Intrathoracic Impedance Monitoring, Audible Patient Alerts, and Outcome in Patients With Heart Failure

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Background—Heart failure is associated with frequent hospitalizations, often resulting from volume overload. Measurement of intrathoracic impedance with an implanted device with an audible patient alert may detect increases in pulmonary fluid retention early. We hypothesized that early intervention could prevent hospitalizations and affect outcome.

Methods and Results—We studied 335 patients with chronic heart failure who had undergone implantation of an implantable cardioverter-defibrillator alone (18%) or with cardiac resynchronization therapy (82%). All devices featured a monitoring tool to track changes in intrathoracic impedance (OptiVol) and other diagnostic parameters. Patients were randomized to have information available to physicians and patients as an audible alert in case of preset threshold crossings (access arm) or not (control arm). The primary end point was a composite of all-cause mortality and heart failure hospitalizations. During 14.9±5.4 months, this occurred in 48 patients (29%) in the access arm and in 33 patients (20%) in the control arm (P=0.063; hazard ratio, 1.52; 95% confidence interval, 0.97–2.37). This was due mainly to more heart failure hospitalizations (hazard ratio, 1.79; 95% confidence interval, 1.08–2.95; P=0.022), whereas the number of deaths was comparable (19 versus 15; P=0.54). The number of outpatient visits was higher in the access arm (250 versus 84; P<0.0001), with relatively more signs of heart failure among control patients during outpatient visits. Although the trial was terminated as a result of slow enrollment, a post hoc futility analysis indicated that a positive result would have been unlikely.

Conclusion—Use of an implantable diagnostic tool to measure intrathoracic impedance with an audible patient alert did not improve outcome and increased heart failure hospitalizations and outpatient visits in heart failure patients.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT 00480077.

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Key Words: cardiography, impedance ■ devices ■ heart failure ■ outcome assessment ■ randomized controlled trial

Heart failure remains one of the largest medical problems of our time.1 It is a very costly disease, and in 2010, its total cost in the United States alone was estimated at $39.2 billion.2 Heart failure–related hospitalizations form the largest part of this cost, and being able to identify patients at risk for hospitalization would be attractive. Most heart failure–related hospitalizations are due to fluid accumulation,3,4 and careful surveillance of fluid status and monitoring of symptoms is important.5 However, early signs and symptoms like dyspnea and fatigue are unspecific, whereas more typical signs like ankle swelling and pulmonary congestion often occur later or remain absent.5 Daily measurement of body weight and natriuretic peptides, both important in heart failure management, has a poor sensitivity in predicting clinical deterioration.6

Clinical Perspective on p ●●●

Cardiac resynchronization therapy and the implantable cardioverter-defibrillator have become standard therapies in heart failure and decreased ejection fraction.1,7,9 In addition to improving prognosis, they offer diagnostic features that...
allow monitoring of several variables, including intrathoracic impedance used to measure changes in thoracic fluid content, intracardiac pressures, heart rate variability, patients’ physical activity level, and arrhythmias. It is unknown whether interventions based on these parameters may improve outcome.

The Diagnostic Outcome Trial in Heart Failure (DOT-HF) was a randomized, controlled trial to investigate whether ambulatory monitoring of intrathoracic impedance and other device-based diagnostic information could improve outcome in heart failure patients who were treated with an implantable cardioverter-defibrillator alone or in combination with cardiac resynchronization therapy. On the basis of earlier work, a fluid detection algorithm (OptiVol) was used in the access arm to alert the patient if a certain level of impedance drop occurred and subsequently to assess the patient according to a recommended algorithm.

Methods

Patient Population
All patients in DOT-HF had undergone implantation of an implantable cardioverter-defibrillator alone or with cardiac resynchronization therapy (InSync Sentry, Concerto, and Virtuoso, Medtronic Inc, Minneapolis, MN). Although these devices have the capability to monitor diagnostic variables (Cardiac Compass), including intrathoracic impedance (OptiVol), the device-based diagnostic information was available only in patients in the access arm (see below). They were at least 18 years of age, had chronic heart failure (New York Heart Association functional class II–IV) despite optimal medical therapy, and an impaired left ventricular ejection fraction (≤35%) at the time of implantation. Patients had been hospitalized for heart failure in the 12 months before device implantation. Enrollment took place within 6 months after device implantation, and only patients in whom an OptiVol-enabled device was successfully implanted were enrolled.

