ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/364474091

Guidelines 2022 SBC Cardiomyopathy of Chagas disease

Conference Paper · October 2022

CITATIONS
0

READS
50

4 authors, including:

Jose Antonio Marin-Neto
University of São Paulo
418 PUBLICATIONS **13,954** CITATIONS
SEE PROFILE

Anis Rassi
Anis Rassi Hospital
313 PUBLICATIONS **9,453** CITATIONS
SEE PROFILE

Some of the authors of this publication are also working on these related projects:

Detecção de Hipertensão Venosa Pulmonar Oculta por meio de Prova de Sobrecarga Volêmica, e Correlação entre o Método Não Invasivo (Dopplerecocardiografia) e a Avaliação Hemodinâmica Invasiva Concomitantes View project

OPTIMIZE TRIAL View project

All content following this page was uploaded by Anis Rassi on 20 October 2022.

The user has requested enhancement of the downloaded file.

NEW GUIDELINE SBC – 2022

CHAGAS HEART DISEASE

Anis Rassi Jr. *MD, PhD, FACP, FACC, FAHA*

Scientific Director, Hospital do Coração Anis Rassi

Goiânia - Brazil

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA 1943

WORLD HEART FEDERATION

Disclosure Statement of Financial Interest

I, **Anis Rassi Jr** DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Adalberto M. Lorga-Filho
Adriana de Jesus Benevides de Almeida Guimarães
Adriana Lopes Latado Braga
Adriana Sarmento de Oliveira
Alberto Novaes Ramos Jr.
Alejandro Luquetti Ostermayer
Alejandro Marcel Hasslocher-Moreno
Alvaro V. L. Sarabanda
Ana Yecê das Neves Pinto
André Assis Lopes do Carmo
André Schmidt
Andréa R. Costa Rodrigues
Andréa Silvestre de Sousa
Angelo Amato Vincenzo de Paola
Anis Rassi Jr.*
Antonio Carlos Sobral de Sousa
Antonio Luiz Pinho Ribeiro
Barbara Maria Ianni
Brivaldo Markman Filho
Carlos Eduardo Rochitte
Carolina Thé Macedo
Charles Mady
Christophe Chevillard
Cláudio Marcelo Bittencourt das Virgens
Cleudson Nery de Castro
Constança Felícia De Paoli de Carvalho Britto
Cristiano Pisani
Dalmo Correia Filho
Daniela do Carmo Rassi
Dario C. Sobral Filho
Dilma do Socorro Moraes de Souza
Dirceu Rodrigues Almeida
Edecio Cunha-Neto
Edimar A. Bocchi
Evandro T. Mesquita
Felix J. A. Ramires
Fernanda de Souza Nogueira Sardinha Mendes
Fernando Bacal
Francisca Tatiana Pereira
Gilberto Marcelo Sperandio da Silva
Giselle de Lima Peixoto
Gláucia M. Moraes Oliveira*
Gustavo Glotz de Lima
Henrique H. Veloso
Henrique Turin Moreira
Hugo Bellotti Lopes
Ibraim Masciarelli Francisco Pinto
João Marcos Bemfica
João Paulo Silva-Nunes
José Antonio Marin-Neto*
José Augusto Soares Barreto-Filho
José Francisco Kerr Saraiva
Joseli Lannes-Vieira
Joselina Luzia Menezes Oliveira
Luciana V. Armaganijan
Luís Claudio Lemos Correia
Luiz Cláudio Martins
Luiz Henrique C. Sangenis
Marco Paulo Barbosa
Marcos Antônio Almeida-Santos
Marcos Vinicius Simões
Maria Aparecida Shikanai-Yasuda
Maria da Consolação Vieira Moreira
Maria de Lourdes Higuchi
Maria do Carmo Pereira Nunes
Maria Rita de Cássia Costa Monteiro
Martino Martinelli Filho
Maurício Ibrahim Scanavacca
Mauro Felippe Felix Mediano
Mayara Maia Lima
Maykon T. Oliveira
Minna Moreira Dias Romano
Nadjar Nitz
Paulo de Tarso Jorge Medeiros
Renato Vieira Alves
Ricardo Alkmim Teixeira
Roberto Coury Pedrosa
Roberto Magalhães Saraiva
Roque Aras
Rosália Morais Torres
Rui Manoel dos Santos Povoa
Sérgio Gabriel Rassi
Sérgio Salles Xavier
Silvia Marinho Martins Alves
Suelene B. N. Tavares
Swamy Lima Palmeira
Telêmaco Luiz da Silva Junior
Thiago da Rocha Rodrigues
Vagner Madrini Junior
Veruska Maia da Costa
Walderez Dutra
Wilson Alves de Oliveira Junior

Chagas Disease: guidelines 2022 (SBC)

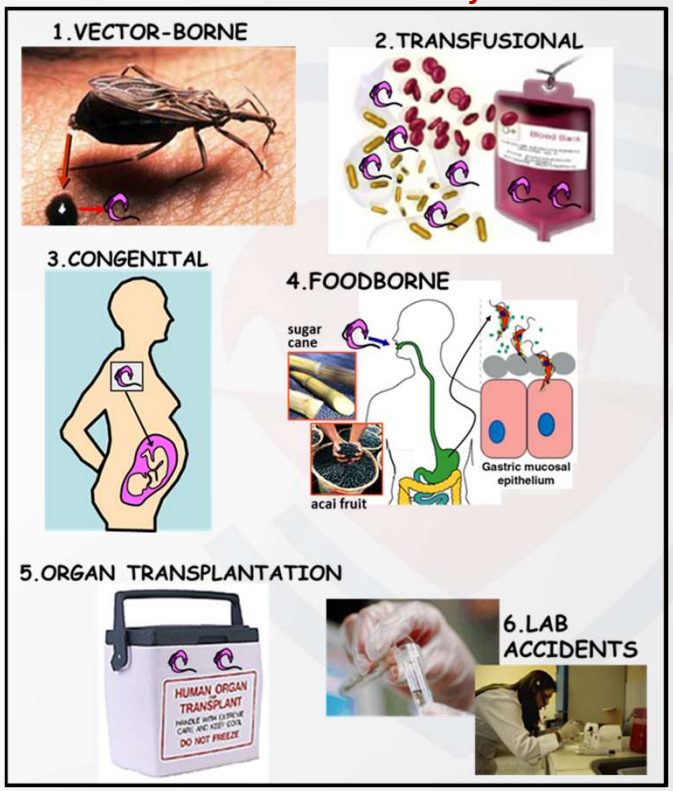
- **Epidemiology and burden of Chagas disease**
- Pathogenesis
- Antiparasitic treatment
- Classification of Chagas disease
- Diagnosis and evaluation of patients with heart disease
- Risk stratification of patients with cardiac disease
- Treatment of heart failure
- Treatment of cardiac arrhythmias
- Challenges in Chagas disease

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

Epidemiology and burden of Chagas disease

- Endemic in 21 countries of Latin America
- Non-endemic in many other countries (USA, Canada, European countries, Japan, Australia) - due to migration
- 70 million people at risk of contracting the infection worldwide
- Overall 6 to 7 million people infected with *T. cruzi*
  - *Argentina: 1.5 mi*
  - *Brasil: 1.2 mi*
  - *Mexico: 0.88 mi*
  - *Bolivia: 0.61 mi*
- Mechanisms of transmission: vectorial, mother-to-child, blood transfusion, orally, organ transplants, accidental infection
- 10,000 to 15,000 deaths each year
- Congenital transmission: 2%-5% (1.12 mi of women at childbearing age are infected)
- Oral transmission: ingestion of food or drink products contaminated with *T. cruzi* (outbreaks in the Amazon region and subtropical Andes) - higher mortality

Mechanisms of transmission



SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

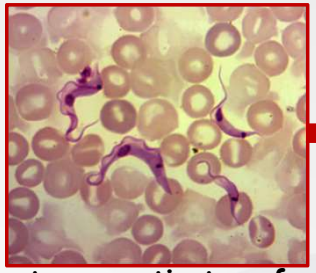
Chagas Disease: guidelines 2022 (SBC)

- Epidemiology and burden of Chagas disease
- **Pathogenesis**
- Antiparasitic treatment
- Classification of Chagas disease
- Diagnosis and evaluation of patients with heart disease
- Risk stratification of patients with cardiac disease
- Treatment of heart failure
- Treatment of cardiac arrhythmias
- Challenges in Chagas disease

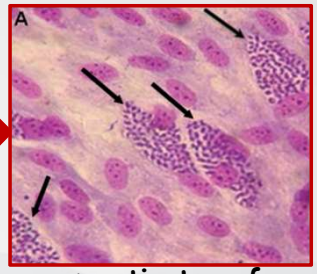
SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

Pathogenesis

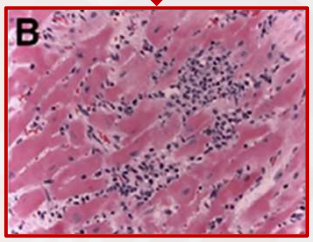
T. cruzi
Low grade chronic infection



trypomastigotes of *T. cruzi* in the blood



amastigotes of *T. cruzi* in cardiac myocytes



inflammation and fibrosis

Continuous inflammatory stimulus
Cross-reactive immune response

platelet aggregation
thrombosis
endothelial dysfunction
intimal proliferation
microvascular spasm

Microvascular ischemia

Mitochondrial dysfunction
Myocardial damage
Fibrosis

Autonomic system denervation

Progressive cardiac dilation
Heart failure

Cardiac arrhythmias
Sudden cardiac death

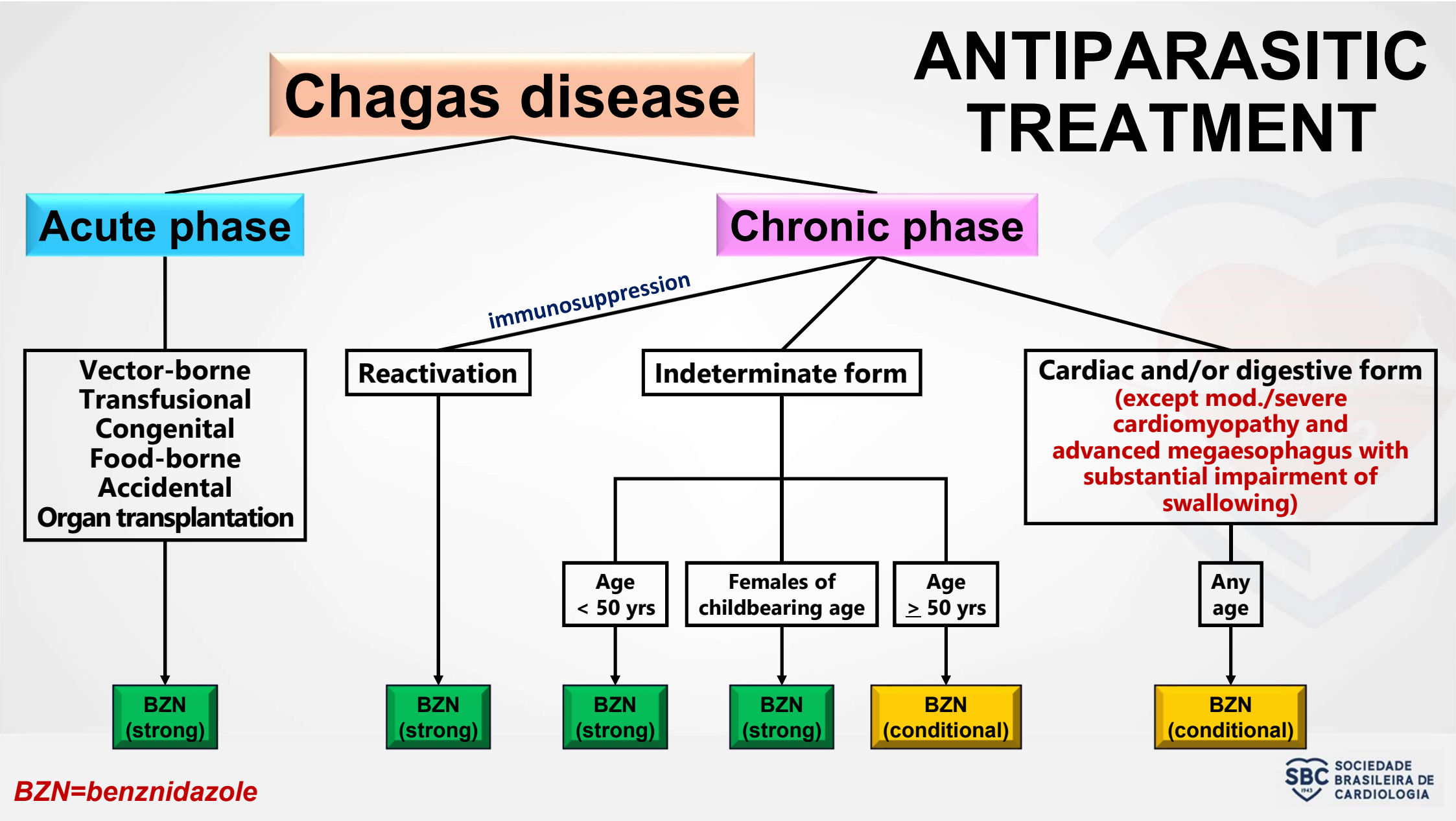
SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

Chagas Disease: guidelines 2022 (SBC)

- Epidemiology and burden of Chagas disease
- Pathogenesis
- **Antiparasitic treatment**
- Classification of Chagas disease
- Diagnosis and evaluation of patients with heart disease
- Risk stratification of patients with cardiac disease
- Treatment of heart failure
- Treatment of cardiac arrhythmias
- Challenges in Chagas disease

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

ANTIPARASITIC TREATMENT



BZN=benznidazole

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

ANTITRYPANOSOMAL TREATMENT

CATEGORY	Symptoms improvement	Negativation of PCR	Negativation of serological tests*	Prevention or delay of heart disease progression	Prevention of congenital transmission
Congenital infection	+++	+++	95-100% (1y)	+++	_
Acute infection	+++	+++	60-80% (3-5y)	+++	_
Children (≤ 12 y) w/ IF	not applicable	+++	50-60% (5-10y)	++	_
Adolescents/adults (13-50y) w/ IF	not applicable	++	25-30% (20-30y)	++	_
Females of childbearing age (15-44y) w/ IF	not applicable	++	not available	not available	+++
Adults (> 50y) w/ IF	not applicable	not available	not available	probably	_
Adults (any age) w/ mild CCCD	+	+	not available	+ (Brazil)	_
Adults (any age) w/ moderate/severe CCCD	no	not available	not available	no	_

IF: indeterminate form; CCCD: chronic cardiomyopathy of Chagas disease.

