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1 **Title:** Potential reductions in mortality and hospitalization with
2 accelerated up-titration and personalized sequencing of therapy
3 in patients with heart failure and reduced ejection fraction.
4

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ABSTRACT

Aims: Previously, guidelines recommend 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. We investigated whether this historical approach is optimal and alternative approaches may improve patient outcomes.

Methods and results: Using data from 6 pivotal trials in HFrEF, we modelled the potential reductions in events that might result from a) more rapid up-titration of therapies used in the conventional order (based on the chronology of the trials), and b) accelerated up-titration and using treatments in different orders than is conventional. 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 7 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 6 fewer deaths at 12 months. The optimal alternative sequences included SGLT2 inhibition and an MRA 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.

Key words: Heart Failure, Pharmacology, Treatment, Mortality, Hospitalization

- 1 **One-sentence Summary:** The standard order in which treatments for heart failure are started
- 2 may not lead to the best patient outcomes and alternative approaches may be better.

INTRODUCTION

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

25

METHODS

Study trials

We used 5 trials conducted in patients with HFrEF to estimate the treatment effects of the 5 life-saving medications. The effects of renin-angiotensin system inhibition (RASi) was based on the Studies of Left Ventricular Dysfunction (SOLVD)-Treatment trial,⁹ the effect of beta-blockers was based on the Metoprolol CR/XL Randomised 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 trial (PARADIGM-HF) and SGLT2 inhibitors on the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF).^{3,4} 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,^{9,12} not receiving a beta-blocker or an MRA, to create a “treatment-naïve” HFrEF population (i.e., patients not receiving any of the 5 pharmacological therapies reducing mortality) and this dataset was used to generate the rates of the clinical outcomes of interest.

Briefly, SOLVD-treatment randomised 2569 heart failure patients who had a left ventricular ejection fraction (LVEF) $\leq 35\%$ 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,

1 the mean daily dose was 16.6 mg for enalapril.⁹ In CHARM-Alternative, 2028 patients who
2 had New York Heart Association (NYHA) class II-IV heart failure and LVEF \leq 40%,
3 intolerant of ACEIs, were randomly assigned to candesartan or placebo. The initial dose was
4 4 mg or 8 mg once daily and the dose was doubled, as tolerated, at a minimum of every 2
5 weeks, to a target dose of 32 mg once daily. A total of 24% of patients in the candesartan
6 group discontinued the study drug for reasons other than death. At 6 months, the mean daily
7 dose among those taking the study drug was 23 mg for candesartan.¹² MERIT-HF enrolled
8 3991 symptomatic heart failure patients with LVEF \leq 40%, receiving standard therapy
9 defined as any combination of diuretics and an ACE inhibitor at enrolment. After a 2-week
10 single-blind placebo run-in period, patients were randomly assigned to metoprolol CR/XL 25
11 mg once daily (or 12.5 mg once daily if in NYHA III-IV) or placebo. The target dose was
12 200 mg once daily and doses were up-titrated over 8 weeks. At the end of the trial, study drug
13 was discontinued in 13.9% of patients in the metoprolol CR/XL group, and the mean daily
14 dose in the metoprolol CR/XL group was 159 mg.¹⁰ EMPHASIS-HF enrolled 2737 patients
15 aged at least 55 years with NYHA class II heart failure and an LVEF \leq 35%, treated with an
16 ACEI or ARB and beta-blocker. Eligible patients were randomly assigned to receive
17 eplerenone 25 mg once daily (increased to 50 mg once daily after 4 weeks) or placebo. The
18 study drug was stopped in 16.3% of patients receiving eplerenone. After completion of the
19 dose-adjustment phase at 5 months, the mean (\pm SD) daily dose of eplerenone was 39.1 \pm 13.8
20 mg among those taking the study drug.¹¹ PARADIGM-HF enrolled 8399 patients with
21 symptomatic heart failure, LVEF \leq 40% and an elevated plasma natriuretic peptide. Patients
22 were required to tolerate the equivalent of enalapril 10 mg daily for at least 4 weeks before
23 screening, along with a stable dose of a beta-blocker (unless contraindicated or not tolerated)
24 and an MRA (if indicated). Patients who tolerated sequential enalapril and sacubitril/valsartan
25 run-in periods were randomized to either sacubitril/valsartan (target dose 97/103 mg twice

1 daily) or enalapril (target dose 10 mg twice daily). Sacubitril/valsartan was discontinued in
2 17.8% of patients for reasons other than death. Among patients taking the study drug, the
3 mean (\pm SD) daily dose was 375 ± 71 mg for sacubitril/valsartan at the final visit.³ In DAPA-
4 HF 4744 patients with NYHA class II-IV symptoms and LVEF $\leq 40\%$, with an elevated
5 plasma natriuretic peptide level, were randomly assigned to either dapagliflozin (10 mg once
6 daily) or placebo. Patients were required to receive guideline-recommended medical and
7 device therapy, including an ACE inhibitor/ARB or sacubitril/valsartan, a beta-blocker and
8 an MRA, unless contraindicated or not tolerated. Dapagliflozin was stopped for reasons other
9 death in 10.5% of patients. At the last assessment, 98.1% of the patients who were still taking
10 dapagliflozin continued to receive the target dose.⁴

