Accelerated and personalized therapy for heart failure with reduced ejection fraction

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Abstract

Aims

Previously, guidelines recommended initiating therapy in patients with heart failure and reduced ejection fraction (HFrEF) in a sequence that follows the chronological order in which trials were conducted, with cautious up-titration of each treatment. It remains unclear whether this historical approach is optimal and alternative approaches may improve patient outcomes.

Methods and results

The potential reductions in events that might result from (i) more rapid up-titration of therapies used in the conventional order (based on the chronology of the trials), and (ii) accelerated up-titration and using treatments in different orders than is conventional were modelled using data from six pivotal trials in HFrEF. Over the first 12 months from starting therapy, using a rapid up-titration schedule led to 23 fewer patients per 1000 patients experiencing the composite of heart failure hospitalization or cardiovascular death and seven fewer deaths from any cause. In addition to accelerating up-titration of treatments, optimized alternative ordering of the drugs used resulted in a further reduction of 24 patients experiencing the composite outcome and six fewer deaths at 12 months. The optimal alternative sequences included sodium–glucose cotransporter 2 inhibition and a mineralocorticoid receptor antagonist as the first two therapies.

Conclusion

Modelling of accelerated up-titration schedule and optimized ordering of treatment suggested that at least 14 deaths and 47 patients experiencing the composite outcome per 1000 treated might be prevented over the first 12 months after starting therapy. Standard treatment guidance may not lead to the best patient outcomes in HFrEF, though these findings should be tested in clinical trials.

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Structured Graphical Abstract

Key Question
Previously, Guidelines recommended initiating therapy in patients with heart failure and reduced ejection fraction in a sequence following the chronological order in which trials were conducted, with cautious up-titrations of each treatment (Sequence 1). Is this historical approach better than alternative ones?

Key Finding
Compared to conventional approach (Sequence 1), modelling an accelerated up-titration schedule (Sequence 1a) and optimized ordering of treatment (Sequences 1b-3) suggested that a larger number of deaths and hospital admissions for worsening heart failure might be prevented over the first 12 months after starting therapy.

Take Home Message
The conventional approach to implementation of the core pharmacological treatments for heart failure and reduced ejection fraction may not be the best and alternative approaches could lead to a substantial reduction in lives lost and hospitalizations for worsening heart failure.

Introduction
In patients with heart failure and reduced ejection fraction (HFrEF), two further pharmacological approaches—inhibition of neprilysin and sodium–glucose cotransporter 2 (SGLT2)—have been shown to improve survival when added to the original ‘core’ therapies of a renin–angiotensin system blocker, a beta-blocker, and a mineralocorticoid receptor antagonist (MRA).\(^1\)\(^-\)\(^5\) Until recently, treatment guidelines and associated prescribing guidance advocated using these therapies according to the chronology of the trials, i.e. starting with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), adding a beta-blocker, adding an MRA, switching to sacubitril/valsartan (i.e. adding a neprilysin inhibitor) and, following precedent, SGLT2 inhibition would be added last (although that was not the case in the 2021 ESC guideline).\(^1\)\(^,\)\(^2\)\(^,\)\(^6\) It was also recommended that patients should be titrated to the ‘target’ dose (or maximally tolerated dose below that) of the first therapy before starting the second and so on.\(^1\)\(^,\)\(^2\) But is this the correct approach? If it is accepted that each of these five life-saving therapies acts
independently and that their effects are additive, then the goal should be to start as many therapies as quickly as possible, especially as each of them exhibits benefit early after initiation (within <30 days). A relevant consideration here is the number of titration steps and the time taken to achieve the evidence-based dose. Clearly, this varies greatly between, for example, beta-blockers and SGLT2 inhibitors (SGLT2i), where the former requires up to four titration steps, over 6–12 weeks, and the latter is used in a single fixed dose for all patients.1–3 Using efficacy data from randomized controlled trials, we have modelled the impact of more rapid up-titration of therapy used in conventional order, and of using the life-saving treatments in different orders. Starting two treatments simultaneously has also been suggested.6–8 We have attempted to quantify the potential reductions in hospital admissions and deaths that might result from alternative approaches by modelling these.6–8

**Methods**

**Study trials**

We used five trials conducted in patients with HFrEF to estimate the treatment effects of the five life-saving medications. The effects of renin–angiotensin system inhibition (RASI) were based on the Studies of Left Ventricular Dysfunction (SOLVD)-Treatment trial,4 the effect of beta-blockers was based on the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF),10 MRAs on the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF),11 angiotensin receptor–neprilysin inhibition (ARNI) on the Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial,3 and SGLT2i on the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF).6 We used the combined cohort of patients randomized in the placebo arm both from SOLVD-Treatment and the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative trial,6 not receiving a beta-blocker or an MRA, to create a ‘treatment-naïve’ HFrEF population (i.e. patients not receiving any of the five pharmacological therapies reducing mortality) and this data set was used to generate the rates of the clinical outcomes of interest.

