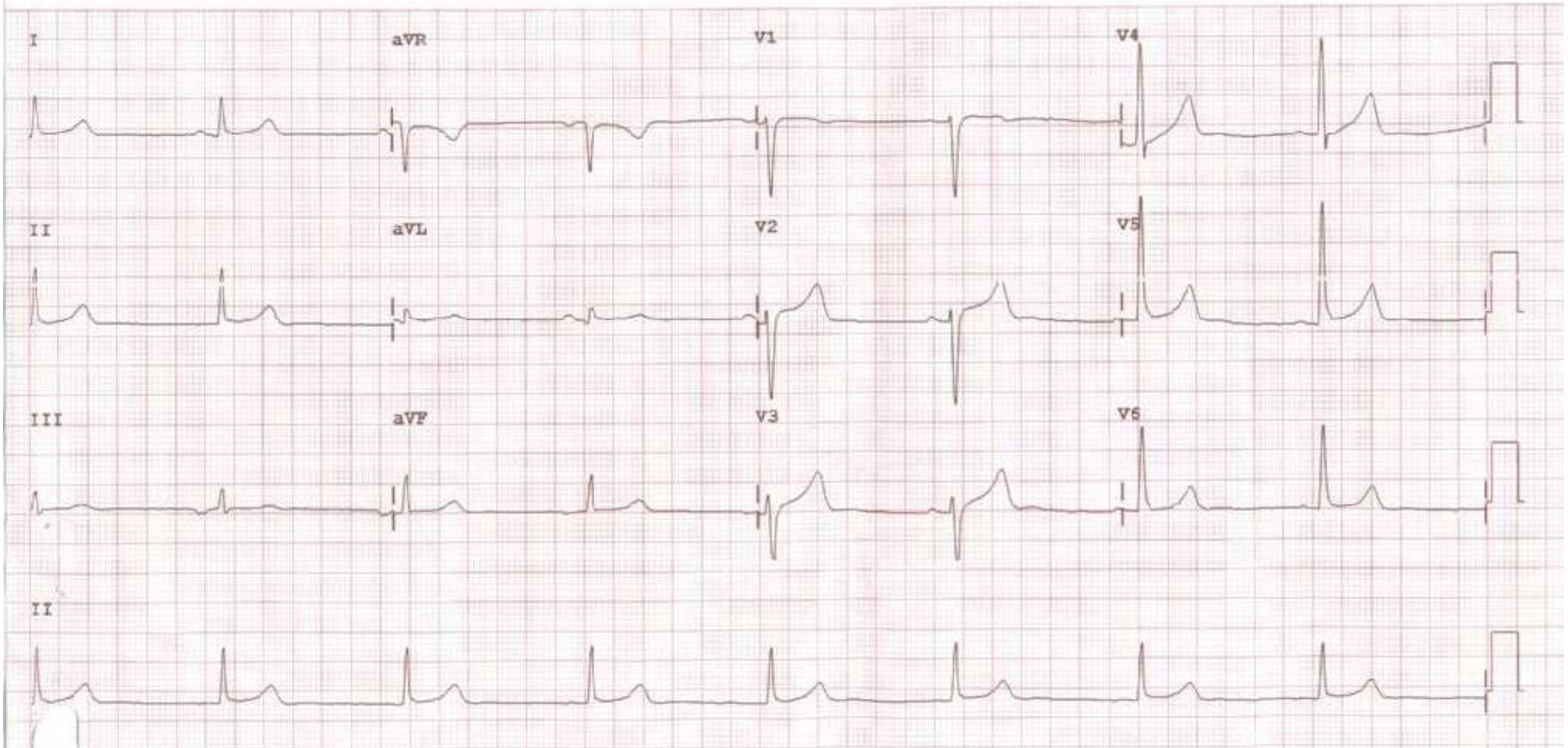
RN.01/02/1965 30/7/2008 07:29:40 MATIAS, NARCISO CARDOSO HCRP
43 Anos Masc Raça: Mulato
Dept°: CARDIOLOGIA
Quarto:

Freq 48
PR 156
QRSD 90
QT 476
QTc 425

--EIXO--
P -27
QRS 48
T 45

Campo 1 PRE CATE
Campo 2 LEO

FIDC



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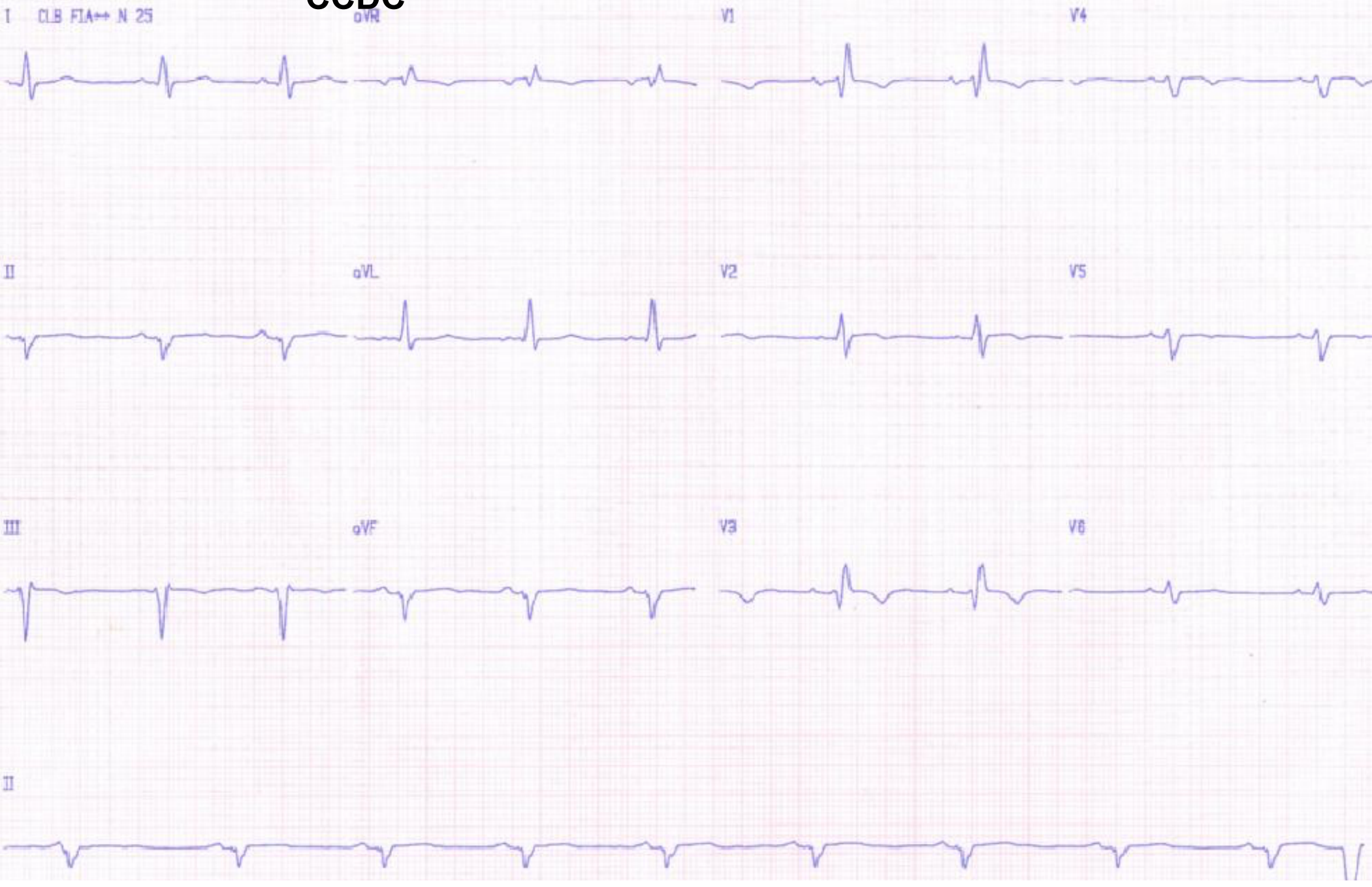
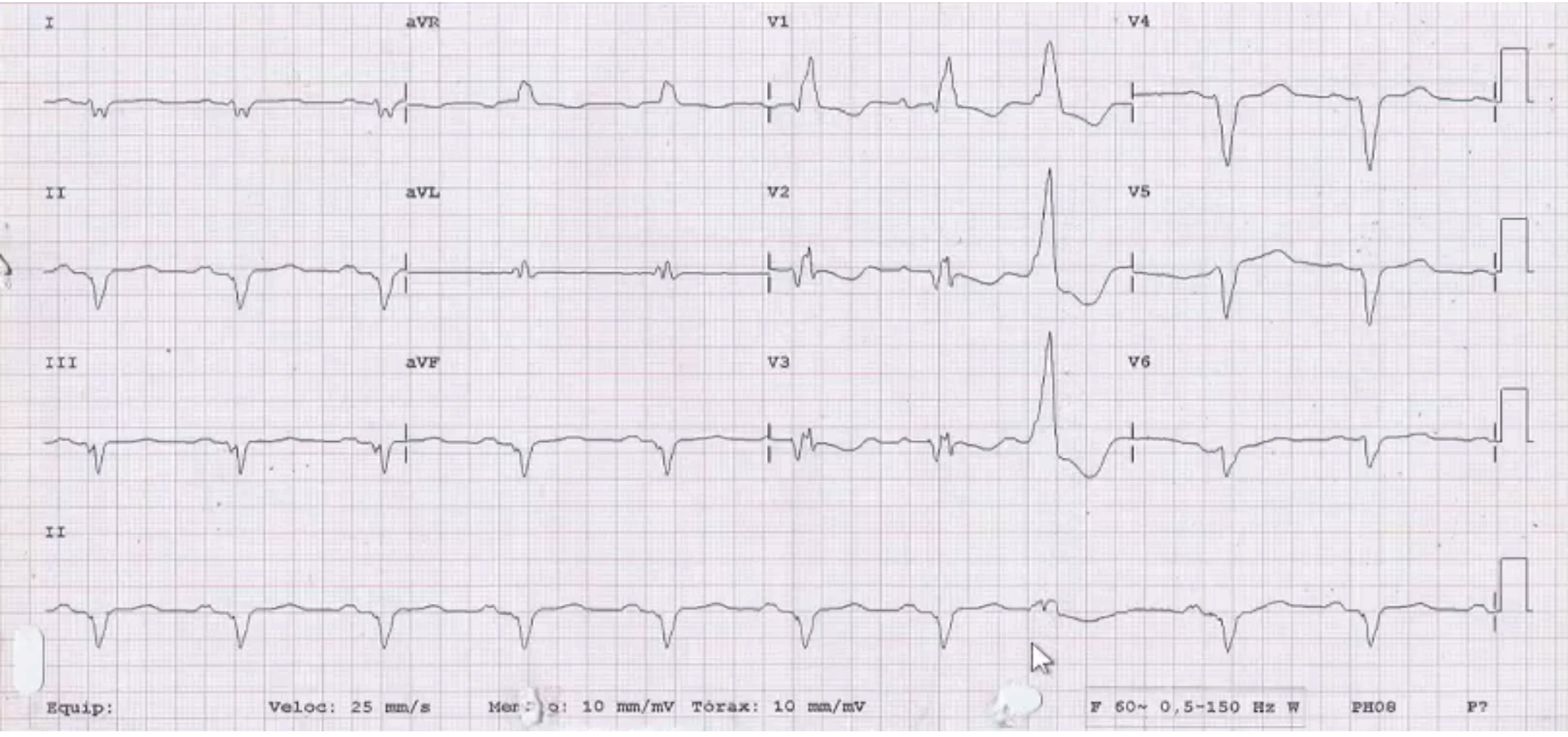
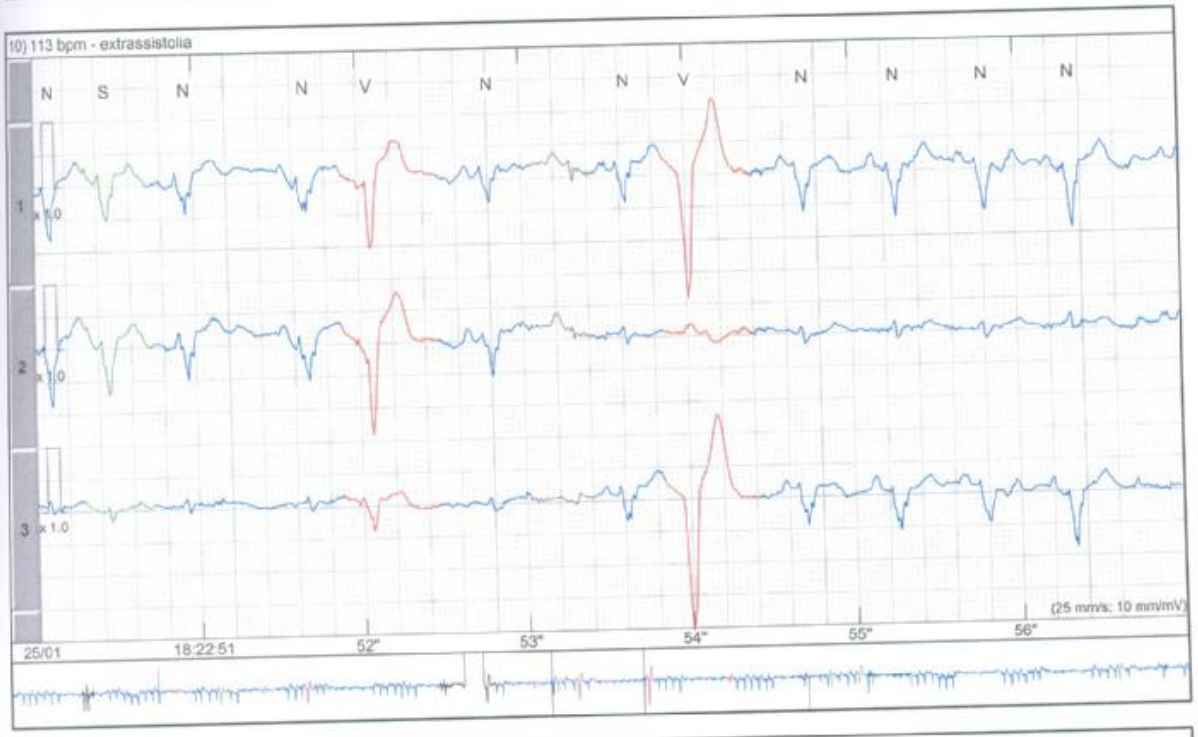
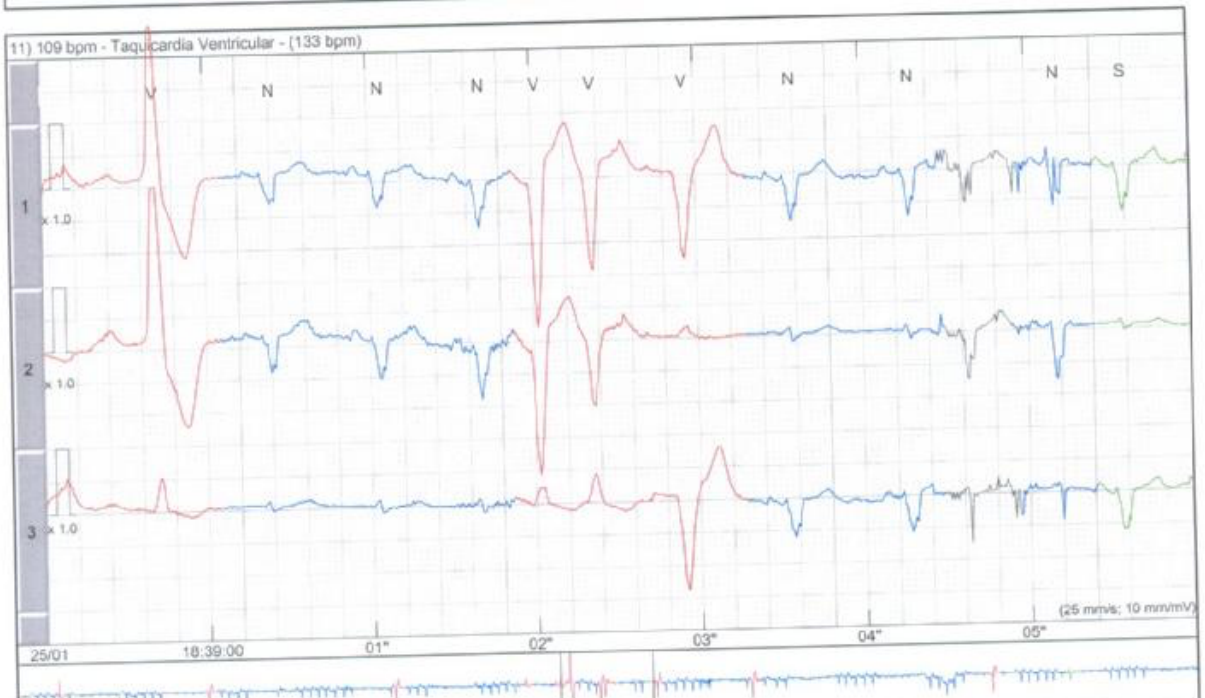