11

12 **Outcomes of interest**

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

22

23 **Statistical analysis**

24 We used the Kaplan-Meier estimates to generate the event rates for clinical outcomes of
25 interest in the treatment-naïve HFrEF cohort. As the risk of heart failure hospitalization was

1 relatively high early after randomization and lower thereafter, the risks of heart failure
2 hospitalization and the composite of heart failure hospitalization or cardiovascular death were
3 estimated separately within 6 months and beyond 6 months. The published hazard ratios on
4 the outcomes of interest for the various therapies tested in the trials listed above were used as
5 their treatment effects, with one exception.^{3, 4, 9-11, 13} The hazard ratio for the composite of
6 heart failure hospitalization or cardiovascular death was not reported in MERIT-HF and the
7 hazard ratio for a composite of heart failure hospitalization or all-cause death was used
8 instead.¹⁰

9

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

24

1 We estimated the event probability and mean event-free time lost at 1 year, 2 years and 3
2 years in patients receiving none of the treatments examined and then in patients treated with
3 the medications started in the sequences described above (see Supplementary methods for
4 detailed information). Our analysis made several assumptions, including that the survival
5 times for the clinical outcomes follows an exponential survival distribution, i.e., the hazard
6 (or event rate) is constant over time. For all-cause death and cardiovascular death, a constant
7 rate was used throughout the follow-up, and for the composite of heart failure hospitalization
8 or cardiovascular death and heart failure hospitalization individually, a constant rate was
9 applied to within 6 months and thereafter with two different rates for each of these periods.
10 We also assumed that in this cohort, the adherence rate to, and the average daily dose of, each
11 of the 5 life-saving medications was the same as those reported in the randomized trials
12 testing these drugs (Table 1), that the relative risk reduction with each medication is
13 independent and additive (i.e., the benefit of each therapy is constant, regardless of any of or
14 the combination of background treatment), and that the hazards in the with- and without-
15 treatment groups for each medication were proportional. In our primary analysis, we assumed
16 that each treatment exerted its full effect from halfway through its up-titration period (and
17 had no effect before that); we also conducted two sensitivity analyses, one assuming the full
18 effect of each medication was present from the commencement of treatment and the other
19 that the full effect was only evident once the medication was fully titrated. We also examined
20 the mean event-free time lost by calculating the area under the time-event-probability curve
21 by 1 year, 2 years and 3 years.¹⁴ The mean event-free time lost at a certain time point
22 indicates by the time point examined the average event-free time lost for one patient. For
23 example, by 1 year 100 out of 1000 patients died, assuming the event rate is constant, the
24 mean event-free time (i.e., survival time) lost at 1 year is approximately 0.6 months for one
25 patient on average and is around 50 years for 1000 patients in total. We also calculated the

1 differences in event probability and mean event-free time gain in Sequence 2-12 compared to
2 conventional Sequence 1, Sequence 1a and Sequence 1b. Separately, we compared the
3 sequences using starting combinations of treatment (Sequences using duos 1-6), compared
4 with Sequence 1b.

5

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

RESULTS

Event rates in “treatment-naïve” HFrEF 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 summarised in Table 1.

Titration schedules and drug sequences examined

Figure 1, shows the conventional sequence of treatments (Sequence 1) using, in order a RASi, beta-blocker, MRA, ARNI (switching from a RASi) and 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

1 treatment exerted its full effect from halfway through the up-titration period (the other
2 scenarios are described in Supplementary material online, Tables S1 and S2).

3
4 The results of applying each of the different treatment sequences on the two endpoints of
5 interest are shown in Figure 2a (heart failure hospitalization or cardiovascular death) and
6 Figure 2b (all-cause death) and the difference in numbers of events and event-free survival
7 after 12 months in Table 2 (the differences in these outcomes over 24 and 36 months are
8 described in the Supplementary material online, Table S3).

9
10 The results of applying the different treatment sequences starting with two drugs
11 simultaneously are also shown in Figures 1 and 3 and the difference in numbers of events and
12 event-free survival after 12 months in Table 3.

13

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

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

21

22 **Impact of accelerating up-titration and changing the order of drug-sequencing**

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

1 The first option considered (Sequence 1b) was starting with an ARNI rather than a RASi, and
2 up-titrating all drugs rapidly, as in sequence 1a. Because this avoided starting with a RASi
3 and later switching to an ARNI, the total time taken for up-titration was reduced from 16 to
4 12 weeks. Compared with sequence 1a, sequence 1b was estimated to result in approximately
5 8 fewer patients experiencing heart failure hospitalization or cardiovascular death, and 1 less
6 death, in the first 12 months after starting treatment.