Briefly, SOLVD-Treatment randomized 2569 heart failure patients who had a left ventricular ejection fraction (LVEF) ≤35% to receive either enalapril or placebo after a 3-week run-in period during which patients received single-blind enalapril for 2–7 days followed by single-blind placebo for 14–17 days. At randomization, the initial dose was 5 mg twice daily (or 2.5 mg twice daily if patients had difficulty tolerating this) and up-titrated to a maximum of 10 mg twice daily (or 5 mg twice daily) after 2 weeks. By the end of the trial, 32.5% of patients in the enalapril group stopped taking the study drug. Among patients taking the study drug, the mean daily dose was 16.6 mg for enalapril.11 In CHARM-Alternative, 2028 patients who had New York Heart Association (NYHA) Classes II–IV heart failure and LVEF ≤40%, intolerant of ACEIs, were randomly assigned to candesartan or placebo. The initial dose was 4 or 8 mg once daily and the dose was doubled, as tolerated, at a minimum of every 2 weeks, to a target dose of 32 mg once daily. A total of 24% of patients in the candesartan group discontinued the study drug for reasons other than death. At 6 months, the mean daily dose among those taking the study drug was 23 mg for candesartan.12

The MERIT-HF enrolled 3991 symptomatic heart failure patients with LVEF ≤40%, receiving standard therapy defined as any combination of diuretics and an ACEI at enrolment. After a 2-week single-blind placebo run-in period, patients were randomly assigned to metoprolol CR/XL 25 mg once daily (or 12.5 mg once daily if in NYHA Classes III and IV) or placebo. The target dose was 200 mg once daily and doses were up-titrated over 8 weeks. At the end of the trial, study drug was discontinued in 13.9% of patients in the metoprolol CR/XL group, and the mean daily dose in the metoprolol CR/XL group was 159 mg.10 The EMPHASIS-HF enrolled 2737 patients aged at least 55 years with NYHA Class II heart failure and an LVEF ≤35%, treated with an ACEI or ARB and beta-blocker. Eligible patients were randomly assigned to receive eplerenone 25 mg once daily (increased to 50 mg once daily after 4 weeks) or placebo. The study drug was stopped in 16.3% of patients receiving eplerenone. After completion of the dose-adjustment phase at 5 months, the mean ± standard deviation (SD) daily dose of eplerenone was 39.1 ± 13.8 mg among those taking the study drug.11 The PARADIGM-HF enrolled 8399 patients with symptomatic heart failure, LVEF ≤40% and an elevated plasma natriuretic peptide. Patients were required to tolerate the equivalent of enalapril 10 mg daily for at least 4 weeks before screening, along with a stable dose of a beta-blocker (unless contraindicated or not tolerated) and an MRA (if indicated). Patients who tolerated sequential enalapril and sacubitril/valsartan run-in periods were randomized to either sacubitril/valsartan (target dose 97/103 mg twice daily) or enalapril (target dose 10 mg twice daily). Sacubitril/valsartan was discontinued in 17.8% of patients for reasons other than death. Among patients taking the study drug, the mean ± SD daily dose was 375 ± 71 mg for sacubitril/valsartan at the final visit.6 In DAPA-HF, 4744 patients with NYHA Classes II–IV symptoms and LVEF ≤40%, with an elevated plasma natriuretic peptide level, were randomly assigned to either dapagliflozin (10 mg once daily) or placebo. Patients were required to receive guideline-recommended medical and device therapy, including an ACEI/ARB or sacubitril/valsartan, a beta-blocker, and an MRA, unless contraindicated or not tolerated. Dapagliflozin was stopped for reasons other than death in 10.5% of patients. At the last assessment, 98.1% of the patients who were still taking dapagliflozin continued to receive the target dose.4

**Outcomes of interest**

The primary endpoint was all-cause death in SOLVD-Treatment and MERIT-HF, and the composite of cardiovascular death or heart failure hospitalization in CHARM-Alternative, EMPHASIS-HF, and PARADIGM-HF. The primary endpoint in DAPA-HF was a composite of cardiovascular death or worsening heart failure, although this differed little from cardiovascular death or heart failure hospitalization, which was the first secondary endpoint. Therefore, in the present analyses, the outcomes of interest were the composite of cardiovascular death or heart failure hospitalization and all-cause death. Cardiovascular death and heart failure hospitalization, as individual outcomes, were also examined and presented in the Supplementary material online.

