Prediction of major cardiovascular events in heart failure patients with active cardiac devices

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Conflict of Interest - Disclosure

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed

Affiliation/Financial Relationship	Company
1. Honoraria for lectures	ADAC, Astra Zeneca, Biotronik, BNK, Impulse Dynamics, Novartis, Pfizer
2. Honoraria for advisory board activities	Astra, Impulse Dynamics
3. Participation in clinical trials	Biotronik, Edwards
4. Research funding	Biotronik, Edwards
5. Financial shares and options	none

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Parameters to predict worsening of heart failure

Prediction of major cardiovascular events in heart failure patients with active cardiac devices

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Parameters to predict worsening of HF

	Predictor for	Publication
Occurrence of AF	Short-Term Destabilization, HR=1,48	Opasich, Am J Cardiol 2001, n=2701
	Sudden Cardiac Death, p=0,013	Middlekauff, Circulation 1991, n=390
Occurrence of ventricular episodes (> 4 VES)	Sudden Cardiac Death, p=0,025	Madsen, Int J Cardiol 1997
	Short-Term Destabilization, HR = 1,19	Opasich, Am J Cardiol 2001, n=584
	Sudden Cardiac Death, Pump Failure	Szabo, Eur Heart J 1994, n=211

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Parameters to predict worsening of HF

	Predictor for	Publication
Increase of mean heart rate	Increase of mortality	Lechat, Circulation 1997 (CIBIS), n=557
Increase of mean heart rate at rest (MHRR)	Increase of cardiovascular mortality rate	Kannel, Am Heart J 1987 (Framingham)
Increase of MHRR by 1 bpm	1,5% increase of risk for all-cause-mortality	Lechat, Circulation 2001 (CIBIS II)
Increase of MHRR by 1 bpm	1,8% increase of risk for re-hospitalisation	Lechat, Circulation 2001, n=2539

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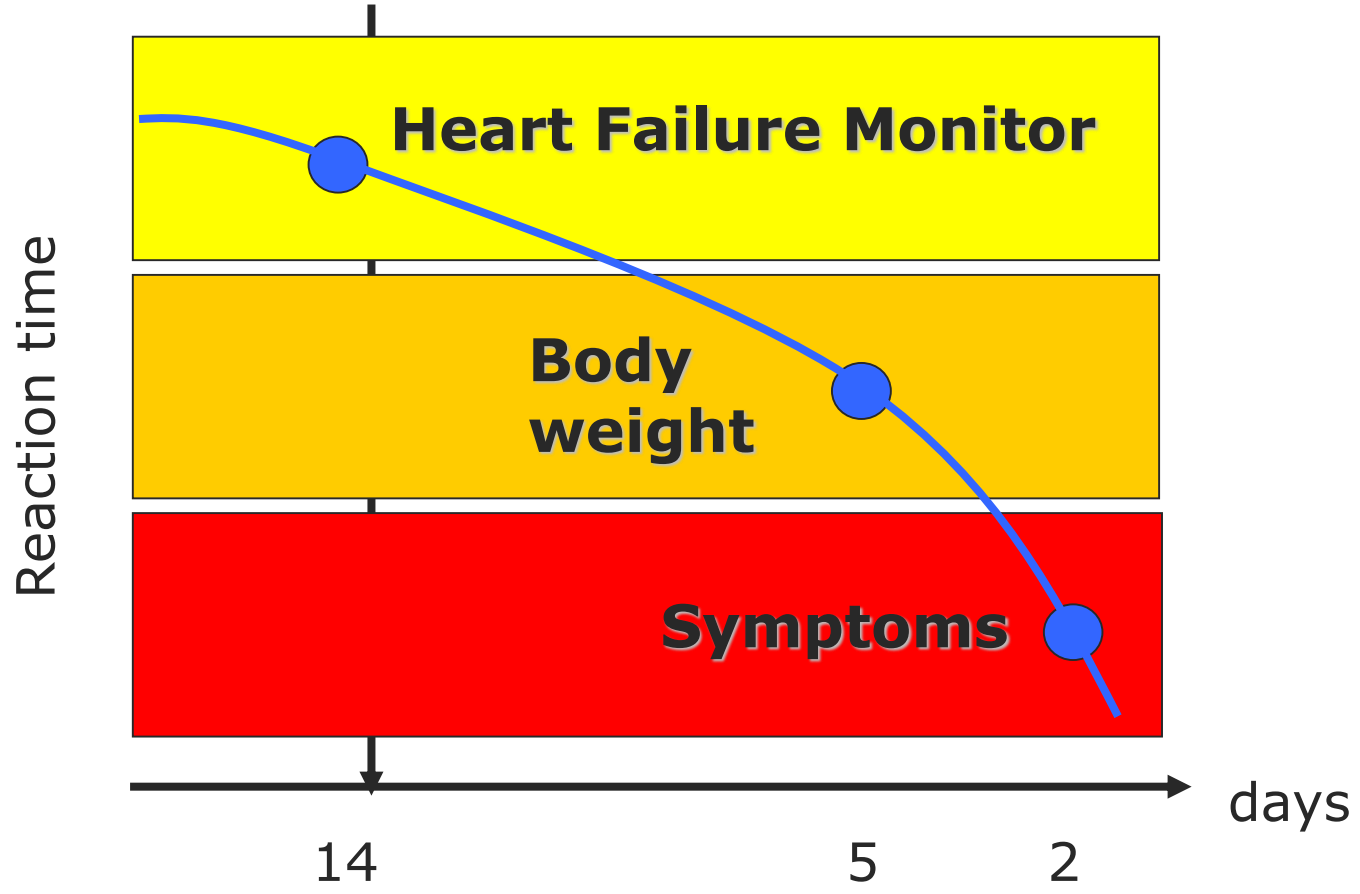
Concept of an early indicator to recognize acute decompensated heart failure (ADHF)



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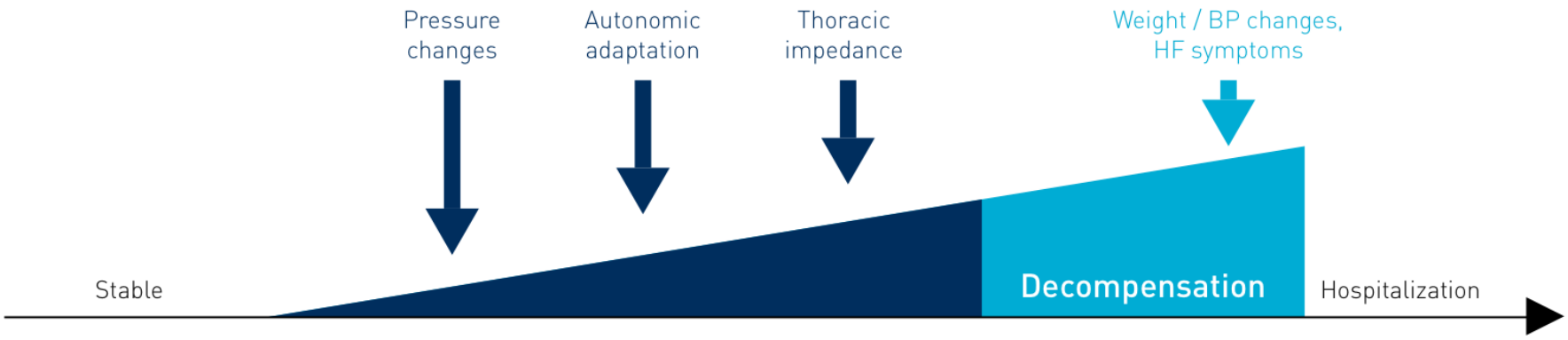
Key of HF Management:
Early Detection of Subclinical Decompensation

Advantages of Home Monitoring

- Monitors potential physiologic changes that occur prior to symptoms
- Automatic data collection, with no patient involvement



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Extensive Heart Failure Diagnostics

