AZIENDA OSPEDALIERO UNIVERSITARIA
Santa Maria della Misericordia di Udine

Luncheon Panel - 25/oct/2012

The "Hemodynamic Approach" to improve CRT Response

Clinical benefit from hemodynamic continuous CRT optimization: from CLEAR to RESPOND-CRT

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Osp. S. Maria della Misericordia - **UDINE**

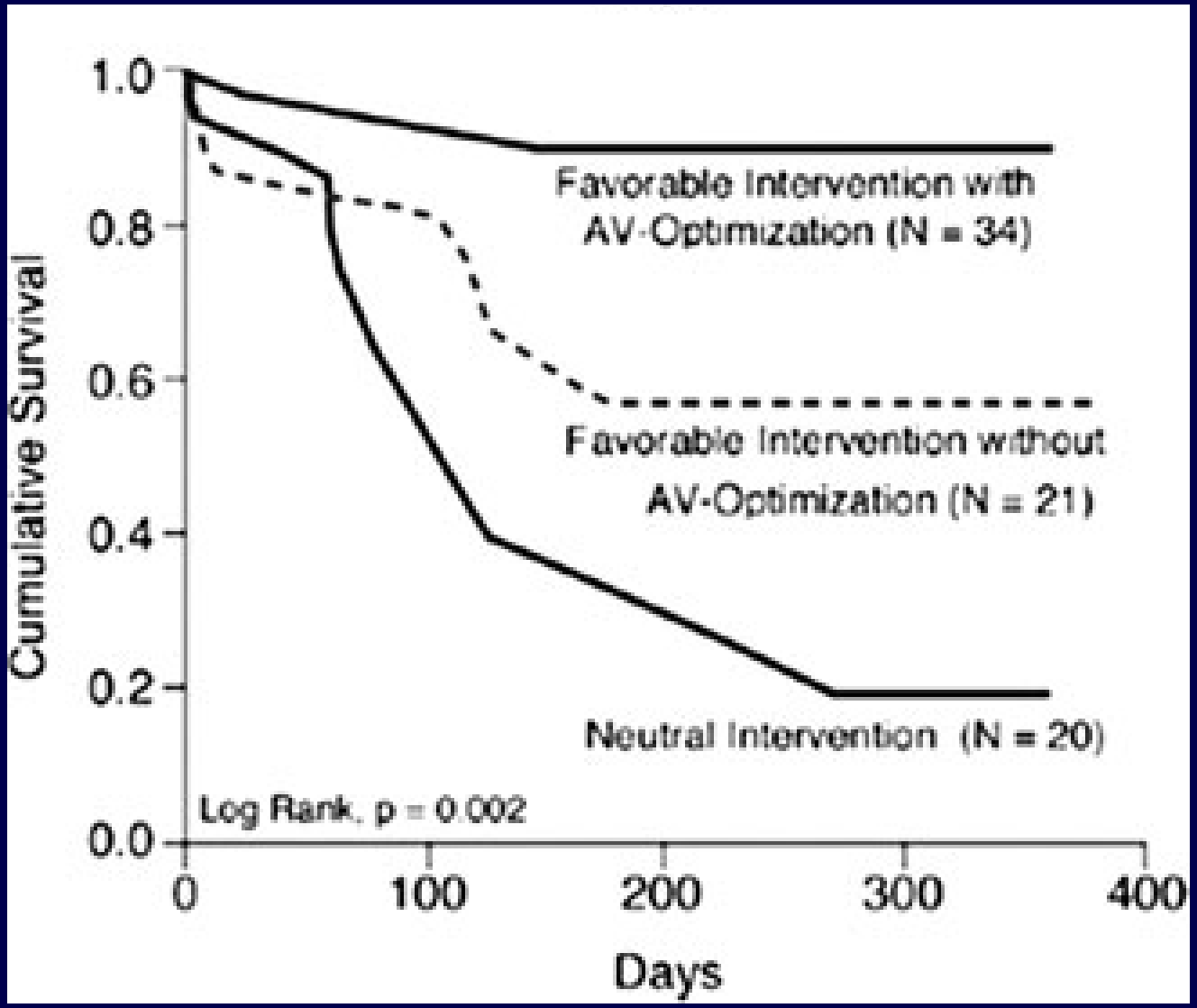
Device-based (IEGM) methods ⇒ NON-Inferiority vs. Echo

	QuickOpt (SJM)	SmartDelay (BSx)	AdaptivCRT (Mdt)
AVD optimization	Only **@ REST**; Paced & sensed	Only **@ REST**; Paced & sensed	Only **@ REST**; Paced & sensed
VVD optimization	OK	OK	OK (LV synchro or BiV)
In-clinic (@ FU) vs. Ambulatory (automatic)	**In-clinic**	**In-clinic**	**Ambulatory** (dowloadable sw)
Outcomes from trials: SAFETY	OK	OK	OK (dowloadable sw)
Outcomes from trials: EFFICACY	AV & VV opt @ FU visits **NOT INFERIOR to clinical practice** (0 or 1 echo) clinically @ 1Y (FREEDOM)	AV opt @ FU visits **EQUIVALENT to ECHO-guided or Empiric** programming, structurally & functionally @ 6M (SMART-AV)	Adaptive-CRT approach is **NON-INFERIOR to Echo-optimized BiV**, clinically @ 6M (AdaptivCRT)

V-V optimization

Author/Study (year)	Study methods	Results
Sogaard P et al (2002)	VV optimization (echo) vs simultaneous	Acute improvements in LV ejection fraction
Rhythm II ICD (2006-2009)	VV optimization (echo) vs simultaneous	Acute: improvements in LVEF 6-months FU: no more improvements
DECREASE HF (2007)	VV optimization (echo) vs simultaneous vs LV only	No advantages of sequential biv. Pacing vs simultaneous biv. pacing
INSYNC III (2005)	VV optimization (echo) vs simultaneous	Improvement in stroke volume and 6 min walk test but not in QoL or NYHA class
Khan FZ et al (2011)	AV/VV optimization (echo) vs AV optimization only	Acute: ↑20% in CO in pts with LV lead sites adjacent to (not at or remote from) the sites of latest activation

