Prediction of readmissions and mortality in patients with heart failure: lessons from the IMPEDANCE-HF extended trial

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Abstract

Aims Readmissions for heart failure (HF) are a major burden. We aimed to assess whether the extent of improvement in pulmonary fluid content ($\Delta$PC) during HF hospitalization evaluated by lung impedance (LI), or indirectly by other clinical and laboratory parameters, predicts readmissions.

Methods and results The present study is based on pre-defined secondary analysis of the IMPEDANCE-HF extended trial comprising 266 HF patients at New York Heart Association Class II–IV and left ventricular ejection fraction $\leq$ 35% randomized to LI-guided or conventional therapy during long-term follow-up. Lung impedance-guided patients were followed for 58 ± 36 months and the control patients for 46 ± 34 months ($P < 0.01$) accounting for 253 and 478 HF hospitalizations, respectively ($P < 0.01$). Lung impedance, N-terminal pro-brain natriuretic peptide, weight, radiological score, New York Heart Association class, lung rales, leg oedema, or jugular venous pressure were measured at admission and discharge on each hospitalization in both groups with the difference defined as $\Delta$PC. Average LI-assessed $\Delta$PC was 12.1% vs. 9.2%, and time to HF readmission was 659 vs. 306 days in the LI-guided and control groups, respectively ($P < 0.01$). Lung impedance-based $\Delta$PC predicted 30 and 90 day HF readmission better than $\Delta$PC assessed by the other variables ($P < 0.01$). The readmission rate for HF was lower if $\Delta$PC > median compared with $\Delta$PC $\leq$ median for all parameters evaluated in both study groups with the most pronounced difference predicted by LI ($P < 0.01$). Net reclassification improvement analysis showed that adding LI to the traditional clinical and laboratory parameters improved the predictive power significantly.

Conclusions The extent of $\Delta$PC improvement, primarily the LI based, during HF-hospitalization, and study group allocation strongly predicted readmission and event-free survival time.

Keywords Heart failure; Monitoring heart failure; Lung impedance; Residual pulmonary congestion; Heart failure readmission

Introduction

Readmissions due to worsening heart failure (HF) during the months following hospitalization for HF are frequent and are influenced by residual congestion. Haemodynamic monitoring was found to reduce re-hospitalizations due to recurrent HF but is invasive and expensive. The ultrasound method for assessment of pulmonary congestion also seems encouraging in light of recently published data and supports the contention that residual pulmonary congestion on discharge is among the primary causes for readmissions after discharge. However, this method is operator dependent and somewhat semi-quantitative. While the change in the level of blood N-terminal pro-brain natriuretic peptide (NT-proBNP) during hospitalization for HF was found to be a useful predictor of readmissions, using of NT-proBNP to guide
therapy is controversial.8,9 Finally, a promising method to monitor and assess lung fluid content is the lung impedance (LI) technique.10–14 The recently published randomized IMPEDANCE-HF trial demonstrated the efficacy of LI-guided monitoring in the treatment of HF patients15 and has shown that LI-guided therapy decreased hospitalizations for HF as well as HF-associated and all-cause mortality. The trial has also confirmed that a significant proportion of HF patients were discharged with residual excess pulmonary fluid.

Based on data from the IMPEDANCE-HF trial, which was extended for an additional year, we sought to evaluate the relationship between changes in pulmonary fluid content during HF hospitalization and post-discharge outcomes. We aimed to compare the accuracy of the LI-based method with other methods used to assess improvement of patients during HF hospitalization in order to predict time to next HF hospitalization and mortality.

Methods

The following analysis of the IMPEDANCE-HF extended trial was based on the data collected during the index hospitalization for HF and the clinical data from the post-hospital follow-up course. The IMPEDANCE-HF extended trial was a randomized controlled single-blinded trial of chronic systolic HF patients. Patients were eligible for participation if they were older than 18 years, had a left ventricular ejection fraction ≤ 35% with New York Heart Association (NYHA) functional Class II–IV, and have been hospitalized for HF within 12 months of recruitment15 (ClinicalTrials.gov NCT01315223). The study required optimal medical therapy for HF according to current guidelines.16 Patients had to be followed for at least 12 months. Exclusion criteria included implantation of a cardiac resynchronization device within the preceding 3 months and the presence of advanced chronic kidney disease (estimated glomerular filtration rate < 25 mL/min per 1.73 m²). All patients provided written informed consent. Half of the patients (n = 133) were assigned to the active LI-guided treatment arm where clinicians were unblinded to LI values and could base therapy on LI level during these monthly outpatient clinic visits. The medical protocol of treating LI-guided patients according to LI changes was described.15 The other half of patient population was assigned to the control arm where LI values were recorded but not conveyed to the clinical treatment team. Hence, LI was measured in all patients at each monthly outpatient clinic visit. In the case of hospitalization, LI was recorded in all patients at admission and discharge, but this information was not conveyed to the treating physician. After discharge, patients were scheduled for an additional visit within 7–10 days. Following this visit, treatment of patients was resumed according to assignment group.

Analysis of data from the IMPEDANCE-HF trial showed that the probability of HF readmissions in the LI-guided and the control groups as assessed by LI and NT-proBNP was lower in the former, but the difference was not significant. The rate of HF hospitalizations in the groups and the number of patients at the termination of IMPEDANCE-HF trial were used to calculate sample size and period of trial extension in order to reach statistical significance. Therefore, the local institutional review board and data and safety monitoring board committees allowed to proceed with the identical treatment protocol as applied in the IMPEDANCE-HF trial for one additional year (IMPEDANCE-HF extended trial).

