


From PDC to integral quantitative metrics: an innovative approach to assessing adherence to combination pharmacotherapy in outpatient practice

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Abstract

Introduction: Current methods for assessing adherence to combination therapy based on aggregated measures (e.g., PDC, proportion of days covered) poorly capture treatment intensity and sustainability over time. We attempted to describe adherence trajectories for combination therapy using integral metrics. Aim: To develop a set of integral metrics analogous to key pharmacokinetic (PK) parameters – area under the concentration-time curve (AUC, area under the curve), maximum concentration (C_{max}), and time to maximum concentration (T_{max}) – to assess adherence to combination therapy as time-based exposure on the PDC methodology among outpatients.

Materials and Methods: As a specific example and a substrate for method development, we used results from a retrospective pharmacoepidemiologic cohort study of patients with heart failure (HF) who had experienced an acute myocardial infarction. Data were extracted from the Unified Medical Information and Analytical System of Moscow (Russia). Three patients with a follow-up duration of ≥ 24 months were randomly selected. We analyzed benefit-covered electronic prescription fills for key HF therapy classes and calculated adherence for each class using PDC across four half-year intervals. We constructed a stepwise trajectory of combination therapy as the function $N(t)$, where N is the number of therapy classes for which the patient was covered at a given time point based on dispensed supply (accounting for days' supply and overlaps), and t is follow-up time. By analogy with the "concentration-time" curve, we considered $N(t)$ as a dynamic "therapy class coverage curve" and used it to calculate PK-analog adherence metrics: exposure to actually dispensed combination therapy, AUC $N(t)$ (class-months); normalized AUC_{norm} (0-1); C_{max} $N(t)$ (number of classes); and T_{max} $N(t)$ (months). In addition, we set a target threshold of $N(t) \geq 3$, determined the time to first attainment, T_{opt} $N(t)$, and calculated the time (or proportion of time) with $N(t) \geq k$, denoted as TN $(t) \geq k$. We also quantified therapy "losses" between intervals based on a decrease in the modal value of $N(t)$ and failure to reach the threshold over the follow-up period.

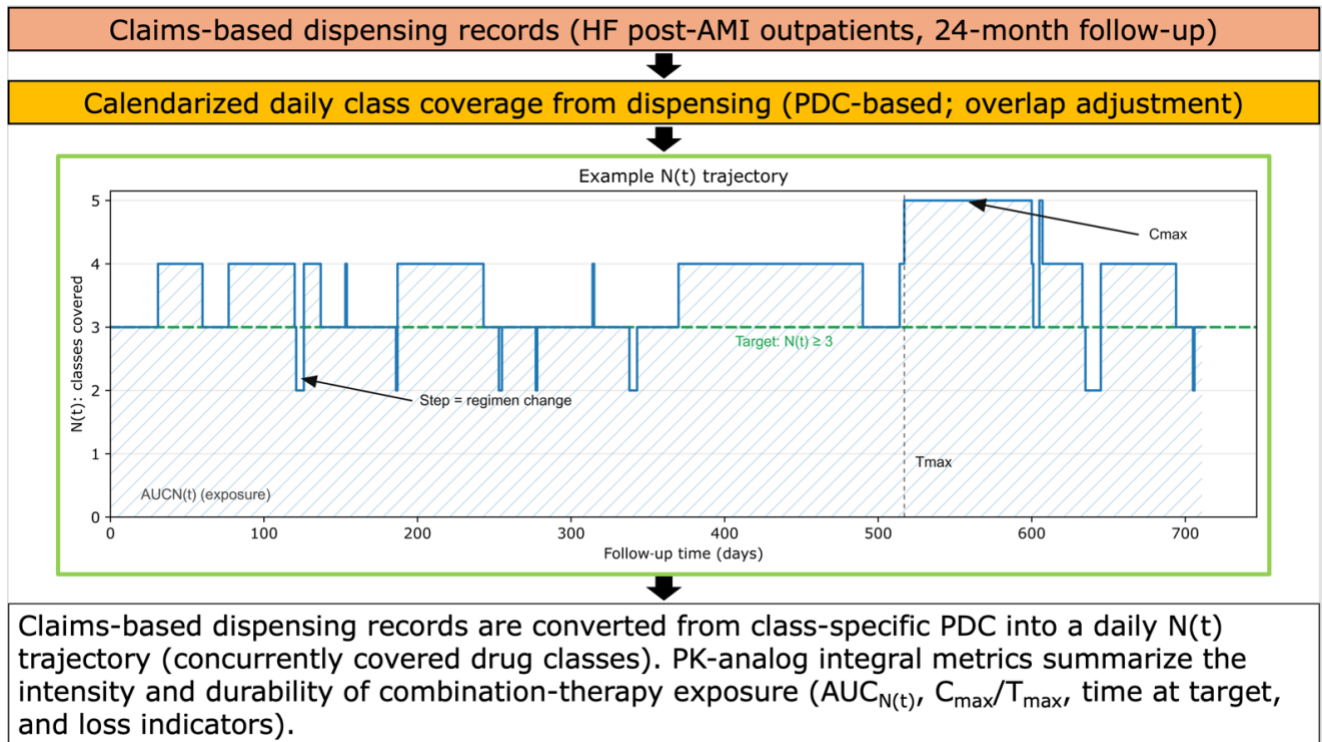
Results: AUC $N(t)$ values were 26.0, 87.37, and 36.67 class-months, and AUC_{norm} values were 0.27, 0.74, and 0.39 in patients with internal IDs 13, 39, and 110, respectively. The proportion of time with $N(t) \geq 3$ was 0.079, 0.96, and 0.23 (1.9, 22.9, and 5.5 months), and the modal $N(t)$ values by half-year corresponded to patterns of 2→0, 3→3→4→4, and 3→2→1→0. The