***percentage and time after treatment**

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

BENEFIT Trial (n=2,854)

Brazil, Argentina, Colombia, Bolivia, and El Salvador

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 1, 2015 VOL. 373 NO. 14

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 0.96 (95% CI, 0.63 to 1.45) at 5 or more years; and in Argentina and Bolivia, the odds ratio was 2.63 (95% CI, 1.89 to 3.66) at 2 years and 2.79 (95% CI, 1.99 to 3.92) at 5 or more years (P<0.001 for interaction). However, the rates of PCR conversion did not correspond to effects on clinical outcome (P=0.16 for interaction).

CONCLUSIONS

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. (Funded by the Population Health Research Institute and others; ClinicalTrials.gov number, NCT00123916; Current Controlled Trials number, ISRCTN13967269.)

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, and updated on September 10, 2015, at NEJM.org.

N Engl J Med 2015;373:1295-306.
DOI: 10.1056/NEJMoa1507574
Copyright © 2015 Massachusetts Medical Society.

Chronic Chagas cardiomyopathy: a review of the main pathogenic mechanisms and the efficacy of aetiological treatment following the BENznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) trial

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

[1]Hospital do Coração Anis Rassi, Goiânia, GO, Brasil
[2]Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Clínica Médica, Divisão de Cardiologia, Ribeirão Preto, SP, Brasil

Chagas cardiomyopathy is the most frequent and most severe manifestation of chronic Chagas disease, and is one of the leading causes of morbidity and death in Latin America. Although the pathogenesis of Chagas cardiomyopathy is incompletely understood, it may involve several mechanisms, including parasite-dependent myocardial damage, immune-mediated myocardial injury (induced by the parasite itself and by self-antigens), and microvascular and neurogenic disturbances. In the past three decades, a consensus has emerged that parasite persistence is crucial to the development and progression of Chagas cardiomyopathy. In this context, antiparasitic treatment in the chronic phase of Chagas disease could prevent complications related to the disease. However, according to the results of the 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

BENEFIT trial

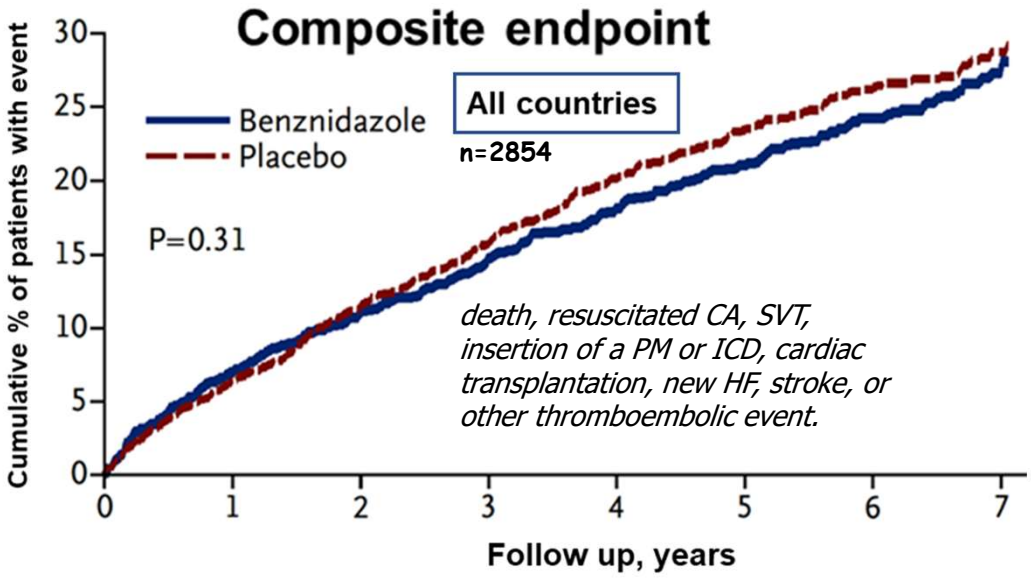
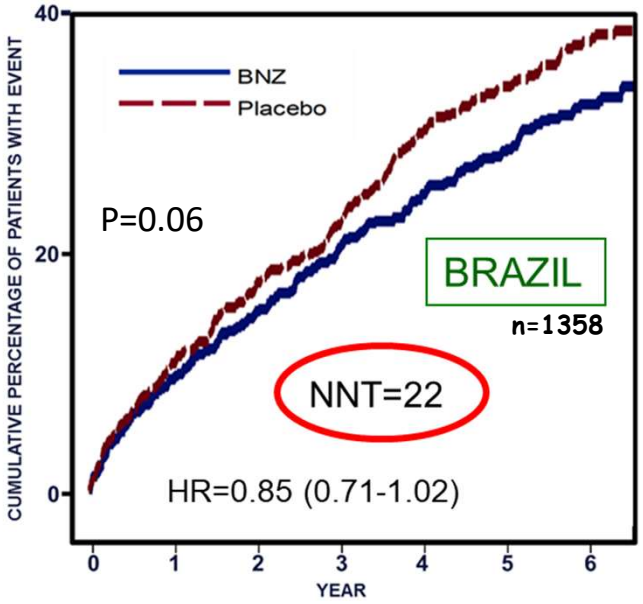


Table 2. Primary Outcome and Its Components, Hospitalizations, and Deaths.

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)	—
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



	BENZNI-DAZOLE+	PLACE-BO	HR	OR	95% CI
Primary outcome (5.4y)	33.2%	37.6% (NNT=22)	0.85		0.71-1.02
Negativation of PCR (EOT)	86.3%	24.3% (NNT=2)		7.20	4.53-11.4

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

N Engl J Med 2015;373:1295-306.
Mem Inst Oswaldo Cruz. 2017;112:224-35.

BENEFIT Trial: Adverse Events of Benznidazole

N=2.854
Age: 55±11 years

Table 3. Adverse Events and Laboratory Abnormalities.*

Cohort and Event	Adverse Events Leading to Drug Interruption			Serious Adverse Events Leading to Drug Interruption		
	Benznidazole (N=1431)	Placebo (N=1423)	P Value	Benznidazole (N=1431)	Placebo (N=1423)	P Value
	no./total no. (%)			*no./total no. (%)*		
Patients completing follow-up visits through end of study-treatment period	1429/1431 (99.9)	1422/1423 (99.9)		1429/1431 (99.9)	1422/1423 (99.9)	
Any adverse event	342/1429 (23.9)	135/1422 (9.5)	<0.001	119/1429 (8.3)	20/1422 (1.4)	<0.001
Cutaneous rash	137/1429 (9.6)	18/1422 (1.3)	<0.001	58/1429 (4.1)	2/1422 (0.1)	<0.001
Gastrointestinal symptoms	112/1429 (7.8)	41/1422 (2.9)	<0.001	26/1429 (1.8)	9/1422 (0.6)	0.004
Nervous system symptoms including peripheral neuropathy	52/1429 (3.6)	19/1422 (1.3)	<0.001	14/1429 (1.0)	6/1422 (0.4)	0.07
Leukopenia†	2/1429 (0.1)	2/1422 (0.1)	1.0	1/1429 (0.1)	0	NA
Permanent treatment discontinuation	192/1429 (13.4)	51/1422 (3.6)	<0.001	96/1429 (6.7)	15/1422 (1.1)	<0.001
Patients completing 60-day visit‡	1123/1431 (78.5)	1194/1423 (83.9)		0	0	NA
Alanine aminotransferase >2× ULN	55/1123 (4.9)	19/1194 (1.6)	<0.001	0	0	NA
Alanine aminotransferase >3× ULN	20/1123 (1.8)	9/1194 (0.8)	0.03	0	0	NA

* NA denotes not applicable, and ULN upper limit of the normal range.
† Leukopenia was defined as a neutrophil count of less than 1900 cells per cubic millimeter.
‡ Data are shown for patients who completed the 60-day study visit and had available values for alanine aminotransferase at that visit.

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

Chagas Disease: guidelines 2022 (SBC)

- Epidemiology and burden of Chagas disease
- Pathogenesis
- Antiparasitic treatment
- **Classification of Chagas disease**
- Diagnosis and evaluation of patients with heart disease
- Risk stratification of patients with cardiac disease
- Treatment of heart failure
- Treatment of cardiac arrhythmias
- Challenges in Chagas disease

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

Chagas Heart Disease

Normal Systolic Function and Classification of Heart Failure (HF) by Left Ventricular Ejection Fraction (LVEF)

CATEGORY	CRITERIA
Preserved global systolic function	• LVEF ≥ 55% - without segmental WMA - with segmental WMA
HF with mildly reduced EF (HFmrEF)	• LVEF 41%-54%
HF with reduced EF (HFrEF)	• LVEF ≤ 40%
HF with improved EF (HFimpEF)	• Baseline LVEF < 40%, with a second measurement of LVEF > 40% and at least a 10 point increase from baseline

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

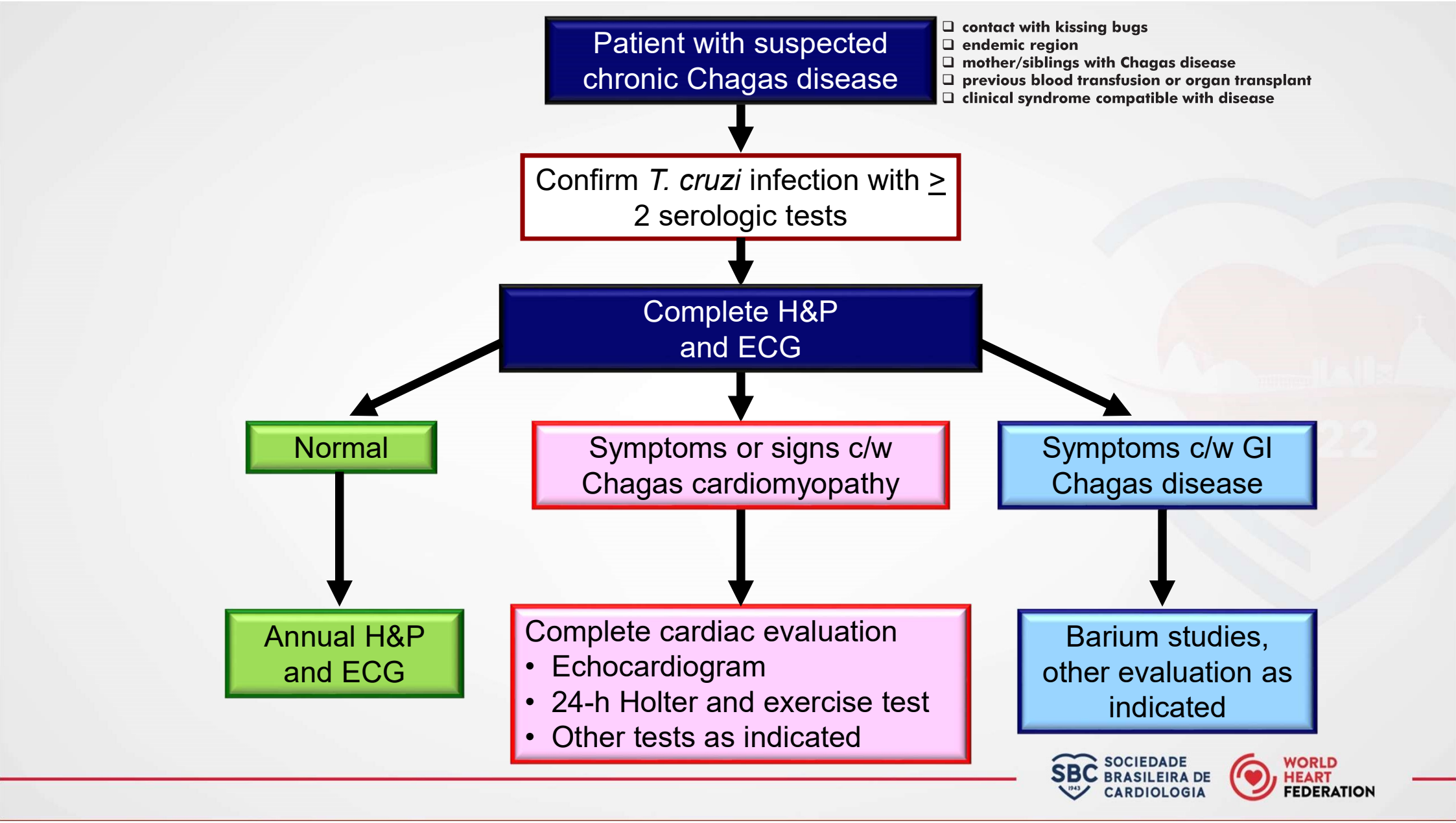
EVOLUTIVE STAGES OF CHRONIC CHAGAS DISEASE

	INDETERMINATE FORM	CHRONIC CHAGAS CARDIOMYOPATHY			
	Stage A	Stage B1	Stage B2	Stage C	Stage D
Characteristics	Asymptomatic; No heart disease or gastrointestinal involvement; At risk for heart disease (30%)	Structural heart disease; Normal global LV function; No symptoms or signs of HF	Structural heart disease; Impaired global LV function; No symptoms or signs of HF	Structural heart disease; Impaired global LV function; Symptoms or signs of HF (current or prior)	Structural heart disease; Impaired global LV function; Refractory HF, despite OMT, and need of specialized therapy
ECG	Normal	Abnormal	Abnormal	Abnormal	Abnormal
Segmental WMA	Usually absent	Can be present	Can be present	Can be present	Usually absent
LVEF (Eco – Simpson)	≥ 55%	≥ 55%	< 55% (usually 41%-54%)	< 55% (usually ≤ 40%)	Usually ≤ 25%
Functional class (NYHA)	Not applicable	I	I	I, II, III or IV	IV
Cardiomegaly (Chest X-ray)	Absent	Absent	Can be present	Usually present	Present
Complex ventricular arrhythmias (Holter 24h)	Usually absent	Can be present	Usually present	Present	Present
Myocardial fibrosis (LGE at MRI)	Can be present	Usually present	Usually present	Present	Present

Chagas Disease: guidelines 2022 (SBC)

- Epidemiology and burden of Chagas disease
- Pathogenesis
- Antiparasitic treatment
- Classification of Chagas disease
- **Diagnosis and evaluation of patients with heart disease**
- Risk stratification of patients with cardiac disease
- Treatment of heart failure
- Treatment of cardiac arrhythmias
- Challenges in Chagas disease