CCDC


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
Equip:
Veloc: 25 mm/s
Mer : o: 10 mm/mV Torax: 10 mm/mV
F 60~ 0,5-150 Hz W
PH08
P?

Nº do Exame	Paciente:	Código
72631	Luiz César de Faria	A06-0021
	Data do Exame: 25/01/2006 10:39:49	





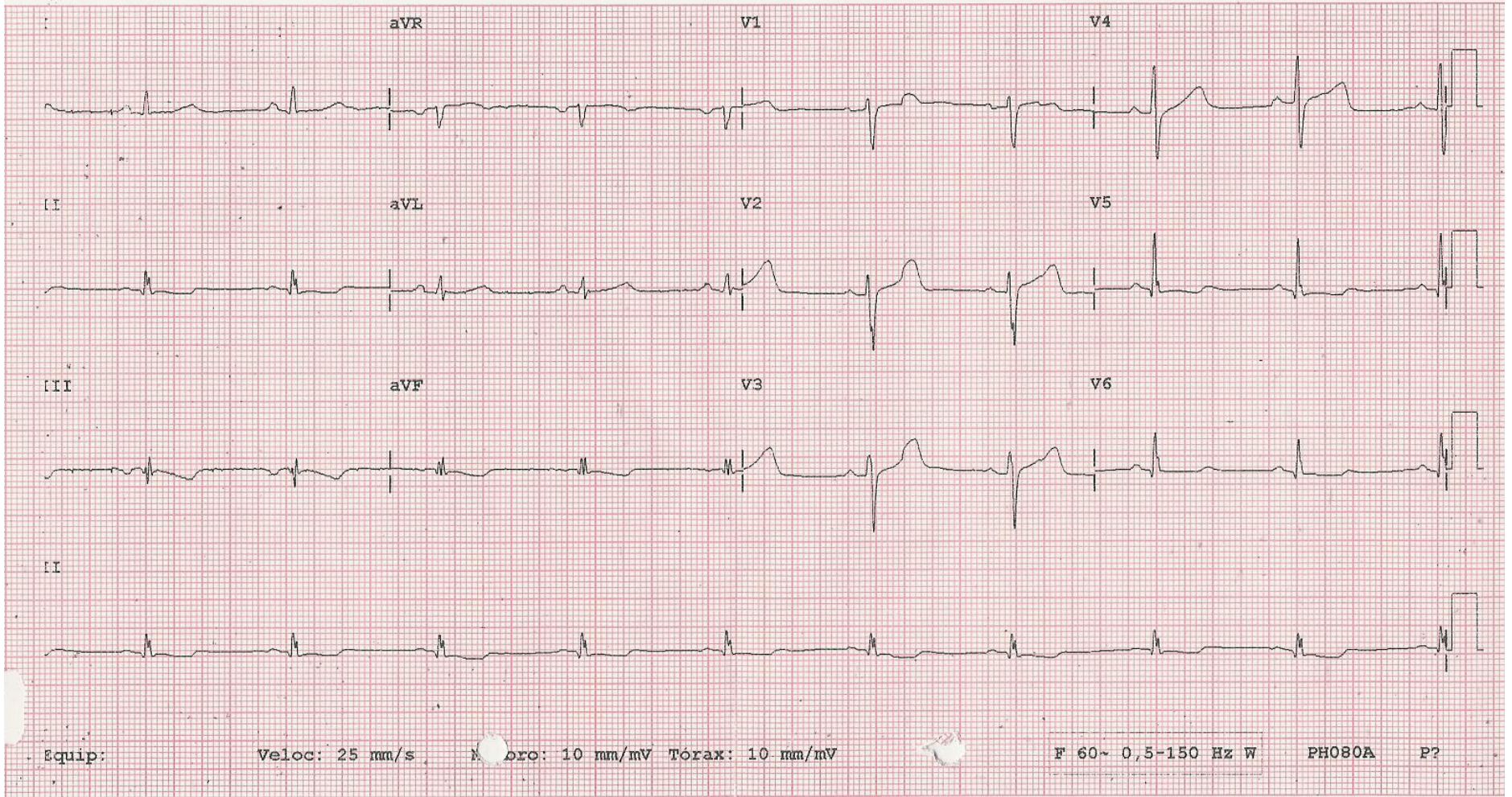
D977019I 27/11/2010 10:15:42 Teodoro da Silva, Dionisio
Masc 9/5/1957 Masc

	. POSSÍVEL ARRITMIA ATRIAL, FREQ A 121	Ps múltiplos
Freq 59	. BAIXA VOLTAGEM EM DERIVS FRONTAIS	todas derivs frontais <0,5 mV
PR 156	. ALTERAÇÃO NA REPOLARIZAÇÃO	infra ST e T alter
QRSD 94	. SUPRADESNIV MÍNIMO DO ST, DERIVS ANTERIORES	ST >0,08 mV, V1-V4
QT 436	. OSCILAÇÃO DA LB NAS DERIVS V4	
QTc 432		

--EIXO--
P -12
QRS 8
T -55

- ECG ALTER -

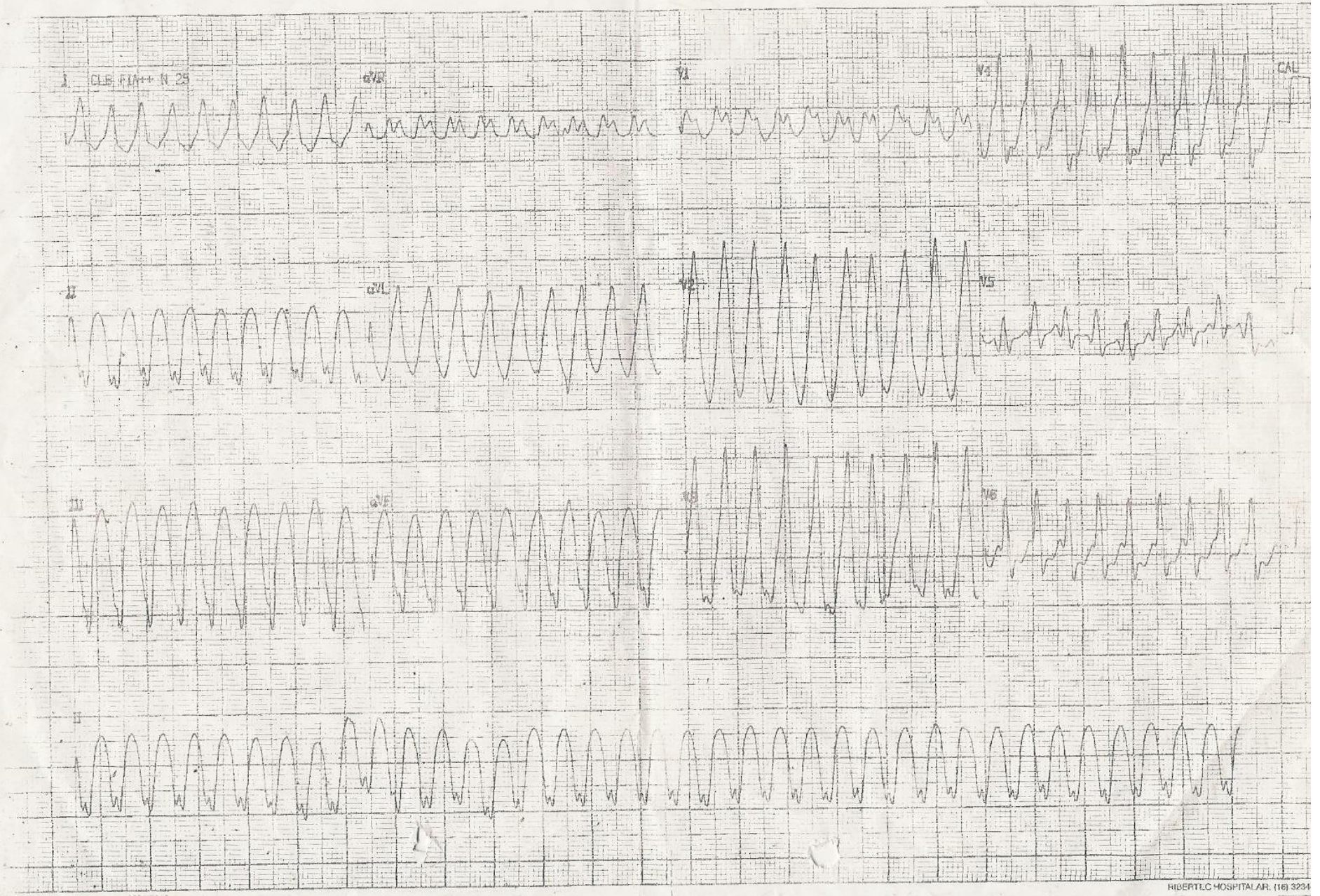
Diagnóstico não confirmado



Equip: Veloc: 25 mm/s Ganho: 10 mm/mV Tórax: 10 mm/mV F 60~ 0,5-150 Hz W PH080A P?