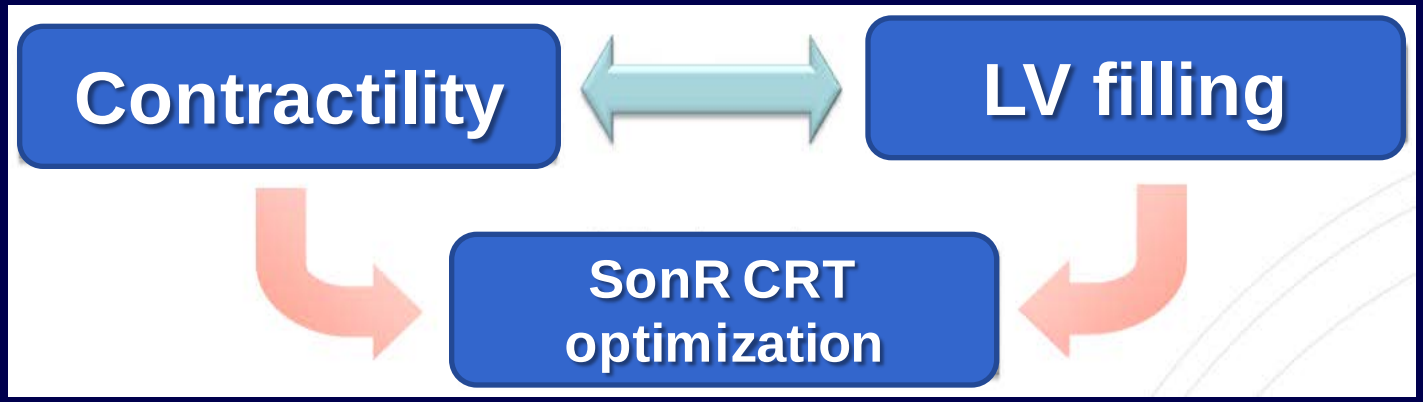
Pts successfully optimized ("favorable" intervention) w/wo AV optimization vs "neutral" intervention after CRT



Mullens W et al J Am Coll Cardiol 2009:53;765-73

SonR technology (ex-PEA) ⇒

Endocardial acceleration sensor (correlated with LVdP/dt): combining LV contractility & LV filling to optimize CRT settings



Delnoy, Europace 2008

A totally NEW concept : a hemodynamic-driven method for ambulatory CRT optimization

The CLEAR pilot study

*« **CL**inical **E**valuation on **A**dvanced **R**esynchronization »*

CRT-PM pts randomized to PEA-method or Clinical Practice

1-ary endpoint: **% Clinical Response to CRT** @ 1-year based upon a "Clinical Composite Criterion" (CCC) *

- CCC composed by:
  - All-cause Mortality
  - HF hospitalization
  - NYHA functional class
  - Quality of Life (EuroQOL)
- Definition of **"Responder Patient"**:
  - Alive, &
  - Never HF-hospitalized, &
  - NYHA class ≥ -1, &/or
  - QOL score ≥ 10%

2-ary endpoints:

- Mortality & HFH

- Variations (baseline to 1Y FU) in:
  - NYHA class
  - QOL score
  - LVEF
  - LV reverse remodeling
  - QRS duration

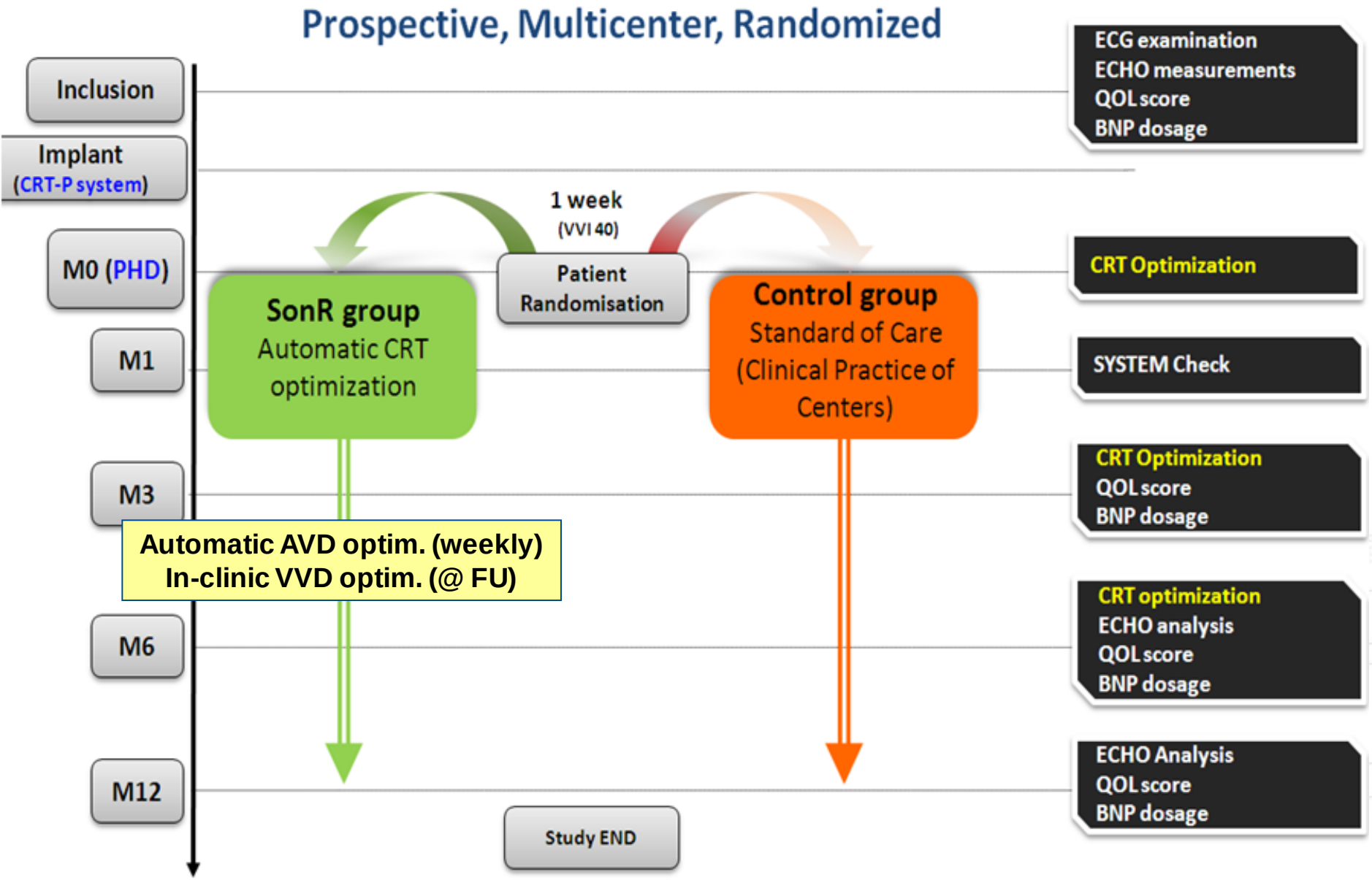
Packer M. Journal of Cardiac Failure 2001

