Telemonitoring in heart failure: IN TIME and beyond

Gerhard Hindricks

University of Leipzig
- Heart Center -
Dept. of Electrophysiology
Presenter Disclosure Information

Gerhard Hindricks has received honoraria for lectures from Biosense, Stereotaxis, St. Jude Medical, Biotronik.

Gerhard Hindricks is a member of the Advisory Board / consultant for Biosense, St. Jude Medical, Biotronik.
Telemedicine and heart failure: Expectations

- Guide heart failure therapy
- Early detection of HF worsening
- Prevention of HF decompensation
- Reduction of mortality, especially HF mortality
- Reduction of hospitalizations, especially HF hospitalizations
- Improvement of QoL
- Reduction of treatment costs
Telemonitoring and heart failure: Tele HF-Study

- 1653 pts. (61 yrs, 50% CAD, 50% NYHA III) with recent HF hospitalization were randomized to telemonitoring or conventional treatment

- Interactive automatic voice response system
  - weight and clinical symptoms

  Primary outcome parameter was mortality and any re-hospitalization

- Secondary outcome parameters: heart failure re-hospitalization, days in hospital, no. of hospitalizations

Chaudhry SI et al., NEJM 2011
Telemonitoring and heart failure: Tele HF-Study

Graph showing the probability of freedom from readmission or death over days since enrollment. The hazard ratio for readmission or death with telemonitoring is 1.04 (95% CI, 0.91–1.19) with a P-value of 0.58.

Chaudhry SI et al., NEJM 2011
Telemonitoring and heart failure: Tele HF-Study

Heart failure and home monitoring: the In Time Trial

Chaudhry SI et al., NEJM 2011
Telemonitoring and heart failure: Tele HF-Study

• Potential explanations for negative study outcome:
  - not the right patients selected/included
  - not the optimal monitoring parameter
  - not the optimal mode of monitoring
  - patient compliance and time windows

• Telemonitoring simply does not improve HF therapy
Automatic impedance alert: Dot HF- Study

- Prospective randomized evaluation of thoracic impedance based automatic patient alert to improve outcome in NYHA III ICD/CRT patients

- Primary endpoint was heart failure hospitalization and all cause mortality

- 335 pts. included [18% ICD, 82% CRT]

- Alert in case of preset impedance threshold crossing

- Follow up was 14.9 months

van Veldhuisen et al., Circulation 2011
Dot HF- Study: Hospitalization for heat failure

van Veldhuisen et al., Circulation 2011
Dot HF- Study: all cause mortality

Hazard ratio, 1.24 (CI, 0.63-2.44)
P = 0.54

van Veldhuisen et al., Circulation 2011
Heart failure and home monitoring: the In Time Trial

Pulmonary artery pressure monitoring: Champion Trial

Abraham WT et al., Am Heart J 2011
Pulmonary artery pressure monitoring: Champion Trial

Abraham WT et al., Lancet 2011
Wireless implantable hemodynamic monitor (W-IHM) was placed percutaneously in 550 pts. with advanced heart failure

Single blinded design; primary endpoint was heart failure related hospitalizations

83 HF hospitalizations occurred in 270 “on” pts.

120 HF hospitalization occurred in 280 “off” pts.

Use of W-IHM data reduced HF hospitalizations by 39%

Abraham WT et al., Lancet 2011
Heart failure and home monitoring: the In Time Trial

Pulmonary artery pressure monitoring: Champion Trial

---

**A**
- **Control group (254 hospital admissions for heart failure)**
- **Treatment group (158 hospital admissions for heart failure)**

Hazard ratio 0.63
(95% CI 0.52–0.77);
p<0.0001

**B**
- **Control group (138 patients with event)**
- **Treatment group (107 patients with event)**

Hazard ratio 0.73
(95% CI 0.57–0.94);
p=0.0146

---

**Number at risk**
- **Control group**
  - 280
  - 267
  - 252
  - 215
  - 179
  - 137
  - 105
  - 67
  - 25
  - 10
  - 0

- **Treatment group**
  - 270
  - 262
  - 244
  - 210
  - 169
  - 131
  - 108
  - 82
  - 29
  - 5
  - 1

---

Abraham WT et al., Lancet 2011
Heart failure and home monitoring: the In Time Trial

Home monitoring and heart failure: Background

Desai AS and Stevenson LW; NEJM 2010
A highly reliable RF transmitter integrated into the ICD device sends patient and device data on command.