7

8 The next options considered also used an ARNI rather than a RASi in the various drug
9 sequences examined and, in each of these sequences, the total time taken for up-titration was
10 always 12 weeks. The most effective alternative approaches (Sequences 2-5 versus Sequence
11 1b) resulted in further reductions in fatal and non-fatal events over 12 months. Sequences 3,
12 4, and 5 enabled treatment with all 4 drugs most quickly (7 weeks) and sequences 2, 3 and 5
13 enabled the initiation of 3 drugs by 3 weeks.

14

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

22

23 The best alternative sequence for reducing all-cause mortality was Sequence 3
24 (SGLT2i/MRA/beta-blocker/ARNI). Compared with Sequence 1b, Sequence 3 was estimated
25 to prevent approximately 5 deaths per 1000 patients treated for 12 months; Sequences 4 and 5

1 resulted in slightly smaller gains compared to Sequence 3 (the same findings were seen for
2 cardiovascular death - Supplementary material online, Table S4). If Sequence 3 was
3 compared with the conventional approach (Sequence 1), the number of patients avoiding
4 premature death was approximately 14 per 1000, reflecting the impact of both more rapid up-
5 titration and different ordering of the treatments examined.

6

7 The cumulative risk reduction with each sequence of therapies is shown graphically for the
8 composite of heart failure hospitalization or cardiovascular death and all-cause mortality in
9 Figures 2a and 2b.

10

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

15

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

21

22 **Impact of initiating two therapies simultaneously**

23 Lastly, we examined the impact of starting two therapies simultaneously, keeping the more
24 rapid up-titration timeline for each drug (although starting two treatments together further

1 shortened the time taken to fully-titrate all treatments by up to 4 weeks), as shown in Figure 1
2 and Table 3.

3

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

11

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

18

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

23

1 The cumulative risk reduction with each sequence of therapies is shown graphically for the
2 composite of heart failure hospitalization or cardiovascular death and all-cause mortality in
3 Figures 3a and 3b.

4

5 The other scenarios, as described above, are shown in Supplementary material online, Tables
6 S7-S10.

DISCUSSION

1
2 Our findings show that the conventional approach to implementation of the core
3 pharmacological treatments for HFrEF may not be the best and that alternative approaches
4 could lead to a substantial reduction in lives lost and hospital admissions for worsening heart
5 failure. Specifically, our modelling suggests that at least 14 more people per 1000 treated
6 might survive the first year after diagnosis, and triple that number of patients avoid a first
7 hospital admission for worsening heart failure or death from a cardiovascular cause, if
8 therapy was initiated in a different sequence and up-titrated in a faster, but realistic, manner.
9 These findings remained robust in a variety of sensitivity analyses, although are based on
10 modelling of the results of trials in a patient cohort.

11
12 The conventional stepwise approach to therapy in guidelines recommends that each treatment
13 is added in a sequence reflecting the chronological order in which trials were conducted.^{1,2}
14 However, if the effects of our life-saving therapies are mechanistically distinct, independent
15 and additive, the order in which treatments are added should not depend on which trial was
16 done first but on other considerations such as the size of the effect, speed of onset of benefit
17 and time taken to up-titrate to the target dose. This philosophy also argues for the
18 implementation of as many effective therapies as possible, as rapidly as possible. If they act
19 independently, additively and quickly (which is what the evidence shows), then the goal
20 should be to protect the patient with all these treatments, as soon as that can be done,
21 practically.^{6-8, 15} To put it bluntly, delays in maximising pharmacological protection means
22 lives lost.

23
24 Consequently, we modeled two alternatives to the current approach to treatment. One was to
25 maintain the conventional sequence of therapies and shorten the time taken to up-titrate each

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

11

12 The new sequences included both the more rapid up-titration and sequencing of the therapies
13 of interest in a different order. When examining new treatment sequences, we did not
14 consider starting with a RASi alone as that approach has the least overall mortality benefit
15 (hazard ratio 0.84, 95% confidence interval: 0.74-0.95) and the greatest inherent delay in
16 completing initiation of all 5 life-saving therapies.⁶⁻⁸ Instead, we only considered using a
17 RASi combined with a neprilysin inhibitor (i.e., sacubitril/valsartan) as the reduction in
18 mortality with this dual therapy is large (hazard ratio 0.72, 0.61-0.85, in an imputed placebo
19 analysis)¹³ and it is well-tolerated as initial treatment.¹⁶⁻¹⁸ However, this approach was not as
20 beneficial as the alternative new sequences examined. In part, this was because the attainment
21 of the target dose of sacubitril/valsartan involves two or three titration steps (depending on
22 the starting dose), with checks of electrolytes and renal function at each dose-step, and even
23 with an accelerated regimen, we estimated 5 weeks were required for dose-titration.¹⁶⁻¹⁸ The
24 most effective alternative sequences were those starting either with SGLT2i or an MRA,
25 reflecting the fact that the former treatment is administered in a single fixed dose and the