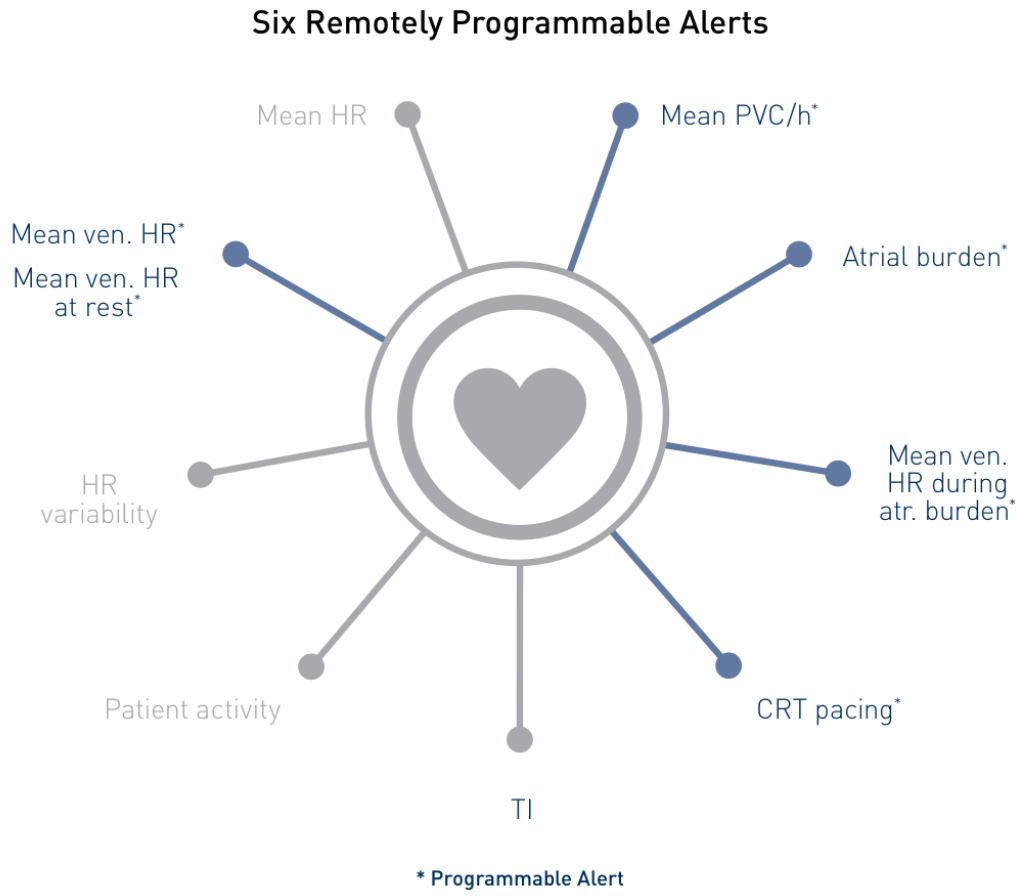
Early Detection and Monitoring

Early detection of subclinical decompensation

- Mean heart rate daily/night
- Heart rate variability
- Patient activity
- Thoracic impedance (TI).

Monitoring potential triggers for decompensation

- Atrial burden, VT and VF
- Mean HR during atrial burden
- PVC/H
- CRT pacing percentage



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Evaluation of HM algorithms in HF patients

Prediction of major cardiovascular events in heart failure patients with active cardiac devices

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Potential Benefit by Home Monitoring

Table 1 Baseline characteristics of 377 patients included in predictor development

Parameter	*n* = 377
Age (years), mean (SD)	66.2 (10.0)
Female, %	21.5
LVEF (%), mean (SD)	24.5 (7.5)
% of patients with LVEF ≤35%	90.7

Potential value of automated daily screening of cardiac resynchronization therapy defibrillator diagnostics for prediction of major cardiovascular events: results from Home-CARE (Home Monitoring in Cardiac Resynchronization Therapy) study

Stefan Sack[1*†], Christian Michael Wende[2‡], Herbert Nägele[3], Amos Katz[4], Wolfgang Rudolf Bauer[5], Craig Scott Barr[6], Klaus Malinowski[7], Harald Schwacke[8¶], Francisco Leyva[9§], Jochen Proff[10], Sergey Berdyshev[11], and Vincent Paul[12‖]

[1]Cardiology Department, Universitätsklinikum Essen, Essen, Germany; [2]St. Elisabeth Klinik, Saarlouis, Germany; [3]St. Adolf-Stift, Reinbek, Germany; [4]Cardiology Department, Barzilai Medical Centre, Ashkelon, Israel; [5]Cardiology Department, Universitätsklinikum Würzburg, Germany; [6]Cardiology Department, Russels Hall Hospital, Dudley, UK; [7]Cardiology Department, Helios Klinikum Aue GmbH, Aue, Germany; [8]Innere Abteilung, Allgemeines Krankenhaus Altona, Hamburg, Germany; [9]Good Hope Hospital, Sutton Coldfield, UK; [10]Biotronik SE & Co. KG, Berlin, Germany; [11]Biotronik SE & Co. KG, Berlin, Germany; and [12]Cardiology Department, St. Peter's Hospital/St. George's, Chertsey, UK

European Journal of Heart Failure (2011) **13**, 1019–1027

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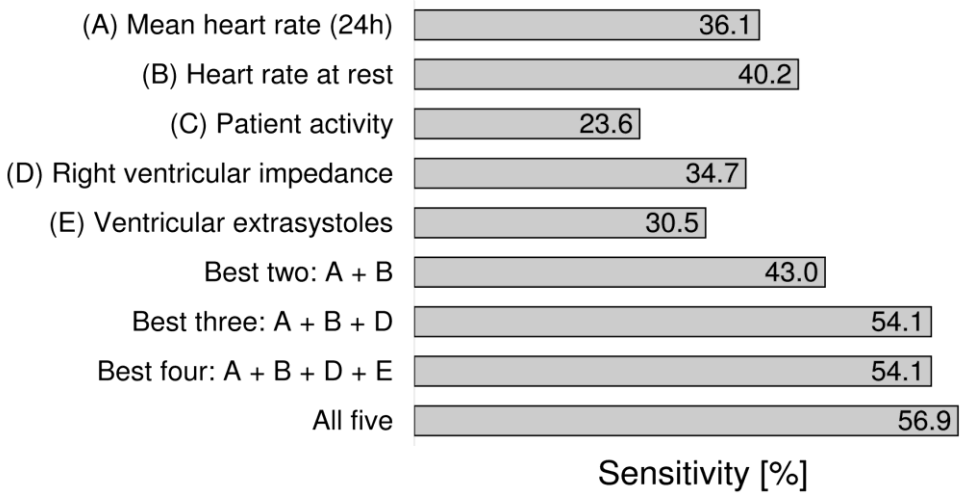
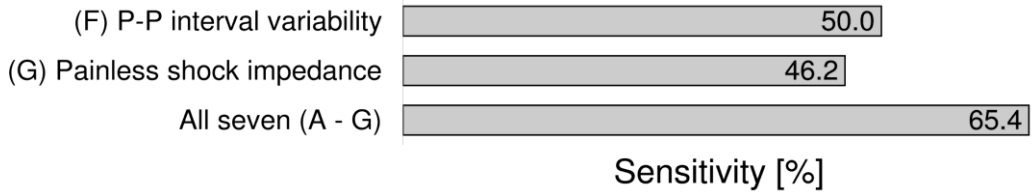
Major cardiovascular events were detected with a sensitivity of 65.4% and a specificity of 99.5% with the enhanced predictor

Basic five-parameter predictor* (sensitivity of 56.9%)



All sensitivity values were calculated retrospectively for the target specificity of 99.5%.

Enhanced seven-parameter predictor** (sensitivity of 65.4%)



*combinations of two, three and four parameters were made by adding the next best individual parameter
**sensitivities for two new parameters and for combination of all seven parameters

Sack S et al. Eur Heart Fail J 2011

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Combined Heart Failure Device Diagnostics Identify Patients at Higher Risk of Subsequent Heart Failure Hospitalizations

Results From PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) Study

David J. Whellan, MD, MHS,* Kevin T. Ousdigian, MSEE, MSIE,† Sana M. Al-Khatib, MD, MHS,‡ Wenji Pu, PHD,† Shantanu Sarkar, PHD,† Charles B. Porter, MD,§ Behzad B. Pavri, MD,* Christopher M. O'Connor, MD,‡ for the PARTNERS Study Investigators