Dionisio

16h20' — 22/11/10



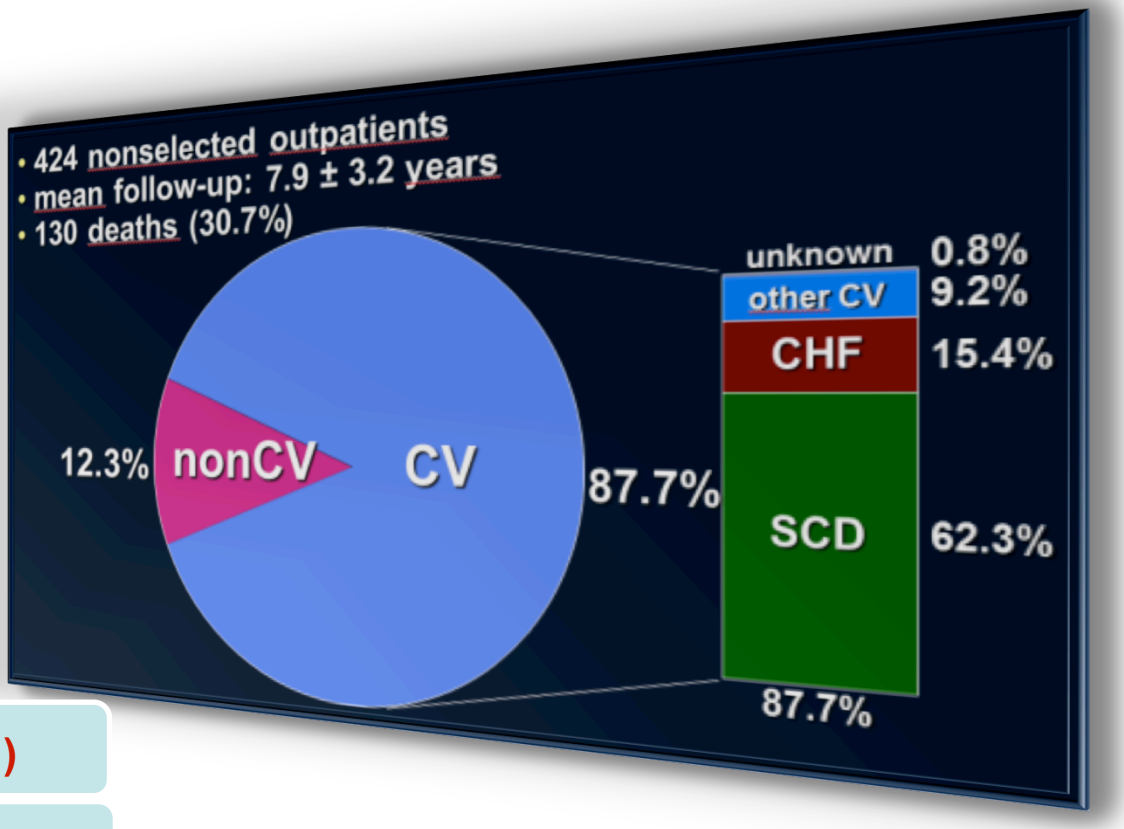
ORIGINAL ARTICLE

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

Anis Rassi, Jr., M.D., Ph.D., Anis Rassi, M.D., William C. Little, M.D., Sérgio S. Xavier, M.D., Ph.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., Ph.D., and Maurício I. Scanavacca, M.D., Ph.D.

Risk Factors for Death in Patients with Chagas Heart Disease:

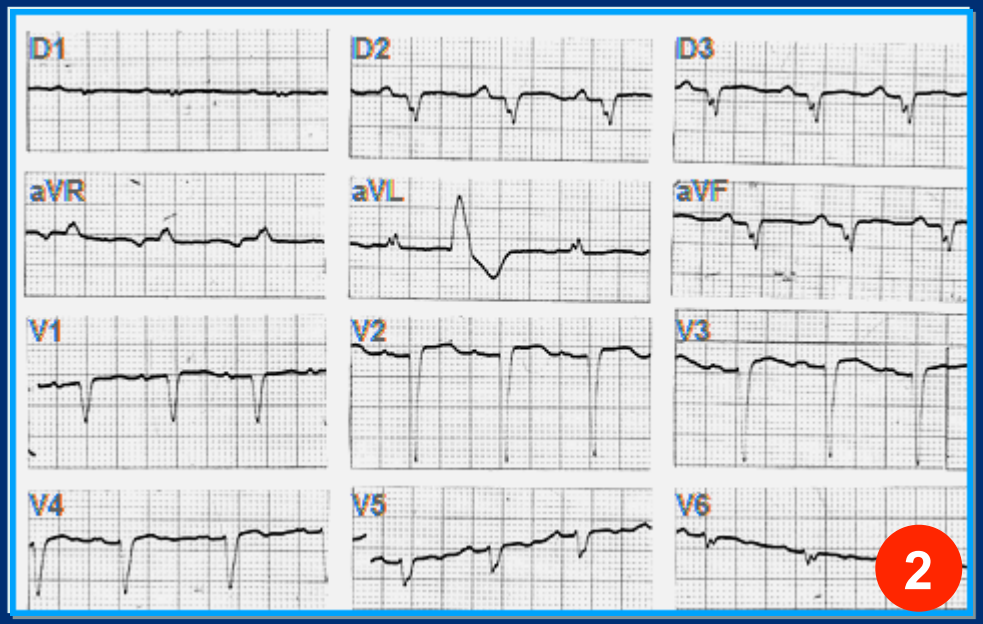
RASSI score: a multivariate analysis of 424 patients

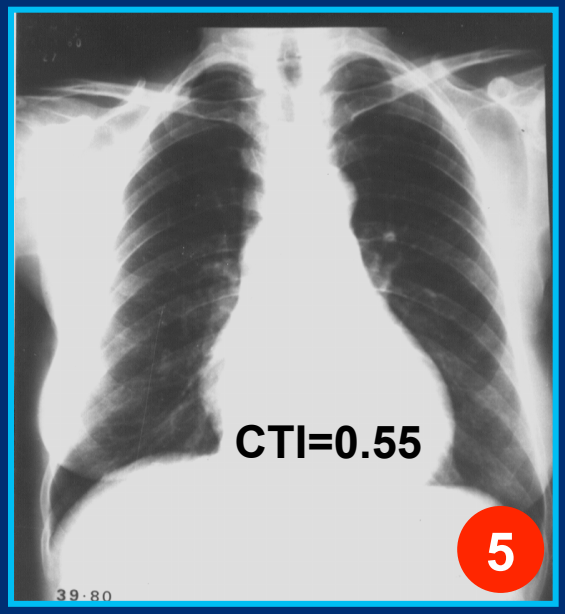


Risk Factor	HR (95% CI)
NYHA class III or IV	4.05 (2.46-6.67)
Cardiomegaly	3.43 (2.06-5.72)
Segmental or global WMA	2.46 (1.26-4.79)
Nonsustained VT	2.15 (1.28-3.62)
Low QRS voltage	1.87 (1.03-3.37)
Male gender	1.72 (1.06-2.81)

Annual mortality rate = 3.9%
Annual SCD rate = 2.4%

Rassi A Jr et al. NEJM 2006; 355: 799-808



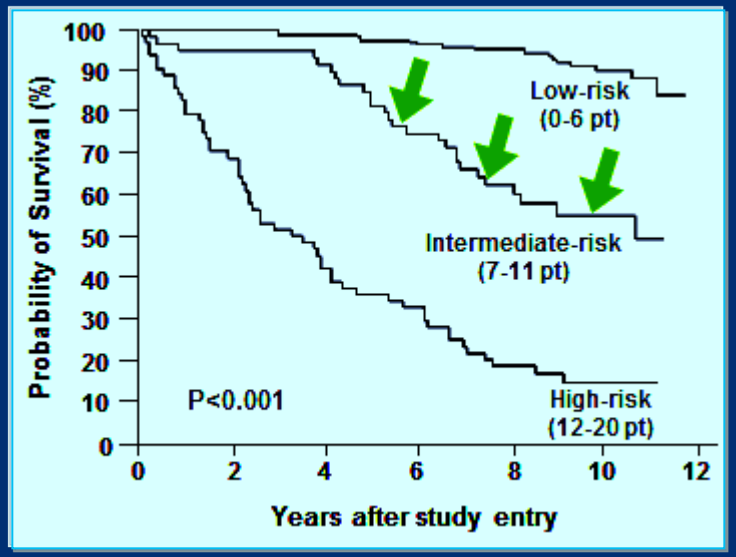


NYHA Class II

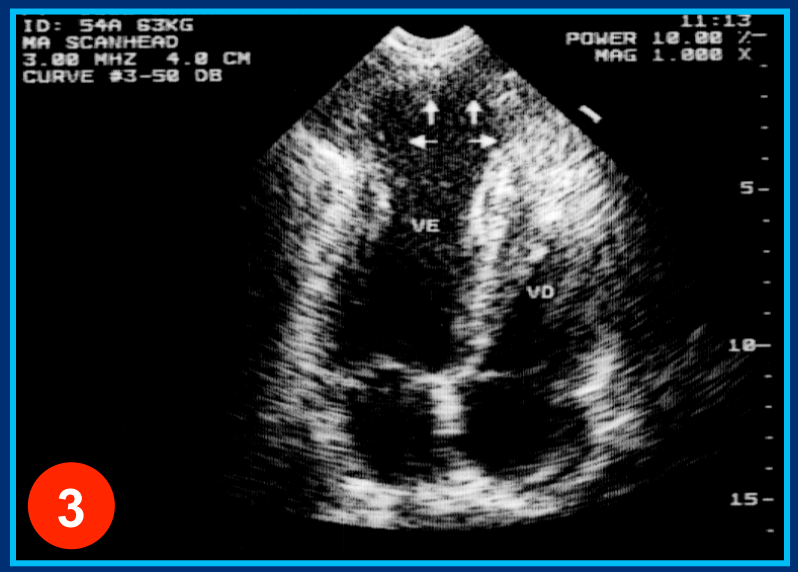
0

Female gender

0



10 points



24-h HOLTER (NSVT-)

