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Improved 30 day heart failure rehospitalization prediction through the addition of device-measured parameters

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Abstract

Aims This study aimed to improve in-person clinical evaluation on the day of heart failure (HF) hospitalization discharge by adding device-measured parameters to predict 30 day HF rehospitalization risk in cardiac resynchronization therapy-defibrillator (CRT-D) patients.

Methods and results In a cohort of Medicare patients with CRT-Ds, the independent prognostic value of four device-measured parameters was assessed relative to typical clinical parameters associated with rehospitalization risk. Medicare registry, claims, and Medtronic CareLink® Network data for these patients were analysed using logistic regression modelling and net reclassification methods. Among 1563 CRT-D patients, 411 patients had 607 HF hospitalization events during a median 6.3 years of follow-up. Compared with clinical variables alone, impedance measurements resulted in a 28% improvement between the predicted probabilities of having vs. not having a 30 day HF rehospitalization (relative integrated discrimination improvement = 0.28) and a net 42% improvement in the classification of 30 day HF rehospitalization events and non-events after an index HF hospitalization (net reclassification index = 0.42; 95% CI: 0.10, 0.74).

Conclusions In CRT patients, intrathoracic impedance measurements improve prediction of 30 day HF rehospitalization over clinical characteristics alone. The present study provides supportive data for the routine evaluation of intrathoracic impedance prior to discharge in patient with CRT devices. Furthermore, the models developed in this study could be used to design interventions to improve compliance with Medicare reimbursement guidelines regarding 30 day HF rehospitalization.

Keywords Cardiac resynchronization therapy; Rehospitalization; Heart failure; Registry; Risk stratification

Introduction

Frequent hospitalizations place considerable suffering on patients living with heart failure (HF), as well as burden on clinicians managing these patients.1 Many HF patients experience severe, acute episodes of symptoms including fatigue, dyspnoea, oedema, sudden weight gain, and chest pain, which require immediate treatment and/or hospitalization. While more HF-related hospitalizations themselves have been associated with poorer outcomes,2,3 there is also an economic burden to the health care system in treating these patients. As of 2012, these costs stood at $20.9 billion in direct treatment costs and a further $9.8 billion in indirect, or lost productivity, costs.4 In an effort to reduce the frequency of rehospitalizations, the Centers for Medicare & Medicaid Services (CMS) instituted their Hospital Readmissions Reduction Program (HRRP) in 2012, which financially penalizes providers who have excessive 30 day rehospitalization rates.5 Therefore, development of criteria that can identify patients at higher risk of 30 day readmission is of critical importance, such that better interventions or more frequent monitoring strategies can be developed and employed.

A review of 30 day rehospitalization models reveals that most are of limited usefulness, with only modest
discrimination between patients with and without imminent rehospitalizations after discharge from an index event.\textsuperscript{6–8} Even the CMS administrative model used for evaluating excessive HF-related rehospitalization rates displays a c-statistic of only 0.60.\textsuperscript{6} Clinical models are typically comprised of many variables, including patient demographics (e.g. patient age and sex), co-morbidities (e.g. diabetes mellitus and hypertension), patient clinical characteristics (e.g. New York Heart Association [NYHA] class and left ventricular ejection fraction [LVEF]), and serum biomarkers (e.g. blood urea nitrogen and creatinine). Data recorded by cardiac resynchronization therapy-defibrillator (CRT-D) devices have the potential to improve 30 day HF rehospitalization risk prediction for patients with moderate to advanced HF; however, there is an unmet need to evaluate how device-measured data can improve clinical prediction models in large cohorts. The present study addresses this need by evaluating device-based and clinical prediction models in a retrospective cohort study of CMS patients in which administrative, clinical, and device-measured data have been combined into a single dataset. We hypothesized that typical 30 day HF rehospitalization models utilizing clinical-only evaluation can be improved upon by the inclusion of one or more CRT-D device-measured parameters.

