Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial

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Summary

Background An increasing number of patients with heart failure receive implantable cardioverter-defibrillators (ICDs) or cardiac resynchronisation defibrillators (CRT-Ds) with telemonitoring function. Early detection of worsening heart failure, or upstream factors predisposing to worsening heart failure, by implant-based telemonitoring might enable pre-emptive intervention and improve outcomes, but the evidence is weak. We investigated this possibility in IN-TIME, a clinical trial.

Methods We did this randomised, controlled trial at 36 tertiary clinical centres and hospitals in Australia, Europe, and Israel. We enrolled patients with chronic heart failure, NYHA class II–III symptoms, ejection fraction of no more than 35%, optimal drug treatment, no permanent atrial fibrillation, and a recent dual-chamber ICD or CRT-D implantation. After a 1 month run-in phase, patients were randomly assigned (1:1) to either automatic, daily, implant-based, multiparameter telemonitoring in addition to standard care or standard care without telemonitoring. Investigators were not masked to treatment allocation. Patients were masked to allocation unless they were contacted because of telemonitoring findings. Follow-up was 1 year. The primary outcome measure was a composite clinical score combining all-cause death, overnight hospital admission for heart failure, change in NYHA class, and change in patient global self-assessment, for the intention-to-treat population. The trial is registered with ClinicalTrials.gov, number NCT00538356.

Findings We enrolled 716 patients, of whom 664 were randomly assigned (333 to telemonitoring, 331 to control). Mean age was 65.5 years and mean ejection fraction was 26%. 285 (43%) of patients had NYHA functional class II and 378 (57%) had NYHA class III. Most patients received CRT-Ds (390; 58.7%). At 1 year, 63 (18.9%) of 333 patients in the telemonitoring group versus 90 (27.2%) of 331 in the control group (p=0.013) had worsened composite score (odds ratio 0.63, 95% CI 0.43–0.90). Ten versus 27 patients died during follow-up.

Interpretation Automatic, daily, implant-based, multiparameter telemonitoring can significantly improve clinical outcomes for patients with heart failure. Such telemonitoring is feasible and should be used in clinical practice.

Funding Biotronik SE & Co. KG.

Introduction

In selected patients with heart failure and left ventricular systolic dysfunction, treatment with implantable cardioverter-defibrillators (ICDs) or cardiac resynchronisation therapy defibrillators (CRT-Ds) reduces all-cause mortality and hospital admissions for heart failure and other major cardiovascular events.1,2 These devices afford the chance to automatically monitor physiological and technical data.2,3 Early detection of worsening heart failure, or of upstream factors predisposing to worsening heart failure, by a telemonitoring implant could enable pre-emptive medical intervention and improve outcomes beyond those achieved with stand-alone implantable devices, but the evidence is weak.2,4 The predisposing factors and precursors for poor clinical outcome or heart failure exacerbation include ventricular tachyarrhythmia, defibrillation shocks, onset of atrial fibrillation, low heart rate variability, low percentage of biventricular pacing, change in patient activity, abnormal sensing and other technical issues, lung fluid accumulation, and some haemodynamic variables.2,5 We did the INfluence of home moniTToring on mortality and morbidity in heart failure patients with IMpaired IEFventricular function (IN-TIME) trial to evaluate the incremental benefit of automatic multiparameter telemonitoring for patients with heart failure treated with an ICD or a CRT-D.

Methods

Study design and participants

We did this randomised controlled trial at 36 tertiary clinical centres, in Australia (one site), Europe (33 sites), and Israel (two sites; appendix). Details of the trial design have been published previously.6 Consenting patients who were at least 18 years old were enrolled if they had chronic heart failure lasting for at least 3 months, New York Heart Association (NYHA) functional class II or III, a left ventricular ejection fraction of no more than 35%, and an indication for dual-chamber ICD or CRT-D treatment according to European guidelines. Patients were excluded if they had uncontrolled hypertension, permanent atrial fibrillation, or rare adverse disorders
such as restrictive or infiltrative or hypertrophic cardiomyopathy, constrictive pericarditis, acute myocarditis, tricuspid valve replacement, severe mitral regurgitation, or symptomatic aortic stenosis.19

After a run-in phase of 1 month, patients were randomly assigned if they had stable optimal drug treatment, automatic data telemonitoring accomplished on at least 80% of all days (or a corrective action initiated if <80%), no acute coronary syndrome or cardiac surgery or stroke in the past 6 weeks, and no planned cardiac surgery within the next 3 months.

