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Heart Failure Invasive Remote Monitoring: a Retrospective Evaluation of a Real-World Remote Monitoring Program

Sérgio Miguel Leal Campos

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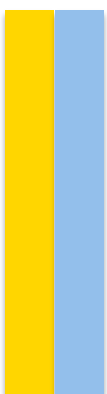

Heart failure invasive remote monitoring: a retrospective evaluation of a real-world remote monitoring program

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

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Porto, junho de 2024

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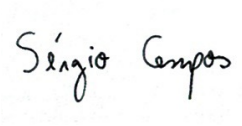

(Sérgio Miguel Leal Campos)

Orientador

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RESUMO

Introdução: Os programas de monitorização remota de Insuficiência Cardíaca (IC) procuram recolher e reconhecer parâmetros relacionados com IC a partir de dispositivos eletrónicos cardíacos implantáveis (DECI), o que permite uma intensificação terapêutica precoce, potencialmente prevenindo a descompensação adicional e reduzindo a pressão das hospitalizações nos sistemas de saúde.

Objetivo: Caracterizar os doentes com IC e a carga de alertas do programa de monitorização remota de IC em ambulatório no nosso centro e compará-la com coortes do mundo real previamente publicadas, bem como avaliar a associação dos alertas do algoritmo TriageHF® com as descompensações da IC.

Métodos: Este estudo observacional retrospetivo incluiu doentes seguidos num programa de monitorização remota invasiva de IC em ambulatório com o algoritmo TriageHF® (Medtronic) entre fevereiro de 2022 e julho de 2023. O algoritmo TriageHF® permite que os DECI recolham e integrem dados dos sensores de modo a estratificar os doentes quanto ao risco de internamento por IC nos 30 dias seguintes. Recolhemos dados sobre o número de alertas (alertas de alto risco) e o tipo de dados do sensor que acionou o alerta. Avaliamos ainda a duração de dias contínuos sob alerta de alto risco. Os *outcomes* clínicos considerados foram visitas não planeadas ao serviço de urgência (SU) com tratamento diurético intravenoso (IV), internamentos por IC, mortalidade por todas as causas e um composto que incluiu todos esses eventos.

Resultados: Houve um total de 77 alertas de alto risco individuais durante o tempo de seguimento mediano de 1,7 anos dos 134 doentes (0,44 alertas por doentes-ano). Os parâmetros anormais mais comuns a acionar o *score* de risco foram a impedância pulmonar medida pelo Optivol™ (n=70), a atividade do doente (n=57) e a frequência ventricular noturna (n=49). O subgrupo de doentes com IC que eventualmente apresentaram um alerta TriageHF® foi notavelmente similar ao subgrupo sem qualquer alerta, à exceção de superior prevalência de doença renal crónica, história de acidente vascular cerebral (AVC) e uso de furosemida. A taxa de eventos foi de 1,1% por mês. O tempo em alto risco constituiu 3,2% da duração total do seguimento. Ocorreram 6 eventos durante dias de alto risco (taxa de eventos de 7,9% por mês contra 0,8% por mês durante dias de risco padrão). Globalmente, avaliando a presença de alertas de alto risco enquanto teste isolado para a predição de eventos adversos, a sensibilidade e o valor preditivo positivo (VPP) foram subótimas, enquanto a especificidade e o valor preditivo negativo (VPN) foram notavelmente satisfatórias (≥68%), particularmente na predição de internamento por IC e de visitas não planeadas ao SU.

Conclusão: O algoritmo TriageHF® identificou períodos de alerta nos quais a incidência de eventos adversos relacionados com IC foi significativamente superior à do período sem alerta. Este achado,

aliado às especificidade e VPN aceitáveis na predição de descompensação de IC, sugere um papel importante na gestão dos recursos clínicos limitados para o crescente número de doentes com IC. A carga de alertas foi baixa, o que suporta a viabilidade da implementação de programas de monitorização remota mesmo em contextos de cuidados de saúde com poucos recursos humanos. Os alertas de monitorização remota podem também representar uma oportunidade de otimização da terapêutica médica direcionada por *guideline* (TMDG).

Palavras-chave: insuficiência cardíaca, descompensação, monitorização remota invasiva, algoritmo, CDI, TRC

ABSTRACT

Introduction: Heart failure (HF) remote monitoring programs seek to collect and recognize HF-related parameters from cardiac implantable electronic devices (CIED), that allow an early therapeutic intensification, potentially avoiding further decompensation and reducing the burden on the health care systems.

Purpose: Characterize the HF patients and the alert burden of the outpatient remote monitoring HF program at our center and compare it with real-world published cohorts, as well as evaluate the association between the TriageHF® algorithm alerts and the HF decompensations.

Methods: This retrospective observational study enrolled patients followed at an outpatient invasive remote monitoring HF program with the TriageHF® (Medtronic) algorithm between February 2022 and July 2023. The TriageHF® algorithm enables CIED to collect and integrate sensor data to stratify the patients' risk of hospitalization in the next 30 days. We collected data on the number of alerts (high-risk alerts) and the type of sensor data that was driving the alert. We also evaluated the duration of continuous days under high-risk alert. The considered clinical outcomes were unplanned emergency room (ER) visits with intravenous (IV) diuretic treatment, HF hospitalizations, all-cause death and clinical outcomes as a compositive of all these events.