Methods

Study population

For this analysis, we used a combination of Medicare ICD registry and Medtronic CareLink\textsuperscript{®} data from patients implanted with an OptiVol\textsuperscript{®}-enabled Medtronic CRT-D device implanted from January 2005 to April 2006. The OptiVol\textsuperscript{®} algorithm measures a patient’s intrathoracic impedance between the right ventricular lead tip and the device on a daily basis. A representative patient intrathoracic impedance trend is shown in Figure 1 and is described in more detail elsewhere.\textsuperscript{9} Patients without at least one CareLink\textsuperscript{®} transmission and at least one HF-related hospitalization event before Medicare follow-up ended in December 2011 were excluded from the analysis. Additional information regarding health maintenance organization (HMO) or managed care organization (MCO) coverage were added from the Medicare Beneficiary File. As described elsewhere, the de-identified data were matched between the Medicare and CareLink\textsuperscript{®} datasets on the basis of patient sex, age at implant, date of implant, device model, and de-identified (three-digit) ZIP code.\textsuperscript{10} We excluded those patients with any HMO/MCO coverage as indicated in the Medicare Beneficiary File, as we specifically looked at hospitalization outcomes recorded by Medicare, which may have been significantly underestimated for these patients.

Endpoint definition

A primary ICD-9-CM diagnosis code of 428.x within 30 days of an index hospitalization constituted a 30 day rehospitalization event. Per CMS guidelines on rehospitalization, any HF-related hospitalization event during the follow-up period classified by a primary ICD-9-CM diagnosis code of 428.x for a given patient qualified as an index hospitalization if there were 30 days of device monitoring information available.

![Figure 1] Representative patient intrathoracic impedance trend. The OptiVol\textsuperscript{®} fluid index is the accumulated difference between the daily impedance value and the reference value. Intrathoracic impedance declines with increased ventricular volumes and pressures.\textsuperscript{9}
following discharge. As a result, a single patient may have several index hospitalization events, and a rehospitalization event may also count as the index event for the next 30 day interval.

**Exposure definition**

Data from the Medtronic CareLink® network from CRT-D devices implanted in the January 2005 to April 2006 time frame were queried to determine the values of daily impedance, reference impedance, time in atrial tachycardia/atrial fibrillation (AF), night heart rate, and percent bi-ventricular pacing on the day of discharge from an index hospitalization. To compare with prior literature, the previously defined device-measured parameters on the day of discharge (daily intrathoracic impedance > 8 Ω below reference impedance, AF burden > 6 h, CRT pacing < 90%, and night heart rate > 80 bpm) were then applied and coded as indicator variables for use in modelling outcomes.\(^1\) Similarly, if device-measured data were missing from the CareLink® data for a specific device parameter on the day of discharge, it was considered that that diagnostic criterion was not met (298 missing, 49.1%).

**Covariates**

We examined all the available variables in the Medicare ICD registry at the time of device implant, including patient sex, bundle-branch block morphology, cardiomyopathy origin (ischaemic Y/N), LVEF, systolic blood pressure (SBP), diastolic blood pressure (DBP), diabetes mellitus, smoking status, chronic kidney disease (CKD), end-stage renal disease, and the prescription of digoxin, beta-blockers, diuretic, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, amiodarone, or warfarin. We also calculated patient age and duration of HF at the time of the index hospitalization.

**Statistical analysis**

We employed a bootstrap approach to identify predictors associated with a 30 day HF rehospitalization event.\(^2\) The method involved splitting our cohort into derivation and validation samples. For the purposes of this analysis, we randomly selected two-thirds of our cohort to derive the model and held the other third for subsequent validation of the model. We then used PROC MULTTEST in SAS v9.4 to generate 1000 datasets with the same number of observations as the original dataset, randomly selecting patients for each dataset from our derivation cohort with replacement. As the main outcome of interest was rehospitalization within 30 days, we used logistic regression modelling with stepwise backwards selection using only the available clinical covariates from the Medicare data in each of these 1000 datasets using a P-value threshold of 0.05 for a parameter to remain in the model. Any variable selected in more than 50% of the 1000 model iterations was included in our final model. A model with these final parameters was then tested in the remaining validation portion of our cohort.