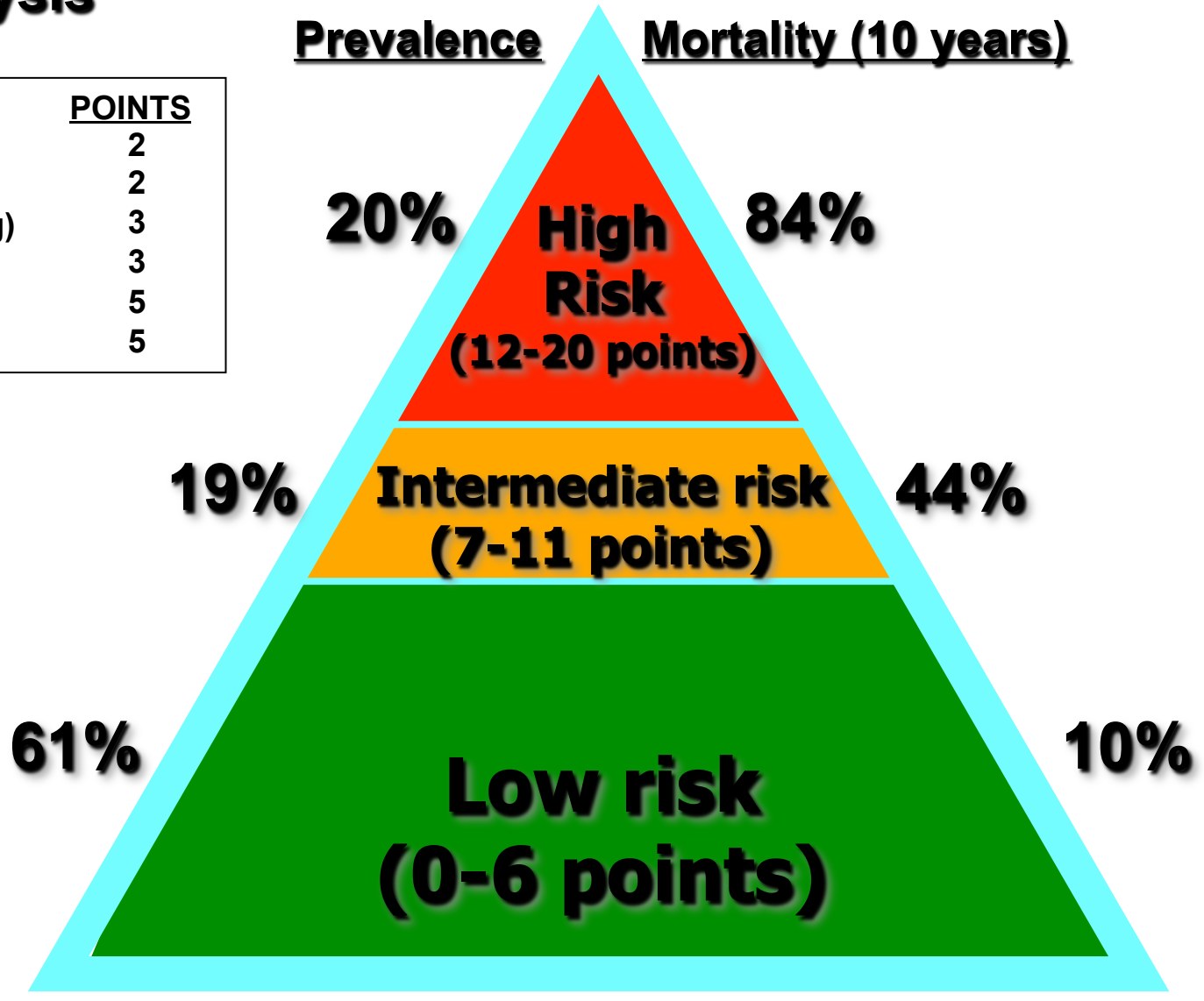
0

Chagas Heart Disease: Risk of Death

Multivariate analysis

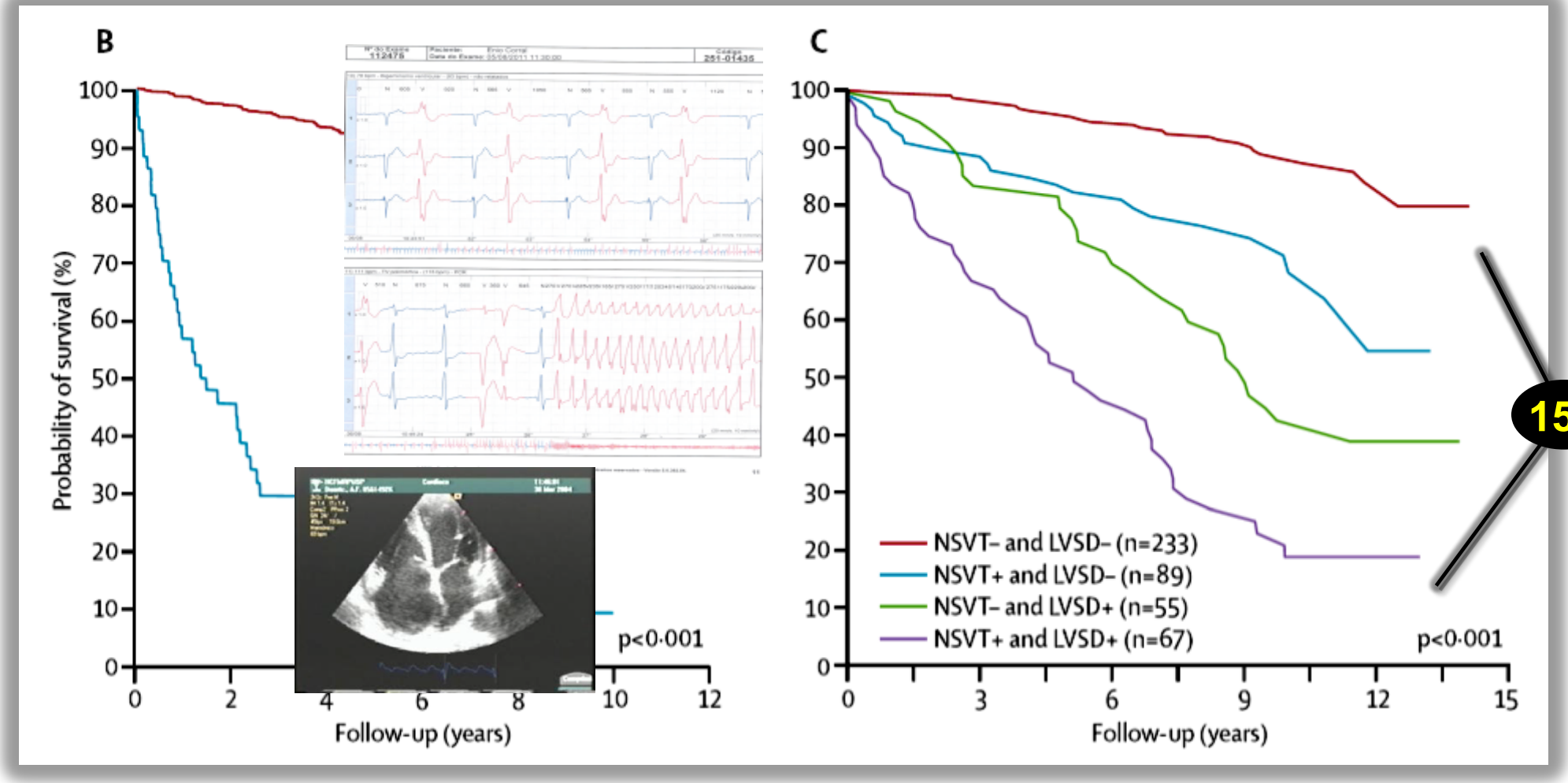
RISK FACTORS	POINTS
1) Male gender	2
2) Low QRS voltage (ECG)	2
3) NSVT (24-h Holter monitoring)	3
4) LV dysfunction (Echo)	3
5) Cardiomegaly (chest x-ray)	5
6) NYHA class III/IV	5

Rassi's score



NEJM 2006; 355: 799-808

PREDICTORS OF MORTALITY IN CHAGAS HEART DISEASE



Rassi Jr A, Rassi A, Marin-Neto JA
Lancet 2010; 375: 1388-402

NSVT = nonsustained ventricular tachycardia (Holter)
LVSD = left ventricular systolic dysfunction (echo)

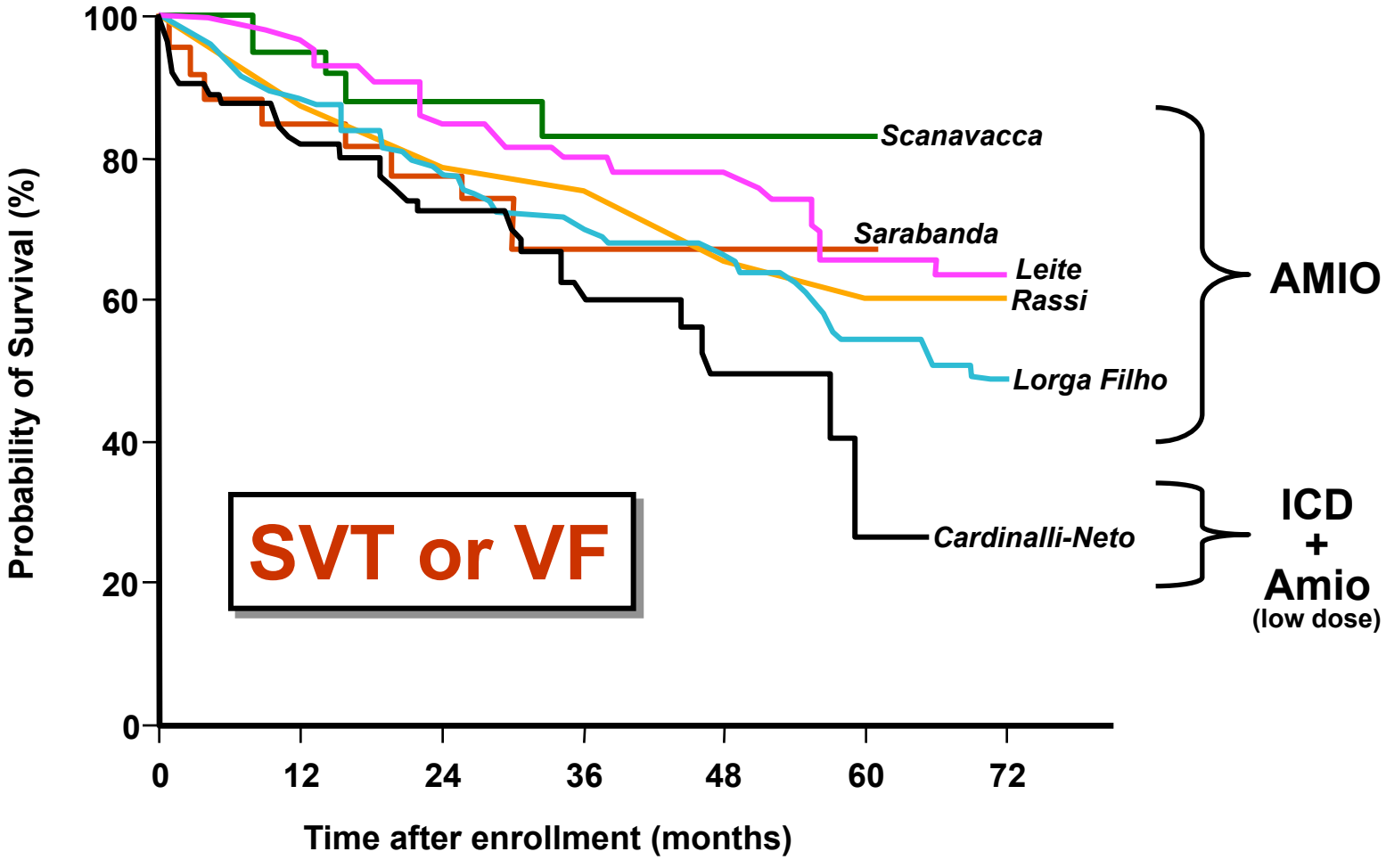
AMIO & ICD in patients with Chagas heart disease

Observational studies

Implantable Cardioverter-Defibrillators in Patients with Chagas Heart Disease: Misperceptions, Many Questions and the Urgent Need for a Randomized Clinical Trial

ANIS RASSI JR., M.D., PH.D.

