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# A randomized study of remote monitoring and fluid monitoring for the management of patients with implanted cardiac arrhythmia devices

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**Aims** Only limited comparative data exist on the benefits of fluid monitoring (FM) combined with remote monitoring (RM) regarding morbidity and mortality of heart failure (HF) patients. This prospective single-centre randomized pilot study aimed to estimate the influence of RM in combination with FM on HF hospitalizations as well as ventricular tachyarrhythmias and mortality.

**Methods and results** Patients with standard indication for implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy and defibrillator were implanted with devices capable of RM and FM, and were followed for 15 months. Subjects were randomly allocated to RM including OptiVol and predefined management of alerts (remote group), or standard in-office visits every 3 months (control group). A total of 176 patients (77% male; 66 ± 12 years; left ventricular ejection fraction (LVEF) 32 ± 11%; ischemic cardiomyopathy 50%; CRT device 50%; primary prevention 85%) were analysed. Cox proportional hazard analysis on the time to first HF-related hospitalization showed a hazard ratio of 1.23 [0.62–2.44] ($P = 0.551$) favouring the control group. In the remote group, 13 patients (15%) experienced ICD shocks vs. 10 patients (11%) in the control group ($P = 0.512$). The average time to first ICD shock was 212 ± 173 days in the remote arm and 212 ± 143 days in the control arm ($P = 0.994$). The Kaplan–Meier estimate of mortality after 1 year was 8.6% (eight deaths) in the remote group vs. 4.6% in the control group (six deaths; $P = 0.502$).

**Conclusion** In a single-centre randomized pilot study of RM in combination with FM, no significant influence on HF-related hospitalizations, ICD shocks, or mortality was found.

**Keywords** Heart failure • Cardiac decompensation • Fluid monitoring • OptiVol fluid index • Remote monitoring • Telemedicine



## Introduction

Heart failure (HF) is a highly prevalent disease with substantial morbidity and mortality. Consequently, the disease is an important healthcare issue with the majority of costs attributed to HF hospitalizations.[1] Efforts continue to detect fluid accumulation early to prevent hospitalization for acute cardiac decompensation. As clinical signs of HF deterioration are often unreliable, device-based sensors have been developed for the continuous monitoring of the patients' HF status. One such approach is the continuous measurement of intrathoracic impedance with an implanted cardiac arrhythmia device. While first investigations showed promising results,[2–4] larger and randomized trials revealed disappointing outcomes.[5,6] A valid option for improving the fluid monitoring (FM) feature might be additional use of remote monitoring (RM), as timely measures of wireless fluid overload alerts may avert cardiac decompensation and HF hospitalization. So far, only limited comparative data exist on the benefits of wireless FM regarding morbidity and mortality of HF patients.

This prospective single-centre randomized pilot study aimed to evaluate the influence of RM in combination with wireless FM using OptiVol alerts (Medtronic, Minneapolis, MN, USA) on time to first

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## What's new?

- So far only few tools for monitoring patients with chronic heart failure (HF) to identify early cardiac deterioration exist.
- Continuous measurement of intrathoracic impedance with an implanted cardiac arrhythmia device might improve the management of HF patients.
- So far data investigating the impedance measurement are conflicting.
- Furthermore, only limited comparative data exist on the benefits of fluid monitoring (FM) combined with remote monitoring regarding morbidity and mortality of HF patients.
- This prospective randomized pilot study adds important information to the value of device-based FM combined with telemedical support for the early detection of HF decompensation to reduce hospitalizations.
- Our data show no significant influence on HF related hospitalizations, ICD shocks, or mortality

HF-related hospitalization as well as tachyarrhythmia occurrences and mortality when compared with standard clinical care.

# Methods

## Patient selection

A detailed description of the study design has been published previously.[7] In brief, patients aged >18 years in need for an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy and defibrillator (CRT-D) according to current guidelines or patients with a previously implanted device without FM feature and a replacement indication for battery depletion were included in the study after written informed consent. Heart failure or a history of decompensated HF hospitalization was not a prerequisite for inclusion. Medtronic devices with telemonitoring capabilities and OptiVol alert (Concerto or Consulta CRT-D, Virtuoso or Secura ICD-DR) were used. Exclusion criteria were permanent atrial fibrillation, a life expectancy ≤15 months, pregnancy, and participation in another study.