numeric profiles were consistent with the stepwise $N(t)$ trajectories and reflected three distinct adherence patterns.

Conclusion: The proposed PK-associated approach enabled quantification of complex adherence trajectories for combination therapy in HF by representing them as an interpretable set of integral numeric metrics. These metrics characterize time-based exposure to combination therapy while accounting for adherence. The results support the conceptual validity of the method and may serve as a basis for further studies of its prognostic value.

Graphical Abstract



Keywords

heart failure; acute myocardial infarction; medication adherence; proportion of days covered (PDC); combination therapy; treatment trajectories; integral metrics of combination-therapy exposure; pharmacokinetic approach

Introduction

In real-world clinical practice, adherence to combination pharmacotherapy is traditionally assessed using pharmacoepidemiologic approaches based on prescription data and aggregated measures such as PDC (proportion of days covered), MPR (medication possession ratio), and persistence. However, because these measures are averaged over long follow-up periods, they poorly reflect within-period treatment-use trajectories and concurrent adherence across multiple drug classes.

As a result, complex adherence trajectories are “compressed” into a single aggregated percentage, which complicates assessment of how real-world pharmacotherapy affects disease course and outcomes. In the context of the ongoing discussion of disease-modifying therapy, where the focus is shifting toward the intensity and durability of treatment use (Dixit et al. 2021; Malgie et al. 2023), it is reasonable to apply an innovative approach that transfers pharmacokinetic (PK) concepts to the description of adherence trajectories for multicomponent therapy. Metrics such as the area under the concentration-time curve (AUC, area under the

curve), maximum concentration (C_{max}), and time to maximum concentration (T_{max}) can be adapted to describe the dynamics of combination-treatment implementation.

This approach makes it possible to represent the number of active drug classes and their combinations over time as an adherence exposure curve for combination therapy. It also enables the development of new integral metrics derived from that curve: the AUC of combination-therapy exposure, time to reach an optimal therapy level, the maximum therapy level (number of drug classes), and the proportion of treatment time at the target (maximum) level. These metrics provide both quantitative and qualitative characterization of adherence to prescriber recommendations at the individual-patient level.

The aim: To develop a set of integral metrics analogous to key pharmacokinetic (PK) parameters – area under the concentration-time curve (AUC, area under the curve), maximum concentration (C_{max}), and time to maximum concentration (T_{max}) – to assess adherence to combination therapy as time-based exposure on the PDC methodology among outpatients.

Materials and Methods

Study design

This work was primarily methodological and aimed to develop formal metrics describing the time-varying implementation of combination therapy based on adherence data. To develop and illustrate the method, we analyzed longitudinal adherence trajectories to combination therapy in three patients. These patients were randomly selected from the database of a retrospective pharmacoepidemiologic cohort study of patients with chronic heart failure (HF) after acute myocardial infarction (AMI) (Fitilev et al. 2024, 2025).

Data sources

Patient data were obtained from the Unified Medical Information and Analytical System (UMIAS) of Moscow (Russia). We recorded information on prescribing and on the actual dispensing of benefit-covered electronic prescriptions for medications.

Study population

The analysis included three randomly selected patients with internal IDs 13, 39, and 110 who had experienced AMI, were diagnosed with HF, and had data on prescribing and actual dispensing of benefit-covered prescriptions for the main pharmacotherapy classes. Eligible patients had at least 24 months of follow-up after the index event.

Therapy classes and initial adherence metrics

We considered the key HF therapy classes: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), angiotensin receptor–neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors).

