



***R*esynchronization/Defibrillation  
for *A*mbulatory Heart *F*ailure *T*rial**

**Cardiac Resynchronization Therapy for  
Mild-to-Moderate Heart Failure**

George Wells

University of Ottawa Heart Institute  
Department of Epidemiology and Community Medicine  
University of Ottawa



- 
1. Brief background information on device therapy
  2. Work leading up to RAFT
  3. Review RAFT design
  4. Review RAFT results
  5. Role of RAFT in determining effect of CRT on mortality
  6. Future analyses



# The Stages of Heart Failure: NYHA Classification

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In order to determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.



# Device Therapy

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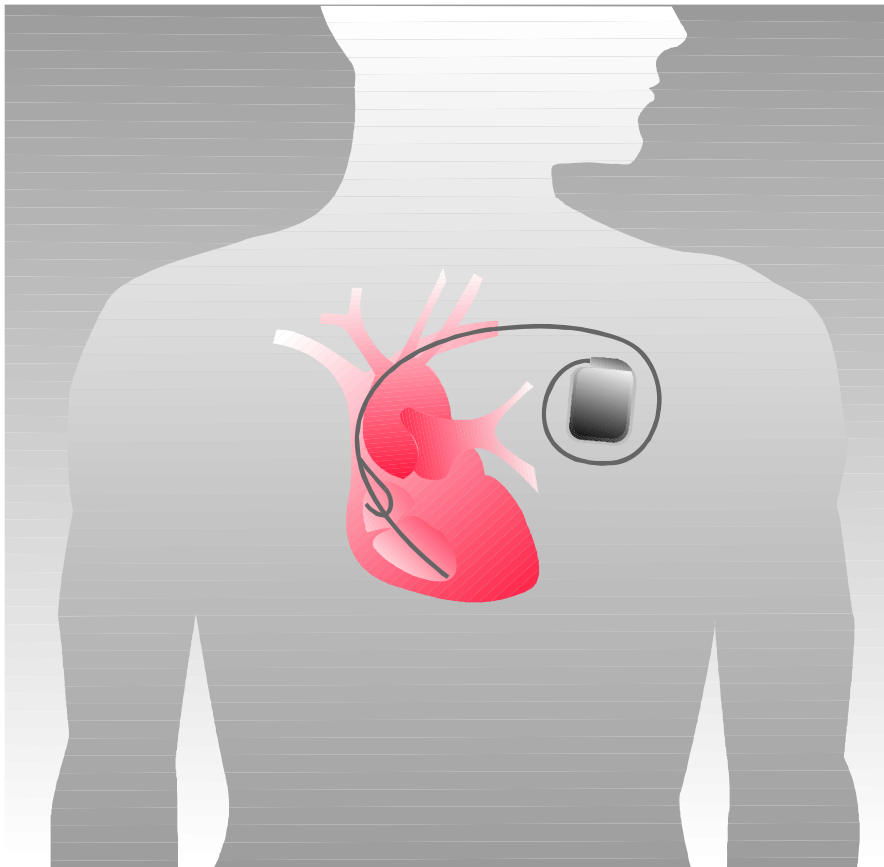
- Implantable **C**ardioverter **D**efibrillator (ICD)
- Cardiac **R**esynchronization **T**herapy (CRT)



# ICD Overview

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## Small device - Pectoral site

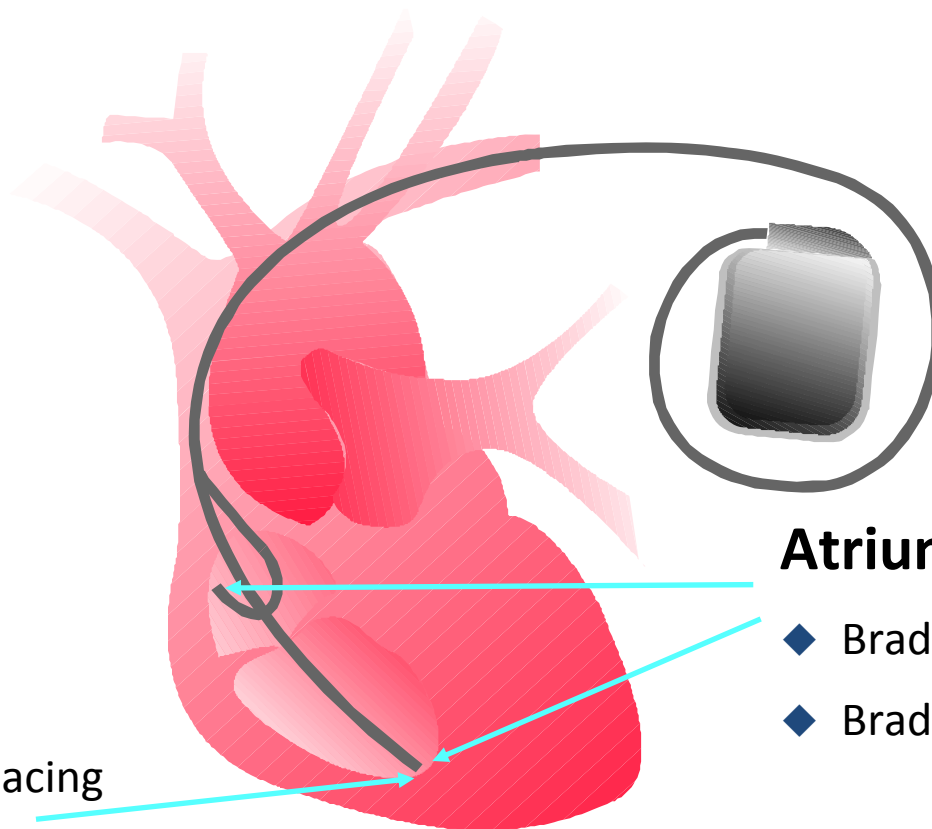


- First-line therapy for VT/VF patients
- AT/AF Therapy
- Heart Failure patients
- Transvenous, single incision
- Local anesthesia; conscious sedation
- Short hospital stays
- Few complications
- Perioperative mortality < 1%
- Programmable therapy options
- Single- or dual-chamber therapy
- Battery longevity up to 9 years



# Therapies Provided by Dual Chamber ICDs

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## Ventricle

- ◆ VT prevention
- ◆ Antitachycardia pacing
- ◆ Cardioversion
- ◆ Defibrillation

## Atrium & Ventricle

- ◆ Bradycardia sensing
- ◆ Bradycardia pacing



# Ventricular Dysynchrony and Cardiac Resynchronization

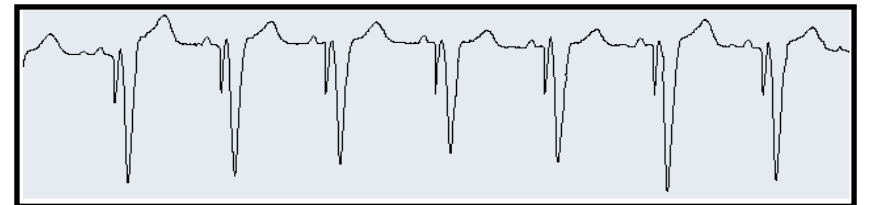
- **Ventricular Dysynchrony**

- Electrical: Inter- or Intraventricular conduction delays typically manifested as left bundle branch block
- Structural: disruption of myocardial collagen matrix impairing electrical conduction and mechanical efficiency
- Mechanical: Regional wall motion abnormalities with increased workload and stress—compromising ventricular mechanics



- **Cardiac Resynchronization**

- Therapeutic intent of atrial synchronized biventricular pacing
  - Modification of interventricular, intraventricular, and atrial-ventricular activation sequences in patients with ventricular dysynchrony
  - Complement to optimal medical therapy