**Statistical analysis**

Kaplan–Meier estimates were used to generate the event rates for clinical outcomes of interest in the treatment-naïve HFrEF cohort. As the risk of heart failure hospitalization was relatively high early after randomization and lower thereafter, the risks of heart failure hospitalization and the composite of heart failure hospitalization or cardiovascular death were estimated separately within 6 months and beyond 6 months. The published hazard ratios on the outcomes of interest for the various therapies tested in the trials listed above were used as their treatment effects, with one exception.3,4,9–11,13 The hazard ratio for the composite of heart failure hospitalization or cardiovascular death was not reported in MERIT-HF and the hazard ratio for a composite of heart failure hospitalization or all-cause death was used instead.10

The conventional sequence (i.e. Sequence 1) used in this study was first a RASI, up-titrated for 6 weeks, followed by a beta-blocker up-titrated
over 6 weeks, then an MRA over 4 weeks, switching from the RASi to an ARNI over 6 weeks and, lastly, adding SGLT2i, with a final patient evaluation 2 weeks later. The accelerated version of this sequence (Sequence 1a) introduced treatments in the same order but accelerated the speed of up-titration as follows: RASi over 4 weeks, beta-blocker over 4 weeks, MRA over 2 weeks, ARNI over 5 weeks, and then SGLT2i, with a final patient evaluation 1 week later. Using the same accelerated up-titration timeline as in Sequence 1a, we further examined 12 other sequences, which excluded treatment with a RASi alone, replacing this in all cases with an ARNI (the combination of RASi and a neprilysin inhibitor), i.e. sacubitril/valsartan. The order of drugs starting with an ARNI followed by a beta-blocker, an MRA, and then SGLT2i is described as Sequence 1b and the 11 additional options as Sequences 2–12. Lastly, given recent suggestions about the possibility of starting two treatments simultaneously, we also examined sequences with various combinations of two drugs started in combination followed by the remaining two.6–8

We estimated the event probability and mean event-free time lost at 1, 2, and 3 years in patients receiving none of the treatments examined and then in patients treated with the medications started in the sequences described above (see Supplementary material online for detailed information). Our analysis made several assumptions, including that the survival times for the clinical outcomes follows an exponential survival distribution, i.e. the hazard (or event rate) is constant over time. For all-cause death and cardiovascular death, a constant rate was used throughout the follow-up, and for the composite of heart failure hospitalization or cardiovascular death and heart failure hospitalization individually, a constant rate was applied to within 6 months and thereafter with two different rates for each of these periods. We also assumed that in this cohort, the adherence rate to, and the average daily dose of, each of the five life-saving medications was the same as those reported in the randomized trials testing these drugs (Table 1), that the relative risk reduction with each medication is independent and additive (i.e. the benefit of each therapy is constant, regardless of any of or the combination of background treatment), and that the hazards in the with and without treatment groups for each medication were proportional. In our primary analysis, we assumed that each treatment exerted its full effect from halfway through the up-titration period (and had no effect before that); we also conducted two sensitivity analyses, one assuming the full effect of each medication was present from the commencement of treatment and the other that the full effect was only evident once the medication was fully titrated. We also examined the mean event-free time lost by calculating the area under the time–event–probability curve by 1, 2, and 3 years.14 The mean event-free time lost at a certain time point indicates by the time point examined the average event-free time lost for one patient. For example, by 1 year, 100 out of 1000 patients died, assuming the event rate is constant, the mean event-free time (i.e. survival time) lost at 1 year is \( \approx 0.6 \) months for one patient on an average and is around 50 years for 1000 patients in total. We also calculated the differences in event probability and mean event-free time gain in Sequences 2–12 compared with conventional Sequences 1, 1a, and 1b. Separately, we compared the sequences using starting combinations of treatment (sequences using duos 1–6), compared with Sequence 1b.

All analyses were performed using Stata version 16 (College Station, TX, USA).

Results

Event rates in the ‘treatment-naïve’ heart failure and reduced ejection fraction population

In the ‘treatment-naïve’ HFrEF population (SOLVD-Treatment and CHARM-Alternative), the rate of the composite of heart failure hospitalization or cardiovascular death was 460 per 1000 person-years within 6 months and 200 per 1000 person-years beyond 6 months. The rate for HF hospitalization was 310 per 1000 person-years within 6 months and 130 per 1000 patient-years thereafter. The rates for all-cause death and cardiovascular death were 150 and 130 per 1000 person-years throughout, respectively. Using these event rates, the estimated survival curves based on an exponential survival distribution agreed rather well with the observed Kaplan–Meier curves, albeit a modest underestimation, for the clinical outcomes of interest (Supplementary material online, Figure S1).