CLEAR study: inclusion criteria

- HF pts in sinus rhythm, NYHA class III / IV
- LVEF < 35% & LVEDD ≥ 30 mm/m^2
- QRS duration:
  - > 150ms or
  - 120ms < QRS < 150ms & docum. dyssynchrony

  Fulfill 2 out of 3 criteria among:
    - *Aortic PreEjection Delay > 140 ms*
    - *InterV Mechanical Delay > 40 ms*
    - *Delayed activation of PL LV wall (after MV opening)*
- Under optimal & stable medical therapy (1-month before inclusion) at max tolerated dosage
- CMP of any etiology

CLEAR study: DESIGN



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

CLEAR study: OUTCOMES

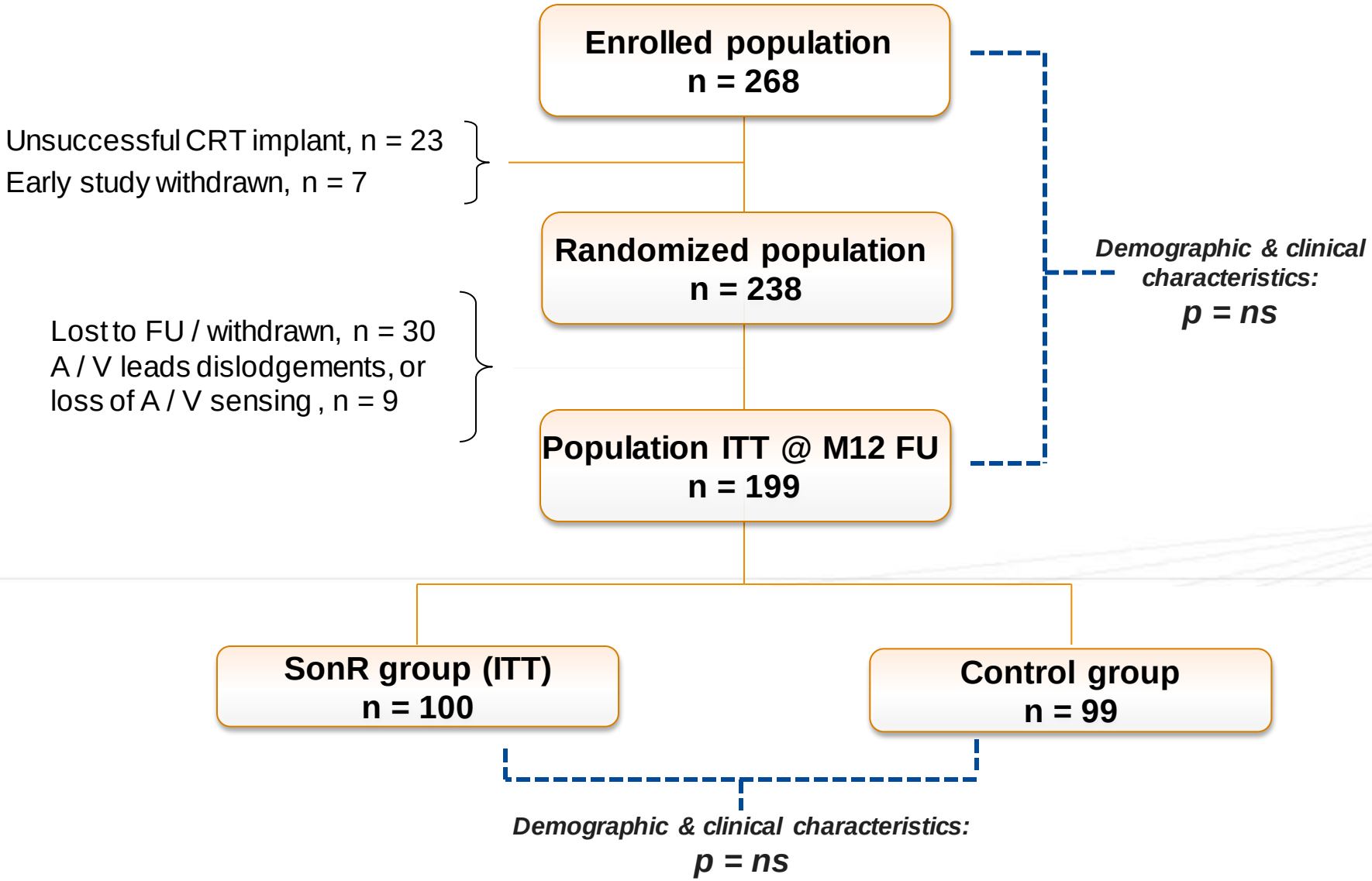
Begin / End	**2005 / 2009**
GL for inclusion	ESC HF 2005
Technology	**CRT-PM** + MiniBest **(RV, PEA)**
1-ary Endpoint (@12M)	Packer's combined (all-cause death / HFH / NYHA / QoL)
Target (randomization)	**PEA vs "Clinical Practice"**
Size (n)	**n = 268 pts**

51 Centers in 8 European Countries

Per-Protocol Outcomes (HRS 2010)

Intention-to-Treat Outcomes (Europace 2012)

CLEAR study: Pts' FLOWCHART
(Intention-To-Treat)



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

CLEAR study: Pts' FLOWCHART
(Per-Protocol)

SonR group @ 1Y FU (ITT)
n = 100

Control Group @ 1Y FU (ITT)
n = 99

n = 24 pts: CRT optimization algorithm under-performing due to **over-protection mechanisms**:

1. Ectopic activity
2. Sinus Tachycardia
3. Spontaneous conduction
4. Fusion complexes

n = 6 pts: investigators' choice
n = 13 pts: BEST sensor related issues

SonR group (PP)
n = 57

Control group (PP)
n = 99

CLEAR: demography (Per-Protocol)