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA


Patient with suspected chronic Chagas disease
❑ contact with kissing bugs
❑ endemic region
❑ mother/siblings with Chagas disease
❑ previous blood transfusion or organ transplant
❑ clinical syndrome compatible with disease
Confirm T. cruzi infection with ≥ 2 serologic tests
Complete H&P and ECG
Normal
Symptoms or signs c/w Chagas cardiomyopathy
Symptoms c/w GI Chagas disease
Annual H&P and ECG
Complete cardiac evaluation
• Echocardiogram
• 24-h Holter and exercise test
• Other tests as indicated
Barium studies, other evaluation as indicated

Diagnostic steps for cardiac evaluation in Chagas disease

- **Step 1** — Serological tests (ELISA, IIF, HAI)
- **Step 2** — History, physical exam, ECG
- **Step 3** — Chest X-ray and echo ⊕ 24-hr Holter and exercise test

---

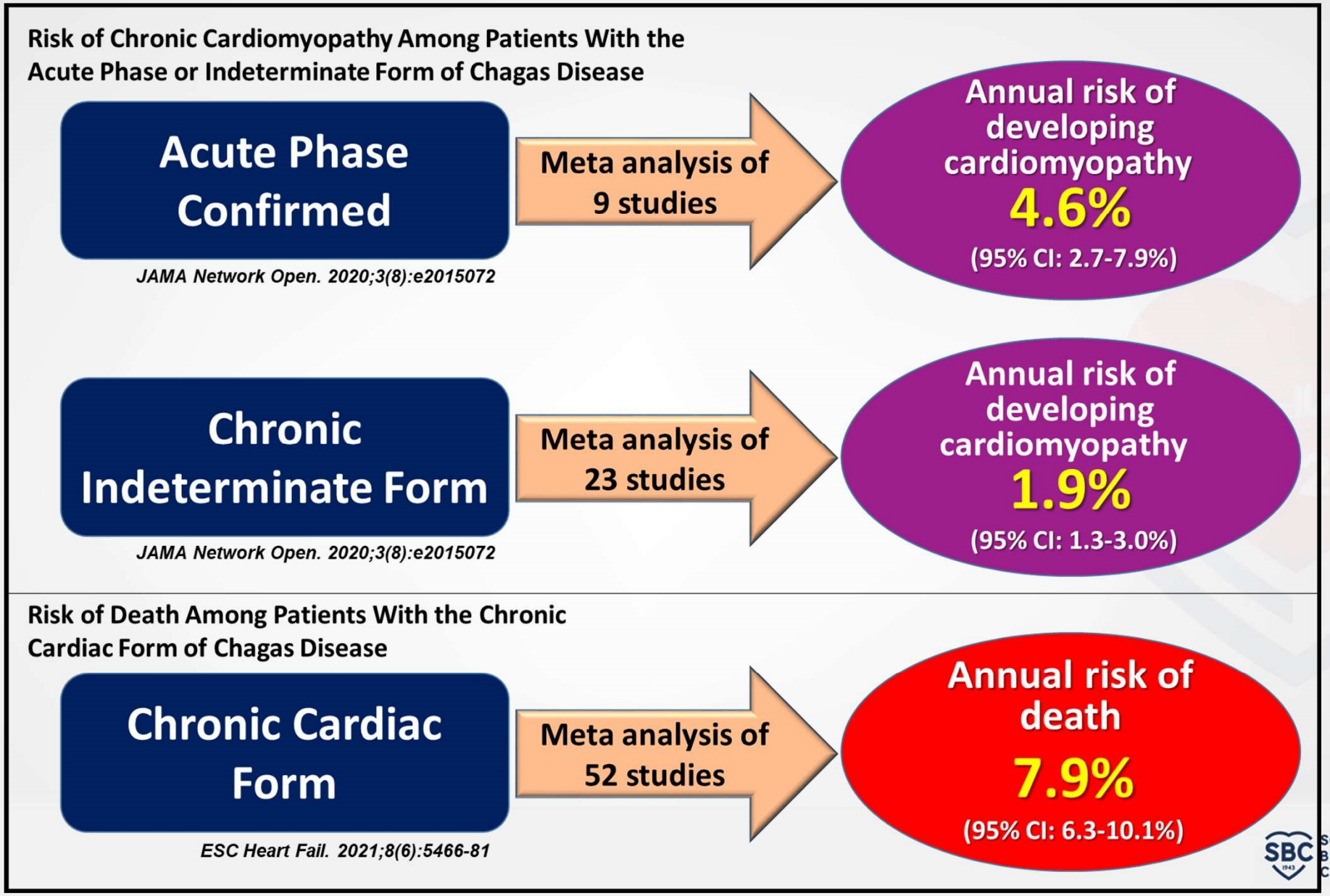
- **Step 4** — Other tests as needed (cardiac MRI, BNP, tissue doppler echo, EPS, scintigraphy, coronary angiography etc)

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

Chagas Disease: guidelines 2022 (SBC)

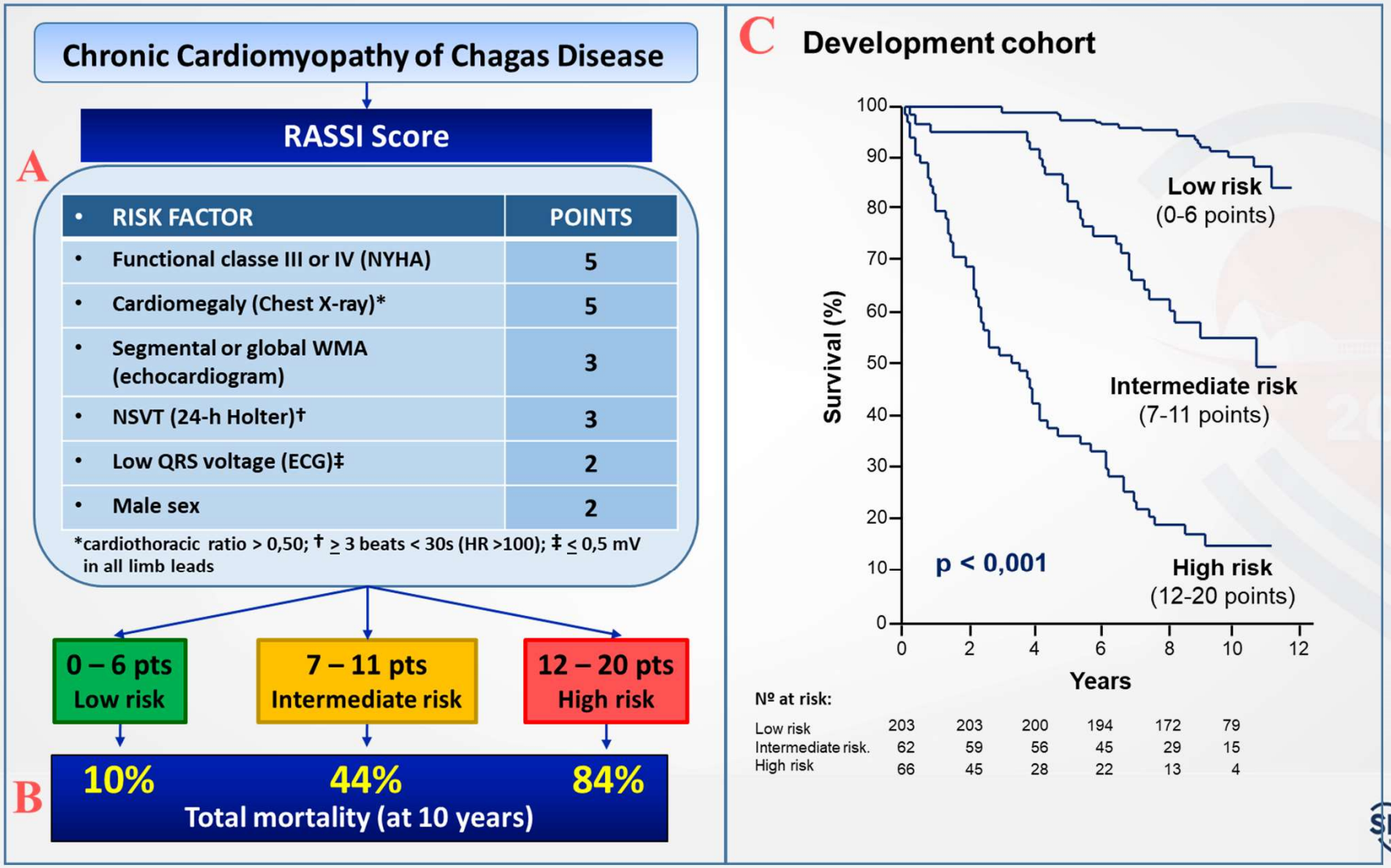
- Epidemiology and burden of Chagas disease
- Pathogenesis
- Antiparasitic treatment
- Classification of Chagas disease
- Diagnosis and evaluation of patients with heart disease
- **Risk stratification of patients with cardiac disease**
- Treatment of heart failure
- Treatment of cardiac arrhythmias
- Challenges in Chagas disease

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA



SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

***RASSI score**. **(A)** Risk factors and points; **(B)** Total mortality at 10 years in the subgroups of low, intermediate and high risk; **(C)** Kaplan-Meier survival curves.*



SOCIEDADE BRASILEIRA DE CARDIOLOGIA

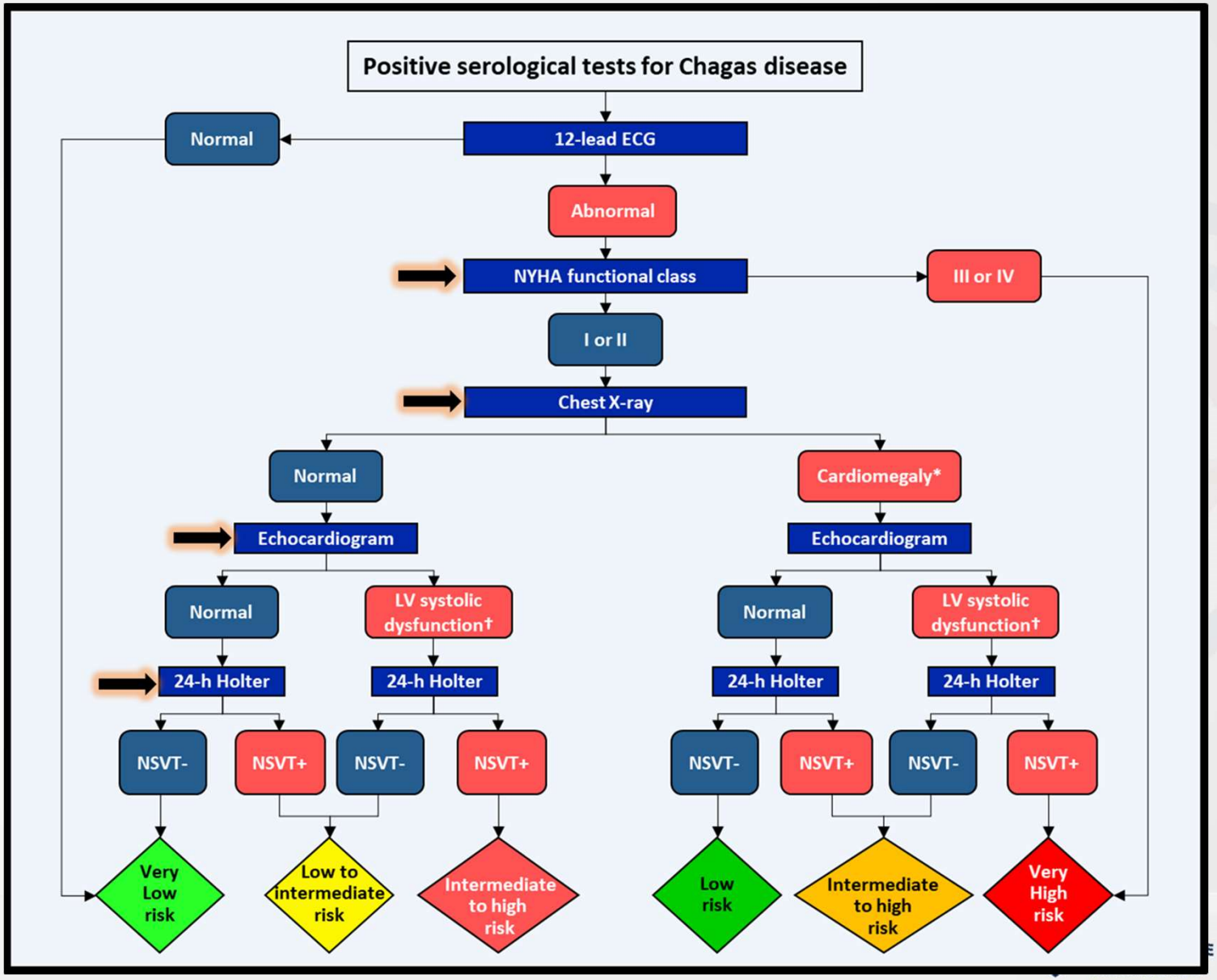
RASSI score: results in the original cohort (Hospital São Salvador, Goiânia) and external validation in four different cohorts

Author	Study Period	Study Location	Nº of patients	Outcome	% Outcome (5 years)			% Outcome (10 years)			C Statistic
					Low risk (0-6 pts)	Intermediate risk (7-11 pts.)	High risk (12-20 pts.)	Low risk (0-6 pts.)	Intermediate risk (7-11 pts.)	High risk (12-20 pts)	
Rassi A Jr. et al.	1986-1991	Hospital São Salvador (Goiânia)	331*	Total mortality	2 (0-5)	18 (8-28)	63 (51-75)	10 (5-14)	44 (31-57)	84 (74-93)	0,84†
Rassi A Jr. et al.	1990-2001	Hospital Evandro Chagas (RJ)	153	Total mortality	0	15 (1-28)	53 (31-75)	9 (2-16)	37 (16-59)	85 (63-100)	0,81†
Rocha MOC & Ribeiro AL	1998-2006	Universidade Federal de Minas Gerais	158	Total mortality	3 (1-7)	10 (4-22)	67 (30-90)	NA	NA	NA	0,84
Benchimol Barbosa PR et al.	1995-2003	Hospital Universitário Pedro Ernesto (RJ)	100	Cardiac mortality or VT§ //	4 (1-11)¶	42 (18-83)¶	50 (6-100)¶	28 (18-43)	58 (29-100)	75 (15-100)	0,79†
				Cardiac mortality#	NA	NA	NA	NA	NA	NA	0,81†
Senra T et al.	2001-2011	Instituto do Coração - INCOR (SP)	130	Total mortality, cardiac transplant, appropriate therapy from ICD or resuscitated of CA//	16	42	76	NA	NA	NA	NA
				Total mortality#	11	33	57,5	NA	NA	NA	NA