Patients provided written informed consent. The study was done in compliance with good clinical practice guidelines and the Declaration of Helsinki, including approval of the study protocol by appropriate national and local ethics committees.

Randomisation and masking

Patients were randomly assigned (1:1) to receive telemonitoring in addition to standard care or to standard care without telemonitoring for 12 months. The randomisation was done through a centralised, concealed process implemented by the sponsor and stratified by site. The random allocation sequence with variable and randomised block size (sizes four or six) was computer generated and concealed from the sites. After reporting implantation date and the serial number of the implanted device, the site received the patient’s group allocation by fax. Investigators were not masked to treatment allocation. Patients were masked to allocation unless they were contacted because of telemonitoring findings.

Procedures

Patients received a commercially available Lumax dual-chamber ICD or CRT-D (Biotronik SE & Co. KG, Berlin, Germany), equipped with a Biotronik Home Monitoring function. At a set time every day (typically 0300 h) or on detection of tachyarrhythmia, the devices transmitted cumulative and last-saved diagnostic data.14,15 A small portable patient device receives the data and relays them automatically over mobile telephone links to the Biotronik Home Monitoring Service Center (Berlin, Germany). Data from all countries were processed automatically and posted on a secure internet site accessible to patients’ physicians.

In the telemonitoring group, transmitted data were reviewed by study investigators according to their clinical routine. In parallel, transmitted data were reviewed by a central monitoring unit composed of trained study nurses and supporting physicians, located at the Heart Center Leipzig (Germany). The role of this unit was to ensure the awareness of investigational sites to pre-defined medical events such as ventricular and atrial tachyarrhythmia episodes, low percentage of biventricular pacing, increase in the frequency of ventricular extrasystoles, decreased patient activity, and abnormal intracardiac electrogram.16

On working days, the central monitoring unit redundantly forwarded these events and standard technical safety notifications issued by the telemonitoring system to investigational sites. The investigational site had to confirm receipt of the reports within 48 h, otherwise the message was repeated.

A clinical response to telemonitoring observations was done at the discretion of investigators. When contacting patients on the basis of telemonitored data, the investigators did a standardised telephone interview to establish whether the patient’s overall condition or dyspnoea had worsened, whether the patient was regularly taking prescribed drugs, and whether the patient’s weight had increased by more than 2 kg over the preceding 3 days. In addition to the interview, the investigators reported whether an additional clinical follow-up was scheduled and whether a visit to the family doctor was recommended.

In the control group, no study participant had access to telemonitoring data until study completion. All patients were treated according to European guidelines. The need for follow-up visits was decided by the treating physician except for the mandatory 12-month visit after randomisation (at the end of follow-up). At each clinical follow-up, NYHA classification was re-assessed and patients graded their overall condition as unchanged or slightly, moderately, or markedly worsened, or improved since randomisation (global self-assessment).17

Outcomes

The primary outcome was worsening of a composite clinical score at 12 months in the intention-to-treat population.23 Designed specifically for patients with heart failure, this score combines the occurrence of a major clinical event (death or hospital admission for heart failure), as objective evidence of change in clinical...
status, with NYHA functional classification, which relies on the physician as the observer, and the global self-assessment, which relies on the patient as the observer. Accordingly, the patient’s status was classified as worsened if they died, had unplanned overnight admission to hospital associated with worsening heart failure, had worse NYHA functional class, or had moderately to markedly worse self-reported overall condition compared with at randomisation.\textsuperscript{13–15} Otherwise, the patient’s status could be unchanged or improved—both positive outcomes, given that heart failure is a progressive disease. Although new, this score has been used in several large studies of patients with heart failure receiving cardiac resynchronisation treatment.\textsuperscript{13–15}

The clinically relevant secondary outcome measures were all-cause mortality and hospital admission because of worsening heart failure in the intention-to-treat population. An endpoint committee (appendix), masked to treatment allocation, judged endpoints and verified the composite clinical score for each patient.

