Sistema Socio Sanitario

Ospedale Niguarda

Regione Lombardia

Device-based optimization improve CRT patient outcome

Dr. Maurizio LUNATI

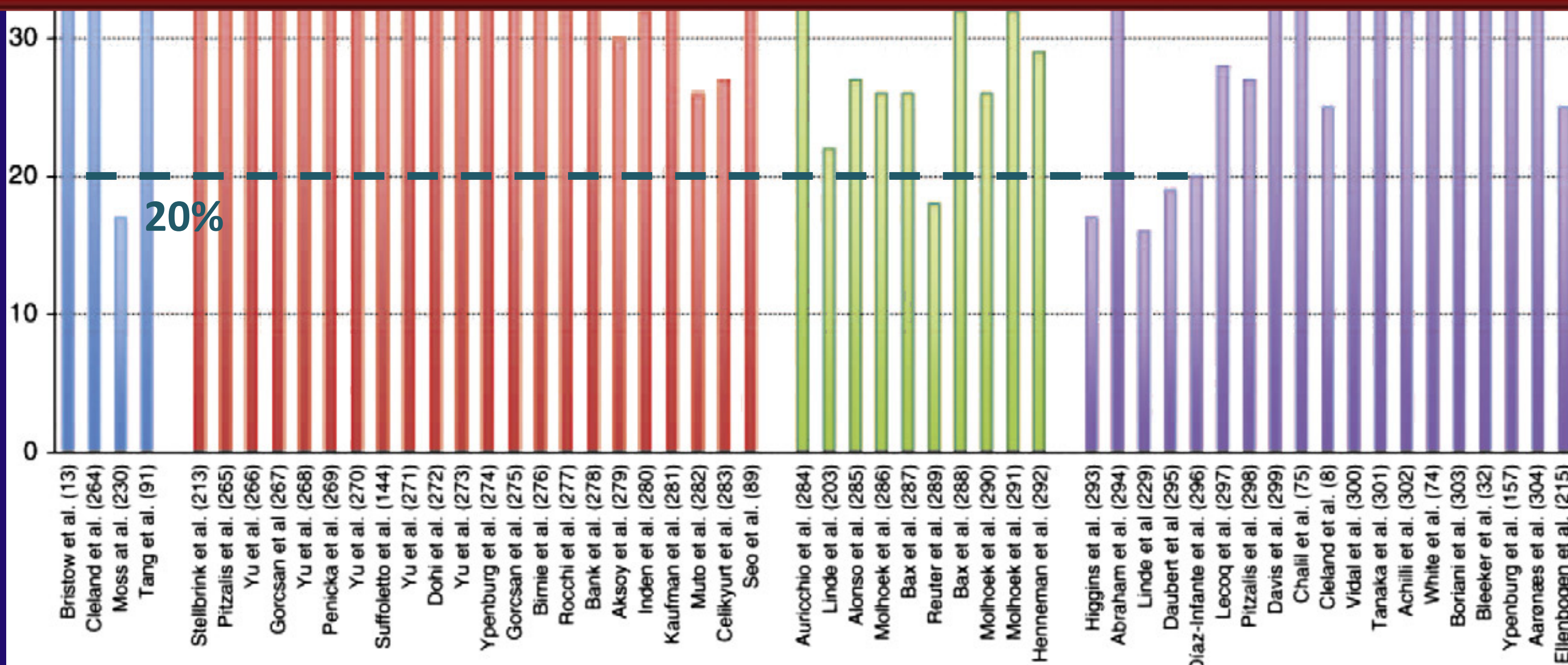
UO Cardiologia 3 - Elettrofisiologia

ASST GOM Niguarda - **MILANO**

NON-Responders in CRT: still an issue …

With an extensive adoption of CRT, it is more & more evident that, even in wide QRS pts, approx. 30% of pts (up to 40-50% in some reports) do NOT reap the expected clinical benefits …

Jaffe LM, Morin DP. ***CRT: history, present status, and future directions.***
Ochsner J. 2014 Winter;14(4):596-607



Daubert JC & al. Heart Rhythm 2012 (CRT consensus document)

The origin of NON-Response is multi-factorial …

… many “mistakes”, from post-implant to FU

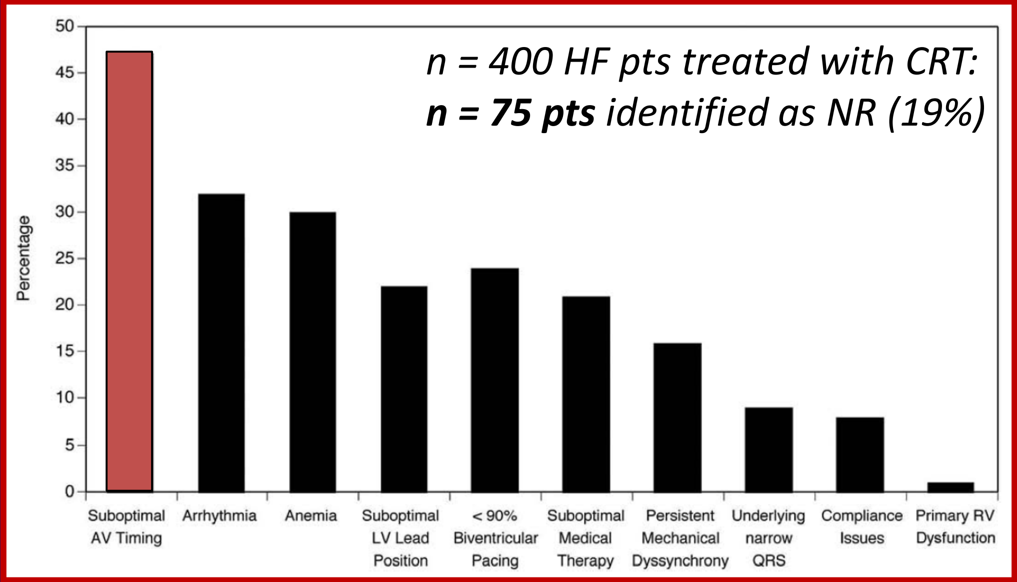
Koneru S & al. JACC 2015;65(10_S) – JACC online

Post-implant CRT (**PRE-DISCHARGE**):
n = 2196 pts with **out-of-the-box** CRT settings:

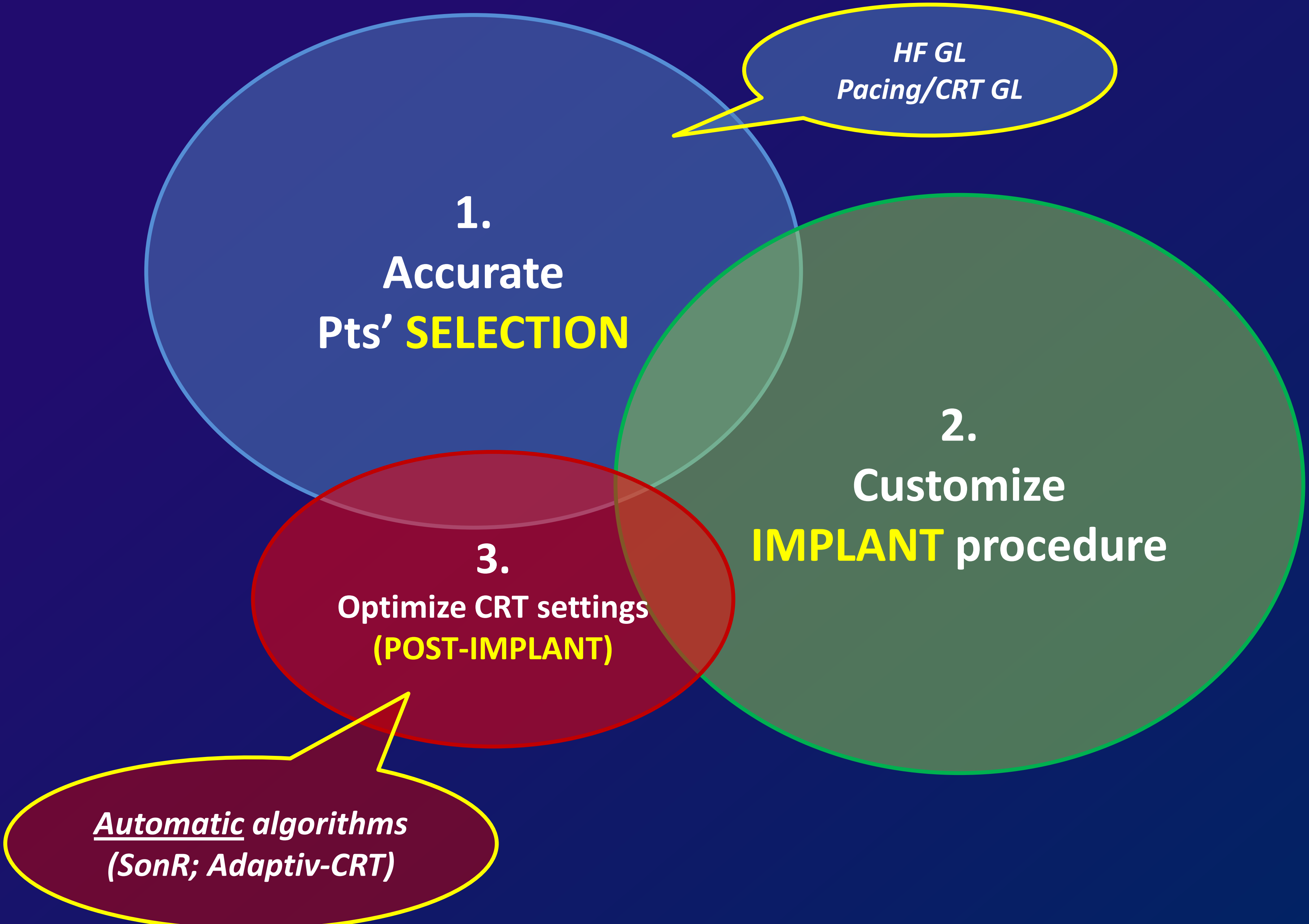
47% of pts present with **diastolic dysfunction** @ echo
(generally correctable by AVD &/or VVD reprogramming)

Mullens W et al. JACC 2009;53:765-73

During **FU** of CRT pts (up to 6M),
47% of Non-Responders
showed NON-optimal AVD …



Leverages to REDUCE the rate of NON-Responders?