The Cardio Messenger relays data to the Service Center using integrated cellular, and/or standard telephone technology for unsurpassed mobility and coverage.

Data is stored and formatted into a Cardio Report with informative trends, charts, parameters, IEGMs and graphs.

Critical patient and device data is transmitted immediately to the physician via Internet, E-mail, pager, cell phone, or fax. Trend analysis and status reporting are delivered on a periodic basis.
Home monitoring and heart failure: concept

- Automatic acquisition and transmission of data during follow-up
- No direct patient involvement
- Immediate access to data
- Short intervention times
- Automatic control / assessment of intervention result
- Which data are predictive for heart failure outcome?
Home monitoring and heart failure: Home Care Study

• Retrospective evaluation of parameters indicative for heart failure decompensation and death

• 377 patients with advanced heart failure were followed for 12 months after HM CRT device implantation

• Pre-defined parameters were assessed in the time window of 25 – 3 days before hospitalization or death

• Sensitivity and specificity for prediction of (I) hospitalization and (II) death were calculated

Sack S et al., Eur J Heart Fail 2011
### Heart failure and home monitoring: the In Time Trial

### Home monitoring and heart failure: Home Care Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n = 377</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>66.2 (10.0)</td>
</tr>
<tr>
<td>Female, %</td>
<td>21.5</td>
</tr>
<tr>
<td>LVEF (%), mean (SD)</td>
<td>24.5 (7.5)</td>
</tr>
<tr>
<td>% of patients with LVEF ≤35%</td>
<td>90.7</td>
</tr>
<tr>
<td>LVEDD (mm), mean (SD)</td>
<td>67.8 (15.8)</td>
</tr>
<tr>
<td>Aetiology of heart failure, %</td>
<td></td>
</tr>
<tr>
<td>Ischaemic (of which, myocardial infarction)</td>
<td>55.7 (75.2)</td>
</tr>
<tr>
<td>Non-ischaemic</td>
<td>44.3</td>
</tr>
<tr>
<td>NYHA class, %</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0.8</td>
</tr>
<tr>
<td>II</td>
<td>14.9</td>
</tr>
<tr>
<td>III</td>
<td>74.8</td>
</tr>
<tr>
<td>IV</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Sack S et al., Eur J Heart Fail 2011
Home Care: sensitivity to detect major CV event

A

(A) Mean heart rate (24h) 36.1
(B) Heart rate at rest 40.2
(C) Patient activity 23.6
(D) Right ventricular impedance 34.7
(E) Ventricular extrasystoles 30.5

Best two: A + B 43.0
Best three: A + B + D 54.1
Best four: A + B + D + E 54.1
All five 56.9

Sensitivity [%]

B

(F) P-P interval variability 50.0
(G) Painless shock impedance 46.2

All seven (A - G) 65.4

Sensitivity [%]

Sack S et al., Eur J Heart Fail 2011
Home Care Study: results

- Retrospective sensitivities for individual parameters ranged from 23.6 – 50%.

- Optimal combination of parameters increased sensitivity to 65.4% for cardiovascular hospitalization and death with a 99.5% specificity

- This corresponds to 1.83 false-positive detections per patient-year of follow-up

- These results need to be confirmed in prospective studies

Sack S et al., Eur J Heart Fail 2011
The In Time Trial

- Prospective, randomized, controlled, international
- 720 HF patients, 50 centers

- 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

Hindricks et al.; Lancet 2014, in press
Each patient is classified by the end of the study as:
  – Improved
  – Unchanged
  – Worse

Based on events such as:
  – 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 assessment score
  – Discontinuation of study protocol due to worsening heart failure, treatment failure or lacking therapeutic response

Primary end point: Packer Score

Heart failure and home monitoring: the In Time Trial
The In Time Study: Secondary end points

