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ORIGINAL RESEARCH ARTICLE

Prediction of worsening heart failure events and all-cause mortality using an individualized risk stratification strategy

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Abstract

Aims This study aimed to examine the clinical utility of a multisensor, remote, ambulatory diagnostic risk score, TriageHF™, in a real-world, unselected, large patient sample to predict heart failure events (HFEs) and all-cause mortality.

Methods and results TriageHF risk score was calculated in patients in the Optum® database who had Medtronic implantable cardiac defibrillator device from 2007 to 2016. Patients were categorized into three risk groups based on probability for having an HFE within 6 months (low risk $<$5.4%, medium risk $\geq$5.4 $<$ 20%, and high risk $\geq$20%). Data were analysed using three strategies: (i) scheduled monthly data download; (ii) alert-triggered data download; and (iii) daily data download. Study population consisted of 22 901 patients followed for 1.8 ± 1.3 years. Using monthly downloads, HFE risk over 30 days incrementally increased across risk categories (odds ratio: 2.8, 95% confidence interval: 2.5–3.2 for HFE, $P < 0.001$, low vs. medium risk, and odds ratio: 9.2, 95% confidence interval: 8.1–10.3, $P < 0.001$, medium vs. high risk). Findings were similar using the other two analytic strategies. Using a receiver operating characteristic curve analysis, sensitivity for predicting HFE over 30 days using high-risk score was 47% (alert triggered) and 51% (daily download) vs. 0.5 per patient year unexplained detection rate. TriageHF risk score also predicted all-cause mortality risk over 4 years. All-cause mortality risk was 14% in low risk, 20% in medium risk, and 38% in high risk.

Conclusions TriageHF risk score provides a multisensor remote, ambulatory diagnostic method that predicts both HFEs and all-cause mortality.

Keywords Heart failure; Congestive; Remote monitor

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Introduction

Despite significant improvements in management, patients with heart failure (HF) continue to have reduced life expectancy, frequent hospitalizations, poor quality of life, and substantial limitations in exercise capacity.[1,2] Management of HF patients is challenged by the ability to identify which patients are at the highest risk of recurrent HF events (HFEs). It is common for risk to change in a dynamic fashion on HF patients over time; detecting these changes in risk when patients are evaluated in person only infrequently is critical. This requires an ability to predict changing risk patterns in an ambulatory setting, using remote, continuous monitoring. To achieve this goal, implantable, sensor-based metrics have been developed, and their utility in accurately predicting HF decompensations has been examined previously both individually and in a combinatorial fashion.[3–18] However, these studies have been performed in highly selected, limited populations, focused almost exclusively on HF hospitalizations. The effects of co-morbidities on predictive accuracy have not been fully examined. In this study, we sought to address these limitations by combining data from the Optum® electronic health record (EHR) de-identified database and data from Medtronic CareLink™ Network. The purpose of this study was

to (i) examine the utility of one multi-parameter integrated diagnostic (TriageHF) in a real-world, unselected, large patient sample to validate its accuracy in predicting HFEs using current generation devices; (ii) validate the accuracy of TriageHF in the presence of co-morbidities that may alter risk prediction; and (iii) determine whether TriageHF predicts all-cause mortality.

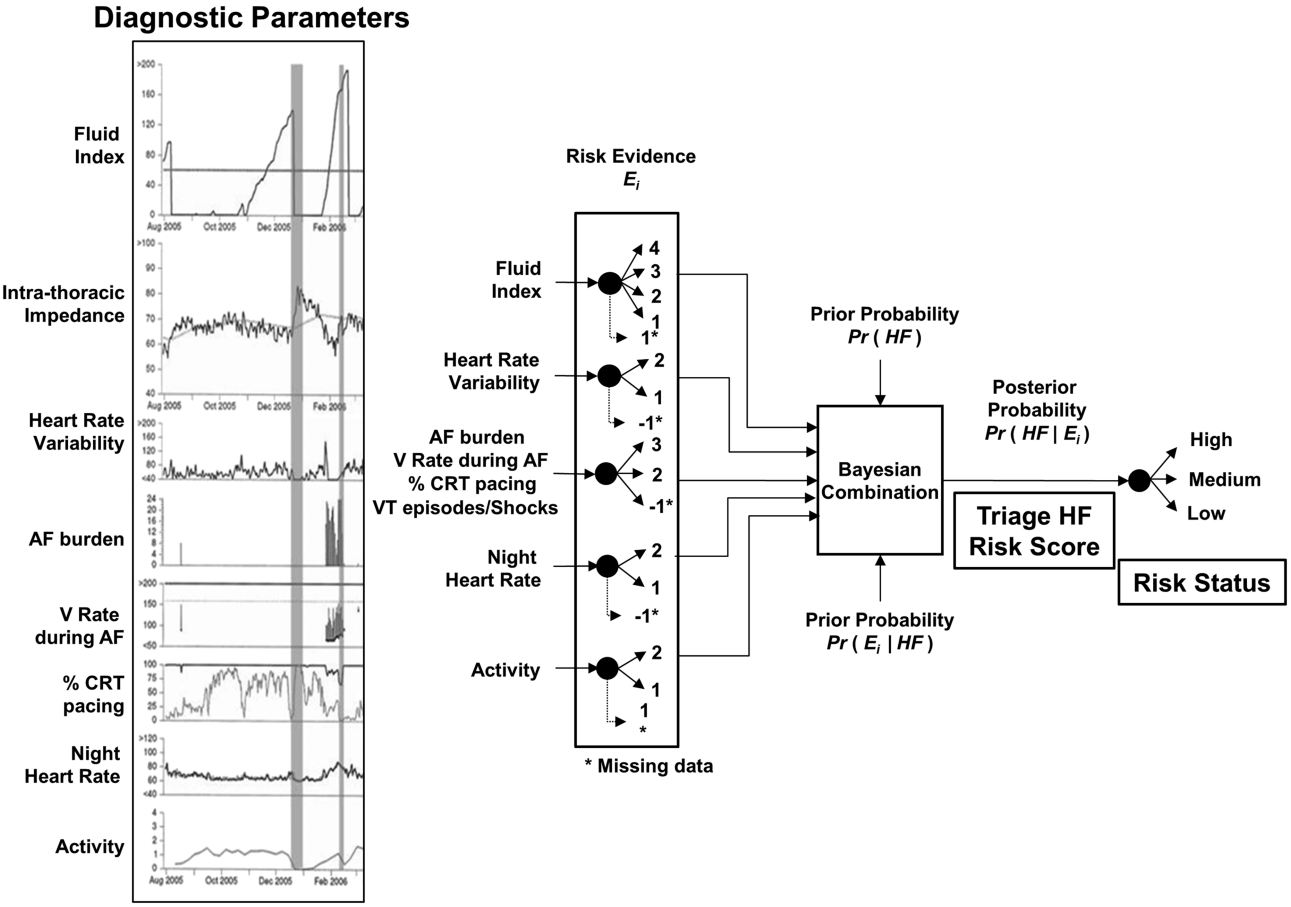
Methods

The TriageHF risk score

Sensors in Medtronic implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy with defibrillator (CRT-D) devices included intrathoracic impedance, intracardiac electrogram, and accelerometer. These sensors were used to derive the following measurements: fluid index based on intrathoracic impedance, heart rate variability, atrial fibrillation burden, ventricular rate during atrial fibrillation, per cent CRT pacing, ventricular tachycardia episodes/shocks, night-time heart rate, and activity. All of these individual diagnostic parameters have been previously shown to have univariate discriminatory power for identifying the risk for the occurrence of an HFE.[3–10]