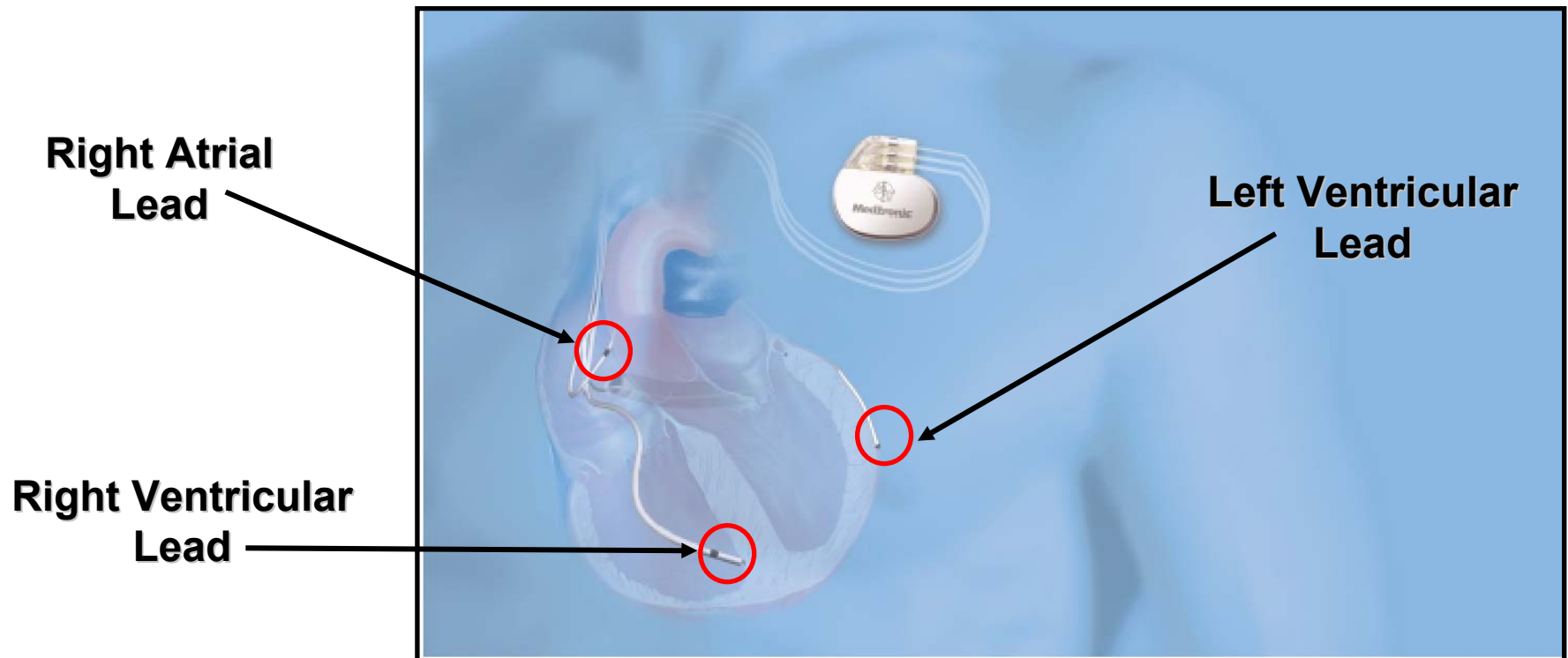


# Achieving Cardiac Resynchronization

**Mechanical Goal: Atrial-synchronized bi-ventricular pacing**

- **Transvenous Approach**

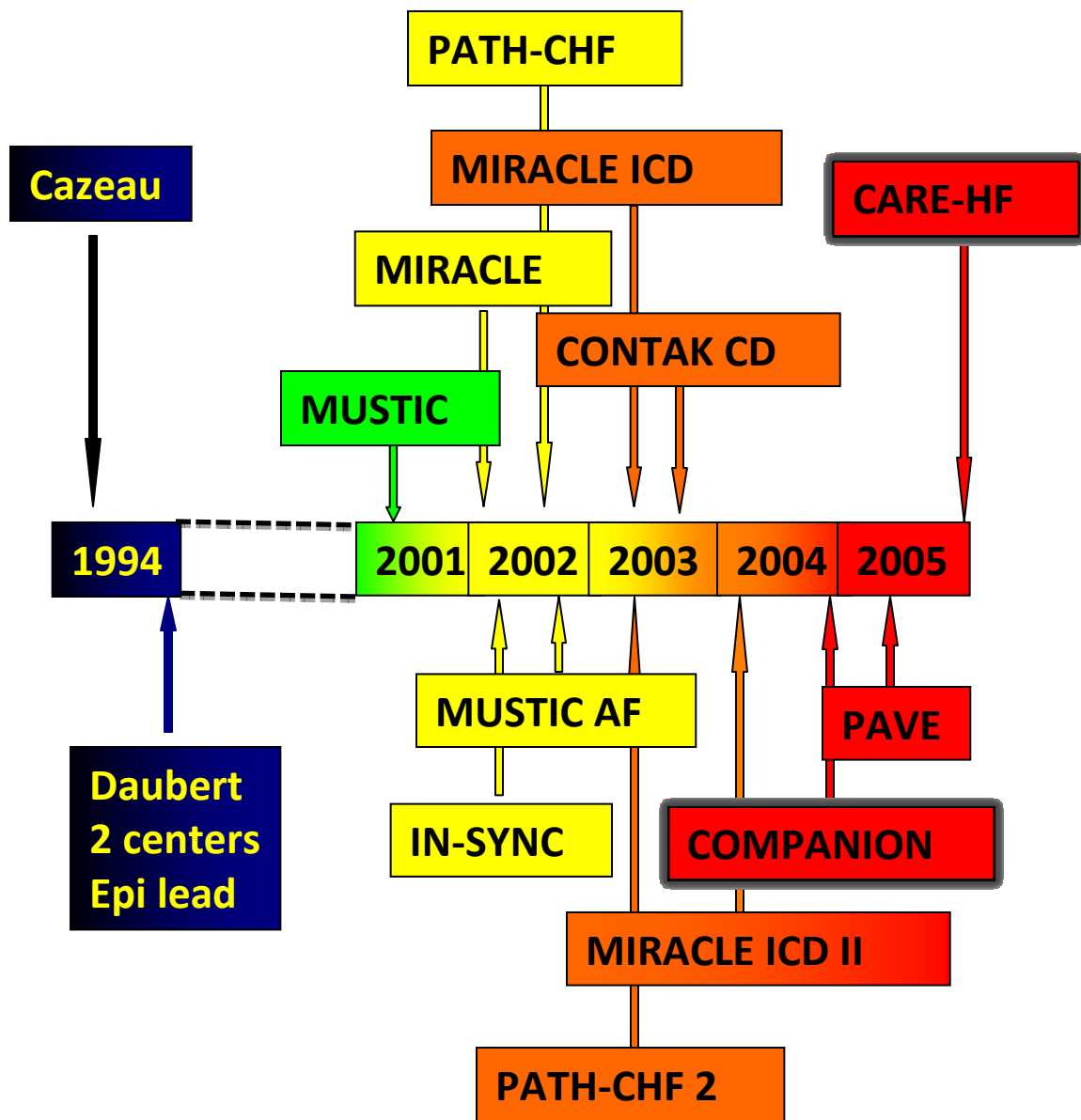
- Standard pacing lead in RA
- Standard pacing or defibrillation lead in RV
- Specially designed left heart lead placed in a left ventricular cardiac vein via the coronary sinus







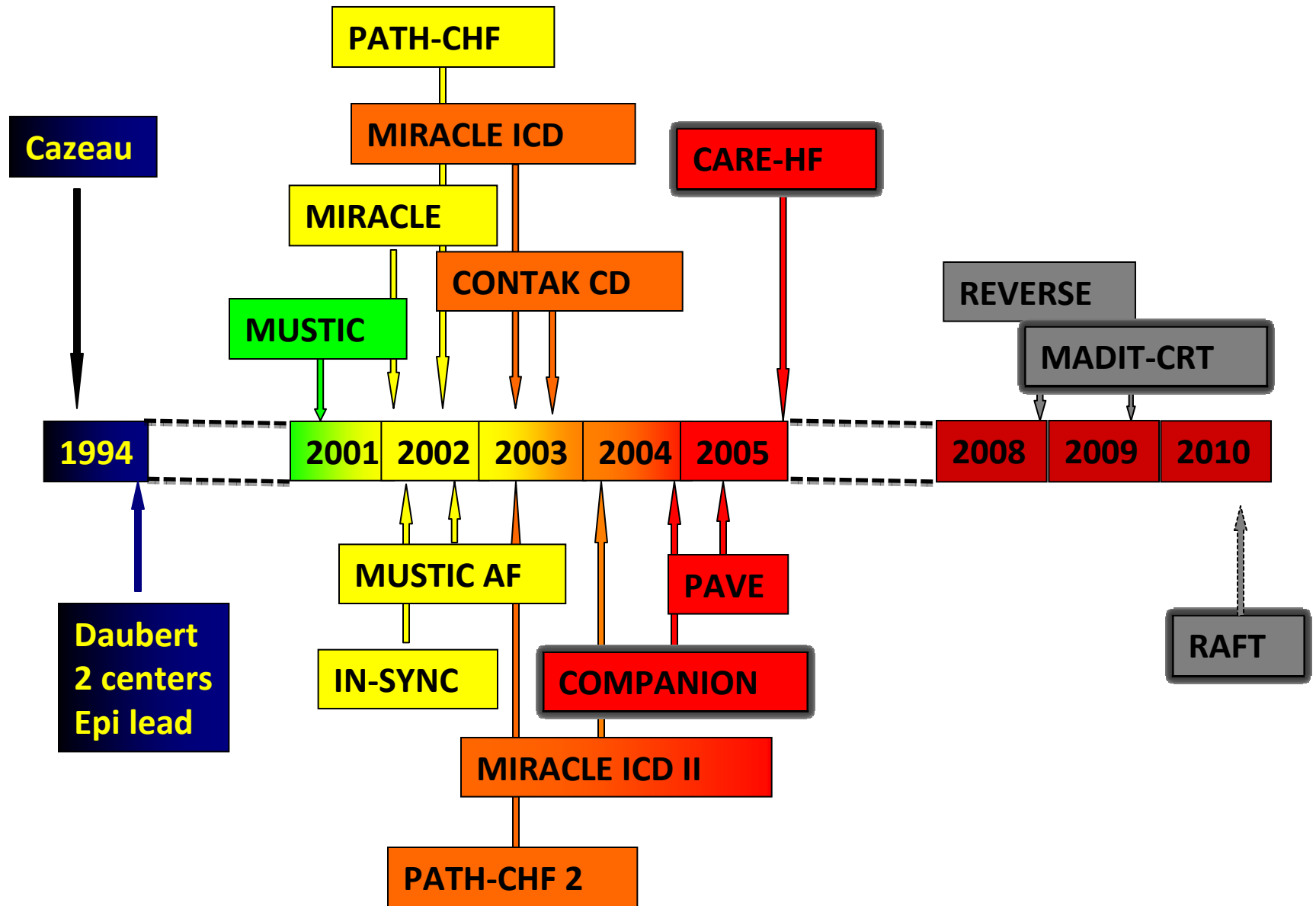
- 
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# CRT

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- In NYHA class III, ambulatory IV patients with LV dysfunction and wide QRS
    - Improve HF symptoms
    - Improve QOL
    - Increase exercise capacity
    - Reverse LV remodeling - ↓ LV size, ↑ LVEF
    - Reduce mitral regurgitation