Mean ± SD	**Included n = 268**	**SonR group n = 57**	**Control group n = 99**	**p**
Age (yrs)	73.3±9.3	71.8±9.5	74.2±9.2	ns
Gender (% F)	35	42	32	ns
LVEF (%)	26.7±8	27.2±8	26.1±7.7	ns
QRS width (ms)	162±30	166±19	160±25	ns
NYHA class	3.0±0.2	3.02±0.22	3.05±0.26	ns
Cardiomyopathy, n, (%)				
▪ Idiopathic	74 (47)	26 (46)	48 (49)	ns
▪ Ischemic	58 (37)	19 (33)	39 (39)	ns
▪ Valvular	14 (7)	7 (12)	7 (7)	ns
▪ Other	13 (8)	3 (5)	5 (5)	ns

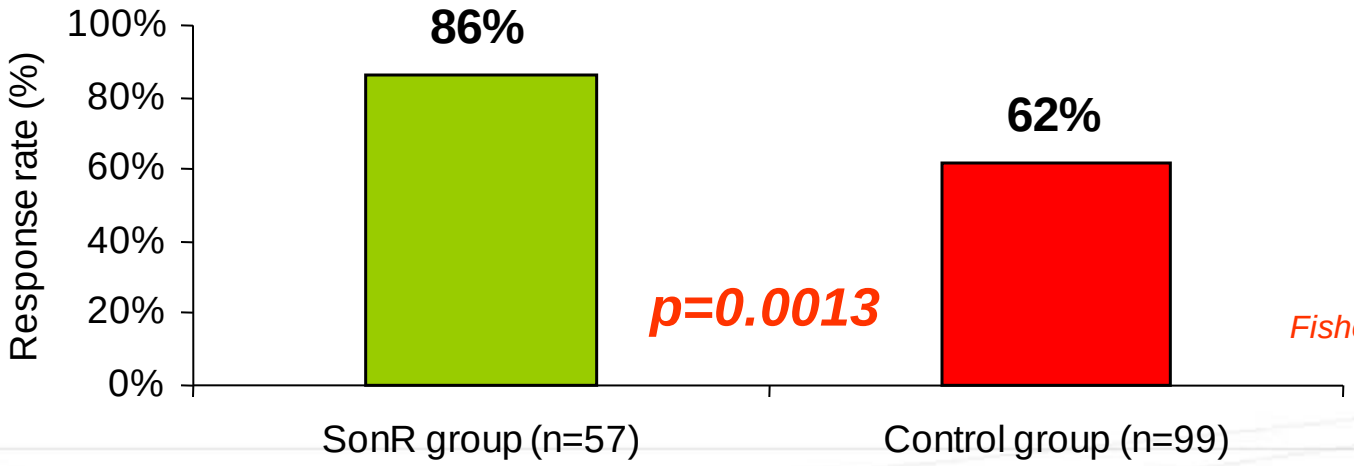
The two groups (SonR vs. Controls) are **still comparable** in the statistical analysis with **Per-Protocol** approach

First Results: ***CLEAR study*** *(* ***Per-Protocol*** *)*

HRS 2010 May, Denver - US; Prof. L. Padeletti

Primary Endpoint:
Clinical response rate to CRT @ 1Y

(composite criterion)*



Fisher's exact test

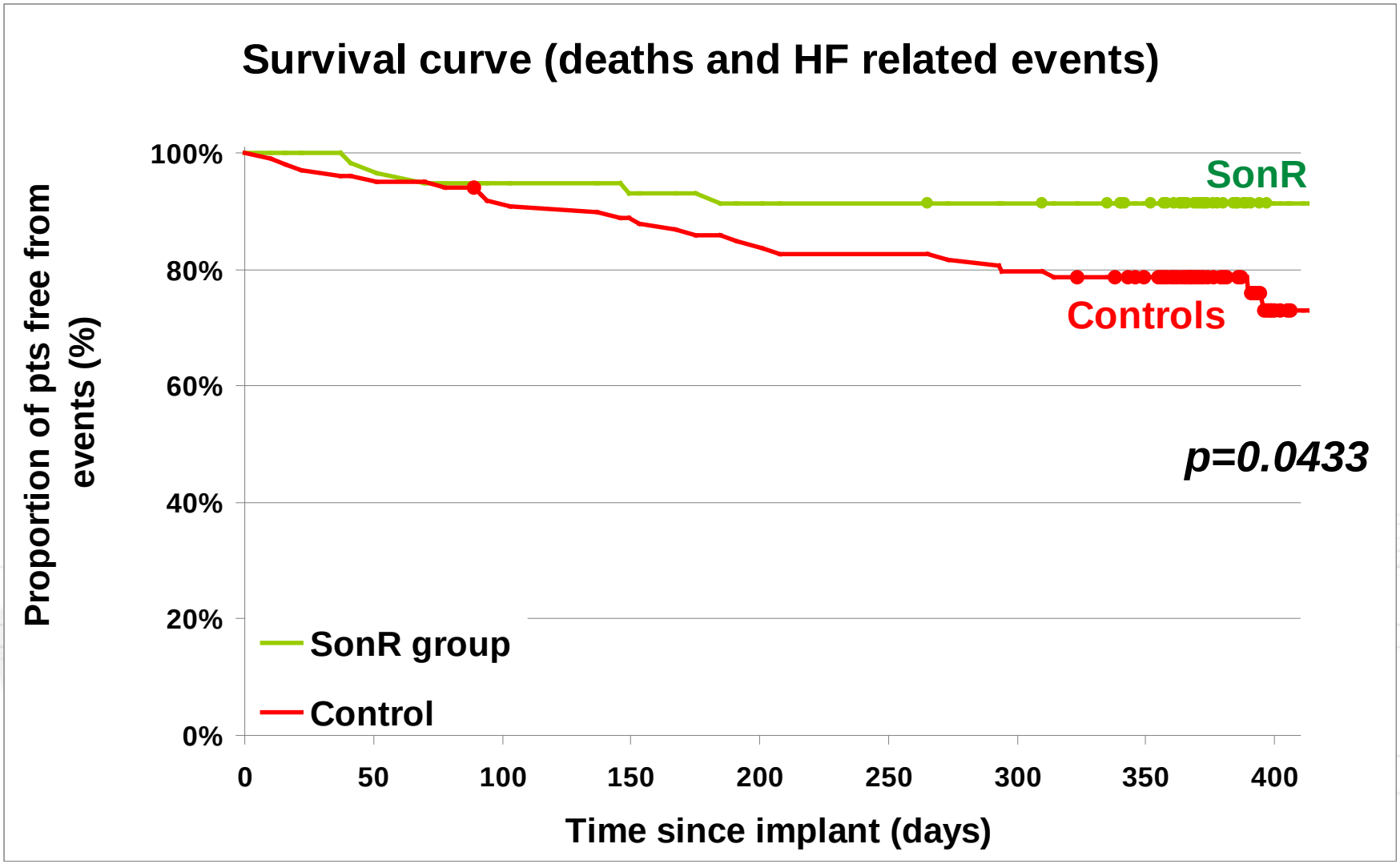
**Composite criterion including:*
NYHA functional class, death from any cause, hospitalizations for management of HF, and QOL score