From the Division of Cardiology, Anis Rassi Hospital, Goiânia, Goiás, Brazil



J Cardiovasc Electrophysiol 2007;18:1241-3

Systematic Review and Meta-Analysis of Clinical Outcome After Implantable Cardioverter-Defibrillator Therapy in Patients With Chagas Heart Disease

Fabio Mahamed Rassi, MD,[a,b] Lucas Minohara, MD,[b] Anis Rassi, Jr, MD, PhD,[a] Luis Claudio Lemos Correia, MD, PhD,[c] José Antonio Marin-Neto, MD, PhD,[d] Anis Rassi, MD,[a] Antonio da Silva Menezes, Jr, MD, PhD[b]

ABSTRACT

OBJECTIVES The goal of this analysis was to pool data from published studies on outcomes after implantable cardioverter-defibrillator (ICD) therapy in patients with Chagas heart disease (CHD).

BACKGROUND CHD is characterized by a high burden of ventricular arrhythmias and an increased risk of sudden cardiac death. The indications for ICD are not well established.

METHODS An extensive literature search without language restrictions was performed to identify all studies on ICD therapy in patients with CHD. A random effects model was used to calculate percentages and 95% confidence intervals (CIs).

RESULTS Of 397 articles screened, 13 studies (all observational) were included. There were 1,041 patients (mean age at implantation 57 ± 11 years; 64% men), most of whom (92%) received an ICD for secondary prevention. Antiarrhythmic medication consisted of amiodarone (79%) and beta-blockers (44%). Overall, the annual all-cause mortality rate was 9.0% (95% CI: 6.9 to 11.7) in 2.8 ± 1.9 years of follow-up, and the annual sudden cardiac death rate was 2.0% (95% CI: 1.3 to 3.3) in 2.6 ± 1.9 years. In addition, 24.8% (95% CI: 15.7 to 37.0) of patients received 1 or more appropriate interventions (shocks or antitachycardia pacing), 4.7% (95% CI: 3.2 to 6.9) received inappropriate shocks, and 9.1% (95% CI: 5.5 to 14.7) had electric storms annually.

CONCLUSIONS In patients with an ICD, annual all-cause mortality rate was 9%. Appropriate ICD interventions and electric storms were frequent, occurring at a rate of 25% and 9% per year, respectively. Inappropriate ICD shocks were not infrequent (5% per year). The benefits and risks of ICD therapy in patients with CHD should be carefully weighed until data from better studies become available. (J Am Coll Cardiol EP 2019;■:■-■) © 2019 by the American College of Cardiology Foundation.

RESULTS: Of 397 articles screened, 13 studies (all observational) were included. There were 1041 patients (mean age at implantation, 57±11 years; 64% men), most of whom (92%) received an ICD for secondary prevention. Antiarrhythmic medication consisted of amiodarone (79%) and beta-blockers (44%). Overall, the annual all-cause mortality rate was 9.0% (95% CI

Annual rates

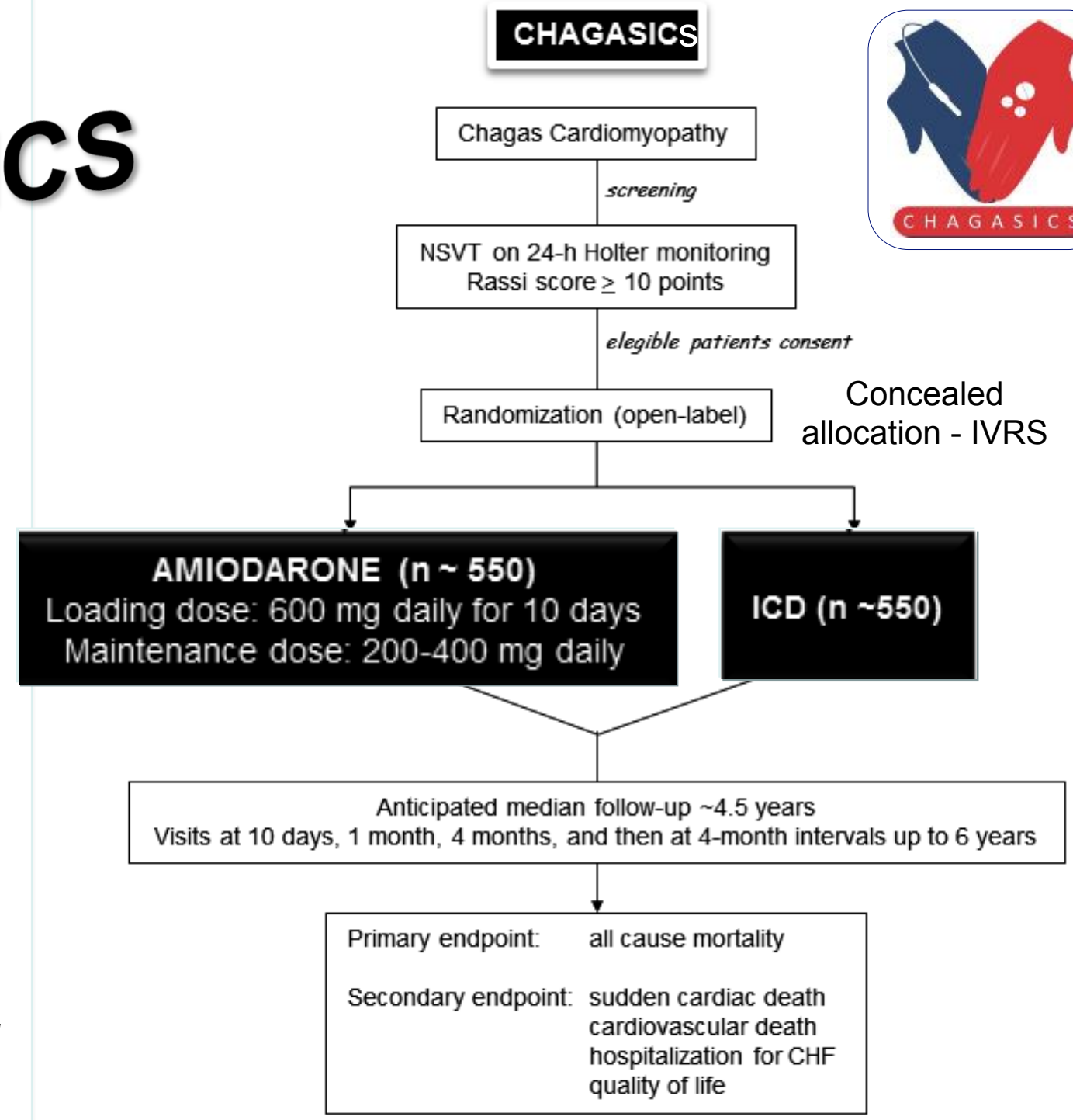
Mortality = 9%
ICD interventions 30%
Electrical storm = 9.1%

CONCLUSION: In patients with an implanted ICD, annual all-cause mortality rate was 9%. Appropriate ICD interventions and electrical storms were frequent, occurring at a rate of 25% and 9% per year, respectively. Inappropriate ICD shocks were not infrequent (5% per year). The benefits and risks of ICD therapy in patients with CHD should be carefully weighed, until data from better studies become available.

JACC – Clinical Electrophysiology 2019

CHAGASICS

ICD vs Amiodarone in the Primary Prevention of Death in Chagas Cardiomyopathy



Martinelli M, Rassi Jr A, Marin-Neto JA et al; CHAGASICS Investigators, ***American Heart Journal 2013; 166: 976-982***

Evidência e Adoção de Terapêutica

AAS no IAM

	Terapêutica	
	Adotada	Não adotada
Com Evidência "Definitiva" de Benefício	Certo	Erro α

Evidência e Adoção de Terapêutica

Antiarrítmico classe I profilático no IAM

	Terapêutica Adotada	Terapêutica Não adotada
Com Evidência "Definitiva" de Malefício	Erro β	Certo

Evidência e Adoção de Terapêutica

	Terapêutica	
	Adotada	Não adotada
Sem Evidência Definitiva	Chance de acerto	Risco de α
	Risco de β	Chance de acerto

Medicina
Embasada
Em Evidências

Decisão
Compartilhada

Pathogenesis of Chronic Chagas Heart Disease

- Chronic Chagas disease is a true infectious process leading to low-grade but virtually incessant myocarditis triggered by the parasite persistence and superimposed adverse immune reaction

- Autonomic disturbances
- Microvascular derangements

} Ancillary

- Parasite-dependent inflammation *
- Immune reaction to parasite persistence

EXPERIMENTAL SUPPORT FOR TRYPANOCIDAL THERAPY IN CHRONIC CHAGAS' HEART DISEASE

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2005, p. 1521–1528 Vol. 49, No. 4
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.4.1521–1528.2005

Treatment with Benznidazole during the Chronic Phase of Experimental Chagas' Disease Decreases Cardiac Alterations

Simone Garcia,[1,2] Carolina O. Ramos,[1] Juliana F. V. Senra,[1] Fabio Vilas-Boas,[3] Maurício M. Rodrigues,[4] Antonio C. Campos-de-Carvalho,[2] Ricardo Ribeiro-dos-Santos,[1] and Milena B. P. Soares[1]*

Centro de Pesquisas Gonçalo Moniz, Fundação Oswaldo Cruz,[1] and Hospital Santa Izabel,[3] Salvador, Bahia, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro,

These results demonstrate that treatment with benznidazole in the chronic phase of infection prevents the development of severe chronic cardiomyopathy, despite the lack of complete parasite eradication. In addition, our data highlight the role of parasite persistence in the development of chronic Chagas' disease and reinforce the importance of T. cruzi elimination …

Etiologic Treatment in the Chronic phase of Chagas Disease (Asymptomatic Patients)

Metanalysis of 5 RCTs (n=756)

Author, year	Population	Treatment	
Andrade 1996 (Brazil)	Children	BZD	Follow up 12-48 mo
Coura, 1997 (Brazil)	Adults	(n=27) (n=24)	
Gianella, 1997 - Bol		ALOP(n=18) PCB (n=22)	
Apt, 1998 (	Adults	ALOP(n=187) ITRA (n=217) PCB (n=24)	
Arg	Children	BZD (n=55) PCB (n=51)	

Only 5 RCTs, 756 patients, no hard clinical outcomes reported.

Villar J ar LA, Marin-Neto JA, Ebrahim S, Yusuf S. Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection (Cochrane Review) In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.

Journal of Antimicrobial Chemotherapy (2009) **64**, 1139–1147
doi:10.1093/jac/dkp357
Advance Access publication 9 October 2009

JAC

Use of benznidazole to treat chronic Chagas' disease: a systematic review with a meta-analysis

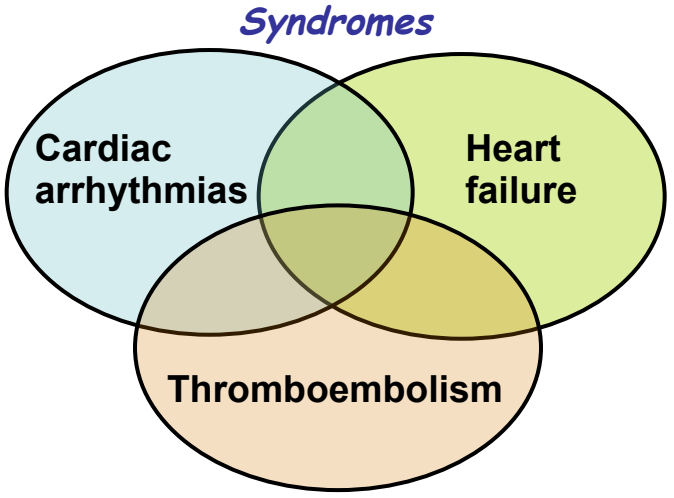
José A. Pérez-Molina[1]*, Ana Pérez-Ayala[1], Santiago Moreno[2], M. Carmen Fernández-González[2], Javier Zamora[3] and Rogelio López-Velez[1]