Medication adherence was assessed by calculating PDC for each drug class using the following formula:

$$PDC = \frac{\text{number of days covered by dispensed prescriptions}}{\text{total number of days in the measurement period}} \times 100\%.$$

The observation period for PDC calculation was defined as the interval from the index date to the corresponding time point (6, 12, 18, and 24 months). The PDC measurement window was bounded by the date of the first dispensing of the medication under a benefit-covered prescription and the relevant time point.

When dispensings overlapped, the remaining supply from the previous dispensing was carried forward to subsequent days (“overlap adjustment”). Thus, we used a PDC calculation with adjustment for overlapping dispensing dates (Fitilev et al. 2024).

Construction of adherence trajectories for combination therapy

For each patient, based on PDC data over the measurement period, we generated: (1) a Gantt chart illustrating, in days, the duration of episodes of use of the key therapy classes and the gaps between them; (2) a heat map of the patient’s medication coverage for individual classes and for their combination, aggregated by weeks; and (3) a step plot of the daily coverage volume for the key drug classes.

Calculation of PK-analog metrics

The adherence trajectory for combination therapy was described using the function $N(t)$, where N denotes the number of key pharmacological classes available concurrently (on hand), and t denotes the calendar day of follow-up. $N(t)$ encoded the multi-component nature of therapy over time and captured transitions between regimens with less and more complete combination therapy (e.g., below vs above the threshold $N(t) \geq 3$). By analogy with classical pharmacokinetics, $N(t)$ was treated as an analogue of the concentration–time curve (instead of drug concentration, we considered the number of classes concurrently available over time).

An analogue of the area under the pharmacokinetic concentration–time curve was $AUCN(t)$, the total area under the $N(t)$ curve over the observation period, interpreted as the integral exposure to the combination therapy actually implemented. The value of $AUCN(t)$ was directly proportional to the number of drug classes available concurrently and was calculated as the sum, across all time segments, of the product of the number of classes available in each segment and its duration ($AUC_{N(t)} = \sum N_i \times \Delta t_i$).

To improve comparability of $AUCN(t)$ across patients, it was normalized to its theoretically maximal value under perfect adherence. Thus, the normalized AUC_{norm} ranged from 0 to 1 and indicated what fraction of the “ideal” multicomponent–therapy exposure a patient had.

As an analogue of C_{max} in pharmacokinetics, we proposed the metric $C_{max}N(t)$, defined as the maximum value of $N(t)$, i.e., the greatest number of key drug classes that were available concurrently on at least one day of follow-up. The time of its first attainment was defined as $T_{max}N(t)$; conceptually, it corresponded to T_{max} on a PK curve and allowed us to distinguish early versus late escalation to the most complete regimen. In addition, a clinical target adherence threshold was specified ($N(t) \geq k$, primarily $k=3$); for this threshold, we calculated the time to first attainment $T_{opt}N(t)$ and the time spent at a level not below the threshold ($TN(t) \geq k$). These characteristics were considered analogous to “time in therapeutic range,” but applied not to the concentration of a single drug, rather to the completeness of the implemented combination of classes.

To account for the direction of changes in combination therapy over time, we described indicators of adherence “losses”: a decrease in the modal value of $N(t)$ between adjacent 6-month intervals (e.g., $3 \rightarrow 2 \rightarrow 1 \rightarrow 0$ or $3 \rightarrow 2 \rightarrow 1 \rightarrow 0$) and failure to achieve the target level $N(t) \geq k$ over the entire observation period.

Given the pilot nature of the study, the statistical analysis was intentionally limited to descriptive methods. PK-analog metrics were presented as absolute values, summary tables, and various types of plots, without formal hypothesis testing or modeling of associations with clinical outcomes. The main goal of the analysis was to demonstrate the interpretability and internal consistency of the proposed PK metrics with visually distinguishable adherence–trajectory patterns, rather than to assess their prognostic value.

Statistical analysis

In view of the pilot and predominantly methodological design of the study, the statistical analysis was deliberately confined to descriptive approaches. The proposed pharmacokinetic-analog adherence metrics were reported as absolute values and summarized using tabular and graphical trajectory-based representations, without formal hypothesis testing or the development of models evaluating their association with clinical outcomes. This strategy was chosen to establish the conceptual interpretability and internal consistency of the proposed metric framework.

Software

All computations and visualizations were performed in Python 3.13.2 (packages: dataclasses, datetime, calplot, os, matplotlib, numpy, pandas, pathlib, re, typing).

Results

In the first step, we analyzed adherence trajectories for combination therapy in patients with heart failure (HF), which are presented in Figures 1–3.

Figure 1 shows Gantt charts illustrating the duration of use of the main HF therapy classes in three patients over the follow-up period. Episodes of continuous coverage by each class are shown as green bars, and gaps lasting ≥ 7 days are indicated by red hatching. The charts allow visual assessment of the persistence of combination therapy, as well as the frequency and magnitude of gaps in the use of individual classes for each patient.