Statistical analysis

We postulated that the number of patients with worsened clinical status would differ significantly between the two study groups. We calculated that a sample size of 620 patients was needed to detect a difference in the proportion with worsened clinical status of 10 percentage points (30% in the control group, 20% in the telemonitoring group) with a statistical power (1–β) of 80%.\textsuperscript{10} However, fewer patients than expected were admitted to hospital halfway through the study in an ad hoc masked review. We therefore amended the protocol to enrol 720 patients, to provide 85% power.

We imputed missing data for NYHA classification or global self-assessment by last observation carried forward. We used logistic regression and Cox regression models to calculate odds ratios (ORs) for the composite clinical score and hazard ratios (HRs) for mortality. We analysed time-to-event data with the Kaplan-Meier method and compared them with the log-rank test. Continuous data were non-normally distributed and so were compared with the Mann–Whitney–Wilcoxon rank sum test. We compared categorical data, including the primary endpoint with the exact Pearson’s \( \chi^2 \) test. We considered a two-sided p value of less than 0.05 as statistically significant. We did the analyses with SPSS (version 22).

This study is registered with ClinicalTrials.gov, number NCT00538356.

Role of the funding source

The funder assisted in study design, data collection, data analysis, and preparing this report. They had no role in data interpretation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From July 24, 2007, to Dec 17, 2010, 716 patients were enrolled, of whom 664 were randomly assigned (figure 1): 333 to the telemonitoring group, 331 to the control group. Characteristics at enrolment were reasonably well balanced between the two groups (table 1). Mean age at enrolment was 65·5 years (SD 9·4), and 536 (81%) patients were men. Mean left ventricular ejection fraction was 26% (SD 7%). 582 (88%) of 664 patients completed follow-up, 37 died (6%), and 45 (7%) terminated the study prematurely (figure 1). All patients received their allocated treatment. Mean length of follow-up until regular or premature study termination was 335 days (SD 79) in the telemonitoring group and 326 days (SD 90) in the control group. 238 patients (all in the telemonitoring group) were contacted during follow-up as a result of telemonitoring findings, and so were unmasked to their treatment allocation.

<table>
<thead>
<tr>
<th>Characteristics at enrolment</th>
<th>Telemonitoring group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65·3 (9·3)</td>
<td>66·8 (9·6)</td>
</tr>
<tr>
<td>Men</td>
<td>274 (82·3%)</td>
<td>262 (79·2%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>26·6% (6%)</td>
<td>26·7% (7%)</td>
</tr>
<tr>
<td>NYHA†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>150 (45·2%)</td>
<td>135 (40·8%)</td>
</tr>
<tr>
<td>Class II</td>
<td>182 (54·8%)</td>
<td>196 (59·2%)</td>
</tr>
<tr>
<td>Intrinsics QRS duration (ms)</td>
<td>135 (33)</td>
<td>133 (36)</td>
</tr>
<tr>
<td>Implantated device</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
<td>190 (57·1%)</td>
<td>200 (60·4%)</td>
</tr>
<tr>
<td>Dual-chamber ICD</td>
<td>143 (42·9%)</td>
<td>131 (39·6%)</td>
</tr>
<tr>
<td>Primary prevention indication for defibrillator</td>
<td>265 (79·6%)</td>
<td>260 (78·5%)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>233 (70·0%)</td>
<td>225 (68·0%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>34 (10·2%)</td>
<td>27 (8·2%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>242 (72·7%)</td>
<td>221 (66·8%)</td>
</tr>
<tr>
<td>Paroxysmal or persistent atrial fibrillation</td>
<td>76 (22·8%)</td>
<td>92 (27·9%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>48 (14·4%)</td>
<td>46 (13·9%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>131 (39·3%)</td>
<td>135 (40·8%)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>99 (29·7%)</td>
<td>100 (30·2%)</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>317 (95·2%)</td>
<td>303 (91·5%)</td>
</tr>
<tr>
<td>ACE inhibitor or angiotensin-converting enzyme blocker</td>
<td>307 (92·2%)</td>
<td>286 (86·4%)</td>
</tr>
<tr>
<td>( \beta ) blocker</td>
<td>304 (91·3%)</td>
<td>304 (91·8%)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>30 (9·0%)</td>
<td>42 (12·7%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>66 (19·8%)</td>
<td>61 (18·4%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>30 (9·0%)</td>
<td>40 (12·1%)</td>
</tr>
<tr>
<td>Any antiarrhythmic drug</td>
<td>45 (13·5%)</td>
<td>61 (18·4%)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>41 (12·3%)</td>
<td>41 (12·4%)</td>
</tr>
<tr>
<td>Lipid-lowering drug</td>
<td>249 (74·8%)</td>
<td>228 (68·9%)</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>218 (65·5%)</td>
<td>207 (62·5%)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>106 (31·8%)</td>
<td>97 (29·3%)</td>
</tr>
</tbody>
</table>