Diastolic optimization (AVD) in AVB/CRT pts:
Approaches & Methods

Antonini L & al. Europace 2012 (background & critical review)

Table 1 Methods for atrioventricular setting

References and methods	Methodology	Type	Used in	Compared	Trials
Ismer[5]					
Ritte					RACLE,[3] [3]
					[9]
Me					
Ishi					
Au					
DF					
MI-					
LV					
Ao					
IdP					
Do					
MP					
FPP					
ICG[20]			CRT		
PEA[21]	Mechanical acceleration	Automatic	DDD, CRT	Ritter	CLEAR[22]
Quick Opt[23]	Intracardiac electrogram	Automatic	CRT	Ao VTI, Standard	FREEDOM[24]
EEHF[25]	Intrinsic measures	Automatic	CRT	Standard, Ritter, Ao VTI	
SMARTDelay[26]	Intracardiac electrogram	Automatic	CRT	DFT, Standard	SMARTAV[27]
Standard	Fixed predefined	Fixed	DDD, CRT	Ao VTI, Doppler d*P*/dt, EEHF, DFT, Ritter	

<u>NON-device</u>-based methods

(formulas or iterative)

- Very efficient to **observe ACUTE EFFECTS**, BUT …
- Inter- & Intra-Operator variability
- Controversial outcomes *(long-term performance ?)*
- Optimization in specific in-Lab conditions *(at rest)*
- Resource-consuming *(manpower / equipments)*
- Repeated assessments needed over time ⇒

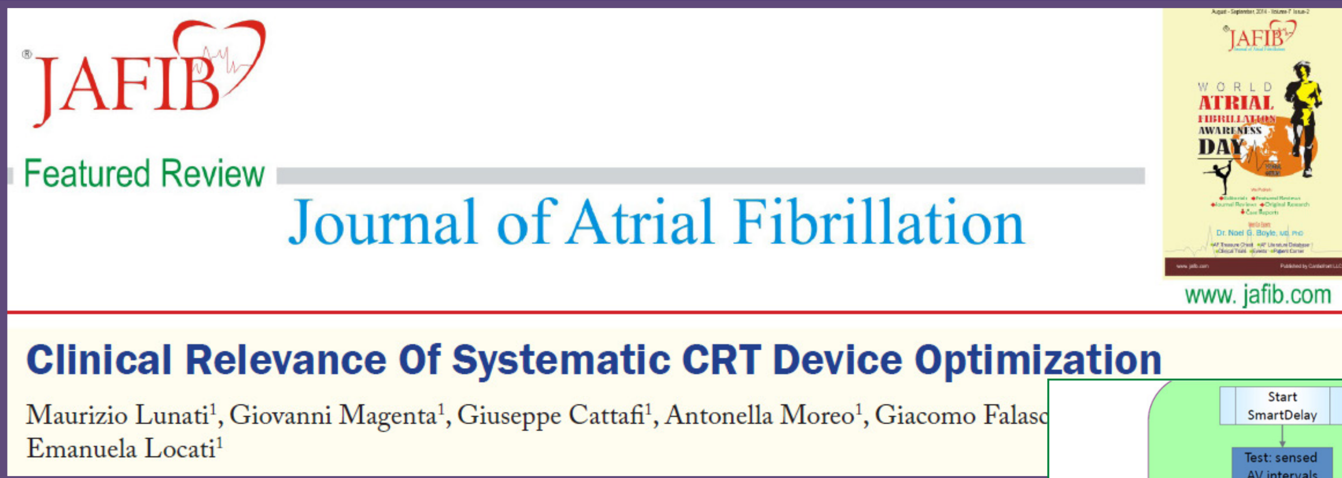
several imits to their applicability in routine clinical practice

FORMULAS (pre-defined)

ITERATIVE methods

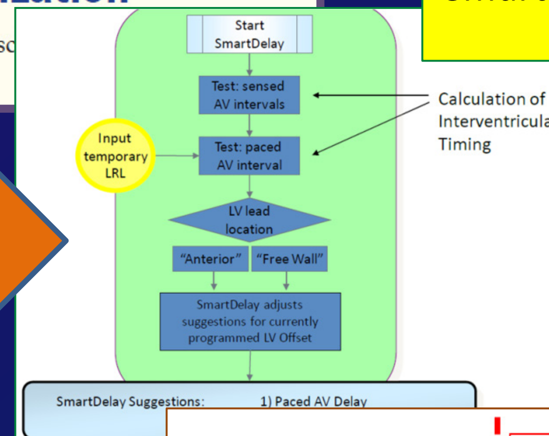
AUTOMATIC methods

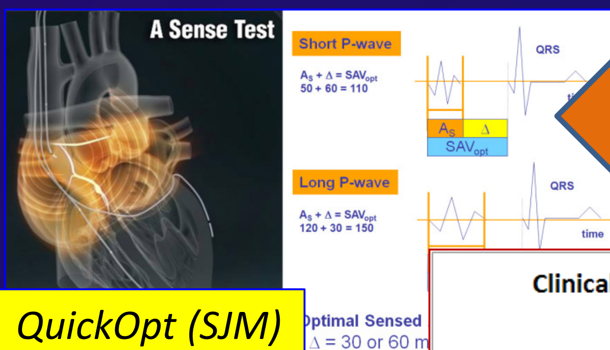
DEVICE-based tools to OPTIMIZE AVD & VVD


JAFIB
Featured Review
Journal of Atrial Fibrillation
www. jafib.com
Clinical Relevance Of Systematic CRT Device Optimization
Maurizio Lunati[1], Giovanni Magenta[1], Giuseppe Cattafi[1], Antonella Moreo[1], Giacomo Falasc
Emanuela Locati[1]

Lunati M & al.
JAFIB 2014 Aug/Sep
Vol. 7(2)

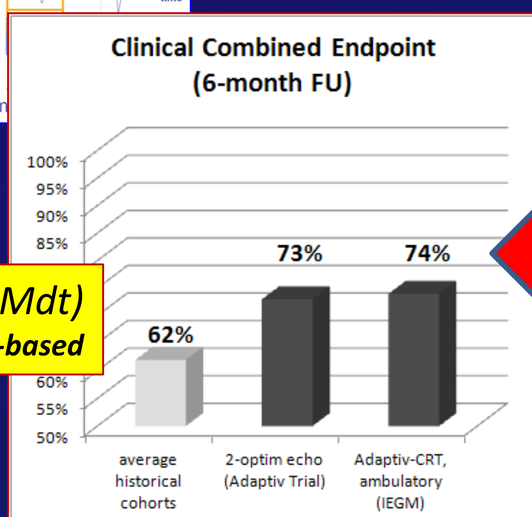
SmartDelay (BSx)
IEGM-based





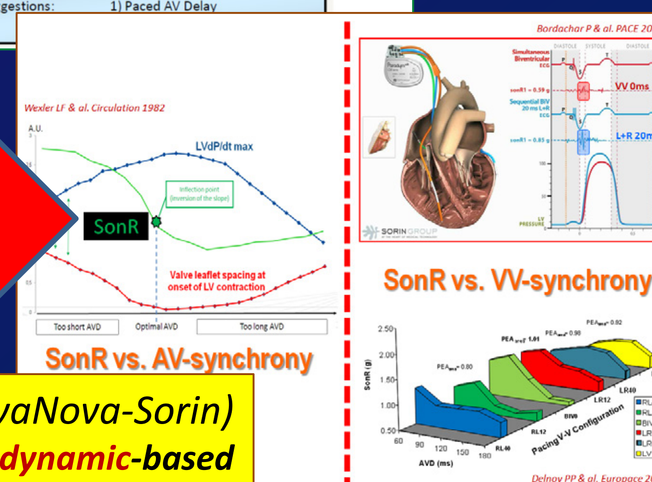
QuickOpt (SJM)
IEGM-based

"In-Clinic" (only @ FU visit)



Adaptive-CRT (Mdt)
IEGM-based

Automatic



SonR (LivaNova-Sorin)
Hemodynamic-based

IEGM-based Optimization Method

AdaptivCRT algorithm (Mdt): PRINCIPLES

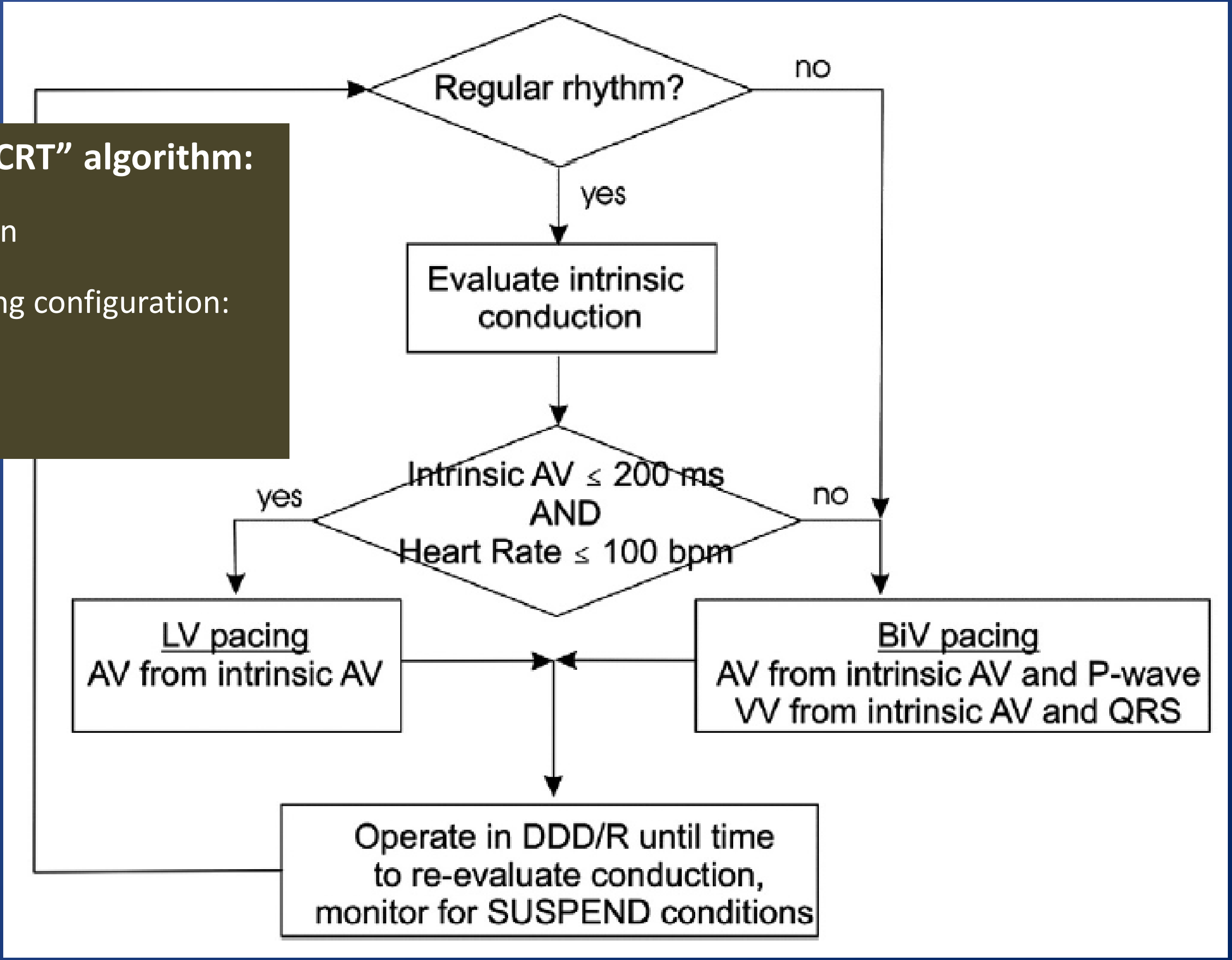
Based upon a PATHOPHYSIOLOGY assumption:

In pts with true-LBBB (with a spontaneous RV activation front), a LV pacing "synchronized" with the RV front is a warranted option, as an alternative to standard BiV pacing

KEY elements of the "AdaptivCRT" algorithm:

1. evaluation of intrinsic conduction

2. determination & update of pacing configuration:
   - LV or BiV
   - AV delays (p/s)
   - VV delay



Krum H & al. Am Heart J 2012

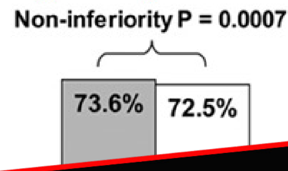
IEGM-based Optimization Method

AdaptivCRT algorithm (Mdt): OUTCOME @ 6M FU

Martin DO &al. Heart Rhythm 2012 Jul [Epub ahead of print]

RESULTS: the study met all 3 non-inferiority 1-ary objectives:

a) **% CLINICAL RESPONSE** to CRT @ 6M (Packer's combined endpoint):



Outcome @ 6M FU:

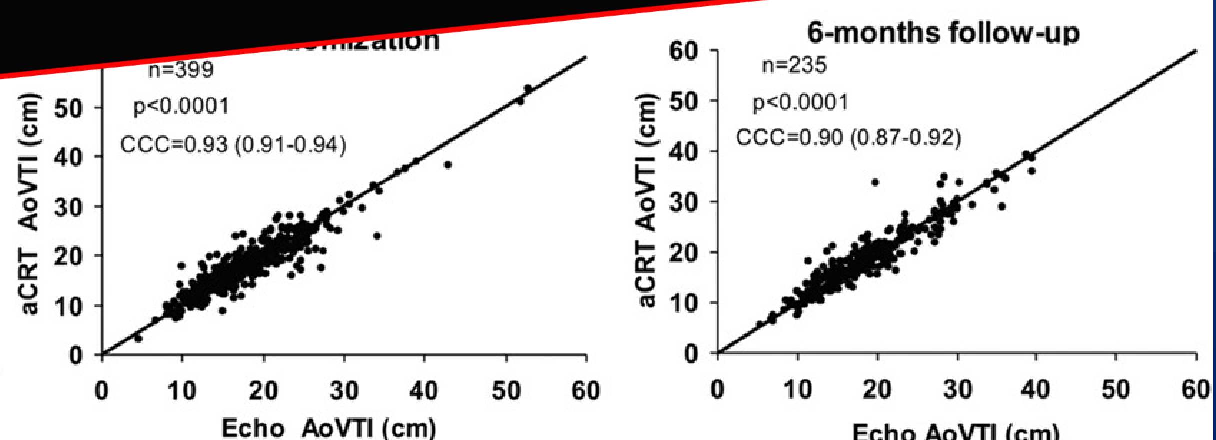
SAFETY &

NON-Inferiority vs. Echo optimization

b) a-CRT an

high Conc

after);



c) a-CRT did **NOT result in inappropriate device settings.**

Adaptive-CRT sub-groups: pts with normal AV conduction

Sub-analisi Adaptive-CRT: "synchronized LV pacing"

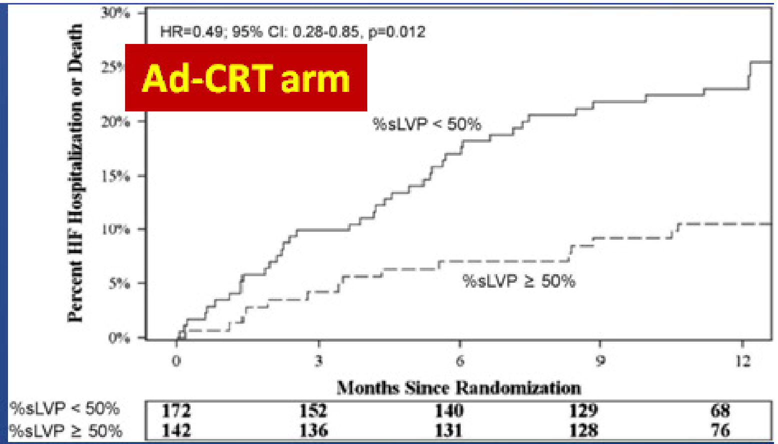
OBJECTIVE

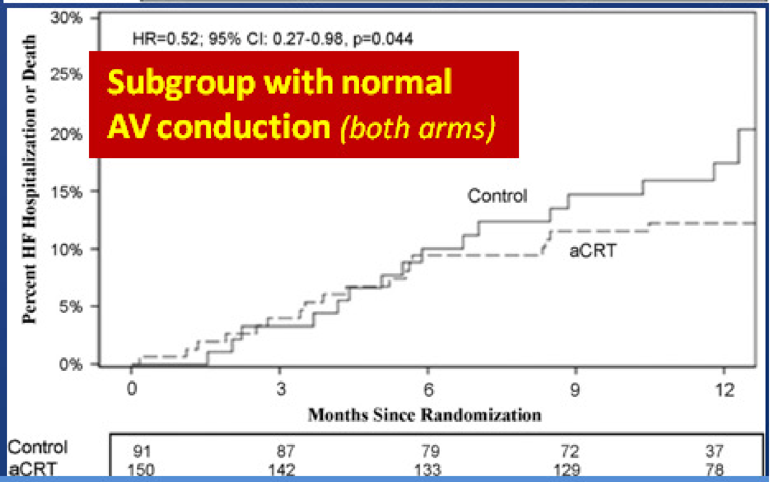
To examine whether synchro-LVP resulted in better clinical outcomes.

METHODS

Stratification by % synchro-LVP and multivariate Cox proportional hazards model used to assess the relationship between % synchro-LVP and clinical outcomes.

Outcomes were compared between pts in the Adaptive-CRT arm and control pts stratified by intrinsic AVD at randomization





Clinical outcomes with synch…
Analysis of the adaptive CRT…

David Birnie, MD, MB, ChB,* Bernd Lemke, M…
Kathy Lai-Fun Lee, MD,‖ Maurizio Gasparini, M…
John Gorcsan III, MD,†† Mahmoud Houmsse, …
Alex Sambelashvili, PhD,§§ David O. Martin, M…

Birnie D & al. Heart Rhythm 2013

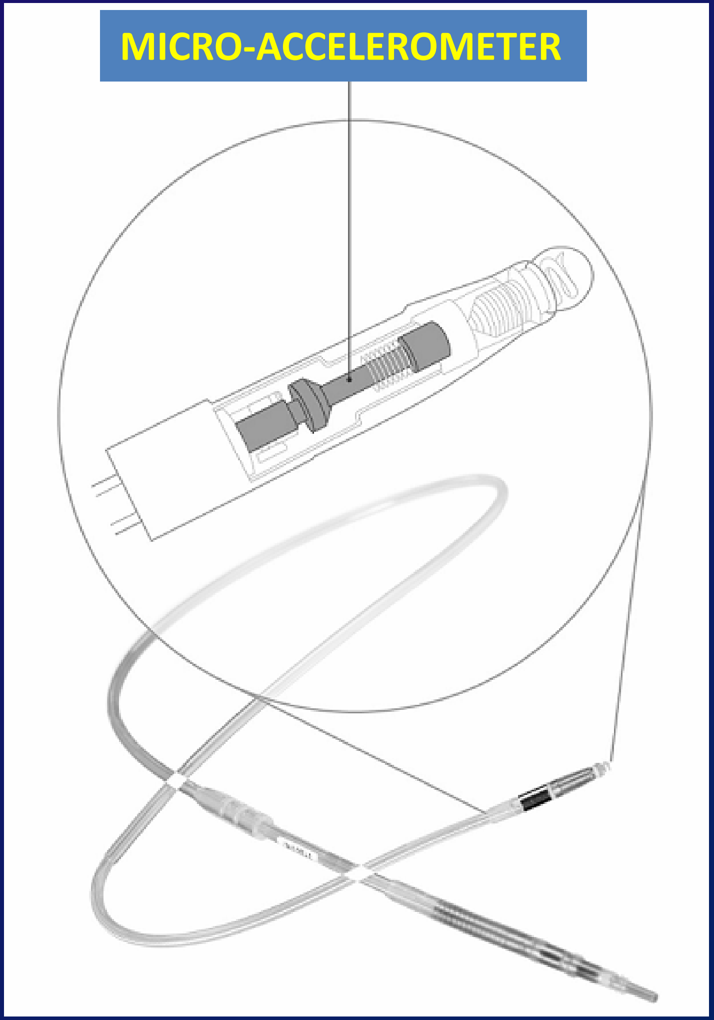
Conclusion

Higher % synchronized-LVP was independently associated with superior clinical outcomes.

