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ORIGINAL RESEARCH

Comparison of Quadruple Therapy Sequencing Strategies for Heart Failure With Reduced Ejection Fraction

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BACKGROUND: Guidelines unanimously recommend quadruple therapy for patients with heart failure with reduced ejection fraction (HFrEF), yet direct comparative evidence is lacking to recommend a specific order of initiating and titrating these agents (or "sequencing strategy"). In the absence of randomized evidence, we aimed to compare the 1-year efficacy and harms of proposed HFrEF quadruple therapy sequencing strategies using a microsimulation model.

METHODS: We conducted a microsimulation study to compare 6 different HFrEF medication sequencing strategies (emulating the range of conventional, 2-drug, and rapid or simultaneous strategies), each with 2 versions (twice-weekly/weekly medication adjustments), applied to treatment-naïve outpatients with HFrEF. We modeled death; total heart failure hospitalization (including recurrent events); the composite of death or first heart failure hospitalization; and adverse drug events (bradycardia, hyperkalemia, hypotension, and renal impairment) at 1 year.

RESULTS: At 1 year, an estimated 15.3 per 100 patients died without treatment compared with 6.9 per 100 patients with the conventional sequence adjusted biweekly, and 5.2 to 6.4 per 100 patients with other sequencing strategies. The incidence of heart failure hospitalization decreased from 31.5 per 100 patients without treatment to 11.4 per 100 patients with conventional sequencing adjusted biweekly, and 7.3 to 9.4 per 100 patients with other strategies. The cumulative incidence of total adverse drug events per 100 patients was 14.2 to 16.0 across sequencing strategies.

CONCLUSIONS: For treatment-naïve outpatients with HFrEF, sequencing strategies that started 2 to 4 medications on the first visit, followed by titration biweekly or weekly, were associated with lower risk of death and heart failure hospitalization, and similar risk of treatment-related adverse events, at 1 year compared with conventional sequencing.

Key Words: heart failure ■ implementation ■ pharmacotherapy ■ sequencing ■ simulation

Pharmacotherapy consisting of "quadruple therapy" with a renin–angiotensin system inhibitor (ideally an angiotensin receptor blocker–neprilysin inhibitor [ARNI]), β blocker, mineralocorticoid receptor antagonist (MRA), and sodium–glucose cotransporter 2 inhibitor (SGLT2I) is the cornerstone of management of heart failure (HF) with reduced ejection fraction (HFrEF).[1] Each of these medication classes is supported by evidence from randomized controlled trials (RCTs) demonstrating clinically important reductions in death and HF hospitalizations added to the standard of care of the era in which the RCTs were conducted.[2] International clinical practice guidelines unanimously recommend quadruple therapy, yet none has proposed a specific order of initiation and titration (or "sequencing strategy") of these agents, reflecting

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CLINICAL PERSPECTIVE

What Is New?

- Various approaches can be taken to initiate and titrate guideline-directed medical therapy for heart failure with reduced ejection fraction ("sequencing strategies"), but these have never been compared head-to-head in a randomized trial.
- In this microsimulation study comparing 12 different sequencing strategies for heart failure with reduced ejection fraction, 1-year risk of death and heart failure hospitalization decreased with a greater number of medications initiated on the first visit, plateauing at 2 medications started on the first visit.

What Are the Clinical Implications?

- More rapid or intensive sequencing strategies to implement quadruple therapy for heart failure with reduced ejection fraction improve outcomes compared with slower approaches but with diminishing returns beyond 2 medications started on the first visit.

Nonstandard Abbreviations and Acronyms

ARNI	angiotensin receptor blocker–neprilysin inhibitor
HFrEF	heart failure with reduced ejection fraction
MRA	mineralocorticoid receptor antagonist
SGLT2I	sodium–glucose cotransporter 2 inhibitor
SOLVD	Studies of Left Ventricular Dysfunction
STRONG-HF	Safety, Tolerability, and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies

the lack of direct evidence comparing different sequencing strategies.[1]