Particular attention should be paid to the chart for patient 39 (2024-04 to 2024-06), where two drug classes that should not be used concomitantly (ACEi/ARB and ARNI) appeared in the combination-therapy coverage trajectory. A detailed review of the source medical records revealed that the ACEi that had already been obtained was discontinued and a new agent, an ARNI, was prescribed.

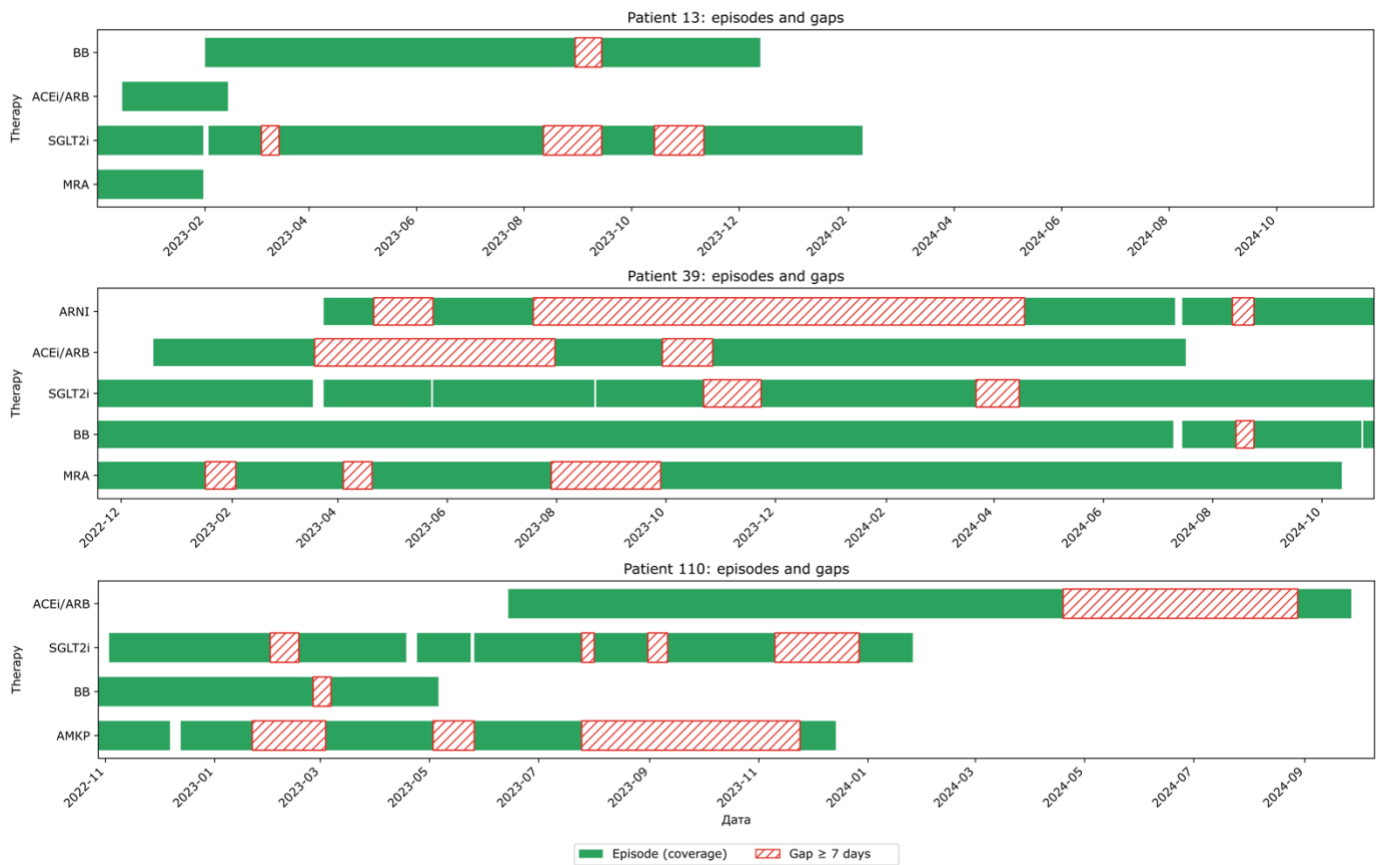


Figure 1. Gantt charts illustrating, in days, the duration of episodes of use of key HF therapy classes and the gaps between them in patients with HF post-AMI. **Note:** HF – heart failure; AMI – acute myocardial infarction; ACEi – angiotensin-converting enzyme inhibitors; ARB – angiotensin II receptor blockers; ARNI – angiotensin receptor–neprilysin inhibitor; BB – β -blockers; MRA – mineralocorticoid receptor antagonists; SGLT2i – sodium–glucose cotransporter 2 inhibitors.