Inpatient study protocol

Patients hospitalized for HF underwent LI measurement within the first 16 h from admission and on discharge. Their vital signs, weight, jugular venous pressure (JVP), leg oedema (0–4 points according to the level of lower limb swelling), extent of lung rales (0—no rales, 1—basilar rales, 2—up to third of the lower lung field, 3—up to half of the lower lung field, and 4—rales beyond half of the lung field), and oximetry were recorded, and NYHA class was assessed. Chest radiographs (CXRs) were performed at hospital admission and discharge and interpreted by a radiologist and cardiologist. The 10-point radiological score (RS) was applied to assess the CXR13 when RS = 0 signifies no congestion; RS of 1–4 represents evolving interstitial congestion; and RS in the range of 5–10 is compatible with mild, moderate, or severe alveolar oedema. Jugular venous pressure was graded according to a modified Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial scale,12 that is, maximal level of venous pulsation above sternal angle <3 cm was defined as JVP = 0, a level of 3–5 cm as JVP = 1, 5–8 cm as JVP = 2, 8–11 cm as JVP = 3, and level of venous head >11 cm as JVP = 4. N-terminal pro-brain natriuretic peptide measurement was not an obligatory part of the protocol at the beginning of the study but was included in the protocol later during the study. N-terminal pro-brain natriuretic peptide was measured within 16 h after admission for HF and at discharge. Chest radiographs and NT-proBNP samples were used to substantiate the cause of admission, the degree of pulmonary congestion, and extent of improvement during hospitalization. Medical therapy administered during hospitalization was documented. Lung impedance was the focus of the present study; therefore, the degree of improvement in pulmonary fluid content (ΔPC) during hospitalization was defined as the difference between measured LI at admission and at discharge. Similarly, the difference between admission and discharge values of ΔNT-proBNP, weight (ΔW), ΔRS, ΔNYHA, lung rales (ΔLR), leg oedema (ΔLE), and ΔJVP were used as comparators to assess clinical improvement of patients during HF hospitalization. In despite of the fact that changes in ‘clinical’ parameters do not reflect directly changes in lung fluid content, the same abbreviation

DOI: 10.1002/ehf2.12330

ESC Heart Failure 2018; 5: 788–799
(ΔPC) was used for ΔLI and for other parameters for the sake of simplicity. The ΔPC assessed by different parameters at the current HF hospitalization was utilized to calculate the predicted time only to the next HF hospitalization.

**Lung impedance measurements and presentation**

A non-invasive impedance device was used in this study to assess the lung fluid content. Unlike the existing impedance devices, the present device has the ability to differentiate a true signal from the lungs (positive signal) from the noise signal of surrounding chest wall, which is at least an order of magnitude larger. The sensitivity of this device to measure small accumulation of lung fluid has allowed the initiation of preemptive LI-guided treatment long before the appearance of the initial clinical signs of lung oedema and attendant deterioration.10–14 A method to determine individual normal or ‘dry’ baseline LI for each HF patient has been previously reported.14 Baseline LI for each patient was calculated upon entry to the study and was used to calculate a new parameter, the ΔLIR = [(current LI/BLI) – 1] × 100%. When pulmonary fluid content above the dry baseline is present, the electrical resistance of the lung tissue falls, and LI values are lower than BLI. In this case, the ΔLIR values are negative, and these were computed for each patient at admission for HF and at discharge.

Hospitalized patients were usually admitted and treated in the internal medicine departments of the two hospitals participating in the IMPEDANCE-HF extended trial. The decisions regarding admission and discharge, as well as the choice of treatment during hospitalization, were at the discretion of the hospital staff with no interaction or influence by the study team. The hospitalization was considered to be related to HF if the following criteria were fulfilled: (i) the main diagnosis at discharge in the medical record was HF exacerbation; (ii) the presence of clinical signs indicating worsening HF in comparison with pre-hospitalization visit such as increased dyspnoea or in the level of lung rales, the degree of JVP or leg oedema, the presence of clinical signs indicating worsening HF in comparison with pre-hospitalization visit such as increased dyspnoea or in the level of lung rales, and LI values are lower than BLI. In this case, the ΔLIR values are negative, and these were computed for each patient at admission for HF and at discharge.

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**Statistical analysis**

The pre-defined purposes of the present analyses were (i) to find out if the degree of ΔPC during index HF hospitalization, as assessed by the different parameters, could predict time to the next HF hospitalization, as well as to HF-associated and all-cause mortality and (ii) to compare the predictive accuracy of the different parameters to identify defined outcomes.

Analyses were conducted according to intention to treat. Continuous variables were expressed as mean and standard deviation, if normally distributed according to the Kolmogorov–Smirnov and visual inspection tests, or median and interquartile range, if not conforming to a normal distribution. Comparisons between normally distributed continuous variables of two groups were performed by the two-sample t-test and between abnormally distributed independent continuous variables by the Mann–Whitney U test. Spearman method was used for calculation of correlations. Comparing of cumulative HF-related hospitalizations during the entire follow-up between groups was achieved by the Andersen–Gill model and additionally checked by using the Prentice, Williams, and Peterson model. Analysis of survival was performed by the Kaplan–Meier method (log-rank test). Analysis of time from discharge after HF-related hospitalization to the next HF hospitalization was carried out by the Andersen–Gill model. Multivariate regression analyses were used for the exploration of the predictive accuracy of different methods of pulmonary congestion assessment on the time of readmissions. Stepwise adjustment was applied to predict the time interval to the next HF readmission with standardized β coefficient, which compares the strength of the effect of each individual independent variable with the dependent variable. The continuous and categorical net reclassification improvement analysis was used to test the informational gain obtained by adding LI to predict future HF readmissions. We have applied two models to evaluate informational gain of LI. In the first model, LI was added to the parameters proved by multivariate analyses to be independent predictors of HF readmissions. In the second model, LI was added to all parameters tested in this study. The SPSS 21.0 statistical package, StatSoft Inc. (version 12.5), and R statistics version 3.2.3 were used for analysis.

**Results**

Baseline demographic, clinical, and laboratory data of the 266 patients randomized to the LI-guided and control groups (n = 133 each) in the IMPEDANCE-HF extended trial are presented in Table 1. Figure 1 shows a flow chart of patients enrolled in the trial and details the rate and cause of hospitalizations. Lung impedance-guided patients were followed for 58 ± 36 months and the control patients for 46 ± 34 months (P < 0.01) accounting for 253 and 478 HF hospitalizations, respectively (P < 0.01). The rate of HF readmissions was similar in the IMPEDANCE-HF extended trial (39 vs. 94 per 100 patients × year; Figure 1) to the primary IMPEDANCE-HF trial (41 vs. 94 per 100 patients × year.
in the LI-guided and control groups, respectively). Upper respiratory tract infections, myocardial ischaemia, arrhythmias, uncontrolled hypertension, and non-adherence to medical therapy or diet were identified as the precipitating factors for deterioration of HF in two-thirds of patients in both groups.

A significant difference between the cumulative risk ratio for HF readmissions of study groups during the entire follow-up period was observed (Figure 2A). During the study period, there were 23 and 57 HF-related deaths \( (P < 0.01) \) and 56 and 76 all-cause deaths \( (P < 0.01) \) in the LI-guided and the control groups, respectively. The rate of HF-related mortality was 3.6 per 100 patients \( \times \) year in the LI-guided group and 11.1 per 100 patients \( \times \) year in the control group \( (P < 0.01) \), while all-cause mortality was 8.7 and 14.9 per 100 patients \( \times \) year \( (P < 0.01) \) in these groups, respectively (Figure 2B and C).