## OptiVol fluid index

The OptiVol fluid index has been described in detail elsewhere.[4,8] In brief, the device determines a representative impedance daily and compares this with a roving reference value. Whenever daily impedance drops below the reference, a cumulative, absolute difference is calculated, and called fluid index. Crossing a programmable threshold indicates a possible fluid overload of the patient, and an OptiVol alert is triggered.

## Study design and protocol

This randomized, single-centre, prospective pilot study complies with the Declaration of Helsinki, and the study protocol was approved by the Institutional Ethics Committee. All patients gave their written informed consent. Patients receiving CRT-D or DR-ICD implants or replacements were randomized to RM including OptiVol ON (remote arm) vs. RM OFF (standard arm) and followed for 15 months. In both groups, the audible OptiVol alert was disabled. Patients in the remote arm, however, were connected to the Medtronic CareLink network. The OptiVol fluid index threshold was set to the nominal 60 Ω at implantation and remained unchanged during follow-up. In case of an automatic alert transmission, a pre-specified clinical decision routine was activated as detailed in *Figure 1*. Evaluation of the clinical status of the patients included assessment of symptoms such as dyspnoea, weight gain, oedema, activity status, and fatigue.

In the control group, standard in-office visits were performed every 3 months.

## Aims

The aim of this study was to estimate the influence of RM in combination with FM using OptiVol alerts on the time to first HF-related hospitalization as well as tachyarrhythmia occurrence and mortality when compared with standard clinical care.

## Data analysis

Statistical analysis was performed using commercial software. Unless otherwise noted, all data are reported as mean ± SD. Differences in baseline characteristics were evaluated using a Student's *t*-test, a $\chi^2$ test, or a Fisher's exact test, where appropriate. For time to first HF-related hospitalization, time to first ICD shock, and time to death a Cox proportional hazard analysis, and a Kaplan–Meier survival analysis with log-rank test were performed. A *P*-value of $<0.05$ was considered statistically significant.

# Results

## Patient characteristics

Between December 2007 and April 2011, a total of 180 patients were included. Two patients were not randomized because the planned device was eventually not implanted. Another two patients withdrew their consent soon after implantation. Thus, after exclusion of the described 4 patients, a total of 176 patients were analysed. Baseline characteristics are summarized in *Table 1*. At inclusion, there were 73 patients (83.9%) in the remote arm in functional NYHA class II or higher, comparing with 82 patients (93.2%) in the control arm, respectively. A CRT device was implanted in half of the patients in both groups.

## OptiVol alerts, urgent visits, and hospitalizations

A total of 174 OptiVol alerts (94 in CRT patients and 80 in ICD patients) in 68 patients (35 patients with CRT and 33 patients with ICD) occurred in the remote group (i.e. 78% of the remote group patients). Of these, 93 alerts (54 in CRT patients and 39 in ICD patients) were classified as true positive based on clinical assessment of the circumstances but not on the basis of a later required hospitalization. In 74 of these cases, ambulatory patient management was clinically possible, whereas in 19 cases hospitalization was required. All decisions were made by the investigators.

One additional hospitalization occurred without prior OptiVol alert. Thus, in total, 20 patients in the remote group and 22 patients in the control group were hospitalized for worsened HF during the follow-up period. As shown in *Figure 2*, Cox proportional hazard analysis on the time to first HF-related hospitalization showed a hazard ratio of 1.231 ([0.621–2.438]; $P = 0.551$). The mean number of emergency department visits was not significantly different between the two groups (RM group 0.10 ± 0.25 vs.

control group 0.10 ± 0.23; $P = 0.7295$). The mean number of urgent care visits, however, differed statistically significant with 0.30 ± 0.50 visits in the remote group and 0.10 ± 0.30 visits in the control group ($P = 0.0332$).