The TriageHF risk score was generated by combining these parameters into a single risk score (*Figure 1*). The details of the development and validation of the TriageHF risk score have been published previously.[13] The TriageHF risk score was expressed on a scale of 0% to 100% probability of having an HFE within 6 months. Low risk was defined as any probability score $<5.4\%$, medium risk was defined as a probability range from $\geq 5.4\%$ to $<20\%$, and high risk was defined as a probability $\geq 20\%$.[13,14] The risk score was predefined in previous studies[13] and was chosen such that 10–15% of monthly download risk scores were high risk, and the medium-risk score was chosen such that all fluid index alerts will be medium risk.

FIGURE 1 Schematic showing how individual diagnostic parameters are combined using a Bayesian analysis to generate an integrated diagnostic risk score 'TriageHF' and the resulting risk status. AF, atrial fibrillation; CRT, cardiac resynchronization therapy; V, ventricular; VT, ventricular tachycardia.



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Data cohort and endpoints

Patients with Medtronic ICD or CRT-D implants with OptiVol2.0 feature were selected from the Optum EHR de-identified database from 2007 to 2016. Patients with selected co-morbidities based on clinical history prior to implant were examined. Patients were only included in this co-morbidity sub-analysis if they had ≥180 days of EHR-derived clinical follow-up before the implant to ascertain clinical history.

Heart failure events were used as the endpoint in the data analysis and were defined as inpatient, observation unit or emergency room stay with primary diagnosis of HF and intravenous diuresis administration. Primary diagnosis of HF was ascertained based on International Classification of Diseases 9/10 codes shown in *Table A1*. Mortality data were all-cause mortality.

Data analysis

Data for this study were analysed using three different strategies to predict HFEs and mortality: (i) physician-directed scheduled monthly data downloads to calculate TriageHF risk score; (ii) alert-triggered downloads, OptiVol™ alert with risk further categorized using TriageHF score (this strategy can be chosen as an alternative to scheduled monthly data download in devices where the OptiVol alert is approved for use); and (iii) simulated daily download schedule to calculate TriageHF risk score (this strategy is under development but was performed in this study to provide comparisons with the currently available systems from other manufacturers). These three strategies were used to predict short-term (30 days) HFEs and long-term (4 years) all-cause mortality.

The purpose of using three data download/analyses methods was to provide diagnostic capabilities tailored to the preferences of the providers and the needs of the individual patients. This approach allows providers to choose the frequency of downloads and the choice of an alert for exception-based management approaches. In some circumstances, monthly downloads are appropriate, and for others, a more frequent download is necessary. The alert-based method allows providers to examine data only after an alert is present (exception-based surveillance). The goal of our analysis was to provide performance results that highlighted the relative accuracy of different approaches to support the utility of provider and patient tailored remote monitoring.

Scheduled monthly downloads

The TriageHF risk score was computed when a monthly scheduled remote wireless transmission was received by the Medtronic CareLink Network. At each data download, the previous 30 day period was examined to determine if at any time during the 30 day time period the TriageHF risk score was above a selected risk threshold. In addition, the 30 days following the download was examined to determine if there was an HFE. A generalized estimating equation (GEE) model with a binomial distribution with logit link and autoregressive correlation structure was used to compare HFEs for different HF risk score groups. A receiver operating characteristic curve of sensitivity and specificity of monthly download will also be reported.

Alert-triggered downloads

When the OptiVol fluid index score crossed a selected threshold (60 Ω·days), an OptiVol alert occurred and a remote wireless transmission was received by the Medtronic CareLink Network. Then, the TriageHF risk score was calculated and classified as medium risk or high risk. Once OptiVol reached 60 Ω·days, TriageHF risk score was never less than medium. For the alert-triggered remote transmission data analysis model, sensitivity and unexplained detection rate were reported. Sensitivity was defined as the percentage of HFEs preceded by a day with TriageHF exceeding a specific threshold within the last 30 days. Unexplained detections were TriageHF high-risk detections not followed by an HFE within 30 days. Specificity cannot be defined using this methodology because true negative cannot be defined. Sensitivity and unexplained detection rate were calculated using a GEE model. For sensitivity, a binomial distribution with logit link and exchangeable correlation structure was used, and for unexplained detection rate, a negative binomial distribution with log link was used.

The time period OptiVol fluid index remained above threshold (with a 'high' TriageHF risk status for at least 1 day during this time period) and 30 days following the date that the OptiVol alert was reset was examined to determine if there was an HFE; this represents a TP; if no HFE occurred, this represents an FP or an 'unexplained detection'. The computed unexplained detection rate was calculated as the FPs per year of patient monitoring across all patients. If an HFE occurred and during the preceding 30 days there was no day during which the OptiVol was above threshold and the TriageHF risk score was high, this represents an FN: Sensitivity = TP (TP + FN). Receiver operating characteristic curve analysis of sensitivity vs. unexplained detection for OptiVol alert followed by TriageHF is reported.

Daily data download

Currently, TriageHF based on a daily remote wireless transmission to the Medtronic CareLink Network is not an available application. However, device models are being developed to have this capability in the future. Data were available from the current study that allowed analytic modelling of the performance of a daily data download model and a TriageHF alert system. In the current study, any remote wireless transmission received by the Medtronic CareLink Network contained 425 days' worth of previous daily data.

Modelling data from each day as a daily remote wireless transmission to the Medtronic CareLink Network, a TriageHF risk score was calculated for each day. Sensitivity and unexplained detection rate were calculated as described earlier.