Fifty-two patients (39%) of the LI-guided group were not hospitalized for HF at all during follow-up, whereas the other 81 patients were hospitalized 253 times (one HF admission every 18.8 months). Of the latter, 228 HF-associated hospitalizations (90%) were available for analysis of predictive accuracy of future readmissions (Figure 1). In the control group, 37 patients (28%) were not hospitalized for HF during follow-up \( (P = 0.05) \), while 96 patients were hospitalized 478 times for HF (one HF admission every 9.2 months). Of these, 417 HF hospitalizations (87%) were available for analysis (Figure 1).

**Table 1 Baseline patient characteristics**

| Variable                              | All patients \( (n = 266) \) | LI-guided group \( (n = 133) \) | Control group \( (n = 133) \) |
|---------------------------------------|-------------------------------|---------------------------------|-------------------------------|
| Age                                   | 67.6 ± 9.9                     | 67.5 ± 11.7                     | 67.7 ± 10.5                   |
| Male (%)                              | 85                             | 82                              | 87                            |
| Ejection fraction, median \( \text{IQR} \) | 30 (25–30)                     | 30 (25–30)                      | 30 (25–30)                    |
| NYHA functional capacity              |                               |                                 |                               |
| II (%)                                | 47                             | 48                              | 46                            |
| III (%)                               | 30                             | 29                              | 31                            |
| IV (%)                                | 23                             | 23                              | 23                            |
| Ischaemic aetiology (%)               | 71                             | 66                              | 75                            |
| S/P coronary artery bypass graft (%)  | 22                             | 17                              | 26                            |
| Atrial fibrillation/flutter (%)       | 26                             | 27                              | 25                            |
| Diabetes mellitus (%)                 | 52                             | 52                              | 53                            |
| Hypertension (%)                      | 74                             | 75                              | 74                            |
| Hyperlipidaemia (%)                   | 74                             | 75                              | 73                            |
| Chronic renal failure (%)             | 33                             | 34                              | 33                            |
| Smoking (%)                           | 40                             | 41                              | 39                            |
| ICD, n (%)                            | 83 (31)                        | 42 (32)                         | 41 (31)                       |
| CRT-D, n (%)                          | 107 (40)                       | 53 (40)                         | 54 (41)                       |
| ACE-I or ARB (%)                      | 96                             | 96                              | 96                            |
| Beta-blockers (%)                     | 91                             | 92                              | 90                            |
| MRA (%)                               | 61                             | 65                              | 58                            |
| Nitrates (%)                          | 47                             | 48                              | 46                            |
| Statin (%)                            | 84                             | 86                              | 83                            |
| Aspirin (%)                           | 77                             | 78                              | 76                            |
| Digoxin (%)                           | 36                             | 39                              | 33                            |
| Diuretics                             | 95                             | 96                              | 95                            |
| Furosemide equivalent dose \( \text{mg/day} \) | 97                             | 99                              | 95                            |

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRT-D, cardiac resynchronization therapy defibrillator; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; JVP, jugular vein pressure; LI, lung impedance; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.
function of the extent of ΔPC improvement of the different assessed variables presented by quartiles or medians. The data demonstrate that patients of both study groups were equally congested on admission regardless of the variable assessed. A finding, which was consistent for all variables of ΔPC assessment, was that larger improvements in ΔPC led to longer delays to next readmission. Table 3 and Supporting Information, Table S2 show the readmission rate at different intervals of time after HF hospitalization according to quartiles or medians of ΔPC improvement. Decongestion during

Figure 1  Flow chart for the IMPEDANCE-HF extended trial. *P < 0.01 between lung impedance (LI)-guided and control groups. IHD, ischaemic heart disease.

Figure 2  (A) Cumulative incidence of hospitalizations due to heart failure (HF, by Anderson–Gil Model). (B) The Kaplan–Meier curve of HF-associated mortality. (C) The Kaplan–Meier curve of all-cause mortality. Hazard ratio (HR) of hospitalizations due to heart failure evaluated by Prentice, Williams, and Peterson model was 2.5 [95% confidence interval (CI): 1.2–1.8, P = 0.0001]. LI, lung impedance; RR, relative risk.
Table 2 Parameters for assessment of the pulmonary fluid content (ΔPC) improvement during HF hospitalizations and time from discharge to readmission

| Variable                  | Li-guided group | Control group |
|---------------------------|-----------------|---------------|
|                           | 1               | 2             | 3             | 4             | 1, 3 | 2, 4 |
|                           | n               | Mean ± SD     | n             | Mean ± SD     | P    |
| Differences of patient’s lung impedance (ΔLIR in %) between HF admission and discharge |                 |               |               |               |      |
| ΔLIR at admission          | 228             | –44.4 ± 7.4   | 417           | –45.1 ± 8.8   | 0.31 |
| ΔLIR at discharge          | 228             | –32.5 ± 11.1  | 417           | –36.0 ± 11.6  | <0.01|
| Q1: ΔLIR < 4.7%            | 47              | 12.1 ± 8.1    | 658 ± 903     | 417           | 9.2  ± 6.2 | 305 ± 581 | <0.01 | <0.01 |
| Q2: 4.7% < ΔLIR ≤ 9.8%     | 55              | 3.0 ± 1.2     | 16 ± 30       | 116           | 2.7  ± 1.4 | 13 ± 25   | 0.23  | 0.48  |
| Q3: 9.8% < ΔLIR ≤ 13.7%    | 48              | 7.7 ± 1.6     | 65 ± 54       | 107           | 7.0  ± 1.6 | 68 ± 110  | <0.01 | 0.85  |
| Q4: ΔLIR > 13.7%           | 78              | 12.8 ± 1.4    | 338 ± 198     | 114           | 12.2 ± 1.4 | 198 ± 268 | 0.05  | <0.01 |
| Differences of patient’s NT-proBNP [ΔNT-proBNP] (pg/mL) between HF admission and discharge |                 |               |               |               |      |
| NT-proBNP at admission     | 178             | 15 159 ± 100  | 372           | 16 497 ± 8987 | 0.13 |
| Time from admission to NT- |                 | 2.8 ± 1.9     |               | 2.7 ± 1.4     | 0.27 |
| proBNP test (h)            | 114             | 10.411 ± 8461 |               |               |      |
| NF-proBNP at discharge     | 178             | 7945 ± 6605   | 320           | 16 497 ± 8987 | 0.13 |
| ΔNT-proBNP                 | 178             | 7511 ± 100  | 320           | 6117 ± 5352   | 0.01 |
| ΔNT-proBNP ≤ median        | 90              | 1906 ± 1282   | 186           | 2020 ± 1351   | 0.5  |
| ΔNT-proBNP > median        | 88              | 13 811 ± 6419 | 134           | 9739 ± 4920   | 0.01 |
| ΔNT-proBNP ≤ 50%           | 98              | 2357 ± 2896  | 153           | 3826 ± 3540   | 0.01 |
| ΔNT-proBNP > 50%           | 80              | 12 233 ± 7379 | 167           | 9372 ± 5649   | 0.01 |

