Hindricks et al., presented at ESC, Rome 2016

# Daily Remote Monitoring of Implantable Cardioverter-Defibrillators:

Insights from the Pooled Patient-Level Data from Three Randomized Controlled Trials (IN-TIME, ECOST, TRUST)[1]

## Study Design

- Meta-analysis of three randomized controlled trials utilizing a remote monitoring system with daily transmission verification (BIOTRONIK Home Monitoring®)
- To verify the mortality findings of Parthiban et al.[2] and to explore mechanism of clinical benefit
- 2405 patients at 181 centers mainly in the USA, France and Germany

## Key Result

- Home Monitoring with daily transmission verification significantly reduced all-cause death and the composite endpoint of all-cause death or worsening heart failure (WHF) hospitalization.

| Clinical Endpoint (at 12 Months) | Relative Risk Reduction | Absolute Risk Reduction | |
|---|---|---|---|
| All-cause death | 38% ↓ | 1.9% ↓ | $p < 0.05$ |
| All-cause death or WHF hospitalization | 36% ↓ | 5.6% ↓ | $p < 0.01$ |

- Similar magnitudes of absolute risk reductions for WHF and cardiovascular endpoints suggest that the benefit of Home Monitoring is driven by the prevention of heart failure exacerbation.

## Clinical Relevance

- This analysis confirms the significant mortality benefit with BIOTRONIK Home Monitoring to be valid for all kind of ICD patients, independent from NYHA class, device type or any other baseline variable.
- The comparison of combined, cause-specific endpoints strongly indicates "prevention of heart failure exacerbation" as the specific mechanism for the observed clinical benefits.

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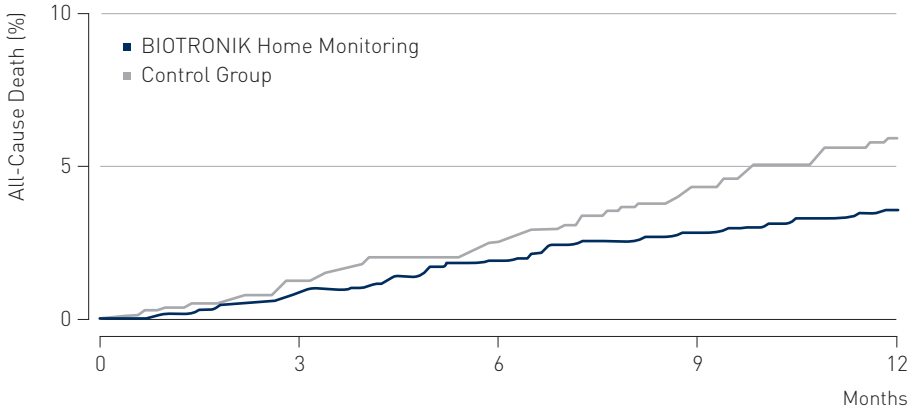
# BIOTRONIK Home Monitoring Is Associated with a Significant Reduction of Clinically Relevant Endpoints