1 latter has a maximum of two dose steps.^{4, 5, 11} The slight differences between the various
2 sequences tested, for the two outcomes examined, reflected the smaller effect of SGLT2i on
3 all-cause mortality (hazard ratio 0.83, 0.71-0.97), compared with an MRA (0.76, 0.62-0.93),
4 balanced against the delay in up-titrating to the full dose of the latter.^{4, 5, 11} Although beta-
5 blockers are the most effective treatment at reducing mortality (hazard ratio 0.66, 0.53-0.81)
6 they have the slowest up-titration regimen, reflecting legacy concerns about using these drugs
7 in HFrEF.^{10, 19} Recommended starting doses are between one-sixteenth and one-eighth of the
8 “target dose”, with doubling dose steps typically recommended at not less than 2-weekly
9 intervals.^{1, 2} However, even with the shortening of the up-titration period to 4 weeks in our
10 accelerated dosing approach, a “beta-blocker first” strategy did not result in better outcomes
11 than the alternative sequencing approaches, although it had been anticipated that it would.⁶⁻⁸
12 Likewise, the additional benefit of starting two therapies simultaneously, as has been
13 advocated recently, had modest incremental benefit.⁶⁻⁸

14
15 Our study involved modelling the results of trials in an untreated patient cohort and was
16 designed to illustrate how accelerating up-titration and different approaches to the order in
17 which treatments is sequenced might lead to different outcomes. In this modelling we made
18 several assumptions, including that the adherence rate to, and the average daily dose of, each
19 of the 5 life-saving medications were the same as those reported in the randomized trials
20 testing these drugs. Given the adoption of these life-saving drugs in real-world practice is not
21 as adequate as that observed from clinical trials, the maximum gains from these life-saving
22 drugs were likely to be lower in real-world scenarios than observed in this study. We did not
23 examine every permutation of all possible variables related to treatment sequencing and
24 others might further optimize outcome. For example, we only considered starting a new
25 therapy after the dose of the previous treatment had been maximized. Yet we do not know,

1 whether a month after diagnosis of HFrEF, is it better to be on a full dose of one therapy or to
2 be on a low dose of three. Although clinical experience has taught us that some of the up-
3 titration regimens recommended in guidelines are too conservative for many patients, the
4 potential benefit of faster titration must be weighed against the potential danger of inducing
5 intolerance and not achieving the “target dose”, especially as there is a dose-related benefit
6 for at least some therapies.^{20, 21} There is also the practical consideration of checking blood
7 chemistry, repeatedly, in a short time window (although, again, our approach here may also
8 be too conservative in many patients). Some of the sequences examined may be more suitable
9 for some patients than others and additional considerations relevant to tolerability, such as
10 blood pressure and kidney function, must be considered, along with synergies between drugs
11 (e.g. the slowed rate of decline in glomerular filtration rate and reduction in hyperkalaemia
12 with neprilysin and SGLT2 inhibition).²²⁻²⁴ An accelerated introduction of multiple
13 treatments may not be as feasible in elderly patients with multi-morbidity. However, the
14 examples provided are offered as a challenge to the conventional, conservative, approach to
15 pharmacological treatment of patients with HFrEF in the outpatient setting to illustrate why
16 this probably does not best serve our patients.⁶⁻⁸ A particular order of use of treatments might
17 not suit all patients equally and tailoring the sequence to patient characteristics may also be
18 appropriate.²⁵

19
20 There are additional limitations to analyses. The assumption underlying our approach is that
21 all patients with HFrEF should receive every effective treatment if tolerated. Some patients
22 may no longer have symptoms after only one or two treatments are introduced and may have
23 exhibited substantial improvement in left ventricular ejection fraction. Perhaps such
24 individuals do not need the addition of a third or fourth treatment? However, we know that all
25 three of the original foundational therapies are beneficial in patients with left ventricular

1 systolic dysfunction, irrespective of symptoms and this is likely true for neprilysin and
2 SGLT2 inhibition as well.²⁶⁻²⁹ Furthermore, although ejection fraction may increase with
3 treatment, complete recovery is uncommon.³⁰ Even if this imaging measure appears to have
4 normalized, ventricular architecture, function and electrical stability probably have not and
5 de-escalation of neurohumoral antagonist therapy results in worse outcomes.^{30, 31}

6

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

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6

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FIGURE LEGENDS

1

2 **Figure 1.** Medication sequences and duration of up-titration periods (Sequences 1, 1a, 1b, 2-
3 5, and duos 1-6)

4 **Figure 2a.** Cumulative incidence of the composite of HF hospitalization or CV death, after
5 the cumulative introduction of disease-modifying medications, assuming the effect of
6 treatment starts midway through the up-titration period for each medication (Sequences 1, 1a,
7 1b, 2-5)