We excluded patients who were scheduled for or had undergone cardiac surgery in the last 90 days and those who were listed for heart transplantation. Further exclusion criteria were a recent (<40 days) myocardial infarction, a life expectancy of <1 year, severe pulmonary or renal disease, use of inotropic drug therapy, complex and uncorrected congenital heart disease, and participation in another trial or disease management program in which remote monitoring or implanted technology was used.

All patients gave their written informed consent, and the study protocol was approved by the Institutional Review Board and/or Medical Ethics Committee of each center.

Study Design
After a 1-month waiting period to allow postoperative clinical stabilization, resolution of pocket edema, and automatic calibration of the impedance reference, patients were randomized in equal numbers to the access arm using a management strategy with access to all device-based diagnostic information, including an auditable patient alert for increased pulmonary fluid retention (see below), or to a control arm in which this information and an alert were not available. The group assignment was not blinded; control group patients knew that the audible fluid alert was programmed off. Device integrity alerts were programmed on for all patients.

Data were collected at enrollment, randomization, and scheduled follow-up visits at 3 and 6 months and every 6 months thereafter until study closure or subject exit. Additional data were collected at all unscheduled visits, hospitalizations, telephone contacts, and device system modifications, as well as during adverse events, study deviations, study exit, or death.

Whenever there was a device alert, the protocol always required a patient-physician contact (Figure 1). Patients in both arms who presented to study centers in the context of a clinical heart failure decompensation and patients in the access arm who had received a fluid alert of their device (see below) were treated according to a standardized intervention algorithm providing detailed recommendations concerning further diagnostic tests and treatment. In patients allocated to the access arm, this included advice for a thorough review of the OptiVol and Cardiac Compass trends. Of note, only changes in intrathoracic impedance with OptiVol could generate an audible alert. Other parameters were available only when the entire Cardiac Compass was reviewed, which required an office visit. On the basis of the available data and the clinical evaluation, patients were managed according to standardized intervention algorithm.

Monitoring of Intrathoracic Impedance and Other Diagnostic Features
Fluid status monitoring with OptiVol was based on calculations of the average daily intrathoracic impedance measured between the right ventricular defibrillation electrode and the device can. Intrathoracic impedance drops with an increase in pulmonary fluid content, which can be used to track changes in fluid status over time by comparison with a reference impedance derived from a moving average algorithm. When daily impedance values consistently fall below the reference, the difference accumulates in the OptiVol fluid index. When this index crossed a programmed threshold, patients in the access arm were alerted either by an audible tone from the device or by a hand-held patient indicator (patient check). An alarm threshold of 60 Ω-days was preset on the basis of earlier work. Other diagnostic parameters were available only when the entire Cardiac Compass (providing trends on heart rate variability, physical activity, arrhythmia incidence, percentage ventricular pacing, and other diagnostic information) was reviewed, which required an outpatient visit.

End Points
The primary end point of the study was to assess whether heart failure patient management with OptiVol and other diagnostic information from Cardiac Compass in addition to standard clinical assessment (access arm) would lead to a reduction in the combined end point of all-cause mortality or heart failure hospitalization compared with standard clinical assessment alone (control arm). Heart failure hospitalization was defined as a nonelective hospital
admission associated with signs and symptoms of congestion requiring at least 1 overnight stay in hospital during which the patient was treated with an augmentation of oral diuretic or the administration of intravenous diuretics, vasodilators, or inotropes. End points were adjudicated by an independent blinded End Point Advisory Committee; this committee did not review or adjudicate other collected data such as arrhythmias. Accumulated study data were periodically reviewed by a Data and Safety Monitoring Board. Thus, 335 patients were assigned to the access arm (n = 168), and 1 patient was dropped out between enrollment and randomization (302 patients). Africa, the Middle East, and Asia. Nine patients dropped out between enrollment and randomization (i.e., were enrolled but not randomized), and 1 patient was excluded because of a major violation of eligibility criteria. Thus, 335 patients were assigned to the access arm (n = 168) or the control arm (n = 167; Table 1). A Consolidated Standards of Reporting Trials (CONSORT) diagram of the study is presented in Figure 2. At the time of implantation, 31% of patients were in New York Heart Association functional class II, 62% were in class III, and 7% were in class IV. On enrollment, the majority were in New York Heart Association class II, and there were no differences in baseline characteristics between groups.