Estimates of effects of key therapies on mortality and hospitalization

The clinical trials used, and treatment effects from these incorporated in the models, are summarized in Table 1.

Titration schedules and drug sequences examined

Figure 1 shows the conventional sequence of treatments (Sequence 1) using, in order a RASi, a beta-blocker, an MRA, an ARNI (switching from a RASi), and an SGLT2i. Figure 1 also shows (i) an accelerated approach to up-titration of the conventional sequence (Sequence 1a), (ii) drug sequencing starting with an ARNI (sacubitril/valsartan), rather than a RASi, and up-titrating all drugs rapidly, as in Sequence 1a (Sequence 1b), and (iii) the four new treatment sequences found to be most advantageous over the accelerated conventional sequence (Sequences 2–5). In Sequences 2–5, the order in which the treatments of interest were used was varied from Sequence 1b. The principal scenario reported here assumes that each treatment exerted its full effect from halfway through the up-titration period (the other scenarios are described in Supplementary material online, Tables S1 and S2).

The results of applying each of the different treatment sequences on the two endpoints of interest are shown in Figure 2A (heart failure hospitalization or cardiovascular death) and 2B (all-cause death) and the difference in numbers of events and event-free survival after 12 months in Table 2 (the differences in these outcomes over 24 and 36 months are described in the Supplementary material online, Table S3).

The results of applying the different treatment sequences starting with two drugs simultaneously are also shown in Figures 1 and 3 and the difference in numbers of events and event-free survival after 12 months in Table 3.

Impact of accelerating up-titration of conventional order of drug sequencing

The first comparison examined accelerating the conventional approach to initiating and up-titrating therapy (Sequence 1a vs. Sequence 1). Inspection of Figure 1 shows that this accelerated approach reduced the time for up-titration from 24 to 16 weeks. As can be seen from Table 2, using this accelerated titration timeline in 1000 patients was estimated to result in 23 fewer patients experiencing heart failure hospitalization or cardiovascular death, and 7 fewer deaths, in the first 12 months after starting treatment (Structural graphical abstract).
Impact of accelerating up-titration and changing the order of drug sequencing

The next comparisons examined the use of the various medications of interest in a different order, keeping the more rapid up-titration timeline for each.

The first option considered (Sequence 1b) was starting with an ARNI rather than a RASI, and up-titrating all drugs rapidly, as in Sequence 1a. Because this avoided starting with a RASI and later switching to an ARNI, the total time taken for up-titration was reduced from 16 to 12 weeks. Compared with Sequence 1a, Sequence 1b was estimated to result in approximately eight fewer patients experiencing heart failure hospitalization or cardiovascular death, and one less death, in the first 12 months after starting treatment.

The next options considered also used an ARNI rather than a RASI in the various drug sequences examined and, in each of these sequences, the total time taken for up-titration was always 12 weeks.

The most effective alternative approaches (Sequences 2–5 vs. 

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**Table 1** Summary of trials of using the medications in this study