JACC Vol. 55, No. 17, 2010
April 27, 2010:1803–10

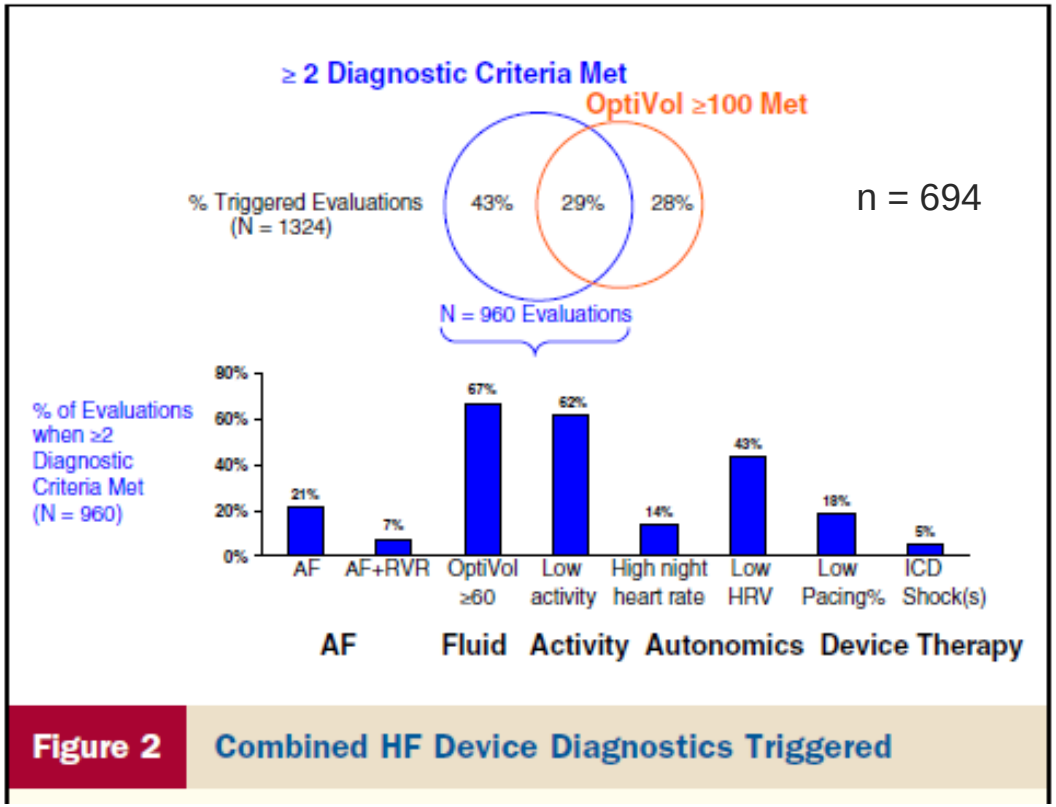
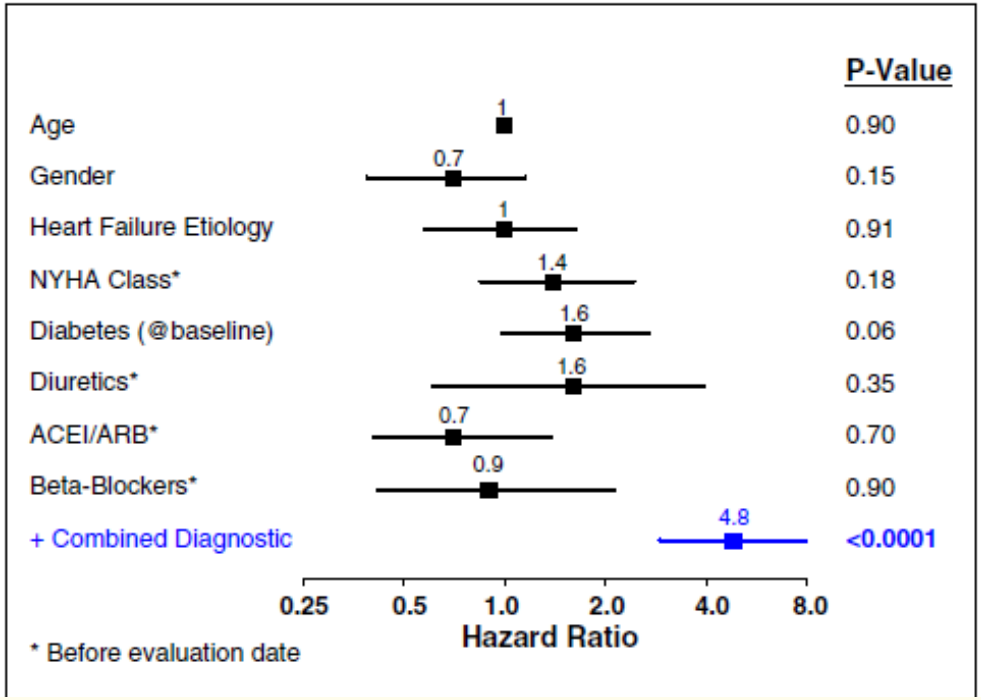
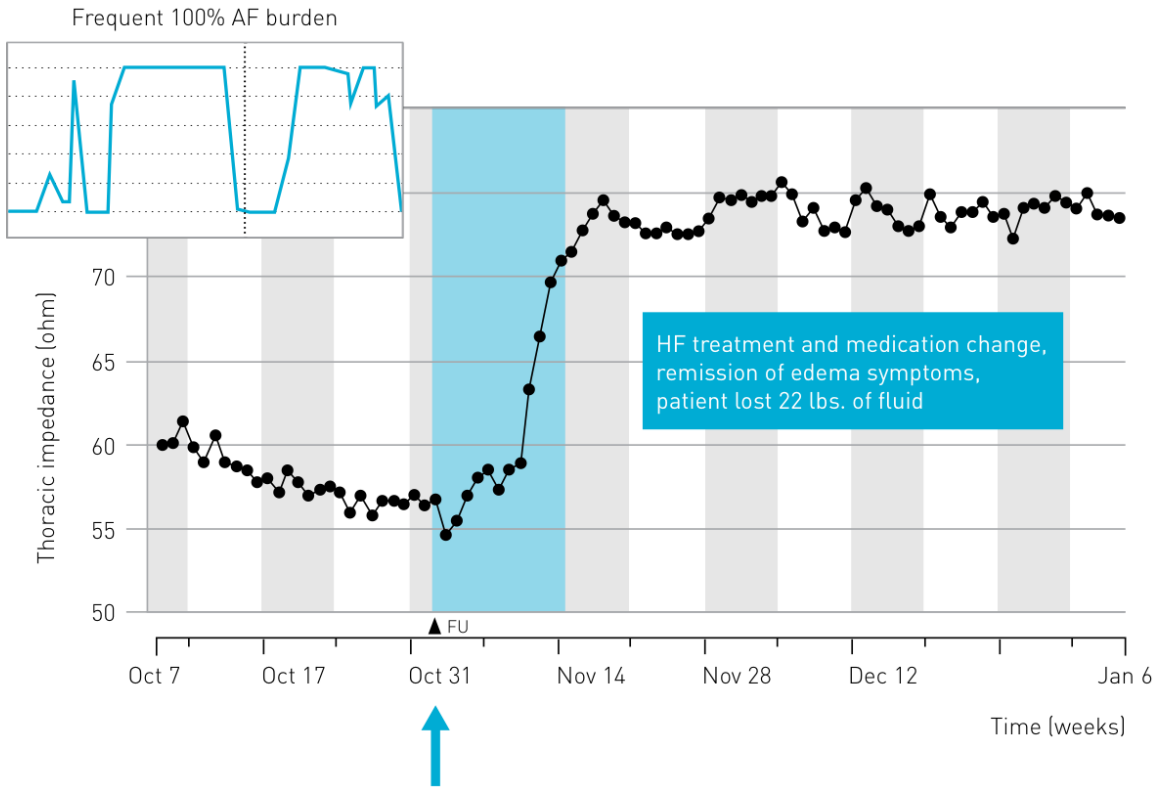


Figure 2 Combined HF Device Diagnostics Triggered



Patients with a positive combined HF device diagnostic had a 4.8-fold increased risk of an HF event within 30 days

Patient Case: Detecting Decompensation



- Patient hospitalized due to severe dyspnea at rest. X-ray confirmed lung edema. Device statistics showed AF burden increased and TI trending down.

* García-Fernández FJ et al.; Biomed TEch 2010; 55 (Supl. 1)

- TI – thoracic impedance

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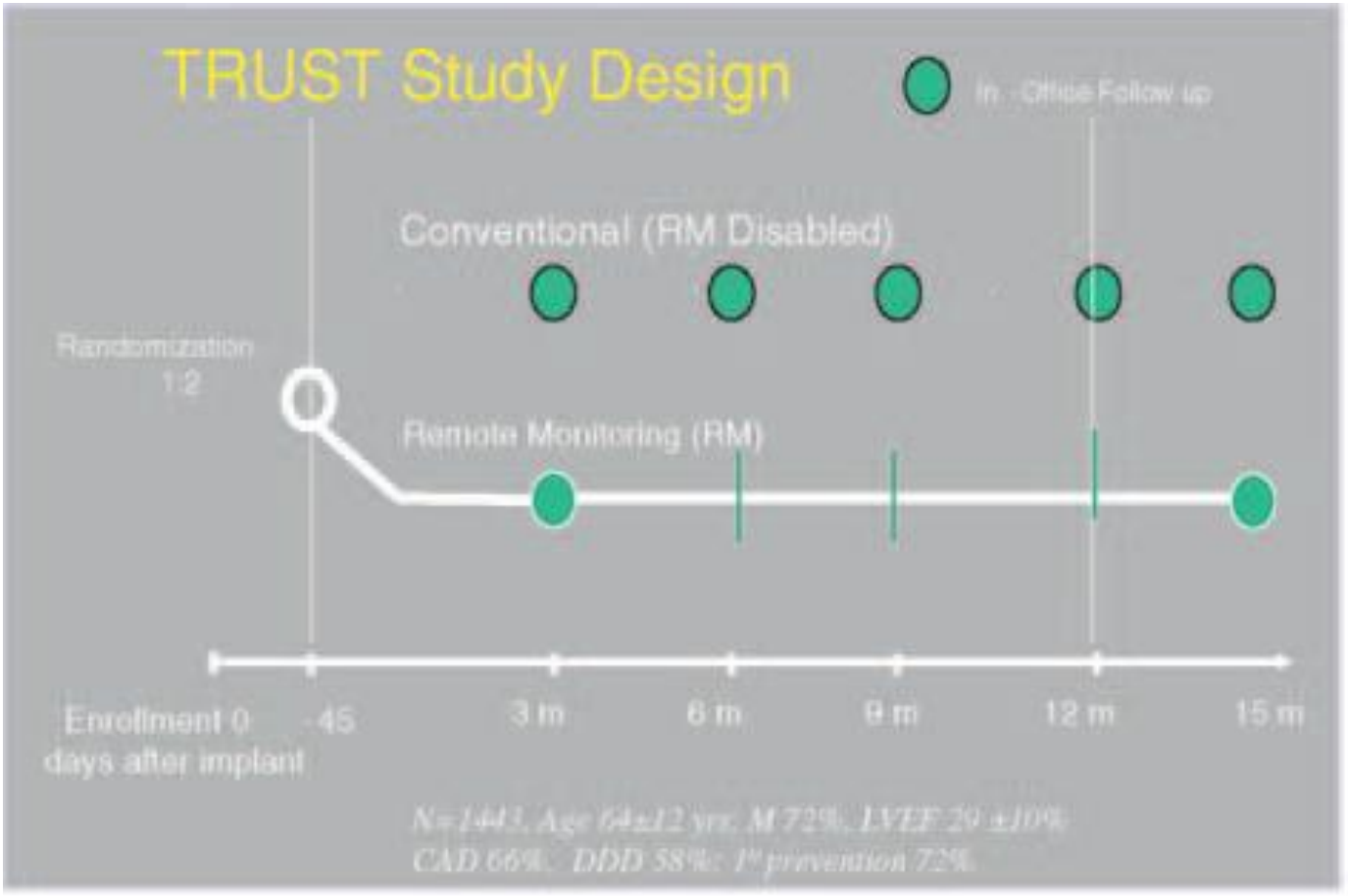
Evaluation of efficacy and safety of remote monitoring for ICD follow-up: the TRUST trial