*The numbers in parentheses correspond to the 95% CI. *multivariate model applied to 331 patients from the original cohort with 424 patients (patients with missing data were excluded); †referring to 10 years; §defined as 3 or more successive beats; //primary outcome; ¶outcome at 50 months; #secondary outcome; ICD - implantable cardioverter-defibrillator; N - number; NA - not available; CA - cardiac arrest; VT - ventricular tachycardia.*

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

Risk Stratification Algorithm in Chagas Disease

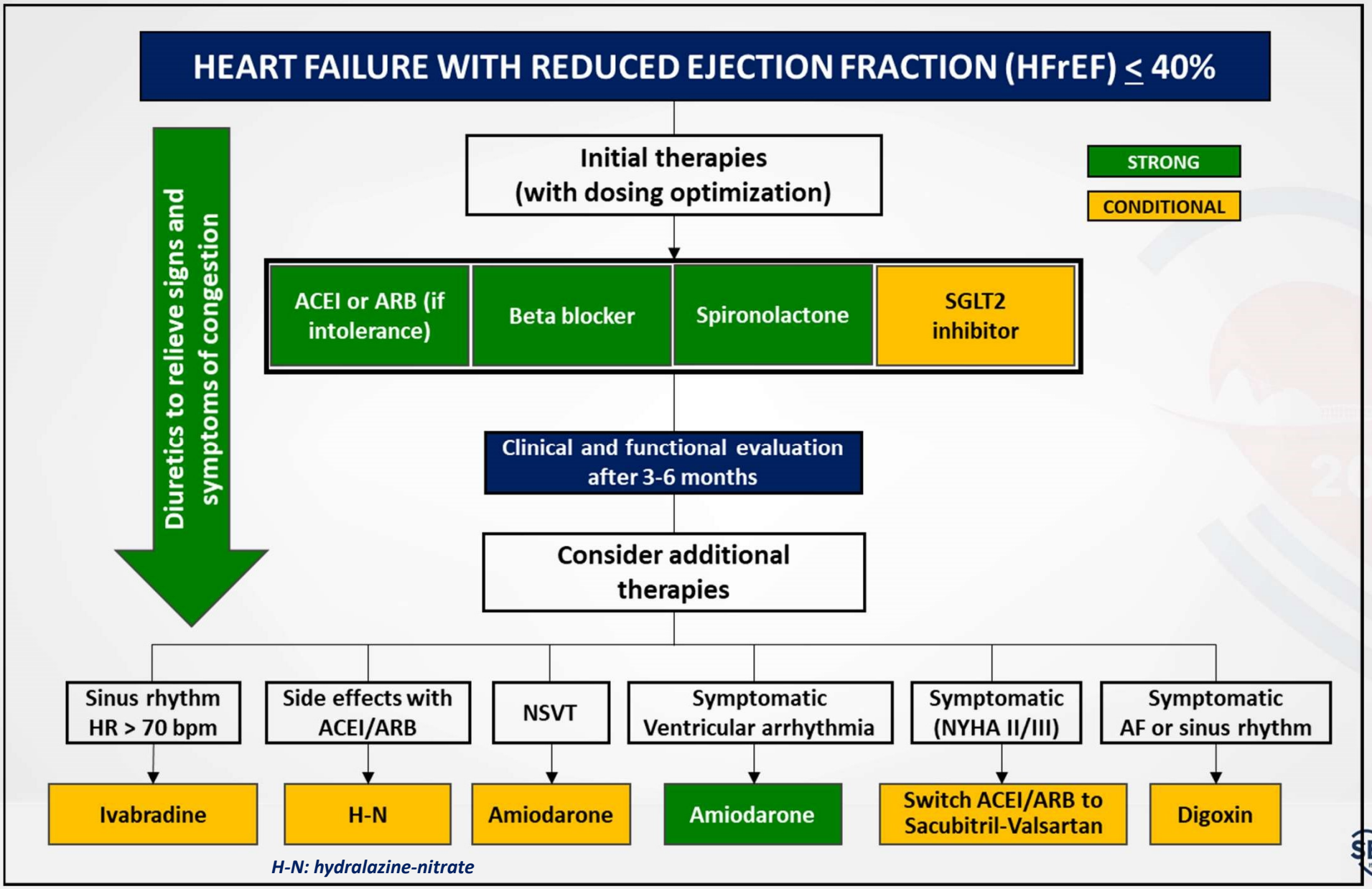


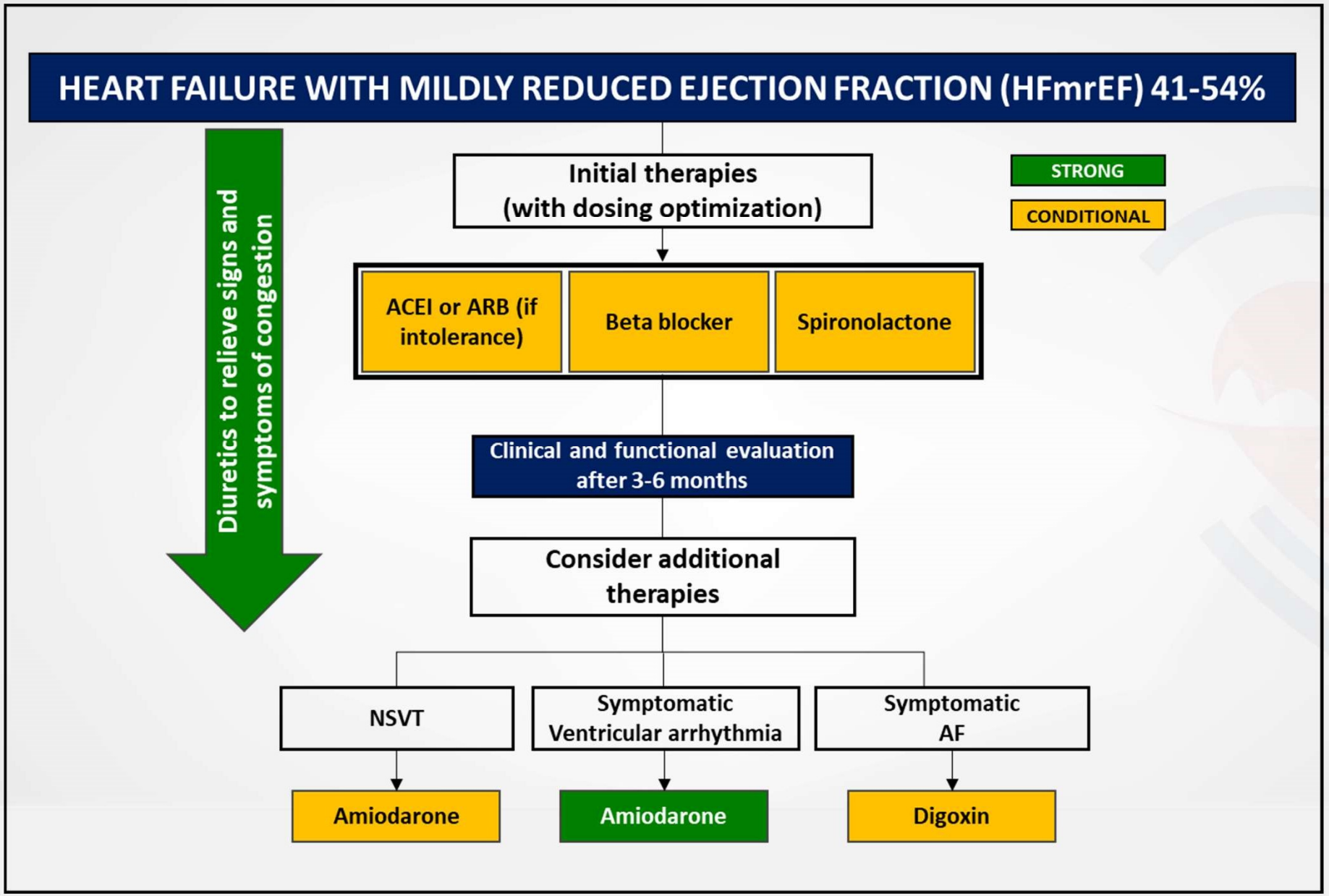
*NSVT: non-sustained ventricular tachycardia; LV: left ventricular. *can be replaced by LV diastolic diameter > 60 mm on echocardiography; †global or segmental. Adapted from Rassi A Jr, Rassi A, Rassi SG. Predictors of mortality in chronic Chagas disease. Circulation. 2007;115:1101-8.*

Chagas Disease: guidelines 2022 (SBC)

- Epidemiology and burden of Chagas disease
- Pathogenesis
- Antiparasitic treatment
- Classification of Chagas disease
- Diagnosis and evaluation of patients with heart disease
- Risk stratification of patients with cardiac disease
- **Treatment of heart failure**
- Treatment of cardiac arrhythmias
- Challenges in Chagas disease

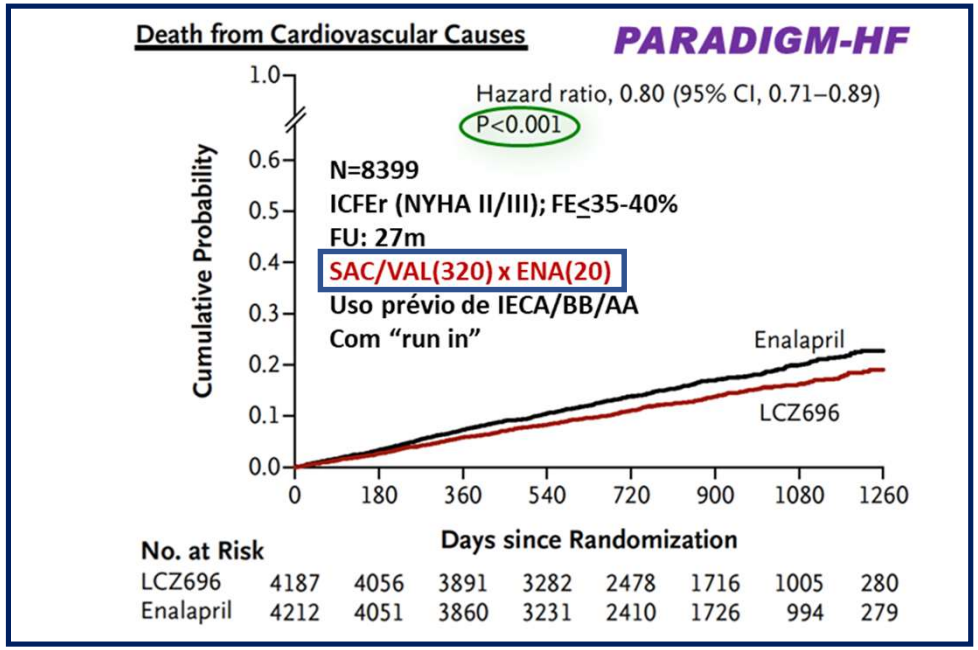
SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

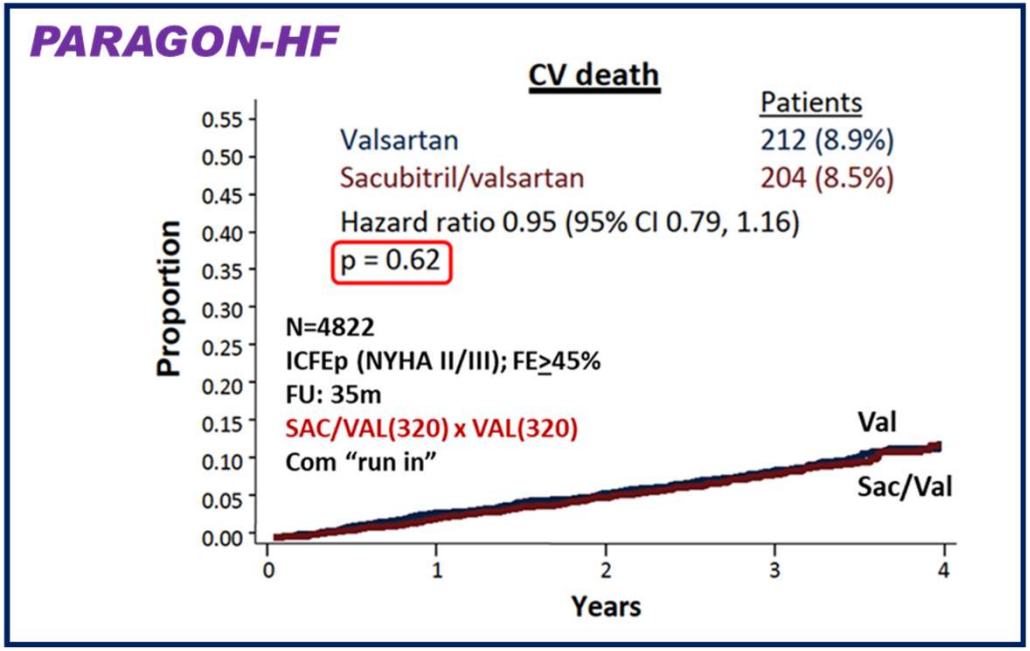

HEART FAILURE WITH REDUCED EJECTION FRACTION (HFrEF) ≤ 40%
Initial therapies (with dosing optimization)
STRONG
CONDITIONAL
Diuretics to relieve signs and symptoms of congestion
ACEI or ARB (if intolerance)
Beta blocker
Spironolactone
SGLT2 inhibitor
Clinical and functional evaluation after 3-6 months
Consider additional therapies
Sinus rhythm HR > 70 bpm
Side effects with ACEI/ARB
NSVT
Symptomatic Ventricular arrhythmia
Symptomatic (NYHA II/III)
Symptomatic AF or sinus rhythm
Ivabradine
H-N
Amiodarone
Amiodarone
Switch ACEI/ARB to Sacubitril-Valsartan
Digoxin
H-N: hydralazine-nitrate