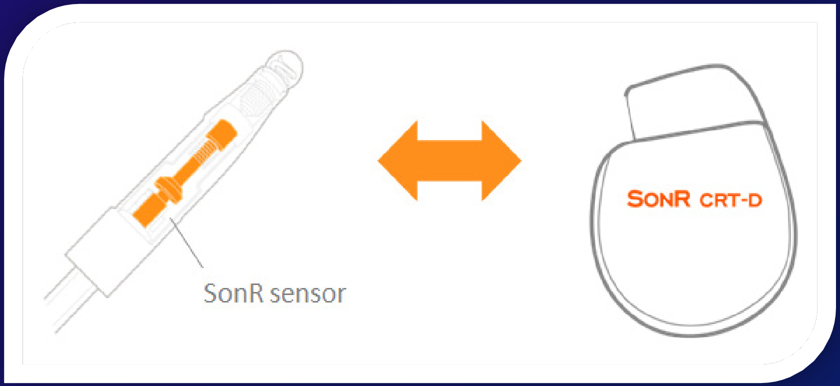
In pts with normal AV conduction, the Adaptive-CRT algorithm provided mostly synchronized-LVP and demonstrated better clinical outcomes compared to echo-optimized BiV-pacing

1. SonR sensor
2. Algorithm for automatic hemodynamic optimization

SonR sensor
It consists of a **micro-accelerometer** realized in the tip of the SonRtip atrial lead. The signal detected by the sensor correlates with a **global myocardial contractility**

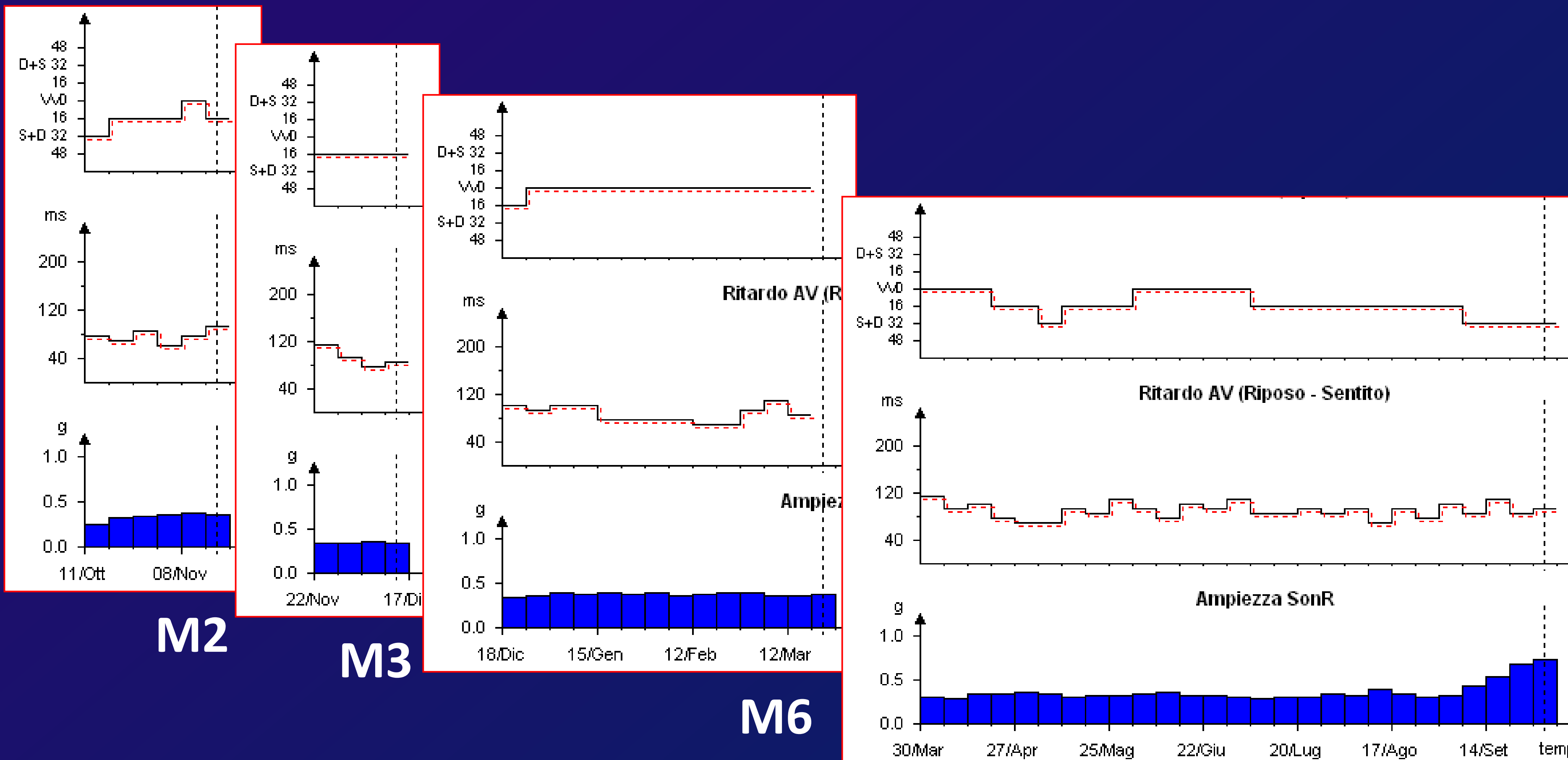


SonR SYSTEM (SonRtip + CRT-D):
is able to **optimize** (every week, **automatically**) the AV & VV delays, at rest & under effort



WEEKLY-BASED info (SonR SYSTEM telemetry):

- Trend of OPTIMAL AVD & VVD
- Trend of average contractility



M2 M3 M6 M12

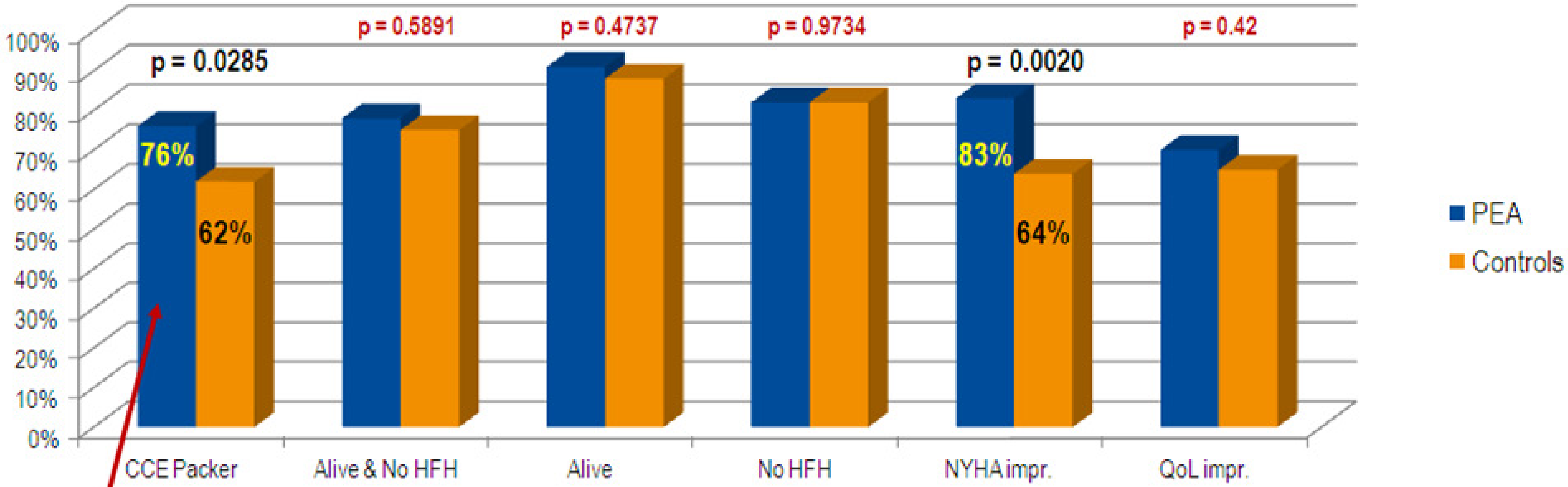
FU of a patient implanted with a CRT-D SonR SYSTEM:

Telemetry interrogation of the device @ 2, 3, 6 and 12M post-implant

CLEAR pilot trial *(ITT analysis: n=100 SonR vs. n=99 Controls)*

CLINICAL EFFICACY (SonR vs. Std of Care)

Ritter P & al. Europace 2012 (risultati studio CLEAR)



COMBINED:
All-cause Mortality / HF-events / NYHA / QoL

Conclusion

The optimization of CRT by an automated PEA-based method in sinus-rhythm patients significantly improved clinical outcomes from CRT-P after 1 year of follow-up, mainly driven by improvements in NYHA class. These encouraging observations warrant further studies of the PEA sensor on a larger scale, using CRT-D devices to comply with current international treatment guidelines.

Ritter P & al. A randomized pilot study of CRT optimization in SR pts using a PEA sensor vs standard methods. Europace 2012.

CLEAR pilot trial LIMITATIONS → Respond-CRT

	CLEAR (2005-10)	
Incl Criteria / Clinical EP	NYHA III/IV / Packer's combined	
Technology	(**PEA**) **CRT-P** + MiniBest, RV tip	
Size (n)	n = 286 pts	
Target (randomization)	PEA vs Clinical Practice	
NYHA & QoL	**NO BLINDING**	
Clinical Efficacy **@ 12M FU**	76% vs 62% (ITT, favors PEA)	

The **RESPOND-CRT** study was conducted to **confirm** the outcomes from the CLEAR pilot trial, in a more extended population of **CRT-D pts** and with a more **robust methodology**, to show that:

- the **SonRtip** lead is **SAFE**
- the AV/VV Automatic Optimization with **SonR is at least EFFECTIVE as Echo optimization** in improving the **rate of clinical response** to CRT

Design & INCLUSION criteria

RESPOND-CRT STUDY

DESIGN

International, multicenter, randomized (2:1), prospective, double-blinded trial

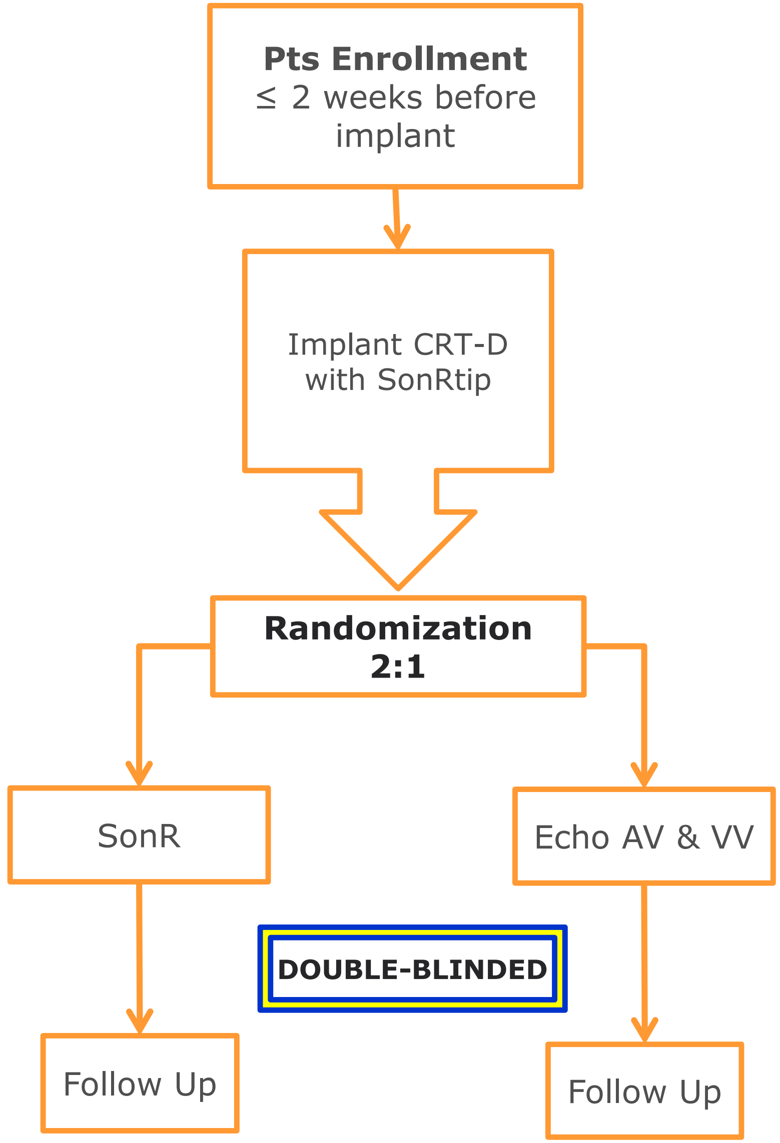
PATIENTS

→ LVEF ≤ 35%
→ QRS ≥ 120 ms (LBBB) or QRS ≥ 150 ms (Non-LBBB)
→ NYHA III or IV-ambul.
→ Permanent AF pts excluded