HF, heart failure; LI, lung impedance; ΔLIR, lung impedance ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q1–Q4, quartiles 1–4: 0 ≤ Q1 ≤ 25th percentile, 25 < Q2 ≤ 50th percentile, 50 < Q3 ≤ 75th percentile, and Q4 > 75th percentile; SD, standard deviation.

HF admissions as evaluated by changes in all assessed variables was a significant predictor for readmissions in both groups (P < 0.01).

Discharge with minimal or small improvement in lung fluid content ([Q1 + Q2] or ≤median) conferred a high risk for readmission in both groups, especially during the first 30 and 90 days after the index hospitalization (Table 3 and Supporting Information, Table S2). In contrast, those who achieved moderate or large improvement in ΔPC ([Q3 + Q4] or >median) on discharge, regardless of the method used to demonstrate this change, were readmitted less frequently (P < 0.01). Assignment to the LI-guided group resulted in a significant decrease in readmissions across all time intervals (Table 3).

Table 3 Frequencies of HF readmissions at different time intervals as a function of pulmonary fluid content (ΔPC) improvement between admission and discharge

| Variable                  | Group          | n of readmissions | n of discharges on corresponding quartiles/medians |
|---------------------------|----------------|------------------|---------------------------------------------------|
| Rate of HF readmissions as a function of lung impedance improvement (ΔLIR) |                 | n               | P within group                                    |
| Q1: ΔLIR ≤ 4.7%           | Li-guided      | 42/47 (89%)      | 0/47 (0%)                                          | <0.01 |
| Q2: 4.7% < ΔLIR ≤ 9.8%    | Control        | 112/116 (97%)    | 0/116 (0%)                                        | <0.01 |
| Q3: 9.8% < ΔLIR ≤ 13.7%   | Li-guided      | 19/55 (35%)      | 0/55 (0%)                                         | <0.01 |
| Q4: ΔLIR > 13.7%          | Control        | 50/107 (47%)     | 0/107 (0%)                                        | <0.01 |
| Rate of HF readmissions as a function of NT-proBNP (pg/mL) improvement |                 | n               | P within group                                    |
| ΔNT-proBNP ≤ median       | Li-guided      | 7/114 (6%)       | 12/114 (11%)                                      | <0.01 |
| ΔNT-proBNP > median       | Control        | 33/114 (29%)     | 55/114 (71%)                                      | <0.01 |
| ΔNT-proBNP ≤ 50%          | Li-guided      | 0/78 (0%)        | 12/78 (15%)                                      | <0.01 |
| ΔNT-proBNP > 50%          | Control        | 6/80 (7%)        | 42/80 (53%)                                      | <0.01 |

FU, follow-up; HF, heart failure; LI, lung impedance; ΔLIR, lung impedance ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q1–Q4, quartiles: 0 ≤ Q1 ≤ 25th percentile, 25 < Q2 ≤ 50th percentile, 50 < Q3 ≤ 75th percentile, and Q4 > 75th percentile.

*P < 0.05, between groups for the same parameter at the same quartile or median.
shift of the readmissions to a later time point. This result was found to be consistent for all methods of ΔPC assessment but appeared most pronounced for ΔPC evaluated by LI (Table 3 and Supporting Information, Table S2). Table 4 and Supporting Information, Table S3 present the probability of HF hospitalizations as a function of the degree in ΔPC improvement within and between groups. The discriminative accuracy of ΔPC to predict HF readmission was higher when assessed by LI and was consistently better for patients of the LI-guided group (P < 0.01) regardless of the method used to assess ΔPC.

The accuracy of the different methods for ΔPC calculation to predict the time interval to the next HF readmission, based on data obtained at the current HF hospitalization, was also compared by multivariate regression analysis. Age, gender, left ventricular ejection fraction, and glomerular filtration rate at the beginning of the study were also included in multivariate analyses. All variables in the LI-guided group (n = 175) and control group (n = 317) demonstrated acceptable collinearity (variance inflation factors range between 1.3 and 3.7 for different combinations of variables). Stepwise adjustment demonstrated that in the LI-guided group, only ΔLI and ΔLE could independently predict the time interval to the next HF readmission with standardized β coefficient of 0.39 for LI and 0.26 for leg oedema (P < 0.01). In the control group, only ΔLI and ΔNT-proBNP could predict independently the time to next HF readmission with standardized β coefficients of 0.34 and 0.17, respectively (P < 0.01).

ΔPC and time to heart failure readmission and mortality

Figure 3A demonstrates the probable time from discharge to the next hospitalization as a function of the degree of improvement in lung fluid content [ΔPC = (ΔLI admission − ΔLI discharge)] in both groups. It is evident that practically all patients of both groups discharged with minimal or mild degree of improvement in lung fluid content (ΔPC ≤ median) were readmitted within 4–5 months (P = 0.3). On the other hand, patients of both groups discharged with moderate and high level of pulmonary decongestion (ΔPC > median) demonstrated a low rate of readmission, which was lower in the LI-guided group than in the control group (P < 0.01). Conversely, patients of both groups discharged with minimal and small (ΔPC ≤ median) improvement in lung fluid status had a higher probability for HF-associated and all-cause death within 3 months after discharge compared with patients who enjoyed moderate and large improvement (ΔPC > median) in lung fluid content (Figure 3B and C). Again, time from discharge to possible death due to HF was longer in the LI-guided group than in the control group (P ≤ 0.05).

In-hospital treatment, length of hospital stays, and readmissions

We have found no difference in the mean dosage of furosemide administered at the ED or during hospitalization per day per patient between the LI-guided and control groups. The length of hospital stay tended to be longer in the control group, but this did not reach statistical significance (5.3 vs. 5.7 days, respectively, P = 0.5).