Figure 2 presents heat maps of weekly aggregated medication coverage for three patients for individual classes and for their combination ($k \geq 3$). Color intensity reflects the degree of coverage (0 to 1) within a given week: patient 13 had short and disconnected episodes of combination therapy, patient 39 had sustained and long-term coverage with most classes and periods of a full combination of ≥ 3 -4 classes, whereas patient 110 showed marked fragmentation with alternating weeks of complete absence of coverage.

The step plots in Figure 3 show that the value of the function $N(t)$ (the number of key therapy classes available concurrently) remains constant within an interval and changes in a stepwise manner at the time of an event (initiation, discontinuation, addition, or removal of a class). This representation clearly visualizes real “stairs” in treatment-regimen changes: exactly when a class was added or discontinued, and how long the patient remained at each $N(t)$ level. This pattern highlights the discrete nature of patient decisions. The figure shows stepwise $N(t)$ trajectories over 24 months post-AMI: patient 13 exhibited an early decrease in adherence intensity followed by discontinuation of combination therapy; patient 39 showed relatively high and increasing adherence with episodes of short gaps; patient 110 demonstrated marked adherence fragmentation with frequent changes in the number of drugs and prolonged periods of de-escalation.

A comparison of the three patients’ adherence trajectories to the prescribed treatment showed that the visually distinguishable “stairs” of treatment-regimen changes differed substantially in duration, maximal level, and time to achieving combination therapy: from low and short-lived implementation of the main drug classes (patient 13), through moderate but unstable adherence (patient 110), to early and relatively sustained optimization with high total exposure (patient 39). It was precisely this initial visual analysis of $N(t)$ trajectories and their obvious resemblance to pharmacokinetic concentration–time curves that motivated us to develop PK-analog integral metrics of adherence to combination therapy ($AUCN(t)$, AUC_{norm} , $C_{maxN(t)}$, $T_{maxN(t)}$, $ToptN(t)$, $TN(t) \geq k$, and “loss” indicators). These metrics made it possible to formalize these intuitive clinical patterns and move from descriptive visualization to a formal quantitative analysis.