We evaluated discrimination improvement of adding device-measured parameters to the clinical variable-only model by examining the change in area under the curve (AUC), net reclassification index (NRI), and integrated discrimination improvement (IDI) described by Pencina et al.\(^3\)\(^4\)\(^5\) NRI and IDI measures of reclassification provide additional information over the AUC, which often requires new predictive variables to have enormous effect sizes to provide improvement of the model.\(^5\)\(^6\) NRI and IDI measures provide the percentage improvement of correctly classifying those patients with events associated with an additional predictor, as well as the changes in sensitivity with the new predictor, given a fixed specificity. To avoid the dilemma of defining meaningful risk categories for NRI calculation, a category-free method was employed to calculate NRI, and any change upward or downward in the probability of a rehospitalization event for a given patient between models was counted.\(^6\)\(^7\) Model calibration was assessed through the Hosmer–Lemeshow \(\chi^2\) statistic.

To validate the model developed from the bootstrapping process, we applied that model to both the validation and full patient cohorts and calculated AUC, NRI, and IDI statistics. One thousand datasets from the full cohort were generated using bootstrapping, and the AUC for this model was determined in each bootstrap dataset. We then calculated the 2.5th, 50th, and 97.5th percentiles of the resulting AUC distribution.

**Results**

A total of 607 index hospitalizations were observed in our cohort of 1563 patients matched between the Medicare and CareLink® datasets over a mean follow-up of 6.3 years. Figure 2 shows that 297 patients experienced a single index hospitalization, 69 experienced two hospitalizations, and 45 more than two. Another hospitalization event occurred within 30 days after 17.6% of index hospitalizations (107 thirty-day rehospitalizations/607 index hospitalizations). Characteristics of patients with and without 30 day rehospitalizations are shown in Table 1. Those who did not experience a 30 day HF-related hospitalization event were younger; had HF for a shorter duration before implant; had lower LVEF; had lower SBP and DBP; were less likely to be diagnosed with CKD at baseline; were more likely to be prescribed digoxin, warfarin, and diuretics; and also had a

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different distribution of NYHA class at baseline than those who did. These observed differences in these parameters were all formally tested for statistical significance in the modelling process, described above.

The results of our model-building process are summarized in Table 2. Our derivation cohort (n = 346 initial index events and 72 total rehospitalizations) was run through the bootstrap variable selection process, where the variables of diuretic prescription (selected in 90.3% of bootstrap models), diagnosis of CKD (89.7%), NYHA HF class (83.2%), patient sex (77.6%), device-measured impedance criterion (66.5%), prior coronary artery bypass graft (65.5%), duration of HF at the time of the index hospitalization (63.9%), atrial fibrillation (55.5%), and prescription of warfarin (52.3%) were stepwise backwards selected by more than 50% of the bootstrap model datasets for inclusion into the model. In the validation cohort, 35 patients were rehospitalized during the 30 days after discharge, and the only clinical variables that were significantly associated with rehospitalization were CKD diagnosis and duration of HF at the time of the index hospitalization. Diuretic prescription, patient sex, NYHA class, and prior coronary artery bypass graft procedure were not significant.

All models showed appropriate calibration using the Hosmer–Lemeshow $\chi^2$ statistic, with values ranging from 5.33 to 9.33 depending on the exact cohort and model parameters in question. Figure 3 shows the plot of expected probabilities of failure vs. observed for the bootstrap-selected model in the validation cohort, as well as the full cohort.

Also shown in Table 2, the calculated AUC for the logistic model in the validation cohort including clinical and device-measured data was 0.78 (95% CI: 0.69, 0.87). The inclusion of device-measured data in the model resulted in an NRI value of 0.42 (95% CI: 0.10, 0.74) relative to the model without device-measured data, indicating a significant net 42% improvement in correctly classifying both patients with and without 30 day HF hospitalization events. For reference, the absolute IDI value was 0.047 (95% CI: 0.002, 0.092), and the relative IDI was 0.28, indicating a 28% improvement in the mean probabilities between events and non-events.