Net reclassification improvement analyses

Net reclassification improvement analyses were performed to assess whether ΔPC measured by LI provided informational gain to predict HF admissions beyond the traditional methods of direct and indirect assessment of changes in pulmonary decongestion (Table 5 and Supporting Information, Table S4). In the first model, values of ΔPC assessed by LI added significant predictive accuracy to that provided by changes in LE in the LI-guided group and to NT-proBNP dynamics in the control group. These were the only variables found by multivariate analyses to independently predict time to HF hospitalization. In the second model, LI-assessed ΔPC values were added to

Table 4 Probability of HF readmissions as a function of the degree in pulmonary fluid content improvement during index HF hospitalization assessed by various parameters

| Variable                                      | LI-guided group | Control group | Control (c)/LI-guided (g) groups |
|-----------------------------------------------|-----------------|---------------|---------------------------------|
| Risk of HF readmission assessed by changes in lung impedance (ΔLI admission − ΔLI discharge) |                 |               |                                 |
| ΔLI: ≤ median vs. > median                    | 21.4            | <0.01         | 16.0                            |
| Risk of HF readmission assessed by changes in NT-proBNP (ΔNT-proBNP) between admission and discharge |                 |               |                                 |
| ΔNT-proBNP: ≤ median vs. > median             | 1.7             | 0.06          | 3.7                             |
| ΔNT-proBNP: ≤ 50% vs. > 50%                   | 2.6             | <0.01         | 8.2                             |

CI, confidence interval; HF, heart failure; HR, hazard ratio; LI, lung impedance; ΔLI, lung impedance ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide.
dian. (C) Survival from all-cause death of patients discharged following admission due to HF according to mean improvement in pulmonary fluid content (ΔPC), assessed by lung impedance (LI). The hazard ratio (HR) of the LI-guided patients with ΔPC ≤ median for admission due to recurrent HF was 22.1 (95% confidence interval (CI): 13.8–35.1, \( P < 0.01 \)) compared with that of the LI-guided patients with ΔPC > median. The HR of the control group with ΔPC ≤ median to experience re-hospitalization for HF was 31.2 (95% CI: 20.0–48.8, \( P < 0.01 \)) higher than that of the control group with ΔPC > median, and that of the control group with ΔPC > median was 2.0 (95% CI: 1.3–3.3, \( P < 0.01 \)) higher than that of the LI-guided group ΔPC > median. (B) Survival from HF-associated death after admission for worsening HF according to mean ΔPC, assessed by LI. The HR of the LI-guided patients with ΔPC ≤ median of HF death was 27.7 (95% CI: 10.2–75.1, \( P < 0.01 \)) compared with that of the LI-guided patients with ΔPC > median. The HR of the control group with ΔPC ≤ median for HF-associated death was 34.6-fold (95% CI: 13.7–87.4, \( P < 0.01 \)) higher than that of the LI-guided group with ΔPC > median, and that of the control group with ΔPC > median was 2.7 (95% CI: 1.1–5.6, \( P = 0.05 \)) higher than that of the LI-guided group ΔPC > median. (C) Survival from all-cause death of patients discharged following admission due to HF according to mean improvement in ΔPC as assessed by LI. The HR of all-cause mortality of the LI-guided patients with ΔPC ≤ median compared with that of the LI-guided group with ΔPC > median was 14.1 (95% CI: 7.0–28.4, \( P < 0.01 \)), whereas the HR of the control group with ΔPC ≤ median and that of the control group with ΔPC > median were 12.6 (95% CI: 6.6–24.2, \( P = 0.13 \)) and 1.2 (95% CI: 0.7–2.1, \( P = 0.13 \)) higher, respectively, than that of the LI-guided group ΔPC > median. In all analyses, the LI-guided group with the ΔPC > median was used as a reference group.

![Figure 3](image)

**Table 5** Impact of LI on prediction of HF readmissions calculated by NRI and IDI

| Name of index                          | 30 day readmissions | 90 day readmissions |
|----------------------------------------|---------------------|---------------------|
|                                        | Index | 95% CI | \( P \)-value | Index | 95% CI | \( P \)-value |
| LI-guided group: Model A. LI added to leg oedema (continues variables were used for analyses) |       |        |              |       |        |              |
| NRI                                    | 1.52  | 1.34–1.69 | <0.0001 | 0.38  | 0.05–0.71 | 0.026    |
| NRI for events (1–3)                   | 0.85  | 0.72–0.98 | <0.0001 | 0.32  | 0.01–0.62 | 0.040    |
| NRI for non-events (2–4)               | 0.67  | 0.56–0.78 | <0.0001 | 0.06  | –0.08 to 0.21 | 0.383   |
| IDI                                    | 0.50  | 0.43–0.57 | <0.0001 | 0.02  | 0.01–0.04 | 0.005    |
| LI-guided group: Model A. LI added to leg oedema (variables were grouped in category for analyses) |       |        |              |       |        |              |
| NRI                                    | 1.30  | 1.07–1.53 | <0.0001 | 0.67  | 0.42–0.93 | <0.0001  |
| NRI for events (1–3)                   | 0.56  | 0.35–0.76 | <0.0001 | 0.74  | 0.52–0.95 | <0.0001  |
| NRI for non-events (2–4)               | 0.74  | 0.64–0.85 | <0.0001 | –0.06 | –0.21 to 0.08 | 0.380   |
| IDI                                    | 0.47  | 0.40–0.55 | <0.0001 | 0.02  | 0.01–0.03 | 0.027    |
| Control group: Model A. LI added to NT-proBNP (continues variables were used for analyses) |       |        |              |       |        |              |
| NRI                                    | 1.09  | 0.90–1.27 | <0.0001 | 0.48  | 0.32–0.65 | <0.0001  |
| NRI for events (1–3)                   | 0.65  | 0.51–0.79 | <0.0001 | 0.88  | 0.76–0.99 | <0.0001  |
| NRI for non-events (2–4)               | 0.44  | 0.31–0.56 | <0.0001 | –0.39 | –0.51 to 0.28 | 0.28    |
| IDI                                    | 0.22  | 0.17–0.26 | <0.0001 | 0.01  | 0.0001–0.001 | 0.041  |
| Control group: Model A. LI added to NT-proBNP (variables were grouped in category for analyses) |       |        |              |       |        |              |
| NRI                                    | 1.15  | 0.96–1.34 | <0.0001 | 0.41  | 0.15–0.67 | 0.0017   |
| NRI for events (1–3)                   | 0.33  | 0.16–0.50 | 0.0002  | 0.36  | 0.14–0.59 | <0.0015  |
| NRI for non-events (2–4)               | 0.88  | 0.74–0.90 | <0.0001 | 0.05  | –0.08 to 0.17 | 0.45   |
| IDI                                    | 0.29  | 0.24–0.34 | <0.0001 | 0.01  | –0.01 to 0.01 | 0.13   |