In the absence of evidence-informed recommendations, several groups have proposed alternative HFrEF pharmacotherapy sequencing strategies, incorporating practical and theoretical considerations, including ease-of-use, additive effects on efficacy outcomes, and subtractive effects on safety outcomes.[3–7] None of these sequencing strategies have been prospectively compared with each other or to a conventional sequencing strategy. The STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) trial is the only RCT evaluating HF pharmacotherapy sequencing strategies, and was conducted in the era where triple therapy (angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker, β blocker, and MRA) was the standard of care.[8] Given the large number of potential permutations, it would be infeasible to compare all of these proposed sequencing strategies in 1 or even several RCTs. A recent study compared 1-year outcomes of HFrEF pharmacotherapy sequencing strategies using a modeling strategy.[7] The model included a limited range of proposed sequencing strategies and did not account for adverse drug events.[7] This study demonstrated that simply changing the sequencing strategy to reach the same final combination could improve patient outcomes; however, it did not capture adverse drug events that could attenuate such benefits or consider some of the more recently proposed and promising sequencing strategies, including "cluster" and "simultaneous" sequencing.[3–7]

In the absence of empirical evidence, carefully conducted modeling studies that synthesize the best available evidence and translate the findings to clinical and policy-relevant outcomes can narrow the evidence gap. Using a microsimulation model, we previously demonstrated that more rapid sequencing strategies were cost effective compared with conventional sequencing strategies in Canada using a public payer perspective and lifetime horizon.[5] Because novel sequencing strategies may differ most within the first year in terms of both efficacy and safety, we aimed to model death, HF hospitalizations, and adverse drug events in the first year after HFrEF diagnosis.

METHODS

All data used to generate this model are included in the published article and references in Table 1.[9–31] We conducted an individual-based state-transition microsimulation modeling study to compare the 1-year cumulative incidence of death, total HF hospitalization, composite of death or first HF hospitalization, and adverse drug events (bradycardia, hyperkalemia, hypotension, and renal impairment) with 6 different HFrEF pharmacotherapy sequencing strategies, each with 2 versions depending on weekly or biweekly medication adjustments, applied to treatment-naïve outpatients with HFrEF.

Model Overview and Inputs

We selected an individual-based state-transition microsimulation model over a Markov model due to its ability to track individual patient histories, which allowed

Table 1. Model Inputs

Variable	Value	Range	Reference
Clinical outcome event rates per week			
Death			
Outpatient	0.003265156	0.001–0.007	9
In-hospital	0.089925	0.023–0.195	
Outpatient correction factor to account for in-hospital death	0.8	…	9
HF hospitalization	0.006768	0.002–0.015	9
Adverse drug event rates per week (proportion dose limiting)*			
Bradycardia	0.000177 (0.078)	0.002–0.154	10
Hypotension	0.000463 (0.393)	0.008–0.778	11
Hyperkalemia	0.000026 (0.143)	0.003–0.283	11
Renal impairment	0.001168 (0.146)	0.003–0.289	12, 14
Treatment effect size (compared to placebo) as risk ratio			
Death			
ACEI/ARB—subtarget dose	0.90	0.82–0.98	13
ACEI/ARB—target dose	0.85	0.80–0.90	15, 16
ARNI—all doses	0.72	0.64–0.81	17–19
β Blockers	0.65	0.57–0.74	20, 21
MRA	0.83	0.77–0.88	22
SGLT2I	0.87	0.77–0.98	23
HF hospitalization			
ACEI/ARB—subtarget dose	0.82	0.72–0.92	13
ACEI/ARB—target dose	0.71	0.65–0.77	15, 16
ARNI	0.56	0.49–0.64	17–19
β Blockers	0.63	0.56–0.71	20, 21
MRA	0.80	0.70–0.92	22
SGLT2I	0.69	0.61–0.78	23
Bradycardia			
β Blockers	3.54	2.19–5.42	24
Hypotension			
ACEI/ARB	1.49	1.29–1.71	13, 15, 16
ARNI	2.32	1.91–2.80	25, 26
β Blockers	1.24	0.92–1.64	24
MRA	1	…	14, 27
SGLT2I	1	…	23, 28, 29
Hyperkalemia			
ACEI/ARB	2.23	1.65–3.00	13
ARNI	2.43	1.74–3.40	25, 26
MRA	2.03	1.78–2.31	14
SGLT2I	0.82	0.71–0.95	30
Renal impairment			
ACEI/ARB	1.33	1.12–1.57	13, 15, 16
ARNI	1.24	0.97–1.58	25, 26
MRA	1	…	14
SGLT2I	0.63	0.59–0.67	31

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HF, heart failure; MRA, mineralocorticoid receptor antagonist; and SGLT2I, sodium-glucose cotransporter-2 inhibitor.