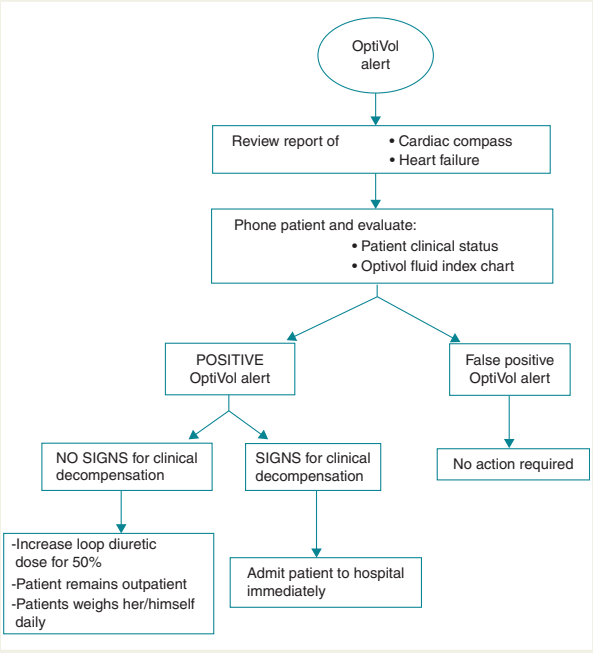


**Figure 1** Pre-specified clinical decision routine activated by an automatic OptiVol alert transmission. (Reprinted with permission from Ref. 7.)

## Ventricular tachyarrhythmias and mortality

In the remote group, 13 patients (15%) experienced ICD shocks vs. 10 patients (11%) in the control group. Inappropriate shocks were delivered in four cases in two patients (2%) in the remote arm and in two cases in two patients (2%) in the control arm. Reasons for inappropriate therapy were atrial fibrillation with fast ventricular rate ($n = 3$), sinus tachycardia ($n = 1$), lead failure ($n = 1$), and electrocauterization upon non-cardiac surgery ($n = 1$). The average time to first ICD shock was 212 ± 173 days in the RM arm and 212 ± 143 days in the control arm ($P = 0.994$). Kaplan–Meier analysis for time to first ICD shock revealed no significant difference between the two groups ($P = 0.512$) (*Figure 3*).

A total of eight patients in the remote arm when compared with six patients in the control arm died during follow-up. In each group, one death was classified as sudden cardiac and three deaths as non-sudden cardiac death. Non-cardiac deaths occurred once in the remote group and twice in the control group. Three deaths in the remote group could not reliably be classified. The Kaplan–Meier estimate of all-cause mortality after 1 year was 8.6% in the remote group vs. 4.6% in the control group. No significant difference could be observed for time to death between the two groups ($P = 0.502$) (*Figure 4*).

# Discussion

The main finding of our study is that device-based FM combined with RM has no favourable effect when compared with standard clinical care on the time to first HF-related hospitalization as well as tachyarrhythmia occurrences, or mortality.

**Table 1 Patient characteristics**

| | All ($n = 176$) | Remote ($n = 87$) | Control ($n = 89$) | *P*-value |
|---|---|---|---|---|
| # Male (%) | 136 (77.3%) | 70 (80.5%) | 66 (74.2%) | 0.3702 |
| Mean age (± SD) | 65.9 (± 12.0) | 66.0 (± 12.0) | 65.9 (± 12.1) | 0.9485 |
| Mean LVEF (± SD) | 31.9 (± 10.8) | 32.7 (± 11.4) | 31.1 (± 10.2) | 0.328 |
| Mean QRS duration (± SD) | 136 (± 129) | 149 (± 179) | 123 (± 38) | 0.2811 |
| # LBBB (%) | 66 (37.5%) | 31 (35.6%) | 35 (39.3%) | 0.6429 |
| # RBBB (%) | 13 (7.4%) | 5 (5.7%) | 8 (9.0%) | 0.5664 |
| # NYHA I (%) | 19 (10.9%) | 13 (14.9%) | 6 (6.8%) | 0.0945 |
| # NYHA II (%) | 80 (45.7%) | 40 (46.0%) | 40 (45.5%) | 1 |
| # NYHA III (%) | 71 (40.6%) | 32 (36.8%) | 39 (44.3%) | 0.3566 |
| # NYHA IV (%) | 4 (2.3%) | 1 (1.1%) | 3 (3.4%) | 0.6207 |
| # Ischaemic cardiomyopathy (%) | 90 (51.1%) | 51 (58.6%) | 39 (43.8%) | 0.0521 |
| # Coronary artery disease (%) | 94 (53.4%) | 48 (55.2%) | 46 (51.7%) | 0.6536 |
| # Hypertension (%) | 118 (67.0%) | 62 (71.3%) | 56 (62.9%) | 0.2642 |
| # Diabetes (%) | 48 (27.3%) | 24 (27.6%) | 24 (27.0%) | 1 |
| # Persist./parox. AF (%) | 52 (29.5%) | 22 (25.3%) | 30 (33.7%) | 0.2496 |
| # CRT ICD (%) | 88 (50.0%) | 44 (50.6%) | 44 (49.4%) | 1 |
| # Primary prevention (%) | 149 (84.7%) | 71 (81.6%) | 78 (87.6%) | 0.3006 |
| # Secondary prevention (%) | 27 (15.3%) | 16 (18.4%) | 11 (12.4%) | 0.3006 |