TriageHF and mortality risk

From the day of device implant or start of available diagnostic data to 6 months after TriageHF risk score initialization, TriageHF risk score was calculated. The maximum value of the TriageHF risk score for each patient during 6 months was determined to group patients into high, medium, and low risk and was followed from 6 months after implant until the end of the study period. Any mortality that occurred between implant and 6 months after implant was censored. A Cox proportional hazards model was used to compare mortality for different HF risk score groups after adjusting for age, gender, and clinical history of hypertension, myocardial infarction, coronary artery disease, diabetes, HF, atrial fibrillation, vascular disease, renal dysfunction, and stroke or transient ischaemic attack. All-cause mortality over 4 years after 6 month evaluation is presented using Kaplan–Meier plots. In addition, data are presented examining mortality combined with HFE.

All patients provided consent to use their de-identified device data for research purposes when they sign up for Medtronic CareLink Network. The centres that allowed use of their patient data for research purposes then consent to storage of patient data in a de-identified Medtronic Discovery Link data warehouse. The de-identified Optum database was used as per contractual arrangement between Optum and Medtronic under which Optum has broad consent in using de-identified data for research purposes. The merging of the two de-identified database was performed by a third party such that the overall merged database stays de-identified to all three parties. The Institutional Review Board at the Medical University of South Carolina guidelines judge this study to fall into the category of non-human research, and therefore, no institutional review board approval was indicated. This was a retrospective real-world data analysis and not a clinical study and hence is not registered in ClinicalTrials.gov.

Results

Patient population

A total of 22 901 patients had 1.8 ± 1.3 years of follow-up with OptiVol2.0 enabled ICD/CRT-D devices; 52% had an ICD, and 48% had a CRT-D device. The average age of patients was 66 ± 12 years, and 71% were male. Detailed baseline demographics are shown in *Table 1*. This entire cohort of patients was included for risk assessment based on scheduled monthly downloads. Of the total 462 107 monthly downloads, a total of 3168 monthly evaluations (0.7%) in 2102 patients had an HFE in the next 30 days.

After additional analysis-related exclusions, such as requiring valid device data on all 30 days prior to an HFE and available EHR data 30 days after last day of diagnostic alert, a total of 21 356 patients with 1.5 ± 1.2 years of follow-up were included for the risk assessment based on alert-triggered downloads. In this cohort, a total of 1812 patients (8.5%) had 2853 HFEs during included follow-up. Further, for analysing the relationship between baseline TriageHF and subsequent long-term mortality and HFE rate that required at least 6 months of device data to evaluate baseline risk, a total of 22 542 patients with 1.7 ± 1.3 years of follow-up were included of which 2489 patients (11%) died during follow-up.

Risk assessment based on scheduled monthly downloads

There was an incremental increase in the risk of an HFE occurring in the 22 901 patient population based on the TriageHF risk score category. Thirty day risk of HFE was 0.25% in low-risk group, 0.70% in medium-risk group [odds ratio: 2.8, 95% confidence interval (CI): 2.5–3.2, $P < 0.001$], and 2.23% in the high-risk group (odds ratio: 9.2, 95% CI: 8.1–10.3, $P < 0.001$), *Figure 2* and *Table A2*. This stepwise pattern of increasing risk was present in patient subgroups defined by coexistent co-morbidities (*Figure 3* and *Table A2*). Patients who had a higher risk of future event included patients with and without a previous history of an HFE prior to device implant, history of hypertension, diabetes, coronary artery disease, myocardial infarction, vascular disease, atrial fibrillation, renal dysfunction, stroke/transient ischaemic attack, and BNP $>$ 547 vs. $<$547 pg/mL (median value). Regardless of the co-morbidity present, the risk of having a future HFE increased in a stepwise fashion in patients with low vs. medium and medium vs. high TriageHF risk score.

The receiver operating characteristic curve plotting the GEE estimate based on the TriageHF score from monthly downloads is shown in *Figure A1*. Each value plotted represents a TriageHF risk score from 100% (bottom left) to 0% (top right); TriageHF high-risk score (20%) and medium-risk score (5.4%) are circled. The sensitivity and specificity for the high risk were 39% and 89% respectively vs. 85% sensitivity and 44% specificity for medium risk. The differences between high-risk and medium-risk score sensitivities and specificities are statistically different ($P < 0.001$ for both).

Risk assessment based on alert-triggered downloads

Using a nominal OptiVol threshold of 60 Ω·days for the fluid index remote care alert coupled with the High TriageHF risk score, 47% of the HFEs were predicted in 30 days prior to event (i.e. sensitivity) with an unexplained detection rate of

Table 1 Baseline demographics of patients in the data analysis cohorts

	All patients (N = 22 901)[a]	Patients with180 day EHR data prior to implant (N = 20 397)[b]	Patient with no history of HF event (N = 17 476)	Patient with history of HF event (N = 2921)
Mean age (SD)	66 (12)	67 (12)	67 (12)	66 (12)
Male gender	16 371 (71%)	14 537 (71%)	12 569 (72%)	1968 (67%)
Hypertension	15 450 (67%)	14 856 (73%)	12 229 (70%)	2627 (90%)
HF	14 276 (62%)	13 628 (67%)	10 707 (61%)	2921 (100%)
Diabetes	7623 (33%)	7378 (36%)	5915 (34%)	1463 (50%)
CAD	14 574 (64%)	13 936 (68%)	11 444 (65%)	2492 (85%)
MI	7365 (32%)	7021 (34%)	5569 (32%)	1452 (50%)
Vascular disease	2643 (12%)	2597 (13%)	2019 (12%)	578 (20%)
Atrial fibrillation	8222 (36%)	7947 (39%)	6479 (37%)	1468 (50%)
Renal dysfunction	5211 (23%)	5083 (25%)	3739 (21%)	1344 (46%)
Stroke/TIA	4289 (19%)	4175 (20%)	3354 (19%)	821 (28%)
Device type				
ICD	11 878 (52%)	10 448 (51%)	9168 (52%)	1280 (44%)
CRT-D	11 023 (48%)	9949 (49%)	8308 (48%)	1641 (56%)
Medications[c]				
ACE-I/ARB	16 118 (70%)	15 210 (75%)	12 512 (72%)	2698 (92%)
Beta-blockers	11 998 (52%)	11 247 (55%)	9315 (53%)	1932 (66%)
Diuretics	15 085 (66%)	14 105 (69%)	11 279 (65%)	2826 (97%)
Spironolactone	6558 (29%)	6192 (30%)	4631 (27%)	1561 (53%)
Sacubitril/valsartan	194 (1%)	177 (1%)	108 (1%)	69 (2%)
Vasodilator/nitrate	12 767 (56%)	11 897 (58%)	9489 (54%)	2408 (82%)
AAD	16 919 (74%)	15 638 (77%)	13 064 (75%)	2574 (88%)
Anticoagulation	9524 (42%)	9002 (44%)	7340 (42%)	1662 (57%)

AAD, anti-arrhythmic drug; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CRT-D, cardiac resynchronization therapy with defibrillator; EHR, electronic health record; HF, heart failure; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; SD, standard deviation; TIA, transient ischaemic attack.
[a]Data include all patients and did not have any pre-EHR day requirement and include all of the patients that contributed to the monthly analysis.
[b]Data include only patients with 180 days of EHR data prior to implant.
[c]Data include only medications that had been prescribed prior to or day of implant.