- All-cause mortality
- Number of re-hospitalizations (> 1 day) due to worsening heart failure
- Correlation of values of HM parameters with the clinical status
- Incidence and reasons for HM based interventions
- Additional follow ups due to technical HM messages
- HM workflow analysis
Centralized Home Monitoring organization

Central monitoring unit (Heart Center Leipzig)

Alert to specified HM events repeatedly until obtaining feedback

Account of the measures undertaken

Physician (clinic)

Patient call + (if needed) advising FU at the GP or initiating FU at clinic

Answers on phone + (if needed) visit to GP/clinic

Patient

Heart failure and home monitoring: the In Time Trial
Heart failure and home monitoring: the In Time Trial

In Time: Patient flow

716 enrolled

Run-in phase (1 month)

664 randomized
Analysis population

52 excluded before randomization
- 18 consent withdrawal
- 11 inclusion criteria violated
- 7 missing 1-month FU
- 4 death
- 12 other reasons

333 HM

331 Control

82 terminated the study prematurely:
- Total: 30 vs. 52 (HM vs. control)
- Death: 10 vs. 27
- Consent withdrawal: 4 vs. 4
- Lost to FU: 6 vs. 9
- Other reasons: 10 vs. 12

306 regular termination

283 regular termination

Crossover = 0

Hindricks et al.; Lancet 2014, in press
Heart failure and home monitoring: the In Time Trial

In Time: Demographics and medical history of analysis population at enrollment

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>HM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Recruitment</strong></td>
<td>664 (100)</td>
<td>333 (50,2)</td>
<td>331 (49,8)</td>
</tr>
<tr>
<td>Age, years</td>
<td>65,5 ± 9,4</td>
<td>65,3 ± 9,3</td>
<td>65,8 ± 9,6</td>
</tr>
<tr>
<td>Female</td>
<td>129 (19,4)</td>
<td>60 (18)</td>
<td>69 (20,8)</td>
</tr>
<tr>
<td><strong>Aetiology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>458 (69)</td>
<td>233 (70)</td>
<td>225 (68)</td>
</tr>
<tr>
<td>Non-ischemic</td>
<td>206 (31)</td>
<td>100 (30)</td>
<td>106 (32)</td>
</tr>
<tr>
<td><strong>Cardiovascular and pulmonary medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>463 (69,7)</td>
<td>242 (72,7)</td>
<td>221 (66,8)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>72 (10,8)</td>
<td>40 (12,0)</td>
<td>32 (9,7)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>94 (14,2)</td>
<td>48 (14,4)</td>
<td>46 (13,9)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>168 (25,3)</td>
<td>76 (22,8)</td>
<td>92 (27,9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>266 (40,1)</td>
<td>131 (39,3)</td>
<td>135 (40,8)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>199 (30)</td>
<td>99 (29,7)</td>
<td>100 (30,2)</td>
</tr>
</tbody>
</table>

Mean ± SD, or n (%)

Hindricks G et al., Lancet 2014, in press
## Status at enrollment

<table>
<thead>
<tr>
<th>Status at enrollment</th>
<th>All</th>
<th>HM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>172 ± 9</td>
<td>173 ± 9</td>
<td>172 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84 ± 16</td>
<td>84 ± 16</td>
<td>83 ± 16</td>
</tr>
<tr>
<td>BMI</td>
<td>28 ± 4,6</td>
<td>28 ± 4,4</td>
<td>28,1 ± 4,7</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>285 (43)</td>
<td>150 (45,2)</td>
<td>135 (40,8)</td>
</tr>
<tr>
<td>Class III</td>
<td>378 (57)</td>
<td>182 (54,8)</td>
<td>196 (59,2)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>25,8 ± 6,6</td>
<td>26 ± 6,5</td>
<td>25,6 ± 6,6</td>
</tr>
<tr>
<td>Intrinsic QRS duration, ms</td>
<td>134 ± 34</td>
<td>135 ± 33</td>
<td>133 ± 36</td>
</tr>
<tr>
<td>Resting heart rate</td>
<td>70,2 ± 13,8</td>
<td>70,3 ± 13,8</td>
<td>70,1 ± 13,9</td>
</tr>
<tr>
<td>Indication for defibrillator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prophylaxis</td>
<td>525 (79,1)</td>
<td>265 (79,6)</td>
<td>260 (78,5)</td>
</tr>
<tr>
<td>Secondary prophylaxis</td>
<td>139 (20,9)</td>
<td>68 (20,4)</td>
<td>71 (21,5)</td>
</tr>
<tr>
<td>SCA with documented VT/VF</td>
<td>31 (4,7)</td>
<td>13 (3,9)</td>
<td>18 (5,4)</td>
</tr>
<tr>
<td>SCA with inducible VT/VF</td>
<td>26 (3,9)</td>
<td>15 (4,5)</td>
<td>11 (3,3)</td>
</tr>
<tr>
<td>Implanted device</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
<td>390 (58,7)</td>
<td>190 (57,1)</td>
<td>200 (60,4)</td>
</tr>
<tr>
<td>ICD</td>
<td>274 (41,3)</td>
<td>143 (42,9)</td>
<td>131 (39,6)</td>
</tr>
</tbody>
</table>