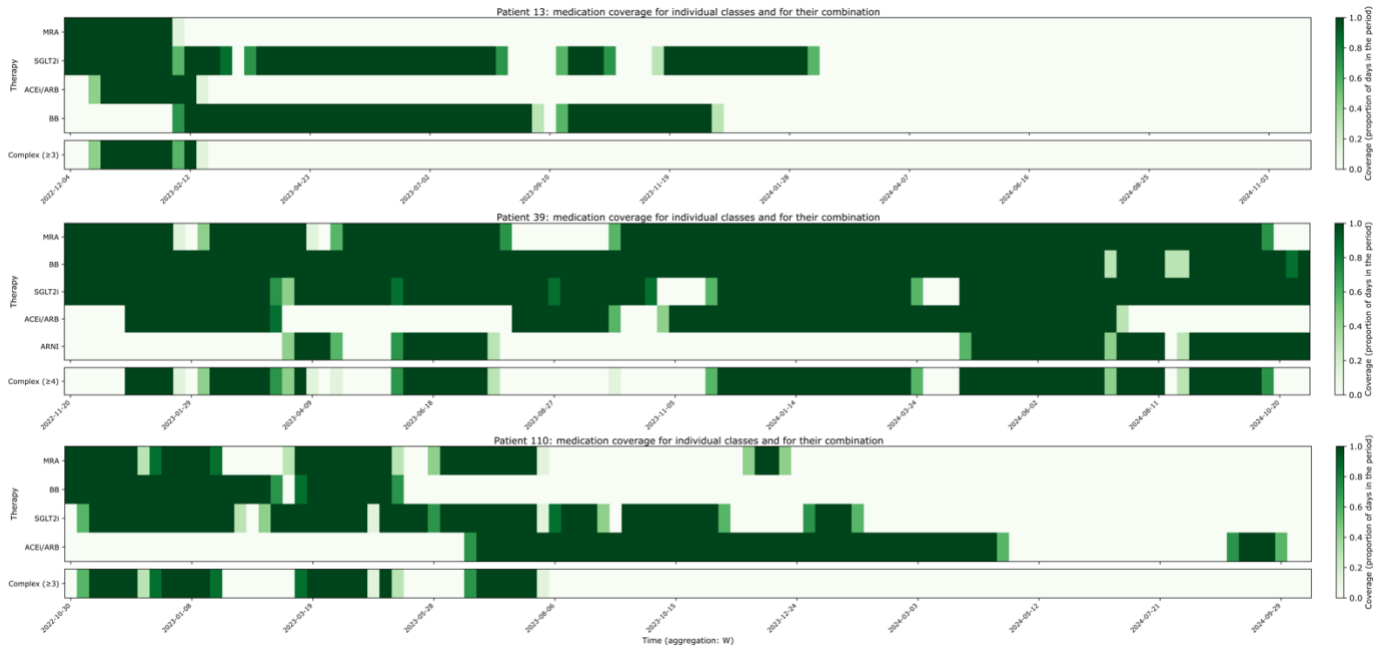


Figure 2. Heat maps of medication coverage in patients with HF post-AMI for key therapy classes and their combination ($k \geq 3$), aggregated by weeks. **Note:** HF – heart failure; AMI – acute myocardial infarction; ACEi – angiotensin-converting enzyme inhibitors; ARB – angiotensin II receptor blockers; ARNI – angiotensin receptor–neprilysin inhibitor; BB – β -blockers; MRA – mineralocorticoid receptor antagonists; SGLT2i – sodium–glucose cotransporter 2 inhibitors.

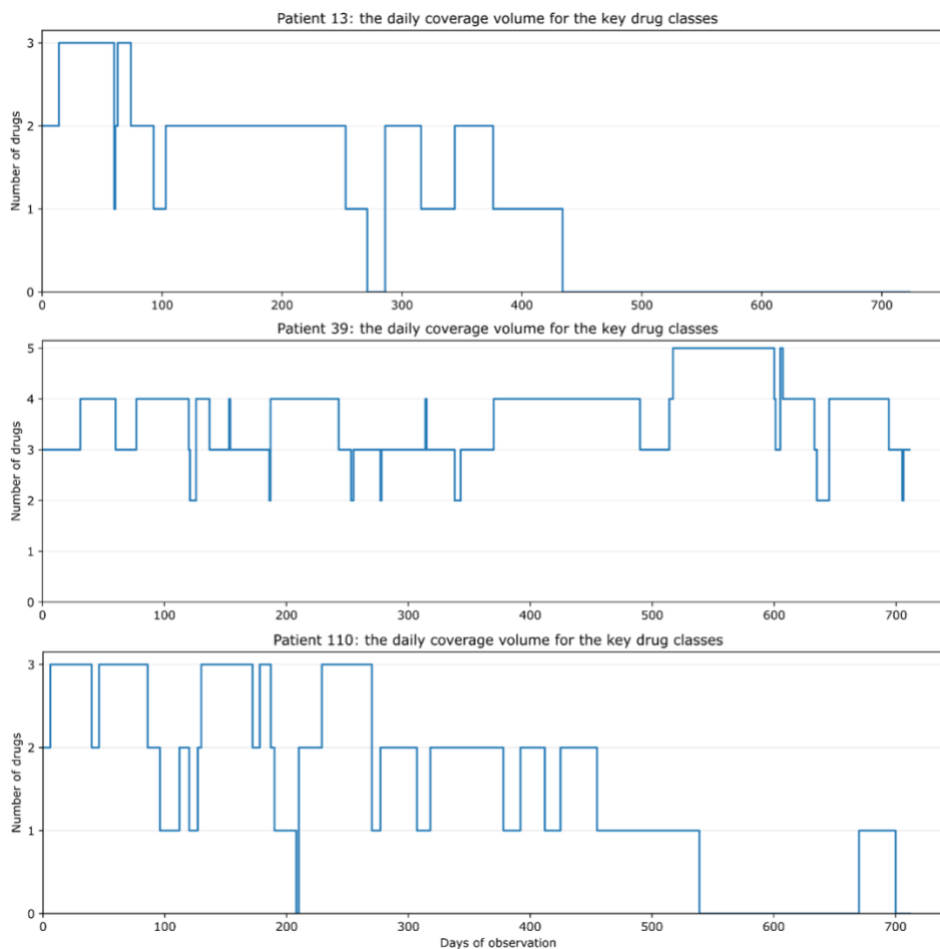


Figure 3. Step plots of the daily coverage volume for key therapy classes in three patients with HF post-AMI. **Note:** HF – heart failure; AMI – acute myocardial infarction; ACEi – angiotensin-converting enzyme inhibitors; ARB – angiotensin II receptor blockers; ARNI – angiotensin receptor–neprilysin inhibitor; BB – β -blockers; MRA – mineralocorticoid receptor antagonists; SGLT2i – sodium–glucose cotransporter 2 inhibitors.

Stage 2 involved the development of PK-analog integral metrics

Two levels of parameters were used: class-level (classes included in combination therapy) and segment-level (0-6, 6-12, 12-18, and 18-24 months). For three patients (13, 39, and 110), we constructed daily $N(t)$ functions and then calculated PK-analog metrics (Table 1).