Results: There was a total of 77 individual high-risk alerts during the median follow-up of 1.7 years of the 134 patients (0.44 alerts per patient-year). The most common abnormal parameters driving the risk score were lung impedance measured by Optivol™ (n=70), patient activity (n=57) and night ventricular rate (n=49). The subset of HF patients who eventually had a TriageHF® alert were remarkably similar to those without any alert, except for the increased prevalence of chronic kidney disease, stroke history and use of furosemide. The event rate was 1.1% per month. The time in high-risk constituted 3.2% of the follow-up duration. 6 events occurred during high-risk days (event rate of 7.9% per month versus 0.8% per month during standard-risk days). Overall, for the presence of high-risk alerts as a standalone test for predicting adverse events, sensitivity and positive predictive value (PPV) were suboptimal, while specificity and negative predictive value (NPV) were remarkably satisfactory (≥68%), particularly in predicting HF hospitalization and unplanned ER visits.

Conclusion: The TriageHF® algorithm identified alert periods in which the incidence of HF-related adverse events was significantly higher than in the non-alert period. This finding, allied with acceptable specificity and NPV in the prediction of HF decompensation, suggests an important role in managing limited clinical resources for the increasing number of HF patients. The alert burden was low, which supports the feasibility of remote monitoring programs implementation even in low human-resource clinical care settings. The remote monitoring alerts may also present an opportunity for optimizing guideline-directed medical therapy (GDMT).

Keywords: heart failure, decompensation, invasive remote monitoring, algorithm, ICD, CRT

LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ACEi	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
CHUdSA	Centro Hospitalar Universitário de Santo António
CIED	Cardiac implantable electronic devices
COPD	Chronic obstructive pulmonary disease
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy with defibrillator
CRT-P	Cardiac resynchronization therapy pacemaker
ER	Emergency room
GDMT	Guideline-directed medical therapy
HF	Heart failure
ICD	Implantable cardioverter-defibrillator
IQR	Interquartile range
IV	Intravenous
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
NPV	Negative predictive value
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PPV	Positive predictive value
SD	Standard deviation
SGLT-2	Sodium-glucose co-transporter 2
SGLT2i	Sodium-glucose co-transporter 2 inhibitor

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INTRODUCTION

Heart failure (HF) is a leading cause of morbimortality and is associated with a substantial economic burden to the health care system[1]. Despite the modern advances in treatments, the rate of hospitalization for HF decompensation remains unacceptably high, with each patient being hospitalized, on average, once every year after the initial diagnosis[2]. Hospitalizations reduce patients' quality of life and longevity and represent the main driver of economic costs related to this disease[3].

Remote patient monitoring seeks to optimally manage health conditions outside healthcare facilities. The use of remote data continuously collected by implanted cardiac devices has gained increased attention as these devices provide insight over several physiological variables primarily implicated in the pathophysiology of HF decompensation and that precede symptoms and weight gain due to congestion[4]. Devices like implantable cardioverter-defibrillators (ICD) and cardiac resynchronization therapy (CRT) are recommended treatment options[5] to a significant proportion of HF patients, regardless of their utility for telemonitoring. The concept underlying all the remote monitoring of these devices in HF is the early recognition by the physician of these actionable data that will allow a timely therapeutic intensification to avoid further cardiac decompensation and hospitalization[4]. Clinical trials aiming to examine the clinical efficacy of these remote patient monitoring strategies using cardiac implantable devices have yielded conflicting results[6,7]. One of the major limitations of these treatment strategies have been the suboptimal sensitivity and specificity of the data that is remotely monitored. The reduced uptake of these remote monitoring risk stratification strategies might be explained by the fear of data overload, a common problem in modern healthcare systems[8]. Real-world data on remote HF monitoring are critical to properly inform healthcare professionals on the expected diagnostic performance of these algorithms in an unselected and diverse HF population and to adequately estimate the resources needed to implement these promising modern strategies.

Our aim was (1) to characterize the HF patients currently being followed at the outpatient invasive remote monitoring HF clinic of Centro Hospitalar Universitário de Santo António (CHUdSA) and compare their clinical and risk profile (mortality and HF hospitalizations) with published cohorts from the remote monitoring studies; (2) to characterize and compare the alert burden with trial and other real-world published cohorts and (3) to evaluate the association of TriageHF® alerts with HF-related clinical outcomes in this clinical setting.

METHODS

Study design and population

We performed an observational retrospective study involving patients followed at the outpatient invasive remote monitoring HF clinic of CHUdSA between February 2022 and July 2023 with the TriageHF® algorithm. By chart review, we collected data of each patient to characterize the baseline clinical profile and HF-related risk. Our variables of interest included demographic (age, sex) and clinically related (New York Heart Association [NYHA] functional class, HF etiology, guideline-directed medical therapy [GDMT], left ventricular ejection fraction [LVEF], plasma concentration of N-terminal pro-B-type natriuretic peptide [NT-proBNP]) characteristics and cardiovascular and non-cardiovascular comorbidities.

This study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study was approved by the Ethics Committee of the CHUdSA (2023.276 [237-DEFI/228-CE]).