Mean ± SD, or n (%)
Heart failure and home monitoring: the In Time Trial

In Time Results: modified Packer Score

<table>
<thead>
<tr>
<th></th>
<th>HM arm (n = 333)</th>
<th>Control arm (n = 331)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsened</td>
<td>18.9%</td>
<td>27.5%</td>
</tr>
<tr>
<td>Improved or unchanged</td>
<td>81.1%</td>
<td>72.5%</td>
</tr>
</tbody>
</table>

* $\chi^2$ test

Hindricks G et al., Lancet 2014, in press
Heart failure and home monitoring: the In Time Trial

In Time Results: CRT D versus ICD

\[ P = 0.58 \]

 CRT-D

RR = 0.75
\[ P = 0.10 \]

ICD

RR = 0.61
\[ P = 0.06 \]

worsened

control

HM

control

HM

30%

23%

23%

14%
Heart failure and home monitoring: the In Time Trial

All-cause mortality

HR: 0.356 (95% CI: 0.172–0.735)
Heart failure and home monitoring: the In Time Trial

Cardiovascular mortality

HR: 0.367  (95% CI: 0.162–0.828)

Cumulative survival

Time from 1-month FU to study termination (days)

Control arm
(21 deaths)

HM arm
(8 deaths)

P = 0.012
(Logrank test)
Transmission reliability and related workload

Transmissions received: > 85 %
additional workload: 0,3 in-hospital visits per patient year

85 % 4 /Jahr 2,2 /Jahr 0,3 /Jahr
306 patient years
Main events triggering further care

Heart failure and home monitoring: the In Time Trial

- Abnormales IEGM: 55
- VES-Trend: 54
- Patientenaktivität: 1
- VT oder Schock: 56
- AT: 109
- % CRT: 92

- Elektrodenparameter: 43
- Klinische Ereignisse: 367
- Übertragung: 821
Main events triggering further care

- Abnormal IEGM: 15%
- Pacing or impedance: 5%
- Transmission: 3%
- VES trend: 7%
- Patient Activity: 0%
- VT or shock: 0%
- % CRT

Heart failure and home monitoring: the In Time Trial
Conclusions

• In-Time is the first implant-based remote monitoring RCT demonstrating significant benefits of implant-based home monitoring for patients with advanced heart failure.

• In the home monitoring arm of the trial:
  - the number of heart failure patients with worsening of the clinical status was significantly reduced.
  - total mortality and cardiovascular mortality were significantly reduced compared to standard care.

• Home monitoring based detection of changes in clinical status or technical events can trigger medical action that prevents worsening of heart failure.
Heart failure and home monitoring: the In Time Trial