ENROLLMENT

→ 125 Centres in Europe, USA, Australia
→ Jan 2012 – Oct 2014
→ End of long-term FU (Oct 2016)

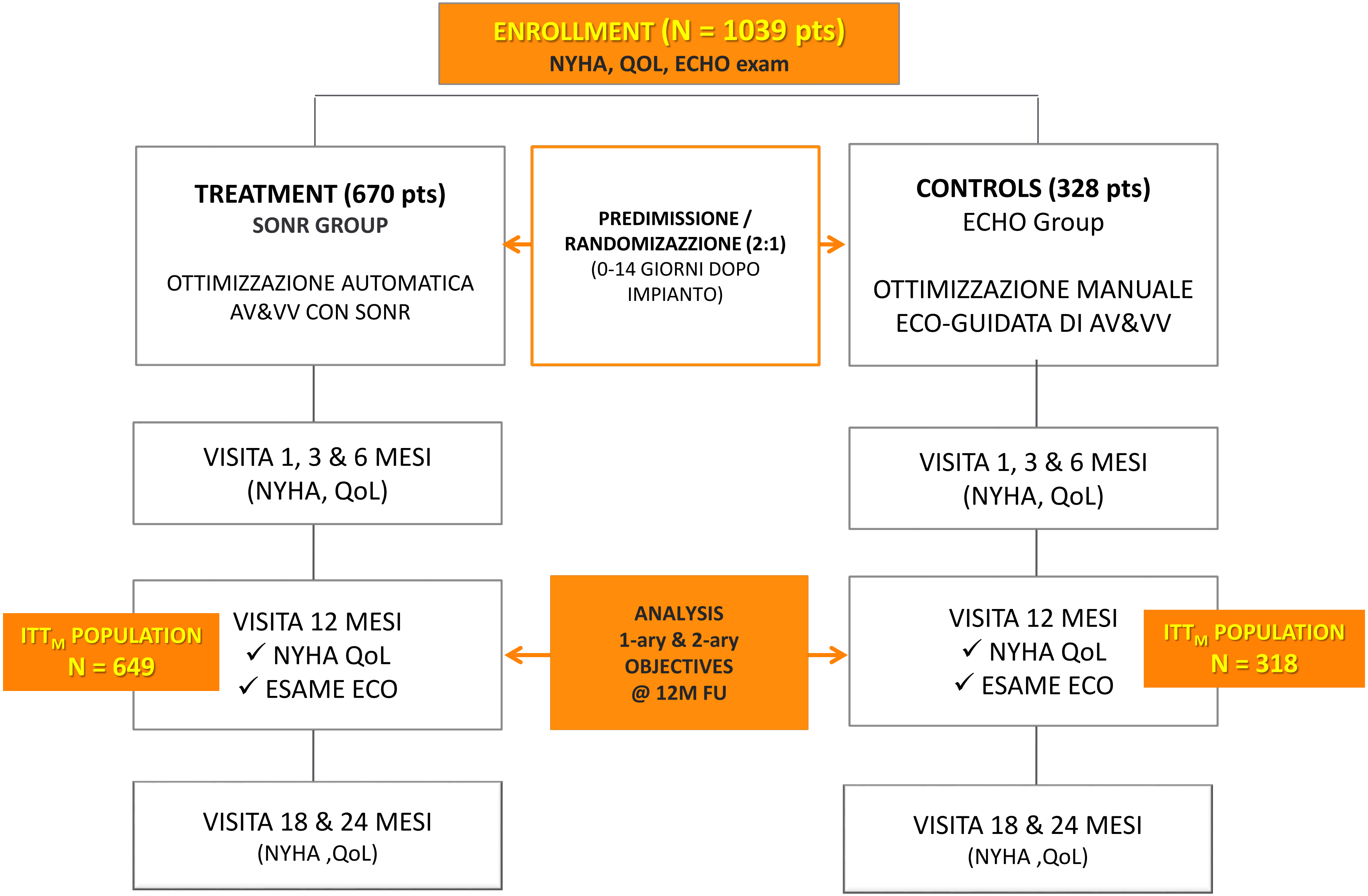
Clinical Endpoint:
DOUBLE-BLINDED judgment
(independent team of
BLINDED investigators)



Brugada J, Brachmann J, Delnoy PP et al. Automatic optimizartion of cardiac resynchroization therapy using SonR-rationale and design of the Clinical trial of the SonRtip lead and Automatic AV-VV optimization Algorithm in the Paradym RF SonR CRT-D (RESPOND CRT) trial. Am Heart J , 2014 ; Vol 167 (4):429-435

Flowchart of included pts

RESPOND-CRT STUDY



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Objectives & Methods

RESPOND-CRT STUDY

1-ARY OBJ, EFFICACY

Non-inferiority in the rate of clinical response, based on a clinical combined criterion assessed @ 12M FU (non-inferiority margin: 10%)

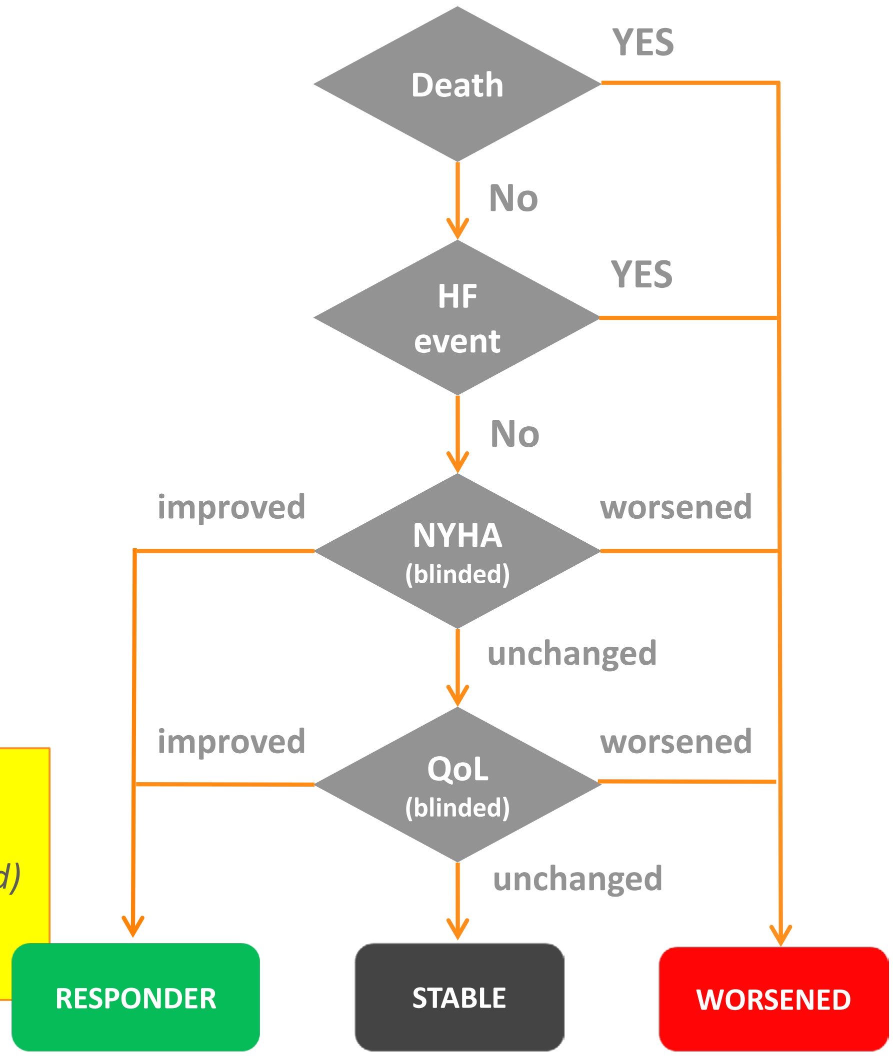
1-ARY OBJ, SAFETY

Free from SonRtip lead-related complications, acutely (0-3 months) & chronically (4-12 months)

2-ARY OBJs

- → HFH & all-cause deaths
- → % of worsened pts
- → 1-ary endpoint subgroups analysis

CRT response assessed by using a hierarchical clinical combined endpoint



"Wide" definition of HF event:

1. *Unplanned HFH*
2. *Urgent visit or ER admission (HF-related)*
3. *Invasive intervention (HF-related)*
4. *Start EV therapy for acute HF*

Brugada J, Brachmann J, Delnoy PP et al. Automatic optimizartion of cardiac resynchroization therapy using SonR-rationale and design of the Clinical trial of the SonRtip lead and Automatic AV-VV optimization Algorithm in the Paradym RF SonR CRT-D (RESPOND CRT) trial. Am Heart J , 2014 ; Vol 167 (4):429-435

Demography (population @ baseline)

RESPOND-CRT STUDY

PTS' CHARACTERISTICS	SonR (n=670)	Echo AV & VV (n=328)	P value
Age (yrs)	**67.2 ±10.2**	**66.6 ±10.2**	0.34
Males	**70.4%**	**65.5%**	0.12
NYHA III	**96.6%**	**95.4%**	0.027
LVEF %	**29.4 ±8.4%**	**29.6±8.0%**	0.78
QRS (ms)	**160.7 ±23.1 ms**	**160.0 ±21.9 ms**	0.65
LBBB	**84.0%**	**88.4%**	0.06
Ischemic CMP	**45.5%**	**42.5%**	0.37
Beta-blockers	**89.4%**	**92.1%**	0.18
ACEI, substit. or ARBs	**89.9%**	**88.7%**	0.58
AF history	**15.6%**	**17.3%**	0.49
Diabetes	**37.3%**	**41.8%**	0.17
Moderate Renal Dysf. (*)	**22.8%**	**24.7%**	0.51

(*) exclusion criterion: GFR<15 ml/min/1.73m^2 or on dialysis

Brugada J et al. Late-Breaking Clinical Trials
Clinical Response to CRT with theSonR Hemodynamic Sensor:
The RESPOND-CRT Randomized Trial,
Presented at Heart Rhythm 2016 - 05/05/16.