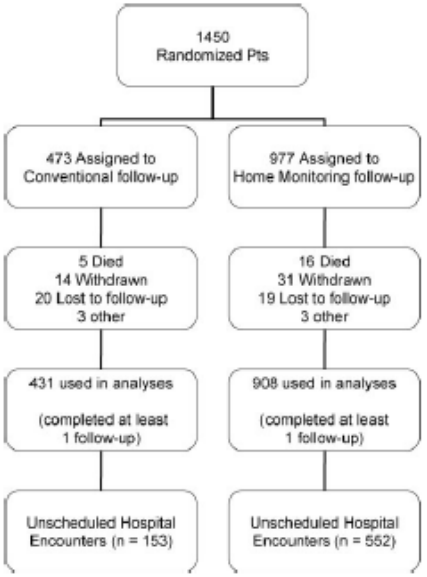
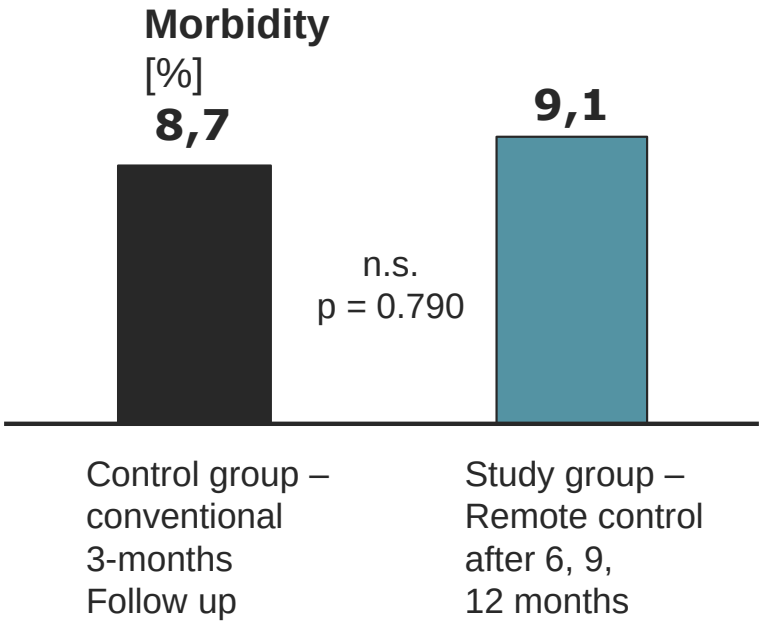


Figure 1. Study patients.

Varma N et al. Circulation 2010:122:325-332

TRUST Trial

Remote control with Home Monitoring are equal safe as conventional follow-ups*



Varma N et al. Circulation 2010;122:325-332

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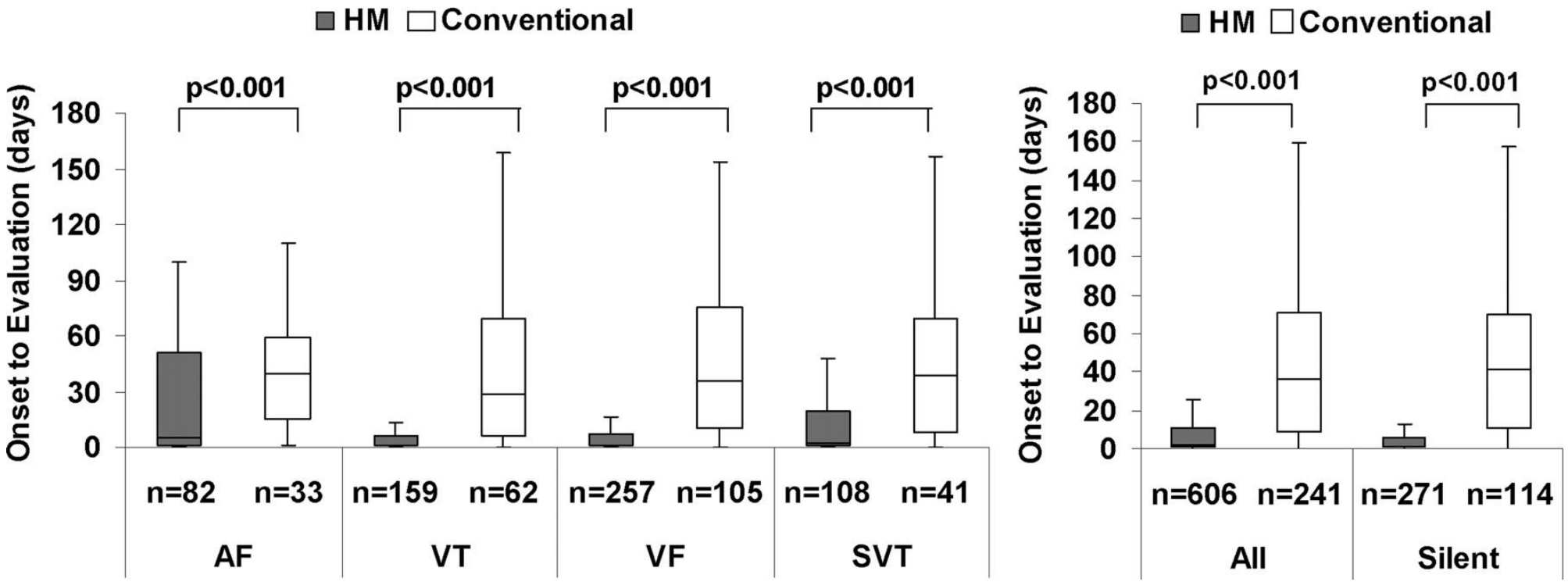
TRUST Trial: Early detection.



Varma N et al. Circulation 2010;122:325-332

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The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) Trial

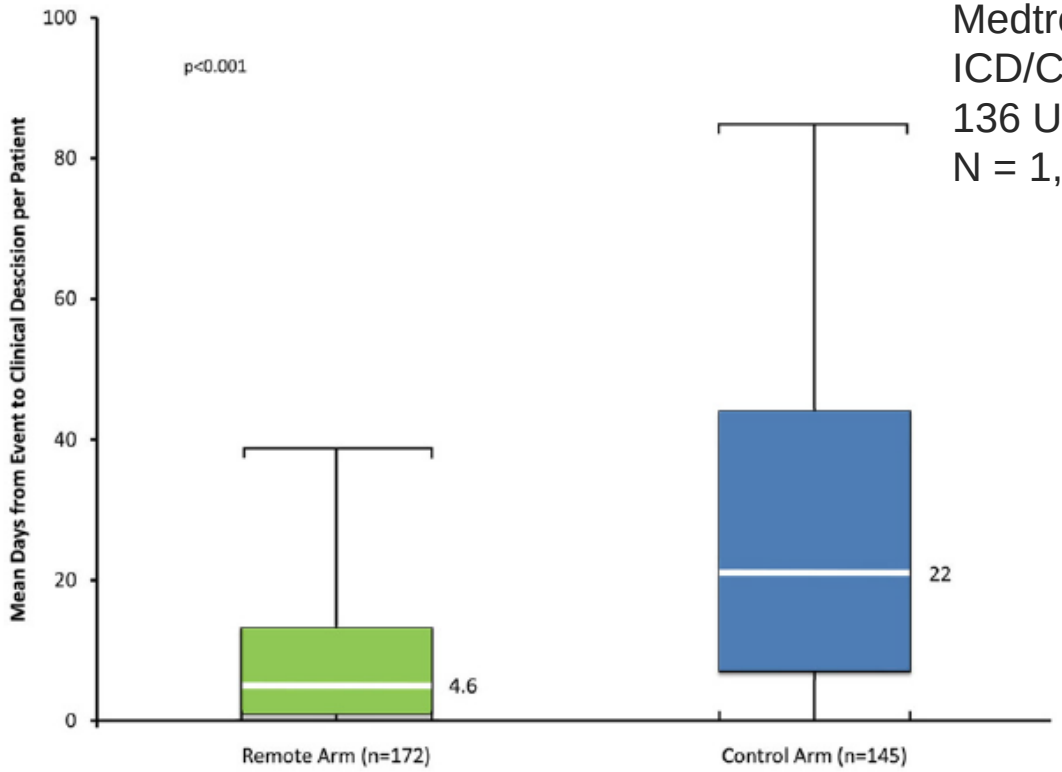
The Value of Wireless Remote Monitoring With Automatic Clinician Alerts