Similar results were observed when applying the bootstrap-selected model to the full cohort. The AUC for the model including device-measured data was 0.77 (95% CI: 0.73, 0.82), and the distribution of observed AUCs with the model applied to bootstrap samples, which were selected from the full cohort instead of the derivation cohort, resulted in a median AUC of 0.81 (2.5th percentile = 0.75, 97.5th percentile = 0.86). The corresponding NRI attributable to the device-measured data in the model was 0.23 (95% CI: 0.07, 0.40), the IDI was 0.026 (95% CI: 0.006, 0.047), and the relative IDI was 0.22, indicating an improvement of 22% in the mean probabilities of events and non-events. Additionally, we applied the model variables and coefficients obtained from the bootstrap variable selection process to the validation sample. The AUC from the validation sample was 0.72, with a Brier score of 0.147, also indicating good calibration.

All patients in the full cohort (n = 607) were dichotomized into ‘high’ (probability of 30 day rehospitalization $\geq 13.3\%$) and ‘low’ (<13.3%) risk on the basis of the predicted probability of an HF-related hospitalization within 30 days as predicted by the reduced bootstrap logistic regression model. A Kaplan–Meier plot showing survival for patients in these categories is shown in Figure 4. The log-rank comparison between risk categories was statistically significant (P-values < 0.0001). Additionally, we compared the predicted and observed probabilities of a 30 day rehospitalization for each risk category in both the derivation and validation samples. The results are presented in Figure 5.

A sensitivity study on the effect of missing impedance data on the day of discharge was also performed by categorizing the impedance criterion as ‘data available, criterion met’, ‘data available, criterion not met’, or ‘data unavailable’. The odds of 30 day rehospitalization for the ‘data available, criterion met’ group were 3.02 times higher than those of the ‘data available, criterion not met’ group (OR 3.02, 95% CI: 1.37, 6.66, P-value 0.0002). Further, the odds for the ‘data unavailable’ group were lower by a factor of 0.55 than those in the ‘data available, criterion not met’ group (OR 0.55, 95% CI: 0.33, 0.90, P-value _x0003C; 0.0001).

Discussion

In a cohort of Medicare patients with CRT-D devices, the addition of the device-measured impedance parameters improves the predictive performance of a logistic regression model for 30 day HF rehospitalization relative to a model with clinical parameters alone, as indicated by observed increases in the NRI and IDI measures. The absolute NRI value of 0.42
indicates a net 42% improvement attributable to device-measured data, and the relative IDI value 0.28 indicates that device-measured parameters increased this difference in mean predicted probabilities of events and non-events by 28%, which represents a large improvement. Given the limitations of NRI and IDI methods in correctly identifying model improvement, we have also included the results of the likelihood ratio tests comparing our final model to the clinical variable-only model. Furthermore, the full bootstrap model in our validation cohort remained robust and well-calibrated. The model developed in the derivation sample performed well in predicting the observed proportions of 30 day rehospitalization events when challenged with a new dataset in the validation sample, with a maximum discrepancy of 1.3 percentage points. Future work to refine these risk categories could involve incorporating longitudinal data on laboratory data and prescription drug information not included in the present dataset.

The intrathoracic impedance criterion increased model performance even with inclusion of influential covariates such as diuretic use and CKD, demonstrating the potential to develop monitoring or interventional strategies guided by

### Table 1 Characteristics of Medicare registry cardiac resynchronization therapy-defibrillator patients with and without 30 day readmission