1-ary objective: **SAFETY endpoint**

RESPOND-CRT STUDY

Rate of dislodgment (0 → 3M) = 1%

SonRtip success rate **at Implant**	SonRtip Complic. Free Rate **0 → 3 months**	SonRtip Complic. Free Rate **4 → 12 months**
99,8%	**98,5%**	**99,8%**
	vs 91% (obj) $p<0.001$	vs 94% (obj) $p<0.001$

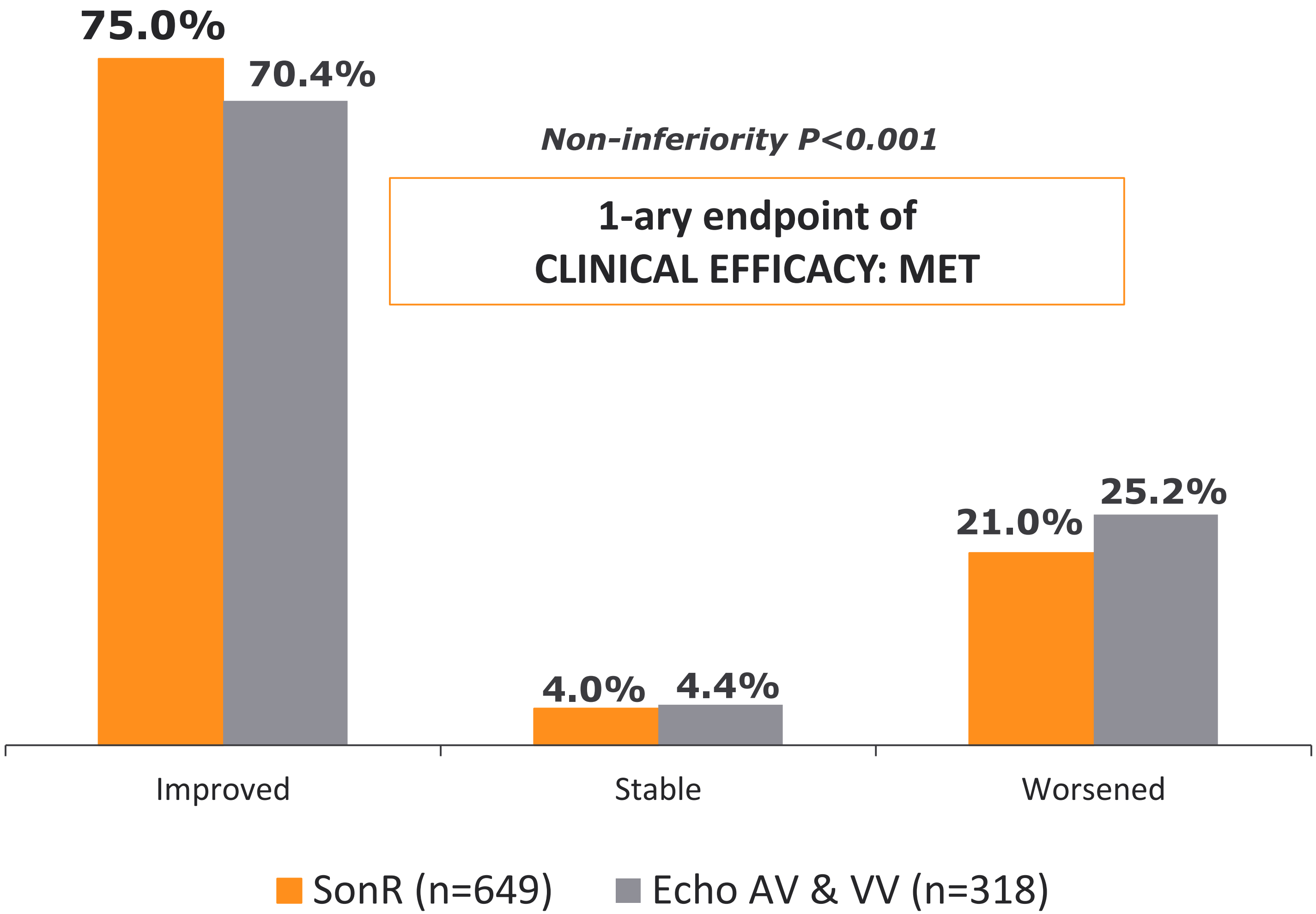
1-ary SAFETY endpoint: MET
(acute & chronic conditions)

Brugada P et al. Late-Breaking Clinical Trials I, Clinical Response to Cardiac Resynchronization Therapy with theSonR Hemodynamic Sensor: The RESPOND-CRT Randomized Trial, Presented at Heart Rhythm 2016 - 05/05/16.

1-ary efficacy obj: **CLINICAL EFFICACY * @ 12M FU**

RESPOND-CRT STUDY

***** % of TRUE RESPONDERS (only "IMPROVED" pts)***

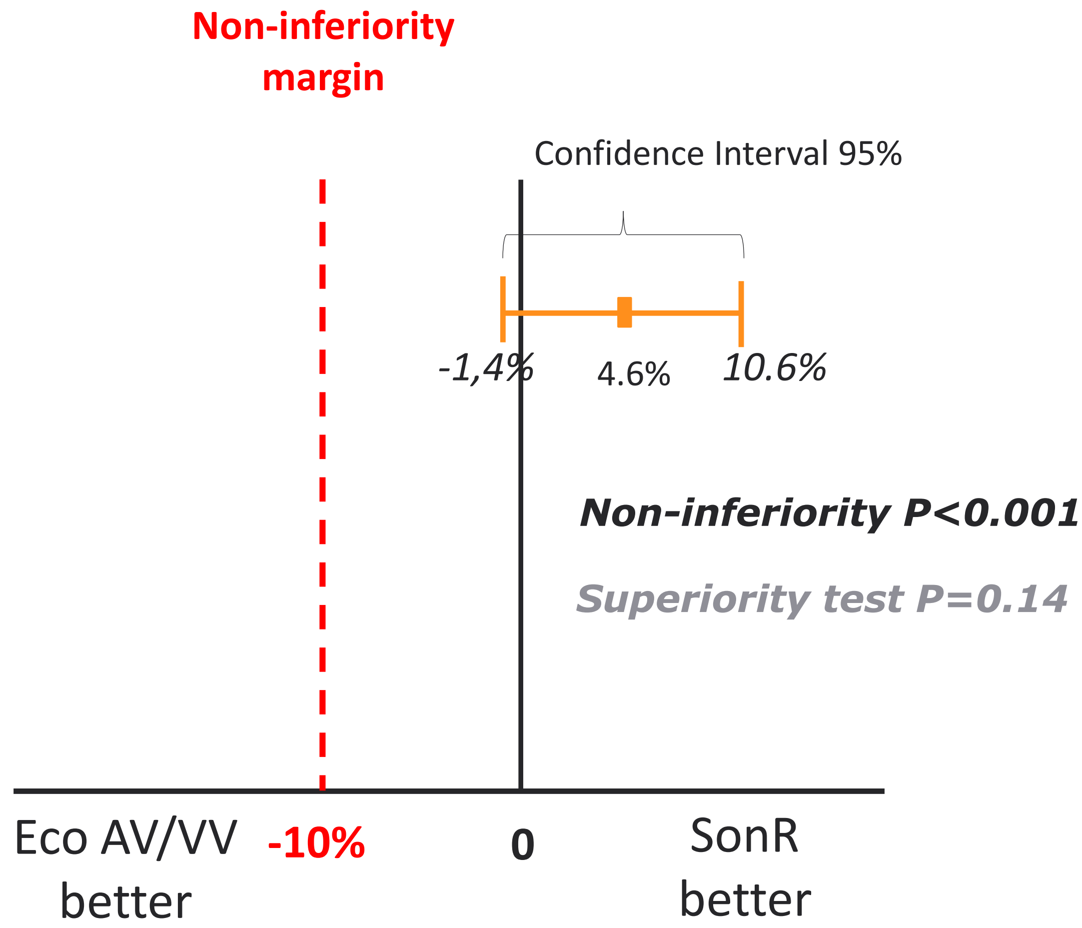


Non-inferiority P<0.001

1-ary endpoint of
CLINICAL EFFICACY: MET

Brugada P et al. Late-Breaking Clinical Trials I, Clinical Response to Cardiac Resynchronization Therapy with theSonR Hemodynamic Sensor: The RESPOND-CRT Randomized Trial, Presented at Heart Rhythm 2016 - 05/05/16.

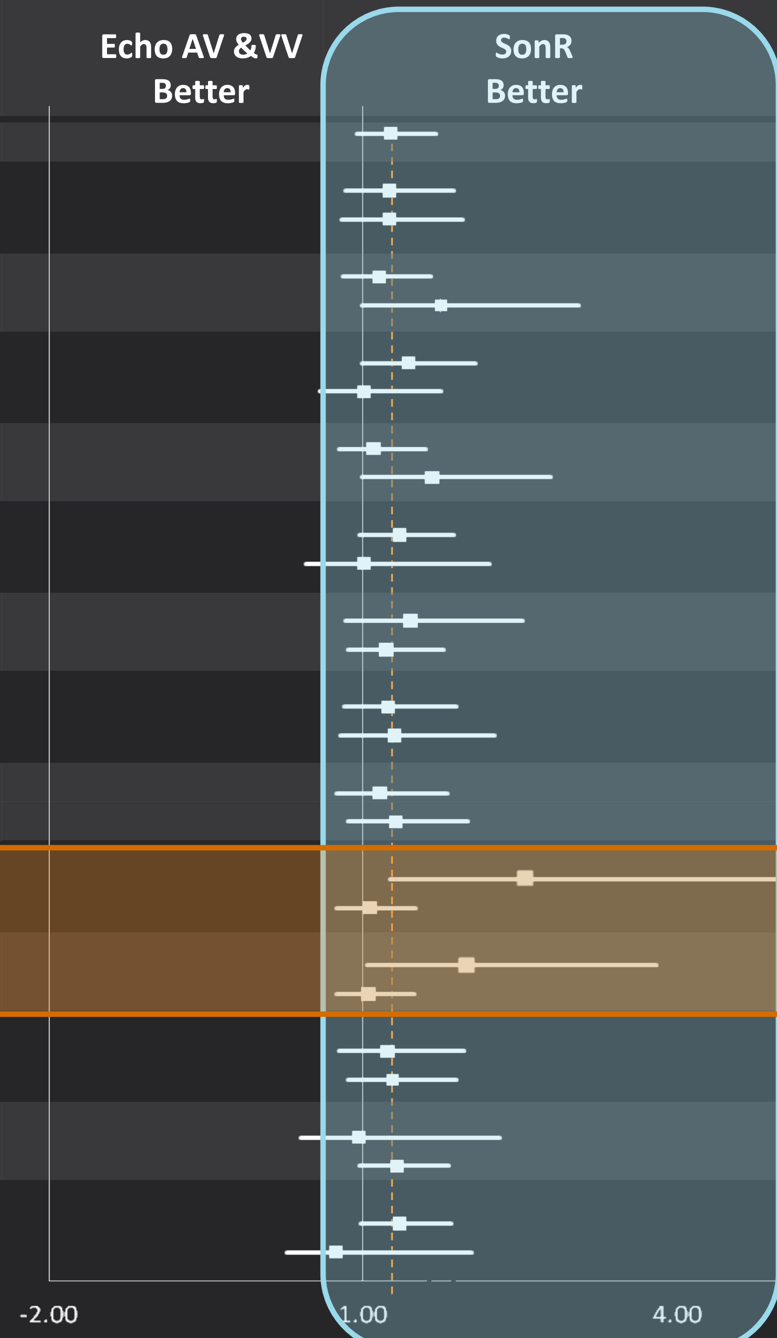
Delta (Rate of Clinical Response) @ 12M FU