George H. Crossley, MD,* Andrew Boyle, MD,† Holly Vitense, PHD,‡ Yanping Chang, MS,§ R. Hardwin Mead, MD,‖ for the CONNECT Investigators

Nashville, Tennessee; Milwaukee, Wisconsin; Minneapolis, Minnesota; and Redwood City, California

Table 2 Baseline Demographics

	Remote (n = 1,014)	In-Office (n = 983)	Total (n = 1,997)
Sex, male	70.5%	71.7%	71.1%
Age, yrs	65.2 ± 12.4	64.9 ± 11.9	65.0 ± 12.1
LVEF, %	28.6 ± 10.0	29.2 ± 10.3	28.9 ± 10.2



Medtronic Care Link
ICD/CRT-D
136 US centers
N = 1,997

Figure 1 Distribution of Time From Clinical Event to Decision per Patient

Box-and-whisker plots show the quartiles with the medians labeled, and the **whiskers** extend to the fifth and 95th percentiles.

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In-Time Trial

The Influence of Implant-Based Home Monitoring on the Clinical Status of Heart Failure Patients with an Impaired Left Ventricular Function

- Randomized, controlled, international, multicenter
- 716 HF patients, 36 investigational sites

– **Inclusion criteria**
  - ICD indications (dual-chamber ICD, CRT-D)
  - Chronic heart failure (≥ 3 months)
  - NYHA Class II or III for 1 month prior to screening
  - LVEF ≤ 35% within 3 months prior to screening
  - Indication for therapy with diuretics

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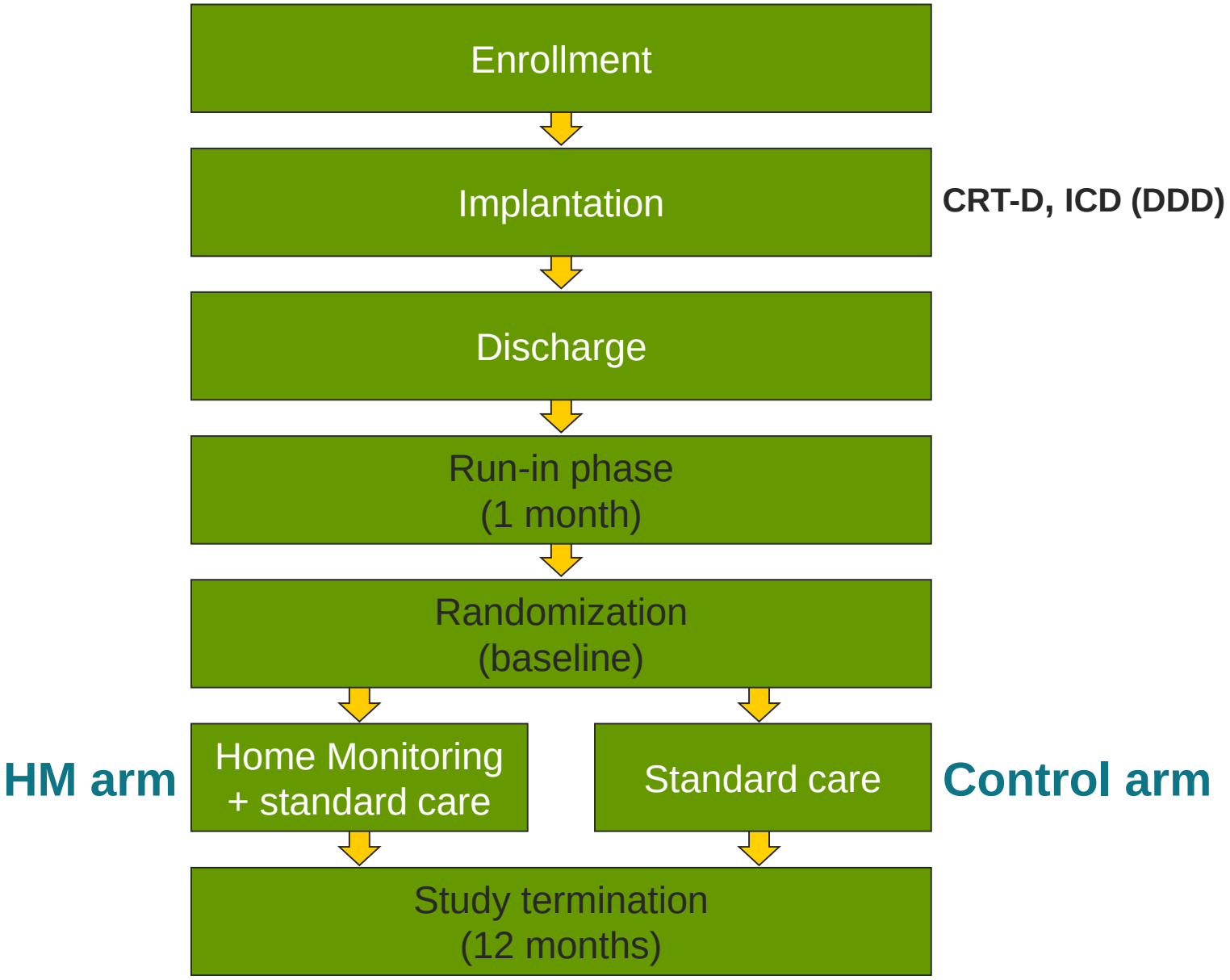
In-Time: Study flow chart



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Primary endpoint: Modified Packer Score

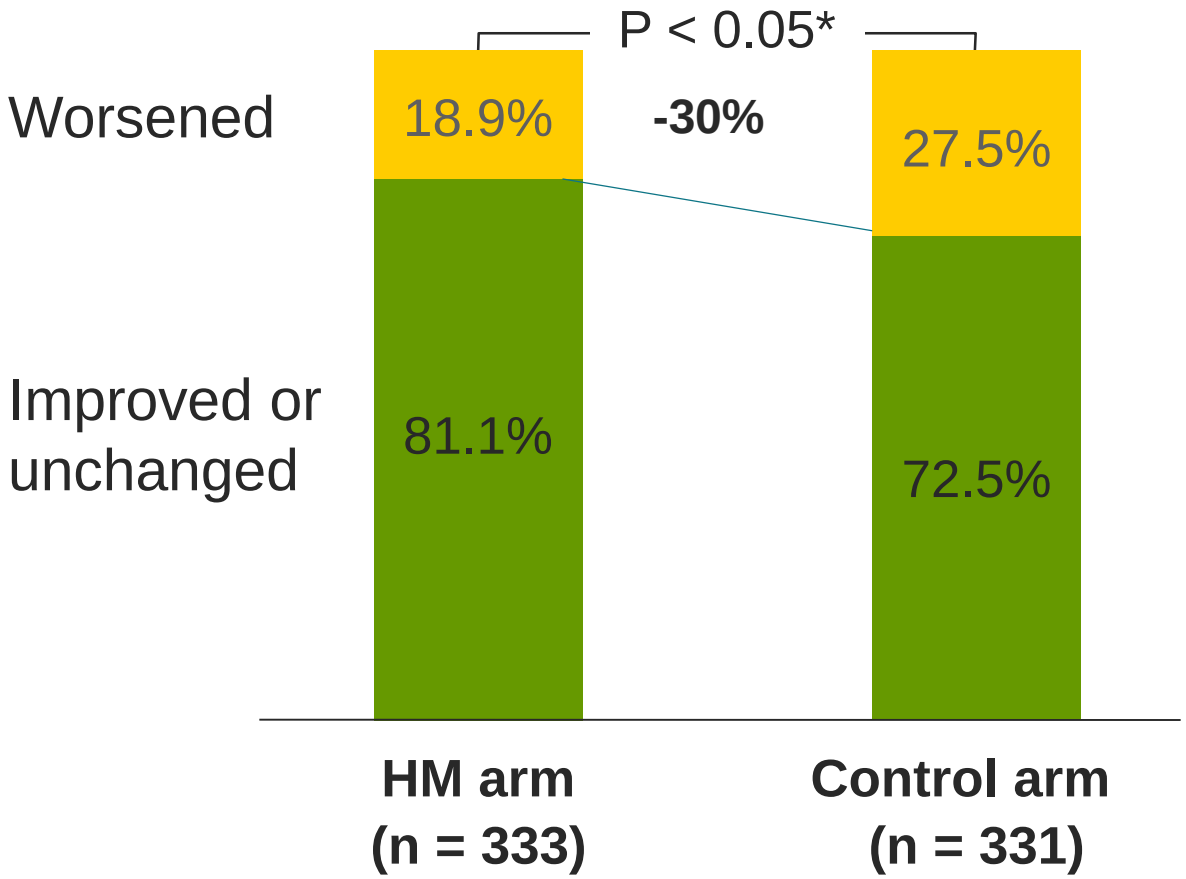
- **Each patient is classified by the end of the study as:**
- Worsened
- Unchanged
- Improved