During the study, in 2 patients in the access arm, the audible alert system was turned off. The impedance threshold was changed in 23 patients.

### Statistical Analysis

The primary end point of the study, all-cause death or hospitalization for heart failure, was analyzed on a time-to-first-event basis with the log-rank test. The hazard ratio (HR) associated with allocation to the access arm relative to control was estimated with corresponding 95% confidence interval (CI) by fitting a Cox proportional hazards model containing the treatment group as a categorical factor. For other clinical end points, the same analysis methods were used. Repeated events survival analysis was performed with the Prentice-Williams-Peterson method with time reset.

We initially estimated that ∼2400 patients would have to be randomized and 868 primary end points accrued to achieve 90% power to demonstrate a reduction in incidence rate of the primary end point. This was based on an assumed control arm event rate of 0.20 events per patient per year, a 20% reduction in the access arm, and an α = 0.05 (2 sided). We planned to do 4 interim analyses. The DOT-HF protocol did not have a specified plan for potential discontinuation of the study because of futility. However, because of slower-than-expected enrollment and the expectation that rapid evolution of monitoring technology (in particular, the availability of remote device monitoring and improvements in the OptiVol fluid algorithm) could lead to interpretation difficulties, the sponsor decided to stop enrollment as of February 2, 2009. However, as suggested by the Steering Committee and the Data and Safety Monitoring Board, it was agreed that follow-up for each patient would be at least 6 months. Patients were therefore followed up until a close-out visit in September 2009. No interim analysis had been done at that time. From stored device data, it was assessed when an alert had occurred in the access arm or would have occurred in the control arm if the alert had been programmed “on.” As a post hoc analysis, hospitalizations and outpatient visits were stratified by the presence or absence of a prior alert condition, which is defined as an actual or an undelivered alert in the 30 days before the event.

The number of outpatient visits was analyzed with a Poisson regression model taking into account the patient’s time on study. Characteristics of outpatient visits were compared by logistic regression with generalized estimating equations to correct for correlation between multiple visits of the same patient.

### Results

#### Patients

In total, 345 patients were enrolled by 72 centers in Europe (302 patients), Africa, the Middle East, and Asia. Nine patients dropped out between enrollment and randomization (i.e., were enrolled but not randomized), and 1 patient was excluded because of a major violation of eligibility criteria. Thus, 335 patients were assigned to the access arm (n = 168) or the control arm (n = 167; Table 1). A Consolidated Standards of Reporting Trials (CONSORT) diagram of the study is presented in Figure 2. At the time of implantation, 31% of patients were in New York Heart Association functional class II, 62% were in class III, and 7% were in class IV. On enrollment, the majority were in New York Heart Association class II, and there were no differences in baseline characteristics between groups.

During the study, in 2 patients in the access arm, the audible alert system was turned off. The impedance threshold was changed in 23 patients.
Primary and Secondary End Points and Clinical Events

During a follow-up of 14.9±5.4 months (median, 14.5 months), 131 primary end points occurred in 81 patients (34 deaths, 1 heart transplantation, and 96 heart failure–related hospitalizations). Of the 81 patients with a primary end point, 48 were in the access arm and 33 in the control arm (HR = 1.24; 95% CI, 0.63–2.44; P = 0.54; Figure 2). Of the 334 outpatient visits (Table 3), 222 were preceded by an alert condition, ie, 196 in the access arm and 26 in the control group (P = 0.001; Figure 3A). A total of 36 patients experienced 50 repeat primary end points, 20 patients with 31 events in the access arm and 16 patients with 19 events in the control arm. Repeat-event survival analysis gives an HR estimate of 1.23 (95% CI, 0.86–1.75; P = 0.25).

