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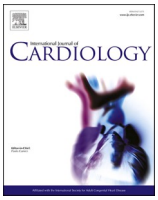

A multistate model of clinical trajectories of heart failure patients with implantable electronic devices followed with remote monitoring: What outcome implications of alerts at long term follow up?

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ABSTRACT

Background: Understanding how baseline conditions influence alerts and adverse events in patients with heart failure (HF) and cardiac implantable electronic devices (CIEDs) under remote monitoring (RM) is crucial for patient management. However, the impact of HF alerts on clinical outcomes remains poorly defined.
Objective: To assess the impact of HF alerts on adverse outcomes and to identify clinical trajectories based on individual baseline risk factors.
Methods: We conducted a single-center, retrospective study including HF patients implanted with a CIED and provided with RM. We modeled patients trajectories using a semi-Markov, four-state framework with six possible transitions, encompassing a HF score alert state, HF Hospitalization (HFH) state and all-cause death. Cox proportional hazards models assessed the effects of baseline covariates on transition rates and evaluated the impact of HF alert occurrence on outcomes, treated as time-dependent covariates.
Results: A total of 511 patients (median age 69.9 years [IQR 61.4–77.1]) were included. During a median follow-up of 1.8 years [IQR 0.7–3.9], 60 patients (11.7%) transitioned to an HF score alert state, of whom 6 (10%) and 12 (20%) respectively experienced an HFH and died without a prior HFH. From the baseline group, 29 patients (5.7%) transitioned directly to death and 53 patients (10.4%) had an HFH. Of the 59 total patients who experienced an HFH, 19 (32%) died during follow-up. The transition to a HF score alert state was significantly associated with all-cause death (HR 6.99, 95% CI 1.89–25.94; $p = 0.004$) while not statistically significant associated with HFH (HR 0.58, 95% CI 0.13–2.69; $p = 0.65$).
Conclusions: Using a multistate model, we characterized clinical trajectories in HF patients and observed the effects of different covariates on transition rates.

1. Introduction

Remote monitoring (RM) of cardiac implantable electronic device (CIED) for the management of patients with heart failure (HF) is increasingly advocated due to its potential to detect disease progression early and enable timely intervention for worsening conditions. In addition to improving patient care, RM may substantially reduce healthcare costs [1–6]. Consequently, a growing number of patients are expected to experience an "alert" state, representing a transition from a baseline stable condition [7,8].

Despite the growing clinical use of RM, current knowledge on the trajectories from baseline to alert states and subsequent adverse events

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in HF patients remains limited. The rate and nature of these transitions may be influenced by various baseline risk factors and clinical characteristics. A better understanding of these dynamics is important for healthcare planning and for developing robust, evidence-based RM protocols.

Moreover, the clinical impact of device-generated alerts on patient outcomes remains matter of debate with contradictory results both from clinical trials and observational registries [9–13].

Multistate models provide a framework to describe and estimate the risk of an individual transitioning between health states [14]. While previous studies have applied these models in various contexts [15,16], comprehensive evaluations in patients with HF and CIEDs are lacking.

The aim of our study was to characterize and quantify the health trajectories of HF patients with CIEDs, from baseline to intermediate alert state and ultimately to adverse events. We also sought to identify the specific determinants of these transitions and evaluate the prognostic impact of transitioning to the alert state on clinical outcomes.

2. Methods

2.1. Study design

The RetrospEctive Analysis of the Clinical ouTcome of patients with cardiac implantable electronic devices followed with Remote Monitoring (REACT-RM) is a single-center, retrospective cohort study designed to investigate clinical trajectories and outcomes in patients with HF who were implanted with CIEDs and enrolled in the RM program at our Institution between September 2014 and October 2024. The main objectives of the study were to quantify specific transitions from alert states to adverse clinical events and to assess the impact of baseline covariates on such transitions.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee, in compliance with national regulations (Protocol Number: 0019717/25).

2.2. Study population

Eligibility criteria for inclusion in the REACT-RM registry required patients to be ≥18 years of age with a clinical diagnosis of HF, defined according to contemporary guideline criteria [17], due to either ischaemic cardiomyopathy (iCMP) or non-ischaemic cardiomyopathy (NiCMP). Patients were included irrespective of left ventricular ejection fraction, thus encompassing the full spectrum of HF phenotypes. All patients had been implanted with a CIED (either an implantable cardioverter defibrillator [ICD] or a cardiac resynchronization therapy defibrillator [CRT—D]) capable of delivering antitachycardia therapies and calculating multiparametric HF scores.