Based on the following elements:

- Death
- Overnight hospitalization for worsening heart failure
- Favorable, unfavorable or no change in NYHA class
- Improvement, deterioration or no change in the patient's global self-assessment score

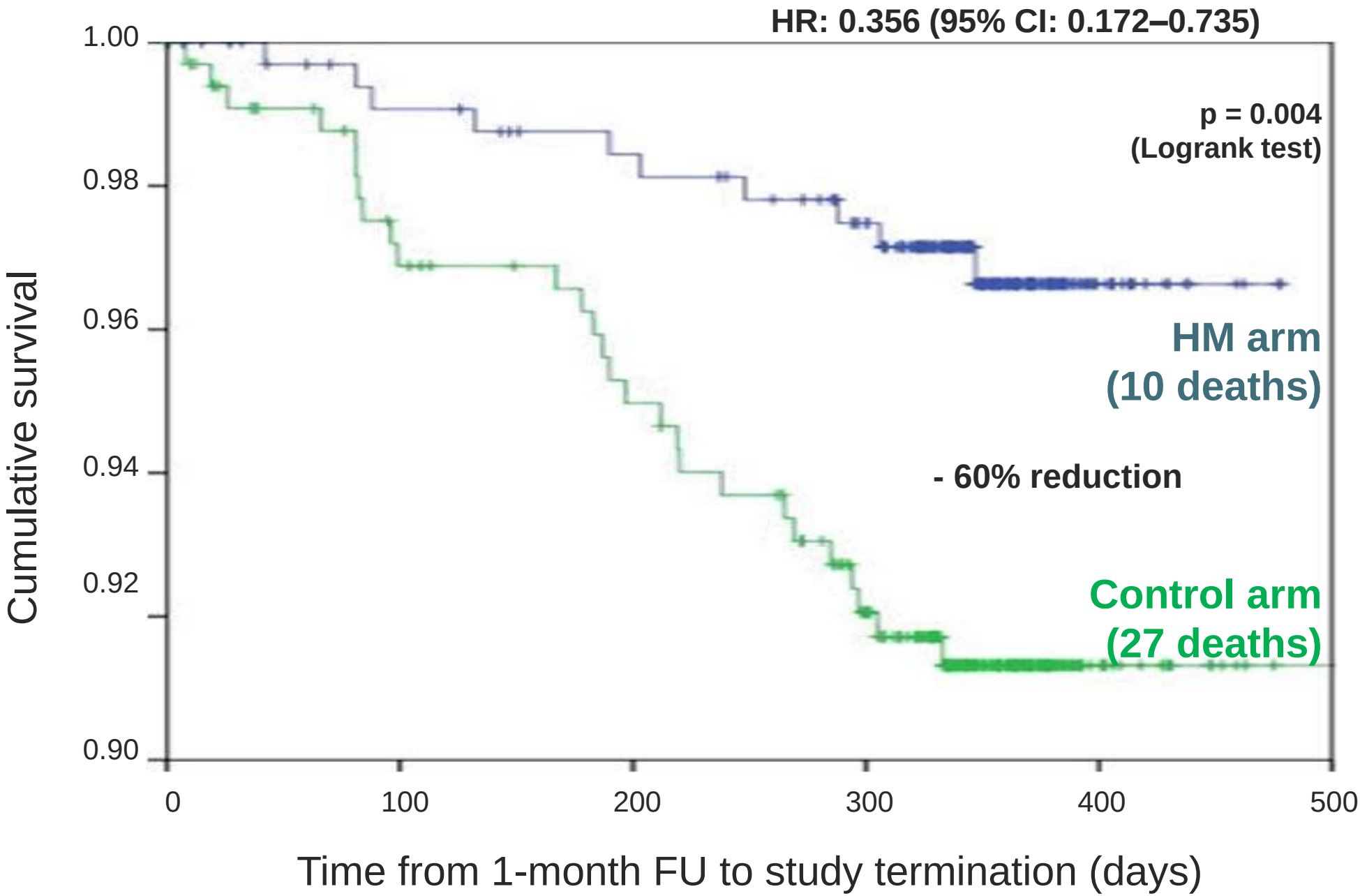
Modified Packer Score

Average FU in HM arm: 11,0 ±2,6 months
Average FU in Control: 10,7 ±3,0 months



* χ^2 test

In-Time Trial: All-cause mortality



Guidelines:
HomeMonitoring With IN-TIME Approach

- ESC Heart Failure Guidelines mention specifically the IN-TIME approach to improve clinical outcome in HF patients

Recommendations for exercise, multidisciplinary management and monitoring of patients with heart failure			
Multiparameter monitoring based on ICD (IN-TIME approach) may be considered in symptomatic patients with HFrEF (LVEF ≤35%) in order to improve clinical outcomes.	IIb	B	630

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Truecoin Meta-Analysis

Prediction of major cardiovascular events in heart failure patients with active cardiac devices

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Truecoin (TRUST, ECOST, IN-TIME)

New meta-analysis confirms and explains significant survival benefit for ICD/CRT-D patients with heart failure

European Heart Journal (2017) **00**, 1–7
doi:10.1093/eurheartj/ehx015

CLINICAL RESEARCH
Arrhythmia/electrophysiology

Daily remote monitoring of implantable cardioverter-defibrillators: insights from the pooled patient-level data from three randomized controlled trials (IN-TIME, ECOST, TRUST)

Gerhard Hindricks[1]*, Niraj Varma[2], Salem Kacet[3], Thorsten Lewalter[4], Peter Søgaard[5], Laurence Guédon-Moreau[3], Jochen Proff[6], Thomas A. Gerds[7], Stefan D. Anker[8], and Christian Torp-Pedersen[9]

Hindricks G, Varma N, Kacet S, Lewalter T, Søgaard P, Guédon-Moreau L, Proff J, Gerds T, Anker S, Torp-Pedersen C.; Daily remote monitoring of implantable cardioverter-defibrillators: Insights from the pooled patient-level data from three randomized controlled trials (IN-TIME, ECOST, TRUST); European Heart Journal 2017, doi:10.1093/eurheartj/ehx015

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New Analysis Pooled Patient-level Data of IN-TIME, ECOST and TRUST Studies

In-TIME

Indication for ICD or CRT-D, heart failure (≥3 months), NYHA class II or III, LVEF ≤35%

ECOST

Indication for ICD, not NYHA class IV

TRUST.

Class 1 indication for ICD, not pacemaker dependent

Pooled patient-level data for death

n=2405

IN-TIME + ECOST+TRUST

Pooled patient-level data for adjudicated death and hospitalization

n=1078

IN-TIME + ECOST

Verifying the mortality findings of Parthiban et al. 2015

by using time-to-event analysis instead of the pooled odds ratio estimates

- All-cause death

Exploring mechanism of clinical benefit

by investigating further clinical endpoints that combine cause-specific death and hospitalizations

- CV death,
- All-cause death or any hospitalisation,
- All-cause death or CV hospitalisation,
- All-cause death or worsening of heart failure (WHF) hospitalisation,
- CV death or CV hospitalisation, and
- WHF death or WHF hospitalisation

Hindricks G, Varma N, Kacet S, Lewalter T, Søgaard P, Guédon-Moreau L, Proff J, Gerds T, Anker S, Torp-Pedersen C.; Daily remote monitoring of implantable cardioverter-defibrillators: Insights from the pooled patient-level data from three randomized controlled trials (IN-TIME, ECOST, TRUST); European Heart Journal 2017, doi:10.1093/eurheartj/ehx015

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Home Monitoring - Meta-analysis confirms and explains significant survival benefit for ICD/CRT-D patients with heart failure

Main Clinical Results

- Home Monitoring is associated with a significant reduction of clinically relevant endpoints
- This clinical benefit is mainly driven by “prevention of heart failure exacerbation”.