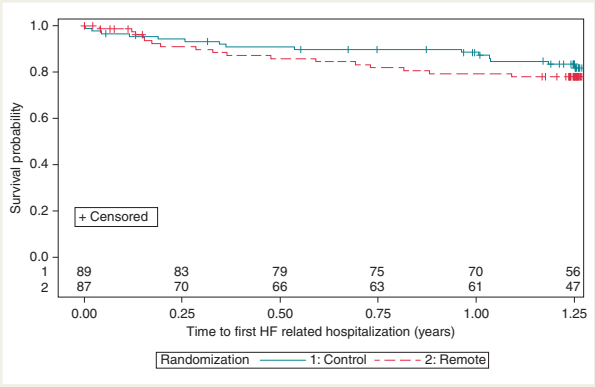


**Figure 2** Kaplan–Meier event probabilities for time to first HF-related hospitalization (*P*-value log-rank test = 0.551).

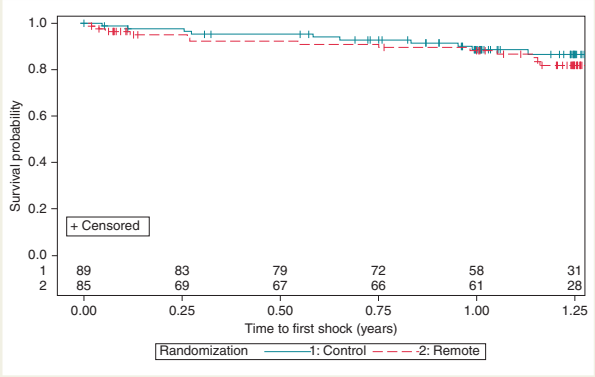


**Figure 3** Kaplan–Meier event probabilities for time to first ICD shock (*P*-value log-rank test = 0.512).

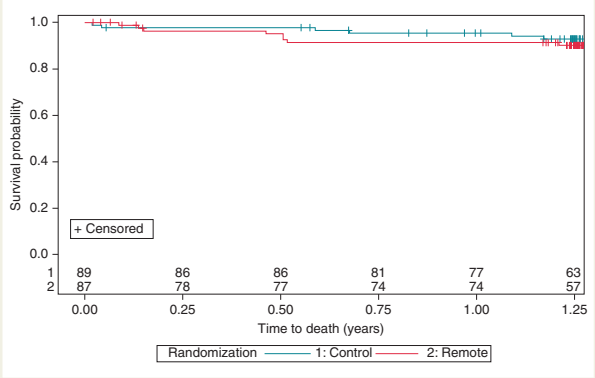


**Figure 4** Kaplan–Meier event probabilities for time to death (*P*-value log-rank test = 0.502).

While the first small or observational studies investigating intrathoracic impedance measurement revealed a sensitivity of 60–77% for detection of a HF related fluid accumulation, they also reported a substantial portion of false-positive detections.[2–4] Another study investigating the alert algorithm was able to demonstrate a reduction of HF hospitalizations[9] in a non-randomized comparison. However, these positive results could not be confirmed in subsequent trials. In the prospective observational SENSE-HF study, sensitivity and positive predictive value of impedance monitoring were considerably low.[5] In the randomized controlled DOT-HF study, the use of impedance measurement did not reduce deaths and HF hospitalizations.[6]

Importantly, all of the investigations mentioned above have not combined FM (without audible alert) with RM for the timely detection of HF deterioration. This combination may overcome shortcomings of the impedance measurement with the audible alert, such as frequent unnecessary outpatient clinic visits due to inadequate alerts, or some overreaction of the treating physician faced with the patients' expectation, who may be concerned by an audible alert. Another important advantage of additional RM might be a further reduction of the time from the device alert to the clinical action taken to prevent manifest decompensation with hospitalization.[10,11] Importantly, larger studies investigating remote telemedical support for HF management but not involving automatic transmissions could not show a benefit.[12,13] Very recently, preliminary data of the IN-TIME study revealed a significant reduction of all-cause mortality and cardiovascular mortality in the RM arm when compared with controls.[14] The combined use of impedance measurement and RM was investigated in the EVOLVO study, demonstrating reduced emergency department or urgent in-office visits by 35% without affecting hospitalizations.[10]