[1]Tro
[2]Infec
Ho

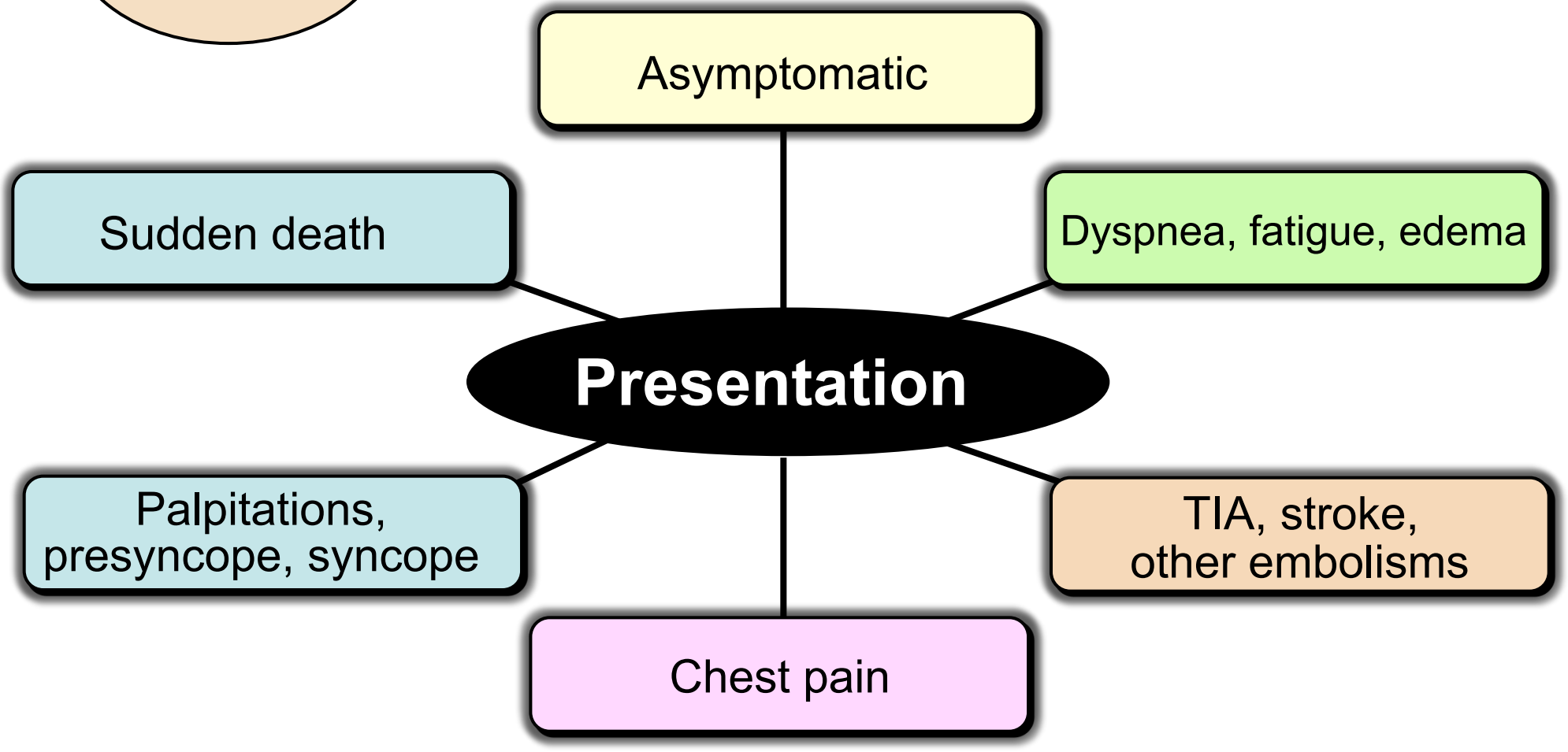
Pacientes tratados com benznidazol tivereram um risco significantemente menor de eventos clínicos (71% menor (84 a 45% menor).
Até 18% de descontinuações do tratamento por efeitos colaterais.

Received 17 June 2009; returned 25 July 2009; revised 8 September 2009; accepted 10 September 2009

Results: **We identified 696 studies, from which we chose 9: 3 clinical trials and 6 observational studies. Compared with placebo or no treatment, benznidazole increases 18-fold the probability of a response to therapy [global odds ratio (OR), 18.8; 95% confidence interval (CI), 5.2–68.3]. This effect was mainly observed in clinical trials (OR, 70.8; 95% CI, 16.4–314), whereas in observational studies it was much less marked (OR, 7.8; 95% CI, 2.1–28.9), and even less so when only observational studies in adults were considered (OR, 6.3; 95% CI, 1.6–24.7). Patients treated with benznidazole had a significantly lower risk of clinical events (OR, 0.29; 95% CI, 0.16–0.53). Up to 18% of patients discontinued treatment due to toxicity (cutaneous reactions followed by gastrointestinal disturbances); this was less common in children than in adults.**



Chagas Cardiomyopathy: Clinical Syndromes and Presentation



"BENznidazole Evaluation For Interrupting Trypanosomiasis"

BENEFIT

Antiparasitic clinical trial

Drug: benznidazole

Population: Chagas' heart disease

- **International**
- **Multicentre**
- **Prospective**
- **Randomized**
- **Double-blind**
- **Placebo-controlled**

Desfecho composto:morte, PCR, TVS, TX, IC, Tromboembolismo

Rationale and design of a randomized placebo-controlled trial assessing the effects of etiologic treatment in Chagas' cardiomyopathy: The BENznidazole Evaluation For Interrupting Trypanosomiasis (BENEFIT)

Jose Antonio Marin-Neto, MD,[a] Anis Rassi, Jr, MD,[b] Carlos A. Morillo, MD,[c] Alvaro Avezum, MD,[d] Stuart J. Connolly, MD,[c] Sergio Sosa-Estani, MD,[e] Fernando Rosas, MD,[f] and Salim Yusuf, MD[c] on behalf of BENEFIT Investigators *Sao Paulo and Goiania, Brazil; Hamilton, Ontario, Canada; Buenos Aires, Argentina; Bogota, Colombia*

2855 Pts followed for at least 3 years (mean = 6 years) – End of Study : 2015

Background Benznidazole is effective for treating acute and chronic (recently acquired) *Trypanosoma cruzi* infection (Chagas' disease). Recent data indicate that parasite persistence plays a pivotal role in the pathogenesis of chronic Chagas' cardiomyopathy. However, the efficacy of trypanocidal therapy in preventing clinical complications in patients with preexisting cardiac disease is unknown.

Study Design BENEFIT is a multicenter, randomized, double-blind, placebo-controlled clinical trial of 3,000 patients with Chagas' cardiomyopathy in Latin America. Patients are randomized to receive benznidazole (5 mg/kg per day) or matched placebo, for 60 days. The primary outcome is the composite of death; resuscitated cardiac arrest; sustained ventricular tachycardia; insertion of pacemaker or cardiac defibrillator; cardiac transplantation; and development of new heart failure, stroke, or systemic or pulmonary thromboembolic events. The average follow-up time will be 5 years, and the trial has a 90% power to detect a 25% relative risk reduction. The BENEFIT program also comprises a substudy evaluating the effects of benznidazole on parasite clearance and an echo substudy exploring the impact of etiologic treatment on left ventricular function. Recruitment started in November 2004, and >1,000 patients have been enrolled in 35 centers from Argentina, Brazil, and Colombia to date.

Conclusion This is the largest trial yet conducted in Chagas' disease. BENEFIT will clarify the role of trypanocidal therapy in preventing cardiac disease progression and death. (Am Heart J 2008;156:37-43.)

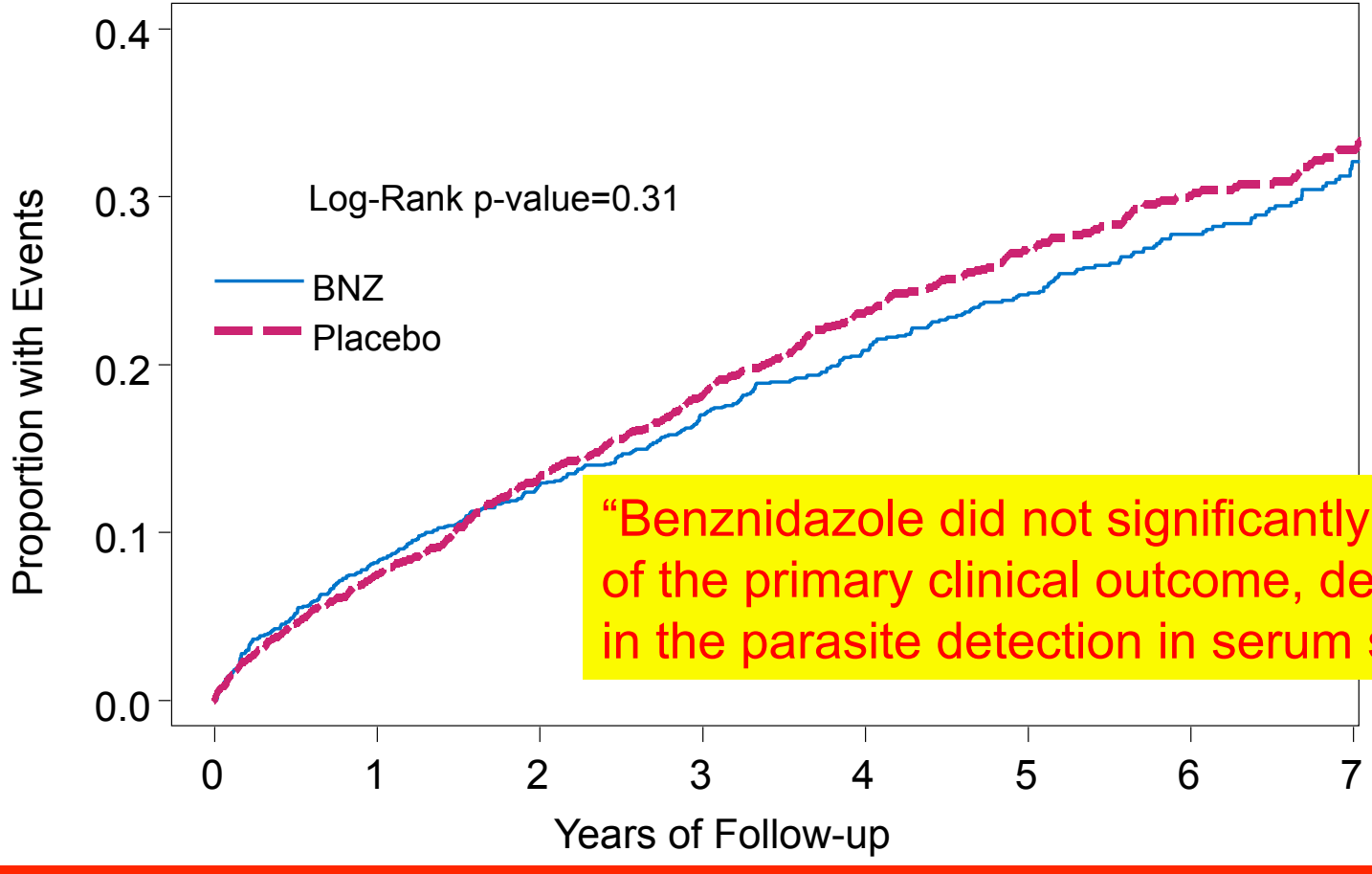
Safety: Adverse Events Leading to Drug Interruption

	BNZ	Placebo	P
Any adverse event	23.9%	9.5%	<0.001
Permanent treatment discontinuation	13.4%	3.6%	< 0.001
Cutaneous rash	9.6%	1.3%	<0.001
Gastrointestinal	7.8%	2.9%	<0.001
Nervous system	3.6%	1.3%	<0.001
Leukopenia < 1.9 $10^3/mm^3$ neutrophil	0.1%	0.1%	1
Alanine aminotransferase >2X ULN	4.9%	1.6%	<0.001

BENEFIT

Primary Outcome

Morillo C, Marin-Neto JA et al
N Engl J Med 2015



"Benznidazole did not significantly reduce the rate of the primary clinical outcome, despite reductions in the parasite detection in serum samples".

"Our findings do not challenge current guidelines that recommend trypanocidal therapy in the early stages of chronic Chagas' infection… and should not detract from the pursuit of goals for exploring more effective or earlier treatments with new drugs or combinations".

