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.

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See **Online** for appendix

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.[3–7] 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.[3–11] 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.[3–11]

We did the INfluence of home moniToring on mortality and morbidity in heart failure patients with IMpaired lEft ventricular 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.[10] 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.[10]

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

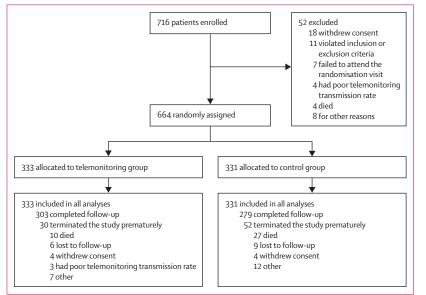Patients received a commercially available Lumax dual-chamber ICD or CRT-D (Biotronik SE & Co. KG, Berlin, Germany), equipped with a Biotronik Home Monitoring function. At a set time every day (typically 0300 h) or on detection of tachyarrhythmia, the devices transmitted cumulative and last-saved diagnostic data.[3,4,8–10] 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.[10] 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).[12]

Outcomes

The primary outcome was worsening of a composite clinical score at 12 months in the intention-to-treat population.[12] 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

Figure 1: Trial profile

716 patients enrolled

52 excluded
 18 withdrew consent
 11 violated inclusion or exclusion criteria
 7 failed to attend the randomisation visit
 4 had poor telemonitoring transmission rate
 4 died
 8 for other reasons

664 randomly assigned

333 allocated to telemonitoring group

331 allocated to control group

333 included in all analyses
 303 completed follow-up
 30 terminated the study prematurely
  10 died
  6 lost to follow-up
  4 withdrew consent
  3 had poor telemonitoring transmission rate
  7 other

331 included in all analyses
 279 completed follow-up
 52 terminated the study prematurely
  27 died
  9 lost to follow-up
  4 withdrew consent
  12 other

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.[12–14] 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.[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%.[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 compared with the Mann–Whitney–Wilcoxon rank sum test. We compared categorical data, including the primary endpoint with the exact Pearson's χ^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.

	Telemonitoring group (n=333)	Control group (n=331)
Age (years)	65·3 (9·3)	65·8 (9·6)
Men	274 (82·3%)	262 (79·2%)
Left ventricular ejection fraction* (%)	26% (6%)	26% (7%)
NYHA†		
Class II	150 (45·2%)	135 (40·8%)
Class III	182 (54·8%)	196 (59·2%)
Intrinsic QRS duration (ms)	135 (33)	133 (36)
Implanted device		
CRT-D	190 (57·1%)	200 (60·4%)
Dual-chamber ICD	143 (42·9%)	131 (39·6%)
Primary prevention indication for defibrillator	265 (79·6%)	260 (78·5%)
Medical history		
Coronary artery disease	233 (70·0%)	225 (68·0%)
Stroke	34 (10·2%)	27 (8·2%)
Hypertension	242 (72·7%)	221 (66·8%)
Paroxysmal or persistent atrial fibrillation	76 (22·8%)	92 (27·9%)
Chronic obstructive pulmonary disease	48 (14·4%)	46 (13·9%)
Diabetes	131 (39·3%)	135 (40·8%)
Renal insufficiency	99 (29·7%)	100 (30·2%)
Drugs		
Diuretic	317 (95·2%)	303 (91·5%)
ACE inhibitor or angiotensin-receptor blocker	307 (92·2%)	286 (86·4%)
β blocker	304 (91·3%)	304 (91·8%)
Calcium channel blocker	30 (9·0%)	42 (12·7%)
Digitalis	66 (19·8%)	61 (18·4%)
Amiodarone	30 (9·0%)	40 (12·1%)
Any antiarrhythmic drug	45 (13·5%)	61 (18·4%)
Nitrate	41 (12·3%)	41 (12·4%)
Lipid-lowering drug	249 (74·8%)	228 (68·9%)
Antiplatelet	218 (65·5%)	207 (62·5%)
Anticoagulant	106 (31·8%)	97 (29·3%)

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**

	Telemonitoring group (n=333)	Control group (n=331)	p value
Worsened	63 (18·9%)	90 (27·2%)	0·013*
Death	10 (3·0%)	27 (8·2%)	0·004*
Overnight admission to hospital for worsening heart failure†	23 (6·9%)	27 (8·2%)	..
Worsened NYHA functional class and global self-assessment	0 (0·0%)	1 (0·3%)	..
Worsened NYHA functional class only	23 (6·9%)	31 (9·4%)	..
Worsened global self-assessment only	7 (2·1%)	4 (1·2%)	..
Improved‡	111 (33·3%)	105 (31·7%)	..
Unchanged	159 (47·8%)	136 (41·1%)	..