Table 1. PK-analogue metrics of combination therapy patients

| Metric | Patient | | |
|--|--------------|--------------|---------|
| | 13 | 39 | 110 |
| N_{0-6} (number of classes) | 2 | 3 | 3 |
| N_{6-12} | 2 | 3 | 2 |
| N_{12-18} | 0 | 4 | 1 |
| N_{18-24} | 0 | 4 | 0 |
| $AUC_{N(t)}$ (class-months) | 26.0 | 87.37 | 36.67 |
| AUC_{norm} | 0.27 | 0.74 | 0.39 |
| $C_{maxN(t)}$ | 3 | 5 | 3 |
| $T_{maxN(t)}$ | not observed | not observed | 0-6 mo |
| $T_{optN(t)} (\geq 3 \text{ classes})$ | 0-6 mo | 0-6 mo | 0-6 mo |
| $T_{N(t) \geq 3}$ (proportion) | 0.079 | 0.96 | 0.23 |
| $T_{N(t) \geq 3}$ (months) | 1.9 | 22.9 | 5.5 |
| Therapy losses [†] | 2→0 | none | 3→2→1→0 |
| Achieved ≥ 3 classes | Yes | Yes | Yes |

Note: [†]Therapy losses indicate transitions between the model time segments (a decrease in $N(t)$ between adjacent observation intervals). PK-analogue metrics – pharmacokinetic analogue metrics. N_{0-6} , N_{6-12} , N_{12-18} , and N_{18-24} are the number of key drug classes available concurrently within the 0-6-, 6-12-, 12-18-, and 18-24-month intervals, respectively. $AUC_{N(t)}$ (class-months) is the area under the $N(t)$ curve over 24 months, and AUC_{norm} is the normalized $AUC_{N(t)}$ (as a fraction of the maximum possible number of class-months over 24 months). $C_{maxN(t)}$ is the maximum observed $N(t)$ value (the peak number of classes available concurrently), and $T_{maxN(t)}$ is the time interval in which $C_{maxN(t)}$ is observed. $T_{optN(t)} (\geq 3 \text{ classes})$ denotes the intervals in which $N(t) \geq 3$. $T_{N(t) \geq 3}$ (proportion) is the proportion of follow-up time with $N(t) \geq 3$, and $T_{N(t) \geq 3}$ (months) is the corresponding absolute duration in months.

The PK-analog metrics consistently captured differences in adherence across the three patients. Exposure to the combination therapy actually implemented ($AUC_{N(t)}$ and AUC_{norm}) was minimal in patient 13 (26 class-months; 0.27) and maximal in patient 39 (87.37 class-months; 0.74), with patient 110 – in between (36.67 class-months; 0.39). This corresponded to a short, long, and moderate-area $N(t)$ “plateau,” respectively.

The highest peak level of coverage with multi-component therapy was achieved by patient 39 ($C_{maxN(t)}=5$), whereas in patients 13 and 110 the maximum was limited to three classes. In patient 110, the peak value occurred in the 0-6-month interval, which coincided with the early “peak” in the step plot reflecting the adherence trajectory.

Time at the target level $N(t) \geq 3$ also differed substantially: patient 39 spent almost the entire follow-up period at this level ($T_{N(t) \geq 3}=0.96$; 22.9 months), patient 110 – about one quarter of the time (0.23; 5.5 months), and patient 13 – a minimal proportion (0.079; 1.9 months). This was consistent with the visual pattern: a sustained above-threshold “plateau” in patient 39, a brief reach of the threshold in patient 13, and a gradual stepwise decline in patient 110. Therapy-loss indicators complemented this picture: patient 39 had no losses, patient 13 showed an abrupt drop (2→0), and patient 110 exhibited stepwise attrition of combination therapy (3→2→1→0).

The combination of these indicators made it possible to distinguish three patterns of combination-therapy implementation: (1 – patient 13) early discontinuation after an initial partial combination, (2 – patient 39) sustained full implementation of combination therapy, and (3 – patient 110) stepwise attrition of an initially more complete regimen.

Thus, the proposed set of PK-analog metrics not only provided a quantitative description of adherence trajectories, but also yielded clinically interpretable patterns of real-world pharmacotherapy.

Discussion

In this study, we propose a two-level approach to describing adherence to combination therapy in HF. At the first level, we introduced a graphically presented function $N(t)$ that reflects the number of concurrently active classes of disease-modifying therapy at each time point. This format aligns the method with trajectory-based approaches to adherence assessment, including those based on group-based trajectory modeling (Alhazami et al. 2020; Chen et al. 2024; Hou et al. 2025), but differs fundamentally in that it encodes the multi-component nature of treatment from the outset. The unit of analysis in our methodology is not an individual medication and not PDC for each class, but the integrated number of implemented classes on each day of follow-up. This makes it possible to directly capture whether a patient is in a “full” or “truncated” state of coverage with combination therapy and how often the patient transitions between these states.