*All incidence rates converted to probabilities for the transition probability matrix.

modeling of medication titrations based on sequencing strategy and emergence of adverse drug events during each cycle. We used a weekly cycle length, corresponding to the minimum titration frequency and median length of HF hospital stay in Canada,[32] with a half-cycle correction (subtracting and adding half of the outcomes to/from the initial and final cycles of the discrete-time model, respectively, to account for the fact that events can occur at any point during the cycle), and a 1-year horizon to assess shorter-term outcomes, consistent with a previous modeling study.[7]

Figure 1 illustrates the model structure, where all patients started in the "outpatient HF" state and could remain in this state, or transition to "HF hospitalization" or "death" states. While in the "outpatient HF" state and still undergoing medication titration, they could transiently experience an adverse drug event (bradycardia,

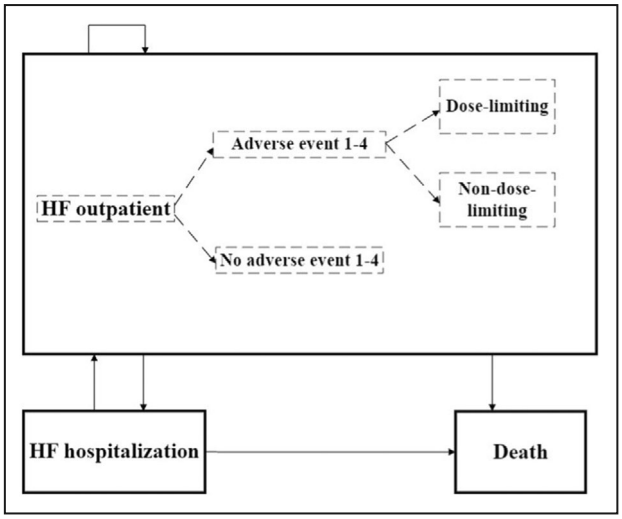

Figure 1. State transition diagram.
State transition diagram for the microsimulation model of pharmacotherapy initiation and titration in patients with HF with reduced ejection fraction. Solid arrows represent transitions between primary health states occurring between cycles. Dashed arrows denote transitions within each cycle while the patient remains in the "HF stable" state. HF indicates heart failure.

hyperkalemia, hypotension, or renal impairment), which could be dose limiting or non–dose limiting (described further below under Sequencing Strategies). Patients hospitalized with HF could transition to the death or outpatient HF state. Probabilities of transitioning to HF hospitalization or death, and experiencing any of the adverse drug events depended on each patient's combination of medications and dose in the current cycle. Table 1 lists model inputs, data sources, and chosen distributions. We used data from placebo-controlled RCTs and meta-analyses of RCTs to estimate the effect of individual medication classes and their doses on state-transition probabilities. Only ACEIs/angiotensin receptor blockers had sufficient direct RCT to model subtarget doses[13]; other medications were modeled as having identical treatment effect sizes for target and subtarget doses. Target doses were based on the maximum doses used in landmark HFrEF RCTs (eg, bisoprolol 10 mg daily), and the subtarget doses were based on minimum doses recommended by guidelines, proportional to the target dose (eg, β blocker starting subtarget dose modeled as 12.5% of target dose to emulate bisoprolol 1.25 mg daily).[33] For ARNIs, which were compared to an active comparator (ACEI), we used the methods by McMurray et al to calculate a putative placebo comparison.[18] All studies provided relative estimates of effect of therapy versus placebo or active comparator on time-to-first HF hospitalization, whereas estimates for total (first and recurrent) HF hospitalizations were infrequently reported but similar to time-to-first event estimates. Because these different analyses generally provide similar results,[34] we used relative estimates from time-to-first-event analyses for all analyses of HF hospitalization.

Study Population

We used a hypothetical cohort of treatment-naïve outpatients with HFrEF without contraindication to quadruple therapy. We derived event rates for death and time to first HF hospitalization in untreated patients from the placebo arm of the SOLVD (Studies of Left Ventricular Dysfunction) treatment trial (baseline mean age, 61 years; 80% men; 32% with New York Heart Association functional class III/IV; mean ejection fraction, 25%; 26% with diabetes; 10% with atrial fibrillation), the only HFrEF RCT with a placebo group with <10% of patients receiving any of the quadruple-therapy agents.[9] Only simulated patient data were used; therefore, we did not require research ethics board approval to conduct this modeling study.