0.48 per patient year of monitoring (*Figure A2*). Compared with using the OptiVol nominal threshold alone, the unexplained detection rate was reduced by 56% (from 1.10 to 0.48 unexplained detection rate per patient year) with a reduction in sensitivity of 17% (from 57% to 47% sensitivity) by adding on the sequential TriageHF risk calculation to the OptiVol-based remote care alert-triggered download.

Risk assessment based on daily data downloads

A high TriageHF risk score occurred in 30 days prior to 51% of the HFEs (i.e. 51% GEE estimate of sensitivity) with an unexplained detection rate of 0.5 per patient year of monitoring (*Figure 4*). A high or a medium TriageHF risk score occurred in 30 days prior to 93% of the HFEs and an unexplained detection rate of 1.7 per patient year of monitoring.

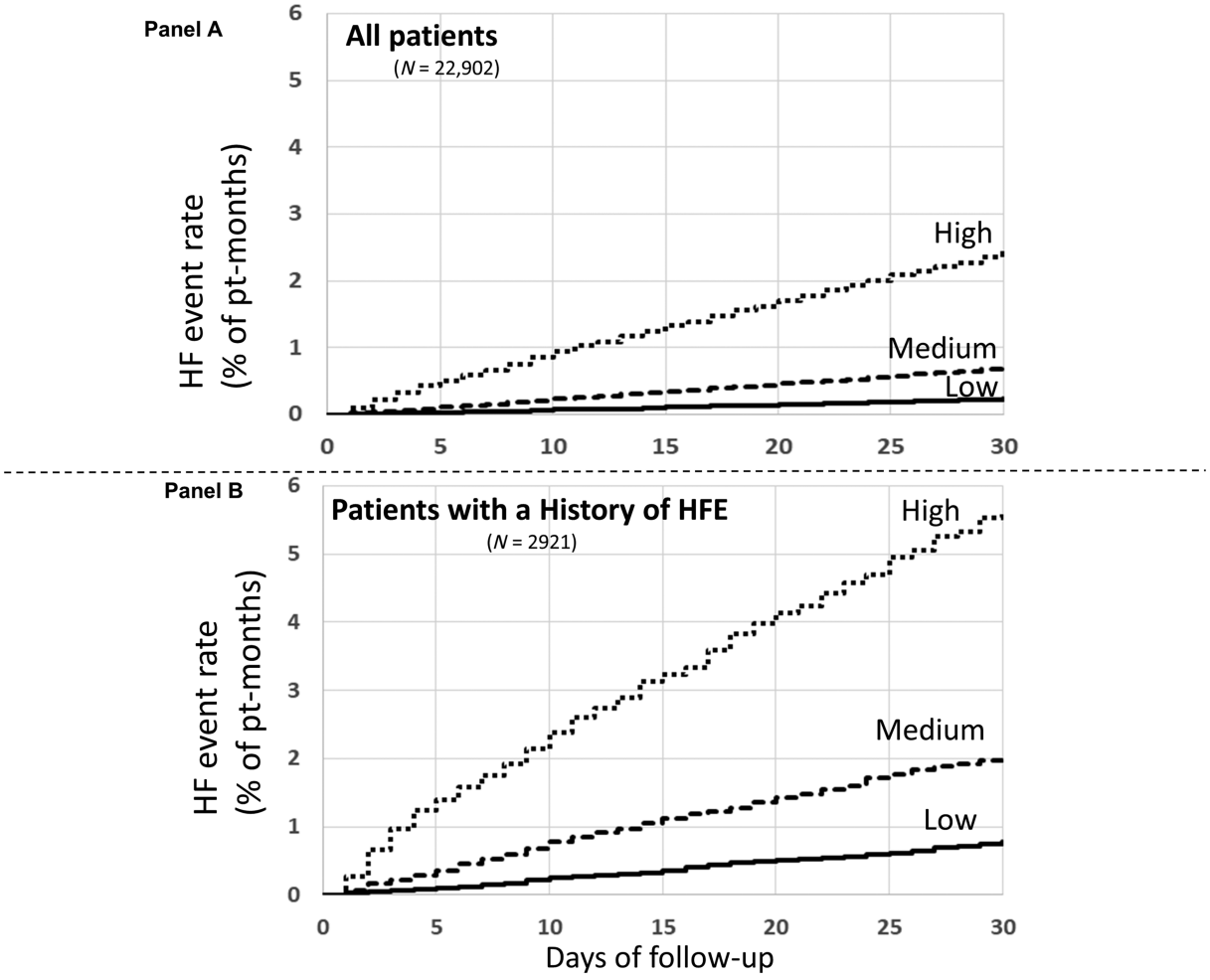
TriageHF risk score and mortality

There was a direct relationship between the TriageHF risk score and mortality over the 4 years of follow-up (adjusted hazard ratio 3.5, 95% CI: 2.8–4.3, $P < 0.001$, in high-risk vs. low-risk score, and adjusted hazard ratio 1.8, 95% CI: 1.4–2.2, $P < 0.001$, in medium-risk vs. low-risk score), adjusted for age, gender, and clinical history of hypertension, myocardial infarction, coronary artery disease, diabetes, HF, atrial fibrillation, vascular disease, chronic kidney disease, and stroke/transient ischaemic attack (*Figure 5*). There was also an incremental increase in the HFE and combined HFE plus mortality across the three risk categories.

Discussion

Data from the current study support the following novel findings: (i) TriageHF risk score provided a sensitive and specific multi-parameter integrated diagnostic measure that predicted the occurrence of HFEs and was applicable to a real-world, unselected, large, patient sample; (ii) the TriageHF risk score retained its accuracy in the presence of co-morbidities that themselves alter risk prediction; and (iii) the TriageHF risk score predicted the all-cause mortality rate.