Of the 34 deaths, 19 occurred in the access arm and 15 in the control arm (HR = 1.24; 95% CI, 0.63–2.44; P = 0.54; Figure 3B). Most deaths (n = 20, 59%) were due to cardiovascular causes, and 18 were considered to be related to heart failure progression. Five deaths were noncardiovascular in origin, and 9 were unknown or could not be classified appropriately. Of these 9 deaths, 6 were not witnessed.

A total of 96 unplanned hospitalizations for heart failure occurred, 60 in the access arm and 36 in the control arm. They were observed in 65 patients, 41 in the access arm and 24 in the control arm (HR = 1.79; 95% CI, 1.08–2.95; P = 0.022; Figure 3C). Of the 60 heart failure hospitalizations in the access arm, 35 (58%) had signs and/or symptoms of decompensation alone, whereas 23 patients who were admitted to the hospital (38%) had signs/symptoms together with an OptiVol alert. In the control arm, in 35 of 36 patients (97%) who were hospitalized for heart failure, there were typical signs and/or symptoms. Cardiac Compass trends were reviewed in 29 of the 60 hospitalizations in the access arm, and in 24 of these 29 (83%), abnormal findings were observed, most commonly related to the OptiVol feature (n = 18; Table 2).

Of the 96 heart failure hospitalizations, 59 were preceded by an OptiVol alert condition (40 in the access group and 19 in the control group) and 37 were not (20 in the access group and 17 in the control group). When the incidence of heart failure hospitalizations with a prior alert condition was compared between the 2 study arms, the HR was 3.02 (95% CI, 1.52–5.98; P < 0.001 for patients in the access group versus those in the control group). In contrast, there was no difference in incidence of heart failure hospitalizations without a prior alert condition (HR = 1.13; 95% CI, 0.56–2.26; P = 0.73).

Overall cardiovascular hospitalizations occurred 189 times, 115 in the access arm and 74 in the control arm. These hospitalizations occurred in 106 patients, 61 in the access arm (36% of group) and 45 in the control arm (27%; HR = 1.45; 95% CI, 0.99–2.14; P = 0.055; Figure 3D).

Although the trial was terminated because of slow enrollment, a post hoc futility analysis indicated that a positive result would have been unlikely. The 95% CI for the HR for the primary end point (0.97–2.37) excludes the 20% reduction that was assumed for sample size determination, so it can be argued that it is unlikely that the study would have ended with a positive outcome if all 2400 patients had been enrolled.

Outpatient Visits

There were 334 outpatient visits, 250 in the access arm and 84 in the control arm (P < 0.0001; Table 3). Of the 250 visits in the access arm, OptiVol threshold crossings (with audible alerts) were present in 144 cases (58%), and in most of them (114 of 144, 79%), the visit was only the result of this alert (Table 3). Of the 334 outpatient visits (Table 3), 222 were preceded by an alert condition, ie, 196 in the access group and 26 in the control group (In the latter group, this was a situation that could have triggered an alert if the alert system had been on) (HR = 6.78; 95% CI, 4.03–11.4; P < 0.001). There were 112 outpatient visits not preceded by an alert condition, ie, 54 in the access group and 58 in the control group (HR = 0.88; 95% CI, 0.55–1.40; P = 0.58).

Patients who had a visit almost always underwent physical examination (90% and 96% in the access and control arms). In the access arm, patients less often had hepatomegaly, positive hepatojugular reflex, and wheezing on physical examination (all P < 0.05) and tended to have less ascites and gallop rhythm (P < 0.10), whereas symptoms of heart failure such as dyspnea, orthopnea, fatigue, dizziness, and reduced activity were similar between arms.