Clinical endpoint (at 12 months)	**relative** risk reduction	**absolute** risk reduction	
All-cause mortality	**38%**	**1.9%**	p<0.05
All-cause mortality or WHF hospitalization	**36%**	**5.6%**	p<0.01

WHF, Worsening Heart Failure

- Hindricks G, J. Proff, N. Varma, S. Kacet, T. Lewalter, P. Sogaard, L. Guedon-Moreau, TA. Gerds, SD. Anker
- Daily remote monitoring of implantable cardioverter-defibrillators: Pooled individual patient data from IN-TIME, ECOST, and TRUST trials suggest a mechanism of clinical benefit, ESC Congress 2016, Rome

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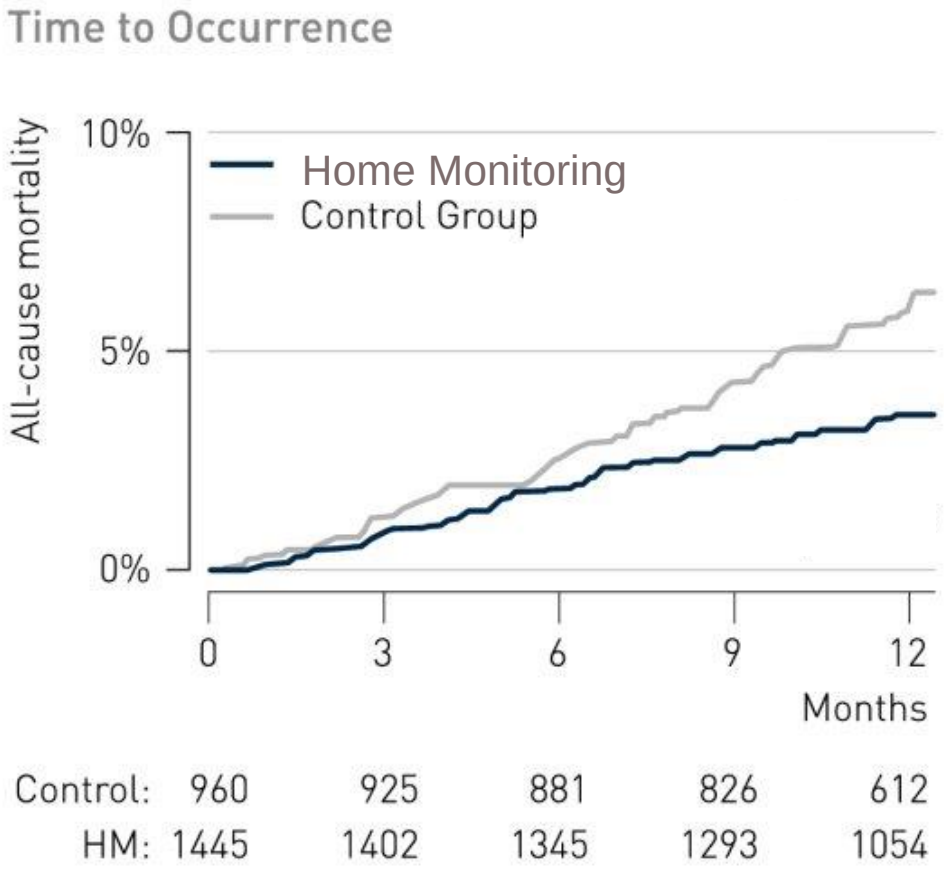
Significant Reduction of All-cause Mortality with Home Monitoring



- 38%

relative reduction of all-cause mortality at 1 year

Relative risk = 0.62

- 95% CI: 0.40 to 0.95

- Hindricks G, J. Proff, N. Varma, S. Kacet, T. Lewalter, P. Sogaard, L. Guedon-Moreau, TA. Gerds, SD. Anker
- Daily remote monitoring of implantable cardioverter-defibrillators: Pooled individual patient data from IN-TIME, ECOST, and TRUST trials suggest a mechanism of clinical benefit, ESC Congress 2016, Rome

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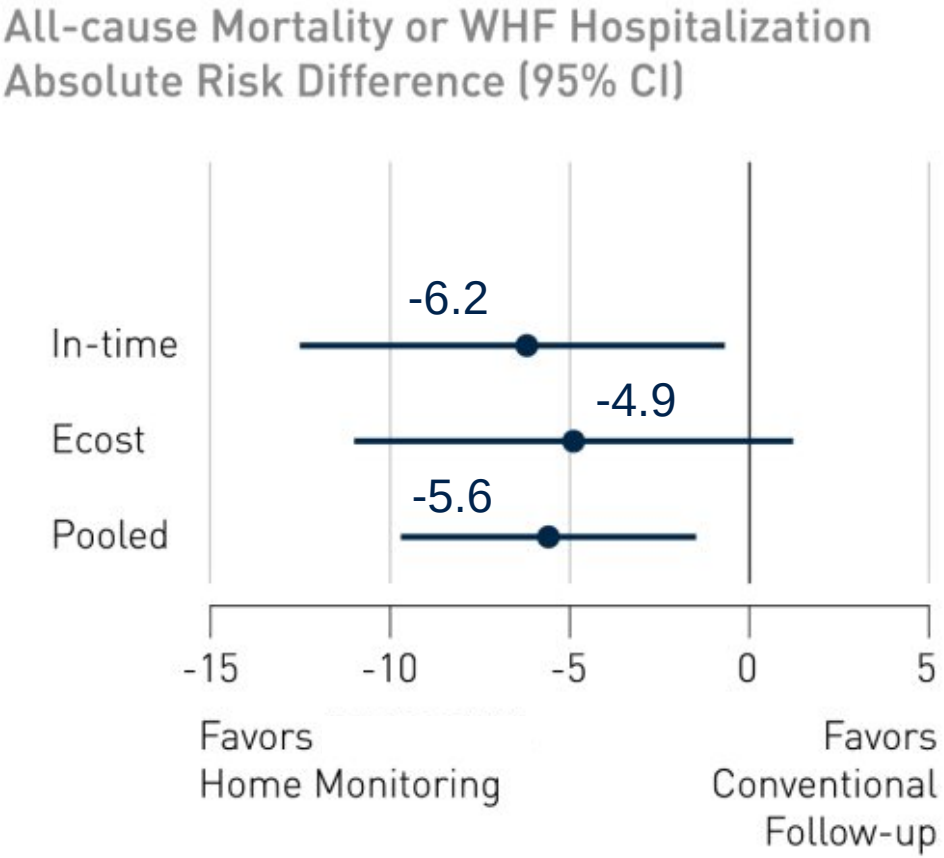
Significant Reduction of All-cause Death or WHF Hospitalization with Home Monitoring



- 5.6%

absolute reduction of all-cause death or WHF hospitalization at 1 year

95% CI: -9.7% to -1.5%
p=0.007

- Hindricks G, J. Proff, N. Varma, S. Kacet, T. Lewalter, P. Sogaard, L. Guedon-Moreau, TA. Gerds, SD. Anker
- Daily remote monitoring of implantable cardioverter-defibrillators: Pooled individual patient data from IN-TIME, ECOST, and TRUST trials suggest a mechanism of clinical benefit, ESC Congress 2016, Rome

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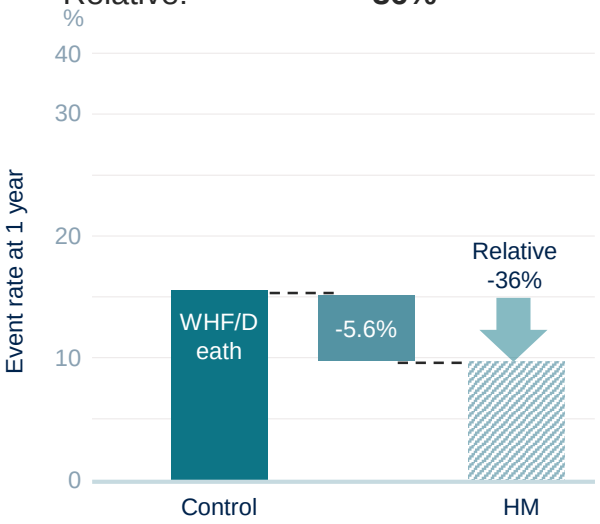
“Prevention of Heart Failure Exacerbation” as the Main Driver for the Observed Benefits

All-cause Mortality or …**WHF** hospitalization — is a subset of … **CV** hospitalization — is a subset of … **any** hospitalization

All-cause mortality or **WHF** hospitalization

Risk reduction

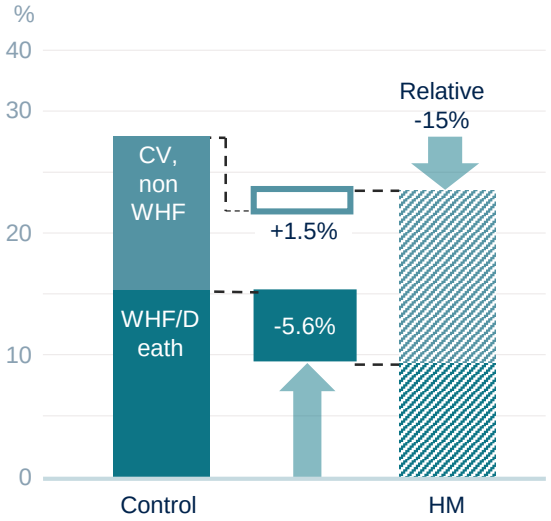
- Absolute: -5.6% (p=0.007)
- Relative: **-36%**