The corrected \( P \)-value for the seven different variables used in the analysis is 0.0071. Categorical variables used for calculation: changes in LI during HF admission (Q1 vs. Q4) and changes in NT-proBNP during HF admission (NT-proBNP ≤ 50% vs. >50%). CI, confidence interval; IDI, integrated discrimination improvement; LI, lung impedance; LIR, lung impedance ratio; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-brain natriuretic peptide.
\( \Delta \text{PC} \) values obtained by measuring changes during admission of NT-proBNP, weight, RS, NYHA, LR, LE, and JVP. Using LI in addition to traditional parameters for assessment of pulmonary decongestion improved informational gain of 30 and 90 day HF admissions in both groups by more than 100% (\( P < 0.01 \), Table 5 and Supporting Information, Table S4).

**Discussion**

The present study was a pre-specified secondary analysis of the IMPEDANCE-HF extended trial. We found that in both study groups, the extent of the pulmonary fluid content decrease during hospitalization for worsening HF, as assessed by LI, demonstrated a higher predictive accuracy for next readmission than all other clinical variables.

The results of the present study show that about half of all patients hospitalized for HF are discharged with only minor or mild improvement in pulmonary fluid content (\( \Delta \text{PC} \leq \text{median} \)). In other words, they are discharged with considerable residual pulmonary fluid content as assessed by the variables used in this study. \( \Delta \text{PC} \) assessed by LI showed that patients discharged with only a minimal (Q1) or mild (Q2) decrease in their pulmonary fluid content had a 94% and 43% probability of being readmitted within 30 days.

Study groups were well matched on entry to the study, but the follow-up period was 25% longer in the LI-guided group who achieved better lung fluid reduction during HF hospitalizations. The longer follow-up period in the LI-guided group could be explained by the better survival in this group. Mean \( \Delta \text{LIR} \) measured at all visits during entire follow-up in both study groups showed that the LI-guided patients were consistently less congested by about 20% (\( P < 0.01 \)). Decreased lung fluid content in the LI-guided group was likely the result of available information regarding lung fluid status of the patients, which was associated with 47% fewer hospitalizations than in control patients. The mean overall NYHA for all clinic visits during the entire follow-up was 2.0 for the LI-guided group compared with 2.3 for the control group (\( P < 0.01 \)). This, again, attests to better decongestive therapy in the LI-guided patients and may explain their improved clinical outcome. More outpatient clinic visits per month were recorded in the LI-guided group than in the control group, but this difference was insignificant (4%, \( P = 0.35 \)) and cannot account for the better clinical outcome in the former.

The degree of the pulmonary congestion at HF admission, as assessed by all parameters, was practically the same, but the extent of improvement in congestion (\( \Delta \text{PC} \)) was more prominent in the LI-guided group. This finding is important especially in light of the fact that all parameters were registered at admission and discharge, but the study physicians and treating physicians were blinded to results. The main objective of the IMPEDANCE-HF extended trial was to prove that LI-guided treatment of HF patients in the outpatient clinic could reduce HF readmissions. Therefore, we wanted to exclude any effect of study team on in-hospital treatment. Therefore, at the stage of study protocol development, it was decided to keep in hospital treatment independent of accessed parameters. The larger improvement in lung fluid content in LI-guided group could be explained by fact that patients of LI-guided group were less sick during the whole period of follow-up. In the LI-guided group, there was a lower incidence of HF hospitalizations, which feasibly resulted in less myocardial micro-damage, less pulmonary congestion, and better NYHA class throughout the follow-up period. This, with some reservations, may lead to the conclusion that patients of LI-guided group were less sick during monitoring period. Additionally, it is important to emphasize that comparison of patients of the LI-guided and control groups discharged with the same level of decongestion (Q1, Q2, Q3, or Q4 of LI-guided vs. respective control subgroups) has shown that time to readmission was practically the same at the Q1 and Q2 levels of improvement but significantly better in the LI-guided for Q3 and Q4 subgroups. This demonstrates that small improvement in pulmonary decongestion does not allow LI-guiding monitoring to confer any beneficial effect on HF admissions. In contrast, discharge of patients with Q3 and Q4 level of decongestion permits enough time to adjust treatment according to LI level and thus effectively prevent readmissions.

The population presently studied was similar to that of other contemporary HF studies\(^6,18–20\) with regard to readmission rate, length of stay, and in-hospital mortality. In-hospital mortality was 4% in the ADHERE registry, 4.7% in the PROTECT registry,\(^7\) 3.8% in the common cohort, and 8.6% for patients readmitted for HF between 60th and 90th days after discharge in the OPTIMIZE-HF registry,\(^19\) 14.3% in the ESCAPE trial,\(^17\) and 16.1% in the present study. The IMPEDANCE-HF trial differs substantially from the other studies by the longer duration of mean follow-up, which was more than 4.5 years. As far as we know, there are no reports relating the extent of pulmonary decongestion during HF hospitalizations to readmission rate. Maggioni et al.\(^21\) using clinical assessment only found that 25% of HF patients showed at discharge signs or symptoms of peripheral and/or pulmonary congestion. The lung impedance method is probably more sensitive than clinical assessment of pulmonary congestion\(^12,22\), hence, we can assume that the incidence of residual pulmonary fluid detected by the lung impedance method would be even higher. In the present study, we obtained a \( \Delta \text{LIR} \) mean value of \(-30\%\) at discharge in the \( \Delta \text{PC} \leq \text{median} \) subgroup, representing significant residual congestion, and mean \( \Delta \text{LIR} = -20\% \) in the \( \Delta \text{PC} > \text{median} \) subgroup when \( \Delta \text{LIR} = 0 \) corresponds to the normal baseline condition. Previously, we have shown that a \( \Delta \text{LIR} \) value of \(-30\%\) is compatible

**Table 5**

| Parameter | Value |
|-----------|-------|
| NYHA class | 2.0 |
| JVP | 2.3 |
| RS | 0.35 |