Patients were also required to have been provided with a RM system compatible with their device. In accordance with institutional practice at our center, RM is routinely activated during the index hospitalization for device implantation.

2.3. Covariates

Baseline covariates were collected at the time of device implantation and RM activation. These included demographic characteristics, type of CIED (ICD or CRT—D), concomitant cardiac conditions, relevant comorbidities, and baseline pharmacological therapy.

All data were extracted from patients' electronic health records by experienced cardiologists and recorded into a dedicated electronic case report form.

Medication data focused on guideline-directed medical therapy (GDMT) for HF, including angiotensin-converting enzyme inhibitors, angiotensin receptor–neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors. Patients were considered to be receiving GDMT if they were prescribed at least three of the aforementioned drug classes at baseline [18].

2.4. Definition of alerts, follow-up and outcomes

All enrolled patients were followed through RM systems from the time of device implantation. We collected data on device-generated alerts triggered by multiparametric HF scores), as defined by each manufacturer's proprietary algorithm. Thresholds used to define multiparametric alerts are detailed in the Supplementary Data (Supplementary Table S1). All alerts were recorded through RM platforms and documented in the patients' electronic health records, ensuring complete traceability regardless of device vendor. Reflecting the real word scenario of this study, alerts were not managed according to predefined protocols; rather, for each alert, a team of electrophysiologists and HF specialists jointly evaluated the patient and determined the appropriate personalized clinical action.

We also collected delivery of appropriate/inappropriate shock therapy [19]. Stored records of electrograms collected before, during and after the episodes were independently reviewed by two expert electrophysiologists for adjudications.

Patients were followed from the date of device implantation until the occurrence of the primary clinical outcome or the end of the follow-up period. For patients who did not experience the primary outcome, the last available date confirming their vital status (e.g., last outpatient visit or hospital admission) was used as the censoring date.

The primary outcomes of the study were all-cause mortality and hospitalization for heart failure (HFH). Outcome data were retrieved from the regional health administrative database, which captures all inpatient and outpatient encounters within the Emilia-Romagna region.

2.5. Statistical analysis

We postulated a Markov, four-state model with six possible transitions. Specifically, all participants entered the initial baseline state at the time of device implantation and RM activation, which was defined as the study entry timepoint. Patients could then transition either to an intermediate state of HF score alert or of HFH (whichever occurred first) or directly to the final absorbing state, defined as the occurrence of all-cause death event. Patients in the intermediate state could subsequently transition to the absorbing state. This defined six possible transitions:

1. Baseline to HF score alert;
2. Baseline to HFH
3. Baseline to death;
4. HF score alert to HFH;
5. HF score alert to death;
6. HFH to death.

We focused on the first occurrence of HF alert or HF hospitalization to maintain a parsimonious and interpretable model structure, given the relatively low number of multiple transitions.

To quantify the effect of baseline risk factors on each transition, we used Cox proportional hazards regression models for each transition. We assumed that each transition was associated with a separate baseline hazard and that covariate effects differed for each transition. The covariates included: age (used as a continuous variable), cardiomyopathy etiology (iCMP versus NiCMP), history of diabetes and chronic kidney disease (CKD) defined by an eGFR <60 mL/min/1.73m^2. The number of covariates included in the model was intentionally restricted in order to avoid overfitting, given the relatively limited number of events observed for some transitions. Variables were selected a priori based on clinical relevance and in light of the increasing recognition of the cardio–kidney–metabolic (CKM) syndrome in HF [20]. A clock-forward approach was used in all models, using time since entry into

the initial state as the time scale. A first sensitivity analysis assessed the robustness of covariate effects under a clock-reset (semi-Markov) approach, where the time scale for each transition was reset to zero upon entry into the current state.

We also performed a second Cox proportional hazards regression to assess the association between HF alert with the risk of adverse outcomes, modeling the HF alert state as a time-dependent covariate. Both univariable and multivariable analyses were performed, the latter adjusted for the covariates listed above. Given the differences among manufacturer-specific HF alert algorithms, we also performed a second sensitivity analysis excluding Abbott/St. Jude devices, whose alert system primarily relies on impedance-based monitoring, in order to assess the robustness of the findings. Due to the large number of tests, all formal comparisons for covariate effects were considered exploratory.