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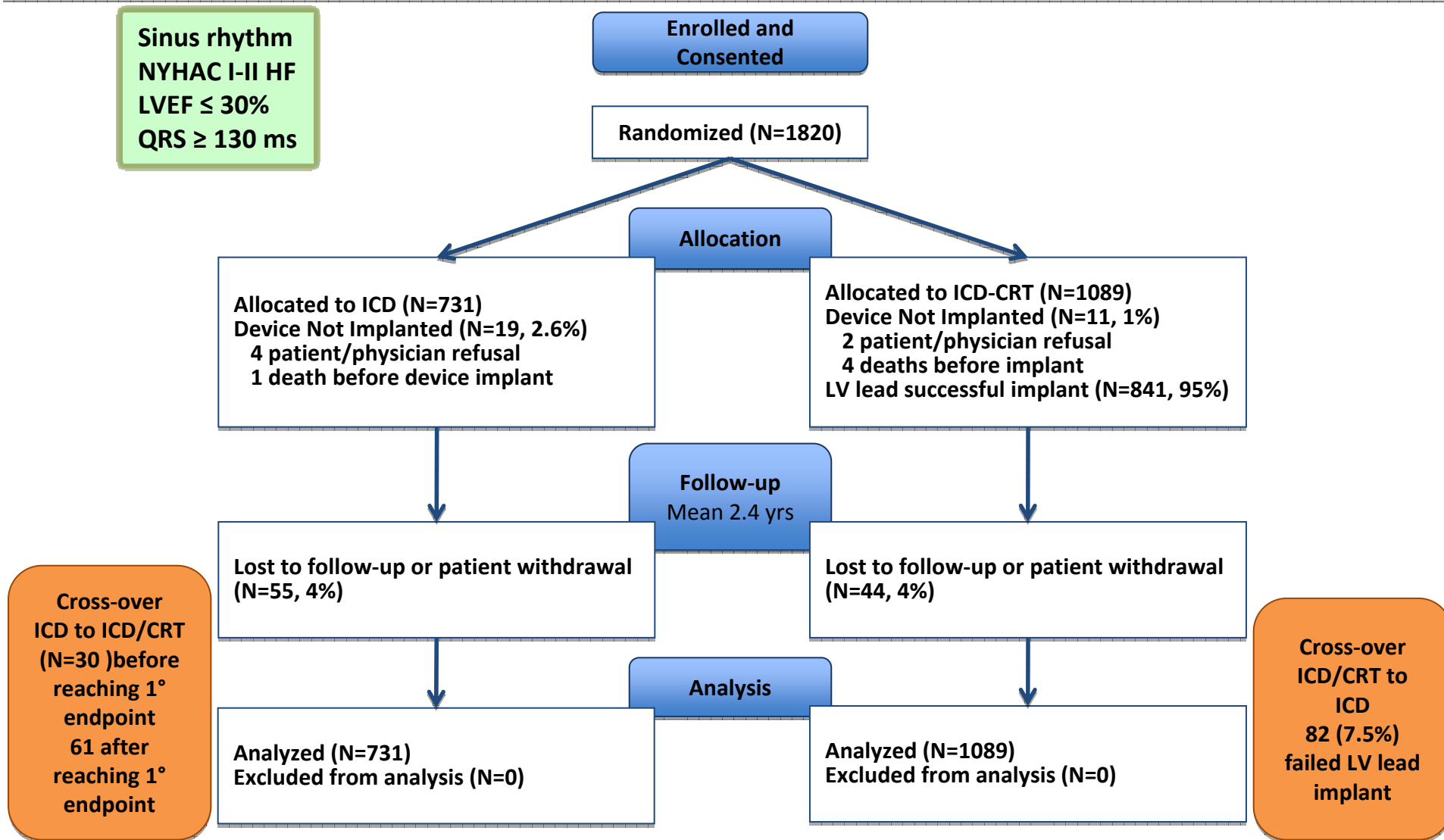
Cardiac-Resynchronization Therapy for the Prevention  
of Heart-Failure Events

Arthur J. Moss, M.D., W. Jackson Hall, Ph.D., David S. Cannom, M.D., Helmut Klein, M.D., Mary W. Brown, M.S.,  
James P. Daubert, M.D., N.A. Mark Estes III, M.D., Elyse Foster, M.D., Henry Greenberg, M.D.,  
Steven L. Higgins, M.D., Marc A. Pfeffer, M.D., Ph.D., Scott D. Solomon, M.D., David Wilber, M.D.,  
and Wojciech Zareba, M.D., Ph.D., for the MADIT-CRT Trial Investigators\*

N Engl J Med 2009;361.

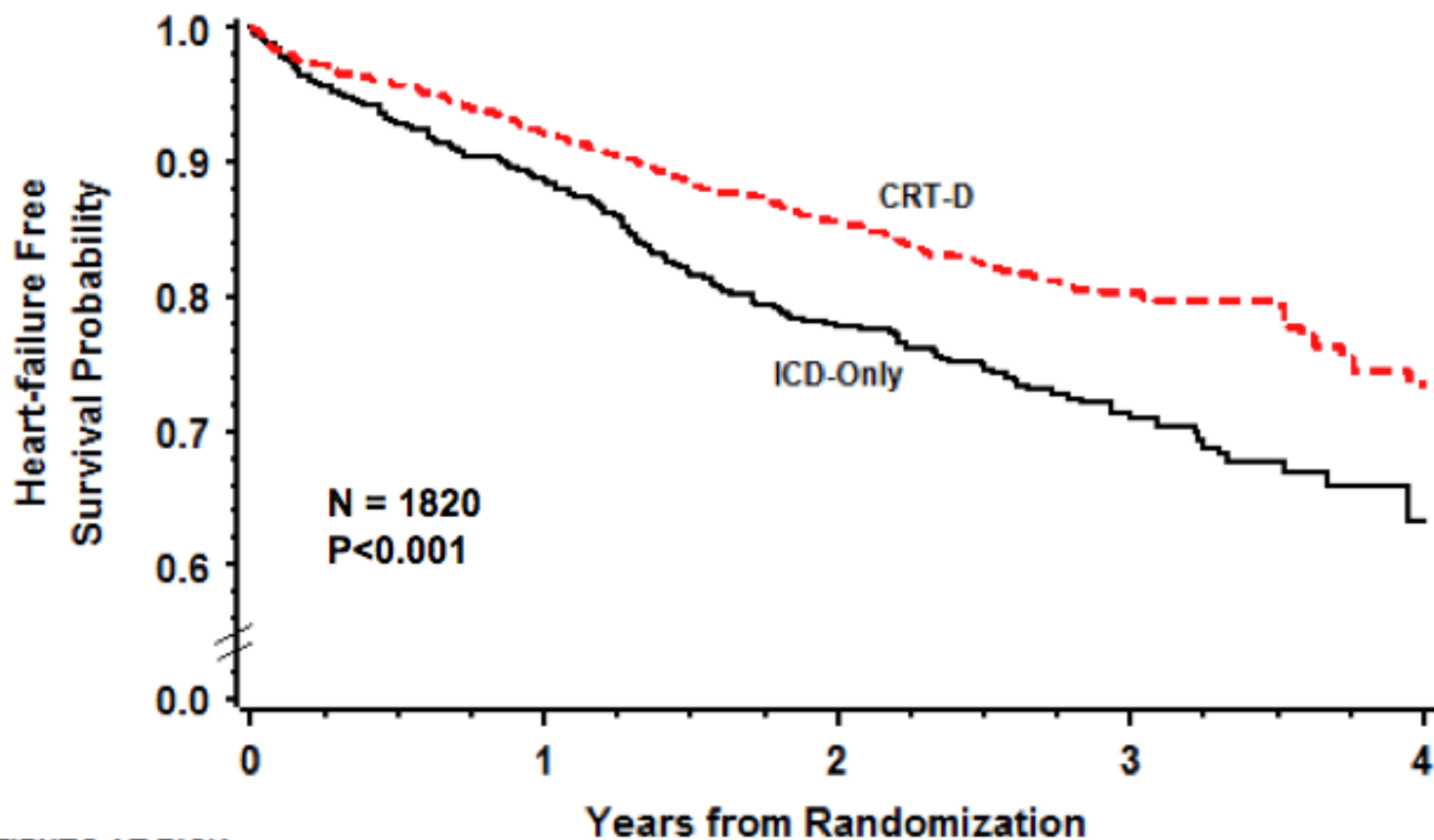


# MADIT-CRT CONSORT Flow Diagram





# MADIT-CRT



## PATIENTS AT RISK

Years from Randomization	ICD-Only	CRT-D
0	731	1089
1	621 (0.89)	985 (0.92)
2	379 (0.78)	651 (0.86)
3	173 (0.71)	279 (0.80)
4	43 (0.63)	58 (0.73)



# Risk of Death or Heart Failure

Variable	ICD-Only Group no. (%)	CRT-ICD Group no. (%)	Hazard Ratio (95% CI) <sup>†</sup>	P Value
All patients	731	1089		
Death or heart failure <sup>‡</sup>	185 (25.3)	187 (17.2)	0.66 (0.52–0.84) <sup>§</sup>	0.001 <sup>§</sup>
Heart failure only	167 (22.8)	151 (13.9)	0.59 (0.47–0.74)	<0.001
Death at any time <sup>¶</sup>	53 (7.3)	74 (6.8)	1.00 (0.69–1.44)	0.99
Patients with ischemic cardiomyopathy (NYHA class I or II) <sup>  </sup>	401	598		
Death or heart failure <sup>‡</sup>	117 (29.2)	122 (20.4)	0.67 (0.52–0.88)	0.003
Heart failure only	105 (26.2)	96 (16.1)	0.58 (0.44–0.78)	<0.001
Death at any time <sup>¶</sup>	35 (8.7)	53 (8.9)	1.06 (0.68–1.64)	0.80
Patients with nonischemic cardiomyopathy (NYHA class II) <sup>  </sup>	330	491		
Death or heart failure <sup>‡</sup>	68 (20.6)	65 (13.2)	0.62 (0.44–0.89)	0.01
Heart failure only	62 (18.8)	55 (11.2)	0.59 (0.41–0.87)	0.01
Death at any time <sup>¶</sup>	18 (5.5)	21 (4.3)	0.87 (0.44–1.70)	0.68





# Question to Address

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Most patients with Low EF, wide QRS, and NHYA class II and III HF are also candidates for ICD.

Does CRT reduce mortality and morbidity in addition to medical therapy and ICD in patients with NYHA class III patients and in patients with NYHA class II patients?



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  3. Review RAFT design



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# Resynchronization/defibrillation for Ambulatory Heart failure Trial (RAFT)



# RAFT Team

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- ***RAFT Investigators***

- A. Tang, G. Wells, M. Talajic, M. Arnold, R. Sheldon, S. Connolly, S Hohnloser, G Nichol, J Rouleau

- ***RAFT Coordinating Centre***

- University of Ottawa Heart Institute
- Coordination Team - G. Wells, A. Tang, P. Theoret-Patrick, M. Luce, L. Yetisir

- ***RAFT committees***

- executive, steering, DSMB, device, adjudication, ECG, publication

- ***RAFT Site Investigators/Coordinators***

- 34 centres



# RAFT

- Idea of a clinical trial put forward in a meeting in Ottawa 1999.





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- Funded by the Canadian Institutes of Health Research, University-Industry program (Medtronic Canada) April 2003.