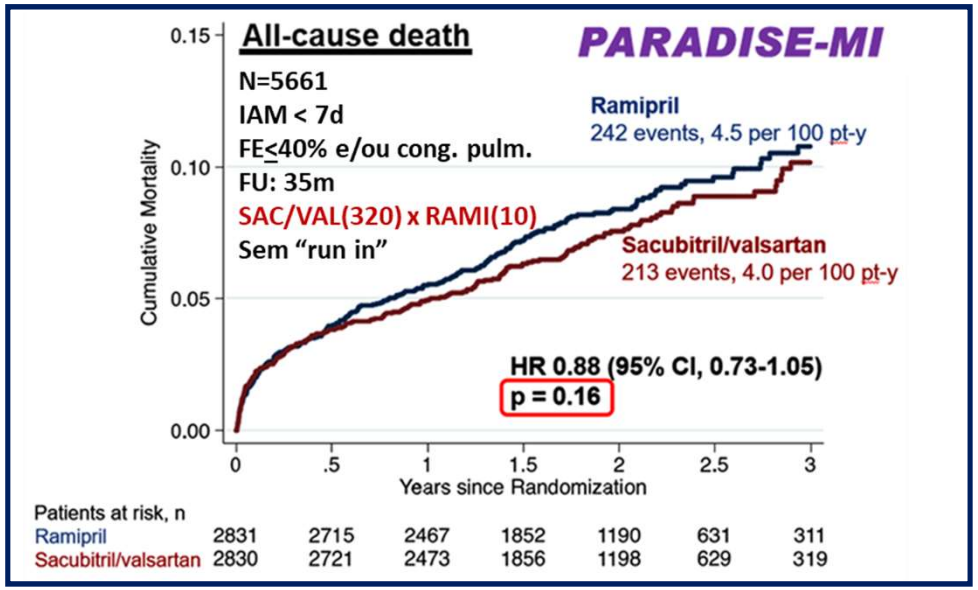


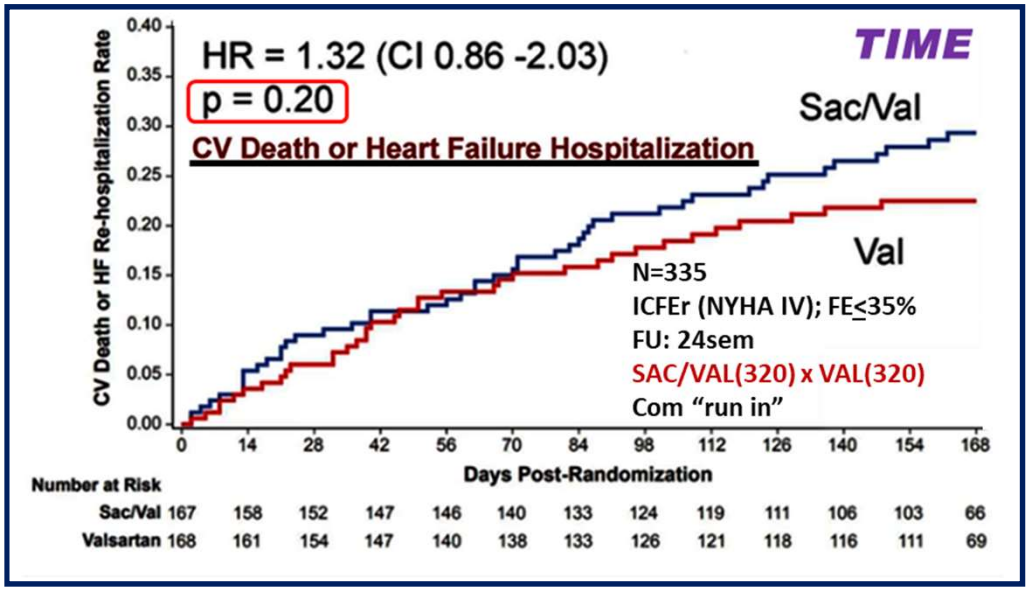
SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

Sacubitril-Valsartan ?

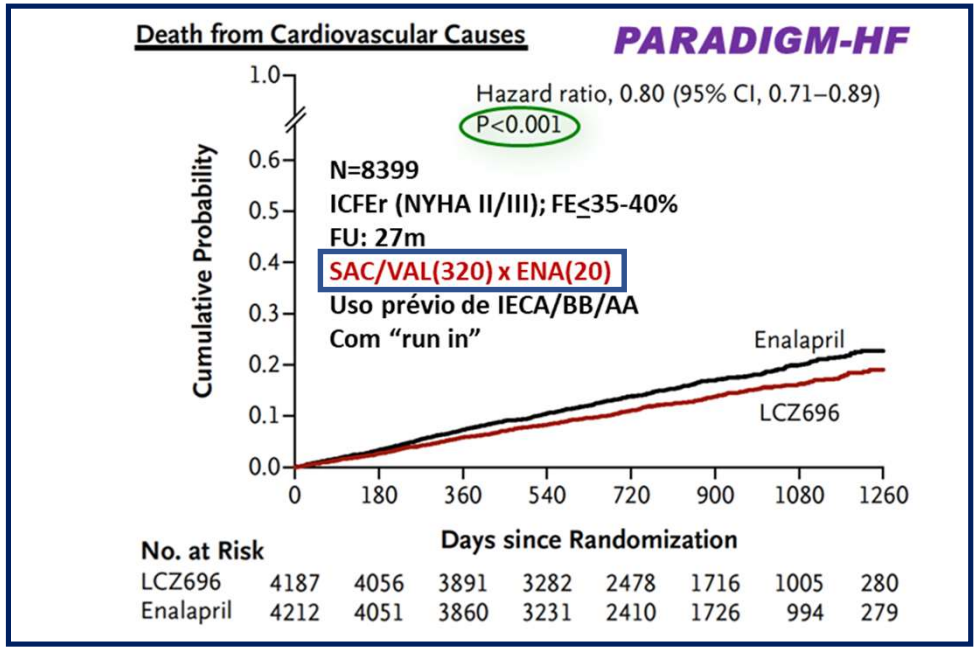


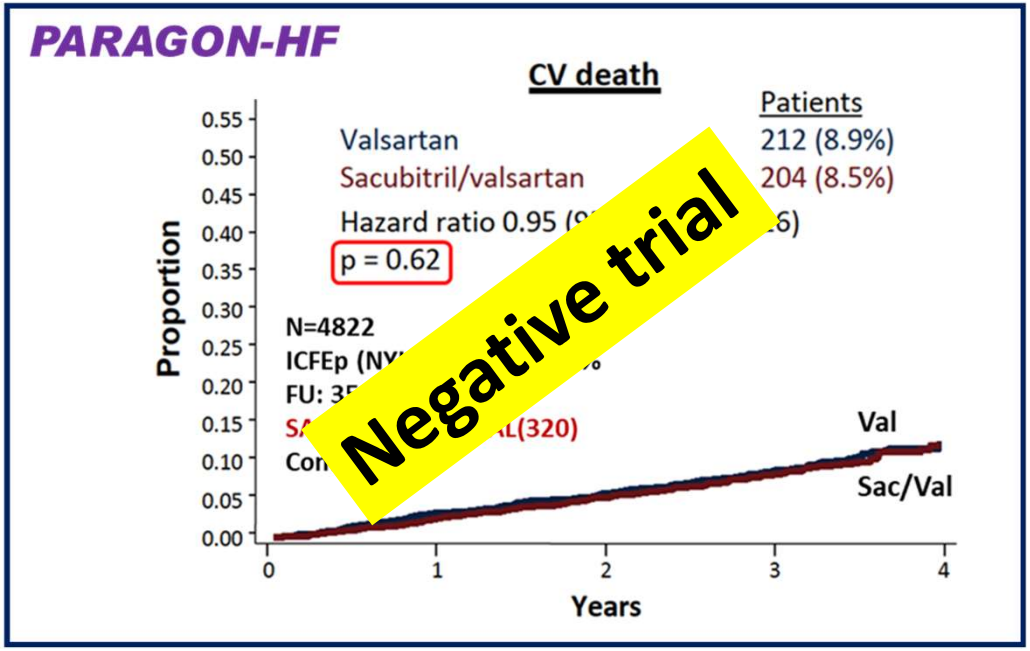


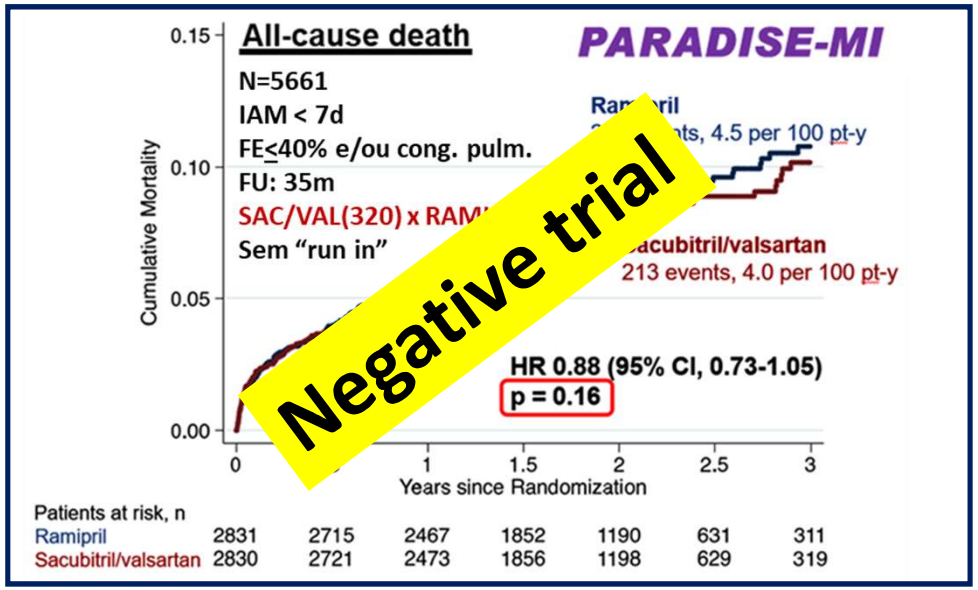


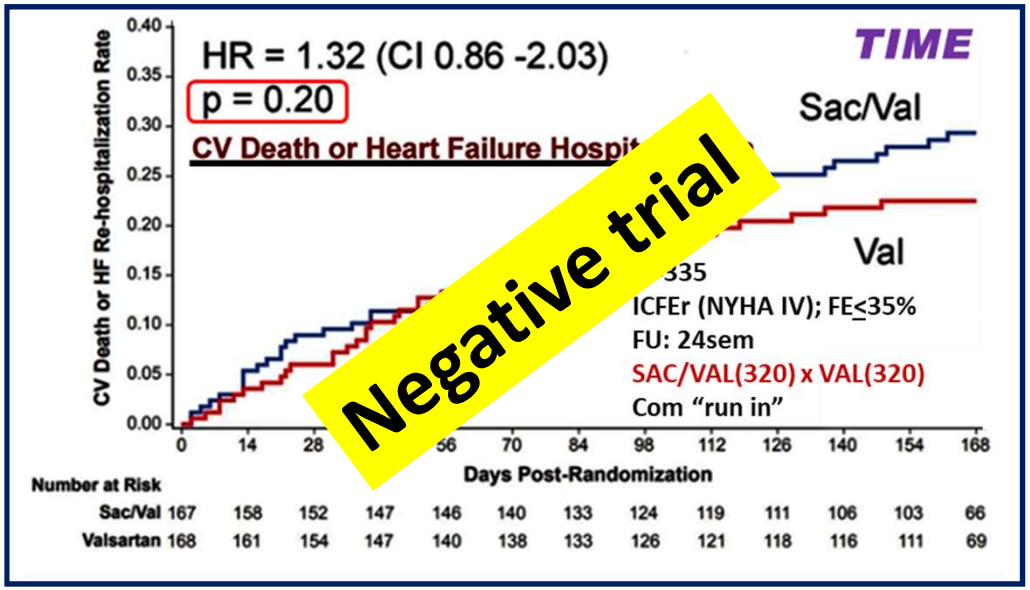


Sacubitril-Valsartan ?









PARACHUTE-HF

Prevention And Reduction of Adverse outcomes in Chagasic Heart failUre Trial Evaluation:
The PARACHUTE-HF Trial

- ❑ **N = 900-1200 patients**
- ❑ **Follow-up = 3 years**

Key Inclusion Criteria:

- •Chagas disease (2 serological tests)
- •Male or female ≥ 18 years of age
- •HFrEF; NYHA Class II-IV
- •LVEF ≤ 40%
- •Increased values of NT-proBNP or BNP
- •With "run in"

Primary Endpoint

PARACHUTE-HF

Hierarchically ordered composite endpoint composed by:

1. **time to CV death**
2. **time to first HF hospitalization**
3. **relative change in NT-proBNP from baseline to Week 12**

For each pair comparison:

Winner based on NTproBNP levels change = more reduction or less increase
To have a winner, the week 12/baseline ratio needs to differs for more than 25% between two subjects.

SACUBITRIL/VALSARTAN(320 mg)
X
ENALAPRIL(20mg) AGAIN?