To estimate the expected time spent in each state, we calculated state-entry probabilities and mean state occupation times at 5 years for representative patient profiles. To study the role of covariates included in the model, we defined four HF phenotypes:

- Age 65 years, NiCMP;
- Age 65 years, iCMP;
- Age 65 years, iCMP, diabetes;
- Age 65 years, iCMP, diabetes, CKD.

We also computed the prediction of state-entry probabilities for the same four HF phenotypes assuming an age of 75 years, while keeping all other covariates unchanged. We conducted a last sensitivity analysis, in which the intermediate HF alert state included also the occurrence of appropriate or inappropriate shock therapies, excluding antitachycardia pacing, since pacing is part of intended arrhythmia management and does not represent a failure event.

Results were reported as hazard ratios (HRs) and 95% confidence intervals (CI). All statistical tests were two-sided, with a p-value <0.05 considered statistically significant. Analyses were performed using R version 4.3.1 (R Core Team 2020, Vienna, Austria) using the mstate package [21].

3. Results

3.1. Study population and transitions

Between September 2014 and October 2024 we included in the analysis 511 participants with a median age of 69.9 years [IQR 61.4–77.1] (Table 1). Of these, 20.7% were female; 33.5% were implanted with a CRT—D, 14.1% were implanted in secondary prevention, 49.9% had iCMP. Among the possible comorbidities 68.3% had hypertension, 28.2% diabetes, 13.5% chronic obstructive pulmonary disease, 18.2% CKD and 35.9% had atrial fibrillation. The median left ventricular ejection fraction was 35.0% [IQR 30.0–45.0] and 57.7% of them were treated with GDMT. Results on other treatments are presented in supplementary material (Supplementary Table S2). During a median follow-up of 1.8 years [IQR 0.7–3.9], 60 patients (11.7%) transitioned to an HF score alert state, of whom 6 (10%) and 12 (20%) respectively experienced an HFH and died without a prior HFH. From the baseline group, 29 patients (5.7%) transitioned directly to death and 53 patients (10.4%) had an HFH. Of the 59 total patients who experienced an HFH, 19 (32%) died during follow-up (Fig. 1). Supplementary Fig. S1 reports the estimates for the sensitivity analysis that combined shock and HF score alerts.

Table 1
Baseline characteristic of the REACT-RM cohort.

	Overall $N = 511$
Age, (median [IQR])	69.9 [61.4, 77.1]
Female, N (%)	106 (20.7)
BMI, (median [IQR])	27.3 [24.7, 30.4]
CRT-D (%)	171 (33.5)
CIED manufacture, N (%)	
Medtronic	215 (42.1)
Biotronik	33 (6.5)
Boston	202 (39.5)
Abbott	61 (11.9)
Secondary prevention (%)	72 (14.1)
Hypertension, N (%)	349 (68.3)
Diabetes, N (%)	144 (28.2)
Ischemic CMP, N (%)	255 (49.9)
COPD, N (%)	69 (13.5)
CKD, N (%)	93 (18.2)
Category of CKD, (%)	
IIIa	25 (5.6)
IIIb	26 (5.8)
IV	21 (4.7)
V	10 (2.2)
Atrial fibrillation, N (%)	183 (35.9)
AF type, N (%)	
Paroxismal	54 (31.2)
Persistent	20 (11.6)
Permanent	99 (57.2)
NYHA class, N (%)	
1	79 (15.5)
2	379 (74.3)
3	50 (9.8)
4	2 (0.4)
LVEF, (median [IQR])	35.0 [30.0–45.0]
GDMT, N (%)	290 (57.7)

Legend. AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; CMP, cardiomyopathy; COPD, chronic obstructive pulmonary disease; CRT—D, cardiac resynchronization therapy defibrillator; GDMT, guideline-directed medical therapy; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAD, peripheral arterial disease; y, years.

3.2. Effect of covariates on transitions and predictions

The detailed effects of baseline covariates on transition-specific hazards are shown in Fig. 2. Increasing age was significantly associated with a higher probability of transitioning from the baseline state to both HF score alert and death. Specifically, each 5-year increase in age was associated with a 22% higher risk of HF score alert (HR 1.22, 95% CI 1.06–1.40) and a 47% higher risk of death (HR 1.47, 95% CI 1.17–1.83).