***Canadian Institutes of Health Research  
University-Industry program***



***Medtronic of Canada***



**Medtronic**



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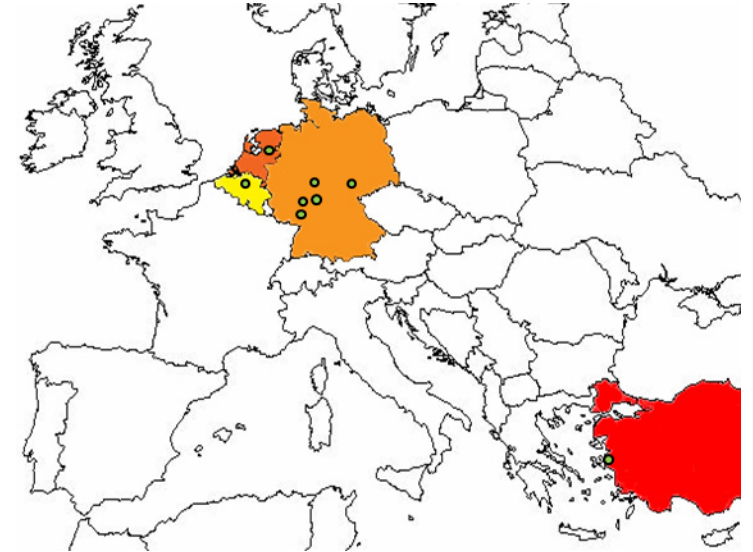
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- Readjustment of sample accounting for 80% NYHA class II to 1800
- 34 centers: 24 centers in Canada, 8 European/Turkey, 2 Australian centers.





# RAFT Centres



Canada	24 centres	1617 patients (90%)
Europe & Turkey	8 centres	137 patients (7.6%)
Australia	2 centres	44 patients (2.4%)



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- Enrollment of 1798 patients completed Feb 2009
- Follow-up completed by August 2010





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- Results announced November 13/14 2010



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ORIGINAL ARTICLE

## Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure

Anthony S.L. Tang, M.D., George A. Wells, Ph.D., Mario Talajic, M.D.,  
Malcolm O. Arnold, M.D., Robert Sheldon, M.D., Stuart Connolly, M.D.,  
Stefan H. Hohnloser, M.D., Graham Nichol, M.D., David H. Birnie, M.D.,  
John L. Sapp, M.D., Raymond Yee, M.D., Jeffrey S. Healey, M.D.,  
and Jean L. Rouleau, M.D., for the Resynchronization–Defibrillation  
for Ambulatory Heart Failure Trial (RAFT) Investigators



# Hypothesis

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## ***Primary Hypothesis***

In patients with mild to moderate heart failure and wide QRS, the addition of CRT to ICD and optimal medical therapy will reduce the primary outcome of total mortality or hospitalizations for heart failure

## ***Secondary Hypotheses***

In patients with mild to moderate heart failure and wide QRS, the addition of CRT to ICD and optimal therapy

- will reduce all cause mortality
- will reduce hospitalization for heart failure



# Outcomes

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- ***Primary Outcome***

- composite of death from any cause or hospitalization for heart failure
- hospitalization for heart failure is defined as an admission to a health-care facility for > 24 hours with worsening heart failure. Hospitalizations > 24 hours were adjudicated by an event committee unaware of the patient treatment allocation

- ***Secondary Outcomes***

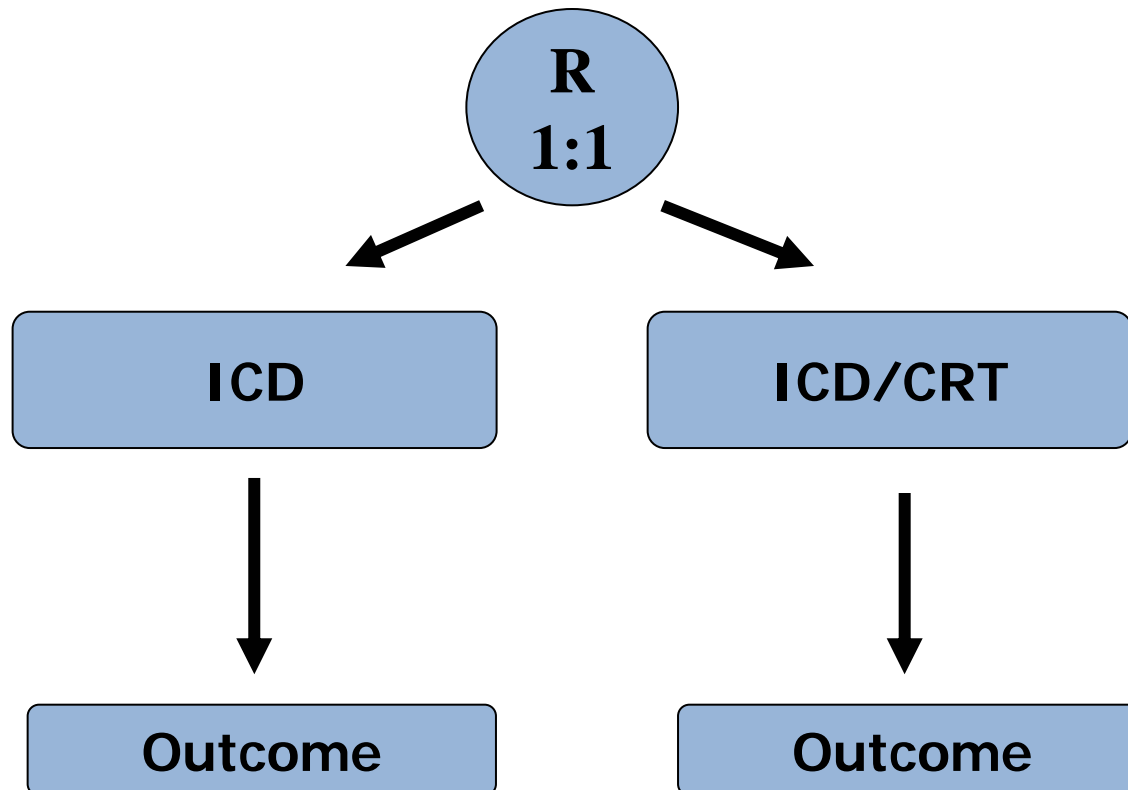
- death from any cause
- death from cardiovascular cause
- hospitalization for heart failure



# Study Design

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- Randomized controlled trial, parallel group
  - Eligible patients were randomly assigned in a 1:1 ratio to receive an ICD or an ICD with CRT







# Key Eligibility Criteria

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- NYHA Class II/III (NYHA Class III not included after Feb 2006)
- QRS duration  $\geq 120$  ms or Paced QRS  $\geq 200$  ms
- LVEF  $\leq 30\%$  by MUGA or LVEF  $\leq 30\%$  and LVEDD  $> 60$ mm by echocardiogram within 6 months of randomization
- ICD indication: 1° or 2° prevention
- Optimal heart failure pharmacological therapy
- Normal sinus rhythm or chronic permanent AF or flutter with a resting ventricular rate  $\leq 60$  bpm and ventricular rate  $\leq 90$  bpm during a 6 minute walk test or intended to perform AV junction ablation



# Randomization


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- Computer generated randomization sequences
- Centralized
  - Allocation Concealment
  - ↓ Selection Bias
- Stratified by
  - Centre
  - Atrial rhythm (permanent atrial fibrillation or flutter versus sinus or atrial pacing)
  - Planned implantation of a single- or dual-chamber ICD



# Blinding

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- Double-Blind
  - The patients and the general health care providers including the team that was responsible for heart failure management and reporting of clinical events were unaware of treatment allocation
  - The arrhythmia team was aware of treatment allocation
-  Performance, Detection, Attrition Bias



# Sample Size - 1800

- The study had a statistical power of 85% to detect a 25% relative reduction in the primary outcome for the CRT/ICD group from an event rate of 11% in the ICD group, given a two-sided  $\alpha$  of 0.05 and taking into consideration an the expected rate of loss-to-follow of 2% and crossover of 7% and 5%

<b>Control Event Rate</b>	<b>11%</b>
<b>MCID</b>	<b>25% RRR</b>
<b>Significance level</b>	<b>0.05 (2 sided)</b>
<b>Power</b>	<b>85%</b>
<b>Loss to follow-up</b>	<b>2%</b>
<b>Crossover</b>	<b>7% CRT/ICD to ICD 5% ICD to CRT/ICD</b>
<b>Test</b>	<b>Log rank</b>
<b>Period</b>	<b>Accrual 4.5 yr, minimum follow-up 1.5 yr</b>
<b>Adjustments</b>	<b>Loss to follow-up. crossover, 2 interim analyses</b>