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). †Adjudicated by an endpoint committee masked to patients' treatment assignment (appendix). ‡Improved NYHA class or moderately to markedly improved self-assessed condition. NYHA=New York Heart Association.

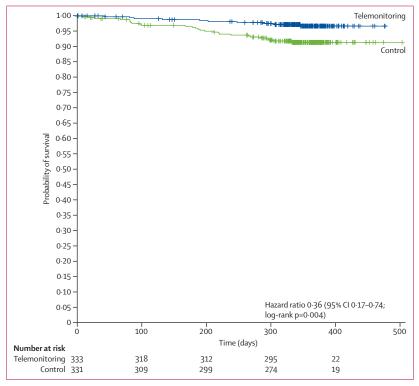*Table 2:* Results for composite clinical score

Figure 2: Kaplan-Meier curves of patient survival

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 in the telemonitoring group was 3·4% versus 8·7% in the control group (log-rank p=0·004; HR 0·36, 95% CI 0·17–0·74; figure 2).

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).

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

	Number of patients		Number of events		Odds ratio (95% CI)		p value	p interaction
	Tele-monitoring group	Control group	Tele-monitoring group	Control group				
Age (years)								0·71
≤67 years	182	170	29	37		0·68 (0·40–1·17)	0·16	
>67 years	151	161	34	53		0·59 (0·36–0·98)	0·042	
LVEF within 3 months of enrolment*								0·58
≤25%	168	166	36	46		0·71 (0·43–1·18)	0·18	
>25%	150	151	25	39		0·57 (0·33–1·01)	0·054	
Sex								0·71
Men	274	262	53	71		0·65 (0·43–0·97)	0·034	
Women	59	69	10	19		0·54 (0·23–1·27)	0·16	
NYHA at enrolment*								0·16
II	150	135	16	29		0·44 (0·23–0·85)	0·014	
III	182	196	47	61		0·77 (0·49–1·21)	0·26	
NYHA at 1 month*								0·53
I–II	233	223	42	54		0·69 (0·44–1·08)	0·11	
III–IV	99	108	21	36		0·54 (0·29–1·01)	0·053	
History of atrial fibrillation*								0·044
No	257	238	50	55		0·80 (0·52–1·24)	0·32	
Yes	76	92	13	35		0·34 (0·16–0·70)	0·003	
Device type								0·58
ICD	143	131	20	30		0·55 (0·29–1·02)	0·058	
CRT-D	190	200	43	60		0·68 (0·43–1·08)	0·10	
ACE/ARB use at enrolment								0·31
No	26	45	9	15		1·06 (0·38–2·93)	0·91	
Yes	307	286	54	75		0·60 (0·41–0·89)	0·011	
All	**333**	**331**	**63**	**90**		**0·63 (0·43–0·90)**	**0·012**	

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.

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 specialised centre for device follow-up or visits to the family doctor were scheduled for 63 patients (19%; table 3), corresponding to 0·32 extra visits per patient-year. The median reaction time after a telemonitoring alert was 1 day (IQR 0–6) to patient contact, and 2 days (IQR 1–14) to follow-up.

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).

	Observation sent to investigational site	Patient contact by investigational site	Further action by investigational site*
Ventricular tachyarrhythmia or shock†	42 (56)	24 (38)	15 (22)
Atrial tachyarrhythmia‡	65 (109)	53 (70)	18 (24)
CRT <80% over 48 h§	35 (91)	28 (63)	15 (26)
Ventricular extrasystole frequency >110 per hour or increasing trend over 7 days	46 (54)	34 (39)	7 (7)
Decreasing trend of patient activity over 7 days	1 (1)	1 (1)	0 (0)
Abnormal IEGM or sensing safety notification¶	34 (51)	20 (25)	14 (15)
Pacing or impedance safety notification‖	26 (43)	13 (14)	5 (5)
Gap in data transmission of >3 days	241 (818)	174 (401)	4 (4)
Total	280 (1225)	238 (641)	63 (99)
Mean per patient-year	4·0	2·1	0·3
Median per patient-year (IQR)	3·0 (1·1–5·7)	1·1 (0·0–3·0)	0·0 (0·0–0·0)