<table>
<thead>
<tr>
<th></th>
<th>RASI</th>
<th>BB</th>
<th>MRA</th>
<th>ARNI</th>
<th>ARNI</th>
<th>SGLT2i</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
<td>SOLVD-treatment</td>
<td>MERIT-HF</td>
<td>EMPHASIS-HF</td>
<td>PARADIGM-HF</td>
<td>PARADIGM-HF vs. SOLVD-treatment and CHARM-alternative</td>
<td>DAPA-HF</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>2569</td>
<td>3991</td>
<td>2737</td>
<td>8399</td>
<td>–</td>
<td>4744</td>
</tr>
<tr>
<td><strong>Study patients</strong></td>
<td>NYHA II–IV, LVEF ≤ 35%</td>
<td>NYHA II–IV, LVEF ≤ 40%</td>
<td>NYHA II, LVEF ≤ 35%</td>
<td>NYHA II–IV, LVEF ≤ 40%</td>
<td>–</td>
<td>NYHA II–IV, LVEF ≤ 40%</td>
</tr>
<tr>
<td><strong>Key baseline therapy</strong></td>
<td>BB 8%, potassium sparing diuretic 9%</td>
<td>RASI 96%, MRA 8%</td>
<td>RASI 94%, BB 87%</td>
<td>RASI 100%, BB 93%, MRA 56%</td>
<td>–</td>
<td>RASI 94%, BB 96%, MRA 71%, ARNI 11%</td>
</tr>
<tr>
<td><strong>Test treatment</strong></td>
<td>Enalapril</td>
<td>Metoprolol CR/XL</td>
<td>Eplerenone</td>
<td>Sacubitril/valsartan</td>
<td>Sacubitril/valsartan</td>
<td>Dapagliflozin</td>
</tr>
<tr>
<td><strong>Control treatment</strong></td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Enalapril</td>
<td>Putative placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Discontinuation percentage in the experimental arm</strong></td>
<td>32.5%</td>
<td>13.9%</td>
<td>16.3%</td>
<td>17.8%</td>
<td>–</td>
<td>10.5%</td>
</tr>
<tr>
<td><strong>Mean daily dose in those taking the study drug/target dose</strong></td>
<td>16.6 mg/20 mg</td>
<td>159 mg/200 mg</td>
<td>39.1 ± 13.8 mg/50 mg</td>
<td>375 ± 71 mg/400 mg</td>
<td>–</td>
<td>98.1% taking the target dose of 10 mg daily</td>
</tr>
</tbody>
</table>

**Cardiovascular death or heart failure hospitalization**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>Treatment vs. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.72 (0.64–0.80)</td>
<td>0.69 (0.60–0.80)*</td>
</tr>
<tr>
<td>0.63 (0.54–0.74)</td>
<td>0.80 (0.73–0.87)</td>
</tr>
<tr>
<td>0.57 (0.50–0.66)</td>
<td>0.75 (0.65–0.85)</td>
</tr>
</tbody>
</table>

**All-cause death**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>Treatment vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.84 (0.74–0.95)</td>
<td>0.66 (0.53–0.81)</td>
</tr>
<tr>
<td>0.76 (0.62–0.93)</td>
<td>0.84 (0.76–0.93)</td>
</tr>
<tr>
<td>0.72 (0.61–0.85)</td>
<td>0.83 (0.71–0.97)</td>
</tr>
</tbody>
</table>

**Cardiovascular death**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>Treatment vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.83 (0.72–0.94)</td>
<td>0.62 (0.50–0.78)</td>
</tr>
<tr>
<td>0.76 (0.61–0.94)</td>
<td>0.80 (0.71–0.89)</td>
</tr>
<tr>
<td>0.66 (0.56–0.79)</td>
<td>0.82 (0.69–0.98)</td>
</tr>
</tbody>
</table>

**Heart failure hospitalization**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>Treatment vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.64 (0.56–0.74)</td>
<td>0.69*</td>
</tr>
<tr>
<td>0.58 (0.47–0.70)</td>
<td>0.79 (0.71–0.89)</td>
</tr>
<tr>
<td>0.51 (0.42–0.61)</td>
<td>0.70 (0.59–0.83)</td>
</tr>
</tbody>
</table>

ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CHARM, Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity; CI, confidence interval; CV, cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PARADIGM-HF, Prospective comparison of ARNI with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure; RASI, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SOLVD, Studies of Left Ventricular Systolic Dysfunction; *= not applicable.

*Hazard ratio for a composite of first HF hospitalization or CV death was not reported in MERIT-HF, thus the hazard ratio for a composite of HF hospitalization or all-cause death was used instead.

*Hazard ratio for HF hospitalization was not reported in MERIT-HF, thus rate ratio was used instead.
Sequence 1b) resulted in further reductions in fatal and non-fatal events over 12 months. Sequences 3, 4, and 5 enabled treatment with all four drugs most quickly (7 weeks) and Sequences 2, 3, and 5 enabled the initiation of three drugs by 3 weeks.

The best sequence for reducing the composite of heart failure hospitalization or cardiovascular death was Sequence 2 (SGLT2i/MRA/ARNI/beta-blocker). Compared with Sequence 1b, Sequence 2 was estimated to prevent 17 patients from experiencing this outcome (Structural graphical abstract); Sequence 3 led to a similar although slightly smaller gain. Consequently, when Sequence 2 was compared with the conventional approach (Sequence 1), the number of patients avoiding an event was almost doubled at 47 per 1000 treated due to both increasing the speed of up-titration and changing the order in which medications were introduced.