8 **Figure 2b.** Cumulative incidence of all-cause death, after the cumulative introduction of
9 disease-modifying medications, assuming the effect of treatment starts midway through the
10 up-titration period for each medication (Sequences 1, 1a, 1b, 2-5)

11 **Figure 3a.** Cumulative incidence of the composite of HF hospitalization or CV death, after
12 the cumulative introduction of disease-modifying medications, assuming the effect of
13 treatment starts midway through the up-titration period for each medication (Sequences using
14 duos 1-6)

15 **Figure 3b.** Cumulative incidence of all-cause death, after the cumulative introduction of
16 disease-modifying medications, assuming the effect of treatment starts midway through the
17 up-titration period for each medication (Sequences using duos 1-6)

1 **SUPPLEMENTARY MATERIAL**

2 **Supplementary methods**

3 Illustration of modelling methods

4

5 **Supplementary Tables**

6 **Table S1.** Event probability and mean event-free time lost for the clinical outcomes at 1 year,
7 2 years and 3 years, according to different medication sequences (Sequences 1, 1a, 1b, 2-12)
8 compared to no treatment, assuming treatment effects starting on the first dose of the
9 medications

10 **Table S2.** Event probability and mean event-free time lost for the clinical outcomes at 1 year,
11 2 years and 3 years, according to different medication sequences (Sequences 1, 1a, 1b, 2-12)
12 compared to no treatment, assuming treatment effects starting at the end of up-titration of the
13 medications

14 **Table S3.** Event probability and mean event-free time lost for the composite of HF
15 hospitalization or CV death and all-cause death at 2 years and 3 years, according to different
16 medication sequences (Sequences 1, 1a, 1b, 2-5) compared to no treatment, assuming
17 treatment effects starting half-way through up-titration of the medications.

18 **Table S4.** Event probability and mean event-free time lost for cardiovascular death and heart
19 failure hospitalization at 1 year, 2 years and 3 years, according to different medication
20 sequences (Sequences 1, 1a, 1b, 2-5) compared to no treatment, assuming treatment effects
21 starting half-way through up-titration of the medications.

22 **Table S5.** Event probability and mean event-free time lost for the composite of HF
23 hospitalization or CV death and all-cause death at 1 year, 2 years and 3 years, according to
24 different medication sequences (Sequences 6-12) compared to no treatment, assuming
25 treatment effects starting half-way through up-titration of the medications.

1 **Table S6.** Event probability and mean event-free time lost for cardiovascular death and heart
2 failure hospitalization at 1 year, 2 years and 3 years, according to different medication
3 sequences (Sequences 6-12) compared to no treatment, assuming treatment effects starting
4 half-way through up-titration of the medications.

5 **Table S7.** Event probability and mean event-free time lost for the clinical outcomes at 1 year,
6 2 years and 3 years, according to different medication sequences (Sequences using duos 1-6)
7 compared to sequence 1b, assuming treatment effects starting on the first dose of the
8 medications.

9 **Table S8.** Event probability and mean event-free time lost for the clinical outcomes at 1 year,
10 2 years and 3 years, according to different medication sequences (Sequences using duos 1-6)
11 compared to sequence 1b, assuming treatment effects starting at the end of up-titration of the
12 medications.

13 **Table S9.** Event probability and mean event-free time lost for the composite of HF
14 hospitalization or CV death and all-cause death at 2 years and 3 years, according to different
15 medication sequences (Sequences using duos 1-6) compared to Sequence 1b, assuming
16 treatment effects starting half-way through up-titration of the medications.

17 **Table S10.** Event probability and mean event-free time lost for cardiovascular death and
18 heart failure hospitalization at 1 year, 2 years and 3 years, according to different medication
19 sequences (Sequences using duos 1-6) compared to Sequence 1b, assuming treatment effects
20 starting half-way through up-titration of the medications.

21

22 **Supplementary Figures**

23 **Figure S1.** Survival curves for the clinical outcomes using the Kaplan-Meier approach and
24 based on an exponential survival distribution in treatment-Naïve patients with HFrEF

25

1 **Figure S2.** Medication sequences and up-titration durations (Sequences 6-12)

2

3 **Figure S3.** Cumulative incidence of the composite of HF hospitalization or CV death, after

4 cumulative introduction of disease modifying medications, assuming treatment effects

5 starting midway through up-titration of the medications (Sequences 6-12)

6

7 **Figure S4.** Cumulative incidence of all-cause death, after cumulative introduction of disease

8 modifying medications, assuming treatment effects starting midway through up-titration of

9 the medications (Sequences 6-12)