TriageHF® algorithm

The TriageHF® algorithm is a validated algorithm that enables ICD and CRT devices to collect and integrate sensor data (thoracic impedance, patient activity, presence of atrial fibrillation, ventricular pacing, treatment for ventricular tachycardia/fibrillation, night ventricular rate, heart rate variability) to stratify the risk of HF hospitalization in the next 30 days. It continuously collects and computes these data and when the hospitalization risk crosses a predefined threshold an alert is sent to the HF clinical team. We collected data on the number of alerts (high-risk alerts) and the type of sensor data that was driving the alert. We also evaluated the duration of continuous days under high-risk alert.

Clinical events

The clinical outcomes considered were unplanned emergency room (ER) visits with the need for intravenous (IV) diuretic treatment, HF hospitalizations and all-cause death. We also evaluated clinical outcomes as a compositive of all these events. All the clinical events were analyzed through a review of the electronic health records.

Data analysis

Continuous variables are expressed as mean ± standard deviation for normally distributed data or median [interquartile range] for nonnormally distributed data. Categorical variables are expressed as number of subjects and proportion [n (%)]. Comparisons between groups were

performed using two-sided unpaired or paired t-tests or Wilcoxon rank sums test for normally and non-normally distributed data, respectively. A two-sided p-value < 0.05 was considered significant. Statistical analyses were done with STATA 12.1 (StataCorp LLC, Texas, USA).

Sensitivity was defined as the number of patients with high-risk alerts and adverse events divided by the total number of patients with adverse events. Specificity was defined as the number of patients without high-risk alerts and no adverse events divided by the total number of patients without adverse events. Positive predictive value (PPV) was defined as the number of patients with high-risk alerts and adverse events divided by the total number of patients with high-risk alerts. Negative predictive value (NPV) was defined as the number of patients without high-risk alerts and no adverse events divided by the total number of patients without high-risk alerts.

RESULTS

Studied population

We studied 134 patients with HF with reduced ejection fraction with an implanted cardiac device (CRT-D/P 82%, ICD 18%) enabled to run the TriageHF® algorithm. Their mean age was 73±11 years and 72% were male. Most of them had a non-ischemic etiology (47%) and were on functional class NYHA II (60%). Their median NT-proBNP plasma concentration was 847 [2348] pg/mL. Regarding comorbidities, 41% were diabetic, 31% had a previous history of acute myocardial infarction, 19% had persistent/permanent atrial fibrillation (29% had paroxysmal). Most of them were on GDMT (91% on beta-blockers; 65% on angiotensin-converting enzyme inhibitor [ACEi] / angiotensin II receptor blocker [ARB]; 21% on angiotensin receptor-neprilysin inhibitor [ARNI]; 44% on sodium-glucose co-transporter 2 inhibitor [SGTL2i]; 56% on mineralocorticoid receptor antagonist [MRA]). Only 19% were followed at a dedicated HF clinic, whereas most of them were followed on general cardiology or cardiac device outpatient consults. Regarding the use of GDMT, the patients followed at a dedicated HF clinic had a significantly better use of MRA (89% versus 49%) and SGLT2i (77% versus 36%) when compared with the patients followed on general cardiology or cardiac device outpatient consults. The demographic and clinical characteristics of the studied population are displayed in Table I and the clinical features of the patients followed at a dedicated HF clinic are displayed in Table II.

Alert characterization

There was a total of 77 individual high-risk alerts during the median follow-up of 1.7 years of the 134 patients, which represents a 0.44 alerts per patient-year. The proportion of patients with at least one alert was 30% (n=40). The proportion of patients with at least 2 alerts was 18% (n=24) and with 3 or more alerts 7% (n=10). The maximal number of alerts any patient had was 5 (1 patient). Among patients who experienced alerts, the mean duration of the alert status was 60±93 days. The most common abnormal parameters driving the risk score were lung impedance measured by Optivol™ (n=70), patient activity (n=57) and night ventricular rate (n=49). The data about TriageHF® alerts are displayed in Table III. The subset of HF patients who eventually had a TriageHF® alert were remarkably similar to those without any alert, except for the increased prevalence of chronic kidney disease, stroke history and use of furosemide (Table IV).

Clinical outcomes

There was a total of 40 events (15 deaths, 10 HF hospitalizations and 15 unplanned ER visits for HF decompensation), occurring in 29 patients. The median follow-up time was 1.7 years. The

death rate was 6.6 deaths / 100 person-years (11.2% over the follow-up period). The overall composite event rate was 17.6 events / 100 person-years. When using the median of NT-proBNP levels (847 pg/mL), patients below the median had a composite event rate of 2.2 events / 100 person-years compared to 41.3 events / 100 person-years in those with an NT-proBNP level above median (the clinical characteristics of the studied patients divided by the NT-proBNP median are displayed in Table V).

TriageHF® performance

Out of the 134 patients, a cumulative total of 2376 months of follow-up data were collected, during which 25 hospitalizations or ER visits due to HF were recorded, translating to an event rate of 1.1% per month. Utilizing the TriageHF® algorithm, a collective sum of 76 months was identified as high-risk, constituting 3.2% of the follow-up duration. There were 19 events during standard-risk days, with an event rate of 0.8% per month, whereas 6 events occurred during high-risk days, representing an event rate of 7.9% per month (Table VI). This denotes an incidence nearly ten times higher in the occurrence of adverse events during high-risk days.