Data are mean (SD) or n (%). ACE=angiotensin-converting enzyme. CRT-D=cardiac resynchronisation therapy defibrillator. ICD=implantable cardioverter-defibrillator. NYHA=New York Heart Association. *Assessed within 3 months before enrolment. †Unknown for one patient in the telemonitoring group.

Table 1: Characteristics at enrolment
At the end of the study, 63 (18·9%) of 333 patients in the telemonitoring group and 90 (27·2%) of 331 in the control group (p=0·013) had worsened composite clinical score (OR 0·63, 95% CI 0·43–0·90; table 2). This difference was mainly driven by the lower mortality in the telemonitoring group than in the control group (ten vs 27 deaths). The Kaplan-Meier estimate of 1-year all-cause mortality was 2·7% in the telemonitoring group and 6·8% in the control group (log-rank p=0·012; HR 0·37, 95% CI 0·16–0·83).

The telemonitoring group and the control group did not differ significantly for the number of hospital admissions for worsening heart failure (44 vs 47, p=0·38) or the number of patients affected (27 vs 34, p=0·35). Likewise, median length of stay in hospital did not differ significantly between groups (8 days, IQR 5–12 vs 7 days 3–10, p=0·21). In exploratory, post-hoc analyses, we recorded no significant difference for worsening NYHA functional class for telemonitoring versus control groups (29 patients vs 35 patients, p=0·43) or for moderate-to-marked worsening self-assessed patient condition (ten patients vs seven patients, p=0·63).

In a post-hoc exploratory analysis, we assessed the primary outcome within subgroups (figure 3). We detected no significant interaction between subgroups and treatment effect, except for history of atrial fibrillation (figure 3): patients with a history of atrial fibrillation were more likely to benefit from telemonitoring than were patients without such a history. The relative benefit of telemonitoring was similar by device type: for patients with ICDs, the composite clinical score worsened in 20 (14·0%) of 143 patients in the telemonitoring group versus 30 (22·9%) of 131 patients in the control group; for patients with CRT-Ds, composite clinical score worsened for 43 (22·6%) of 190 patients versus 60 (30·0%) of 200.

We imputed data for six patients (0·9%) with missing NYHA classification or global self-assessment at 1 year, and it never resulted in worsened primary outcome. Furthermore, of the 15 patients who were lost to follow-up (figure 1), all but two (one in each group) were known to be alive at 1 year because their devices were transmitting data. In a post-hoc sensitivity analysis, neither classification of the six patients with missing data or the 15 patients lost to follow-up as worsened, nor exclusion of these patients from the primary outcome analysis had a significant effect on the p value (data not shown).

In an exploratory analysis, we assessed telemonitoring data and contact with patients in the telemonitoring group (table 3). 1225 observations for 280 patients (84%) were forwarded by the central monitoring unit to investigational sites during 306 cumulative patient-years of follow-up, which corresponds to 4·0 observations per patient year. In response to telemonitoring data, investigators made contact with 238 patients (71%), on 641 occasions (2·1 contacts per patient year). An observation did not result in patient contact when it was repetitive or related to a known