10

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

	RASi	BB	MRA	ARNI	ARNI	SGLT2i
Trial	SOLVD-Treatment	MERIT-HF	EMPHASIS-HF	PARADIGM-HF	PARADIGM-HF versus SOLVD-Treatment & CHARM-Alternative	DAPA-HF
Number of patients	2569	3991	2737	8399	-	4744
Study patients	NYHA II-IV, LVEF≤35%	NYHA II-IV, LVEF≤40%	NYHA II, LVEF≤35%	NYHA II-IV, LVEF≤40%	-	NYHA II-IV, LVEF≤40%
Key baseline therapy	BB 8%, potassium sparing diuretic 9%	RASi 96%, MRA 8%	RASi 94%, BB 87%	RASi 100%, BB 93%, MRA 56%	-	RASi 94%, BB 96%, MRA 71%, ARNI 11%
Test treatment	Enalapril	Metoprolol CR/XL	Eplerenone	Sacubitril/valsartan	Sacubitril/valsartan	Dapagliflozin
Control treatment	Placebo	Placebo	Placebo	Enalapril	Putative placebo	Placebo

Discontinuation percentage in the experimental arm	32.5%	13.9%	16.3%	17.8%	-	10.5%
Mean daily dose in those taking the study drug /target dose	16.6mg/20mg	159mg/200mg	39.1±13.8mg/50mg	375±71 mg/400 mg	-	98.1% taking the target dose of 10 mg daily
Cardiovascular death or heart failure hospitalization						
HR (95% CI) Treatment versus control	0.72 (0.64-0.80)	†0.69 (0.60-0.80)	0.63 (0.54-0.74)	0.80 (0.73-0.87)	0.57 (0.50-0.66)	0.75 (0.65-0.85)
All-cause death						
HR (95% CI) Treatment versus control	0.84 (0.74-0.95)	0.66 (0.53-0.81)	0.76 (0.62-0.93)	0.84 (0.76-0.93)	0.72 (0.61-0.85)	0.83 (0.71-0.97)
Cardiovascular death						
HR (95% CI) Treatment versus control	0.83 (0.72-0.94)	0.62 (0.50-0.78)	0.76 (0.61-0.94)	0.80 (0.71-0.89)	0.66 (0.56-0.79)	0.82 (0.69-0.98)
Heart failure hospitalization						

HR (95% CI)	0.64 (0.56-0.74)	‡0.69	0.58 (0.47-0.70)	0.79 (0.71-0.89)	0.51 (0.42-0.61)	0.70 (0.59-0.83)
Treatment versus control						

ARNI denotes angiotensin receptor neprilysin inhibitor; BB, beta-blocker; CHARM-Alternative, the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity Alternative study; CI, confidence interval; CV, cardiovascular; DAPA-HF, the Dapagliflozin And Prevention of Adverse outcomes in Heart Failure trial; EMPHASIS-HF, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure trial; HR, hazard ratio; LVEF, left ventricular ejection fraction; MERIT-HF, the Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure trial; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PARADIGM-HF, the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SOLVD-Treatment, the Study Of Left Ventricular Dysfunction Treatment trial.

‘-’ denotes 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.

Table 2. Event probability and mean event-free time lost for the composite of HF hospitalization or CV death and all-cause death at 1 year, according to the different medication sequences examined (Sequences 1, 1a, 1b, 2-5), compared to no treatment, assuming the effect of treatment starts half-way through up-titration period for each medication.

Sequence	No treatment	Seq. 1	Seq. 1a	Seq. 1b	Seq. 2	Seq. 3	Seq. 4	Seq. 5
Medication order	None	RASi /BB /MRA	RASi /BB /MRA	ARNI/ BB/ MRA/	SGLT2i /MRA /ARNI	SGLT2i /MRA /BB	SGLT2i /BB /MRA	MRA/ SGLT2i /BB
Up-titration duration (weeks)	-	24	16	12	12	12	12	12
HF hospitalization or CV death								
Event probability, per 1000 persons	280.4	128.8	106.0	98.3	81.5	82.5	87.3	83.6
Difference in event probability compared to Sequence 1, per 1000 persons	151.6	ref	-22.8	-30.5	-47.3	-46.3	-41.5	-45.2

Difference in event probability compared to Sequence 1a, per 1000 persons	174.4	22.8	ref	-7.7	-24.5	-23.5	-18.7	-22.4
Difference in event probability compared to Sequence 1b, per 1000 persons	182.1	30.5	7.7	ref	-16.8	-15.8	-11.0	-14.7
Mean event-free time lost, months	2.09	1.16	0.94	0.87	0.68	0.69	0.75	0.71
Mean gain in event-free time compared to Sequence 1, months	-0.93	ref	0.22	0.29	0.48	0.47	0.41	0.45
Mean gain in event-free time compared to Sequence 1a, months	-1.15	-0.22	ref	0.07	0.26	0.25	0.19	0.23
Mean gain in event-free time compared to Sequence 1b, months	-1.22	-0.29	-0.07	ref	0.19	0.18	0.12	0.16
All-cause death								
Event probability, per 1000 persons	139.3	65.3	57.9	56.5	52.6	51.6	52.1	51.9
Difference in event probability compared to Sequence 1, per 1000 persons	74.0	ref	-7.4	-8.8	-12.7	-13.7	-13.2	-13.4