Non-inferiority one-sided test (margin of 10%), P-values <0.025 were considered statistically significant

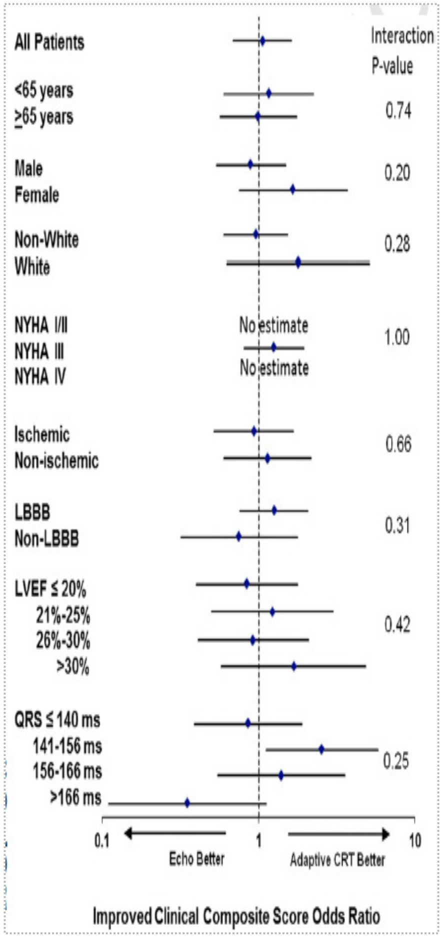
SUBGROUPS: benefit consistently in favour of SonR arm …

VARIABLE		SonR (N=649)	Echo AV & VV (N=318)	P value	Odds Ratio
Overall		75.0%	70.4%		1.26
Age	<68.5years	72.6%	68.1%	0.99	1.25
	≥68.5 years	77.3%	73.2%		1.25
Gender	Male	71.6%	68.6%	0.23	1.15
	Female	83.1%	73.9%		1.74
BMI	<30 kg/m²	76.5%	69.5%	0.30	1.43
	≥30kg/m²	72.2%	72.0%		1.01
LVEF	> 25%	74.7%	72.7%	0.21	1.10
	≤25%	75.8%	65.3%		1.66
QRS morph.	LBBB	76.8%	71.1%	0.51	1.35
	Non LBBB	66.0%	65.8%		1.01
QRS duration	<150 ms	68.0%	59.5%	0.62	1.45
	≥150 ms	77.9%	74.3%		1.22
PR interval	≤200 ms	78.0%	74.0%	0.89	1.24
	>200 ms	71.6%	65.9%		1.30
Cardiomyopathy	Ischemic	69.9%	66.7%	0.70	1.16
	Non-Ischemic	79.1%	74.3%		1.31
History of AF	Yes	70.2%	48.1%	0.03	2.55
	No	75.9%	74.8%		1.06
Renal dysfunction	Yes	61.9%	46.3%	0.07	1.89
	No	79.1%	78.6%		1.03
Diabetes	Yes	72.3%	67.9%	0.90	1.23
	No	76.8%	72.2%		1.28
Smoker	Yes	69.6%	70.6%	0.49	0.96
	No	75.9%	70.4%		1.32
Beta Blocker	Yes	76.1%	70.3%	0.27	1.35
	No	65.7%	72.0%		0.74



Note: P values <0.15 were considered significant for interaction

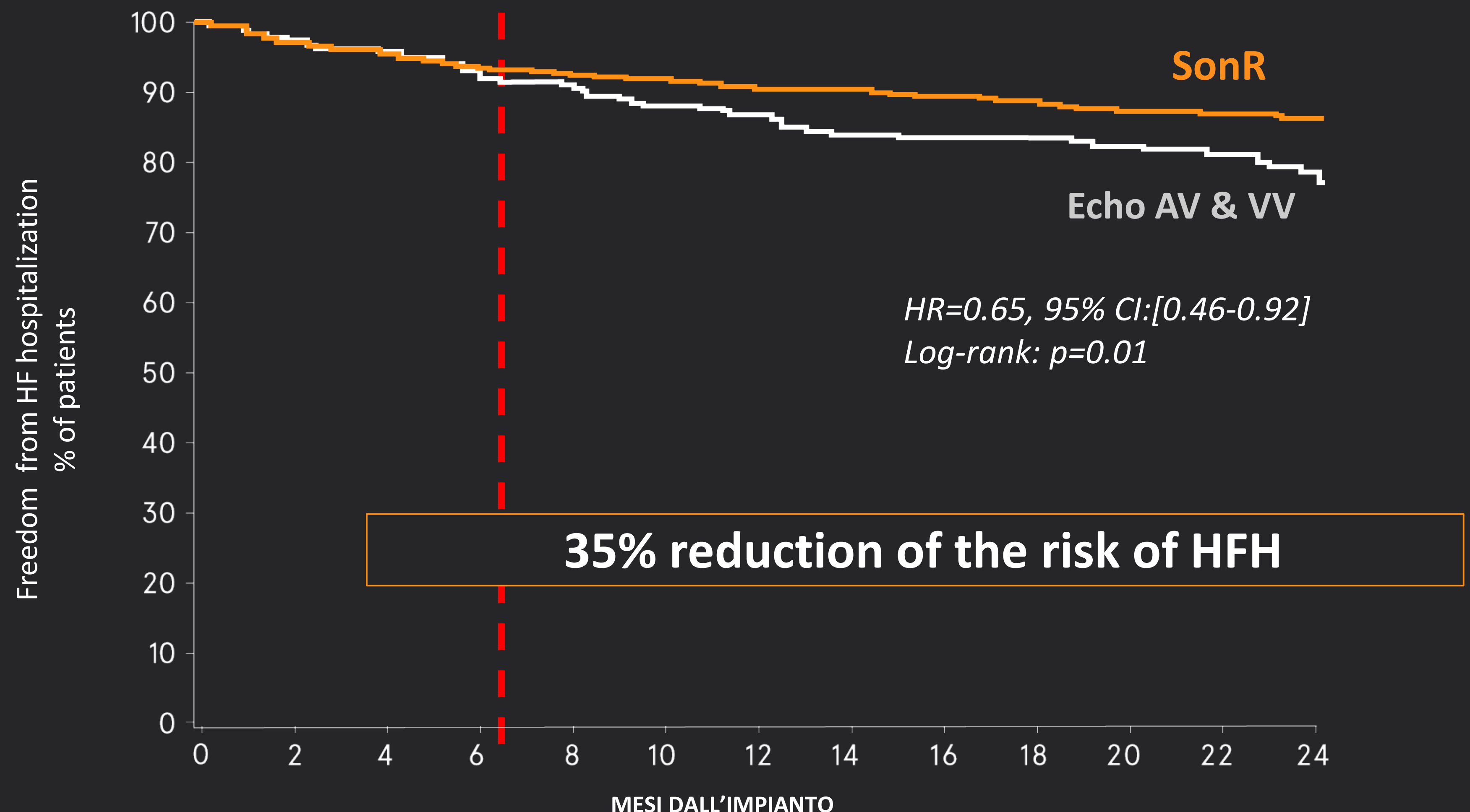
SonR vs. Adaptive-CRT (subgroups analysis)

	SonR	Adaptive CRT
Clinical response	**75% @ 12M FU** (2) (Non-Inf. vs. Echo AV-VV)	**73.5% @ 6M FU** (1) (Non-Inf. vs. Echo AV-VV)
Subgroup analysis	Echo better SonR better	

1. Results of the adaptive CRT trial. Martin DO et al. Heart Rhythm 2012
2. Respond-CRT results. Brugada J et al. HRS 2016 LBCT Session I

(2-ary endpoint, HFH @ 24M FU)