Of the 250 visits in the access arm, a Cardiac Compass review was done in 199 cases (80%). In 156 of these (78%), at least 1 abnormal finding was observed, which was most frequently (85%) an OptiVol threshold crossing (Table 2). Abnormal findings were generally similar to those found during hospitalization for heart failure, with a decrease in patient activity being the second-most-common finding.

In 100 of the 199 visits (50%) in patients in the access arm in whom review of OptiVol and Cardiac Compass trends was done, this review led to a change in medication for heart failure. During outpatient visits, a change of the diuretic dose was more common in patients in the access arm (46%) than in the control arm (31%, P = 0.041).
Discussion

The main finding of the present study is that monitoring of intrathoracic impedance (and other diagnostic parameters) with an implantable device with the additional use of an audible patient alert for possible fluid accumulation did not lead to a reduction of the composite end point of all-cause mortality and heart failure hospitalizations in the outpatient management of patients with heart failure. In fact, using the diagnostic information from OptiVol and Cardiac Compass together with the patient alert led to more hospitalizations and more outpatient visits.

The present study is the first prospectively designed, randomized trial to examine the hypothesis that monitoring of intrathoracic impedance with an implanted device with a patient alert could affect outcome in patients with heart failure. In 2005, Yu et al.10 were the first to demonstrate the feasibility of this concept and showed that hospitalizations for heart failure were generally preceded by a decrease in intrathoracic impedance with an average of >2 weeks, suggesting that there would be a time window for interventions to prevent hospitalizations. Subsequent observational studies confirmed that decreases in intrathoracic impedance were associated with increased risk for heart failure hospitalizations.16–21 Intrathoracic impedance monitoring was also reported to be superior to weight changes in predicting heart failure events (76% versus 23% sensitivity).22 In the present study, the number of hospitalizations increased when more diagnostic information was available and patients were alerted for possible fluid accumulation. The number of patients who were hospitalized solely because of signs and symptoms of heart failure, however, was the same in both groups. Outpatient visits also markedly increased in the access arm, and patients were generally less symptomatic. Interestingly, however, the absolute number of patients with abnormal physical findings again was the same. Together, these findings suggest that a large portion of the extra hospitalizations in the access arm were triggered by alerts that were not associated with typical signs and symptoms of decompensated heart failure.

Patient alerts after crossings of the preset fluid threshold were based on changes in intrathoracic impedance, which may be subject to day-to-day fluctuation.20 For a fluid index threshold of 60 Ω-days, sensitivity was reported to range from 60% to 77%,
but specificity is much lower. Increasing the cutoff value to 100 or 120 Ω-days will increase specificity but decrease sensitivity. It is likely that patients in the access arm would have received fewer alerts, albeit with a higher specificity for volume overload, if we would have set the fluid index threshold higher. Very recently, data from the largest study in this field, the Sensitivity of the InSync Sentry OptiVol Feature for the Prediction of Heart Failure Hospitalization or During Outpatient Visit (SENSE-HF), have become available. Very recently, data from the largest study in this field, the Sensitivity of the InSync Sentry OptiVol Feature for the Prediction of Heart Failure Hospitalization or During Outpatient Visit (SENSE-HF), have become available.23

In previous reports, a considerable proportion of patients had fluid alerts without any clinical evidence for heart failure decompensation alone. Increasing the cutoff value to 100 or 120 Ω-days will increase specificity but decrease sensitivity. It is likely that patients in the access arm would have received fewer alerts, albeit with a higher specificity for volume overload, if we would have set the fluid index threshold higher. Very recently, data from the largest study in this field, the Sensitivity of the InSync Sentry OptiVol Feature for the Prediction of Heart Failure Hospitalization or During Outpatient Visit (SENSE-HF), have become available.23 This study showed a much lower sensitivity of OptiVol to predict heart failure hospitalizations, particularly early (within 2 months) after device implantation, but sensitivity increased to 42% after 6 months. Another way to possibly increase the specificity of device alerts would be to combine intrathoracic impedance monitoring with other device-based diagnostic information, as was done successfully before. However, such a combined algorithm with an audible alert was not available.