|                                | All hospitalizations (n = 607) | Hospitalizations without 30 day readmission (n = 500) | Hospitalizations with 30 day readmission (n = 107) | P-value a |
|--------------------------------|--------------------------------|-------------------------------------------------------|----------------------------------------------------|-----------|
| Age, mean ± SD, years          | 74.0 ± 8.1                     | 73.6 ± 7.9                                            | 75.8 ± 8.4                                         | 0.01      |
| Duration HF, mean ± SD, months | 30.5 ± 29.7                    | 29.2 ± 29.0                                           | 36.5 ± 32.2                                        | 0.02      |
| LVEF, mean ± SD, %             | 23.1 ± 6.4                     | 22.7 ± 6.5                                            | 25.1 ± 5.9                                         | <0.01     |
| QRS duration, mean ± SD, ms    | 156.1 ± 23.6                   | 155.9 ± 23.9                                          | 156.7 ± 22.6                                       | 0.75      |
| SBP, mean ± SD, mm Hg          | 124.8 ± 22.4                   | 123.9 ± 21.9                                          | 129.0 ± 24.4                                       | 0.03      |
| DBP, mean ± SD, mm Hg          | 69.8 ± 12.4                    | 69.3 ± 12.1                                           | 72.0 ± 13.8                                        | 0.04      |
| Heart rate, mean ± SD, bpm     | 70.9 ± 13.7                    | 71.3 ± 14.0                                           | 68.9 ± 11.8                                        | 0.07      |
| Sex, n (%)                     |                                |                                                       |                                                   |           |
| Female                         | 28.0                           | 27.0                                                  | 33.7                                               | 0.23      |
| Male                           | 72.0                           | 73.0                                                  | 67.3                                               |           |
| NYHA class (%)                 |                                |                                                       |                                                   |           |
| I                              | 1.7                            | 1.2                                                   | 3.7                                                |           |
| II                             | 11.0                           | 10.2                                                  | 15.0                                               |           |
| III                            | 72.5                           | 72.0                                                  | 74.8                                               | 0.01      |
| IV                             | 14.8                           | 16.6                                                  | 6.5                                                |           |
| Ischaemic CM (%)               | 65.7                           | 65.4                                                  | 67.3                                               | 0.71      |
| Prior CABG (%)                 | 45.3                           | 44.4                                                  | 49.5                                               | 0.33      |
| BBB morphology (%)             |                                |                                                       |                                                   |           |
| LBBB                           | 71.7                           | 70.2                                                  | 78.5                                               |           |
| RBBB                           | 9.9                            | 9.8                                                   | 10.3                                               | 0.10      |
| Other IVCD                     | 18.5                           | 20.0                                                  | 11.2                                               |           |
| Atrial fibrillation (%)        | 37.4                           | 36.4                                                  | 42.1                                               | 0.27      |
| Ventricular tachycardia (%)    | 18.3                           | 18.4                                                  | 17.8                                               | 0.88      |
| Sudden cardiac arrest (%)      | 2.0                            | 2.0                                                   | 1.9                                                | 0.93      |
| Diabetes mellitus (%)          | 39.5                           | 39.6                                                  | 39.3                                               | 0.95      |
| Prior MI (%)                   | 48.1                           | 46.4                                                  | 56.1                                               | 0.07      |
| Chronic kidney disease (%)     | 45.3                           | 42.0                                                  | 60.8                                               | <0.01     |
| End-stage renal disease (%)    | 1.5                            | 1.4                                                   | 1.9                                                | 0.74      |
| Smoking status (%)             |                                |                                                       |                                                   |           |
| Never                          | 42.3                           | 42.0                                                  | 43.9                                               |           |
| Former                         | 49.1                           | 48.8                                                  | 50.5                                               | 0.48      |
| Current                        | 8.6                            | 9.2                                                   | 5.6                                                |           |
| Medications (%)                |                                |                                                       |                                                   |           |
| Beta-blocker                   | 78.9                           | 78.2                                                  | 82.2                                               | 0.36      |
| ACEI or ARB                    | 74.1                           | 75.2                                                  | 69.2                                               | 0.20      |
| Digoxin                        | 40.5                           | 42.6                                                  | 30.8                                               | 0.02      |
| Diuretic                       | 82.4                           | 84.8                                                  | 71.0                                               | <0.01     |
| Amiodarone                     | 11.7                           | 12.4                                                  | 8.4                                                | 0.20      |
| Warfarin                       | 32.3                           | 34.4                                                  | 22.4                                               | 0.01      |
| Device measurement criteria met (%) |                  |                                                       |                                                   |           |
| Impedance                      | 6.6                            | 4.2                                                   | 15.9                                               | <0.01     |
| Atrial fibrillation            | 17.0                           | 16.8                                                  | 17.8                                               | 0.81      |
| CRT pacing                     | 19.8                           | 17.2                                                  | 24.3                                               | 0.19      |
| Night heart rate               | 18.0                           | 18.8                                                  | 21.5                                               | 0.29      |