^ HRS 2010 May, Denver - US; Prof. L. Padeletti

First Results: ***CLEAR study*** *(Per-Protocol)*

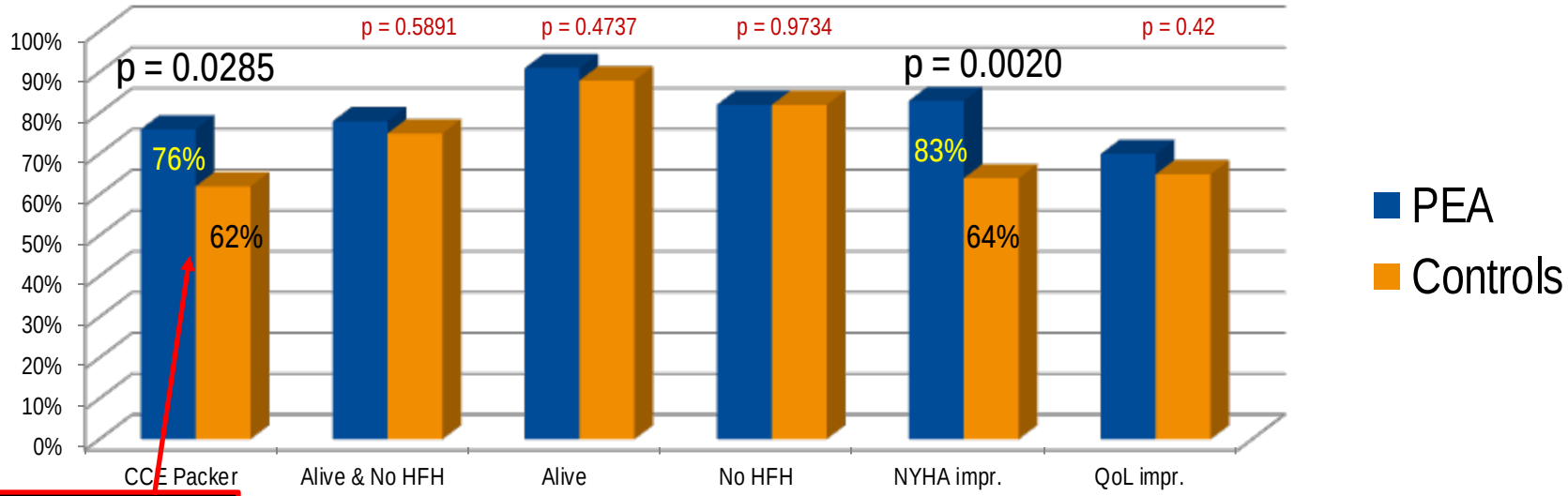
HRS 2010 May, Denver - US; Prof. L. Padeletti

Secondary Endpoint: Hard Endpoints @ 1Y



^ *HRS 2010 May, Denver - US; Prof. L. Padeletti*

CLEAR study (Intention-To-Treat): 1-ary & 2-ary endpoints



COMBINED:
All-cause death / HF-events / NYHA class / QoL

Δ [1Y vs Baseline]: PEA vs Controls

- BNP p = 0.5045
- QRS p = 0.5475
- LVEF p = 0.8482
- LVESD p = 0.5475

Conclusions:

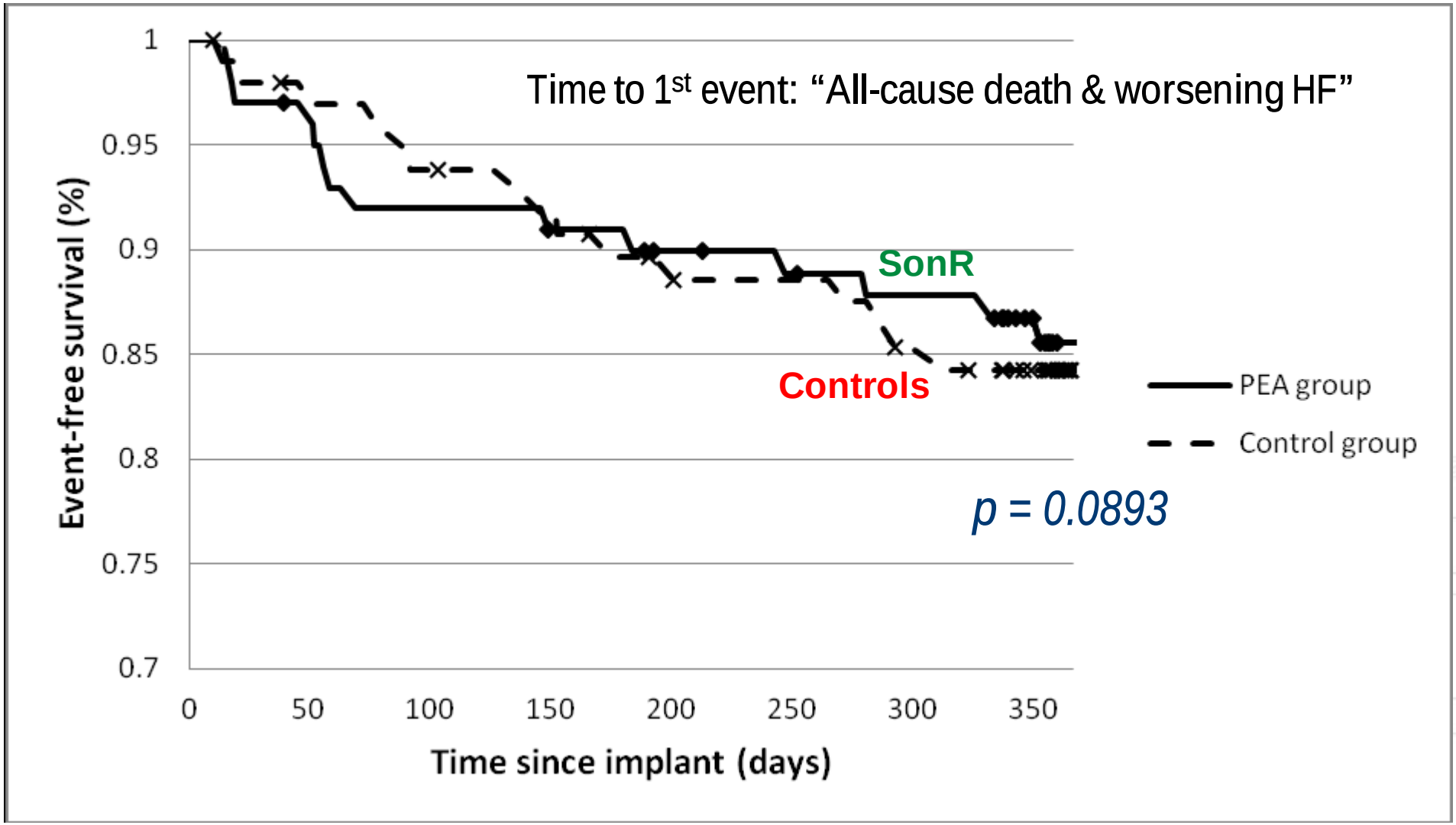
Continuous PEA-based optimization in CRT pts significantly increased the rate of clinical responders with CRT, mainly through an improved NYHA functional class @ 1Y FU