Table VII presents sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the presence of high-risk alerts, as a standalone test, for predicting adverse events. Overall, sensitivity and PPV were suboptimal, while specificity and NPV were remarkably satisfactory, particularly in predicting HF hospitalization and unplanned ER visits.

DISCUSSION

Our study has yielded several noteworthy findings warranting further discussion. First, HF patients with implanted cardiac devices enabled to be enrolled in remote monitoring programs are quite heterogeneous regarding prognosis, which might have clinical implications for the implementation of these programs. Second, most of these patients were not followed in a dedicated outpatient HF clinic and there was an underutilization of guideline-directed medical therapy with prognostic impact. Third, the pattern of abnormal sensing parameters is in line with previously published reports. Lastly, the alert burden was low, which supports the feasibility of integrating these remote programs even in a low-human resource setting.

Previous reports have described monthly HF-related event rates ranging from 0.68% to 1.5%[9-13]. This aligns with the reported rate of 1.1% per month for hospitalizations or ER visits due to HF in our cohort. These studies also consistently demonstrated a substantial increase in the incidence and relative risk of HF events in the 30 days following a high-risk alert, being that the algorithm assessed 10% to 13% of the total months as high-risk[9-11]. In our cohort, distinct from previous reports which considered the maximum monthly score, we evaluated the cumulative duration of continuous days under high-risk alert. This probably explains the comparatively lower percentage of time spent in the high-risk category (only 3% of the time). Nevertheless, our findings corroborate a nearly ten-fold increase in the incidence of HF decompensations during the alert period itself, which supports TriageHF® algorithm as an effective and useful risk stratification tool in HF.

Comparing the clinical characteristics of the studied patients, those who eventually had a TriageHF® alert closely resembled those without any alert, apart from an increased prevalence of chronic kidney disease, use of furosemide and stroke history. This finding might be understood considering HF decompensation and hospitalization risk as a dynamic variable, with significant variations over time, thereby generating growth and descending trends that are better ascertained by longitudinal risk assessment tools, such as the TriageHF® remote monitoring program, rather than through any cross-sectional analysis of the population in follow-up. The association between the presence of chronic kidney disease and stroke history and the notification of a TriageHF® high-risk alert may elucidate the importance of these characteristics as clinical markers of more severe vascular and systemic pathology, leading to an increased risk of HF related-adverse events. Similarly, the association of furosemide usage and the presence of a TriageHF® high-risk alert could be interpreted as the loop diuretic usage being a marker of more severe disease and a subsequent higher risk of HF decompensation and triggering of a high-risk alert.

Regarding high-risk alert diagnostic performance, the low sensitivity and PPV underscores that the TriageHF® algorithm's ability to accurately predict HF decompensation in those with high-risk alert is limited, and clinicians should be cautious when interpreting these alerts in isolation. However, in line with previous studies, we reported a specificity and a NPV of at least 68%, suggesting a role in identifying individuals that may not require immediate intervention or closer monitoring, which helps to optimize limited resources allocation[11,12,14], allowing them to be redirected from patients in their non-high-risk periods to more vulnerable patients in their high-risk periods.

Using this alert-triggered evaluation approach, our data underline a low alert burden at 0.44 alerts per patient-year. This suggests that implementation in real-world settings is feasible without data overload. Although not directly evaluated in our series, we hypothesized that integrating a telephonic call into a standardized protocol for alert management could potentially enhance the diagnostic performance and cost-effectiveness of remote monitoring without substantially increasing workload, as previously described[15].

Risk stratification of heart failure using invasive remote monitoring may also have a promising role for optimizing guideline-directed medical therapy[16]. In our series, baseline medication was suboptimal, particularly regarding the use of MRA and SGLT2i, which were prescribed to only nearly half of the patients. Also, MRA and SGLT2i use was significantly better in patients followed in a dedicated HF clinic (see Table II). Remarkably, medication profiles were similar between patients with and without TriageHF® alerts, except for furosemide, which was more frequently prescribed to patients at higher risk (see Table IV). As such, remote monitoring alerts can serve not only as reminders for diuretic adjustment and symptomatic optimization but also present an opportunity for optimizing GDMT.

Our study has several limitations that should be acknowledged. First, its retrospective nature does not allow us to collect a more detailed clinical data during alert periods. Second, being a single center study, the generalizability of these results to different healthcare settings is limited. Third, the relatively low number of patients and event rate in our cohort may have impacted the estimates of diagnostic performance of the algorithm, particularly for the evaluation of sensitivity. Additionally, the lack of data for low or medium risk score alerts limits our understanding on these different risk strata. Lastly, the absence of data on interventions or treatment modifications during the follow-up precludes the assessment of their potential impact on risk status and outcomes.

CONCLUSIONS

In this real-world evaluation of a population of HF patients with an ICD or a CRT, the TriageHF® algorithm identified alert periods in which the incidence of HF-related adverse events was ten times higher than in the non-alert period. This finding, allied with acceptable specificity and NPV in the prediction of HF decompensation, suggests an important role in managing limited clinical resources for the increasing number of HF patients. The alert burden was low, which supports the feasibility of remote monitoring programs implementation even in low human-resource clinical care settings. The remote monitoring alerts may also present an opportunity for optimizing GDMT (Figure 1).