# Statistical Analysis

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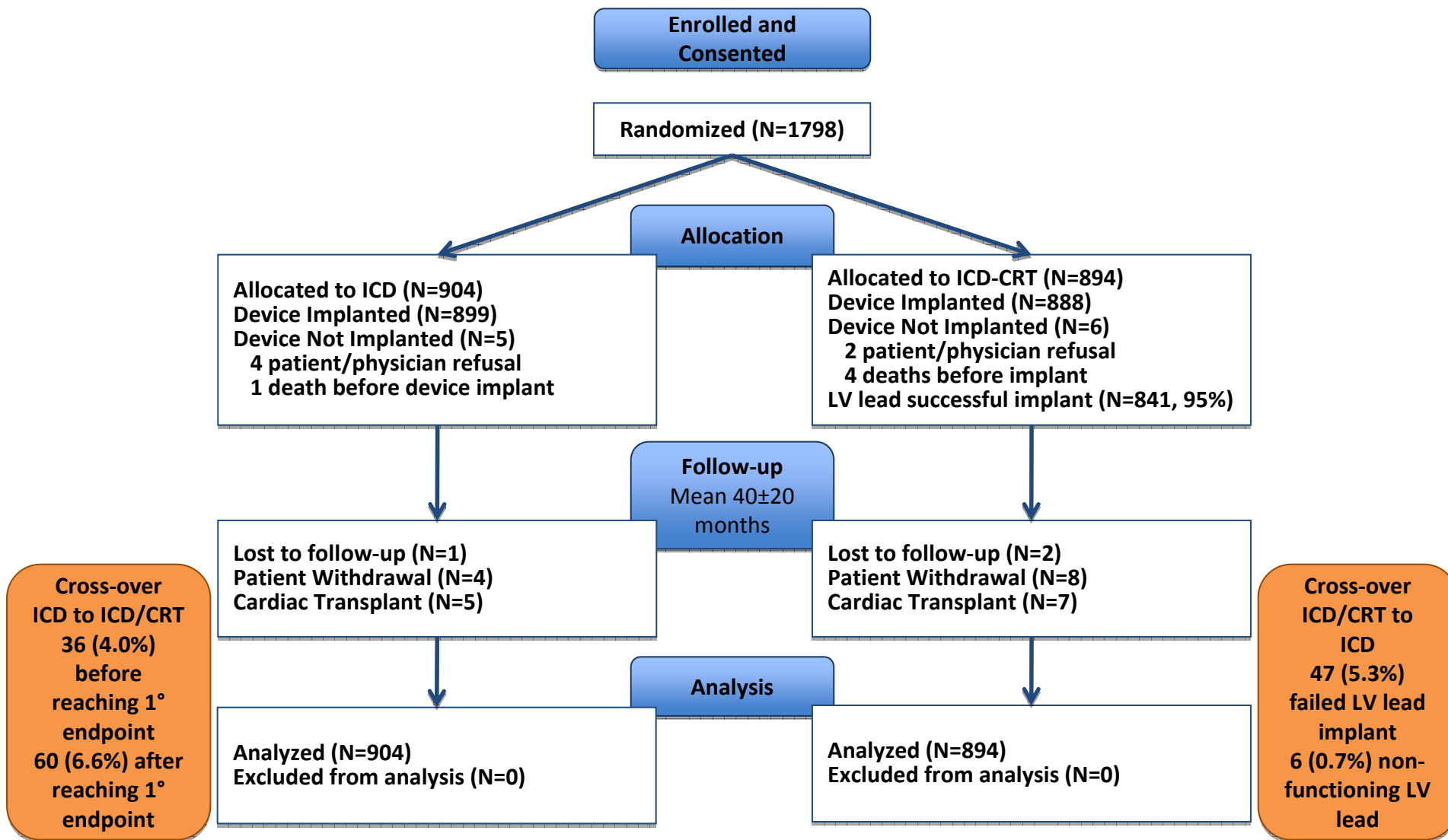
- All analyses conducted according to the intention-to-treat principal
- Baseline characteristics compared descriptively using a priori clinically important difference bounds
- Time to primary and secondary outcomes of the two groups were summarized using Kaplan-Meier curves
  - Curves were compared using log-rank tests
  - Hazard ratio and 95% CI were calculated using the Cox proportional hazards model
  - 5 year actuarial event rates were calculated



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# CONSORT Flow Diagram





# Patient Characteristics at Baseline

Variables	ICD (N=904)	ICD-CRT (N=894)
Age - yr	66.2±9.4	66.2±9.3
Male sex - no. (%)	732 (81.0)	758 (84.8)
Underlying Heart Disease - no. (%)		
Ischemic heart disease	587 (64.9)	614 (68.7)
Nonischemic heart disease	317 (35.1)	280 (31.3)
NYHA class - no. (%)		
Class II	730 (80.8)	708 (79.2)
Class III	174 (19.2)	186 (20.8)
LV Ejection Fraction - %	22.6±5.1	22.6±5.4
Atrial rhythm - no. (%)		
Permanent atrial fibrillation or flutter	115 (12.7)	114 (12.8)
Sinus or atrial paced	789 (87.3)	780 (87.2)
Hypertension - no. (%)	397 (43.9)	402 (45.0)
Diabetes mellitus - no. (%)	313 (34.6)	293 (32.8)
Previous Percutaneous coronary intervention - no. (%)	208 (23.0)	220 (24.6)
Previous CABG - no. (%)	313 (34.6)	293 (32.8)
Current cigarette smoking - no. (%)	127 (14.0)	121 (13.5)
Peripheral vascular disease - no. (%)	90 (10.0)	88 (9.8)
Hospitalization for heart failure in the previous 6 months - no. (%)	223 (24.7)	238 (26.0)
Intrinsic QRS duration		
No. of patients	837	826
Mean – msec.	158.3±24.0	157±23.6
Paced QRS duration		
No. of patients	67	68
Mean - msec	210.0±18.3	206.5±24.0
QRS morphologic type - no. (%)		
Right bundle-branch block	93 (10.3)	68 (7.6)
Left bundle-branch block	643 (71.1)	652 (72.9)
NIVCD	101 (11.2)	106 (11.9)
Ventricular paced	67 (7.4)	68 (7.6)



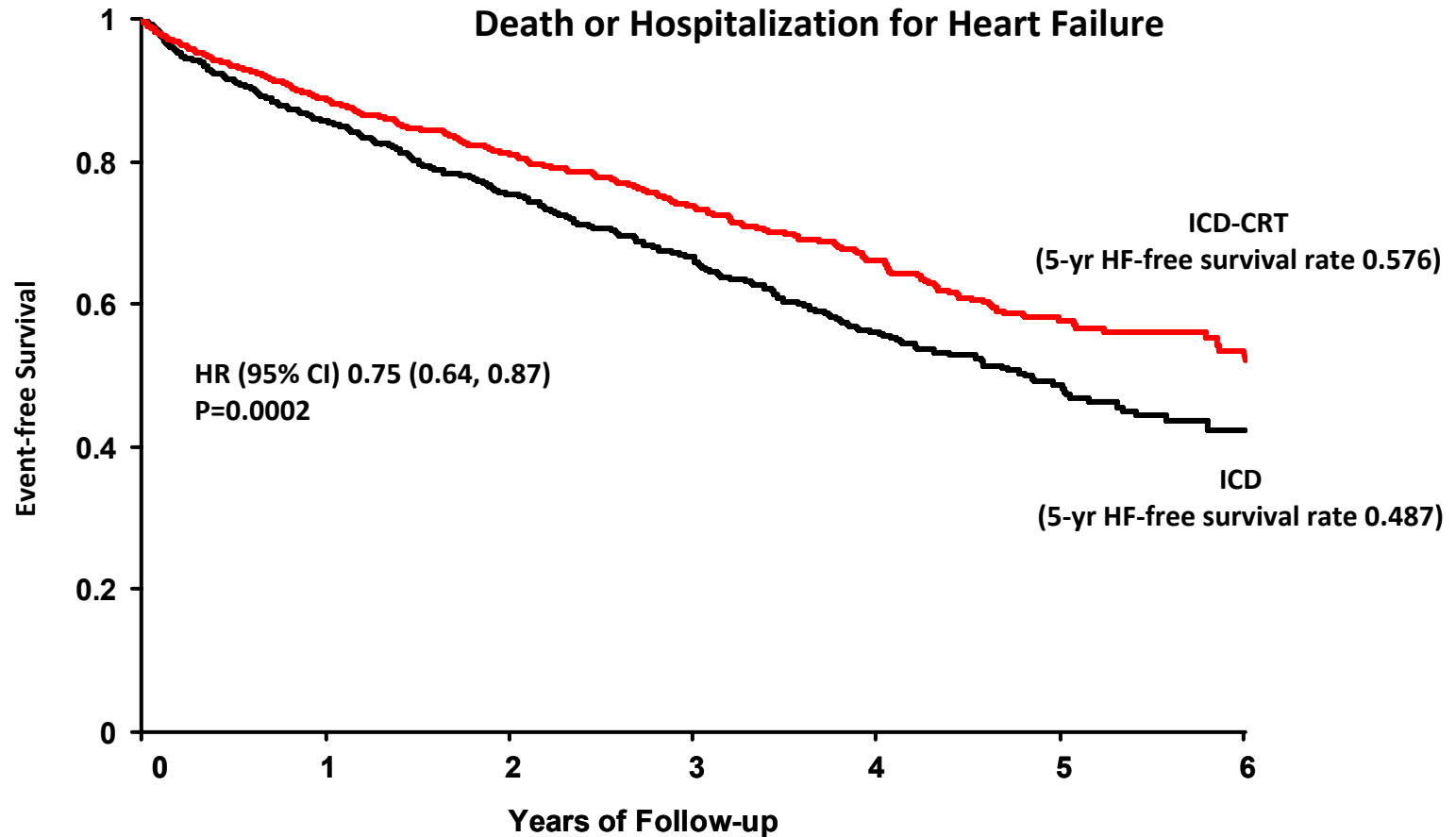


# Patient Characteristics at Baseline

Variables	ICD (N=904)	ICD-CRT (N=894)
<b>Medications - no. (%)</b>		
Beta-blocker	805 (89.0)	808 (90.4)
ACE inhibitor or ARB	878 (97.1)	859 (96.1)
Spirolactone	378 (41.8)	372 (41.6)
Digoxin	319 (35.3)	301 (33.7)
Aspirin	622 (68.8)	584 (65.3)
Warfarin	298 (33.0)	310 (34.7)
Clopidogrel	145 (16.0)	134 (15.0)
Statin	618 (68.4)	607 (67.9)
Diuretics	756 (83.6)	757 (84.7)
Calcium-Channel Blocker	83 (9.2)	101 (11.3)
Amiodarone	124 (13.7)	140 (15.7)
Other antiarrhythmia drug	8 (0.9)	12 (1.3)
<b>6-minute walk test distance</b>		
No. of patients	765	789
Mean - m	354.9±110.1	351.3±106.7
<b>Estimated glomerular filtration rate</b>		
No. of patients	897	885
Rate - ml/min/1.73 m <sup>2</sup>		
<30 - no. (%)	63 (7.0)	57 (6.4)
30-59 - no. (%)	383 (42.7)	398 (45.0)
>60 -no. (%)	516 (50.3)	430 (48.6)