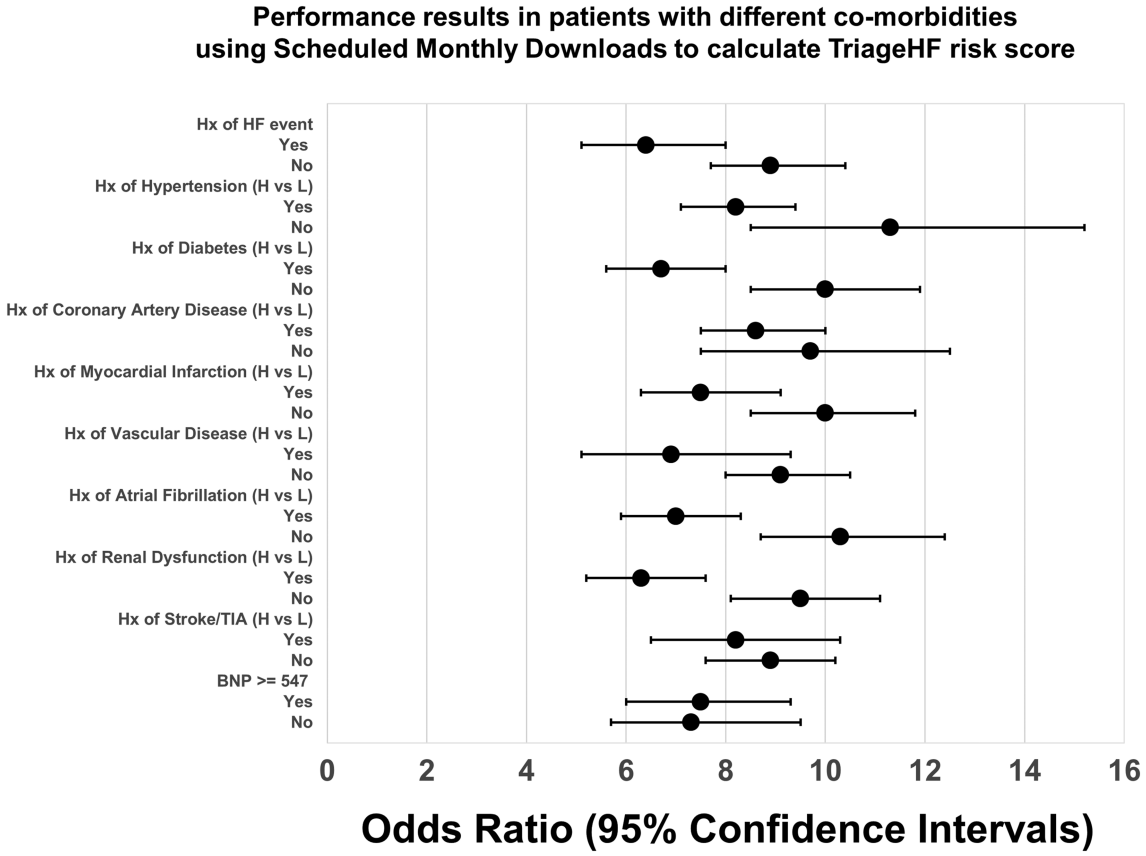
FIGURE 2 Using scheduled monthly download data to derive the TriageHF risk score, heart failure event (HFE) rates (expressed as % of patient months) were plotted for each TriageHF risk score category low, medium, and high for (A) all patients studied and for (B) patients with a previous history of an HFE.



Rationale for numeric value of risk score thresholds

TriageHF risk score thresholds were categorized as low, medium, or high. The exact numeric values for the high TriageHF threshold were chosen, at least in part, to provide a maximum sensitivity rate that corresponded to a minimum rate of unexplained detections. There are clear outcome trade-offs in this design; the higher the target value of sensitivity that is chosen, the higher the resultant corresponding number of unexplained detections will be present. The rationale for the numeric choice made for risk threshold reflected the effects of several factors, including economic, administrative, provider, and patient care-based issues. Previous studies have shown that high rates of unexplained detection (i.e. false positives) lead to unnecessary use of healthcare resources such as increased hospitalizations and emergency room visits and increased burden to outpatient clinic resources needed to evaluate and treat the causes of alerts/detections.[19] In addition, high rates of unexplained detections lead to changes in data management strategies (decreased trust in data validity), potential for overtreatment, and increased patient anxiety. Therefore, lower sensitivity values were chosen to minimize the unexplained detection rate. However, even these lower sensitivity values may provide important opportunities to improve patient care.[20–26] It has also been hypothesized that both avoidance of HFEs and long-term reduction in risk metric scores may improve quality of life scores, improve exercise capacity, and even decrease mortality rates. However, these outcomes are only obtainable if a change in risk score leads to an active change in management and that the change in management is based on a change in the risk score itself, independent of the presence or absence of symptoms and signs of acute decompensated HF.[22] Whether an HF management informed by

FIGURE 3 Performance results in patients with different co-morbidities using scheduled monthly downloads to calculate TriageHF risk score. A stepwise pattern of increased risk was present in all examined patient subgroups comparing the high-risk with low-risk TriageHF risk score, including patients with and without history (Hx) of hypertension, diabetes, coronary artery disease, myocardial infarction, vascular disease, atrial fibrillation, renal dysfunction, stroke/transient ischaemic attack (TIA), and BNP > 547 vs. <547 pg/mL (the population median value). HF, heart failure.



multi-parameter risk metric will lead to improved outcomes needs prospective randomized evaluation.

What change in management strategy should result from a change in remote, continuous, time-varying, multisensor, multi-metric integrated risk scores? At least two management algorithms have been proposed based on physician-directed and, in one case, HF specialty nurse-facilitated, patient management programmes. The 'Multiple Cardiac Sensors for the Management of Heart Failure (Manage-HF, NCT03237858)' study, the 'Integrated Diagnostics Driven Diuretic and Chronic Medication Management for Heart Failure (Intervene-HF, NCT02698241)' study, and 'Algorithm Using LINQ Sensors for Evaluation and Treatment of Heart Failure' (Alleviate-HF, NCT04452149) are ongoing studies. Whether these management algorithms result in safe and effective management awaits completion of these studies. However, data from the Champion study[21] using the pulmonary artery pressure sensor and IN-TIME study[22] using device-based diagnostics support this direction for HF care.

Compare time-varying, multi-parameter, integrated, diagnostic risk scores

High-voltage implanted therapy devices (ICD, CRT, and CRT-D) currently provide remote sensor-based risk algorithms. Beyond TriageHF, a single sensor assessment of intrathoracic impedance uses a cumulative sum-based method to assess accumulating risk as the OptiVol fluid index. An OptiVol risk threshold of 60 Ω·days provided 76% sensitivity and 1.9 unexplained detection per patient year in the FAST Study with an earlier version of OptiVol.[3] The development of OptiVol fluid index paved the way for development of multisensory integrated metrics with higher specificity and lower unexplained detection rates such as TriageHF and HeartLogic™. Each uses a unique list of parameters, some of which are common to both risk metrics and some of which differ between the risk metrics. There are no studies that have directly compared OptiVol vs. TriageHF vs. HeartLogic. However, data from the current study were compared with published studies[6,15] to derive an imputed comparison. Critical to these comparisons

FIGURE 4 Risk assessment based on alert-triggered downloads. TriageHF risk score alert-triggered downloads. The receiver operating characteristic curve of sensitivity vs. unexplained detection rate for TriageHF risk score-based prediction of HF events in a care alert usage model.