## Time to All-Cause Death for Pooled TRUST, ECOST, and IN-TIME Patients



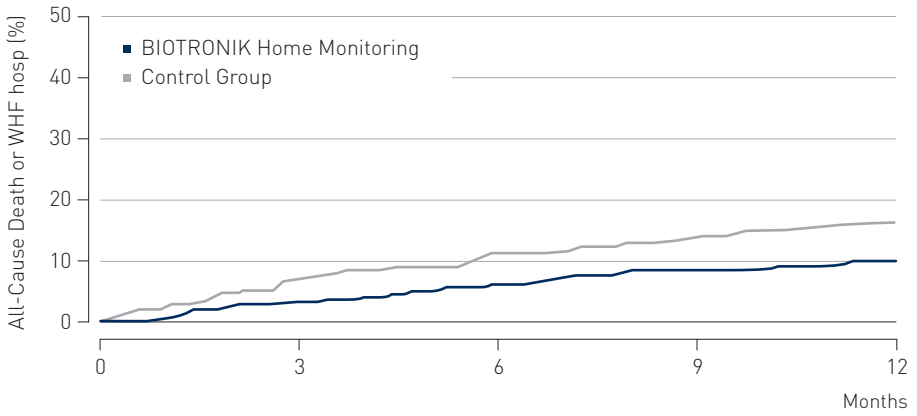

**38%** reduction of relative risk for **all-cause death** at 1 year

Relative risk = 0.62
95% CI: 0.40 to 0.95

Patients at Risk

| | | | | | |
|---|---|---|---|---|---|
| **Control:** | 960 | 925 | 881 | 826 | 612 |
| **HM:** | 1445 | 1402 | 1345 | 1293 | 1054 |

## Time to All-Cause Death or WHF Hospitalization for Pooled ECOST and IN-TIME Patients




**36%** reduction of relative risk for **all-cause death or WHF hospitalization** at 1 year

Relative risk = 0.64
95% CI: 0.45 to 0.89

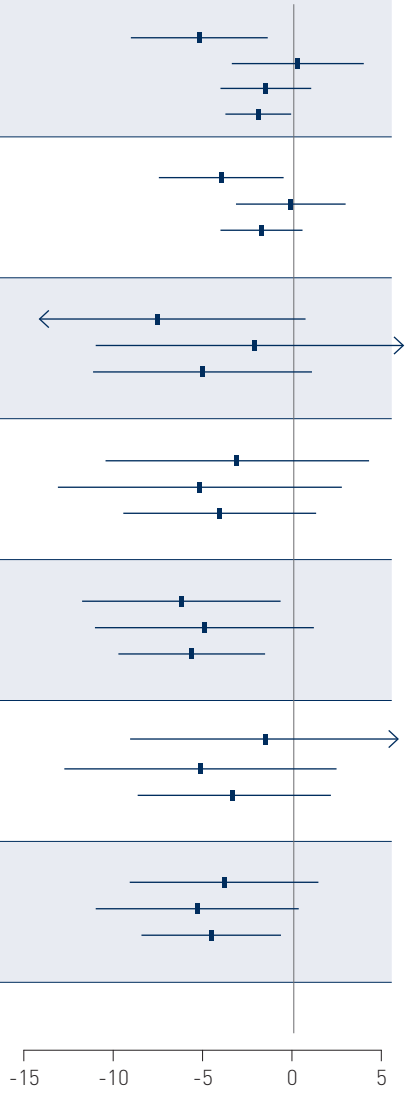
Patients at Risk

| | | | | | |
|---|---|---|---|---|---|
| **Control:** | 534 | 486 | 457 | 436 | 257 |
| **HM:** | 544 | 516 | 495 | 476 | 279 |

# The Clinical Benefits Are Driven by Prevention of Heart Failure Exacerbation

## Absolute Risk Differences (in %) for All Endpoints at 12 Months

| Outcome | Study | Absolute Risk Difference (95% CI) | P-value |
|---|---|---|---|
| All-cause death | IN-TIME | -5.3 (-9.1;-1.5) | |
| | ECOST | 0.3 (-3.4;4.0) | |
| | TRUST | -1.5 (-4.1;1.0) | |
| | Pooled | -1.9 (-3.8;-0.1) | 0.037 |
| CV death | IN-TIME | -4.0 (-7.5;-0.6) | |
| | ECOST | -0.1 (-3.2;2.9) | |
| | Pooled | -1.8 (-4.1;0.4) | 0.11 |
| All-cause death or any hospitalization | IN-TIME | -7.5 (-15.6;0.7) | |
| | ECOST | -2.2 (-11.0;6.7) | |
| | Pooled | -5.0 (-11.1;1.0) | 0.10 |
| All-cause death or CV hospitalization | IN-TIME | -3.1 (-10.5;4.2) | |
| | ECOST | -5.2 (-13.0;2.6) | |
| | Pooled | -4.1 (-9.5;1.2) | 0.13 |
| All-cause death or WHF hospitalization | IN-TIME | -6.2 (-11.8;-0.7) | |
| | ECOST | -4.9 (-11.0;1.2) | |
| | Pooled | -5.6 (-9.7;-1.5) | 0.007 |
| CV death or CV hospitalization | IN-TIME | -1.6 (-9.0;5.9) | |
| | ECOST | -5.2 (-12.7;2.4) | |
| | Pooled | -3.3 (-8.7;2.0) | 0.22 |
| WHF death or WHF hospitalization | IN-TIME | -3.9 (-9.1;1.4) | |
| | ECOST | -5.4 (-11.0;0.3) | |
| | Pooled | -4.6 (-8.4;-0.7) | 0.020 |