Data are number of patients (number of events) unless stated otherwise. Observations were forwarded by the central monitoring unit to investigational sites. CRT=Cardiac resynchronisation treatment. IEGM=intracardiac electrogram. *A scheduled clinical follow-up or a suggested patient visit to their family doctor. †Could include inappropriate detections. ‡The first onset of atrial fibrillation for >30 s, a long atrial arrhythmia episode (≥6 h) with high ventricular rate (>120 beats per minute), or high atrial arrhythmia daily burden (≥50%) on 7 consecutive days. §Percentage of biventricular pacing needed for effective cardiac resynchronisation treatment. ¶Abnormal IEGM:T-wave oversensing, far-field atrial sensing of ventricular activity, or other suspected sensing problem; sensing safety notification: low sensing amplitude or insufficient safety margin on any lead. ‖Pacing safety notification: low safety margin for stimulation on right or left ventricular lead; impedance safety notification: out-of-range impedance of any lead.

Table 3: Results of telemonitoring and clinical reactions

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,[5,16–18] 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 worsen congestive heart failure.[19–21] 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.[22,23]

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.[16,18,24] The commonest cause of inappropriate shocks and of reduced biventricular pacing reduction is atrial fibrillation and other supraventricular tachyarrhythmias,[18,22–25] 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.[3,24–27]

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.[5]

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 clincal 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).[4] 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.[6,7,28] 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.[5]

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.[29–31] A meta-analysis[31] 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,

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Panel: **Research in context**

Systematic review

We searched PubMed with the terms "ICD/CRT-D" or "defibrillator telemonitoring, remote monitoring, or home monitoring", combined with "mortality", "death", "hospitalization", "composite score", "infarction", or "stroke". No up-to-date systematic reviews of the published work exist. Few randomised controlled studies have assessed hard clinical benefits of implant-based multiparameter telemonitoring, mostly as secondary endpoints, and none have shown a significant effect.[4,6,7,28] One observational study[5] of 10 272 patients showed that telemonitoring reduced 1-year and 5-year mortality by 50%.

Interpretation

Our study is the first randomised controlled trial showing a significant benefit of implant-based multiparameter telemonitoring on the clinical status of patients with heart failure. Such telemonitoring is feasible and should be used in clinical practice.

two large trials of external telemedicine devices could not confirm these benefits.[29,30] External devices cannot be easily compared with implant-based telemonitoring 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 telemonitoring. However, teasing out the contribution of each mechanism might be difficult: Inglis and colleagues,[31] 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.[30] 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 telemonitoring observations nor thoroughly recorded clinical actions. The latter limited our ability to analyse the role of treatment changes in the clinical benefit in the telemonitoring group.

The telemonitoring 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.

Contributors
GH designed the study; collected, verified, analysed, and interpreted data; searched previously published work; and wrote the first draft and revised later drafts of the Article. Other members of the Steering Committee (authors MT, BS, TL, MB, JK, SS, and PS) designed the study; collected, verified, and interpreted data; searched the published work; and revised the Article. The remaining authors (MG, UH, AK, JB, AG, DH, and CP) collected and verified data, and revised the Article.

Declaration of interests
GH is a member of the advisory board or consultant in Biotronik, Biosense, St Jude Medical, Stereotaxis, and Cyberheart, and has received honoraria for lectures from these companies except for Cyberheart. JK is a member of the advisory board or consultant in Boston Scientific,

Biosense Webster, GE Healthcare, Siemens Healthcare, and St Jude Medical. He has received honoraria for lectures from Biotronik, Boston Scientific, Biosense Webster, Hansen Medical, Medtronic, and St Jude Medical. PS is a consultant for Biotronik and has received equipment from GE Health Care and from EBR Systems. CP has received personal fees and grants from Biotronik and SJM. The other authors declare no competing interests.