aComparing hospitalizations with and without 30 day readmissions.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BBB, bundle branch block (left, right); CABG, coronary artery bypass graft; CM, cardiomyopathy; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; HF, heart failure; IVCD, interventricular conduction delay; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; SBP, systolic blood pressure.
Table 2  Odds ratios and model performance metrics for probability of 30 day rehospitalization from logistic regression modelling

| Model variables                              | Bootstrap model, derivation sample (n = 418) | Clinical only validation sample (n = 189) | Bootstrap model, validation sample (n = 189) | Clinical-only, full cohort (n = 607) | Bootstrap model, full cohort (n = 607) |
|----------------------------------------------|---------------------------------------------|-----------------------------------------|---------------------------------------------|-------------------------------------|----------------------------------------|
| Reference impedance—daily impedance > 8 Ω  | 4.08 (1.47, 11.27)                          | n/a                                     | 5.09 (1.61, 16.11)                          | n/a                                 | 4.26 (2.01, 8.99)                      |
| Diuretic (Y/N)                               | 0.31 (0.16, 0.61)                            | 0.48 (0.18, 1.32)                       | 0.43 (0.15, 1.20)                           | 0.36 (0.21, 0.61)                    | 0.36 (0.21, 0.62)                      |
| Patient sex (M/F)                            | 3.48 (1.77, 6.84)                            | 0.85 (0.33, 2.17)                       | 0.93 (0.35, 2.44)                           | 1.85 (1.11, 3.10)                    | 2.13 (1.25, 3.62)                      |
| Chronic kidney disease (Y/N)                 | 2.61 (1.42, 4.78)                            | 2.85 (1.20, 6.77)                       | 3.08 (1.26, 7.52)                           | 2.45 (1.52, 3.96)                    | 2.53 (1.55, 4.13)                      |
| NYHA class                                   |                                             |                                         |                                             |                                     |                                        |
| I                                            | 0.24 (0.04, 1.71)                            | 1.29 (0.09, 18.65)                      | 2.18 (0.12, 38.94)                          | 0.44 (0.10, 1.94)                    | 0.53 (0.11, 2.49)                      |
| II                                           | 0.20 (0.03, 1.23)                            | 0.98 (0.08, 11.66)                      | 1.48 (0.10, 21.63)                          | 0.39 (0.10, 1.52)                    | 0.45 (0.11, 1.90)                      |
| IV                                           | 0.06 (0.01, 0.45)                            | 0.40 (0.02, 7.02)                       | 0.60 (0.03, 12.88)                          | 0.13 (0.03, 0.62)                    | 0.15 (0.03, 0.75)                      |
| Duration of HF at index hospitalization (years) | 1.15 (1.05, 1.26)                            | 1.25 (1.09, 1.43)                       | 1.24 (1.08, 1.43)                           | 1.16 (1.09, 1.26)                    | 1.16 (1.08, 1.25)                      |
| Prior CABG procedure                         | 1.88 (1.03, 3.48)                            | 1.60 (0.68, 3.77)                       | 2.14 (0.85, 5.39)                           | 1.58 (0.98, 2.53)                    | 1.75 (1.08, 2.85)                      |
| Baseline AF diagnosis                        | 2.27 (1.20, 4.29)                            | 0.79 (0.30, 2.07)                       | 0.70 (0.26, 1.89)                           | 1.72 (1.04, 2.86)                    | 1.58 (0.94, 2.65)                      |
| Prescription of warfarin                     | 0.48 (0.24, 0.98)                            | 0.35 (0.12, 1.04)                       | 0.36 (0.18, 1.09)                           | 0.39 (0.22, 0.70)                    | 0.42 (0.23, 0.75)                      |
| Discrimination                               |                                             |                                         |                                             |                                     |                                        |
| AUC                                          | 0.79 (0.73, 0.84)                            | 0.76 (0.67, 0.85)                       | 0.78 (0.69, 0.87)                           | 0.75 (0.70, 0.80)                    | 0.77 (0.73, 0.82)                      |
| NRI                                          | n/a                                         | n/a                                     | 0.42 (0.10, 0.74)                           | n/a                                 | 0.23 (0.07, 0.40)                      |
| Absolute IDI                                 | n/a                                         | n/a                                     | 0.047 (0.002, 0.092)                         | n/a                                 | 0.026 (0.006, 0.047)                    |
| Relative IDI                                 | n/a                                         | n/a                                     | 0.28b                                    | n/a                                 | 0.22b                                  |
| Likelihood ratio test $\chi^2$ (P-value)      |                                             |                                         | 6.93 (0.01)b                               |                                     | 13.72 (<0.01)b                         |
| Calibration                                  |                                             |                                         |                                             |                                     |                                        |
| Hosmer-Lemeshow $\chi^2$ (P-value)            | 5.33 (0.72)                                 | 9.20 (0.33)                             | 8.67 (0.37)                                | 7.50 (0.48)                         | 9.33 (0.32)                            |