Similarly, iCMP was associated with a 2.6-fold increased risk of death (HR 2.67 [1.07–6.70]), while the presence of diabetes doubled the risk of experiencing an HFH (2.04 [1.15–3.59]). CKD was associated with a twofold increased risk of HF score alert (HR 2.24 [1.22–4.08]) and a 2.8-fold higher risk of HFH (HR 2.80 [1.53–5.12]), but was not significantly associated with death. None of the examined covariates significantly influenced the risk of transitioning from either intermediate state (HF score alert or HFH) to the final absorbing state of death.

The first sensitivity analysis using a clock-reset approach, reported in Supplementary Fig. S2, showed consistent results with the main analysis for the effect of baseline covariates across all transitions. In the sensitivity analysis combining HF score alerts with shock therapies, overall results were consistent with those of the main analysis (Supplementary Fig. S3). Two additional associations emerged that were not observed in the primary model. Increasing age was significantly associated with a higher risk of transition from the alert state to death (HR 1.65, 95% CI 1.15–2.38), and CKD was associated with an increased risk of transition from the alert state to HFH (HR 4.63, 95% CI 1.12–19.19).

3.3. Association between HF alerts with adverse outcome

Among the six postulated transitions, the transition from the HF score alert state to HFH state showed higher rates of events (IR 7.4 per 100 person-years) compared with the transition directly from the baseline to HFH state (IR 4.3 per 100 person-years) (Fig. 1). However, this association was not significant after adjustment for age,

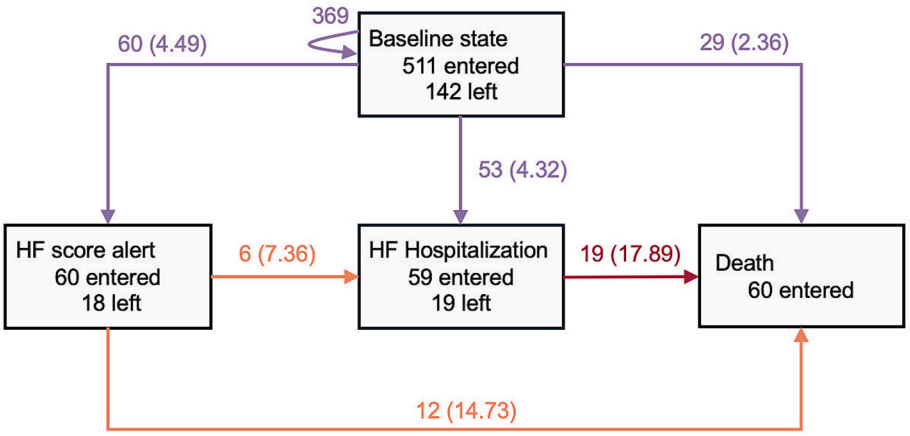

Fig. 1. Transitions from a healthy state to intermediate states and events for all participants.
Data along the arrows represent the number of transitions (incidence per 100 person-years). Entering indicates the number of participants entering each state and leaving indicates the number of participants leaving each state at the end of follow-up. Transitions between states are indicated by arrows.