References
1   Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352:** 225–37.
2   Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary. *Circulation* 2013; **128:** 1810–52.
3   Burri H, Senouf D. Remote monitoring and follow-up of pacemakers and implantable cardioverter defibrillators. *Europace* 2009; **11:** 701–09.
4   Varma N, Epstein AE, Irimpen A, Schweikert R, Love C. Efficacy and safety of automatic remote monitoring for implantable cardioverter-defibrillator follow-up: the Lumos-T Safely Reduces Routine Office Device Follow-up (TRUST) trial. *Circulation* 2010; **122:** 325–32.
5   Saxon LA, Hayes DL, Gilliam FR, et al. Long-term outcome after ICD and CRT implantation and influence of remote device follow-up: the ALTITUDE survival study. *Circulation* 2010; **122:** 2359–67.
6   Crossley GH, Boyle A, Vitense H, Chang Y, Mead RH. The CONNECT (Clinical Evaluation of Remote Notification to Reduce Time to Clinical Decision) trial: the value of wireless remote monitoring with automatic clinician alerts. *J Am Coll Cardiol* 2011; **57:** 1181–89.
7   Landolina M, Perego GB, Lunati M, et al. Remote monitoring reduces healthcare use and improves quality of care in heart failure patients with implantable defibrillators: the evolution of management strategies of heart failure patients with implantable defibrillators (EVOLVO) study. *Circulation* 2012; **125:** 2985–92.
8   Sack S, Wende CM, Nagele H, et al. 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. *Eur J Heart Fail* 2011; **13:** 1019–27.
9   Varma N, Wilkoff B. Device features for managing patients with heart failure. *Heart Fail Clin* 2011; **7:** 215–25.
10   Arya A, Block M, Kautzner J, et al. Influence of home monitoring on the clinical status of heart failure patients: design and rationale of the IN-TIME study. *Eur J Heart Fail* 2008; **10:** 1143–48.
11   Hasan A, Paul V. Telemonitoring in chronic heart failure. *Eur Heart J* 2011; **32:** 1457–64.
12   Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail* 2001; **7:** 176–82.
13   Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio 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.
14   Martin DO, Day JD, Lai PY, et al. Atrial support pacing in heart failure: results from the multicenter PEGASUS CRT trial. *J Cardiovasc Electrophysiol* 2012; **23:** 1317–25.
15   Chung ES, Leon AR, Tavazzi L, et al. Results of the predictors of response to CRT (PROSPECT) trial. *Circulation* 2008; **117:** 2608–16.

16 Moss AJ, Greenberg H, Case RB, et al. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. *Circulation* 2004; **110:** 3760–65.

17 Saxon LA, Bristow MR, Boehmer J, et al. Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. *Circulation* 2006; **114:** 2766–72.

18 Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med* 2008; **359:** 1009–17.

19 Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012; **366:** 120–29.

20 Daubert JC. Introduction to atrial fibrillation and heart failure: a mutually noxious association. *Europace* 2004; **5** (suppl 1)**:** S1–S4.

21 Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003; **107:** 2920–25.

22 Gasparini M, Auricchio A, Metra M, et al. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. *Eur Heart J* 2008; **29:** 1644–52.

23 Hayes DL, Boehmer JP, Day JD, et al. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. *Heart Rhythm* 2011; **8:** 1469–75.

24 Daubert JP, Zareba W, Cannom DS, et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. *J Am Coll Cardiol* 2008; **51:** 1357–65.

25 Koneru JN, Swerdlow CD, Wood MA, Ellenbogen KA. Minimizing inappropriate or "unnecessary" implantable cardioverter-defibrillator shocks: appropriate programming. *Circ Arrhythm Electrophysiol* 2011; **4:** 778–90.

26 Spencker S, Coban N, Koch L, Schirdewan A, Muller D. Potential role of home monitoring to reduce inappropriate shocks in implantable cardioverter-defibrillator patients due to lead failure. *Europace* 2009; **11:** 483–88.

27 Guedon-Moreau L, Kouakam C, Klug D, et al. Decreased delivery of inappropriate shocks achieved by remote monitoring of ICD: a substudy of the ECOST trial. *J Cardiovasc Electrophysiol* 2014; published online March 6. DOI:10.1111/jce.12405.

28 van Veldhuisen DJ, Braunschweig F, Conraads V, et al. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. *Circulation* 2011; **124:** 1719–26.

29 Chaudhry SI, Mattera JA, Curtis JP, et al. Telemonitoring in patients with heart failure. *N Engl J Med* 2010; **363:** 2301–09.

30 Koehler F, Winkler S, Schieber M, et al. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. *Circulation* 2011; **123:** 1873–80.

31 Inglis SC, Clark RA, McAlister FA, Stewart S, Cleland JG. Which components of heart failure programmes are effective? A systematic review and meta-analysis of the outcomes of structured telephone support or telemonitoring as the primary component of chronic heart failure management in 8323 patients: abridged Cochrane review. *Eur J Heart Fail* 2011; **13:** 1028–40.