The best alternative sequence for reducing all-cause mortality was Sequence 3 (SGLT2i/MRA/beta-blocker/ARNI). Compared with
Sequence 1b, Sequence 3 was estimated to prevent \(\approx 5\) deaths per 1000 patients treated for 12 months (Supplementary material online, Table S4). If Sequence 3 was compared with the conventional approach (Sequence 1), the number of patients avoiding premature death was \(\approx 14\) per 1000, reflecting the impact of both more rapid up-titration and different ordering of the treatments examined.
Figure 2 (A) Cumulative incidence of the composite of heart failure hospitalization or cardiovascular death, after cumulative introduction of disease-modifying medications, assuming the effect of treatment starts midway through the up-titration period for each medication (Sequences 1, 1a, 1b, 2–5). The rates of clinical outcomes in treatment-naïve patients were based on the rates among patients who were randomized in the placebo arm in Studies of Left Ventricular Dysfunction-Treatment and who were in the placebo arm of Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity-Alternative and not treated with a beta-blocker or a mineralocorticoid receptor antagonist. The rate for the composite of heart failure hospitalization or cardiovascular death was 460 per 1000 person-years for the first 6 months and 200 per 1000 person-years thereafter. The upward arrows denote the introduction of certain medication at certain time point. The colours of the arrows and the lines indicate different medications, i.e. pink for renin–angiotensin system inhibitor, orange for beta-blocker, green for mineralocorticoid receptor antagonist, red for angiotensin receptor–neprilysin inhibitor, and blue for sodium–glucose cotransporter-2 inhibitor. The grey-dashed horizontal line denotes the probability of the clinical outcome at 12 months. ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CV, cardiovascular; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RASI, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter-2 inhibitor. (B) Cumulative incidence of all-cause death, after cumulative introduction of disease-modifying medications, assuming the effect of treatment starts midway through the up-titration period for each medication (Sequences 1, 1a, 1b, 2–5). The rate for all-cause mortality was 150 per 1000 person-years throughout. Other figure legends are the same as those in (A).
The cumulative risk reduction with each sequence of therapies is shown graphically for the composite of heart failure hospitalization or cardiovascular death and all-cause mortality in Figure 2A and B.

The sequences that had the least mortality benefit, using the principal scenario (the assumption that the treatment had a full effect from halfway through its up-titration period) were those starting with sacubitril/valsartan (Supplementary material online, Tables S5 and S6, Figures S2–S4).

The other two extreme scenarios, assuming the full effect of each treatment was present as soon as it was commenced, or that the full effect of each treatment was only evident once treatment was fully titrated, did not change the ranking of the treatment.
sequences in terms of events avoided, although did change the estimated number of events avoided (Supplementary material online, Tables S1 and S2).

**Impact of initiating two therapies simultaneously**

Lastly, we examined the impact of starting two therapies simultaneously, keeping the more rapid up-titration timeline for each drug (although starting two treatments together further shortened the time taken to fully titrate all treatments by up to 4 weeks), as shown in Figure 1 and Table 3.

Compared with Sequence 1b, the greatest incremental reduction in the composite of heart failure hospitalization or cardiovascular death was with the sequence starting with the combination of SGLT2i plus MRA, followed by an ARNI and then beta-blocker (the sequence SGLT2i plus MRA, followed by a beta-blocker, and then an ARNI was almost as effective). These sequences were estimated...
to prevent 21–22 events per 1000 patients treated over 12 months compared with Sequence 1b (Table 3) and 4–5 more events compared with the best accelerated-sequence described above, i.e. Sequence 2 (Table 2).

For all-cause mortality, an MRA plus beta-blocker, followed by SGLT2i and then an ARNI was most effective (the sequence SGLT2i plus MRA, followed by a beta-blocker and then an ARNI was the second most effective, as for the composite outcome). These sequences were estimated to prevent \( \approx 7 \) deaths per 1000 patients treated over 12 months compared with Sequence 1b (Table 3) and prevent 2 more deaths compared with the best accelerated-sequence described above, i.e. Sequence 3 (Table 2).

Of note, the sequence starting simultaneously with a beta-blocker plus ARNI, followed by SGLT2i and then an MRA, substantially shortened the theoretical total time to full titration of all treatments (to only 8 weeks) but was not particularly effective in further reducing the risk of either outcome.

The cumulative risk reduction with each sequence of therapies is shown graphically for the composite of heart failure hospitalization or cardiovascular death and all-cause mortality in Figure 3A and B.
The other scenarios, as described above, are shown in Supplementary material online, Tables S7–S10.