### Table 2: Results for composite clinical score

<table>
<thead>
<tr>
<th></th>
<th>Telemonitoring group (n=333)</th>
<th>Control group (n=331)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsened</td>
<td>63 (18·9%)</td>
<td>90 (27·2%)</td>
<td>0·032*</td>
</tr>
<tr>
<td>Death</td>
<td>10 (3·0%)</td>
<td>27 (8·2%)</td>
<td>0·004†</td>
</tr>
<tr>
<td>Overnight admission to hospital for worsening heart failure†</td>
<td>22 (6·9%)</td>
<td>27 (8·2%)</td>
<td>—</td>
</tr>
<tr>
<td>Worsened NYHA functional class and global self-assessment‡</td>
<td>23 (6·9%)</td>
<td>31 (9·4%)</td>
<td>—</td>
</tr>
<tr>
<td>Worsened NYHA functional class only</td>
<td>23 (6·9%)</td>
<td>31 (9·4%)</td>
<td>—</td>
</tr>
<tr>
<td>Worsened global self-assessment only</td>
<td>7 (2·1%)</td>
<td>4 (1·2%)</td>
<td>—</td>
</tr>
<tr>
<td>Improved‡</td>
<td>111 (33·3%)</td>
<td>105 (31·7%)</td>
<td>—</td>
</tr>
<tr>
<td>Unchanged</td>
<td>159 (47·8%)</td>
<td>136 (41·1%)</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are n (%). Patients are included only once, in the topmost subcategory. †Also statistically significant difference in a post-hoc multivariable logistic regression model after adjustment for use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (the only substantial imbalance between groups at randomisation; data not shown). ‡Improved NYHA class or angiotensin-converting enzyme inhibitors.

### Figure 2: Kaplan-Meier curves of patient survival

Eight deaths in the telemonitoring group versus 21 in the control group were cardiovascular, including six versus 15 from worsening heart failure, one versus two sudden deaths, and one versus four for other reasons. In a post-hoc analysis, the Kaplan-Meier estimate of 1-year cardiovascular mortality was 2·7% in the telemonitoring group and 6·8% in the control group (log-rank p=0·012; HR 0·37, 95% CI 0·16–0·83).
condition, or when a clinical visit had already been scheduled for the near future.

Short gaps in data transmission were the most frequent observations because patients who were absent from home for 3 or more consecutive days did not usually take along the patient device that relayed data to the central monitoring unit and investigation sites. Taking all telemonitored patients together, transmissions occurred on 85% of days per patient-year. Patient interviews prompted by all categories of events showed a worsened overall condition or progressive dyspnoea for 40 (12%) of 333 patients, deviation in drug use in 51 (15%) of 333 patients, and rapid weight gain in no patients.

In response to telemonitoring data and patient interviews, 99 additional follow-up visits to a specialized centre for device follow-up or visits to the family doctor were scheduled clinical follow-up or a suggested patient visit to their family doctor.

The total number of follow-up controls at investigational sites after the randomisation visit was 958 in the telemonitoring group (corresponding to 3·13 follow-up controls per patient-year) and 844 in the control group (2·86 follow-up controls per patient-year).