Sequencing Strategies

We modeled six HFrEF pharmacotherapy sequencing strategies representing the range of approaches proposed in the literature (Figure 2).[3–6] Sequences mainly varied in number of medications started on the first visit 1 medication in sequences 1 ["conventional"] and 2; 2 medications in sequences 3 (prioritizing SGLT2I to enhance tolerability of other medications) and 4 (prioritizing ARNI plus β blocker as commonly done in practice); 3 medications in sequence 5 ("cluster"); and all 4 medications in sequence 6 ("simultaneous"), and frequency of medication adjustments (biweekly in version a, and weekly in version b). To model the titration process, we divided sequencing strategies into steps and walks (Figure 2). Each step was a unique combination of medications and dose that could be further divided into walks in weekly cycles. For each sequence, patients began in the first walk and could transition through the sequence on the basis of the occurrence of adverse drug events by moving to the next walk (no adverse drug event), staying in the same walk (non–dose-limiting adverse drug event), or deescalating to the last walk of the previous step (dose-limiting adverse drug event) (Figure S1). Across evaluated sequencing strategies, the number of steps ranged from 5 to 13, and the minimum number of weeks to achieve target-dose quadruple therapy ranged from 8 to 24 in version a and 5 to 13 in version b.

Outcomes of Interest

For efficacy, we modeled the incidence of death, total HF hospitalization (first and recurrent events), and the composite of death or first HF hospitalization within each of 53 cycles (1 year) and then calculated the cumulative incidence per 100 patients over 1 year. We also modeled cumulative incidence of total and individual adverse drug events (bradycardia, hyperkalemia, hypotension, renal impairment).

Statistical Analysis

We performed deterministic analyses of 10 000 patients, with the untreated group from the SOLVD treatment trial for reference, to generate cumulative incidences for all outcomes of interest. We generated separate cumulative incidence curves for the outcomes of death and total HF hospitalizations over 1 year. We reported outcomes as mean±SE for the cumulative incidence per 100 patients. The model explicitly accounted for the competing risk of death by treating death as an absorbing state, such that simulated individuals who died could not subsequently experience other events. We further conducted a post hoc probabilistic sensitivity analysis of 10 000 simulations of 10 000 patients.

RESULTS

At 1 year, an estimated 15.3 per 100 simulated patients died without treatment compared with 6.9 per