DOI: 10.1002/ehf2.12330
with mild to moderate alveolar oedema, while a value of
–20% corresponds to mild–moderate interstitial conges-
tion.\textsuperscript{13,14} This explains the absence of rales on lung auscu-
tlation in 52% of patients in the present study, at a time when lung impedance and the chest radiograph
demonstrate interstitial congestion.\textsuperscript{12,13} Only 10% of
\(\Delta PC >\) median subgroup patients were discharged with an acceptable level of, or with no pulmonary congestion
at all, that is, \(\Delta LIR >\) –18%, defined previously as the
threshold level.\textsuperscript{15}

\section*{Comparison of the different methods of in-hospital improvement}

In this study, we evaluated changes in the functional NYHA
class, LR, LE, and JVP as physical signs, weight, RS, and NT-
proBNP as a biochemical marker, and LI as markers of lung
decongestion. We found that all clinical parameters could
contribute to the prediction of HF readmission, but the as-
essment was operator dependent with considerable inter-
observer variability and with a relatively weak predictive
power. Changes in patient weight during HF hospitalization
indicated increased probability for HF readmission. The
mean weight decrease during HF hospitalization was
2.7 kg in the LI-guided group and 2.5 kg in the control
group (\(P < 0.01\)), respectively, nearly the same as observed
in the ASCEND-HF trial.\textsuperscript{20} The radiological score was found
to be a very useful tool to predict HF hospitalization. To
the best of our knowledge, there are no reports on the
use of the CXR to assess the risk of HF readmission. How-
ever, the radiation burden and lack of agreement among
physicians treating HF patients regarding the radiological
score may impede the widespread use of this method.

The usefulness of NT-proBNP measurements during index
HF admission for risk stratification of readmissions was al-
ready investigated.\textsuperscript{7} In our study, we found that insufficient
decrease of NT-proBNP level at discharge compared with its
admission value is a useful predictor of readmission. NT-
proBNP decreased by more than 50% during hospitalization
in more than 42% of patients. Noveau \textit{et al.}\textsuperscript{23} measured
an NT-proBNP decrease of more than 50% in 67% of pa-
tients during HF admissions but could not use this for pre-
diction of readmissions. The predictive accuracy for HF
readmissions assessed by NT-proBNP was weaker than that
for LI (Table 4 and Supporting Information, Table S3).
Therefore, it is not surprising that multivariate regression analysis
has shown that changes in NT-proBNP are not predictive in
the LI-guided group and only borderline predictive in the
control group. Net reclassification improvement analyses
shown that using LI in addition to the classical clinical and
laboratory parameters for predicting HF readmissions im-
proved informational gain by more than 100%.

\section*{Impedance techniques}

Traditional impedance techniques measure the conductivity
of the whole chest, whereas the impedance of the lung is
only a small component (near 10–15%) of this resistance,\textsuperscript{8,15}
and the remainder is that of the chest wall impedance.
Therefore, traditional techniques are not sufficiently sensitive
to measure small changes in lung conductivity at the pre-
clinical stage of evolving pulmonary congestion. Packer
\textit{et al.}\textsuperscript{24} have shown that the traditional impedance scheme
has limited utility for identification of short-term risk of clinical
deterioration. Pacemaker-based devices were also found
to be too insensitive to allow detection of small shifts in pul-
monary fluid content in evolving HF.\textsuperscript{25} The physical basis of
the limited effectiveness of such devices was described in
the work of Charles \textit{et al.}\textsuperscript{26}

In the present study, we used the technique that elimi-
nates noise impedance of the chest wall and calculates the
net lung impedance.\textsuperscript{16} The sensitivity of this approach is
sufficiently high to allow detection of the pre-clinical stage
of evolving pulmonary fluid accumulation and thus permits
pre-emptive adjustment of treatment in LI-guided patients.

\section*{Practical implications}

According to current clinical experience, patients are usually
considered for discharge after initial therapy during the first
4–5 days of hospitalization following the amelioration of
symptoms as a result of the decrease in pulmonary fluid con-
tent. In the present study, as in some others, the median
length of stay was only 4–4.5 days.\textsuperscript{18–20} Current data show
that only half of all patients of both groups achieve \(\Delta PC >\) me-
dian level of decongestion during their hospital stay. The
impedance technique used in this study elicits patients with
insufficient lung fluid decongestion, and the extension of in-
hospital treatment until \(\Delta PC >\) median level is achieved
could allow better readmission rate.

\section*{Conclusions}

The extent of reduction in pulmonary fluid content during HF
hospitalization as measured by lung impedance strongly pre-
dicts readmission rate and event-free survival for HF hospital-
zation, as well as HF-related and all-cause mortality. The
extent of clinical improvement as measured by other vari-
ables used in this study also predicts readmission rates but
significantly less accurately than by lung impedance. The
study shows that about half of HF patients have persistently
increased pulmonary fluid content at discharge and suggests
the intensification of treatment until moderate-level or high-
level decongestion is achieved in order to decrease 30 day
readmissions.
Acknowledgement

We thank Nadia Bordo, MSc, of the Faculty of Industrial Engineering and Management, Technion—Israel Institute of Technology for statistical analysis.

Conflict of interest

M.K.S. is co-founder and member of the board of directors of the CardioSet Startup Company that manufactured and supplied the devices used in the trial.

Funding

None.

References

1. Krumholz HM, Lin Z, Keenan PS, Chen J, Ross JS, Drye EE, Bernheim SM, Wang Y, Bradley EH, Han LF, Normand SL. Relationship between hospital readmission and mortality rates for patients hospitalized with acute myocardial infarction, heart failure, or pneumonia. JAMA 2013; 309: 587–593.

2. Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, Hennen J. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. Arch Intern Med 1997; 157: 99–104.

3. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med 2009; 360: 1418–1428.

4. Cleland JG, Chiswell K, Teerlink JR, Stevens S, Fiuza M, Givertz MM, Davison BA, Mansoor GA, Ponikowski P, Voors AA, Cotter G, Metra M, Massie BM, O’Connor CM. Predictors of post-discharge outcomes from information acquired shortly after admission for acute heart failure: a report from the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) Study. Circ Heart Fail 2014; 7: 76–87.

5. Ciorte S, Rossignol P, Ambrosio G, Garfucchio E, Alunni G, Murrone A, Tritto I, Zannad F, Girerd N. Prognostic value of residual pulmonary congestion at discharge assessed by lung ultrasound imaging in heart failure. Eur J Heart Fail 2015; 17: 1172–1181.

6. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS, CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomized controlled trial. Lancet 2011; 377: 658–666.