In the present study, the most common abnormal finding after review of the diagnostic information provided by OptiVol and Cardiac Compass was a crossing of the fluid index threshold. This finding confirms data from another observational study in which it was also the most sensitive parameter to identify increased risk for heart failure hospitalization. In that study, patients with a fluid index >60 and 100 Ω-days had a 2.7-fold and 3.9-fold increased risk for a subsequent heart failure hospitalization, respectively. These findings suggest that monitoring of intrathoracic impedance may provide useful information for a general risk assessment in heart failure. However, a strategy that triggers healthcare use on the basis of patient alerts for possible fluid overload may not be the appropriate way to incorporate diagnostic device features into routine patient management, as shown here. In contrast to earlier studies, remote patient monitoring via CareLink was not available in the present study, so any review of diagnostic information inevitably required an outpatient visit.

In previous reports, a considerable proportion of patients had fluid alerts without any clinical evidence for heart failure deterioration, and natriuretic peptides were often found not to be increased under such circumstances. One observational, nonrandomized study showed that the number of heart failure hospitalizations was reduced in patients in whom the audible fluid alert was activated. In the present study, OptiVol alerts were present in two thirds of patients who were evaluated during an (unplanned) outpatient visit. However, signs of heart failure were found on physical examination in only a minority of them, and an alert only rarely led to a hospitalization. Nevertheless, a proportion of hospitalizations may well have been driven mainly by the alert and the need of patients (but also physicians) to resolve the situation even

### Table 2. Findings During Cardiac Compass Review at Heart Failure Hospitalization or During Outpatient Visit

<table>
<thead>
<tr>
<th></th>
<th>Access Arm (n=168), n (%)</th>
<th>Control Arm (n=167), n (%)</th>
<th>P, Access vs Control*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total heart failure hospitalizations</td>
<td>60</td>
<td>29 (48)</td>
<td></td>
</tr>
<tr>
<td>Cardiac Compass review done</td>
<td>29 (48)</td>
<td>20 (30)</td>
<td></td>
</tr>
<tr>
<td>Any abnormal observation</td>
<td>24 (83)</td>
<td>18 (62)</td>
<td></td>
</tr>
<tr>
<td>OptiVol index above threshold or impedance shows sustained change</td>
<td>13 (45)</td>
<td>7 (24)</td>
<td></td>
</tr>
<tr>
<td>Decrease in patient activity</td>
<td>13 (45)</td>
<td>7 (24)</td>
<td></td>
</tr>
<tr>
<td>AT/AF</td>
<td>7 (24)</td>
<td>4 (14)</td>
<td>0.05</td>
</tr>
<tr>
<td>High ventricular rates during AT/AF</td>
<td>3 (10)</td>
<td>2 (7)</td>
<td>0.37</td>
</tr>
<tr>
<td>VT/VF episodes or shocks</td>
<td>5 (17)</td>
<td>3 (10)</td>
<td>0.56</td>
</tr>
<tr>
<td>Night heart rate high or increasing</td>
<td>4 (14)</td>
<td>2 (7)</td>
<td>0.37</td>
</tr>
<tr>
<td>Ventricular pacing low (CRT-D)</td>
<td>3 (10)</td>
<td>2 (7)</td>
<td>0.37</td>
</tr>
<tr>
<td>Heart rate variability low or decreasing</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Total outpatient visits</td>
<td>250</td>
<td>199 (80)</td>
<td></td>
</tr>
<tr>
<td>Cardiac Compass review done</td>
<td>199 (80)</td>
<td>156 (78)</td>
<td></td>
</tr>
<tr>
<td>Any abnormal observation</td>
<td>156 (78)</td>
<td>132 (66)</td>
<td></td>
</tr>
<tr>
<td>OptiVol index above threshold or impedance shows sustained change</td>
<td>132 (66)</td>
<td>114 (66)</td>
<td></td>
</tr>
<tr>
<td>Decrease in patient activity</td>
<td>114 (66)</td>
<td>91 (54)</td>
<td></td>
</tr>
<tr>
<td>AT/AF</td>
<td>18 (9)</td>
<td>10 (5)</td>
<td>0.05</td>
</tr>
<tr>
<td>High ventricular rates during AT/AF</td>
<td>10 (5)</td>
<td>7 (4)</td>
<td>0.20</td>
</tr>
<tr>
<td>VT/VF episodes or shocks</td>
<td>14 (7)</td>
<td>9 (5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Night heart rate high or increasing</td>
<td>5 (3)</td>
<td>3 (1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Ventricular pacing low (CRT-D)</td>
<td>8 (4)</td>
<td>5 (3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart rate variability low or decreasing</td>
<td>9 (5)</td>
<td>6 (3)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