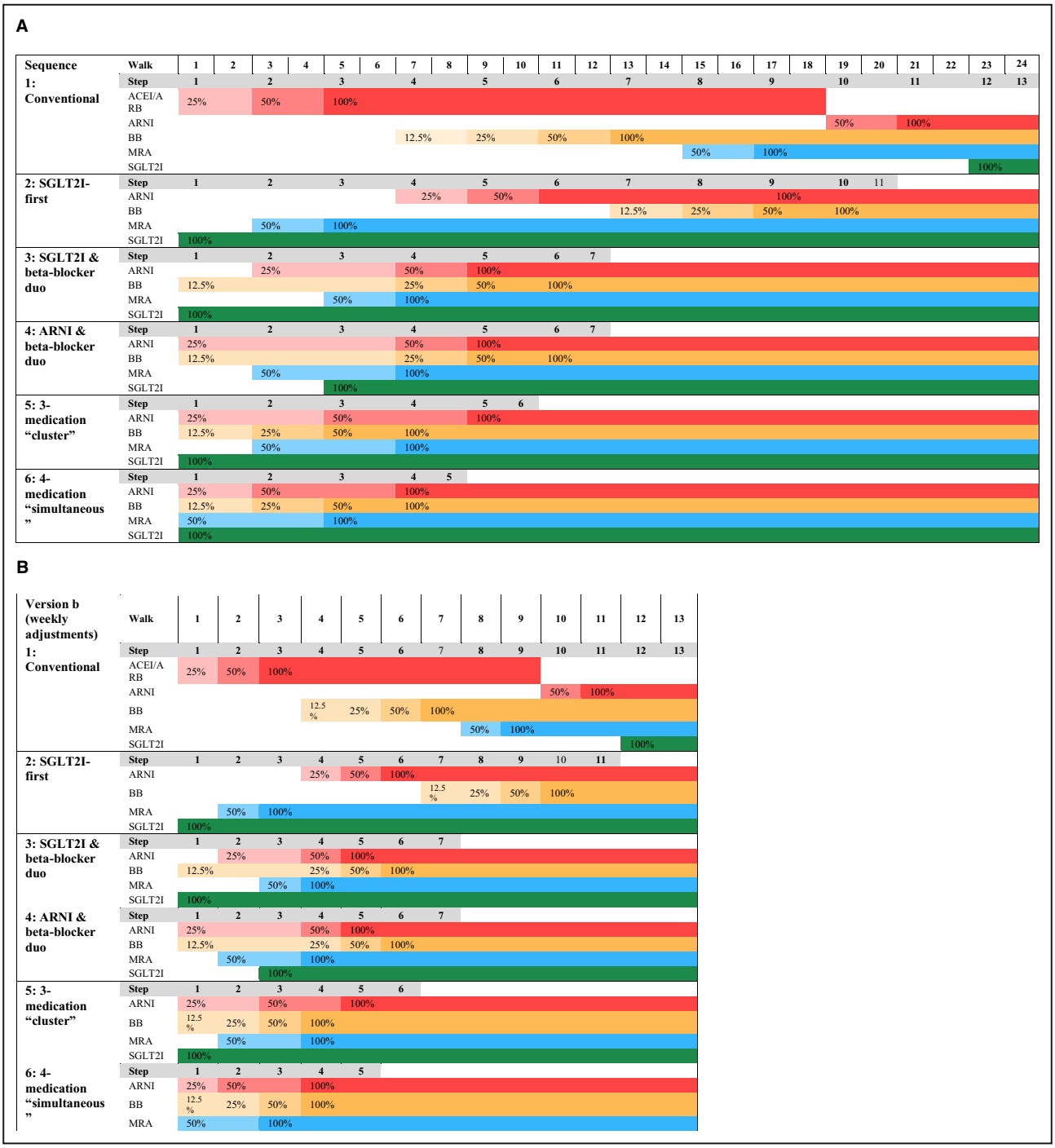

Figure 2. HFrEF pharmacotherapy sequencing strategies.
The figure provides a visual representation of each profile through sequencing steps and walks. Each walk represents 1 wk in practice and 1 cycle in the model, with each step corresponding to a medication adjustment. Thus, each adjustment visit (ie, step) occurs every 2 wk/walks for version a, and every week/walk for version b. **A**, Version a (adjustments every 2 wk); **B**, Version b (weekly adjustments). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction; and SGLT2I, sodium-glucose cotransporter-2 inhibitor. Percentages indicate the percentage of target dose.

100 patients with the conventional sequence adjusted biweekly, and 5.2 to 6.4 per 100 patients with other sequencing strategies (Figure 3A, Table 2). The risk of death decreased with a greater number of medications initiated on the first visit and more frequent medication adjustments; however, this plateaued at 2 medications started on the first encounter. Sequences 3a to 6b (ie, starting 2–4 medications on first encounter titrated