Adverse Events (Fatal & Non-Fatal): **NO significant differences** (PEA vs Controls)

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

CLEAR study (Intention-To-Treat): hard endpoints (p = ns)

PEA group: **n = 100 pz**
Control group: **n = 99 pz**



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

CLEAR study: LIMITATIONS

	CLEAR	LIMITATIONS
Year / GL for inclusion	2005-2009 / ESC HF 2005	-
1-ary Endpoint	Combined Clinical (Packer, JCF 2001)	-
Technology	CRT-PM + MiniBest (RV tip, PEA)	Pts selected for CRT-PM + "non-mature" sensor technology
AV & VV optimization algorithm	• Ambulatory AVD, VVD @ FU visit; • Too many constraints, non-optimal success rate	**1st generation algorithm** *(satisfactory success rate, non optimal)*
Target (randomization)	PEA vs "Clinical Practice"	Too "undefined" control arm
Size (n)	n = 286 pts	**Insufficient power** *(a posteriori judgment)*
NYHA & QoL	NON-blinded assessment	**Too subjective** clinical judgment
Remodeling endpoint	Partially evaluated (result: p = ns)	Echo data available @ 85%
Superiority @ 12M	ITT: 76% vs 62% [Δ = 14%] (observed)	Statistical **significance** driven by **NYHA class** (both ITT & PP); High rate of drop-outs

CLEAR pilot study: CLINICAL messages

- An AMBULATORY continuous optimization of CRT settings (weekly iteration) based upon HEMODYNAMIC principles, when compared to the SoC (= clinical practice), leads to significant CLINICAL results :

  - *Confirms the postulated NON-Inferiority*:

    an automatic device-based method is (at least) clinically equivalent to other non-invasive methods used in the clinical practice

  - *Generates the hypothesis of "Suspected Superiority"*:

    improved endpoints @ 1Y FU (combined & NYHA) are observed,

    whereas isolated hard endpoints are improved only in a PP analysis approach (larger trials needed to confirm …)

Ritter P & al. A randomized pilot study of CRT optimization in sinus rhythm pts using a PEA sensor vs standard methods. Europace 2012, In Press.

From the PEA (RV) to the SonR (RA) technology: SonR system validation (safety / efficacy trial)

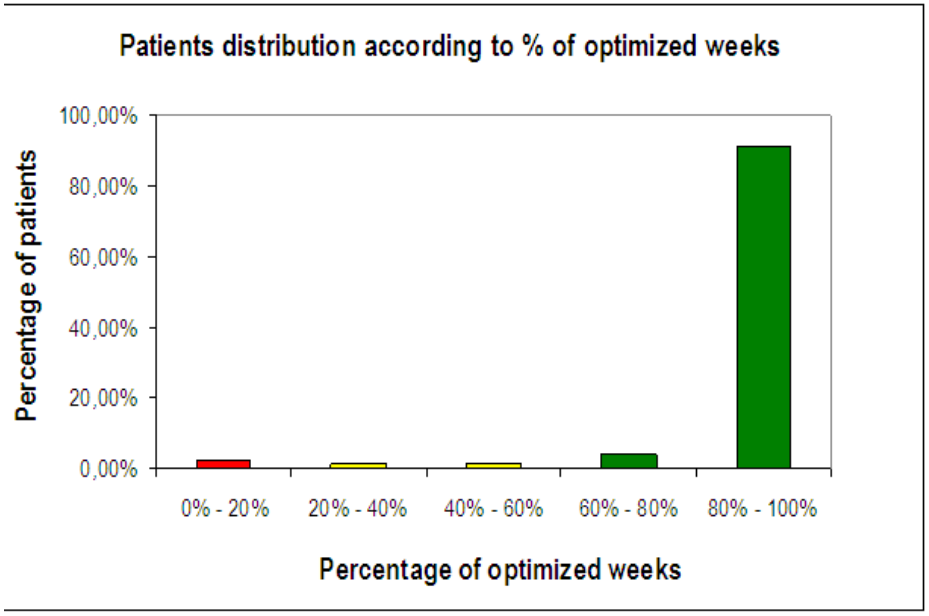
- **n = 99 pts in 22 European selected Centers** (100% data @ M3; 50% data @ M6)
  Standard population of CRT-D indicated pts in sinus rhythm
  (Sep 2010 – May 2011)

- **SAFETY** of the SonR system:
  - No Adverse Events related to the specific SonR system up to M3 FU
  - Safety confirmed **independently upon the RA site**
- **LEAD HANDLING** of the SonRtip atrial lead:
  - Handling feedback largely **positive** from EP-room operators
  - Resulting implant time: **5 to 6 min** *(PEG dissolution included)*
- **ELECTRICAL PERFORMANCES** of the SonRtip RA lead:
  - Independently upon RA site: pacing threshold, sensing amplitude & p/s impedances **STABLE & ACCEPTABLE**, in both acute & CHRONIC condition
- **SonR SIGNAL**:
  - Independently upon RA site: **very good signal amplitude** in 93% of acquisitions
  - **Stable** amplitudes over time