At the second level, the trajectory of the $N(t)$ function was transformed into a compact set of PK-analog metrics ($AUCN(t)$, AUC_{norm} , $C_{max}N(t)$, $T_{max}N(t)$, $T_{opt}N(t)$, $T_{\geq k}N(t)$, and “loss” indicators between half-year periods), which formed a trajectory feature vector that is convenient for use in regression and prognostic models. This is clearly illustrated by the identified patterns: in a patient with sustained multi-component therapy, a high AUC_{norm} , absence of late “losses,” and a long $TN(t) \geq 3$ quantitatively capture the visual $N(t)$ plateau at the level of 3–4 classes. In contrast, in patients with de-escalation ($2 \rightarrow 0$ or $3 \rightarrow 2 \rightarrow 1 \rightarrow 0$), a lower AUC_{norm} , an early $T_{max}N(t)$ and/or $T_{opt}N(t)$, and a cascade of “losses” reflect the descending staircase of the $N(t)$ function and the reduced time at the target level.

Classic PDC and MPR measures computed for individual drugs or classes answer the question, “What proportion of days was the patient on this specific class?” (Fitilev et al. 2024). This is useful for assessing coverage with individual therapy components, but it poorly reflects two critically important aspects of combination treatment: (1) how long the patient was concurrently on ≥ 3 –4 key classes; (2) and how exactly the completeness of this combination changed over time (escalation, stability, de-escalation, fragmentation).

By contrast, the proposed PK-based approach addresses precisely these questions. $AUCN(t)$ and AUC_{norm} characterize the total exposure to a multi-component regimen (“how long and how completely the patient was on combination therapy”), $TN(t) \geq k$ captures the time spent at the clinically targeted level ($N(t) \geq 3$), and the half-year “loss” cascade makes it possible to distinguish sustained from deteriorating regimens. As a result, the method does not duplicate PDC as yet another adherence index; rather, it complements it by capturing a different facet of the phenomenon. Specifically, the focus shifts from “the number of prescription-covered days for each class” to evaluating the “quality” and duration of exposure to combination therapy.

This separation of levels ($N(t)$ as a dynamic trajectory of multi-component treatment and PK metrics as its compact numerical representation), together with a more targeted approach than PDC, makes the method both methodologically transparent and intuitive for clinicians who are accustomed to thinking in terms of exposure, C_{max} , T_{max} and “time at target.”

Clearly, patients with a “sustained and increasing” multi-component therapy pattern can be considered a reference group for analyzing associations between exposure to disease-modifying therapy and outcomes, whereas patterns with de-escalation can be viewed as a target population for interventions (management of adverse effects, educational programs, and organizational measures to support the treatment regimen) (Chien et al. 2025; Hou et al. 2025). In future, using PK metrics in longitudinal cohort and interventional studies will make it possible to test whether $AUCN(t)$ and $TN(t) \geq k$ are associated with survival, hospitalizations, and myocardial remodeling better than classic PDC-like measures.

At the same time, the proposed approach has a number of limitations. First, we treat all classes as having equal “contribution” to the AUC, whereas their effects on outcomes may differ; this may require developing metrics with differentiated weights for specific classes or doses. Second, the analysis was conducted in a single cohort of patients with HF, which may limit the generalizability of the results to other populations and clinical contexts. Third, reconstruction of adherence trajectories to combination therapy was based on claims-based dispensing records and may not fully reflect actual medication intake. Finally, we did not examine a number of potentially important factors (e.g., socioeconomic characteristics, cognitive status, etc.) that may influence therapy-implementation patterns.

Conclusion

The proposed PK-associated approach made it possible to quantify complex adherence trajectories to combination therapy in patients with heart failure by representing them as an interpretable set of integral exposure metrics for the therapy actually implemented. The

developed PK-analog measures (AUCN(t), AUCnorm, CmaxN(t), TmaxN(t), ToptN(t), TN(t)≥k, and “loss” indicators) systematically described multiclass adherence over time and complemented traditional static indicators that focus on individual drugs or averaged values. An illustrative analysis of three contrasting trajectories showed that these metrics captured clinically meaningful patterns of combination-therapy use and may serve as summary measures for subsequent prognostic models and comparative studies of treatment strategies. The results support the conceptual validity of the method and indicate the promise of further evaluation of its prognostic value in larger samples and in clinical-outcome models.

Additional Information

Conflict of interest

The authors declare that they have no conflicts of interest.

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Data availability

All of the data that support the findings of this study are available in the main text.

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