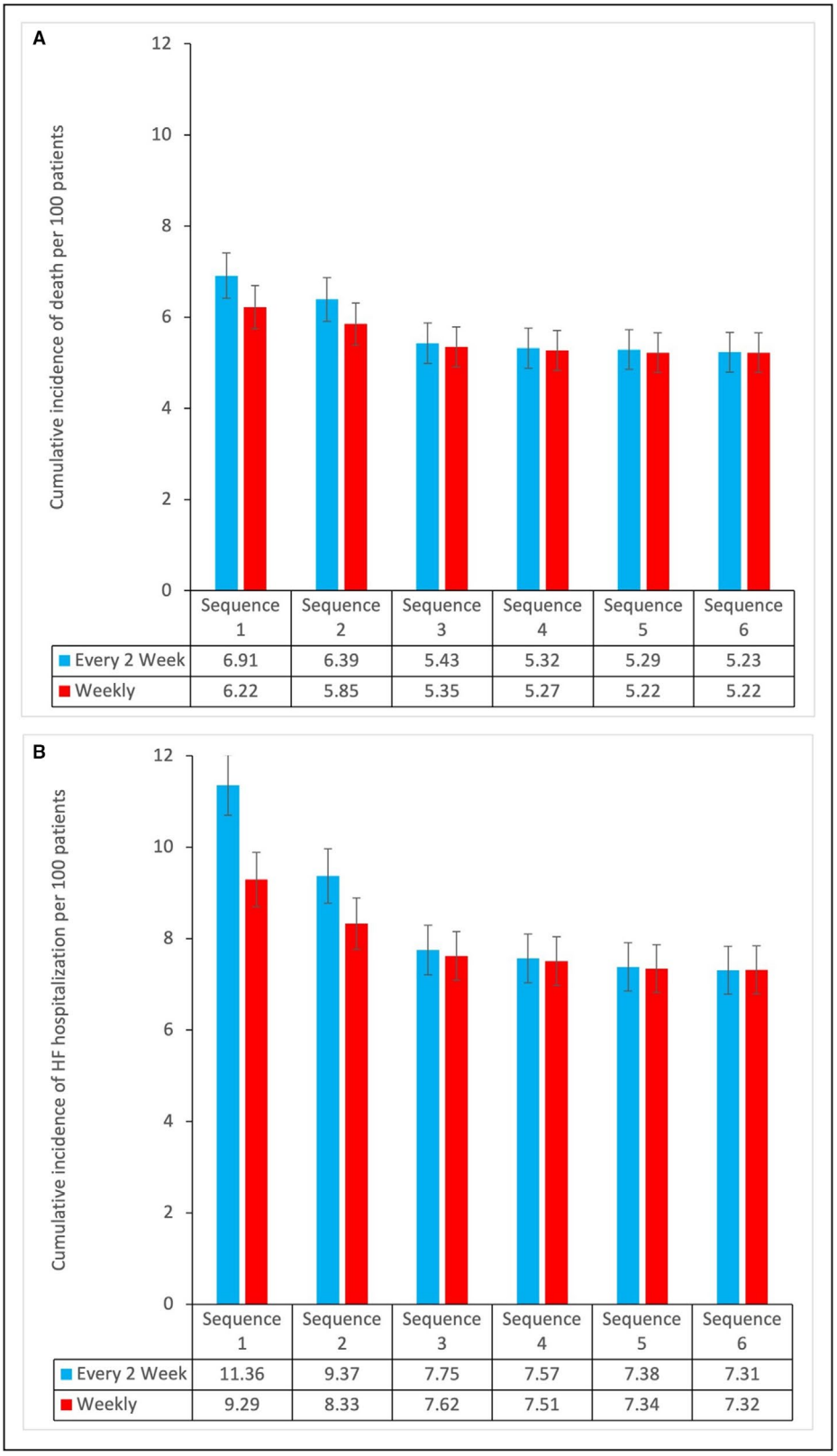

Figure 3. Deaths (A) and total heart failure hospitalizations (B) per 100 patients at 1 year for each sequencing strategy.

Table 2. Cumulative Incidence ±SE per 100 Patients at 1 Year for Each Sequencing Strategy

Outcome	Untreated	Sequencing strategies*										
		1a	1b	2a	2b	3a	3b	4a	4b	5a	5b	6a	6b
Death	15.27±0.360	6.91±0.254	6.22±0.242	6.39±0.245	5.85±0.235	5.43±0.227	5.35±0.225	5.32±0.224	5.27±0.223	5.29±0.224	5.22±0.222	5.23±0.223	5.22±0.222
Total heart failure hospitalizations	31.45±0.557	11.36±0.335	9.29±0.303	9.37±0.304	8.33±0.288	7.75±0.276	7.62±0.274	7.57±0.273	7.51±0.271	7.38±0.269	7.34±0.268	7.31±0.268	7.32±0.268
Composite of death or first heart failure hospitalizations	37.82±0.485	16.44±0.371	14.08±0.348	14.35±0.351	12.97±0.336	12.16±0.327	11.97±0.325	11.89±0.324	11.8±0.323	11.69±0.321	11.61±0.320	11.59±0.320	11.59±0.320
Total adverse drug events	…	15.35±0.389	15.57±0.393	14.19±0.374	14.88±0.383	15.44±0.391	15.57±0.393	16.01±0.398	15.84±0.396	15.69±0.395	15.71±0.395	15.70±0.395	15.71±0.395
Bradycardia	…	2.68±0.163	2.82±±0.169	2.44±0.156	2.72±0.165	2.98±0.173	2.99±0.173	2.98±0.173	2.98±0.173	2.99±0.173	2.99±0.173	2.99±0.173	3.00±0.173
Hyperkalemia	…	0.46±0.068	0.50±0.071	0.51±0.071	0.49±0.070	0.50±0.071	0.50±0.071	0.51±0.071	0.53±0.073	0.51±0.071	0.52±0.072	0.52±0.072	0.52±0.072
Hypotension	…	6.07±0.247	6.78±0.261	6.52±0.256	6.94±0.264	7.15±0.268	7.25±0.270	7.38±0.272	7.36±0.272	7.34±0.272	7.34±0.272	7.33±0.272	7.33±0.272
Renal impairment	…	6.14±0.247	5.47±0.233	4.72±0.217	4.73±0.217	4.81±0.219	4.83±0.219	5.14±0.226	4.97±0.222	4.85±0.220	4.86±0.220	4.86±0.220	4.86±0.220

*Sequences refer to those described in Figure 2. Version a refers to medication adjustments every 2 wk, and version b refers to medication adjustments weekly.

every 1–2 weeks) produced comparable risk of death (5.2–5.4 per 100 patients at 1 year). Figure S2A and S2B illustrates the cumulative incidence of death with each sequence with biweekly or weekly adjustments.