SORIN Group, data on file (unpublished); ITSY05 trial (ad-interim analysis – May 2012)

From the PEA (RV) to the SonR (RA) technology: Last-generation SonR algorithm (CRT optimization)

- (n=99 pts) Automatic CRT Optimization Algorithm with **SonR** (rest & exercise): **Performance over 3M FU**



Optimization @ REST * :

- ✓ **All pts (but 1) optimized between 2 FU:**
  - pt not optimized: >2000 PMTs, 8% PACs, 13 FMS
- ✓ **91,5% of pts with at least 80% of successful weekly optimizations**
- ✓ **83% of pts optimized every week**
- ✓ **Reasons for non-optimizations:**
  - unstable atrial rhythm
  - rhythm abnorm. during scan (PVCs, PACs, PMTs…)

Optimization @ EXERCISE :

- ✓ **20% of pts did NOT reach the condition for optimiz. @ exer. (HR > 90 bpm)**
- ✓ **All pts fulfilling the conditions were successfully optimized**

**Successful optimization = VV optimization & 1 AVD at rest found during the week*

SORIN Group, data on file (unpublished); ITSY05 trial (ad-interim analysis – May 2012)

RESPOND CRT

Clinical Trial of the SonRtip Lead and Automatic AV-VV Optimization Algorithm in the PARADYM RF SonR CRT-D

A multi-center, prospective, randomized, double blind study

Clinical TRial of thE SonRtiP Lead and Automatic AV-VV OptimizatioN Algorithm in the ParaDym RF SonR CRT-D

Target: to **confirm the CLINICAL BENEFIT** from a continuous hemodynamic CRT optimization (weekly ambulatory) with SonR in the clinical practice:
Endpoint: Packer's Clinical Combined ⇒ death / HF-events / NYHA / QoL

Design: multicenter, prospective, **double-blinded**, **randomized** 2-arms (2:1) ⇒
automatic SonR CRT optimization vs. ECHO optimization in pre-discharge only

Inclusion Criteria (n = 582 pts, Eu + US)

- Pt indicated for implantation of a CRT-D system according to the currently available GL
- Severe HF (**NYHA class III / IV**) at inclusion time
- **LVEF ≤ 35%**; **QRS > 120 ms**
- Under stable & optimal medical therapy
- **Sinus rhythm** at inclusion time
- Written Pt's Informed Consent

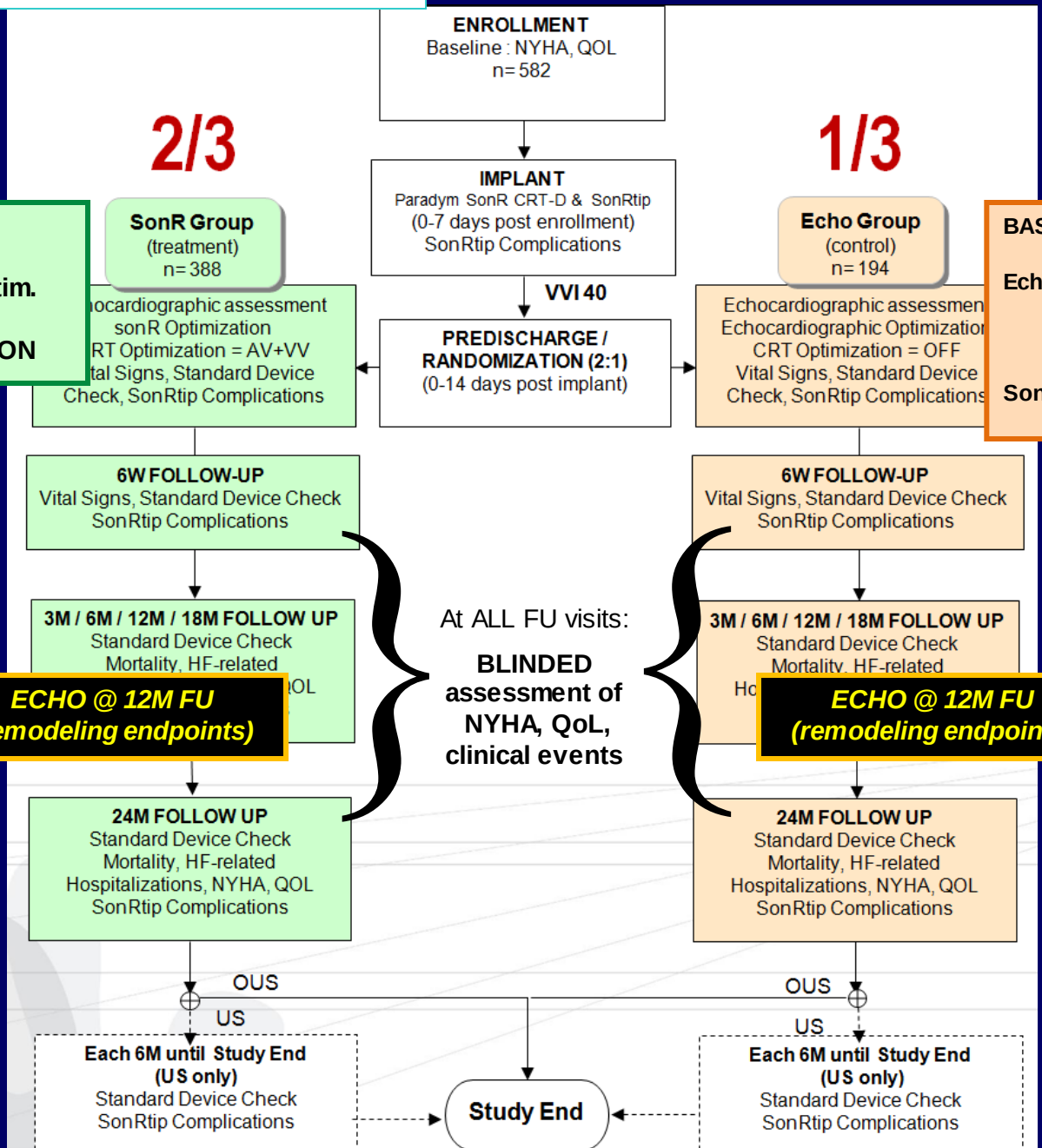
All pts receive the implant of a system with Paradym RF SonR CRTD + SonRtip RA lead

clinicaltrials.gov ID: NCT01534234 (sponsor: SORIN Group)

RESPOND CRT

Clinical TRial of thE SonRtiP Lead and Automatic AV-VV OptimizatioN Algorithm in the ParaDym RF SonR CRT-D

n = 582 pts



BASELINE ECHO

SonR manual CRT optim.