Difference in event probability compared to Sequence 1a, per 1000 persons	81.4	7.4	ref	-1.4	-5.3	-6.3	-5.8	-6.0
Difference in event probability compared to Sequence 1b, per 1000 persons	82.8	8.8	1.4	ref	-3.9	-4.9	-4.4	-4.6
Mean event-free time lost, months	0.86	0.49	0.42	0.41	0.36	0.35	0.36	0.36
Mean gain in event-free time compared to Sequence 1, months	-0.37	ref	0.07	0.08	0.13	0.14	0.13	0.13
Mean gain in event-free time compared to Sequence 1a, months	-0.44	-0.07	ref	0.01	0.06	0.07	0.06	0.06
Mean gain in event-free time compared to Sequence 1b, months	-0.45	-0.08	-0.01	ref	0.05	0.06	0.05	0.05

ARNI denotes angiotensin receptor neprilysin inhibitor; BB, beta-blocker; CV, cardiovascular; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor; ref, reference; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

The detailed illustration of sequences 1, 1a, 1b, and 2-5 examined can be seen in Figure 1.

Table 3. Event probability and mean event-free time lost for the composite of HF hospitalization or CV death and all-cause death at 1 year according to different medication sequences (Sequences using duos 1-6) with two medications initiated simultaneously compared to Sequence 1b, assuming treatment effects starting half-way through up-titration of each medication.

Sequence	Seq. 1b	Seq. duo 1	Seq. duo 2	Seq. duo 3	Seq. duo 4	Seq. duo 5	Seq. duo 6
Medication order	ARNI/ BB/ MRA/ SGLT2i	SGLT2i+MRA/ BB/ ARNI	SGLT2i+MRA/ ARNI/ BB	SGLT2i+BB/ MRA/ ARNI	BB+ARNI/ SGLT2i/ MRA	MRA+BB/ SGLT2i/ ARNI	MRA+ARNI/ SGLT2i/ BB
Up-titration duration (weeks)	12	11	11	11	8	10	10
HF hospitalization or CV death							
Event probability, per 1000 persons	98.3	77.5	76.6	82.4	82.5	79.2	78.5
Difference in event probability compared to Sequence 1b, per 1000 persons	ref	-20.8	-21.7	-15.9	-15.8	-19.1	-19.8
Mean event-free time lost, months	0.87	0.64	0.63	0.69	0.70	0.66	0.65

Mean gain in event-free time compared to Sequence 1b, months	ref	0.23	0.24	0.18	0.17	0.21	0.22
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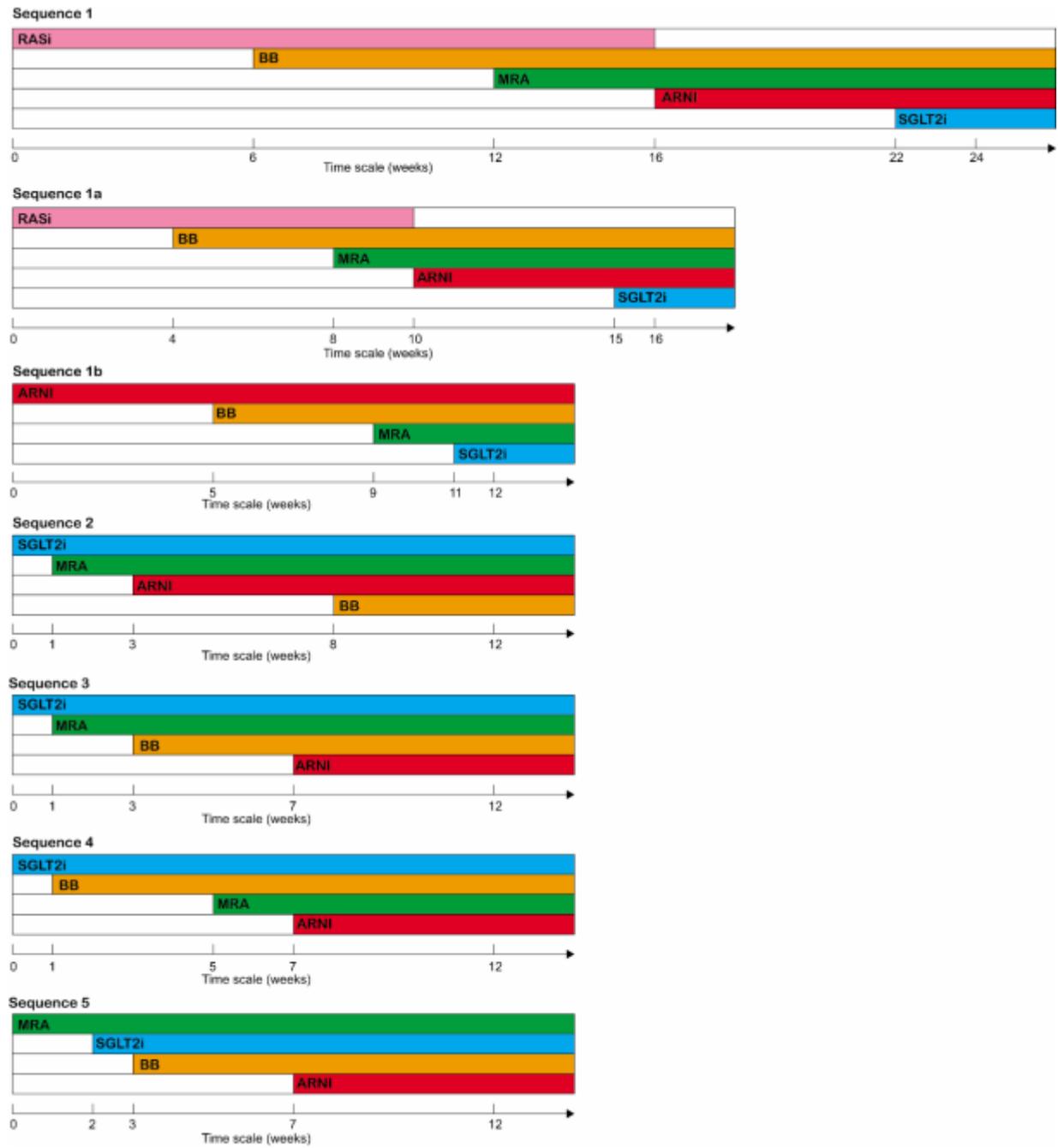
All-cause death