# Kaplan-Meier Estimates of the Primary Outcome

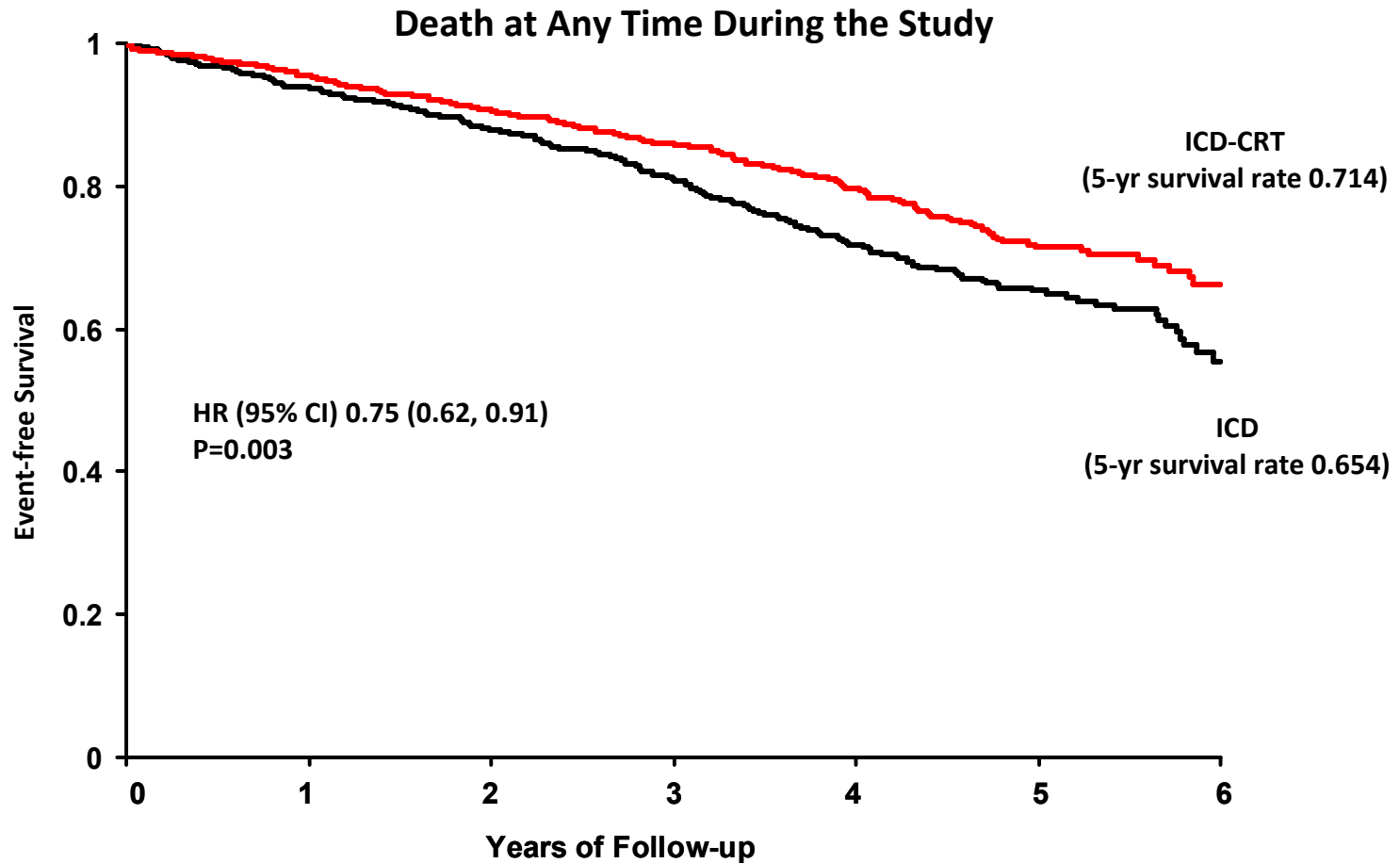


**No. at Risk**

ICD/CRT	894	790	615	429	278	130	41
ICD	904	770	572	384	214	101	19



# Kaplan-Meier Estimates of All cause Mortality



No. at Risk

ICD/CRT	894	849	685	502	333	167	53
ICD	904	841	670	482	289	149	35



# Risk of Death or Hospitalization for Heart Failure

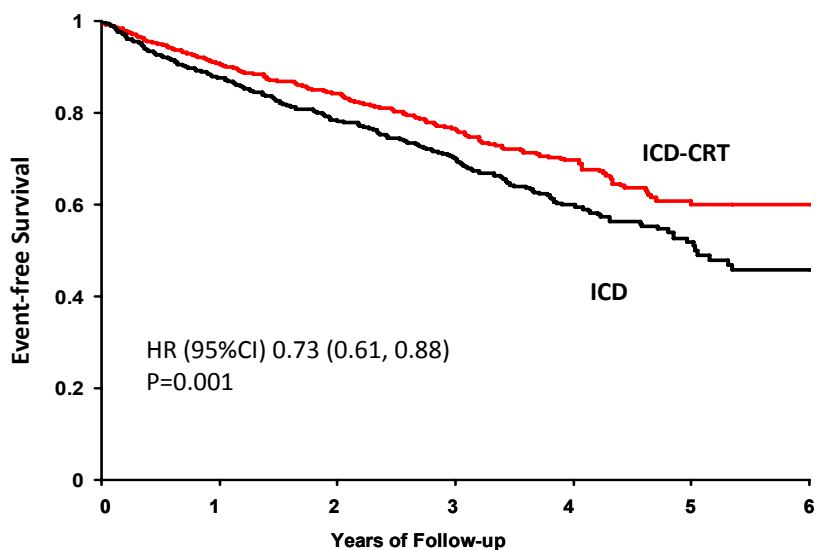
Outcomes	ICD only (N=904)	ICD-CRT (N=984)	Hazard Ratio (95% CI)	P Value
<b>All patients</b>				
<b>Primary outcome</b>				
Death or hospitalization for heart failure	364 (40.3)	297 (33.2)	0.75 (0.64-0.87)	0.0002
<b>Secondary Outcomes</b>				
Death from any cause	236 (26.1)	186 (20.8)	0.75 (0.62-0.91)	0.003
Death from cardiovascular cause	162 (17.9)	130 (14.5)	0.76 (0.60-0.96)	0.019
Hospitalization for heart failure	236 (26.1)	174 (19.5)	0.68 (0.56-0.83)	<0.0001
<b>NYHA class II patients</b>				
No. of patients	730	708		
<b>Primary outcome</b>				
Death or HF hospitalization	253 (34.7)	193 (27.3)	0.73 (0.61-0.88)	0.001
<b>Secondary Outcomes</b>				
Death from any cause	154 (21.1)	110 (15.5)	0.71 (0.56-0.91)	0.006
Death from cardiovascular cause	100 (13.7)	74 (10.5)	0.73 (0.54-0.99)	0.043
Hospitalization for heart failure	159 (21.8)	115 (16.2)	0.70 (0.55-0.89)	0.003
<b>NYHA class III patients</b>				
No. of patients	174	186		
<b>Primary outcome</b>				
Death or hospitalization for heart failure	111 (63.8)	104 (55.9)	0.76 (0.58-0.99)	0.04
<b>Secondary Outcomes</b>				
Death from any cause	82 (47.1)	76 (40.9)	0.79 (0.58-1.08)	0.135
Death from cardiovascular cause	62 (35.6)	56 (30.1)	0.77 (0.54-1.10)	0.154
Hospitalization for heart failure	77 (44.3)	59 (31.7)	0.63 (0.45-0.88)	0.006



# Kaplan-Meier Estimates of the Primary Outcome and Death by NYHA Class

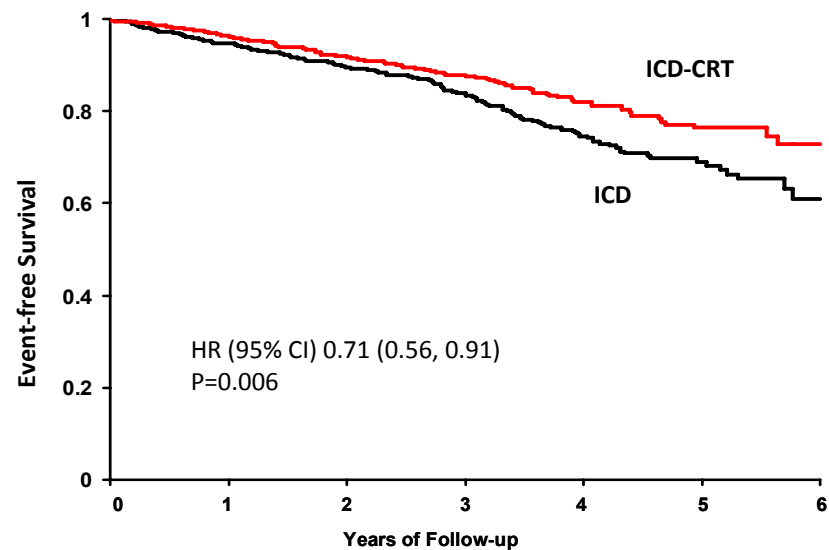
## NYHA Class II

Death or Hospitalization for Heart Failure



No. at Risk	0	1	2	3	4	5	6
ICD/CRT	708	640	488	315	181	70	15
ICD	730	638	465	299	146	57	6

Death from any cause



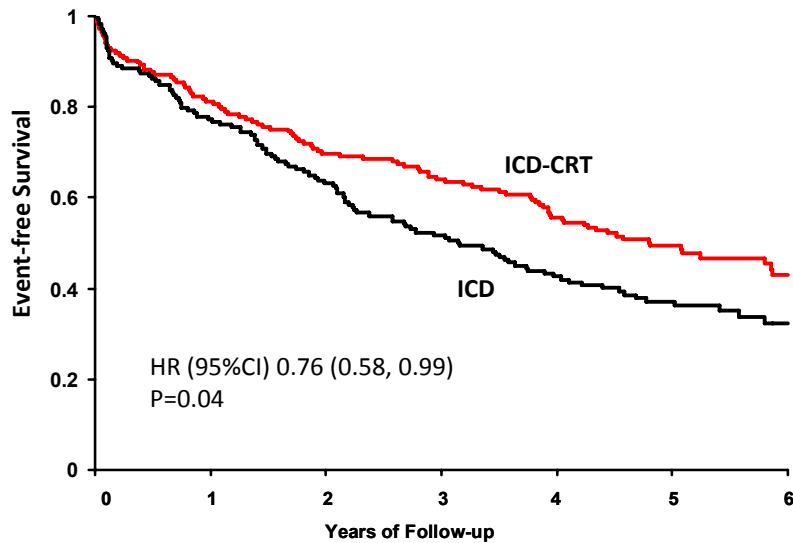
No. at Risk	0	1	2	3	4	5	6
ICD/CRT	708	679	530	361	206	89	20
ICD	730	687	533	366	189	83	13