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Number of events</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥67 years</td>
<td>Tele-monitoring</td>
<td>182</td>
<td>0·68 (0·40–1·12)</td>
<td>0·16</td>
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<tr>
<td></td>
<td>Control group</td>
<td>179</td>
<td>0·59 (0·36–0·98)</td>
<td>0·042</td>
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<tr>
<td>≥75 years</td>
<td>Tele-monitoring</td>
<td>351</td>
<td>0·71 (0·43–1·18)</td>
<td>0·18</td>
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<tr>
<td></td>
<td>Control group</td>
<td>346</td>
<td>0·57 (0·33–1·01)</td>
<td>0·034</td>
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<tr>
<td>LVEF within 3 months of enrolment*</td>
<td>Tele-monitoring</td>
<td>29</td>
<td>0·65 (0·43–0·97)</td>
<td>0·026</td>
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<tr>
<td></td>
<td>Control group</td>
<td>34</td>
<td>0·54 (0·23–1·27)</td>
<td>0·16</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Tele-monitoring</td>
<td>274</td>
<td>0·69 (0·44–1·08)</td>
<td>0·11</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>262</td>
<td>0·54 (0·29–1·01)</td>
<td>0·053</td>
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<td>Women</td>
<td>Tele-monitoring</td>
<td>59</td>
<td>0·69 (0·44–1·08)</td>
<td>0·11</td>
</tr>
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<td></td>
<td>Control group</td>
<td>69</td>
<td>0·54 (0·29–1·01)</td>
<td>0·053</td>
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<tr>
<td>NYHA at enrolment*</td>
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<tr>
<td>I–II</td>
<td>Tele-monitoring</td>
<td>150</td>
<td>0·69 (0·44–1·08)</td>
<td>0·11</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>150</td>
<td>0·54 (0·29–1·01)</td>
<td>0·053</td>
</tr>
<tr>
<td>III</td>
<td>Tele-monitoring</td>
<td>182</td>
<td>0·69 (0·44–1·08)</td>
<td>0·11</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>196</td>
<td>0·54 (0·29–1·01)</td>
<td>0·053</td>
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<tr>
<td>NYHA at 1 month*</td>
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<td></td>
<td></td>
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<tr>
<td>I–II</td>
<td>Tele-monitoring</td>
<td>233</td>
<td>0·80 (0·52–1·24)</td>
<td>0·32</td>
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<tr>
<td></td>
<td>Control group</td>
<td>223</td>
<td>0·34 (0·16–0·70)</td>
<td>0·003</td>
</tr>
<tr>
<td>III–IV</td>
<td>Tele-monitoring</td>
<td>99</td>
<td>0·69 (0·44–1·08)</td>
<td>0·11</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>108</td>
<td>0·34 (0·16–0·70)</td>
<td>0·003</td>
</tr>
<tr>
<td>History of atrial fibrillation*</td>
<td>Tele-monitoring</td>
<td>76</td>
<td>1·06 (0·58–1·93)</td>
<td>0·91</td>
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<tr>
<td></td>
<td>Control group</td>
<td>72</td>
<td>0·60 (0·41–0·99)</td>
<td>0·011</td>
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<tr>
<td>Device type</td>
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</tr>
<tr>
<td>ICD</td>
<td>Tele-monitoring</td>
<td>143</td>
<td>0·69 (0·44–1·08)</td>
<td>0·11</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>131</td>
<td>0·54 (0·29–1·01)</td>
<td>0·053</td>
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<tr>
<td>CRT-D</td>
<td>Tele-monitoring</td>
<td>190</td>
<td>0·69 (0·44–1·08)</td>
<td>0·11</td>
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<tr>
<td></td>
<td>Control group</td>
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<td>0·54 (0·29–1·01)</td>
<td>0·053</td>
</tr>
<tr>
<td>ACE/ARB use at enrolment</td>
<td>Tele-monitoring</td>
<td>26</td>
<td>1·06 (0·58–1·93)</td>
<td>0·91</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>45</td>
<td>0·60 (0·41–0·99)</td>
<td>0·011</td>
</tr>
<tr>
<td>No</td>
<td>Tele-monitoring</td>
<td>257</td>
<td>0·80 (0·52–1·24)</td>
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</tr>
<tr>
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<td>Control group</td>
<td>238</td>
<td>0·34 (0·16–0·70)</td>
<td>0·003</td>
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<tr>
<td>Yes</td>
<td>Tele-monitoring</td>
<td>76</td>
<td>1·06 (0·58–1·93)</td>
<td>0·91</td>
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<tr>
<td></td>
<td>Control group</td>
<td>92</td>
<td>0·60 (0·41–0·99)</td>
<td>0·011</td>
</tr>
<tr>
<td>Device type</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>Tele-monitoring</td>
<td>143</td>
<td>0·69 (0·44–1·08)</td>
<td>0·11</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>131</td>
<td>0·54 (0·29–1·01)</td>
<td>0·053</td>
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<tr>
<td>CRT-D</td>
<td>Tele-monitoring</td>
<td>190</td>
<td>0·69 (0·44–1·08)</td>
<td>0·11</td>
</tr>
<tr>
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<td>200</td>
<td>0·54 (0·29–1·01)</td>
<td>0·053</td>
</tr>
<tr>
<td>ACE/ARB use at enrolment</td>
<td>Tele-monitoring</td>
<td>26</td>
<td>1·06 (0·58–1·93)</td>
<td>0·91</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>45</td>
<td>0·60 (0·41–0·99)</td>
<td>0·011</td>
</tr>
</tbody>
</table>