In our study, we were not able to show a benefit of impedance monitoring combined with RM when compared with a control group despite a predefined management routine of alerts. In contrast to the EVOLVO study,[10] our study showed more urgent care visits in the remote group when compared with the controls. Although we classified 93 OptiVol alerts as true positive, and ≈80% of these alerts were manageable without the need for hospitalization, this did not translate into a reduction of HF-related hospitalizations when compared with standard treatment. Several reasons may account for this. First, as HF hospitalizations could not be used anymore as a gold standard when aiming to avoid them, not all alerts may have been correctly classified. Secondly, the natural course of impending HF deterioration may not always lead to manifest cardiac decompensation, but also to spontaneous improvement of HF and return to stable conditions. In this context, the aim of the study of an early intervention to prevent hospitalization might have been counteracted by early detections of HF decompensation necessitating in-patient treatment in the remote group. The same patient in the control group might have spontaneously improved without the need for hospitalization and unnoticed by a physician. Finally, cardiac decompensation may be more complex than the assumption of a prolonged subclinical period of linear HF deterioration before manifest decompensation, thus measurable with intrathoracic impedance.[15] Indeed, in our study 19 of the positive alert patients were clinically diagnosed as an already manifest cardiac decompensation that required hospitalization. These cases suggest a shorter subclinical period before decompensation without a genuine chance to intervene.

Results reported by Singh *et al.*[16] suggested that worsening clinical conditions such as hospitalization for HF are associated with an

increased risk of ICD shock delivery. Furthermore, an increased risk for first and recurrent HF events after ICD discharge has been found.[17] Several investigations have also shown that appropriate as well as inappropriate ICD discharges negatively impact on mortality.[18] Thus, improvement of HF status as well as early detection of device-related problems using telemonitoring should be capable of impacting on the rate of inappropriate and appropriate ICD shock deliveries on the one hand. On the other hand, a reduction of ICD discharges could positively influence HF-related hospitalization and mortality. In the present study, however, we were not able to see a significant difference of ICD shock deliveries between the remote and the control arms. This is in line with previously published data from Landolina *et al.*[10]. However, in their study as well as in ours, the number of events might not have been high enough for sufficient discrimination.

So far, only limited data are available concerning mortality and intrathoracic impedance monitoring or telemonitoring use. Previous studies investigating the impact of impedance monitoring or telemonitoring on HF hospitalizations or death revealed no significant differences between the control and treatment groups.[6,12] These studies are in line with our data, as we were unable to demonstrate mortality differences between the treatment and control groups. As mentioned earlier, recently results from the IN-TIME trial[14] were presented. A total of 664 patients with implanted cardiac arrhythmia devices were randomly assigned to telemonitoring or standard care and followed for 12 months. A significant reduction of total mortality and cardiovascular mortality of ~65% between the two groups was observed. This risk reduction during 12 months of follow-up is difficult to comprehend in the light of our results, even if our study included only about a quarter of the patients and was as a pilot study not powered for mortality analysis. Currently, two large trials aimed at further elucidating the role of RM combined with FM are under way.[19,20]

## Limitations

The main limitation of our study is the number of patients included. As no significant differences between the treatment groups were found, our results should be interpreted with the caution that they may be due to under-powering. However, we have conducted a uniform single-centre prospective, randomized pilot study with ~180 patients included, thus hypothesis generating conclusions may be drawn from our data. Another potential limitation is the single-centre design of our study. However, the uniform response by a small experienced study group reduces the risk of heterogenous response to OptiVol alerts, which is unavoidable in a multicentre trial. This way, risk of a heterogeneous response as reason for the negative result can be substantially reduced.

# Conclusion

The data of this single-centre prospective randomized pilot trial do not support the use of RM combined with intrathoracic impedance monitoring in patients implanted with cardiac arrhythmia devices for the reduction of hospitalizations, tachyarrhythmia occurrence or mortality. This data need to be confirmed in large randomized trials.

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**Conflict of interest:** L.L. has received research and travel support from Medtronic. D.V. has received lecture fees and travel support from Medtronic. J.S. has received travel support from Medtronic. C.S. and G.H.: none declared. M.Z. has received research funding from Medtronic including this study, as well as from Biotronik and Boston Scientific, has received lecture fees and travel grant support from Medtronic, Boston Scientific, and Biotronik, and has served on advisory boards for Biotronik, Boston Scientific, and Medtronic.

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