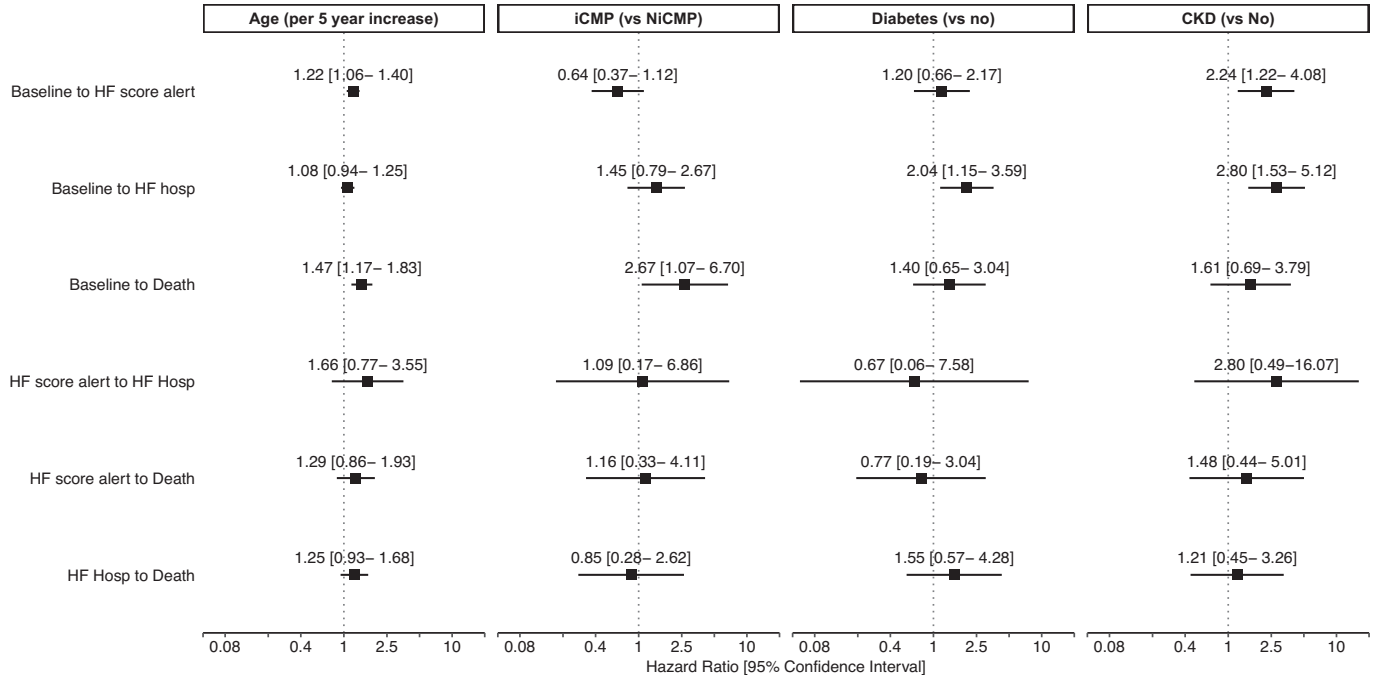

Fig. 2. Forest plots of the association baseline characteristics with transition rates in the multistate model.
Legend. CKD, chronic kidney disease; HF, heart failure; iCMP, ischemic cardiomyopathy; NiCMP, non-ischemic cardiomyopathy.

cardiomyopathy etiology, diabetes and CKD (HR 0.59, 95% CI 0.05–6.30; $P = 0.659$; Table 2).

By contrast, the transition from HF score alert to death showed higher rates of events (IR 14.7 per 100 person-years) compared with the transition directly from the baseline to death (IR 2.4 per 100 person-years) (Fig. 1) and this resulted in a 7-fold association with an increased risk of the event even after adjustment for confounders (HR 6.99, 95% CI 1.89–25.94; $P = 0.004$; Table 2). Consistent results were observed for the sensitivity analysis that combined HF score alerts with shock therapies (Supplementary Fig. S1 and Supplementary Table S3). Similarly, results remained consistent in the sensitivity analysis excluding Abbott/St. Jude devices (Table 2).

Table 2
Multivariable Cox proportional hazards regression analysis for the association of the HF score alert with HFH and death.

	Main analysis		Sensitivity analysis	
	HR [95% CI]	P-value	HR [95% CI]	P-value
Alert (vs no) for HFH	0.59 [0.05–6.30]	0.650	0.61 [0.06–6.70]	0.690
Alert (vs no) for death	6.99 [1.89–25.94]	0.004	7.76 [1.97–30.60]	0.003

Legend. CI, confidence interval; HFH, heart failure hospitalization; HR, hazard ratio.

3.4. State-entry probabilities

We computed the probabilities of being in each state at 3 years for four different HF patient phenotypes. Results are shown in Fig. 3 and Supplementary Table S4.