Bold indicates model parameters/values that are statistically significant.

*Equation from the bootstrap model in the derivation cohort is given by

$$\text{odds}(30\text{-day Rehospitalization}=1) = -2.54 + 1.40 \times [\text{Impedence Criterion}=1] + -1.16 \times [\text{Diuretics}=1] + 1.25 \times [\text{Male sex}] + 0.96 \times [\text{CKD}=1] + 0.05 \times [\text{NYHA class}=2] + 0.13 \times [\text{NYHA class}=3] + 1.31 \times [\text{NYHA class}=4] + 0.14 \times [\text{Duration of HF at index hospitalization(years)}] + 0.63 \times [\text{Prior CABG}=1] + 0.82 \times [\text{AF}=1] + 0.73 \times [\text{Warfarin}=1]$$

Comparing bootstrap model to clinical-only model.
the intrathoracic impedance to reduce 30 day rehospitalizations in CRT patients. Our model AUCs also compare favourably with previous published data on prediction of 30 day HF rehospitalization and offers a new avenue for exploration in predicting rehospitalization by including device-measured variables. Of note, we did not consider patient death to be a competing risk in this analysis, as the 30 day time frame for patient mortality to compete with an index hospitalization is very short and is not expected to meaningfully affect observed associations. We also did not reevaluate the threshold value for meeting the impedance criterion at hospital discharge (daily impedance value > 8 Ω.

**Figure 3** Calibration plot of clinical-only and bootstrap models. The points in the graph correspond to predicted and observed probabilities of 30 day heart failure (HF) rehospitalization by deciles of predicted risk.

**Figure 4** Kaplan–Meier plot of 30 day heart failure (HF) rehospitalization risk based on dichotomous bootstrap model-predicted risk. The Kaplan–Meier curves for survival free of rehospitalization for the full cohort are shown.
below reference impedance), as we desired a direct comparison with previous literature. The OptiVol® algorithm was updated to Version 2.0 with the Protecta™ line of CRT-D devices in late 2011. However, the impedance measurement implemented in OptiVol® 2.0 has not fundamentally changed from Version 1.0 found in the devices of the current work. Rather, the OptiVol® 2.0 algorithm accounts for individual patient variation and allows for updates to the fluid index value more frequently than Version 1.0. On the basis of this, we believe that the intrathoracic impedance findings of the current work are still directly applicable to more recent devices featuring the more recent OptiVol® 2.0 algorithm.

Since its implementation in 2012, much attention has been given to the Medicare Readmission Reduction Program, which has represented a shift away from the traditional fee-for-service model towards a value-based health care model where reimbursement is determined by patient outcomes. From 2013 to 2017, the number of initial hospitalization diagnoses examined by the programme has increased from three to six, with approximately 79% of hospitals being penalized in 2017 for an estimated $528 million. In addition, there is a direct link to poorer overall outcomes after multiple rehospitalizations. HF treatments themselves help reduce the burden of patient hospitalizations and readmissions; specifically, CRT-D therapy in HF has been demonstrated to both improve survival and decrease all-cause and HF readmissions as compared with ICD therapy alone, both acutely and in long-term settings. Intrathoracic impedance monitoring by these devices has been shown to be superior to weight monitoring in detecting worsening HF, including HF rehospitalizations, and that fluid index values associated with impedance measurements indicate increased risk of impending HF decompensation.