A negative value (reduction) is in favour of Home Monitoring.

# Meta-Analysis of Three Randomized Controlled Trials Utilizing a Remote Monitoring System with Daily Transmission Verification

## Pooled Individual Patient Data from IN-TIME, ECOST and TRUST

| | (a) IN-TIME | (b) ECOST | (c) TRUST |
|---|---|---|---|
| N° of centers | 26 sites in Germany, 10 sites elsewhere[3] | 43 sites in France | 102 sites in USA |
| Patient eligibility | Indication for ICD or CRT-D, heart failure (⩾3 months), NYHA class II or III, LVEF ⩽35% | Indication for ICD, not NYHA class IV | Class 1 indication for ICD, not pacemaker dependent |
| Primary objective | To compare heart failure outcomes using a clinical composite (Packer) score[4] | To compare major CVAEs including all-cause death | To evaluate safety and efficacy of extended IO intervals |
| Follow-up schedule | | | |
| HM group | IO at 12 M, and in-between according to hospital routine | IO at 1-3 M, 15 M, and 27 M. HM replaced IO at 9 M and 21 M | IO at 3 M and 15 M. HM replaced IO at 6 M, 9 M and 12 M |
| Control group | Same as in the HM group | IO at 1-3 M, then every 6 M | IO every 3 M |
| Blinded endpoint committee | Yes | Yes | No |

| Pooled Patient-Level Data | Analyzed Clinical Endpoints (All at 12 Month) |
|---|---|
| Death n=2405 (a+b+c) | ▪ All-cause death |
| Adjudicated death and hospitalization n=1078 (a+b) | ▪ CV death<br>▪ All-cause death or any hospitalization<br>▪ All-cause death or CV hospitalization<br>▪ All-cause death or worsening heart failure (WHF) hospitalization<br>▪ CV death or CV hospitalization<br>▪ WHF death or WHF hospitalization |


1 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: pooled individual patient data from IN-TIME, ECOST, and TRUST trials suggest a mechanism of clinical benefit; ESC 2016

2 Parthiban N, Esterman A, Mahajan R, Twomey DJ, Pathak RK, Lau DH, Roberts-Thomson KC, Young GD, Sanders P, Ganesan AN; Remote Monitoring of Implantable Cardioverter-Defibrillators: A Systematic Review and Meta-Analysis of Clinical Outcomes; J Am Coll Cardiol. 2015 Jun 23;65(24):2591-600.

3 Denmark (3 sites), Czech Republic (2), Israel (2), Australia (1), Austria (1), and Latvia (1).

4 The score combines all-cause death, overnight hospitalization for heart failure, change in NYHA class, and change in patient global self-assessment.


**Abbreviations**: **CI**, confidence interval; **CRT-D**, cardiac resynchronization therapy defibrillator; **CV**, cardiovascular; **CVAE**, cardiovascular adverse event; **ECOST**, Effectiveness and cost of ICDs follow-up schedule with telecardiology; **HM**, Home Monitoring; **hosp**, hospitalization; **ICD**, implantable cardioverter-defibrillator; **IN-TIME**, Influence of Home Monitoring on mortality and morbidity in heart failure patients with impaired left ventricular function; **IO**, in-office; **LVEF**, left ventricular ejection fraction; **M**, months; **NYHA**, New York Heart Association; **TRUST**, Lumos-T safely reduces routine office device follow-up; **WHF**, worsening heart failure

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