For a 65-year-old patient with NiCMP, the probability of remaining in the baseline state at 3 years was 82%, while 9% experienced an HF score alert without subsequent events, 5% experienced an HFH, and 4%

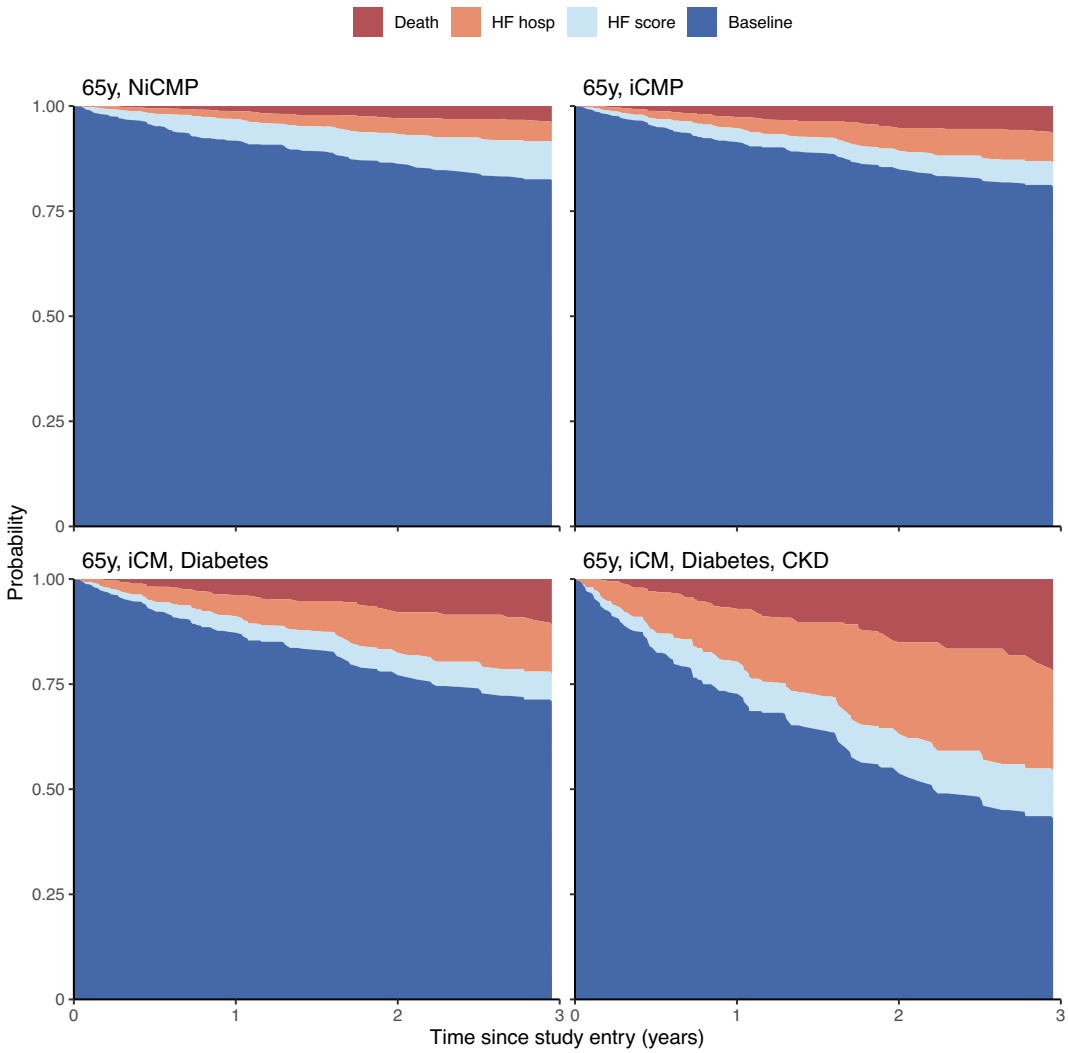

Fig. 3. Stacked predicted state occupancy probabilities with time.
Legend. CKD, chronic kidney disease; HF, heart failure; iCMP, ischemic cardiomyopathy; NiCMP, non-ischemic cardiomyopathy.

died. For patients iCMP, the overall distribution of states was broadly similar, although with a modest increase in adverse events.

The addition of diabetes and CKD led to a stepwise increase in the probability of HFH and death. Specifically, the probability of HFH increased to 12% and 24%, while the probability of death rose to 11% and 22% in patients with iCMP plus diabetes, and iCMP plus diabetes and CKD, respectively. In contrast, the probability of experiencing an HF score alert without subsequent events remained relatively stable across phenotypes.