Table 3: Results of telemonitoring and clinical reactions

<table>
<thead>
<tr>
<th>Observation sent to investigational site</th>
<th>Patient contact by investigational site</th>
<th>Further action by investigational site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular tachyarrhythmia or shock†</td>
<td>42 (56)</td>
<td>24 (38)</td>
</tr>
<tr>
<td>Attrial tachyarrhythmia</td>
<td>65 (99)</td>
<td>53 (70)</td>
</tr>
<tr>
<td>CRT &lt;80% over 48 h‡</td>
<td>35 (91)</td>
<td>28 (65)</td>
</tr>
<tr>
<td>Ventricular extrasystole frequency &gt;110 per hour or increasing trend over 7 days</td>
<td>46 (54)</td>
<td>34 (39)</td>
</tr>
<tr>
<td>Decreasing trend of patient activity over 7 days</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Abnormal EGM or sensing safety notification¶</td>
<td>34 (51)</td>
<td>20 (25)</td>
</tr>
<tr>
<td>Pacing or impedance safety notification</td>
<td></td>
<td>26 (43)</td>
</tr>
<tr>
<td>Gap in data transmission of &gt;3 days</td>
<td>241 (818)</td>
<td>174 (401)</td>
</tr>
<tr>
<td>Total</td>
<td>280 (1225)</td>
<td>238 (641)</td>
</tr>
<tr>
<td>Mean per patient-year</td>
<td>4.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Median per patient-year (IQR)</td>
<td>3.0 (1.1–5.7)</td>
<td>1.1 (0.0–3.0)</td>
</tr>
</tbody>
</table>

Table 3: Results of telemonitoring and clinical reactions

*Data missing for some patients. ACE/ARB=angiotensin-converting enzyme or angiotensin-receptor blocker. CRT-D=cardiac resynchronisation therapy defibrillator. ICD=implantable cardioverter-defibrillator. LVEF=left ventricular ejection fraction. NYHA=New York Heart Association functional class.

Figure 3: Subgroup analyses of worsened composite clinical score

Odds ratios and p values are based on logistic regression. For age and LVEF, we used a median split. *Data missing for some patients. ACE/ARB=angiotensin-converting enzyme or angiotensin-receptor blocker. CRT-D=cardiac resynchronisation therapy defibrillator. ICD=implantable cardioverter-defibrillator. LVEF=left ventricular ejection fraction. NYHA=New York Heart Association functional class.
Discussion

In patients with heart failure treated with ICDs and CRT-Ds, automatic, daily, implant-based telemonitoring of rhythmic and technical parameters had a significantly beneficial effect on the composite clinical score and all-cause mortality. The favourable effect of telemonitoring seemed to arise from careful attention to various kinds of remote data without a single, typical scenario. In our opinion, three mechanisms contributed in parallel to the improved clinical outcome, but their relative contributions are unclear.

One mechanism was early detection of the onset or progression of ventricular and atrial tachyarrhythmias. As shown by several large studies, patients with ventricular tachyarrhythmia have a significantly higher risk of heart failure and non-sudden cardiac death, and need special attention to modify clinical outcomes. Likewise, early detection of atrial tachyarrhythmia, followed by drug treatment, cardioversion, or catheter ablation, reduces stroke and suppresses irregular, rapid ventricular response that might otherwise trigger haemodynamic instability and worsening congestive heart failure. The potential link between atrial fibrillation and the telemonitoring benefit we report from IN-TIME is substantiated by our findings that atrial tachyarrhythmia was the medical telemonitoring observation that most often led to patient contact and that patients with history of atrial fibrillation benefited more from telemonitoring than did the patients without such a history.

The second possible mechanism of telemonitoring benefit was early recognition of suboptimal device function. Achievement of nearly 100% biventricular pacing is highly desirable in cardiac resynchronisation treatment because anything lower hinders left ventricular remodelling and is linked with higher mortality. Similarly, unnecessary defibrillation shocks can have adverse inotropic, arrhythmic, or haemodynamic effects and are associated with a doubled risk of death in the subsequent months. The commonest cause of inappropriate shocks and of reduced biventricular pacing reduction is atrial fibrillation and other supraventricular tachyarrhythmias, emphasising the importance of early detection of these, usually asymptomatic, arrhythmias. Inappropriate shocks can also be triggered by T-wave oversensing, electrical noise from fractured leads, and other sensing disorders that can be noticed in remotely monitored intracardiac electrocardiograms well before they result in shocks.