**In-Time investigational sites (36):**

<table>
<thead>
<tr>
<th>Location</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Australia (1):</strong></td>
<td></td>
</tr>
<tr>
<td>Wahroonga</td>
<td>(Sydney Adventist Hospital)</td>
</tr>
<tr>
<td><strong>Austria (1):</strong></td>
<td></td>
</tr>
<tr>
<td>Innsbruck</td>
<td>(Uni-klinik für Innere Medizin)</td>
</tr>
<tr>
<td><strong>Czech Republic (2):</strong></td>
<td></td>
</tr>
<tr>
<td>Prague</td>
<td>(IKEM)</td>
</tr>
<tr>
<td>Prague</td>
<td>(Na Homolce)</td>
</tr>
<tr>
<td><strong>Denmark (3):</strong></td>
<td></td>
</tr>
<tr>
<td>Aalborg</td>
<td>(Aalborg Hospital)</td>
</tr>
<tr>
<td>Aarhus</td>
<td>(Uni-hospital, Skejby Sygehus)</td>
</tr>
<tr>
<td>Hellerup</td>
<td>(Gentofte Hospital)</td>
</tr>
<tr>
<td><strong>Germany (26):</strong></td>
<td></td>
</tr>
<tr>
<td>Bad Berka</td>
<td>(Zentralklinik Bad Berka)</td>
</tr>
<tr>
<td>Bad Neustadt</td>
<td>(Herz- und Gefäß-Klinik)</td>
</tr>
<tr>
<td>Bad Segeberg</td>
<td>(Segeberger Kliniken)</td>
</tr>
<tr>
<td>Berlin</td>
<td>(Charité – Campus Benjamin Franklin)</td>
</tr>
<tr>
<td>Berlin</td>
<td>(Vivantes Humboldt-Klinikum)</td>
</tr>
<tr>
<td>Berlin</td>
<td>(Vivantes Klinikum am Urban)</td>
</tr>
<tr>
<td>Berlin</td>
<td>(Vivantes Klinikum Neukölln)</td>
</tr>
<tr>
<td>Bielefeld</td>
<td>(Städtische Kliniken Bielefeld Mitte)</td>
</tr>
<tr>
<td>Bonn</td>
<td>(Uni-klinikum Bonn)</td>
</tr>
<tr>
<td><strong>Germany continued</strong></td>
<td></td>
</tr>
<tr>
<td>Coburg</td>
<td>(Klinikum Coburg)</td>
</tr>
<tr>
<td>Detmold</td>
<td>(Klinikum Lippe-Detmold)</td>
</tr>
<tr>
<td>Essen</td>
<td>(Uni-klinikum Essen)</td>
</tr>
<tr>
<td>Hannover</td>
<td>(MH Hannnover)</td>
</tr>
<tr>
<td>Homburg/Saar</td>
<td>(Uni-klinikum des Saarlandes)</td>
</tr>
<tr>
<td>Leipzig</td>
<td>(Herzzentrum Leipzig)</td>
</tr>
<tr>
<td>Leipzig</td>
<td>(Klinikum St. Georg)</td>
</tr>
<tr>
<td>Lübeck</td>
<td>(Uni-klinikum Schleswig-Holstein)</td>
</tr>
<tr>
<td>Lünen</td>
<td>(St. Marienhospital Lünen)</td>
</tr>
<tr>
<td>München</td>
<td>(Augustinum)</td>
</tr>
<tr>
<td>München</td>
<td>(Herzzentrum München-Bogenhaus.)</td>
</tr>
<tr>
<td>München</td>
<td>(Kard. Gem.-Praxis Dr. Mühling)</td>
</tr>
<tr>
<td>München</td>
<td>(Klinikum Schwabing)</td>
</tr>
<tr>
<td>München</td>
<td>(Klinikum Großhadern)</td>
</tr>
<tr>
<td>Nordhausen</td>
<td>(Kard. Gemeinschaftspraxis)</td>
</tr>
<tr>
<td>Paderborn</td>
<td>(St. Vincenz Krankenhaus)</td>
</tr>
<tr>
<td>Pirna</td>
<td>(Klinikum Pirna)</td>
</tr>
<tr>
<td><strong>Israel (2):</strong></td>
<td></td>
</tr>
<tr>
<td>Ashkelon</td>
<td>(Barzilai Medical Center)</td>
</tr>
<tr>
<td>Tel-Hashomer</td>
<td>(Chaim Sheba Medical Center)</td>
</tr>
<tr>
<td><strong>Latvia (1):</strong></td>
<td></td>
</tr>
<tr>
<td>Riga</td>
<td>(P. Stradins Clinical University Hosp.)</td>
</tr>
</tbody>
</table>