7. Michaltik HJ, Yeh HC, Campbell CY, Haq N, Park H, Clarke W, Brotman DJ. Acute changes in N-terminal pro-B-type natriuretic peptide during hospitalization and risk of readmission and mortality in patients with heart failure. Am J Cardio 2011; 107: 1191–1195.

8. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuza M, Houston-Miller N, Januzzi JL, Mark DB, Piña IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O’Connor CM. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA 2017; 318: 713–720.

9. Bajaj NS, Patel N, PrabhU SD, Arora G, Wang Tj, Arora P. Effect of NT-proBNP-guided therapy on all-cause mortality in chronic heart failure with reduced ejection fraction. J Am Coll Cardiol 2018; 71: 951–952.

10. Shochat M, Charach G, Meyler S, Kazatzker M, Mosseri M, Frimerman A, Rabinovich P, Shotan A, Meisel S. Internal thoracic impedance monitoring: a novel method for the preclinical detection of acute heart failure. Cardiovasc Revasc Med 2006; 7: 41–45.

11. Shochat M, Charach G, Meyler S, Kazatzker M, Mosseri M, Frimerman A, Rabinovich P, Shotan A, Meisel S. Prediction of cardiogenic pulmonary edema onset by monitoring right lung impedance. Intensive Care Med 2006; 32: 1214–1221.

12. Shochat M, Shotan A, Blandheim DS, Kazatzker M, Dahan I, Asif A, Shochat I, Rabinovich P, Rozenman Y, Meisel SR. Usefulness of lung impedance-guided pre-emptive therapy to prevent pulmonary edema during STElevation myocardial infarction and to improve long-term outcomes. Am J Cardiol 2012; 110: 190–196.

13. Shochat M, Shotan A, Trachtetgerts V, Blandheim DS, Kazatzker M, Gurovich V, Asif A, Shochat I, Rozenman Y, Meisel SR. A novel radiological score to assess lung fluid content during evolving acute heart failure in the course of acute myocardial infarction and to improve long-term outcomes. Acute Card Care 2011; 13: 81–86.

14. Shochat M, Shotan A, Blandheim DS, Kazatzker M, Dahan I, Asif A, Shochat I, Frimerman A, Rozenman Y, Meisel SR. Derivation of baseline lung impedance in chronic heart failure patients: use for monitoring pulmonary congestion and predicting admissions for...
decompensation. J Clin Monit Comput 2015; 29: 341–349.
15. Shochat MK, Shotan A, Blondheim DS, Kazatsker M, Dahan I, Asif A, Rozenman Y, Kleiner I, Weinstein JM, Framer M, Vasilienko L, Meisel SR. Non-invasive lung IMPEDANCE-guided preemptive treatment in chronic heart failure patients: a randomized controlled trial (IMPEDANCE-HF trial). J Card Fail 2016; 22: 713–722.
16. Ponikowski P, Voors AA, Anker SD, Bueno H, Celano LG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parides JT, Piepsz B, Riley JP, Rosano GM, Ruijike LM, Ruschitzka F, Rutten PH, van der Meer P, Authors/ Task Force Members, Document Reviewers. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18: 891–975.
17. Drazner MH, Anne S, Hellkamp AS, Leier CV, Shah MR, Miller LW, Russell SD, Young JB, Robert M, Califf RM, Nohria A. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circ Heart Fail 2008; 1: 170–177.
18. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005; 149: 209–216.
19. Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O’Connor CM, Pieper K, Sun JI, Yancy C, Young JB, OPTIMIZE-HF. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. JAMA 2007; 297: 61–70.
20. Ambrosy AP, Cerbin LP, Armstrong PW, Butler J, Coles A, DeVore AD, Dunlap ME, Ezekowitz JA, Felker GM, Fudim M, Greene SJ, Hernandez AF, O’Connor CM, Schulte P, Starling RC, Teerlink JR, Voors AA, Mentz RJ. Body weight change during and after hospitalization for acute heart failure: patient characteristics, markers of congestion, and outcomes: findings from the ASCEND-HF trial. JACC Heart Fail 2017; 5: 1–13.
21. Maggioni AP, Dahlofström U, Filippatos G, Chioncel O, Leiro MC, Drozda J, Fruhwald F, Guillestal L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F, Tavazzi L, Heart Failure Association of ESC (HFA). EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail 2010; 12: 1076–1084.
22. Donadio C, Bozzoli L, Colombini E, Pisanu G, Ricciuti G, Picano E, Gargani L. Effective and timely evaluation of pulmonary congestion: qualitative comparison between lung ultrasounds and thoracic bioelectrical impedance in maintenance hemodialysis patients. Medicine (Baltimore) 2015; 94: e473.
23. Noveanu M, Breidhthardt T, Potocki M, Reichlin T, Twerenbold R, Uthoff H, Socrates T, Arenja N, Reiter M, Meissner J, Heinisch C, Stalder S, Mueller C. Direct comparison of serial B-type natriuretic peptide and NT-proBNP levels for prediction of short- and long-term outcome in acute decompensated heart failure. Crit Care 2011; 15: R1.
24. Packer M, Abraham WT, Mehra MR, Yancy CW, Lawless CE, Mitchell JE, Smart FW, Bijou R, O’Connor CM, Massie BM, Pina IL, Greenberg BH, Young JB, Fishbein DP, Hauptman PJ, Bourge RC, Strober BE, Muri M, Schoenen D, Teerlink JR, Levy WC, Trupp RJ, Silver MA. Prospective Evaluation and Identification of Cardiac Decompensation by ICG Test (PREDICT) Study Investigators and Coordinators. Utility of impedance cardiography for the identification of short-term risk of clinical decompensation in stable patients with chronic heart failure. J Am Coll Cardiol 2006; 47: 2245–2252.
25. van Veldhuisen DJ, Braunischweig F, Conraads Y, Ford I, Cowie MR, Jondeau G, Kautzner J, Aguillera RM, Lunati M, Yu CM, Gerritse B, Borggreve M, Investigators DOT-HF. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. Circulation 2011 Oct 18; 124: 1719–1726.
26. Charles CJ, Rademaker MT, Melton IC, Gutfinder D, Eigler NL, Qu F, Troughton RW. Thoracic impedance measures tissue characteristics in the vicinity of the electrodes, not intervening lung water: implications for heart failure monitoring. J Clin Monit Comput 2015; 29: 65–76.

ESC Heart Failure 2018; 5: 788–799
DOI: 10.1002/ehf2.12330