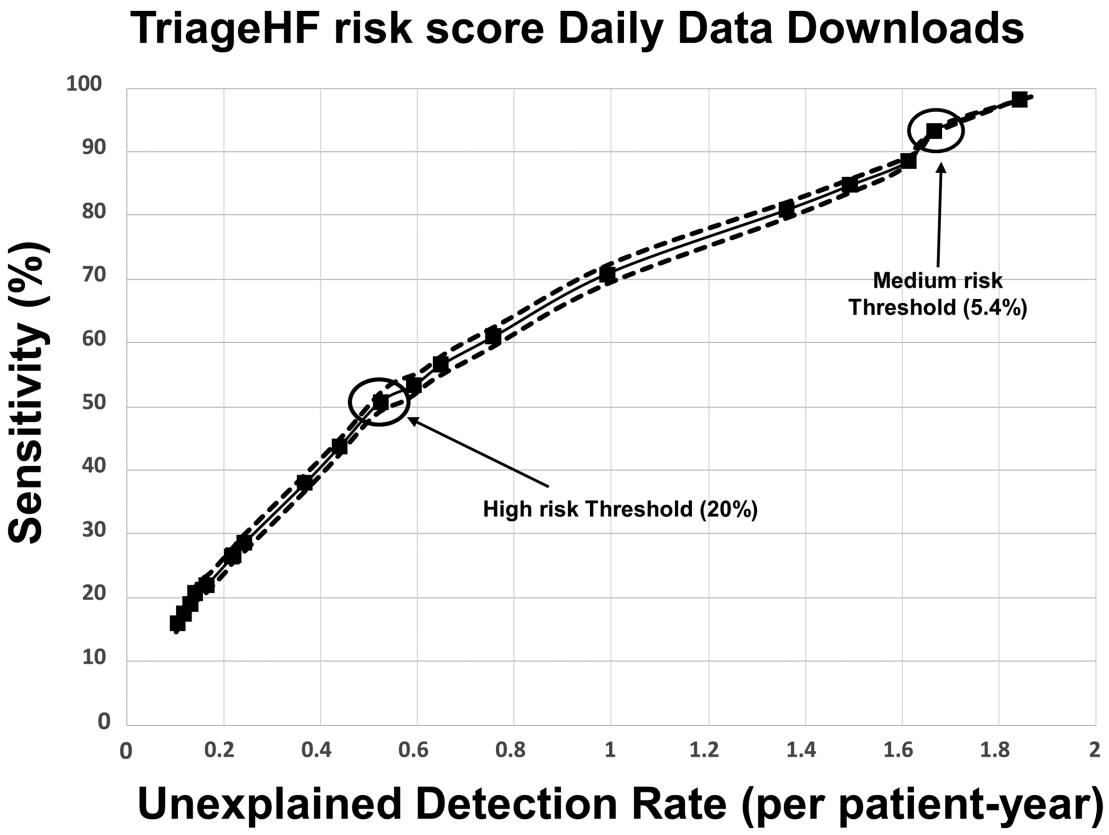
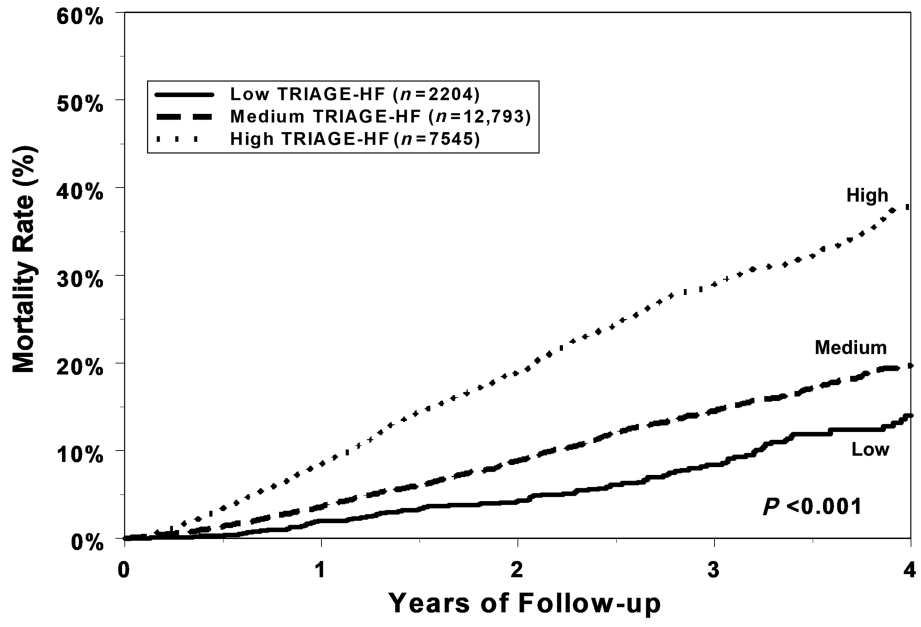


FIGURE 5 Baseline TriageHF risk score predicts all-cause mortality rate over 4 years. There was a direct and linear relationship between the baseline TriageHF risk score category and all-cause-mortality over the 4 years of follow-up. Mortality rate increased as the TriageHF risk score increased from low-risk to medium-risk to high-risk score.



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is the use a common unexpected detection rate to examine sensitivity rate. In *Table A3*, unexplained detection rates of 0.5 or 1.0 per patient year and sensitivities were compared between risk metrics. Remarkably, using 0.5 per patient year unexplained detection rate and a HeartLogic high-risk threshold at 30 or a TriageHF high-risk threshold at 20%, the sensitivity rates were nearly identical at ~50%. We also compared the risk thresholds suggested in previous publications.[6,15] For HeartLogic, the suggested risk threshold was a score of 16. This yielded a sensitivity of 70% and an unexplained detection rate of 1.5 per patient year. Using the same unexplained detection rate of 1.5, the sensitivity for TriageHF was 85%. These data comparisons suggest that the individual metrics selected may be less important than the use of multiple parameters that are integrated into a diagnostic approach. As such, the more the individual sensors/metrics provide orthogonal information, the better the performance is for the integrated combination.

Limitations of the current study

The current study was not prospective, randomized, or blinded and relied on EHRs for identifying clinical endpoints and the presence of co-morbidities. As such, there was neither knowledge of nor control over the use of the data available to guide change in therapy, which may act as confounders for the subsequent course of the disease. Physicians and other providers had knowledge of and potential use of OptiVol fluid index and other individual metrics such as heart rate variability, night-time heart rate, and activity, but each was plotted and examined as separate variables. If physicians acted based on data and prevented HFE, it would reduce sensitivity and increase false alert rate. The performance results derived from a real-world cohort of patients may therefore underestimate the sensitivity and overestimate the unexplained detection rate because the diagnostic data were not blinded from providers who may have acted based on the data and may have prevented HFEs. However, this hypothesis could not be tested in the current data set.