The third possible mechanism of benefit was patient interview prompted by telemonitoring, which occasionally revealed symptomatic worsening or noncompliance to drugs. Patient interviews raised patients’ awareness of relevant developments and encouraged them to take more responsibility for their own health, including adherence to prescribed treatments.

The effects of telemonitoring depend on the reaction of health-care professionals to the transmitted data. To ensure that clinicians reacted appropriately, the central monitoring unit also screened telemonitored data in the study. This unit is redundant when clinical attitude to telemonitoring is appropriate. Because our results are derived from patients at 36 investigational sites in seven countries across a range of geographic and practice settings, the external validity of the study is not a concern unless a health-care system differs substantially from those studied here.

Only one other large, randomised, controlled trial has so far compared mortality for the telemonitoring system we used (n=908) with no telemonitoring (n=431), in a population of patients with milder heart failure than in our study and who were treated solely with ICDs (panel). In that study, 1-year mortality was lower in the telemonitoring group but not significantly so (3·6% vs 5·8%, p=0·17). Other implant-based telemonitoring systems, typically with weekly data transmission, had no effect on hard clinical outcomes in randomised controlled trials. However, in an observational study of 10 272 patients with ICDs or CRT-Ds, both 1-year and 5-year mortality were 50% lower for implant-based remote follow-up with an average of four transmissions per month than with no telemonitoring (p<0·001), but a patient selection bias cannot be excluded.

An alternative to implant-based telemonitoring is patient-managed transmission of data for measures such as bodyweight, blood pressure, and heart rate, measured with external devices and combined with symptom reports. A meta-analysis showed that patient-managed telemonitoring reduces all-cause mortality (risk ratio 0·66, 95% CI 0·54–0·81, p<0·0001; from 2710 patients from 11 clinical studies) and hospital admissions for worsening heart failure (risk ratio 0·79, 95% CI 0·67–0·94, p=0·008; 1570 patients, four studies). As in our study, telemonitoring had a stronger effect on mortality than on hospital admissions. However,
two large trials of external telemedicine devices could not confirm these benefits.29,30 External devices cannot be easily compared with implant-based telenotifying technology because different variables are monitored and patients have different levels of involvement. In principle, implant-based technology enables fully automated transmission of several dozens of parameters, including details of atrial and ventricular arrhythmia episodes.

We will further analyse the data from IN-TIME to investigate the relative contribution and implications of the mechanisms of clinical benefit of telenotifying. However, teasing out the contribution of each mechanism might be difficult: Inglis and colleagues,13 in their meta-analysis of 26 studies with 8323 patients using external telemedicine devices or structured telephone support, concluded that the precise mechanisms by which these interventions produced beneficial effects are unclear but probably relate to a combination of improved implementation of and adherence to guideline treatments, early identification of complications or disease progression, and a positive effect on patient psychology. The number of hospital admissions for worsening heart failure was low in our study but similar to the number in the TIM-HF trial of external telemedicine devices.19 Both studies enrolled patients with chronic heart failure (and no hospital admission within 30 days) and otherwise similar characteristics. Half of the 710 patients in TIM-HF had ICDs and CRT-Ds.

The major limitation of our study was the inability to mask patients and investigators to the treatment allocation. The potential bias inherent in a non-blinded intervention study is a shortcoming; however subjective components of the composite clinical score had much less effect on our results than did mortality. Other limitations were the medium-term length of follow-up and the fact that we neither enforced standardised treatment after telenotifying observations nor thoroughly recorded clinical actions. The latter limited our ability to analyse the role of treatment changes in the clinical benefit in the telenotifying group.

The telenotifying technique presented here is feasible and should be used in clinical practice for patients with heart failure and an indication for an indication for ICD or CRT-D treatment.

References
13 Linde C, Abraham WT, Gold MR, St John Sutton M, Gluho S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008; 52: 1834–43.