# Kaplan-Meier Estimates of the Primary Outcome and Death by NYHA Class

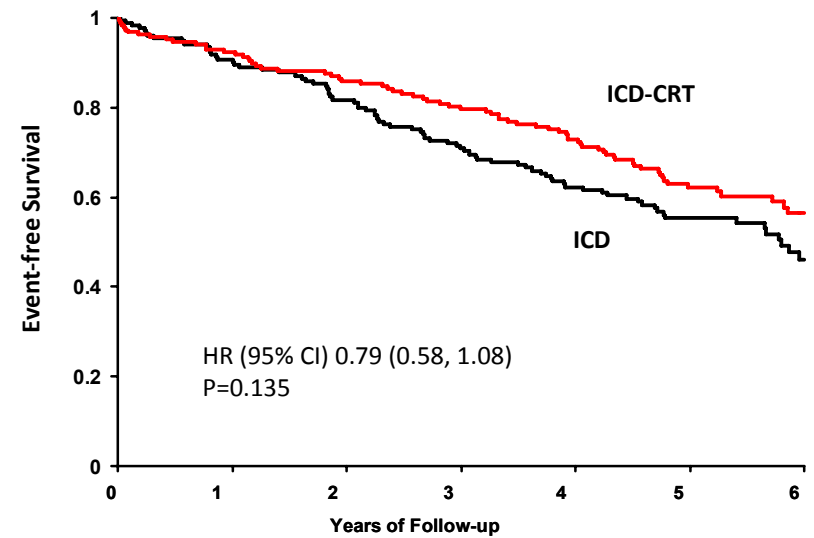
## NYHA Class III

Death or Hospitalization for Heart Failure



No. at Risk	0	1	2	3	4	5	6
ICD/CRT	186	150	127	114	97	60	26
ICD	174	132	107	85	68	44	13

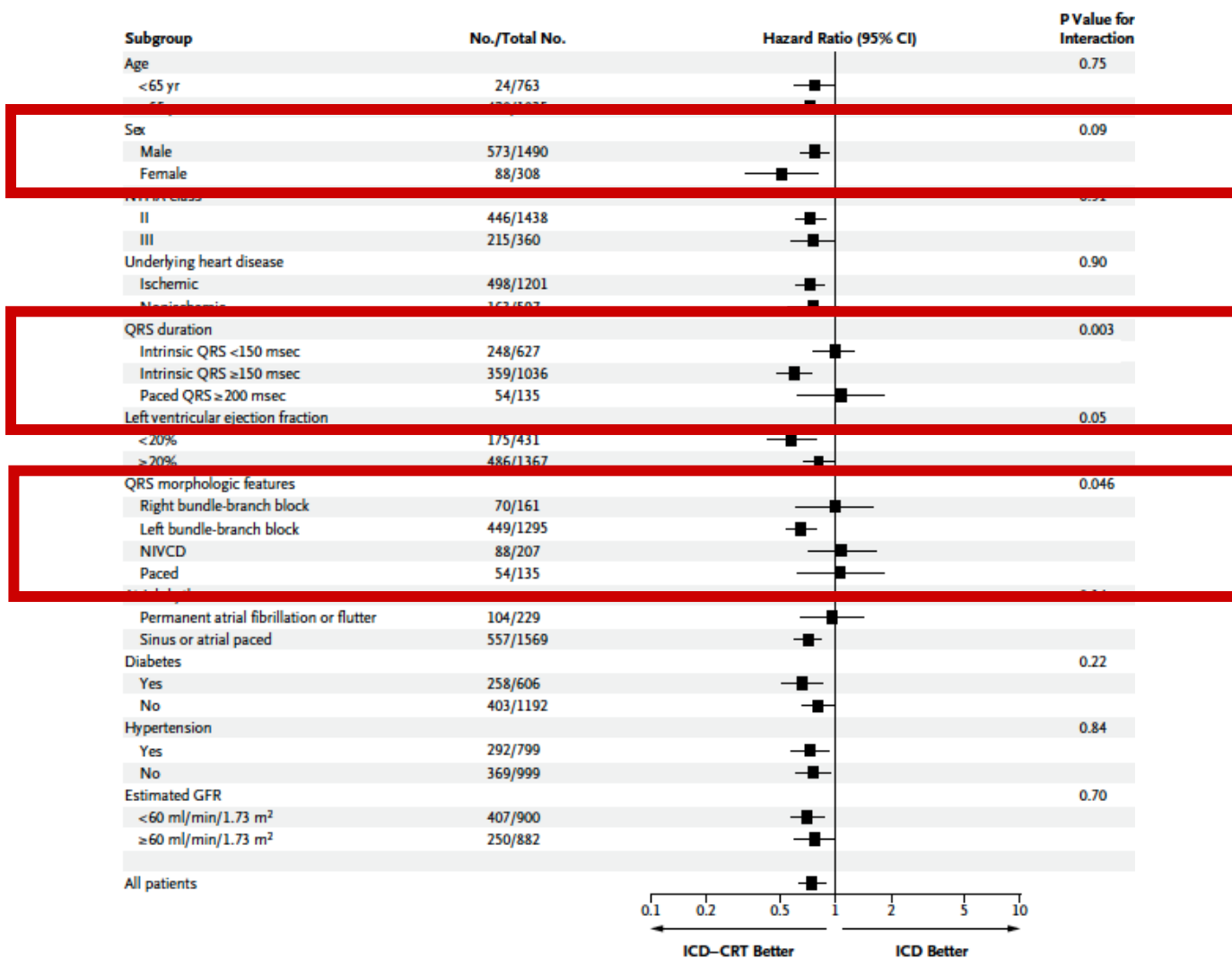
Death from any cause



No. at Risk	0	1	2	3	4	5	6
ICD/CRT	186	170	155	141	127	78	33
ICD	174	154	137	116	100	66	22



# Primary Outcome: Subgroup Analysis





# 30 Days Post Device Implantation Adverse Events

Patients with Adverse Events within 30 Days of Device Implantation			
Adverse Event	ICD (N=899)	ICD-CRT (N=888)	p-value
Hemo/pneumothorax	8 (0.89)	11 (1.24)	0.47
Pocket hematoma	11 (1.22)	14 (1.58)	0.53
Pocket infection	16 (1.78)	21 (2.36)	0.39
Tamponade	2 (0.22)	1 (0.23)	1
Lead dislodgement	20 (2.22)	61 (6.87)	<0.001
Coronary sinus dissection	0 (0.0)	11 (1.24)	<0.001
Device pocket revision	1 (0.11)	4 (0.45)	0.22





# Conclusions

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Among patients with NYHA class II or III heart failure and left ventricular ejection  $\leq 30\%$ , and wide QRS, the addition of CRT to ICD reduces

- Death and hospitalization for heart failure
- All cause mortality
  - with an absolute reduction of 6% over a treatment period of 5 years
  - 14 patients would need to be treated for 5 years to prevent 1 death
- Hospitalization for heart failure
  - 11 patients would need to be treated for 5 years to prevent 1 hospitalization for heart failure



- 
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# Systematic Review

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- **PICO**

- **Population** - mildly symptomatic or advanced HF failure patients
- **Interventions** - CRT/ICD or CRT
- **Comparisons** - CRT vs OMT; CRT/ICD vs ICD
  - (studies comparing CRT with RV pacing or LV pacing not included)
- **Outcome** – mortality

- **Analysis**

- pool RR using random effects model; assess heterogeneity ( $I^2$ )
- optimum information size (OIS) was considered for assessing the minimum amount of information required in the literature for reaching reliable conclusions about CRT



# Flow Diagram: Inclusion and exclusion of Studies

Citations identified in literature  
search after duplicates removed  
**N=2999**

Citations Identified through Other  
Sources (Grey Literature, FDA)  
**N=29**

Total potentially relevant reports identified and  
screened **N= 140**

**N=12** Studies Included in Meta-Analysis

Lozano 2000  
MUSTIC SR 2001  
MIRACLE 2002  
MIRACLE-ICD 2003  
MIRACLE-ICD II 2004  
COMPANION 2004  
CARE-HF 2005  
Vector 2005  
RHYTHM-ICD 2006  
REVERSE (ICD) 2008  
MADIT-CRT 2009  
RAFT 2010

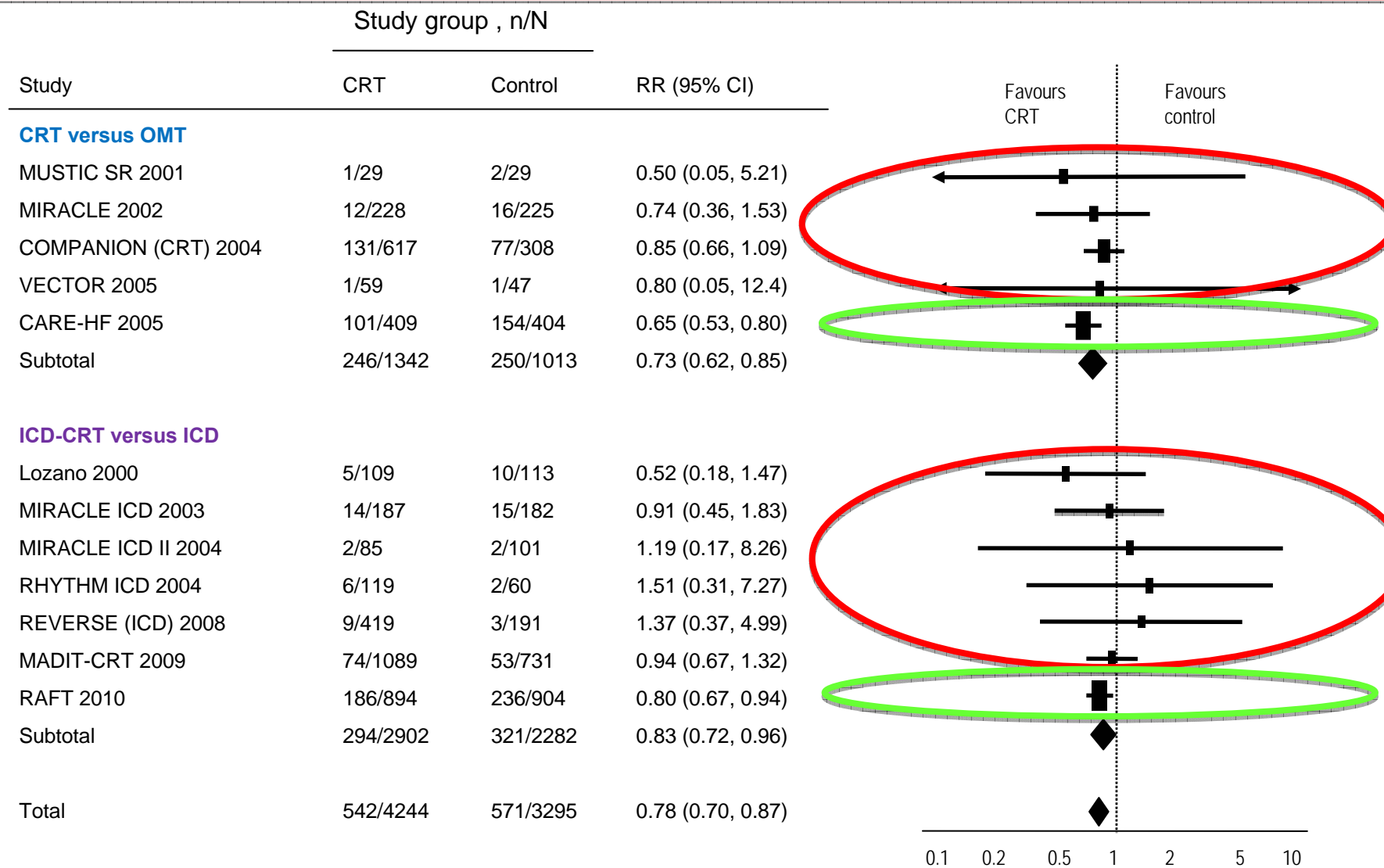
**N=128** Reports Excluded:

Wrong population (n=2)  
Wrong intervention or comparator (n=75)  
No mortality outcome (n=3)  
Wrong study design (n=14)  
Sub-study/Sub-analysis/Extension study (n=17)  
Protocol or rationale paper (n=14)  
Review paper (n=3)



# Meta-analysis of RCT: All cause Mortality

## Effect of CRT added to OMT and CRT added to ICD

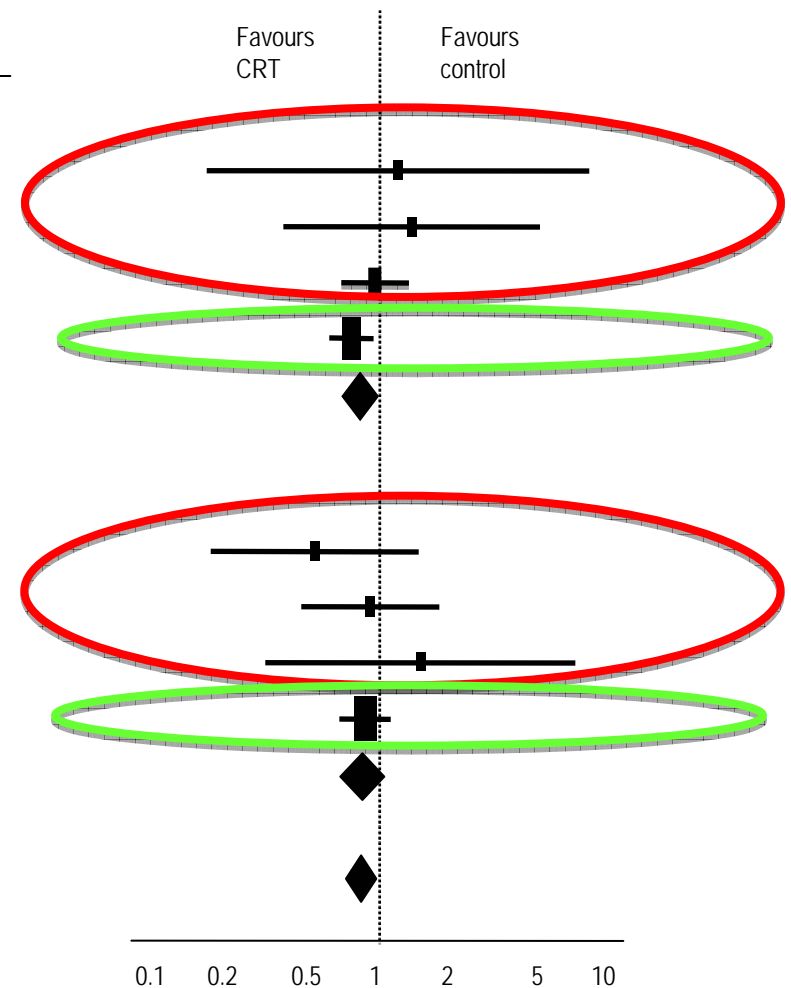




# Meta-analysis of RCT: All cause Mortality

## Effect of CRT added to ICD by NYHA Class

Study	Study group , n/N		RR (95% CI)
	ICD-CRT	ICD	
<b>NYHA Class I and II</b>			
MIRACLE ICD II 2004	2/85	2/101	1.19 (0.17, 8.26)
REVERSE (ICD) 2008	9/419	3/191	1.37 (0.37, 4.99)
MADIT-CRT 2009	74/1089	53/731	0.94 (0.67, 1.32)
RAFT (Class II)	110/708	154/730	0.74 (0.59, 0.92)
Subtotal	195/2301	212/1753	0.80 (0.67, 0.96)
<b>NYHA Class III and IV</b>			
Lozano 2000	5/109	10/113	0.52 (0.18, 1.47)
MIRACLE ICD 2003	14/187	15/182	0.91 (0.45, 1.83)
RHYTHM ICD 2004	6/119	2/60	1.51 (0.31, 7.27)
RAFT (Class III) 2010	76/186	82/174	0.87 (0.69, 1.10)
Subtotal	101/601	109/529	0.86 (0.69, 1.07)
Total	296/2902	321/2282	0.83 (0.72, 0.96)

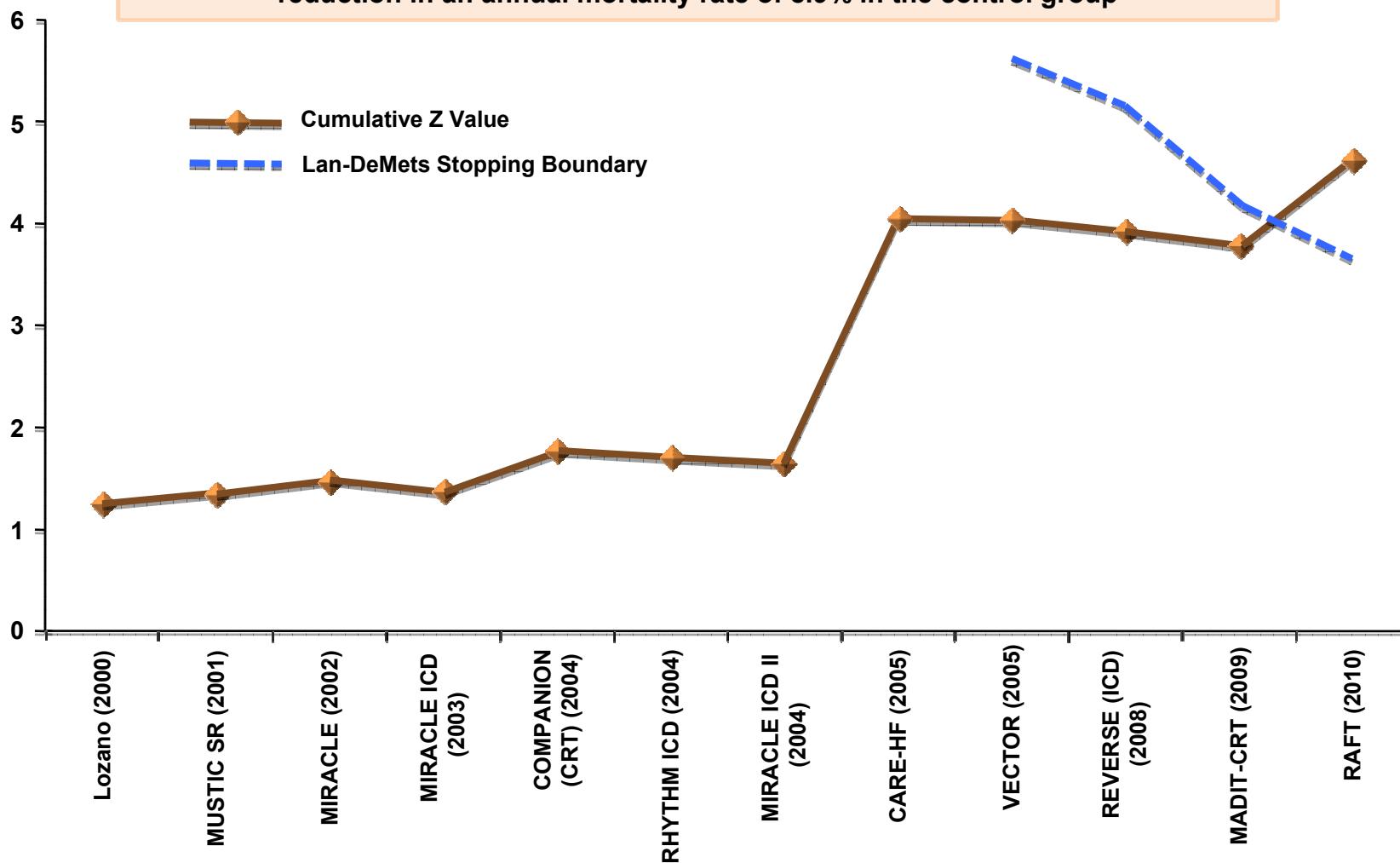




# Optimal Information Size

## Cumulative meta-analysis of CRT added to OMT or ICD

Lan-DeMets monitoring boundary for 2-sided  $\alpha$  value of 0.01, 90% power and a 20% reduction in an annual mortality rate of 8.9% in the control group





# Conclusion

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With this RAFT study results, the cumulative evidence is now conclusive that the addition of CRT to OMT or ICD significantly reduces mortality for patients with mildly symptomatic and advanced heart failure





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1. Brief background information on device therapy
  2. Work leading up to RAFT
  3. Review RAFT design
  4. Review RAFT results
  5. Role of RAFT in determining effect of CRT on mortality



# Future Plan

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- Health economic analysis to determine the cost-effectiveness of CRT
- Network meta-analysis
- Is CRT effective in patients with permanent AF?
- What is the effect of CRT on ventricular arrhythmia and atrial arrhythmia?
- What is the relationship of QRS width and CRT benefit?
- Is CRT effective in patients with RBBB?
- What is relationship between LV lead location and CRT effective?



# **R**esynchronization/Defibrillation for **A**mbulatory Heart **F**ailure **T**rial

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