When older patients were considered (75 years; Supplementary Table S5 and Supplementary Fig. S4), the probabilities of all adverse events further increased across phenotypes. In particular, among 75-year-old patients with iCMP, diabetes, and CKD, only 31% remained in the baseline state at 3 years, 13% experienced an HF score alert without subsequent events, 19% were hospitalized for HF, and 36% died.

4. Discussion

In this single-centre retrospective analysis derived from the REACT-RM registry, we sought to characterize transition rates from a stable clinical state to alert and subsequent adverse events, along with the factors influencing these transitions. Our analysis suggest three main observations: i) several baseline conditions were associated with the probability of different transitions, with CKD being one of the most important factors across all postulated transitions. The interplay of these conditions also markedly affects the predicted probabilities of occupying each clinical state over a 3-year follow-up; ii) HF score alerts marked an increase in the rate of subsequent event of HFH and all-cause death; iii) this association remained statistically significant for all-cause death but was no longer significant for HFH after multivariable adjustment.

RM is recommended for the management of patients with HF implanted with CIEDs [17,22]. In recent years, we observed a steep increase in the number of incoming alerts, which burdens both in-office and remote visits [23]. Therefore, informing clinicians about clinical trajectories of HF patients with CIEDs has several clinical and practical implications. Our multistate analysis allowed us to show, accounting for various transitions, the effect of numerous covariates on each transition. In particular, we observed in this analysis that CKD had a significant impact on different transition rates. This factor is somewhat expected. Indeed, CKD considerably complicates the management of HF patients, making the initiation and subsequent titration of GDMT more difficult [24]. This makes patients more prone to a more pronounced disease trajectory [25–27].

Indeed, we found in our prediction analysis that the addition of CKD to a patient profile with iCMP and common associated conditions (such as diabetes) increased substantially the probability of reaching an adverse state. When different patient phenotypes were compared, the

presence of CKD and diabetes in older patients with iCMP was associated with the highest 3-year death probability (36%), whereas younger patients with NiCMP and no comorbidities had the lowest (4%), with a 82% likelihood of remaining in the baseline state. These results illustrate how clinical profiles shape disease trajectories and may inform daily practice by supporting tailored follow-up and RM strategies according to patient phenotype [28].

Another aspect of our analysis worth noting is that experiencing an HF score alert is associated with a increased risk of HFH and death, but after adjustment only the association with death remained significant. It should be acknowledged that these findings should be interpreted with caution. In particular, the number of HFH occurring after an HF alert was limited, which may have resulted in unstable estimates and insufficient statistical power to detect a meaningful association. Therefore, these results should be considered exploratory and hypothesis-generating. If confirmed in larger cohorts, the observed pattern may appear somewhat paradoxical. Indeed, inconsistent findings have been previously reported: for instance, the IN-TIME trial showed a significant reduction in the composite outcome for patients randomized to the use of RM [10], whereas other trials, such as MORE-CRT [9], failed to demonstrate a significant effect of this approach. Furthermore, a recent meta-analysis that collected data on the effect of telemedicine in HF showed that considering only remote monitoring via CIEDs, there was no significant reduction in the risk of all-cause death (HR 0.84, 95% CI 0.65–1.08; $I^2 = 56\%$) or heart failure (HR 0.92, 95% CI 0.79–1.06) [29].

One possible interpretation is that RM should primarily be viewed as a clinical tool rather than an intervention per se. Its effectiveness likely depends on how the information provided by the monitoring system is integrated into clinical decision-making and subsequent therapeutic optimization, which may partly explain the heterogeneous results observed across trials.

In this perspective, HF score alerts may simply identify patients who are more clinically fragile, with a higher burden of comorbidities and more advanced disease, which could explain their increased risk of adverse events [30]. If confirmed, these alerts could therefore represent an opportunity to identify higher-risk patients who may benefit from closer clinical surveillance and tailored management strategies. However, it is important to consider that alert duration, resolution and recurrence may influence their prognostic value, aspects that we were unable to explore in the current analysis.

Taken together, our results may have potential clinical implications. First, they may help identify subgroups of patients with a higher risk profile who could benefit from closer clinical surveillance. Second, they may support the concept that timely therapeutic optimization could be particularly relevant in these patients. For example, the STRONG-HF [31] trial demonstrated that rapid up-titration of guideline-directed medical therapy can improve outcomes in selected HF populations. Furthermore, in the MANAGE-HF study [32], patients who received HF therapy optimization within two weeks of an initial alert showed a more rapid recovery of the HeartLogic index.