Conclusions

TriageHF risk score provided a sensitive and specific multi-parameter integrated diagnostic measure that predicted the occurrence of HFEs in an unselected, large patient sample size that validated its predictive accuracy in a real-world population. The TriageHF risk score retained its accuracy in the presence of co-morbidities that themselves alter risk prediction. The TriageHF risk score predicted the rate of all-cause mortality.

Conflict of interest

M.R.Z. served as a consultant to Medtronic. J.K. and S.S. are Medtronic employees. J.B. is a consultant for Abbott, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, and Vifor Pharma.

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Appendix A.

Table A1 ICD-9 and ICD-10 diagnosis codes used to determine history of diseases present prior to device implant

Disease state	ICD-9 or ICD-10 diagnosis codes
Hypertension	401.X, 402.X, 404.X, 403.X, 405.X, I10.X, I11.X, I12.X, I13.X, I15.X
Coronary artery disease	410.X, 411.X, 412.X, 413.X, 414.0X, 414.2, 414.3, 414.4, 414.8, 414.9, I20.X, I21.X, I22.X, I23.X, I25.1X, I25.2, I25.5, I25.6, I25.7, I25.8, I25.9
Diabetes	250.X0, 250.X2, E11.X, 250.X1, 250.X3, E10.X
Heart failure	428.X, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, I50.X, I11.0, I13.0, I13.2
Renal dysfunction	403.X, 404.X, 585.X, N12.X, N13.X, N18.X
Ischaemic stroke/TIA	433.X, 434.X, 436.X, I63.X, I65.X, I66.X, 435.X, G45.0, G45.1, G45.2, G45.8, G45.9
Atrial fibrillation/atrial flutter	427.31, I48.0, I48.1, I48.2, I48.91, 427.32, I48.3, I48.4, I48.92

ICD, International Classification of Diseases; TIA, transient ischaemic attack.

Table A2 Performance results in different patient cohorts

	Number of monthly evaluations (%)			HF event rate (per patient month) GEE estimate (95% CI)			Odds ratio (95% CI)	
Patient cohort	Low	Medium	High	Low	Medium	High	Medium vs. low	High vs. low
All patients	200 587 (43%)	210 400 (46%)	51 120 (11%)	0.25 (0.23–0.27)	0.70 (0.66–0.75)	2.23 (2.08–2.40)	2.8* (2.5–3.2)	9.2* (8.1–10.3)
No Hx of HTN	60 220 (46%)	58 048 (44%)	13 072 (10%)	0.13 (0.10–0.17)	0.43 (0.37–0.50)	1.46 (1.23–1.74)	3.3* (2.5–4.3)	11.3* (8.5–15.2)
Hx of HTN	120 251 (42%)	131 030 (46%)	32 792 (12%)	0.32 (0.29–0.36)	0.84 (0.78–0.90)	2.59 (2.38–2.81)	2.6 (2.3–3.0)	8.2 (7.1–9.4)
No Hx of diabetes	129 307 (47%)	120 665 (44%)	26 855 (10%)	0.19 (0.17–0.22)	0.56 (0.51–0.61)	1.91 (1.72–2.12)	2.9* (2.5–3.4)	10.0* (8.5–11.9)
Hx of diabetes	51 164 (37%)	68 413 (49%)	19 009 (14%)	0.43 (0.37–0.50)	1.00 (0.91–1.09)	2.78 (2.49–3.10)	2.4* (2.0–2.8)	6.7* (5.6–8.0)
No Hx of CAD	65 247 (44%)	66 212 (45%)	15 757 (11%)	0.17 (0.13–0.20)	0.39 (0.33–0.45)	1.58 (1.34–1.85)	2.4* (1.9–3.0)	9.7* (7.5–12.5)
Hx of CAD	115 224 (43%)	122 866 (46%)	30 107 (11%)	0.31 (0.28–0.35)	0.89 (0.83–0.96)	2.63 (2.42–2.86)	2.9* (2.5–3.3)	8.6* (7.5–10.0)
No Hx of MI	125 348 (44%)	129 457 (45%)	30 809 (11%)	0.20 (0.17–0.23)	0.54 (0.49–0.59)	1.95 (1.77–2.15)	2.7* (2.3–3.2)	10.0* (8.5–11.8)
Hx of MI	55 123 (42%)	59 621 (46%)	15 055 (12%)	0.40 (0.34–0.46)	1.10 (1.00–1.21)	2.92 (2.61–3.27)	2.8* (2.4–3.3)	7.5* (6.3–9.1)
No Hx of VASC	163 367 (44%)	167 508 (45%)	39 650 (11%)	0.24 (0.21–0.27)	0.64 (0.59–0.69)	2.14 (1.96–2.32)	2.7* (2.4–3.0)	9.1* (8.0–10.5)
Hx of VASC	17 104 (38%)	21 570 (48%)	6214 (14%)	0.46 (0.36–0.59)	1.32 (1.14–1.52)	3.10 (2.63–3.64)	2.9* (2.2–3.8)	6.9* (5.1–9.3)
No Hx of AF	119 617 (45%)	118 279 (45%)	25 902 (10%)	0.19 (0.16–0.22)	0.56 (0.51–0.61)	1.91 (1.72–2.13)	3.0* (2.5–3.5)	10.3* (8.7–12.4)
Hx of AF	60 854 (40%)	70 799 (47%)	19 962 (13%)	0.40 (0.35–0.46)	0.98 (0.90–1.07)	2.73 (2.46–3.03)	2.5 (2.1–2.9)	7.0 (5.9–8.3)
No Hx of CKD	148 157 (45%)	145 444 (45%)	32 066 (10%)	0.20 (0.18–0.23)	0.52 (0.48–0.57)	1.89 (1.71–2.08)	2.6* (2.2–3.0)	9.5* (8.1–11.1)
Hx of CKD	32 314 (36%)	43 634 (49%)	13 798 (15%)	0.52 (0.44–0.61)	1.36 (1.22–1.50)	3.18 (2.83–3.57)	2.6* (2.2–3.1)	6.3* (5.2–7.6)
No Hx of stroke/TIA	152 082 (44%)	153 997 (45%)	36 112 (11%)	0.24 (0.21–0.26)	0.60 (0.56–0.65)	2.05 (1.87–2.23)	2.6* (2.2–2.9)	8.9* (7.6–10.2)
Hx of stroke/TIA	28 389 (39%)	35 081 (48%)	9752 (13%)	0.39 (0.32–0.47)	1.21 (1.07–1.36)	3.09 (2.68–3.56)	3.1* (2.5–3.9)	8.2* (6.5–10.3)
No Hx of HF event	162 206 (45%)	163 825 (45%)	38 082 (10%)	0.19 (0.17–0.22)	0.51 (0.47–0.55)	1.68 (1.53–1.84)	2.7* (2.3–3.1)	8.9* (7.7–10.4)
Hx of HF event	18 265 (36%)	25 253 (49%)	7782 (15%)	0.85 (0.71–1.02)	2.06 (1.85–2.29)	5.22 (4.63–5.88)	2.4* (2.0–3.0)	6.4* (5.1–8.0)
Hx of low BNP	31 263 (41%)	35 511 (47%)	8612 (11%)	0.33 (0.27–0.41)	0.88 (0.77–1.01)	2.38 (2.01–2.81)	2.7* (2.1–3.4)	7.3* (5.7–9.5)
Hx of high BNP	25 352 (38%)	31 827 (47%)	10 303 (15%)	0.60 (0.50–0.72)	1.72 (1.55–1.90)	4.30 (3.82–4.82)	2.9* (2.4–3.6)	7.5* (6.0–9.3)