TABLES AND FIGURES

Table I – Clinical characteristics of studied patients (n=134).

Mean age, years (±SD)	72.8	11.1
Males, *n* (%)	96	71.6
Etiology,		
- Ischemic, *n* (%)	45	34.4
- Non-Ischemic, *n* (%)	61	46.6
- Combined, *n* (%)	24	18.3
Mean LVEF, % (±SD)	38.4	11.3
Median NT-proBNP, pg/ml (IQR)	847.1	2348.4
Type of device		
- ICD, *n* (%)	24	17.9
- CRT-P, *n* (%)	49	36.6
- CRT-D, *n* (%)	61	45.5
NYHA		
- NYHA 1, *n* (%)	22	16.5
- NYHA 2, *n* (%)	80	60.2
- NYHA 3, *n* (%)	31	23.3
- NYHA 4, *n* (%)	0	0
Medical History		
- Hypertension, *n* (%)	81	69.9
- Diabetes, *n* (%)	54	40.6
- Dyslipidemia, *n* (%)	93	69.9
- Active smoker, *n* (%)	23	17.3
- Coronary Artery Disease, *n* (%)	72	54.5
- History of MI, *n* (%)	41	30.8
- Atrial Fibrillation		
No, *n* (%)	69	53.1
Yes, paroxysmal, *n* (%)	37	28.5
Yes, persistent, *n* (%)	8	6.2
Yes, permanent, *n* (%)	16	12.3
- Chronic Kidney Disease, *n* (%)	40	30.1
- Peripheral Artery Disease, *n* (%)	16	12.0
- Stroke history, *n* (%)	20	15.0
- COPD, *n* (%)	23	17.3
Chronic Medication		
- Beta-blocker, *n* (%)	122	91.0
- ACE inhibitors / ARB, *n* (%)	86	64.7
- Sacubitril/Valsartan, *n* (%)	28	21.1
- SGLT2 inhibitors, *n* (%)	59	44.4
- MRA, *n* (%)	75	56.4
- Furosemide, *n* (%)	104	78.2

-	Digoxin, *n* (%)	17	12.8
-	Ivabradine, *n* (%)	8	6.0

ACE – angiotensin-converting enzyme; ARB – angiotensin II receptor blocker; COPD – chronic obstructive pulmonary disease; MI – myocardial infarction; NYHA – New York Heart Association; CRT-D – cardiac resynchronization therapy with defibrillator; CRT-P – cardiac resynchronization therapy pacemaker; ICD – implantable cardioverter-defibrillator; IQR – interquartile range; LVEF – left ventricular ejection fraction; MRA – mineralocorticoid receptor antagonist; NT-proBNP – N-terminal pro-B-type natriuretic peptide; SD – standard deviation; SGLT-2 - Sodium-glucose co-transporter 2.

Table II – Clinical features of patients followed at a dedicated heart failure [HF] clinic.

	General Cardiology or Cardiac Device Outpatient consult (n=108)		Dedicated HF clinic (n=26)		p-value
Mean age, years (±SD)	73.7	11.1	69.1	9.9	0.059
Males, *n* (%)	76	70.4	20	76.9	0.506
Etiology,					
- Ischemic, *n* (%)	36	34.3	9	34.6	0.967
- Non-Ischemic, *n* (%)	49	46.7	12	46.2	
- Combined, *n* (%)	19	18.1	5	19.2	
Mean LVEF, % (±SD)	38.5	11.3	32.7	10.1	**0.004**
Median NT-proBNP, pg/ml (IQR)	898.2	2450.4	612.0	1782.8	0.956
Type of device					
- ICD, *n* (%)	20	18.5	4	15.4	**0.004**
- CRT-P, *n* (%)	42	38.9	19	73.1	
- CRT-D, *n* (%)	46	42.6	3	11.5	
NYHA					
- NYHA 1, *n* (%)	19	17.8	3	11.5	
- NYHA 2, *n* (%)	66	61.7	14	53.8	0.290
- NYHA 3, *n* (%)	22	20.6	9	34.6	
- NYHA 4, *n* (%)	0	0	0	0	
Medical History					
– Hypertension, *n* (%)	65	60.7	16	61.5	0.940
– Diabetes, *n* (%)	45	42.1	8	30.8	0.487
– Dyslipidemia, *n* (%)	77	72.0	16	61.5	0.299
– Active smoker, *n* (%)	16	15.0	7	26.9	0.260
– Coronary Artery Disease, *n* (%)	57	53.8	15	57.7	0.719
– History of MI, *n* (%)	32	29.9	9	34.6	0.641
– Atrial Fibrillation					
No, *n* (%)	58	55.8	11	42.3	
Yes, paroxysmal, *n* (%)	25	24.0	12	46.2	0.098
Yes, persistent, *n* (%)	8	7.7	0	0	
Yes, permanent, *n* (%)	13	12.5	3	11.5	
– Chronic Kidney Disease, *n* (%)	32	29.9	8	30.8	0.931
– Peripheral Artery Disease, *n* (%)	12	11.2	4	15.4	0.558
– Stroke history, *n* (%)	14	13.1	6	23.1	0.201
– COPD, *n* (%)	17	15.9	6	23.1	0.385
Chronic Medication					
– Beta-blocker, *n* (%)	96	88.9	26	100.0	0.075
– ACE inhibitors / ARB, *n* (%)	70	65.4	16	61.5	0.710
– Sacubitril/Valsartan, *n* (%)	19	17.8	9	34.6	0.059
– SGLT2 inhibitors, *n* (%)	39	36.4	20	76.9	**0.001**
– MRA, *n* (%)	52	48.6	23	88.5	**0.001**
– Furosemide, *n* (%)	84	78.5	20	76.9	0.861
– Digoxin, *n* (%)	13	12.1	4	15.4	0.658