ClinicalTrials.gov Identifier: NCT04023227

Observational studies of CRT in CCCD

CHARACTERISTICS	Araujo et al. 2014	Menezes et al. 2018	Martinelli et al. 2018			Scorzini et al. 2018			Passos et al. 2019	
População	CCCD	CCCD	CCCD	ICM	DCM	CCCD	ICM	OTHER	CCCD	No-CCCD
Nº of patients	72	50	115	134	177	42	13	43	13	41
Male sex (%)	ND	56	65	83	51	59.5	92	56	31	66
Mean age, years	ND	63	57	68	60	60	66	58	65	62
Intraventricular block:										
-Induced LBBB (%)	15	30	74	31	17	21	0	5	NA	NA
-Spontaneous LBBB (%)	47	30	11	63	78.5	39	92	87	NA	NA
-Non-LBBB (%)	38	40	15	7	4.5	39	8	8	NA	NA
CRT-D (%)	ND	74	23.5	33	26	31	31	26	0	0
Atrial fibrillation or flutter (%)	0	16	25	16	15	14	15	14	0	0
NYHA class III/IV (%)										
• Pre-CRT	100	82	82	82	88	87.5	67	80	77	63
• Post-CRT	13	18	43.5	26	26	50	33	24	NA	NA
Mean LVEF (%)										
• Pre-CRT	27	29	26	26	24	26	27	24	27	26
• Post-CRT	44	39	27	28	29	26	34	30	NA	NA
Mean QRS duration, ms										
• Pre-CRT	148	150	163	164	162,5	161	154	160	NA	NA
• Post-CRT	ND	116	ND	ND	ND	139	134	135	NA	NA
LVEDD, mm										
• Pre-CRT	66	ND	66	69	74	68	68	73	NA	NA
• Post-CRT	65	ND	68	68	71	65	65	69	NA	NA
Mean follow-up, months	47	61	29	29	29	27	42	35	15	15
Non-responders (%)	33	34	43.5	26	26	47	33	35	NA	NA
Annual mortality (%)	9.0	9.2	25.4	11.3	10.4	25.6	4.8	13.9	18.4	3.2

LBBB: complete left bundle branch block; CCCD: chronic cardiomyopathy of Chagas disease; DCM: dilated cardiomyopathy; IMC: ischemic cardiomyopathy; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; NA: not available; CRT: cardiac resynchronization therapy; CRT-D: CRT + ICD

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

Indication for CRT in CCCD

Summary of recommendations	Grade of recommendation	Level of evidence
Symptomatic HF, NYHA class II and III, with LVEF ≤ 35%, in sinus rhythm, with LBBB morphology and QRS duration ≥ 130ms, despite optimal medical therapy, to reduce morbidity and mortality.	Conditional	B

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

Chagas Disease: guidelines 2022 (SBC)

- Epidemiology and burden of Chagas disease
- Pathogenesis
- Antiparasitic treatment
- Classification of Chagas disease
- Diagnosis and evaluation of patients with heart disease
- Risk stratification of patients with cardiac disease
- Treatment of heart failure
- **Treatment of cardiac arrhythmias**
- Challenges in Chagas disease

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

SECONDARY PREVENTION

Aborted CA (VF)
Any SVT
Syncope + Inducible SVT

+ Structural Heart Disease = ICD

1996-2005

PRIMARY PREVENTION

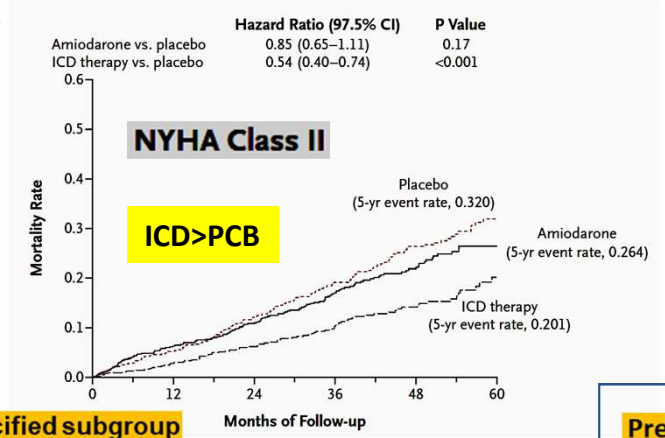
Ejection Fraction ≤ 35%

+ Structural Heart Disease = ICD

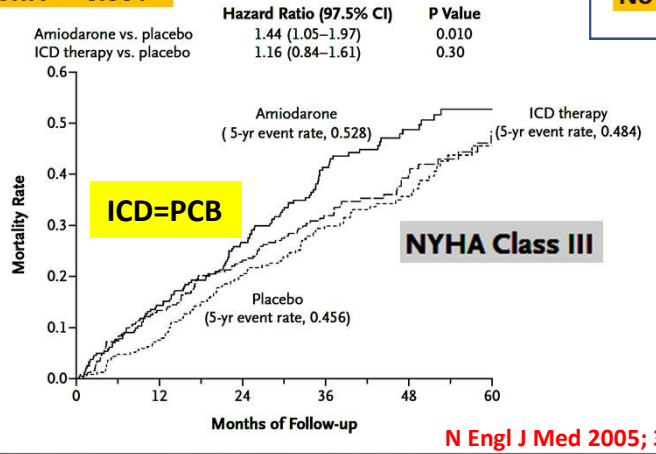
Scientific evidence???

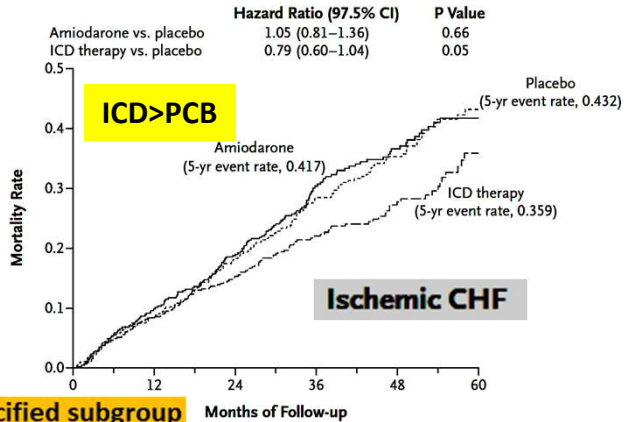
One-size fits all: *what`s good for the gander is good for the goose*

3.8y

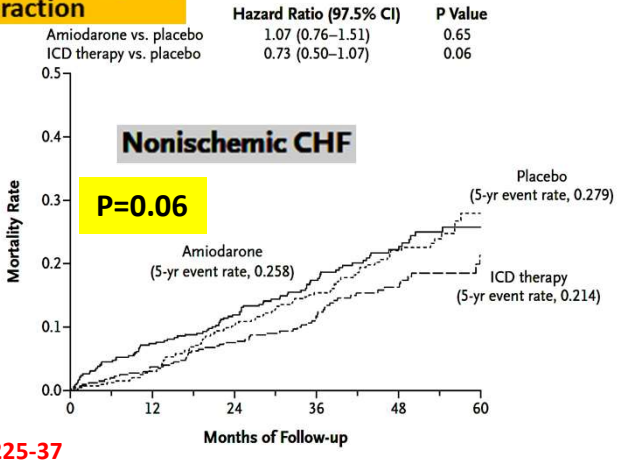


Prespecified subgroup
Interaction: P < 0.001

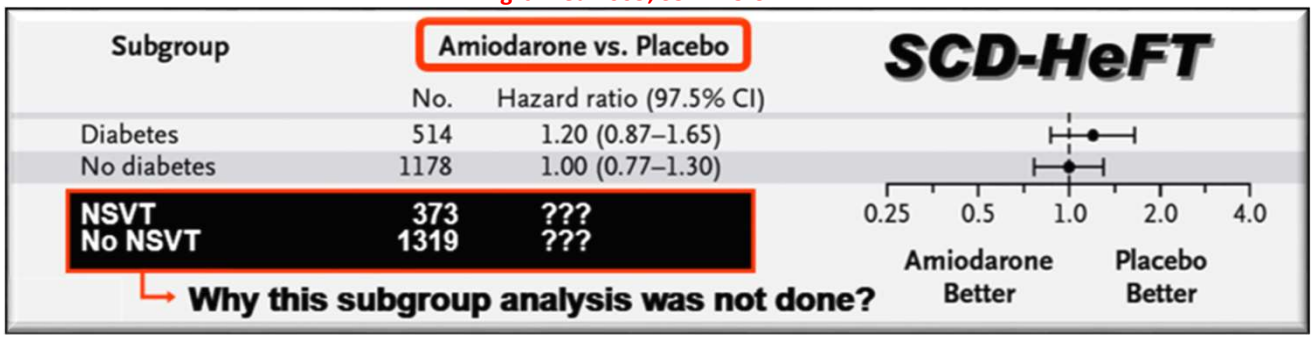


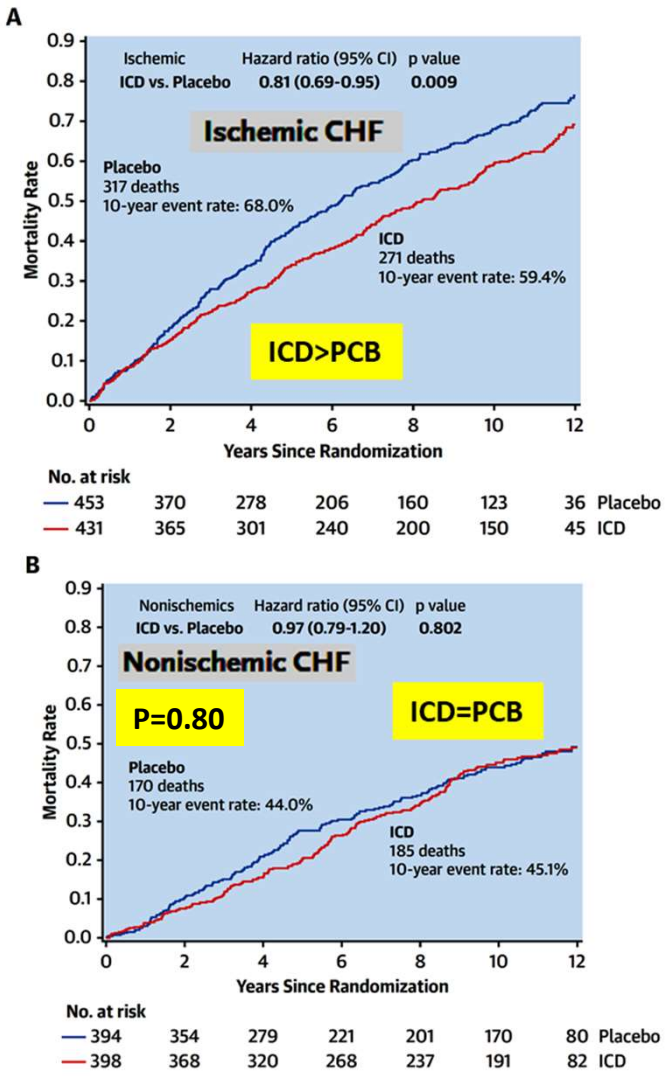


Prespecified subgroup
No interaction



N Engl J Med 2005; 352:225-37



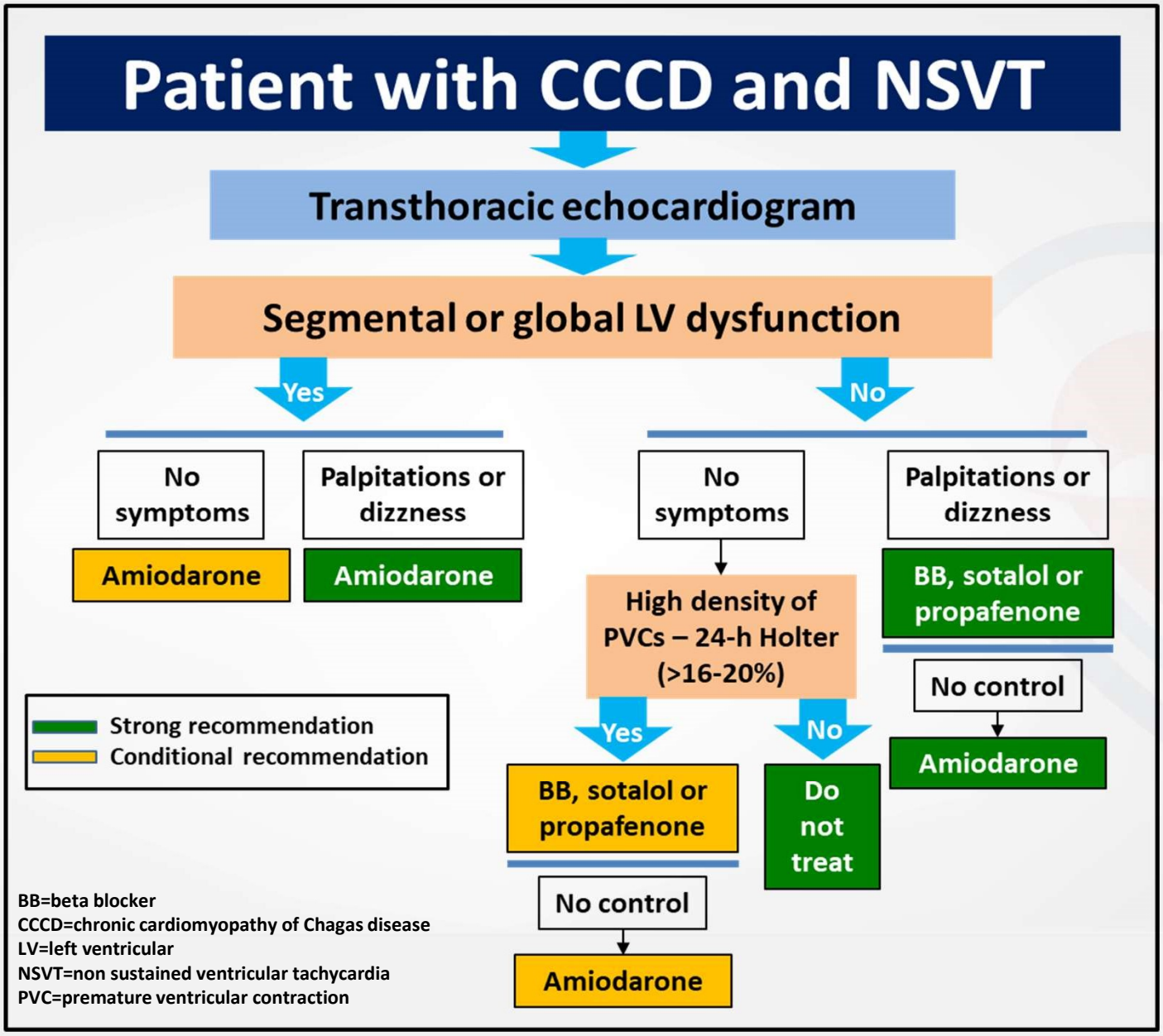


SCD-HeFT

Long-Term Outcomes (11y)

J Am Coll Cardiol 2020;76:405-15

PRIMARY PREVENTION



BB=beta blocker
CCCD=chronic cardiomyopathy of Chagas disease
LV=left ventricular
NSVT=non sustained ventricular tachycardia
PVC=premature ventricular contraction

SBC SOCIEDADE BRASILEIRA DE CARDIOLOGIA

Primary Prevention

CHAGASICS: Study design

Chagas heart disease

≥ 1 episode of NSVT on 24h Holter (HR

Rassi score ≥ 10

Age between 18 and

III

RASSI SCORE

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

Trial stopped because of low enrollment of patients (n=323)

CHronic use of Amiodarone aGAinSt Implantable cardioverter-defibrillator therapy for primary prevention of death in patients with Chagas cardiomyopathy Study: Rationale and design of a randomized clinical trial

Martino Martinelli, MD, PhD,[a,b] Anis Rassi, Jr., MD, PhD,[b,h] José Antonio Marin-Neto, MD, PhD,[c,h] Angelo Amato Vincenzo de Paola, MD, PhD,[d,h] Otávio Berwanger, MD, PhD,[e,h] Maurício Ibraim Scanavacca, MD, PhD,[f,h] Roberto Kalil, MD, PhD,[g,h] and Sérgio Freitas de Siqueira, Eng, MsC[a,h]
São Paulo, and Goiânia, Brazil

Background The implantable cardioverter defibrillator (ICD) is better than antiarrhythmic drug therapy for the primary and secondary prevention of all-cause mortality and sudden cardiac death in patients with either coronary artery disease or idiopathic dilated cardiomyopathy. This study aims to assess whether the ICD also has this effect for primary prevention in chronic Chagas cardiomyopathy (CCC).