Discussion

Our findings show that the conventional approach to implementation of the core pharmacological treatments for HFrEF may not be the best and that alternative approaches could lead to a substantial reduction in lives lost and hospital admissions for worsening heart failure. Specifically, our modelling suggests that at least 14 more people per 1000 treated might survive the first year after diagnosis, and triple that number of patients avoid a first hospital admission for worsening heart failure or death from a cardiovascular cause, if therapy was initiated in a different sequence and up-titrated in a faster, but realistic, manner (Structural graphical abstract). These findings remained robust in a variety of sensitivity analyses, although they are based on modelling of the results of trials in a patient cohort.

The conventional stepwise approach to therapy in guidelines recommends that each treatment is added in a sequence reflecting the chronological order in which trials were conducted. However, if the effects of our life-saving therapies are mechanistically distinct, independent, and additive, the order in which treatments are added should not depend on which trial was done first but on other considerations such as the size of the effect, speed of onset of benefit, and time taken to up-titrade to the target dose. This philosophy also argues for the implementation of as many effective therapies as possible, as rapidly as possible. If they act independently, additively,
been shown to be practicable and safe in a variety of studies.16 and SGLT2i for 1 week) are feasible in many patients and have already weeks, beta-blocker for 4 weeks, MRA for 2 weeks, ARNI for 5 weeks, the early gains, given the incremental bene

<table>
<thead>
<tr>
<th>Medication order</th>
<th>Seq. 1b</th>
<th>Seq. duo 1</th>
<th>Seq. duo 2</th>
<th>Seq. duo 3</th>
<th>Seq. duo 4</th>
<th>Seq. duo 5</th>
<th>Seq. duo 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up-titration duration (weeks)</td>
<td>12</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>8</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>HF hospitalization or CV death</td>
<td>Ref</td>
<td>−20.8</td>
<td>−21.7</td>
<td>−15.9</td>
<td>−15.8</td>
<td>−19.1</td>
<td>−19.8</td>
</tr>
<tr>
<td>Mean event-free time lost (months)</td>
<td>0.87</td>
<td>0.64</td>
<td>0.63</td>
<td>0.69</td>
<td>0.70</td>
<td>0.66</td>
<td>0.65</td>
</tr>
<tr>
<td>All-cause death</td>
<td>ref</td>
<td>0.23</td>
<td>0.24</td>
<td>0.18</td>
<td>0.17</td>
<td>0.21</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean event-free time lost with Sequence 1b (months)</td>
<td>0.41</td>
<td>0.34</td>
<td>0.35</td>
<td>0.34</td>
<td>0.34</td>
<td>0.33</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean gain in event-free time compared with Sequence 1b (months)</td>
<td>0.07</td>
<td>0.06</td>
<td>0.07</td>
<td>0.07</td>
<td>0.08</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

The abbreviations are the same as those in Figure 2. The detailed illustration of sequences using duos 1–6 examined can be seen in Figure 1.

Accelerated and personalized therapy for HFrEF

and quickly (which is what the evidence shows), then the goal should be to protect the patient with all these treatments, as soon as that can be done, practically.6–8,15 To put it bluntly, delays in maximizing pharmacological protection means lives lost.

Consequently, we modelled two alternatives to the current approach to treatment. One was to maintain the conventional sequence of therapies and shorten the time taken to up-titrage each treatment to its target dose. The other was to consider several different orders in which treatments could be sequenced, using the accelerated up-titration schedule. Shortening the time taken to up-titration alone accounted for around half the total estimated reduction in deaths and hospitalizations we calculated was possible with the optimum treatment approach identified. This, of course, was entirely expected—the more rapidly each of the drugs in question can be added, the greater the early gains, given the incremental benefit of these treatments. We believe that the shortened titration periods modelled (RASi for 4 weeks, beta-blocker for 4 weeks, MRA for 2 weeks, ARNI for 5 weeks, and SGLT2i for 1 week) are feasible in many patients and have already been shown to be practicable and safe in a variety of studies.16–18