AT indicates atrial tachycardia; AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation; and CRT-D, cardiac resynchronization therapy with a defibrillator.

### Table 3. Outpatient Visits

<table>
<thead>
<tr>
<th></th>
<th>Access Arm (n=168), n (%)</th>
<th>Control Arm (n=167), n (%)</th>
<th>P, Access vs Control*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total visits</td>
<td>250</td>
<td>84</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Primary reason for visit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs/symptoms of cardiac decompensation alone</td>
<td>11 (4)</td>
<td>22 (26)</td>
<td></td>
</tr>
<tr>
<td>OptiVol threshold crossing (exclusive)</td>
<td>114 (46)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Signs/symptoms and OptiVol crossing</td>
<td>30 (12)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Intervention algorithm (exclusive)</td>
<td>11 (4)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Other reason</td>
<td>84 (34)</td>
<td>57 (68)</td>
<td></td>
</tr>
<tr>
<td>Findings on physical examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination done</td>
<td>225 (90)</td>
<td>80 (95)</td>
<td>0.19</td>
</tr>
<tr>
<td>Rales</td>
<td>33 (15)</td>
<td>7 (9)</td>
<td>0.31</td>
</tr>
<tr>
<td>Edema</td>
<td>46 (18)</td>
<td>10 (12)</td>
<td>0.48</td>
</tr>
<tr>
<td>Wheezing</td>
<td>4 (2)</td>
<td>5 (6)</td>
<td>0.037</td>
</tr>
<tr>
<td>Gallop rhythm</td>
<td>9 (4)</td>
<td>8 (10)</td>
<td>0.08</td>
</tr>
<tr>
<td>Murmurs (systolic/diastolic)</td>
<td>46 (20)</td>
<td>18 (23)</td>
<td>0.13</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>27 (12)</td>
<td>11 (14)</td>
<td>0.50</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>16 (7)</td>
<td>13 (16)</td>
<td>0.034</td>
</tr>
<tr>
<td>Positive hepatojugular reflex</td>
<td>8 (4)</td>
<td>6 (8)</td>
<td>0.038</td>
</tr>
<tr>
<td>Ascites</td>
<td>8 (4)</td>
<td>8 (10)</td>
<td>0.061</td>
</tr>
</tbody>
</table>

*Characteristics of outpatient visits were compared with logistic regression models with generalized estimating equation correction to account for correlation between multiple visits from the same patient.† No statistical test was performed because protocol differences between arms.
in the absence of signs and symptoms. An OptiVol alert (at this threshold) thus may not be very specific for the detection of fluid overload and imminent cardiac decompensation.11

Although changes in intrathoracic impedance overall are associated with an increased risk, questions remain regarding its clinical use (especially early after device implantation)23; in particular, the value of an audible alert in this setting is unclear. A number of studies examining the value of monitoring intrathoracic impedance are currently ongoing and will clarify the place of this technology in the management of patients with heart failure.

Recently, favorable results have been reported on the value of intracardiac pressure recordings. In 1 small open-label study in 40 patients,26 management of heart failure patients with the use of left atrial pressure recordings (through the use of an intracardiac sensor lead inserted during transseptal cardiac catheterization) was associated with a favorable clinical course. In another study of 550 patients,27 Abraham et al used a small wireless implantable device to monitor pulmonary artery hemodynamics. These investigators reported a significant reduction in heart failure–related hospitalizations after 6 months (the primary end point of the study), which appeared to increase further over time. These favorable findings, together with earlier data,12 suggest that monitoring intracardiac pressures may be potentially useful in managing patients with heart failure.