Similarly, the incidence of HF hospitalization decreased from 31.5 per 100 patients with no treatment to 11.4 per 100 patients with conventional sequencing adjusted biweekly (Figure 3B, Table 2). This was further reduced to 7.3 to 9.4 per 100 patients with more rapid sequencing strategies. The incidence of HF hospitalization decreased with a greater number of medications initiated on the first visit and more frequent medication adjustments, with sequences 3a to 6b producing comparable incidence of HF hospitalization (7.3–7.7 per 100 patients). Figure S2C and S2D illustrates the cumulative incidence of HF hospitalization with each sequence with biweekly or weekly adjustments.

Adverse drug events ranged from 14.2 to 16.0 per 100 patients across all sequences (Table 2). Among these, hypotension was most common (6.1–7.4 per 100 patients) and increased with number of agents at initial visits and more frequent adjustments. Sequences 4a through 6b were similar owing to the neutral impact of MRAs and SGLT2Is on hypotension in the model. Renal impairment ranged from 4.7 to 6.1 per 100 patients and was lowest in sequences that initiated an SGLT2I earlier. Bradycardia occurred in 2.4 to 3.0 per 100 patients and was highest in sequences 3a through 6b, which all initiated a β blocker on the first visit. Hyperkalemia was infrequent with all sequences (≈0.5 per 100 patients).

In post hoc analyses, sequences starting with the combination of an SGLT2I plus either an ARNI or MRA on first visit performed similarly to other 2-drug combinations (ie, sequences 3–4; Table S1). A post hoc probabilistic sensitivity analysis was nearly identical to the deterministic analysis, with greater precision (smaller SEs) by nature of the multiple simulations (Table S2).

DISCUSSION

This microsimulation modeling study compared 6 HFrEF pharmacotherapy quadruple therapy sequencing strategies with biweekly or weekly medication adjustments among treatment-naïve outpatients with HFrEF. Overall, sequencing strategies that started 2 to 4 medications on initial encounter reduced the risk of death and HF hospitalization at 1 year compared with a conventional quadruple therapy sequencing strategy. Moreover, weekly medication adjustments numerically outperformed biweekly adjustments; however, this advantage diminished and was not meaningfully different when ≥2 medications were initiated on the first visit. Medication-related adverse events were infrequent, and differences were minimal between sequencing strategies. Overall,

there were diminishing returns in terms of both death and HF hospitalization with greater intensity and rapidity. Differences were minimal and of unclear clinical relevance between sequencing strategies that started between 2 and 4 medications at once, all of which were designed to achieve ARNI-based target-dose quadruple therapy within 12 weeks.

The STRONG-HF trial is the only RCT that compared different HF pharmacotherapy sequencing strategies.[8] STRONG-HF randomized 1078 hospitalized patients with HF to a multimodal "high-intensity care" intervention arm that included initiation and titration of triple therapy (ACEI/angiotensin receptor blocker/ARNI, β blocker, and MRA) within 2 weeks of hospital discharge, or a usual care arm that seldom resulted in medication adjustments.[8] Notably, few if any patients were treatment-naïve at randomization, and all initiated medications while in hospital. This high-intensity care intervention reduced the composite of death or HF hospitalization at 6 months by a relative 34%, which translated to an absolute risk reduction of 6.3% in the subgroup of patients with HFrEF.[8] A subsequent modeling study estimated that implementation of this intervention to rapidly start ARNI-based quadruple therapy within the first 2 weeks after discharge by a pharmacist-led HF medication optimization program would be cost effective in the United States.[35]

The present study corroborates and expands the findings from a previous modeling study that used data from 5 RCTs to compare the impact of various HFrEF pharmacotherapy sequencing strategies on death and the composite of cardiovascular death or HF hospitalizations at 1 year.[7] The sequencing strategies tested within this model started with 1 or 2 medications on initial visit and fully titrated an agent before adding the subsequent medication. Notably, this study did not model adverse drug events or dose-dependent effects on efficacy.[7] Expanding from this, our study used event estimates derived from meta-analyses of RCTs for each medication class, with dose-dependent effect estimates for renin–angiotensin system inhibitors, and used microsimulation to model the interdependence between outcomes and medication adjustments. Despite these methodological differences, the risk of death at 1 year was comparable between our studies for those sequences evaluated in both (eg, 6.5% and 5.1%, respectively, with strategies analogous to our sequences 1a and 4b).[7] The present study further extends comparisons to the promising cluster and simultaneous sequencing strategies, medication adjustment frequencies for each strategy, and perhaps most importantly, the interaction between these 2 strategy considerations. Our findings demonstrate comparable efficacy and safety of these sequencing strategies that start 2, 3, or 4 medications on the initial visit.