All-cause mortality or **CV** hospitalization

Risk reduction

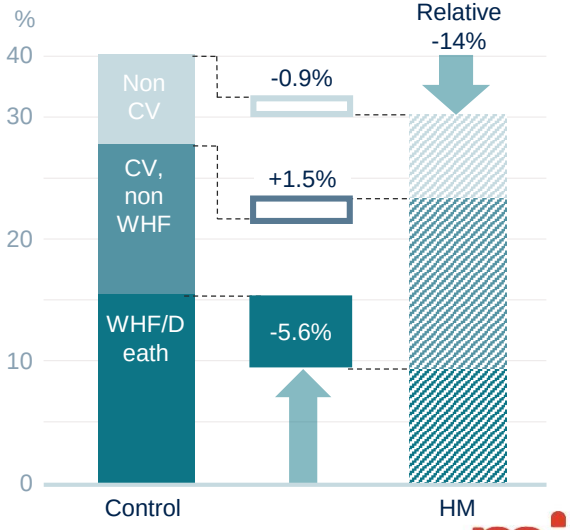
- Absolute: -4.1% (p=n.s.)
- Relative: **-15%**



All-cause mortality or **any** hospitalization

Risk reduction

- Absolute: -5.0% (p=n.s.)
- Relative: **-14%**



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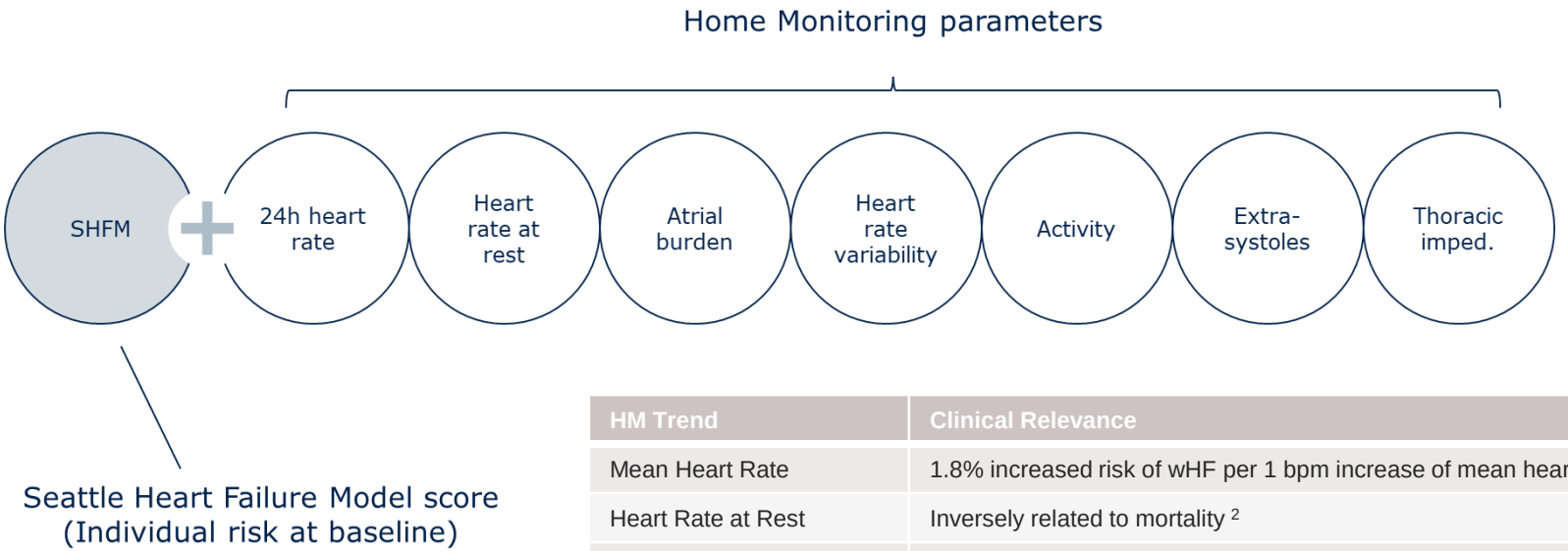
BIO.Detect HF IV Study (SELENE HF)
Heart Failure Index Derivation

Index Derivation

- Development of a logistic model including proper transformations of the home monitoring variables and adjusting with a baseline index
- Calculation of the composite index



HM Trend	Clinical Relevance
Mean Heart Rate	1.8% increased risk of wHF per 1 bpm increase of mean heart rate[1]
Heart Rate at Rest	Inversely related to mortality [2]
Atrial Burden	Well assessed predictor of wHF [3]
Heart Rate Variability	HRV reduction is associated with wHF [4]
Activity	Inability to maximal exercise for at least 4 minutes predicts death and wHF [5]
Extrasystolies	Associated with 5.5-fold increased risk of cardiovascular death [6]
Thoracic impedance	Congestion is the most common cause for hospitalization due to HF and readmission[7]

1: Lechat P et al. Circulation 2001; 103: 1428-1433
2: Hori M et al. Journal of Cardiology 60 (2012)86-90
3: Middlekauf HR et al. Circulation 1991; 84: 40-48
4: Fantoni C et al. J Am Coll Cardiol. 2005; 46(10):1875-1882
5: Madsen BK et al. Int J Cardiol. 1997; 58(2):151-62
6: Le VV et al. Ann Noninvasive Electrocardiol. 2010;15(1):56-62
7: Gheorghiade M et al. Am J Med 2006;119 (12 Suppl 1):S3–S10

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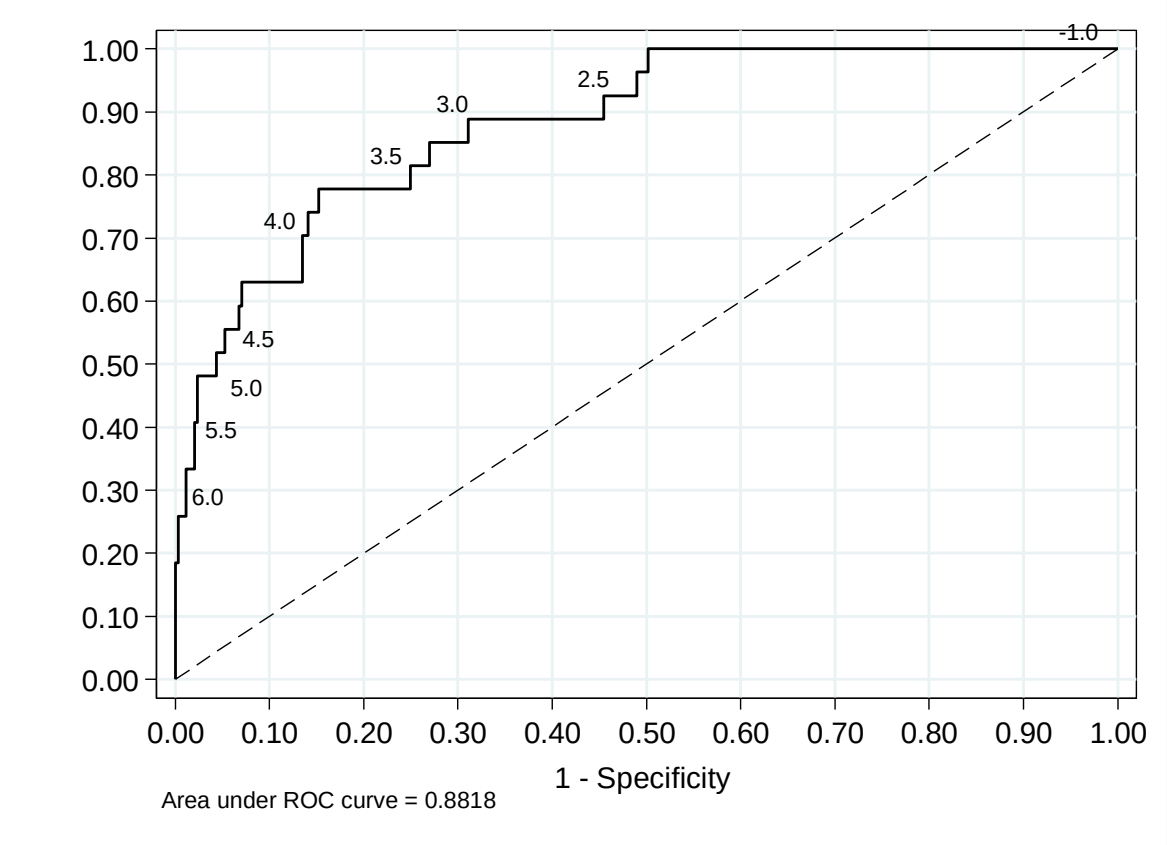
BIO.Detect HF IV Study – Index Derivation Results

Receiver Operating Curve (ROC)

- Area under curve (AUC) : 0.88
- Odds Ratio (OR)
  for index unitary increase : 2.72 (confidence interval (CI): 1.79-3.75; p<0.001)



True positive rate (sensitivity) is plotted against false postive rate (1-specificity)

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Conclusion

- Home Monitoring can be used to predict worsening of HF in ICD/CRT-D population with impaired LV Function.
- Parameters adressed in the Heart Failure Monitor are solid when used as a combined multi-factor analysis
- Patients well being and survival can be improved with Home Monitoring

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