The present study has a number of limitations. First, only a small proportion of patients that we aimed to include were actually enrolled because the study was terminated prematurely, although we believe that the data draw a clear picture. Nevertheless, it cannot be excluded that if we would have enrolled the originally planned 2400 patients, a very different result could have been obtained. (It must be noted that a similar study in managing patients with heart failure.

Second, we used 60 Ω-days as the cutoff for our OptiVol device, and we cannot excluded that a different threshold would have shown other results. Third, we have not implemented statistical methods to account for multiple testing of secondary end points, which must be taken into account in the interpretation of statistical results. Fourth, optimal use of Cardiac Compass and OptiVol requires experience with these diagnostic tools, and many centers use a multidisciplinary approach in which expertise in the field of both heart failure and electrophysiology is available28; it cannot be excluded that this was not always the case in each participating site in the present study.

Conclusions

In the present study, the use of an implantable diagnostic tool to measure intrathoracic impedance with a patient alert did not improve outcome in the outpatient management of patients with heart failure. Further studies are needed to examine what the place of diagnostic device-based features may potentially be in heart failure.

Appendix

Participents of the DOT-HF Study

Steering Committee: Martin Borggrefe (cochair), Dirk J. van Veldhuisen (cochair), Frieder Braunischweig, Viviane Conraads, Ian Ford, Martin Cowie, Guillaume Jondeau, Josef Kautzner, Roberto Muñoz Aguilera, Maurizio Lunati, Cheuk Man Yu, and Burt Gerris. Data and Safety Monitoring Board: Lars Ryden (chair; Stockholm, Sweden), Hans We del (Gothenburg, Sweden), and Hein J.J. Wellens (Maastricht, the Netherlands). End Point Advisory Committee: Kristian Thygesen (Aarhus, Denmark) and Barry Uretsky (Little Rock, AR). A list of participating centers is provided in the online-only Data Supplement.

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Disclosures

Drs Van Veldhuisen, Braunischweig, Conraads, Ford, Cowie, Kautzner, Yu, and Borggrefe report that they have received research funding, consultancy fees, or honoraria from Medtronic and from other device companies. Dr Muñoz Aguilera reports having received payments from service on a speakers’ bureau. Dr Gerris is an employee of Medtronic Inc. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Heart failure is associated with frequent hospitalizations, often because of volume overload. It is difficult, however, to identify patients at risk for hospitalization, and signs and symptoms are often unspecific. Measurement of intrathoracic impedance with an implantable device with an audible patient alert may detect increases in pulmonary fluid retention early. In the Diagnostic Outcome Trial in Heart Failure (DOT-HF), we studied patients with chronic heart failure who had undergone implantation of an implantable cardioverter-defibrillator alone or with cardiac resynchronization therapy. All devices featured a monitoring tool to track changes in intrathoracic impedance (OptiVol) and other diagnostic parameters. Patients were randomized to have information available to physicians and patients as an audible alert in case of preset threshold crossings (access arm) or not (control arm). The primary end point was a composite of all-cause mortality and heart failure hospitalizations. The study showed that the use of an implantable diagnostic tool to measure intrathoracic impedance with an audible patient alert did not improve outcome and in fact increased outpatient visits and heart failure hospitalizations in this population. These findings may have important implications. Although changes in intrathoracic impedance have been associated in a large number of studies with an increased risk for cardiovascular events in patients with heart failure, questions remain about its clinical use, sensitivity, and specificity. Moreover, the audible alert in particular seems to have played a role in the increased number of outpatient visits and heart failure hospitalizations.
Intrathoracic Impedance Monitoring, Audible Patient Alerts, and Outcome in Patients With Heart Failure

Dirk J. van Veldhuisen, Frieder Braunschweig, Viviane Conraads, Ian Ford, Martin R. Cowie, Guillaume Jondeau, Josef Kautzner, Roberto Muñoz Aguilera, Maurizio Lunati, Cheuk Man Yu, Bart Gerritse, Martin Borggrefe and for the DOT-HF Investigators

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