– Ivabradine, *n* (%)	7	6.5	1	3.8	0.604

ACE – angiotensin-converting enzyme; ARB – angiotensin II receptor blocker; COPD – chronic obstructive pulmonary disease; MI – myocardial infarction; NYHA – New York Heart Association; CRT-D – cardiac resynchronization therapy with defibrillator; CRT-P – cardiac resynchronization therapy pacemaker; ICD – implantable cardioverter-defibrillator; IQR – interquartile range; LVEF – left ventricular ejection fraction; MRA – mineralocorticoid receptor antagonist; NT-proBNP – N-terminal pro-B-type natriuretic peptide SD – standard deviation; SGLT-2 - Sodium-glucose co-transporter 2.

Table III – TriageHF® alerts description.

Total number of high-risk alerts	77	
Abnormal parameters		
- Thoracic impedance (OptiVol™)	70	
- Patient activity	57	
- Presence of atrial fibrillation	12	
- Ventricular pacing	20	
- Treatment for VT/VF	1	
- Night ventricular rate	49	
- Heart rate variability	44	
Number of patients with		
- 1 alert, *n* (%)	16	11.94
- 2 alerts, *n* (%)	14	10.45
- 3 alerts, *n* (%)	8	5.97
- 4 alerts, *n* (%)	1	0.75
- 5 alerts, *n* (%)	1	0.75
Number of patients with		
- At least 1 alert, n (%)	40	29.85
- At least 2 alerts, n (%)	24	17.91
- At least 3 alerts, n (%)	10	7.46
- At least 4 alerts, n (%)	2	1.49
- At least 5 alerts, n (%)	1	0.75

VF – ventricular fibrillation; VT – ventricular tachycardia.

Table IV – Clinical characteristics of studied patients, divided by the occurrence of a TriageHF® alert.

	No TriageHF® alert (n=94)		TriageHF® alert (n=40)		p-value
Mean age, years (±SD)	72.7	10.8	73.2	11.8	0.805
Males, *n* (%)	69	73.4	27	67.5	0.488
Etiology,					
- Ischemic, *n* (%)	33	36.3	12	30.0	0.430
- Non-Ischemic, *n* (%)	41	45.1	20	50.0	
- Combined, *n* (%)	17	18.7	7	17.5	
Mean LVEF, % (±SD)	37.5	11.5	40.6	10.8	0.148
Median NT-proBNP, pg/ml (IQR)	616.0	2423.5	1234.0	2255.5	0.245
Type of device					
- ICD, *n* (%)	15	16.0	9	22.5	0.499
- CRT-P, *n* (%)	42	44.7	19	47.5	
- CRT-D, *n* (%)	37	39.4	12	30.0	
NYHA					
- NYHA 1, *n* (%)	18	19.4	4	10.0	
- NYHA 2, *n* (%)	56	60.2	24	60.0	0.275
- NYHA 3, *n* (%)	19	20.4	12	30.0	
- NYHA 4, *n* (%)	0	0	0	0	
Medical History					
– Hypertension, *n* (%)	52	55.9	29	72.5	0.072
– Diabetes, *n* (%)	34	36.6	19	47.5	0.134
– Dyslipidemia, *n* (%)	62	66.7	31	77.5	0.221
– Active smoker, *n* (%)	15	16.1	8	20.0	0.491
– Coronary Artery Disease, *n* (%)	51	55.4	21	52.5	0.756
– History of MI, *n* (%)	28	30.1	13	32.5	0.784
– Atrial Fibrillation					
No, *n* (%)	48	52.7	21	53.8	
Yes, paroxysmal, *n* (%)	26	28.6	11	28.2	0.938
Yes, persistent, *n* (%)	5	5.5	3	7.7	
Yes, permanent, *n* (%)	12	13.2	4	10.3	
– Chronic Kidney Disease, *n* (%)	20	21.5	20	50.0	**0.001**
– Peripheral Artery Disease, *n* (%)	12	12.9	4	10.0	0.640
– Stroke history, *n* (%)	9	9.7	11	27.5	**0.008**
– COPD, *n* (%)	14	15.1	9	22.5	0.298
Chronic Medication					
– Beta-blocker, *n* (%)	87	92.6	35	87.5	0.389
– ACE inhibitors / ARB, *n* (%)	61	64.9	25	64.1	0.931
– Sacubitril/Valsartan, *n* (%)	20	21.3	8	20.5	0.921
– SGLT2 inhibitors, *n* (%)	42	44.7	17	43.6	0.908
– MRA, *n* (%)	53	56.4	22	56.4	0.998
– Furosemide, *n* (%)	69	73.4	35	89.7	**0.038**
– Digoxin, *n* (%)	12	12.8	5	12.8	0.993
– Ivabradine, *n* (%)	4	4.3	4	10.3	0.185