AF, atrial fibrillation; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; GEE, generalized estimating equation; HF, heart failure; HTN, hypertension; Hx, history; MI, myocardial infarction; TIA, transient ischaemic attack; VASC, vascular disease.
Used the maximum BNP value in the year prior to implant. Converted NT-proBNP to BNP by dividing by 4. Split into two groups using median BNP value of 547.
*P-value <0.001.

Table A3 Comparison of sensitivity using different analytic methods measured at common unexplained detection rates

Analysis method	Sensitivity at unexplained detection rate of 0.5 per patient year	Sensitivity at unexplained detection rate of 1.0 per patient year
OptiVol	40%	54%
OptiVol modified by TriageHF	48%	60%
TriageHF daily download	51%	70%
HeartLogic™ Reference #15	50%	60%

FIGURE A1 TriageHF risk score calculated based on scheduled monthly downloads. The receiver operating characteristic curve of sensitivity vs. specificity for the TriageHF risk score at various thresholds was calculated based on scheduled monthly downloads. The high-risk and medium-risk thresholds are indicated on the curve.

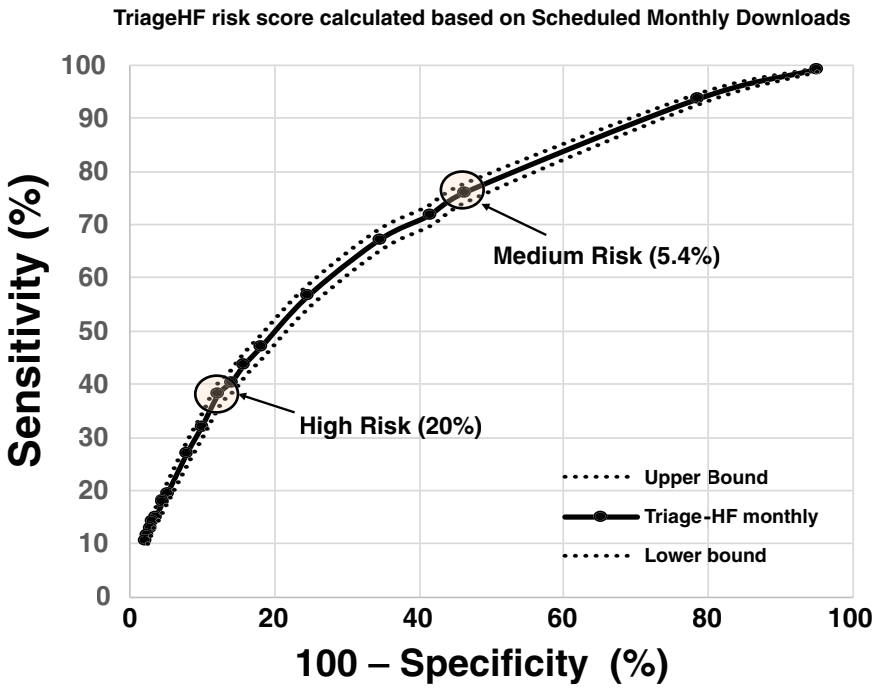
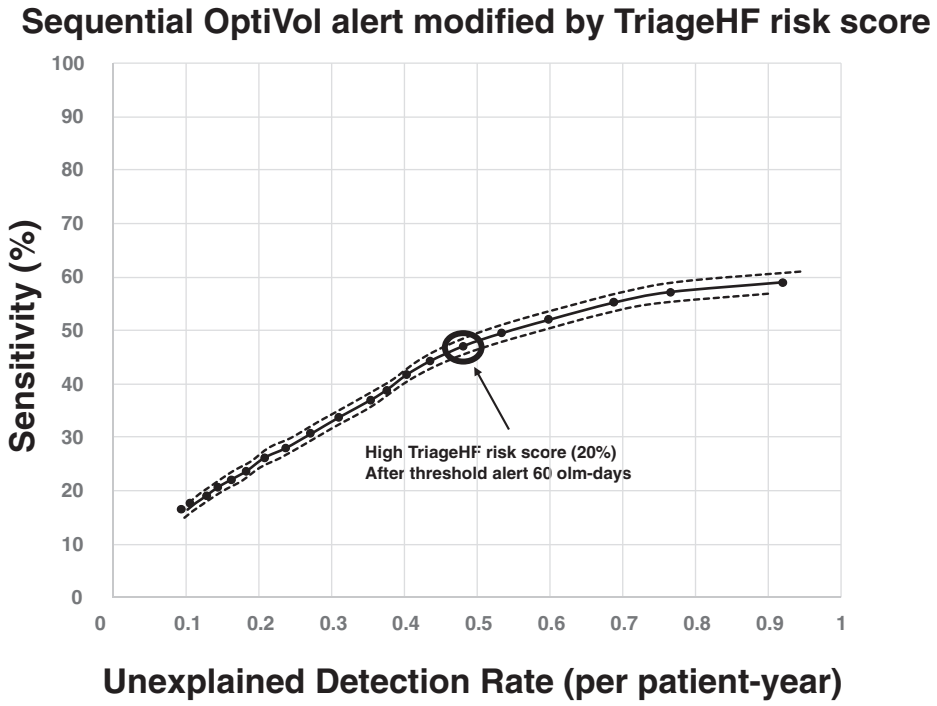


FIGURE A2 Risk assessment based on alert-triggered downloads. Sequential OptiVol alert modified by TriageHF risk score. The receiver operating characteristic curve of sensitivity vs. unexplained detection rate for OptiVol fluid index modified by TriageHF risk score-based prediction of heart failure events in a care alert usage model.



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