Methods In this randomized (concealed allocation) open-label trial, we aim to enroll up to 1,100 patients with CCC, a Rassi risk score for death prediction of ≥10 points, and at least 1 episode of nonsustained ventricular tachycardia on a 24-hour Holter monitoring. Patients from 28 centers in Brazil will be randomly assigned in a 1:1 ratio to receive an ICD or amiodarone (600 mg/d for 10 days, then 200-400 mg/d until the end of the study). The randomization sequence will be generated by computer, and the members of the committees responsible for end point validation and data analysis will be blinded to study assignment. The primary end point is all-cause death, and enrolment will continue until 256 patients have reached this end point. Key secondary end points include cardiovascular death, sudden cardiac death, hospitalization for heart failure, and quality of life. We expect follow-up to last 3 to 6 years, and data analysis will be done on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov number NCT01722942.

Conclusion CHAGASICS is the first large-scale trial to assess the benefit of ICD therapy for the primary prevention of death in patients with CCC and nonsustained ventricular tachycardia, who have a moderate to high risk of death. (Am Heart J 2013;166:976-982.e4.)

Ami

tive
nticenter
Brazilian
Open label

ICD
N = 550

Minimum follow-up: 3 years
Mean follow-up: 4.5 years

Primary end point: all cause mortality (intention-to-treat)

Martino Martinelli, MD, PhD, Anis Rassi Jr, MD, PhD, José Antonio Marin-Neto, MD, PhD, Angelo Amato Vincenzo de Paola, MD, PhD, Otávio Berwanger, MD, PhD, Maurício Ibraim Scanavacca, MD, PhD, Roberto Kalil, MD, PhD, Sérgio Freitas de Siqueira, Eng, MsC, on behalf of the CHAGASICS Investigators, Brazil. Am Heart J 2013; 166: 976-982.

Stable SVT &
SVT with mildly reduced EF

Zero RCT with ICD

SECONDARY PREVENTION ICD TRIALS

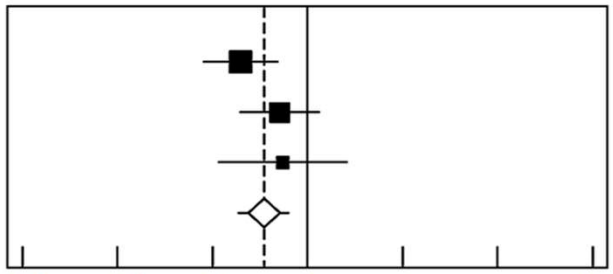
Study	AVID[2]	CASH[3]	CIDS[4]
Years	1993 to 1997	1987 to 1998	1990 to 1997
Patients	1016	191	659
Mean age (years)	65±11	58±11	63±9
Male (%)	78	79	85
Follow-up (months)	18±12	57±34	36
CAD (%)	81	73	83
Nonischemic (%)	15	12	10
LVEF	32±13	46±19	34±14
Presenting arrhythmia (%)			
VF	45	100	45
VT with LOC	21	0	16
VT without LOC (LVEF < 35%)	34	0	24
Syncope	0	0	15
BB (%)	42	0	33
ACE-I/ARB (%)	69	45	NR
One-year mortality (%): Control/ICD	17.7/10.7	15.2/8.1	11.2/9.5
Two-year mortality (%): Control/ICD	25.3/18.4	27.2/17.2	21.0/14.8

LOC: loss of consciousness

META ANALYSIS
AVID, CIDS, CASH

Total mortality

Name	n	Events	HR	95% CI
AVID	1016	80	0·62	0·47, 0·81
CIDS	659	83	0·82	0·61, 1·10
CASH	191	37	0·83	0·52, 1·33
Fixed effects HR = 0·72				95% = 0·60, 0·87



Test for association (U = 11·77 on 1 df) $P = 0·00060$

Test for heterogeneity (Q = 2·37 on 2 df) $P = 0·30550$

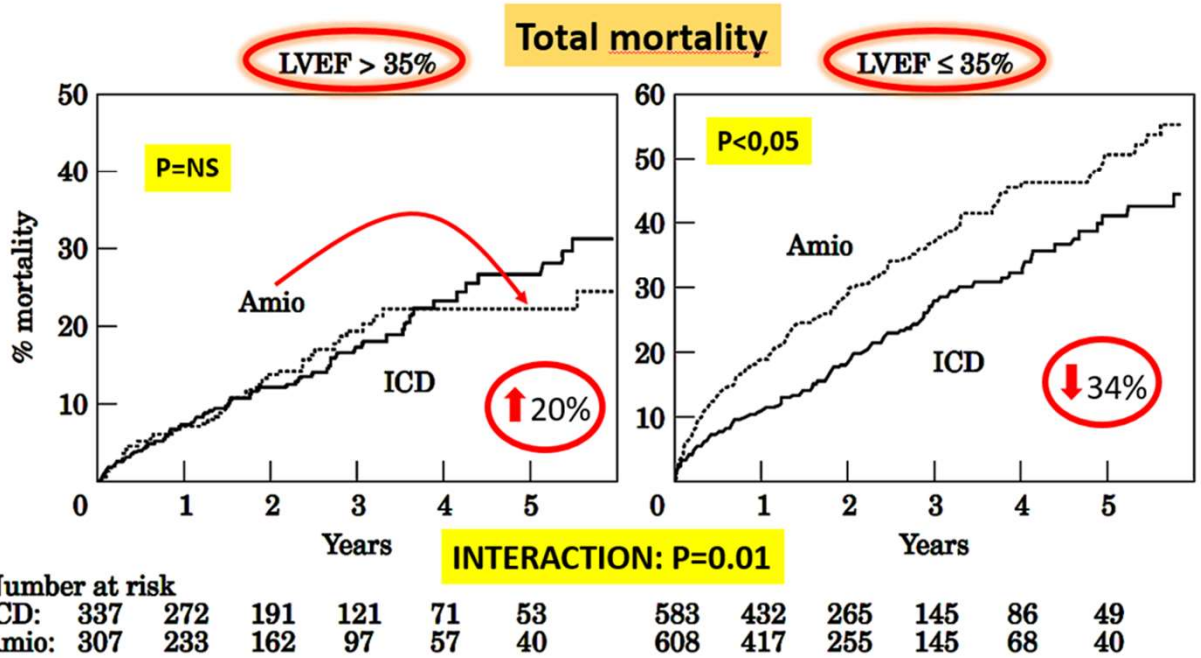


Figure 2 **Cumulative risk of death for patients with left ventricular ejection fraction (LVEF) >35% and ≤35%.**

Table 3 ***Baseline characteristics of patients: pooled database***

	ICD n=934	Amiodarone n=932
Age (years)	63 ± 11	64 ± 10
Male gender (%)	81	82
Left ventricular ejection fraction	34 ± 15	33 ± 14
NYHA class (CHF symptoms) ⩾3	9%	12%
Prior myocardial infarction	69%	69%
Non-ischaemic cardiomyopathy	12%	13%
No heart disease	4%	3%
Presenting arrhythmia		
Ventricular fibrillation	51%	52%
Ventricular tachycardia	44%	43%
Syncope	5%	4%
Randomized in the 'epicardial era'*	9%	8%
Discharge beta-blocker	42%	19%
Discharge ACE inhibitor	63%	64%
Discharge ASA	51%	51%

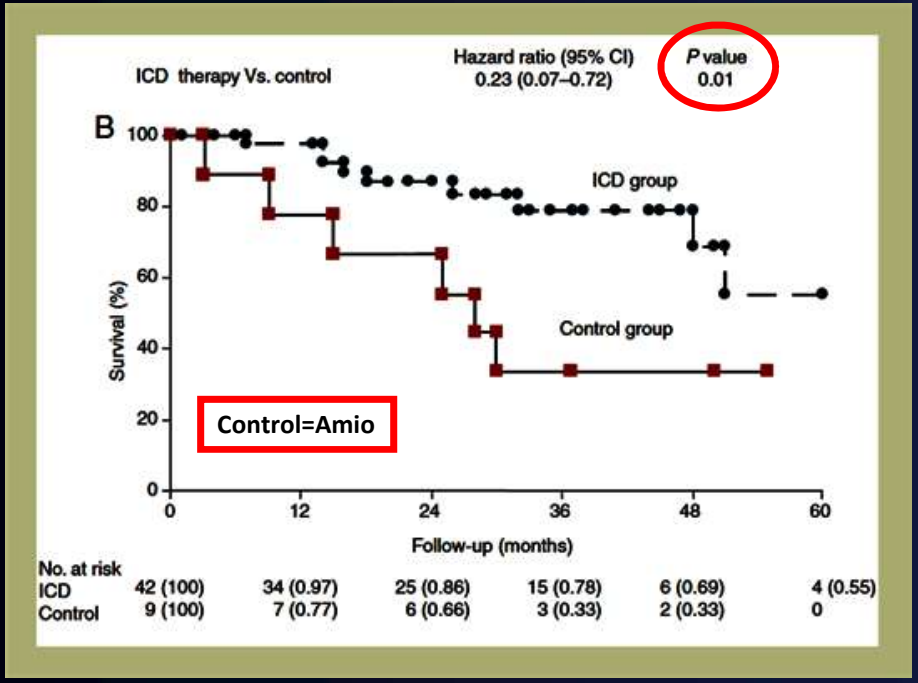
*Randomized before 1 July 1991.
CHF=congestive heart failure; ACE=angiotensin converting enzyme; NYHA=New York Heart Association.

Connolly et al. *Eur Heart J 2000;21:2071-78*

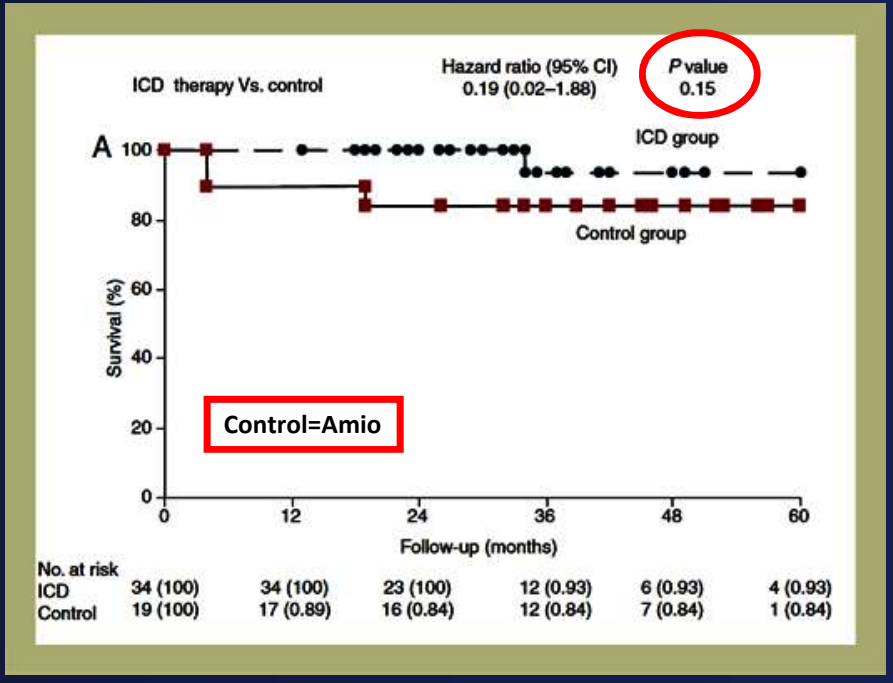
ICD x AMIO in Secondary Prevention (Chagas)

- Observational study (single center in Ribeirão Preto, SP)
- ICD: 76 patients; 48 men; age 57 ± 11 years; LVEF 39 ± 12%; 100% SVT
- AMIO: 28 patients; 18 men; age 54 ± 10 years; LVEF 41 ± 10%; 74% symptomatic SVT, 22% syncope + inducible SVT at EPS, 4% aborted CA
- Mean follow up: 34 months

LVEF < 40% (n=51)



LVEF ≥ 40% (n=53)



Gali WL et al. *Europace* 2014;16:674-80

Implantable cardioverter-defibrillator in Chagas heart disease: A systematic review and meta-analysis of observational studies

Andre A.L. Carmo [a,1], Marcos R. de Sousa [a,1], Juan F. Agudelo [b,1], Eric Boersma [c,1], Manoel O.C. Rocha [a,1], Antonio L.P. Ribeiro [a,*,1], Carlos A. Morillo [d,e,1]

Studies assessing mortality outcomes in patients with CHD and SVT treated w/ ICD implantation or w/ amiodarone.