ACE – angiotensin-converting enzyme; ARB – angiotensin II receptor blocker; COPD – chronic obstructive pulmonary disease; MI – myocardial infarction; NYHA – New York Heart Association; CRT-D – cardiac resynchronization therapy with defibrillator; CRT-P – cardiac resynchronization therapy pacemaker; ICD – implantable cardioverter-defibrillator; IQR – interquartile range; LVEF – left ventricular ejection fraction; MRA – mineralocorticoid receptor antagonist; NT-proBNP – N-terminal pro-B-type natriuretic peptide SD – standard deviation; SGLT-2 - Sodium-glucose co-transporter 2.

Table V – Clinical characteristics of studied patients, divided by N-terminal pro-B-type natriuretic peptide (NT-proBNP) median (above and below 847 pg/mL).

	Below NT-proBNP Median (n=58)		Above NT-proBNP Median (n=58)		p-value
Mean age, years (±SD)	68.8	10.6	75.4	10.6	**0.001**
Males, *n* (%)	42	72.4	43	74.1	0.834
Etiology,					
- Ischemic, *n* (%)	20	35.1	21	36.8	0.351
- Non-Ischemic, *n* (%)	27	47.4	21	36.8	
- Combined, *n* (%)	9	15.8	15	26.3	
Mean LVEF, % (±SD)	39.6	10.4	36.8	12.3	0.181
Median NT-proBNP, pg/ml (IQR)	213.2	304.1	2553.0	2892.0	**<0.001**
Type of device					
- ICD, *n* (%)	15	25.9	8	13.8	0.117
- CRT-P, *n* (%)	28	48.3	26	44.8	
- CRT-D, *n* (%)	15	25.9	24	41.4	
NYHA					
- NYHA 1, *n* (%)	8	13.8	13	22.4	**0.002**
- NYHA 2, *n* (%)	43	74.1	25	43.1	
- NYHA 3, *n* (%)	7	12.1	20	34.5	
- NYHA 4, *n* (%)	0	0	0	0	
Medical History					
– Hypertension, *n* (%)	32	56.2	42	72.4	0.069
– Diabetes, *n* (%)	22	38.6	25	43.1	0.549
– Dyslipidemia, *n* (%)	44	77.2	43	74.1	0.702
– Active smoker, *n* (%)	14	24.6	8	13.8	0.340
– Coronary Artery Disease, *n* (%)	31	54.4	37	63.8	0.305
– History of MI, *n* (%)	17	29.8	22	37.9	0.359
– Atrial Fibrillation					
No, *n* (%)	43	75.4	18	32.7	**<0.001**
Yes, paroxysmal, *n* (%)	11	19.3	22	40.0	
Yes, persistent, *n* (%)	2	3.5	5	9.1	
Yes, permanent, *n* (%)	1	1.8	10	18.2	
– Chronic Kidney Disease, *n* (%)	10	17.5	28	48.3	**0.001**
– Peripheral Artery Disease, *n* (%)	9	15.8	6	10.3	0.386
– Stroke history, *n* (%)	11	19.3	9	15.5	0.593
– COPD, *n* (%)	6	10.5	15	25.9	**0.033**
Chronic Medication					
– Beta-blocker, *n* (%)	53	91.4	54	93.1	0.729
– ACE inhibitors / ARB, *n* (%)	42	72.4	33	57.9	0.102
– Sacubitril/Valsartan, *n* (%)	13	22.4	11	19.3	0.681
– SGLT2 inhibitors, *n* (%)	25	43.2	29	50.9	0.404
– MRA, *n* (%)	34	58.6	34	59.6	0.910
– Furosemide, *n* (%)	40	69.0	50	87.7	**0.015**
– Digoxin, *n* (%)	6	10.3	7	12.3	0.743
– Ivabradine, *n* (%)	4	6.9	1	1.8	0.177

ACE – angiotensin-converting enzyme; ARB – angiotensin II receptor blocker; COPD – chronic obstructive pulmonary disease; MI – myocardial infarction; NYHA – New York Heart Association; CRT-D – cardiac resynchronization therapy with defibrillator; CRT-P – cardiac resynchronization therapy pacemaker; ICD – implantable cardioverter-defibrillator; IQR – interquartile range; LVEF – left ventricular ejection fraction; MRA – mineralocorticoid receptor antagonist; NT-proBNP – N-terminal pro-B-type natriuretic peptide SD – standard deviation; SGLT-2 - Sodium-glucose co-transporter 2.

Table VI – Rate of adverse events (emergency room [ER] visit or heart failure [HF] hospitalization) according to TriageHF® risk.

	No. of months	No. of adverse events (event rate per month)
All	2376	25 (1.1%)
No alert	2300 (96.8%)	19 (0.8%)
High Risk alert	76 (3.2%)	6 (7.9%)

Table VII – Sensitivity, specificity, and positive and negative predictive values of high-risk alerts as a standalone test for adverse events.