SonR AUTOM. optim: ON

SonR ON

Continuous AV/VV optimization

BASELINE ECHO

Echo-based AV/VV optimiz.

- Transmitral flow
- Transaortic flow

SonR AUTOM. optim: OFF

SonR OFF

NO continuous AV/VV optimization (up to 24M FU)

clinicaltrials.gov ID: NCT01534234
(sponsor: SORIN Group)

RESPOND CRT

Clinical Trial of the SonRtip Lead and Automatic AV-VV Optimization Algorithm in the PARADYM RF SonR CRT-D

A multi-center, prospective, randomized, double blind study

Clinical TRial of thE SonRtiP Lead and Automatic AV-VV OptimizatioN Algorithm in the ParaDym RF SonR CRT-D

Objective	Type of obj.	Endpoint definition	Timing
Primary	CRT efficacy	**NON-Inferiority SonR vs Echo @ 6M** *(equivalent % of improved pts)*	**6M**
Primary	CRT safety	% of worsened pts SonR vs Echo *(SonR does not increase % worsened pts)*	**6M**
Primary	Atrial lead safety	Adverse Evente RA-lead-related (SonRtip*)	**6M**
Secondary	CRT efficacy	**Superiority SonR vs Echo @ 12M** *(SonR increases % of improved pts; Δ > 12%)*	**12M**
Secondary	% RA lead complications	% of pts without RA-lead complications (SonRtip*)	**6M / 12M**
Ancillary	All-cause deaths	SonR vs Echo	**≥ 12M**
Ancillary	HF-related events	SonR vs Echo	**≥ 12M**
Ancillary	NYHA class	SonR vs Echo	**≥ 12M**
Ancillary	Score QoL (KCCQ)	SonR vs Echo	**≥ 12M**
Ancillary	LV remodeling	**LVEF, LV volumes, LPEI, Mitral Regurge** *(jet-area)* *(12M vs baseline)*	**12M**

clinicaltrials.gov ID: NCT01534234 (sponsor: SORIN Group)

All pts receive the implant of a system with Paradym RF SonR CRTD + SonRtip RA lead

From the CLEAR pilot study to the RESPOND-CRT trial

	CLEAR	RESPOND-CRT
Begin / End	2005 / 2009	2012 / 2016
CRT GLs for inclusion	ESC HF 2005	HF devices 2010
Inclusion criteria	NYHA III / IV	NYHA III / IV
1-ary Endpoint	Packer's Combined, JCF 2001	Packer's Combined, JCF 2001
Technology	CRT-PM + MiniBest, RV tip (PEA)	CRT-D + SonRtip, RA tip (SonR)
Automatic CRT optimization **algorithm**	• Automatic AVD, VVD @ FU visit; • More constraints, non-optimal % success	• **Automatic** AVD & VVD • Less constraints, increased % success
Target (**randomization**)	PEA vs "Clinical Practice"	**SonR vs Echo** in pre-discharge
Study **Size** (n)	n = 286 pts	n = 582 pts
NYHA & QoL assessment	NON-blinded assessment	BLINDED assessment
Remodeling endpoints	Partially evaluated (result: p = ns)	Mandatory assessment (with an Echo Core-Lab); (12M vs baseline)
Superiority @ 12M	76% vs 62% [Δ = 14%] (observed in the ITT approach)	79% vs 67% [Δ = 12%] (target, FDA agreed)

RESPOND CRT

Clinical Trial of the SonRtip Lead and Automatic AV-VV Optimization Algorithm in the PARADYM RF SonR CRT-D

A multi-center, prospective, randomized, double blind study

Study status:
n = 145/582 pts included (25%)

- Europe (9 Countries):
  Austria, France, Germany, Italy, Netherlands, Portugal, Spain, Switzerland, UK
- Outside Europe:
  Australia & US

Steering Committee INTERNAZIONALE

- Prof. Josep BRUGADA (**chairman**) - Università di Barcellona, ES
- Prof. Johannes BRACHMANN - Coburgo, D
- Dr. Peter Paul DELNOY - Isala Kliniken, Zwolle, NL
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Dr. Francis MURGATROYD - King's Hospital, London, UK

RESPOND-CRT: study amendment

(to be confirmed: November 2012)

- **Preliminary agreement with FDA:**
  OK (September 2012)

- **Study Up-sizing from n = 582 ⇒ n = 1032 pts**
  requested by FDA to strengthen the study:
  - More robust data on **SAFETY** of SonRtip atrial lead
  - More statistical **POWER** for 1-ary & 2-ary objectives

- **LV remodeling @ 12M:**
  mandatory **echocardiography** @ 12M in ALL pts (as an ancillary endpoint)

RESPOND CRT

Clinical Trial of the SonRtip Lead and Automatic AV-VV Optimization Algorithm in the PARADYM RF SonR CRT-D

A multi-center, prospective, randomized, double blind study

clinicaltrials.gov ID: NCT01534234
(sponsor: SORIN Group)

Conclusioni

The technology for an AMBULATORY (automatic) continuous AV & VV optimization based upon HEMODYNAMIC principles:

- has been tested with a first-generation algorithm within the CLEAR pilot study (PEA technology, RV tip), producing (vs. clinical practice) a significant improvement in the rate of clinical response @ 1Y FU (combined endpoint, although NYHA-driven effect)
- has been subsequently re-designed using a new platform (for CRT-D pts), based on detection of the SonR signal in the RA (SonRtip lead), which is shown safe and efficacious
- will be prospectively evaluated in the RESPOND-CRT trial (*clinicaltrials.gov ID: NCT01534234*): international, multicenter, 2-arm randomized: continuous SonR optimization vs. ECHO-optimization in Pre-discharge:
  - Ambitious objective to prospectively demonstrate the LONG-TERM CLINICAL BENEFIT (2 yrs FU) associated with a continuous optimization vs. traditional ECHO-based approach
  - Clinical Endpoint: double-blinded assessment
  - Safety: independent Echo Core-Lab & Event-Board (safety & HF events)