The findings from the present study have implications for both future research and current practice. First, this study, taken together with the study by Shen et al,[7] demonstrates the value of modeling studies to compare different strategies that have not been directly compared in a randomized trial to estimate efficacy and safety, which can subsequently be used to design future comparative trials, including in sample size estimations. Based on the estimated absolute difference of ≤0.6% for the composite of death or HF hospitalizations at 1 year, a trial comparing different contemporary sequencing strategies (starting 2–4 HFrEF medications on the first encounter) would need to be prohibitively large (ie, >12 000 patients per group). This modeling study therefore suggests that such a trial would be impractical and supports more pragmatic designs to evaluate the implementation of guideline-directed medical therapy in HFrEF. Given the comparable risk of death, HF hospitalizations, and individual adverse drug events among these different strategies as long as they achieve quadruple therapy, implementation RCTs comparing different models of care focusing on patient-oriented outcomes (such as quality of life and treatment burden) and medication implementation outcomes (such as the Optimal Medical Therapy Score[36] or its derivatives) could help to bridge the evidence-to-practice gap. In terms of implications for practice, institutions and providers can use our results to identify sequencing strategies that optimally balance outcomes and practical considerations in the local context. Specific considerations when selecting a sequencing strategy to implement in a clinic may include staffing, space, and telehealth capabilities, which may dictate medication adjustment frequency and consistency. Other considerations would include total number of patient encounters, coverage criteria requiring prior medication use (eg, 4 weeks of ACEI/angiotensin receptor blocker before switching to ARNI), and patient-specific considerations. For example, HF clinics with limited staff may select a simultaneous sequencing strategy with biweekly adjustments (sequence 6a) to balance the need to discharge patients promptly while limiting the frequency of medication adjustment visits. Conversely, a primary care or geriatric clinic with a clinical pharmacist–led medication optimization program that primarily cares for older patients with multiple comorbidities may elect a sequencing strategy that starts with 2 or 3 medications, followed by a mix of telehealth and in-person biweekly or weekly follow-ups (sequence 3a/b or 5a/b) to allow for more staggered adjustments and close monitoring. Future studies could extend our modeling strategy to evaluate HFrEF pharmacotherapy sequencing strategies in different contexts, including delivery within different care models, and in specific patient subgroups.

Limitations

Our modeling study has several limitations. First, the model relied on data from RCTs of individual medications compared with placebo to estimate the impact of different medication combinations and assumed that effects were independent and additive.[3–7] We had to make assumptions on the additivity of treatment benefit, and independence of adverse drug events. Evidence supporting these assumptions is relatively robust for the 1-year time horizon of this study.[3–7] To what extent the long-term profile of medications will be similar to their-short term profile needs to be studied empirically. Second, the model assumed that adverse drug events either resolved spontaneously after 1 cycle or led to a temporary reduction in treatment intensity, without allowing for permanent discontinuation of a medication class. However, this approach yielded a conservative estimate of efficacy in patients experiencing adverse drug events by delaying treatment intensification, thereby emulating clinical practice. Third, the model did not account for comorbidities, polypharmacy, and drug reluctance, all of which are common concerns in clinical practice that may impact the baseline risk of events, which warrants further research to extend the generalizability of these findings. Fourth, the present study did not consider cost–utility trade-offs, as this had already been assessed over a lifetime horizon in our previous related work, the findings of which align with the present study.[5]

Conclusions

For treatment-naïve outpatients with HFrEF eligible for ARNI-based quadruple therapy, starting 2 to 4 HFrEF medications on initial encounter reduced the risk of death and hospitalization, and similar risk of treatment-related adverse events, at 1 year compared with a conventional sequencing strategy. Additionally, weekly medication adjustments did not meaningfully outperform biweekly adjustments when ≥2 medications were started in the first week. Clinicians and policymakers can use these findings when developing HFrEF medication optimization programs with sequencing strategy protocols that fit the local practical context.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2
Figures S1–S2

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