		Events - Composite		
		Yes	No	Total
Alert	Yes	10	30	40
	No	19	74	93
	Total	29	104	133

Sensitivity 34.5% | Positive predictive value 25.0% | Specificity 71.2% | Negative predictive value 79.6%

		Death		
		Yes	No	Total
Alert	Yes	2	38	40
	No	13	80	93
	Total	15	118	133

Sensitivity 13.3% | Positive predictive value 5.00% | Specificity 67.8% | Negative predictive value 86.0%

		HF hospitalization		
		Yes	No	Total
Alert	Yes	6	34	40
	No	5	88	93
	Total	11	122	133

Sensitivity 54.5% | Positive predictive value 15.0% | Specificity 72.1% | Negative predictive value 94.6%

		Unplanned ER visits		
		Yes	No	Total
Alert	Yes	8	32	40
	No	5	88	93
	Total	13	120	133

Sensitivity 61.5% | Positive predictive value 20.0% | Specificity 73.3% | Negative predictive value 94.6%

ER – emergency room; HF – heart failure

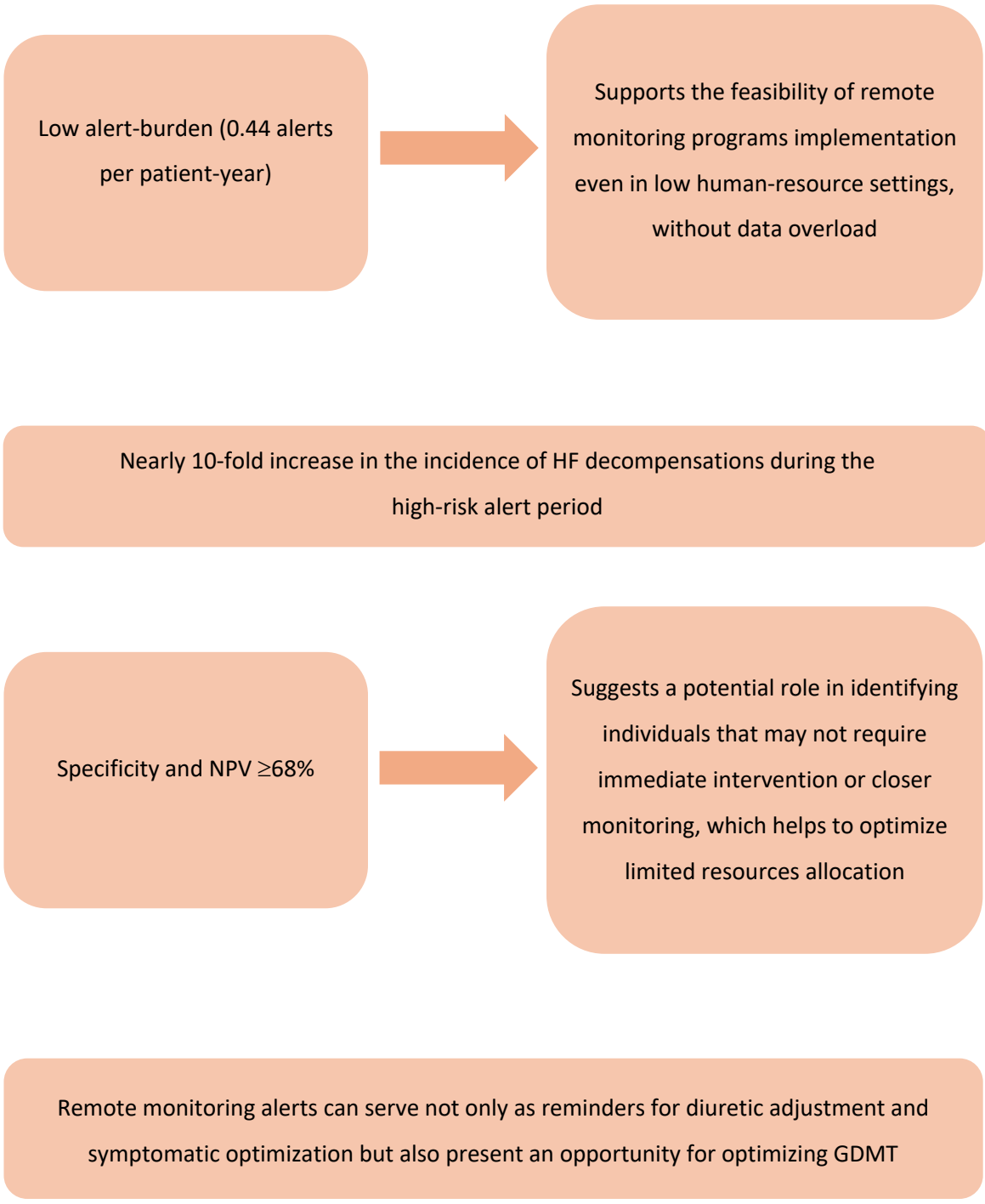

Figure 1 – Take-home messages.
GDMT – guideline-directed medical therapy; HF – heart failure; NPV – negative predictive value.

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