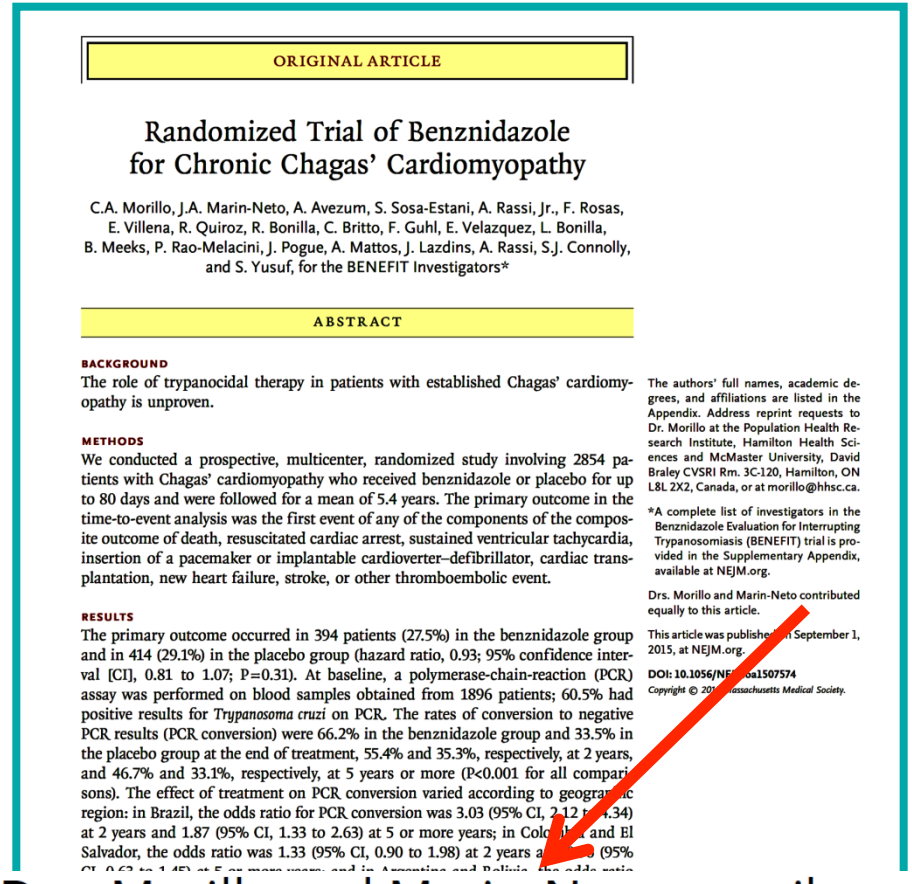
The BENEFIT trial

Conclusion:

Trypanocidal therapy with benznidazole in patients with established Chagas' cardiomyopathy significantly reduced serum parasite detection but did not significantly reduce cardiac clinical deterioration through 5 years of follow-up.

Clear the parasite but do not change disease evolution?!?

This article was published on September 1, 2015, at NEJM



ORIGINAL ARTICLE

Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy

C.A. Morillo, J.A. Marin-Neto, A. Avezum, S. Sosa-Estani, A. Rassi, Jr., F. Rosas, E. Villena, R. Quiroz, R. Bonilla, C. Britto, F. Guhl, E. Velazquez, L. Bonilla, B. Meeks, P. Rao-Melacini, J. Pogue, A. Mattos, J. Lazdins, A. Rassi, S.J. Connolly, and S. Yusuf, for the BENEFIT Investigators*

ABSTRACT

BACKGROUND

The role of trypanocidal therapy in patients with established Chagas' cardiomyopathy is unproven.

METHODS

We conducted a prospective, multicenter, randomized study involving 2854 patients with Chagas' cardiomyopathy who received benznidazole or placebo for up to 80 days and were followed for a mean of 5.4 years. The primary outcome in the time-to-event analysis was the first event of any of the components of the composite outcome of death, resuscitated cardiac arrest, sustained ventricular tachycardia, insertion of a pacemaker or implantable cardioverter–defibrillator, cardiac transplantation, new heart failure, stroke, or other thromboembolic event.

RESULTS

The primary outcome occurred in 394 patients (27.5%) in the benznidazole group and in 414 (29.1%) in the placebo group (hazard ratio, 0.93; 95% confidence interval [CI], 0.81 to 1.07; P=0.31). At baseline, a polymerase-chain-reaction (PCR) assay was performed on blood samples obtained from 1896 patients; 60.5% had positive results for *Trypanosoma cruzi* on PCR. The rates of conversion to negative PCR results (PCR conversion) were 66.2% in the benznidazole group and 33.5% in the placebo group at the end of treatment, 55.4% and 35.3%, respectively, at 2 years, and 46.7% and 33.1%, respectively, at 5 years or more (P<0.001 for all comparisons). The effect of treatment on PCR conversion varied according to geographic region: in Brazil, the odds ratio for PCR conversion was 3.03 (95% CI, 2.12 to 4.34) at 2 years and 1.87 (95% CI, 1.33 to 2.63) at 5 or more years; in Colombia and El Salvador, the odds ratio was 1.33 (95% CI, 0.90 to 1.98) at 2 years and (95%

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Morillo at the Population Health Research Institute, Hamilton Health Sciences and McMaster University, David Braley CVSRI Rm. 3C-120, Hamilton, ON L8L 2X2, Canada, or at morillo@hhsc.ca.

*A complete list of investigators in the Benznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Morillo and Marin-Neto contributed equally to this article.

This article was published on September 1, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1507574

Drs. Morillo and Marin-Neto contributed equally to this article.

This article was published on September 1, 2015, and updated on September 10, 2015, at NEJM.org.

N Engl J Med 2015;373:1295-306.

Evidência e Adoção de Terapêutica

Tratamento Tripanocida para Muitos : risco de erro α é atualmente muito menos aceitável do que o risco de β

	Terapêutica Adotada	Terapêutica Não adotada
Sem Evidência Definitiva	Chance de acerto	Risco de α
	Risco de β	Chance de acerto

MARIN-NETO, JA et alii "Doença de Chagas: Moléstia Negligenciada", in: *Tratado de Prevenção Cardiovascular. Um Desafio Global*. Andrade, JP; Arnett, DK Et alii (editores). Editora Atheneu, São Paulo, 1ª edição, 221 páginas, v. 1, 2014, pp. 111-27.

BENEFIT Trial Results in Brazil

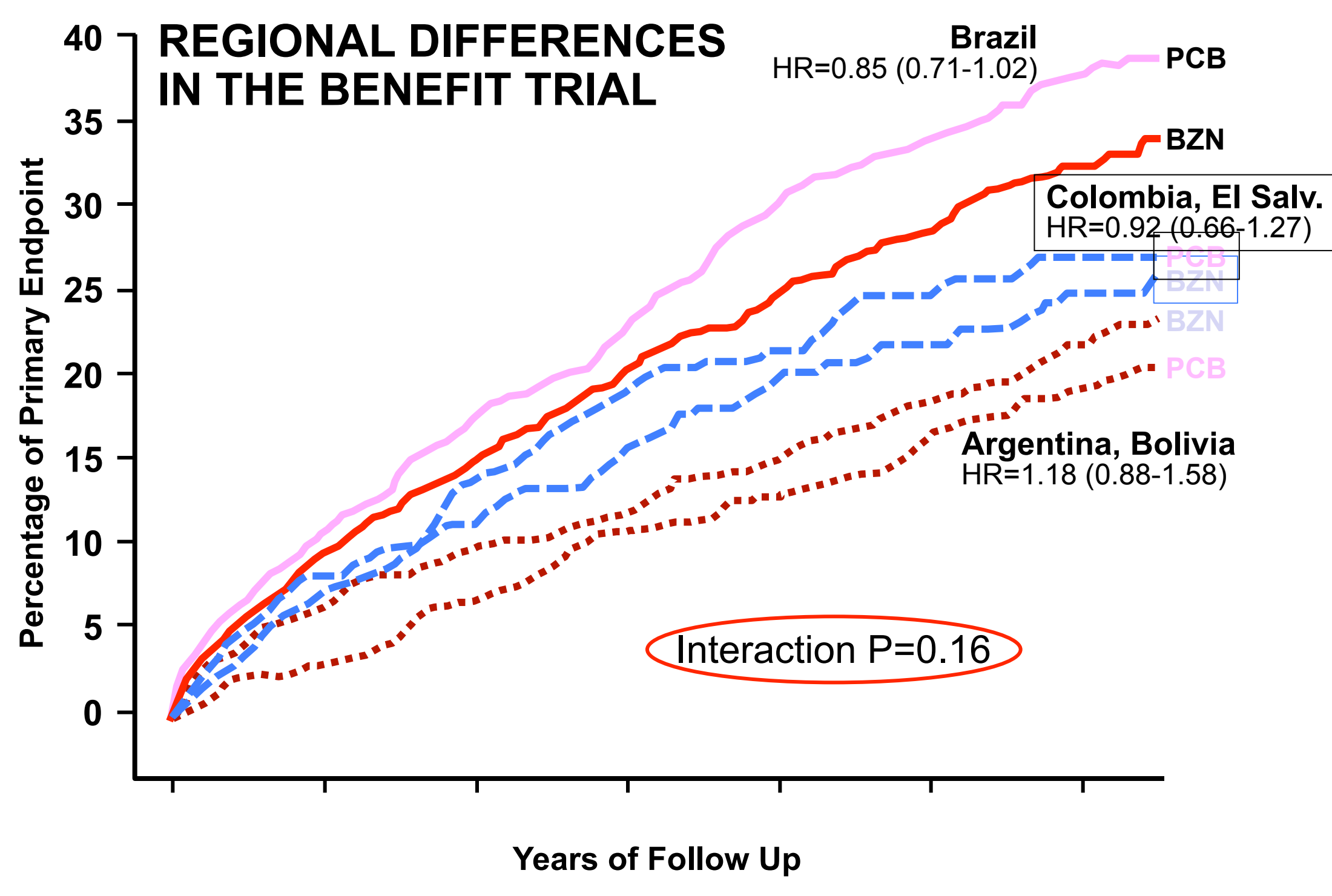
	BENZNIDAZOLE⁺	PLACEBO	HR	OR	95% CI
Primary outcome* (5.4y)	33.2%	37.6%	0.85		0.71-1.02
Negativization of PCR (EOT)	86.3%	24.3%		7.20	4.53-11.4

EOT=end of treatment (5mg/Kg/day for 60 days).

NNT = 23

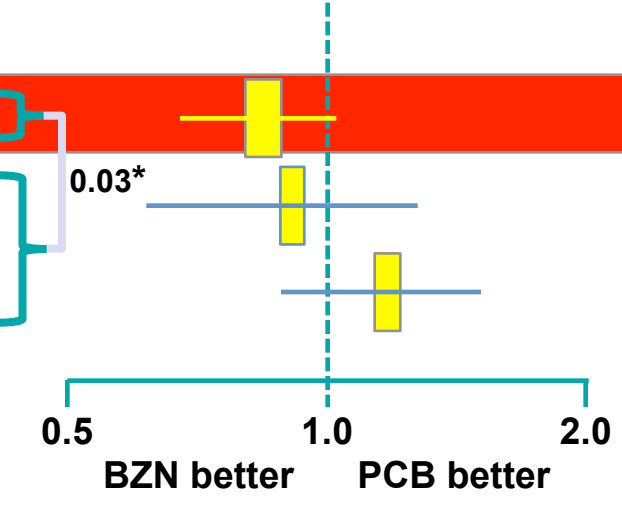
⁺13% of patients interrupted therapy.
*composite of death, resuscitated CA, SVT, insertion of a pacemaker or ICD, cardiac transplantation, new HF, stroke, or other thromboembolic event.