The new sequences included both the more rapid up-titration and sequencing of the therapies of interest in a different order. When examining new treatment sequences, we did not consider starting with a RASI alone as that approach has the least overall mortality benefit [hazard ratio (HR) 0.84, 95% confidence interval (CI) 0.74–0.95] and the greatest inherent delay in completing initiation of all five life-saving therapies.6–8 Instead, we only considered using a RASI combined with a neprilysin inhibitor (i.e. sacubitril/valsartan) as the reduction in mortality in this dual therapy is large (HR 0.72, 0.61–0.85, in an imputed placebo analysis)13 and it is well-tolerated as initial treatment.16–18 However, this approach was not as beneficial as the alternative new sequences examined. In part, this was because the attainment of the target dose of sacubitril/valsartan involves two or three titration steps (depending on the starting dose), with checks of electrolytes and renal function at each dose step, and even with an accelerated regimen, we estimated 5 weeks were required for dose titration.16–18 The most effective alternative sequences were those starting either with an SGLT2i or an MRA, reflecting the fact that the former treatment is administered in a single fixed dose and the latter has a maximum of two dose steps.4,5,11 The slight differences between the various sequences tested, for the two outcomes examined, reflected the smaller effect of SGLT2i on all-cause mortality (HR 0.83, 0.71–0.97), compared with an MRA (HR 0.76, 0.62–0.93), balanced against the delay in up-titrating to the full dose of the latter.4,5,11 Although beta-blockers are the most effective treatment at reducing mortality (HR 0.66, 0.53–0.81), they have the slowest up-titration regimen, reflecting legacy concerns about using these drugs in HFrEF.10,19 Recommended starting doses are between one-sixteenth and one-eighth of the ‘target dose’, with doubling dose steps typically recommended at not <2 weekly intervals.1,2 However, even with the shortening of the up-titration period...
to 4 weeks in our accelerated dosing approach, a ‘beta-blocker first’ strategy did not result in better outcomes than the alternative sequencing approaches, although it had been anticipated that it would.6–8 Likewise, the additional benefit of starting two therapies simultaneously, as has been advocated recently, had modest incremental benefit.6–8

Our study involved modelling the results of trials in an untreated patient cohort and was designed to illustrate how accelerating up-titration and different approaches to the order in which treatments is sequenced might lead to different outcomes. In this modelling, we made several assumptions, including that the adherence rate to and the average daily dose of each of the five life-saving medications were the same as those reported in the randomized trials testing these drugs. Given the adoption of these life-saving drugs in real-world practice is not as adequate as that observed from clinical trials, the maximum gains from these life-saving drugs were likely to be lower in real-world scenarios than observed in this study. We did not examine every permutation of all possible variables related to treatment sequencing and others might further optimize outcome. For example, we only considered starting a new therapy after the dose of the previous treatment had been maximized. Yet we do not know whether a month after diagnosis of HFrEF, is it better to be on a full dose of one therapy or to be on a low dose of three. Although clinical experience has taught us that some of the up-titration regimens recommended in guidelines are too conservative for many patients, the potential benefit of faster titration must be weighed against the potential danger of inducing intolerance and not achieving the ‘target dose’, especially as there is a dose-related benefit for at least some therapies.20,21 There is also the practical consideration of checking blood chemistry, repeatedly, in a short-time window (although, again, our approach here may also be too conservative in many patients). Some of the sequences examined may be more suitable for some patients than others and additional considerations relevant to tolerability, such as blood pressure and kidney function, must be considered, along with synergies between drugs (e.g. the slowed rate of decline in glomerular filtration rate and reduction in hyperkalaemia with nepri-lysin and SGLT2 inhibition).22–24 An accelerated introduction of multiple treatments may not be as feasible in elderly patients with multi-morbidity. However, the examples provided are offered as a challenge to the conventional, conservative, approach to pharmacological treatment of patients with HFrEF in the outpatient setting to illustrate why this probably does not best serve our patients.6–8 A particular order of use of treatments might not suit all patients equally and tailoring the sequence to patient characteristics may also be appropriate.25

There are additional limitations to analyses. The assumption underlying our approach is that all patients with HFrEF should receive every effective treatment if tolerated. Some patients may no longer have symptoms after only one or two treatments are introduced and may have exhibited substantial improvement in LVEF. Perhaps such individuals do not need the addition of a third or fourth treatment? However, we know that all three of the original foundational therapies are beneficial in patients with left ventricular systolic dysfunction, irrespective of symptoms and this is likely true for nepri-lysin and SGLT2 inhibition as well.26–29 Furthermore, although ejection fraction may increase with treatment, complete recovery is uncommon.30 Even if this imaging measure appears to have normalized, ventricular architecture, function, and electrical stability probably have not and de-escalation of neurohumoral antagonist therapy results in worse outcomes.30,31

In summary, compared with conventional up-titration schedules and recommended sequencing of drug therapy in HFrEF, an accelerated up-titration schedule and optimized ordering of treatment could prevent at least 14 deaths and more than three times as many patients experiencing heart failure hospitalization or cardiovascular death per 1000 treated over the first 12 months after starting therapy. Standard treatment guidance may not lead to the best patient outcomes in HFrEF and alternative approaches should be tested in clinical trials.

**Supplementary material**

**Supplementary material** is available at European Heart Journal online.

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