It should be acknowledged, that in our center the management of alerts does not follow a predefined protocol. Rather, patients are managed through a collaborative model involving both HF specialists and electrophysiologists who jointly evaluate alerts and determine the most appropriate clinical actions. As such, our study reflects routine clinical practice in a real-world setting rather than a structured intervention strategy.

While this aspect may limit the external generalizability of our findings, it also provides important information regarding RM alerts in daily practice. Although our analysis cannot directly address treatment strategies, it raises the hypothesis that patients identified through RM alerts may represent a subgroup in whom closer follow-up and therapeutic optimization could potentially be considered. Future prospective studies should specifically evaluate whether early identification of these high-risk patients can translate into improved outcomes through standardized and tailored intervention strategies.

Altogether, these findings highlight the potential of multistate modeling to capture the dynamic nature of HF progression in patients with CIEDs and to generate hypotheses regarding clinically meaningful patient subsets who may benefit from more individualized monitoring and management strategies.

4.1. Strengths and limitations

Our analysis has several strengths: first, the statistical design using multistate models allows detailed evaluation of transition rates and the effect of covariates on each transition. In addition, in our clinical practice, patients are provided with in-hospital RM, allowing thorough observation of the clinical disease course, and our healthcare system, which tracks alerts and events, ensures excellent traceability.

However, several limitations must be acknowledged: first, this is a single-center study, so our results are not necessarily generalizable. Second, the retrospective design does not allow for accounting for all potential residual confounders. Specifically, the multivariable models were adjusted for a limited number of baseline covariates (age, cardiomyopathy etiology, diabetes, and CKD), and therefore residual confounding from other unmeasured or unavailable variables cannot be excluded. Another limitation relates to the alerts we chose, namely shocks and HF scores. For shocks, we decided to evaluate only shocks and not antitachycardia pacing, because the latter is part of therapeutic strategies to resolve arrhythmias and prevent shocks, which is an intended practice. Shocks, on the other hand, typically occur when other strategies fail. For HF scores, we do not have data regarding alert resolution, so we cannot assess false positives or the in-alert time. Additionally, as noted in the Methods, we focused on the first occurrence of each HF alert or HF hospitalization, rather than recurrent events. While multiple alerts and hospitalizations are clinically important and can impact prognosis, this simplification was necessary to maintain a parsimonious and interpretable model structure. Future studies with larger datasets could incorporate recurrent events to more fully capture patient trajectories and the cumulative impact of repeated HF episodes. Lastly, we do not have data on programming of devices which may also influence subsequent clinical outcome [33].

5. Conclusions

In conclusion, using a multistate model, we described potential transitions in patients with HF and CIEDs followed with RM and observed the effects of different covariates on transition rates. We also found that HF score alerts were associated with all-cause death. These findings have important clinical implications for personalizing follow-up via RM and for identifying high-risk patient profiles.

CRediT authorship contribution statement

Davide Antonio Mei: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Jacopo Francesco Imberti:** Conceptualization. **Kevin Serafini:** Investigation, Data curation. **Marco Vitolo:** Software. **Niccolò Bonini:** Conceptualization. **Silvia Gaspard:** Data curation. **Francesco Sbarra:** Data curation. **Igor Diemberger:** Methodology. **Matteo Ziacchi:** Investigation. **Marco Zuin:** Data curation, Conceptualization. **Matteo Bertini:** Formal analysis, Data curation, Conceptualization. **Giuseppe Boriani:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

GB: is the Principal Investigator of the ARISTOTELES project (Applying ARtificial Intelligence to define clinical trajectorieS for personalized predicTiOn and earlydeTEction of comorbidity and muLtimorbidity pattErnS) that received funding from the European Union

within the Horizon 2020 research and innovation program (Grant N. 101080189) and reports small speaker fees from Bayer, Boston, BMS, Daiichi, Sanofi and Janssen outside the submitted work.

MZ received speaker's fees from Abbott, Boston Scientific, Biotronik, Medtronic, Edwards Lifesciences.

The other authors do not have conflict of interests to report

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2026.134458.

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