Secondary prevention

Death Rate Meta-analysis

	Group by Comparison	Study name	Comparison	Rate	Standard error	Lower limit	Upper limit
	amiodarone	Gali et al. 2014	amiodarone	0,110	0,037	0,038	0,182
	amiodarone	Leite et al. 2003	amiodarone	0,093	0,016	0,062	0,124
TOTAL	amiodarone			0,096	0,014	0,067	0,124
	ICD	Di-Toro 2011	ICD	0,103	0,028	0,049	0,157
	ICD	Barbosa et al. 2013	ICD	0,168	0,059	0,052	0,284
	ICD	Martinelli Filho et al. 2012	ICD	0,071	0,013	0,046	0,096
	ICD	Cardinalli-Neto et al. 2007	ICD	0,165	0,030	0,107	0,224
	ICD	Gali et al.. 2014	ICD	0,048	0,015	0,018	0,078
TOTAL	ICD			0,097	0,020	0,057	0,137

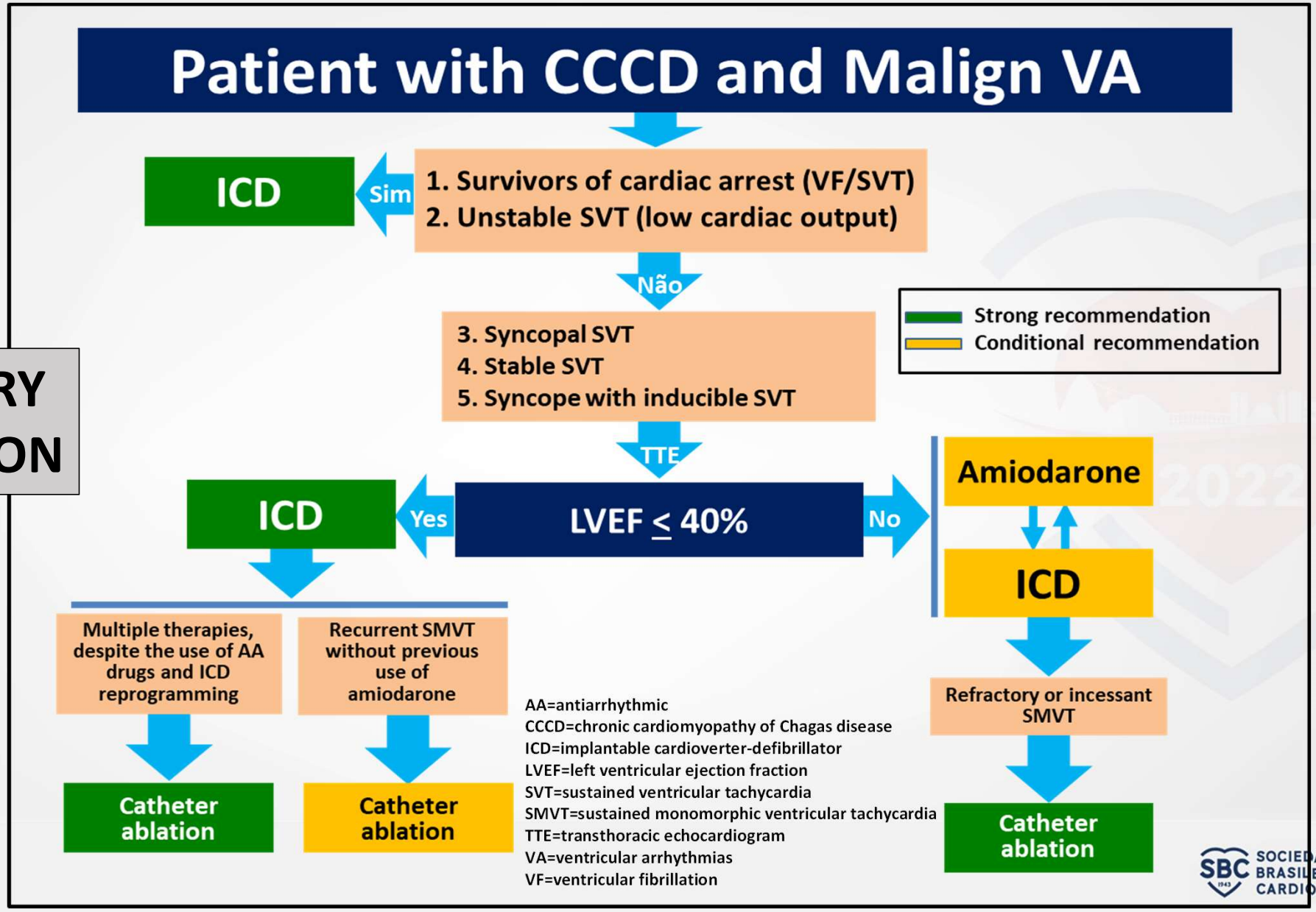
Rate and 95% CI

-0,50 -0,25 0,00 0,25 0,50

Int J Cardiol. 2018 Sep 15;267:88-93.

Conclusion: The best available evidence derived from small observational studies suggests that ICD therapy in secondary prevention of sudden death (VT or resuscitated SCD) is not associated with lower rate of all-cause mortality in patients with ChCM. Randomized controlled trials are needed to answer this question.

SECONDARY PREVENTION



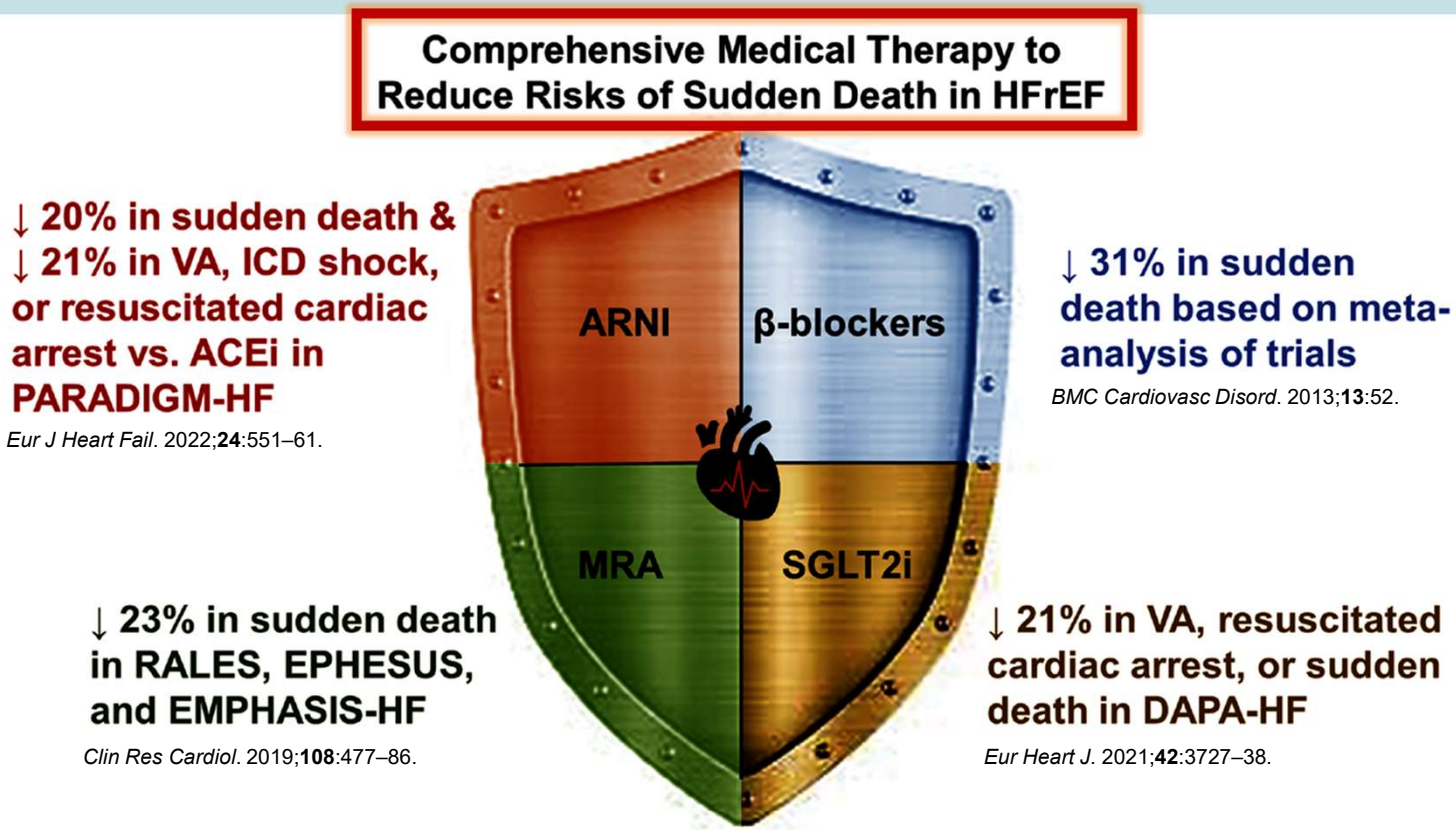


Figure 1 Comprehensive medical therapy to reduce risk of sudden death in heart failure with reduced ejection fraction (HFrEF). Each component of contemporary HFrEF pharmacotherapy has been shown to reduce risk of sudden death, including ARNI (hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.68–0.94), β-blockers (odds ratio 0.69; 95% CI 0.62–0.77), MRA (HR 0.77; 95% CI 0.66–0.89), and SGLT2i (HR 0.79; 95% CI 0.63–0.99).

*European Journal of Heart Failure (2022) **24**, 562–564*

Chagas Disease: guidelines 2022 (SBC)

- Epidemiology and burden of Chagas disease
- Pathogenesis
- Antiparasitic treatment
- Classification of Chagas disease
- Diagnosis and evaluation of patients with heart disease
- Risk stratification of patients with cardiac disease
- Treatment of heart failure
- Treatment of cardiac arrhythmias
- **Challenges in Chagas disease**

70% of people with Chagas don't know they're infected

13 Apr 2021

PAHO Pan American Health Organization World Health Organization Americas

PAHO 120th ANNIVERSARY

Only 1% of those infected are treated annually

In the clinical picture, Chagas disease, as a complicating factor, is hidden in the heart and digestive tract, and therefore, only 1% of those infected are treated annually. Chagas disease must be diagnosed by laboratory tests as the cause in such cases and disorders, which afflict millions of people.

Achieving universal health coverage, including clinical management and counseling for all people diagnosed in the late stages, is essential for controlling the disease and improving the quality of life of those affected.

Under the slogan "Comprehensive and Equitable Health Care and Services for All," this year's World Chagas Disease Day seeks to raise the visibility of the disease and increase and broaden awareness of the importance of improving early detection while expanding diagnostic coverage and equitable access to clinical care for Chagas.

DIAGNOSE

TREAT

SciELO Preprints

Estado da publicação: O preprint foi submetido para publicação em um periódico

Diretriz da Sociedade Brasileira de Cardiologia sobre Diagnóstico e Tratamento de Pacientes com Cardiomiopatia da Doença de Chagas

José Antonio Marin-Neto, Anis Rassi Jr., Gláucia M. Moraes Oliveira, Luís Claudio Lemos Correia, Alberto Novaes Ramos Jr., Alejandro Marcel Hasslocher-Moreno, Alejandro Luquetti Ostermayer, Andréa Silvestre de Sousa Silvestre de Sousa, Angelo Amato Vincenzo de Paola, Antonio Carlos Sobral de Sousa, Antonio Luiz Pinho Ribeiro, Dalmo Correia Filho, Dilma do Socorro Moraes de Souza, Edecio Cunha-Neto, Felix J. A. Ramires, Fernando Bacal, Maria do Carmo Pereira Nunes, Martino Martinelli Filho, Maurício Ibrahim Scanavacca, Roberto Magalhães Saraiva, Wilson Alves de Oliveira Júnior, Adalberto M. Lorga-Filho, Adriana de Jesus Benevides de Almeida Guimarães, Adriana Lopes Latado Braga, Adriana Sarmento de Oliveira, Alvaro V. L. Sarabanda, Ana Yecê das Neves Pinto, André Assis Lopes do Carmo, André Schmidt, Barbara Maria Ianni, Brivaldo Markman Filho, Carlos Eduardo Rochitte, Carolina Thé Macedo, Charles Mady, Christophe Chevillard, Cláudio Marcelo Bittencourt das Virgens, Cleudson Nery de Castro, Constança Felícia De Paoli de Carvalho Britto, Cristiano Pisani, Daniela do Carmo Rassi, Dario C. Sobral Filho, Dirceu Rodrigues Almeida, Edimar A. Bocchi, Evandro T. Mesquita, Fernanda de Souza Nogueira Sardinha Mendes, Francisca Tatiana Pereira, Gilberto Marcelo Sperandio da Silva, Giselle de Lima Peixoto, Gustavo Glotz de Lima, Henrique H. Veloso, Henrique Turin Moreira, Hugo Bellotti Lopes, Ibraim Masciarelli Francisco Pinto, João Carlos Pinto Dias, João Marcos Bemfica, João Paulo Silva-Nunes, José Augusto Soares Barreto-Filho, José Francisco Kerr Saraiva, Joseli Lannes-Vieira, Joselina Luzia Menezes Oliveira, Luciana V. Armaganijan, Luiz Cláudio Martins, Luiz Henrique C. Sangenis, Marco Paulo Barbosa, Marcos Antônio Almeida-Santos, Marcos Vinicius Simões, Maria Aparecida Shikanai-Yasuda, Maria da Consolação Vieira Moreira, Maria de Lourdes Higuchi, Maria Rita de Cássia Costa Monteiro, Mauro Felippe Felix Mediano, Mayara Maia Lima, Maykon T. Oliveira, Minna Moreira Dias Romano , Nadjar Nitz, Paulo de Tarso Jorge Medeiros, Renato Vieira Alves, Ricardo Alkmim Teixeira, Roberto Coury Pedrosa, Roque Aras, Rosália Morais Torres, Rui Manoel dos Santos Povoa, Sérgio Gabriel Rassi, Sérgio Salles Xavier, Silvia Marinho Martins Alves , Suelene B. N. Tavares, Swamy Lima Palmeira, Telêmaco Luiz da Silva Junior, Thiago da Rocha Rodrigues, Vagner Madrini Junior, Veruska Maia da Costa , Walderez Dutra

DOI: https://doi.org/10.1590/SciELOPreprints.4820

Submetido em: 2022-10-11
Postado em: 2022-10-11 (versão 1)
(AAAA-MM-DD)

"363 pages, 965 references and several tables, figures and algorithms"

Sumário

1. Considerações Iniciais
2. Epidemiologia - Atualização no Século XXI
3. Patogênese da Cardiomiopatia da Doença de Chagas
4. Fisiopatologia da Cardiomiopatia - Fases Aguda e Crônica
5. História Natural
6. Diagnóstico da Cardiomiopatia da Doença de Chagas
7. Estratificação de Risco e Prognóstico
8. Condutas Terapêuticas na Forma Indeterminada da Doença de Chagas
9. Tratamento Etiológico da Doença de Chagas
10. Condutas Terapêuticas na Disfunção Ventricular e Insuficiência Cardíaca
11. Condutas Terapêuticas nas Arritmias Cardíacas
12. Condutas para Prevenção e Tratamento de Complicações Tromboembólicas
13. Condutas em Subgrupos Especiais e Abordagem de Problemas Relativos à Gravidez, à Atividade Física, ao Risco Cirúrgico, à Anestesia Geral e à Infecção COVID-19
14. Recomendações para Constituição de Serviços Estruturados para Acompanhamento de Pessoas com Cardiomiopatia Crônica da Doença de Chagas
15. Definição de Cardiopatia Grave e Avaliação Médico-Trabalhista