On the basis of the BENEFIT results, we suggest trypanocidal therapy to treat Brazilian patients with chronic CD, even if there is established cardiomyopathy of mild-to-moderate severity, but not in those with more advanced stages of CCC


REGIONAL DIFFERENCES
IN THE BENEFIT TRIAL
Brazil
HR=0.85 (0.71-1.02)
PCB
BZN
Colombia, El Salv.
HR=0.92 (0.66-1.27)
PCB
BZN
BZN
PCB
Argentina, Bolivia
HR=1.18 (0.88-1.58)
Interaction P=0.16
Percentage of Primary Endpoint
0
5
10
15
20
25
30
35
40
Years of Follow Up

Treatment effect of BZN over hard endpoints was inconsistent across different countries

Country	Total patients	KM at 5.4 ys BZN	KM at 5.4 ys PCB	HR (95% CI)	Interaction P value
Brazil	1358	33.2	37.6	0.85 (0.71-1.02)	
Colombia/El Salvador	580	24.1	25.6	0.92 (0.66-1.27)	0.16
Argentina/Bolivia	916	21.4	18.5	1.18 (0.88-1.58)	0.03*



*not shown by the investigators

Post hoc grouping of countries: may be biased

*Brazil (T cruzi II) compared to all other countries (non T cruzi II) = significant P for interaction

Drug discovery for Chagas disease should consider *Trypanosoma cruzi* strain diversity

Bianca Zingales[1]/+, Michael A Miles[2], Carolina B Moraes[3], Alejandro Luquetti[4], Felipe Guhl[5], Alejandro G Schijman[6], Isabela Ribeiro[7]

(iii) Once promising drug candidates have been identified, they should be checked for broad activity against two or three representatives of each DTU (secondary screens). Priority should be given to DTUs that are more often associated with human infection (TcI_{DOM}, TcII, TcV and TcVI), preferably with dissimilar characteristics regarding geographical origin, replication rates, as this parameter may impact the response to some classes of drugs, and level of susceptibility to BZ or NF. This last item is particularly relevant when any drug candidates are analogues of BZ and/or NF. An extensive list of strains reports susceptibility and natural resistance to the two drugs (Filardi & Brener 1987). There is a large panel of clones representing the different DTUs, from which

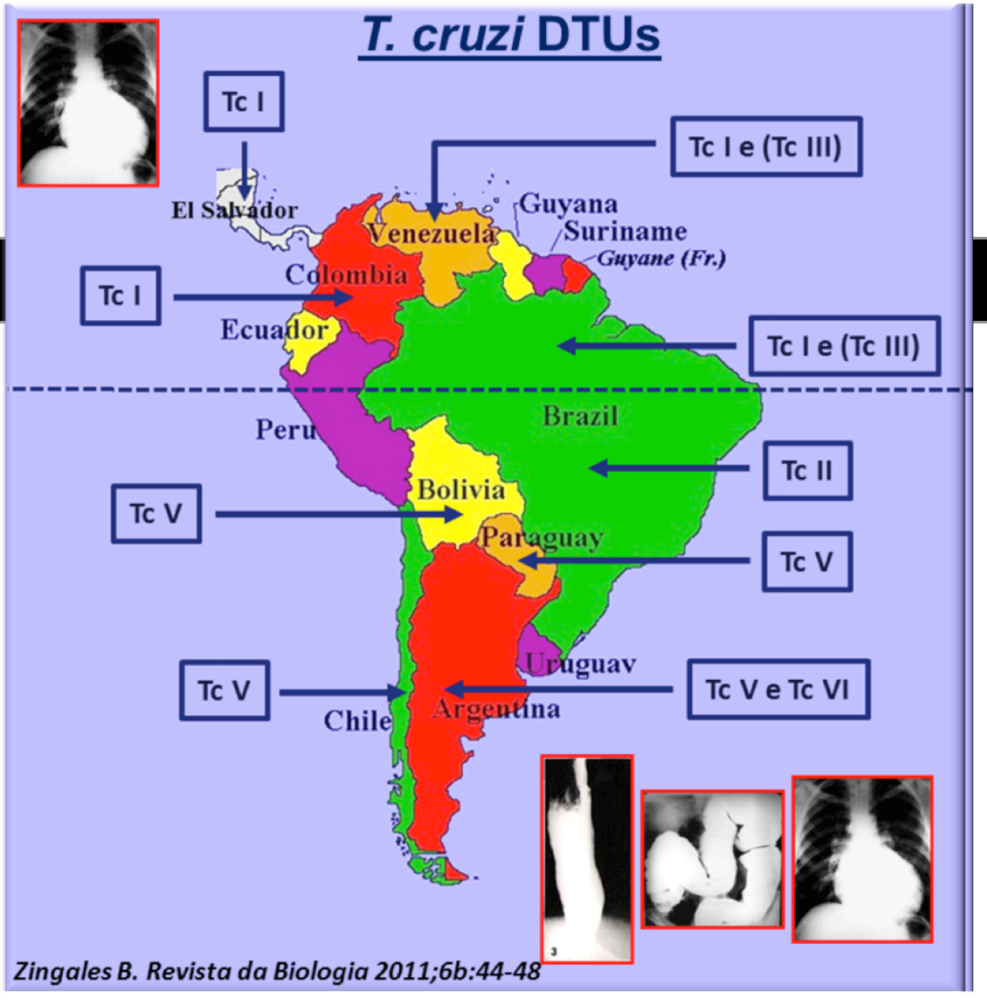


Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Benznidazole (N=1431)	Placebo (N=1423)
Age — yr	55.4±10.7	55.2±11.2
Male sex — no. (%)	726 (50.7)	682 (47.9)
Any abnormal result on electrocardiography — no./total no. (%)	1335/1431 (93.3)	1348/1423 (94.7)
Right bundle-branch block or left anterior fascicular block		
Right bundle-branch block	691/1335 (51.8)	702/1348 (52.1)
Left anterior fascicular block	643/1335 (48.2)	618/1348 (45.8)
Both conditions	465/1335 (34.8)	442/1348 (32.8)
Sinus bradycardia <50 beats/min	159/1335 (11.9)	161/1348 (11.9)
Low-voltage QRS	178/1335 (13.3)	163/1348 (12.1)
ST–T wave changes	393/1335 (29.4)	405/1348 (30.0)
Q waves	45/1335 (3.4)	24/1348 (1.8)
Atrial fibrillation — no. (%)	107 (7.5)	90 (6.3)
Complex ventricular arrhythmia — no. (%)	221 (15.4)	189 (13.3)
Resuscitated cardiac arrest — no. (%)	19 (1.3)	16 (1.1)
Previous heart failure — no. (%)	142 (9.9)	128 (9.0)
New York Heart Association class — no./total no. (%)		
Patients with score	1431/1431 (100)	1421/1423 (99.9)
Class I	1065/1431 (74.4)	1045/1421 (73.5)
Class II	327/1431 (22.9)	343/1421 (24.1)
Class III	39/1431 (2.7)	33/1421 (2.3)
Pacemaker — no. (%)	205 (14.3)	198 (13.9)
Implantable cardioverter–defibrillator — no. (%)	39 (2.7)	31 (2.2)
Stroke or transient ischemic attack — no. (%)	61 (4.3)	62 (4.4)
Systemic or pulmonary embolism — no. (%)	7 (0.5)	11 (0.8)
Echocardiography performed <1 yr before randomization		
Patients with results — no. (%)	1126 (78.7)	1121 (78.8)
Left ventricular ejection fraction		
Mean — %	54.4±14.8	54.6±14.6
Value <40% — no./total no. (%)	200/1126 (17.8)	189/1121 (16.9)
Wall-motion abnormality — no./total no. (%)	431/1126 (38.3)	422/1121 (37.6)

BENEFIT trial

RESULTS: Baseline characteristics were well balanced between the two study groups (Table 1).

→ **Not entirely true**

Imbalance in prognostic factors

Characteristic (RASSI score)	BZN (N=1431)	PCB (N=1423)
Male sex	50.7%	47.9%
Low voltage QRS	13.3%	12.1%
Complex ventricular arrhythmias	15.4%	13.3%
Wall motion abnormalities	38.3%	37.6%
Cardiomegaly	?	?
NYHA class III	2.7%	2.3%

→ **All more frequent in the BZN group**

- Trial results may not be valid if it is not well balanced across prognostic factors.
- P value should be adjusted for imbalances in prognostic baseline characteristics.

Table 2. Primary Outcome and Its Components, Hospitalizations, and Deaths.

Outcome	Benznidazole (N=1431)	Placebo (N=1423)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite outcome	394 (27.5)	414 (29.1)	0.93 (0.81–1.07)	0.31
Death	246 (17.2)	257 (18.1)	0.95 (0.79–1.13)	—
Resuscitated cardiac arrest	10 (0.7)	17 (1.2)	0.58 (0.27–1.28)	—
Sustained ventricular tachycardia	33 (2.3)	41 (2.9)	0.80 (0.50–1.26)	—
New or worsening heart failure	109 (7.6)	122 (8.6)	0.88 (0.68–1.14)	—
Pacemaker or implantable cardioverter–defibrillator	109 (7.6)	125 (8.8)	0.86 (0.66–1.11)	—
Stroke or transient ischemic attack, systemic embolism, or pulmonary embolism	54 (3.8)	61 (4.3)	0.88 (0.61–1.26)	—
Cardiac transplantation	3 (0.2)	9 (0.6)	0.33 (0.09–1.22)	—
Hospitalization				
Any	358 (25.0)	397 (27.9)	0.89 (0.77–1.03)	0.11
For cardiovascular causes	242 (16.9)	286 (20.1)	0.83 (0.70–0.98)	0.03
Death from cardiovascular causes	194 (13.6)	203 (14.3)	0.94 (0.77–1.15)	0.55
Death from or hospitalization for cardiovascular causes	348 (24.3)	380 (26.7)	0.89 (0.77–1.03)	0.13

- **All components of the composite end-point were less frequent in the treated group, although without statistical significance in all but one of them. This was not highlighted in the NEJM discussion, but may bear clinical relevance.**
- **The rate of hospitalization for CV causes was significantly reduced with BZN (p=0.03)**
- **And if recurrent events were included in the analysis?**

Chronic Chagas cardiomyopathy: a review of the main pathogenic

MARIN-NETO, JA et alii "Doença de Chagas: Moléstia Negligenciada", in: *Tratado de Prevenção Cardiovascular. Um Desafio Global*. Andrade, JP; Arnett, DK Et alii (editores). Editora Atheneu, São Paulo, 1ª edição, 221 páginas, v. 1, 2014, pp. 111-27.

Anis Rassi Jr[1]/+, José Antonio Marin-Neto[2], Anis Rassi[1]

[1]Hos
[2]Uni
Dep

We strongly believe that the risk of incurring an alfa-error (not to apply a promising therapy with tolerable side-effects) is much less acceptable than incurring a beta-error (Marin-Neto et al 2015b). On the basis of current evidence, doctor's failure to even consider the possibility of aetiological treatment for their patients is questionable from an ethical standpoint − after all, absence of evidence is not evidence of absence (Altman & Bland 1995)

BENEFIT trial, benznidazole seems to have no benefit for arresting disease progression in patients with chronic Chagas cardiomyopathy. In this review, we give an update on the main pathogenic mechanisms of Chagas disease, and re-examine and discuss the results of the BENEFIT trial, together with its limitations and implications.

Key words: chronic Chagas cardiomyopathy - Chagas heart disease - pathogenesis - aetiological treatment - Benznidazole - BENEFIT trial

Event	Recommendation class	Level of evidence
Antiparasitic treatment in the acute phase of Chagas disease	I	B
Antiparasitic treatment in congenital Chagas disease	I	B
Antipar treat in the chronic phase of Chagas disease in children aged ≤12 years	I	A
Antipar treatment in the chronic phase of Chagas disease with recent infection	IIa	C
Antiparasitic treatment in the chronic phase of Chagas disease with late infection, wtih indeterminate form	IIa	B
Antiparasitic treatment in the chronic phase of Chagas disease with late infection and cardiomyopathy without advanced disease	IIb	C
Antiparasitic treatment in the chronic phase of Chagas disease with advanced cardiac form of the disease	III	C

JC Dias et al - 2 nd Brazilian Consensus on Chagas Disease, Rev Soc Bras Med Trop 2015.

For individuals with Chagas disease aged 19–50 years with no recent documented infection, antiparasitic treatment should be considered on an individual basis, whether in ICF(120) (252) (Class IIa, level of evidence B) or in the determined chronic form, without advanced cardiopathy(42) (120) (252) (295) (296) (297) (298) (Class IIb, level of evidence C).

Specifically, treatment of chronically infected women of childbearing age, when provided before pregnancy, can reduce congenital transmission(104) (109) .

2 nd Brazilian Consensus on Chagas Disease, 2015.