Free from HF Hospitalization



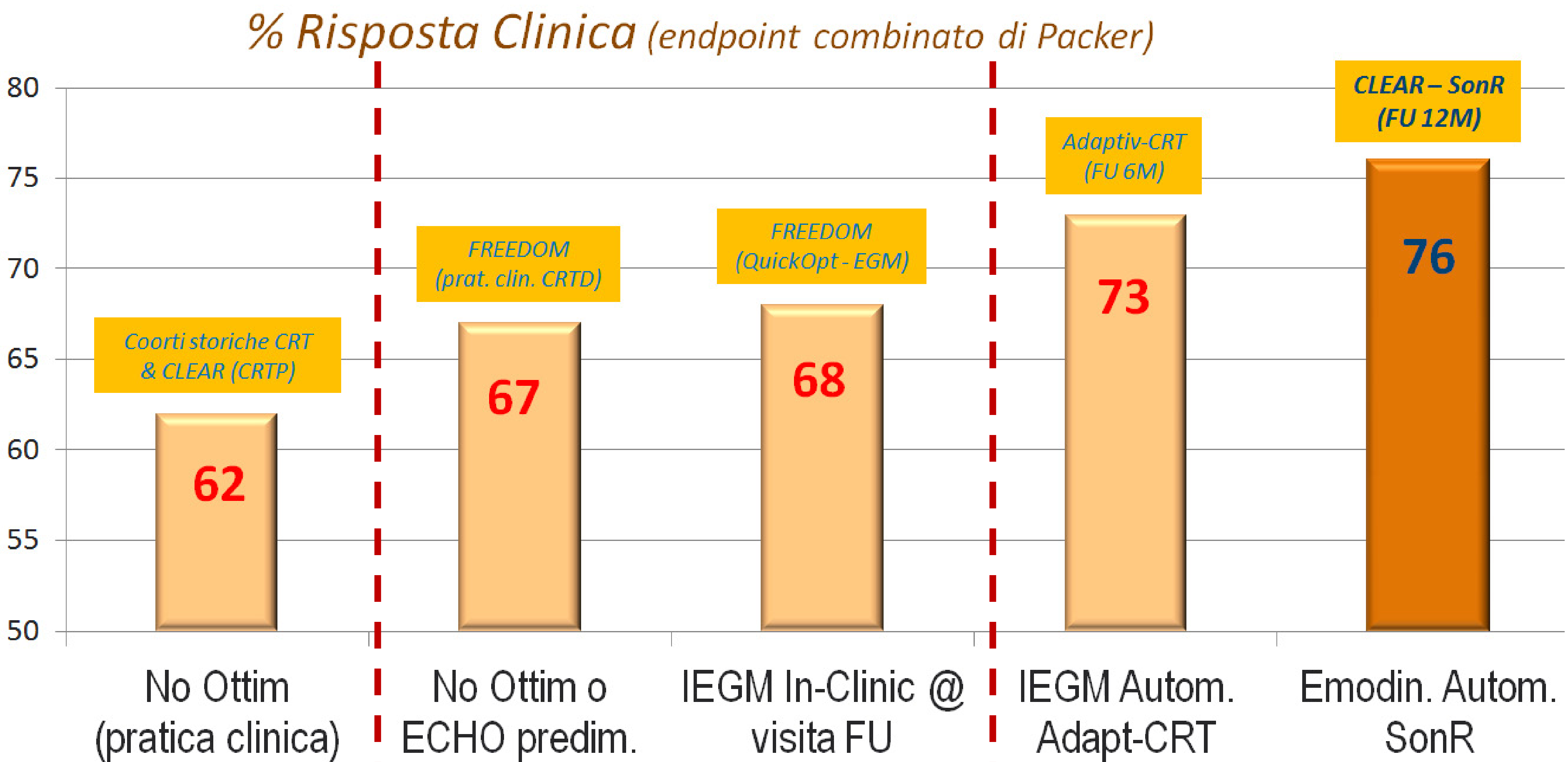
No. at risk

SonR	**670**	**641**	**617**	**600**	**588**	**579**	**498**	**418**	**408**	**339**	**250**	**244**	**135**
Echo	**328**	**315**	**304**	**289**	**277**	**269**	**229**	**191**	**189**	**171**	**119**	**144**	**49**

Brugada P et al. Late-Breaking Clinical Trials I, Clinical Response to Cardiac Resynchronization Therapy with the SonR Hemodynamic Sensor: The RESPOND-CRT Randomized Trial, Presented at Heart Rhythm 2016 - 05/05/16.

CRT settings optimization @ FU and rate of clinical response

RESPOND-CRT (75%) reinforces the CLEAR pilot …



Clinical Practice (NO optimiz.)

Echo or **Manual Optimiz.** (w device) @ in-hospital FU

CONTINUOUS Automatic Optimization (w device)

Outcomes UPDATE @ 18M FU

(ESC congress, Rome 2016)

RESPOND-CRT STUDY

RESPOND CRT *update*

Risk reduction in HF hospitalization and cardiovascular

Conclusions

RESPOND-CRT STUDY

After a complete follow-up of 18 months, results confirm:

Benefits from SonR-SYSTEM sustain over time:

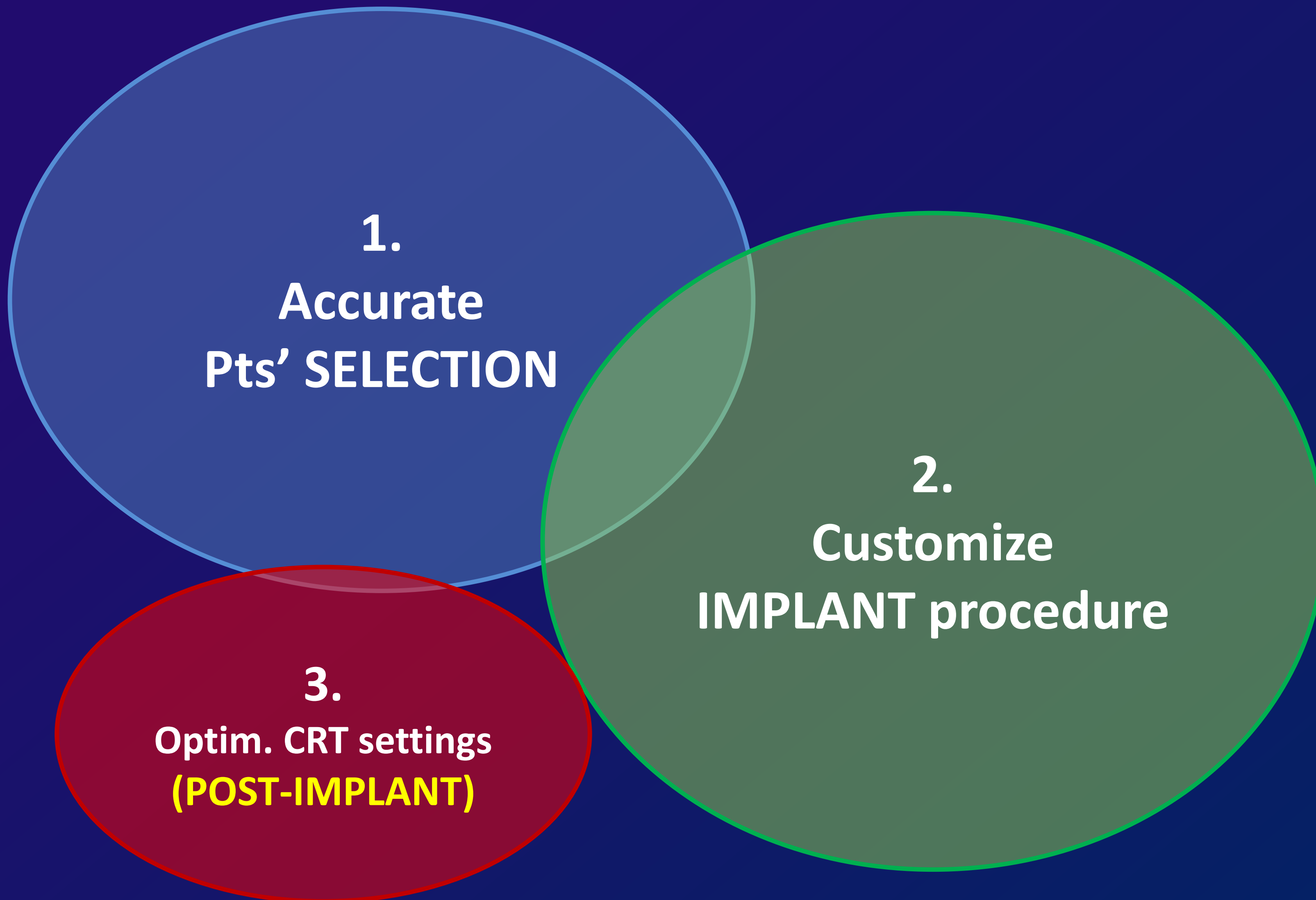
- a consistent risk reduction for HFH (- 33%)

- an additional relevant risk reduction for CV events in some subgroups among the sickest pts (AF history, renal dysf.)

→ **In addition, SonR is associated with a 48% and 41% significant risk reduction in CV deaths or hospitalizations in patients with AF and renal dysfunction, respectively**

Brugada J et al. ESC Congress 2016 (Rome). Respond-CRT UPDATE (slides available @ http://congress365.escardio.org)

OPTIMIZATION matters to reduce the rate of NR !!!



Conclusions (1/2)

CRT still suffers from a **too high rate of NR**;
the role of CRT settings optimization during FU
is still under debate (prognostic impact not clear)

Recent reports underline that a **FREQUENT optimization of CRT settings** ("systematic") confers hemodynamic / clinical benefits

NON-device based methods to optimize CRT (mainly echo) show **limitations** *(repeated assessments, resource-consuming, inter- & intra-op variability)*

Device-based AUTOMATIC methods are available to frequently optimize (daily/weekly) CRT settings on electrical (synchronization of wavefronts) or hemodynamic (maximising contractility) basis

The **Adaptiv-CRT** and **RESPOND-CRT** trials confirmed the clinical benefits from the **automatic optimization** provided by the device algorithms, on a **long-term FU**:

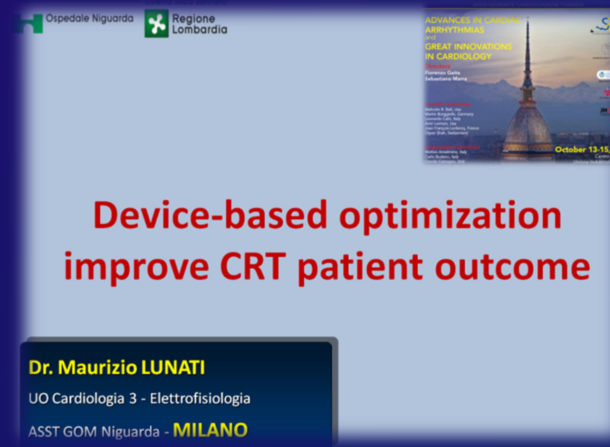
- Adaptiv-CRT: better clinical response (vs. echo) in pts with normal AV conduction

- SonR, risk reduction: 1. HFH in all pts (35% at 2Y FU), indep. upon charact.

2. CV events in the sickest pts (AF history, renal dysf.)

Conclusions (2/2)

Time to change CRT Guidelines ?



2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing

In biventricular pacing ICD patients, it can be beneficial to adjust the therapy to produce the highest achievable percentage of ventricular pacing, preferably above 98%, to improve survival and reduce HF hospitalization.	IIa	B-NR
In biventricular pacing ICD patients, it can be reasonable to activate the algorithms providing automatic adjustment of atrioventricular delay and/or LV-RV offset to obtain a high percentage of synchronized pacing and reduce the incidence of clinical events.	IIb	B-R

Class II-b / B recommendation *(metanalysis from R = randomized trials):*

ALGORITHMS *for* ***AUTOMATIC reprogramming of*** *AVD &/or VVD improve the clinical outcome*

Wilkoff B et al. Heart Rhythm 2016;13(2):e51-e78

Thanks for your attention