Congestion is the primary cause for HF decompensation, and subclinical congestion may be detected days or weeks in advance of an actual decompensation event. The use of data from implanted devices offers a unique opportunity to detect subclinical congestion and impending rehospitalization events through well-known device measures such as intrathoracic impedance, AF burden, and night heart rate. Consistent with subclinical congestion, the present study has found that the intrathoracic impedance value on the day of discharge, which is likely directly related to residual congestion, offers a more robust contribution to our predictive model of 30 day rehospitalization than the other device-measured variables. In this way, intrathoracic impedance measurements on the day of discharge could be used to alter decision making regarding the timing of discharge. In patients for whom intrathoracic impedance is consistently unsatisfactory prior to discharge, referral for evaluation for more advanced HF treatments such as mechanical circulatory support and heart transplantation could be considered. In line with the critical role that subclinical/congestive congestion plays in HF trajectory, we noted that patients who were on diuretics were less likely to experience the outcome of 30 day readmission. It seems very plausible that discharging patients on an appropriate dose of diuretics would be associated with a decreased risk of HF hospitalizations. This highlights the potential use of intrathoracic impedance monitoring to identify patients not discharged on a diuretic who need to be on an outpatient loop diuretic to prevent an HF readmission. We also noted that patients on digoxin were associated with fewer 30 day readmissions. A recent meta-analysis showed a decreased rate of HF admissions with digoxin. The effects of digoxin on mortality are controversial, however, with disparate reports on mortality. For example, one study found a neutral effect of digoxin on mortality, while another meta-analysis published the same year showed an association of digoxin with increased mortality. Another more recent study demonstrated that discontinuation of digoxin prior to discharge was associated with increased risk of the combined endpoint of death and rehospitalization.

Limitations

While our baseline model using only clinical variables was based on commonly observed patient characteristics, it should be noted that these variables were not updated over the follow-up period. Further study is also warranted to determine whether the device-measured intrathoracic impedance criterion provides incremental predictive value over other quantitative measures of kidney function. Our treatment of multiple hospitalizations from a patient did not consider that the probability of a rehospitalization within a 30 day interval might depend on prior hospitalizations a patient experienced. Future work in this area could calculate NRI and IDI accounting for the within-patient correlation of hospitalization and determine 95% confidence intervals via a bootstrap methodology.

We observed a relatively large proportion of missing intrathoracic impedance values on the day of discharge (49.1%). We believe this was due to no formal protocol to interrogate the device on the day of discharge and that regular in-office interrogation would not necessarily capture that specific data point. Because the odds ratio for the impedance criterion was similar before and after adjusting for the presence of missing data (OR 3.02, 95% CI: 1.37, 6.66 vs. OR 4.26, 95% CI: 2.01, 8.99, respectively, P-value for comparison = 0.54), we believe it is a reasonable assumption that a patient did not meet the impedance criterion if device data were missing on the day of discharge.

Device-measured data in patients with HF and CRT can be combined with clinical parameters to improve prediction of 30 day rehospitalization events. Used in this way, CRT device-measured data at the time of discharge from an HF hospitalization could help identify those patients most likely to have a possible benefit from interventions designed to
prevent rehospitalizations. As a result, these findings provide justification for the routine evaluation of intrathoracic impedance on the day of discharge. Further prospective evaluation of such strategies to improve patient outcomes and compliance with CMS guidelines for reimbursement after HF hospitalizations would be of great interest.

**Conclusions**

In CRT patients, intrathoracic impedance measurements improve prediction of 30 day HF rehospitalization over clinical characteristics alone. The present study provides supportive data for the routine evaluation of intrathoracic impedance prior to discharge in patient with CRT devices, and the use of device-measured data could be used to design interventions to improve compliance with Medicare reimbursement guidelines regarding 30 day HF rehospitalization.

**Conflict of Interest**

Dr. Brown and Dr. Warman are both employees of Medtronic PLC. Dr. Bilchick has an External Research Program grant from Medtronic. The other authors have no conflicting interests.

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