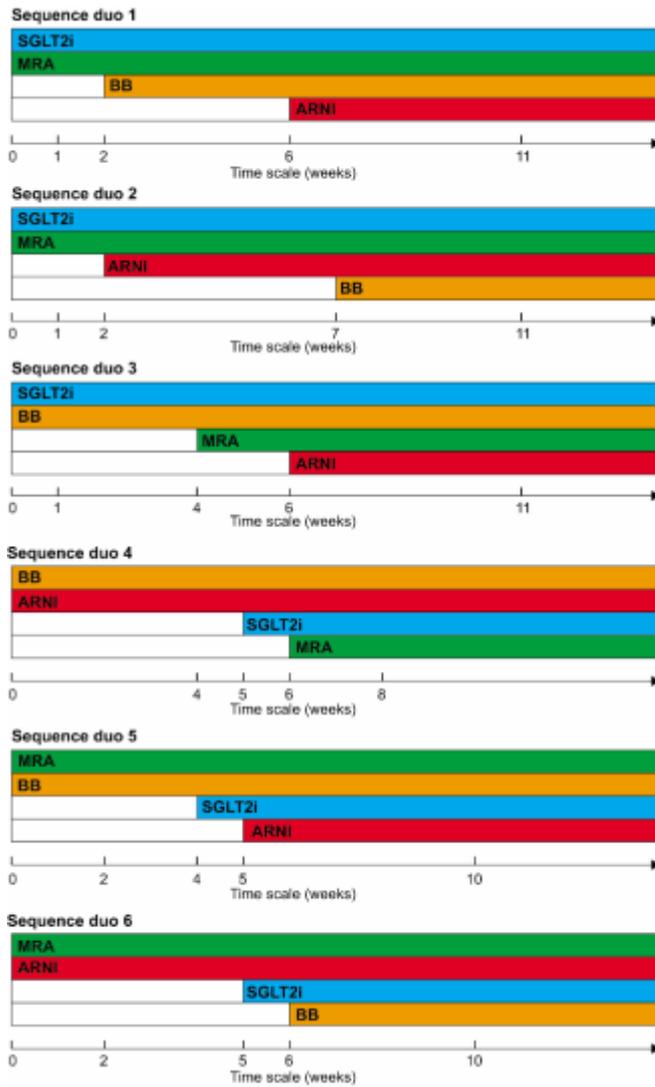
Event probability, per 1000 persons	56.5	50.1	51.1	50.6	50.5	49.8	51.3
Difference in event probability compared to Sequence 1b, per 1000 persons	ref	-6.4	-5.4	-5.9	-6.0	-6.7	-5.2
Mean event-free time lost, months	0.41	0.34	0.35	0.34	0.34	0.33	0.35
Mean gain in event-free time compared to Sequence 1b, months	ref	0.07	0.06	0.07	0.07	0.08	0.06

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.

Figure 1. Medication sequences and duration of up-titration periods (Sequences 1, 1a, 1b, 2-5, and duos 1-6)

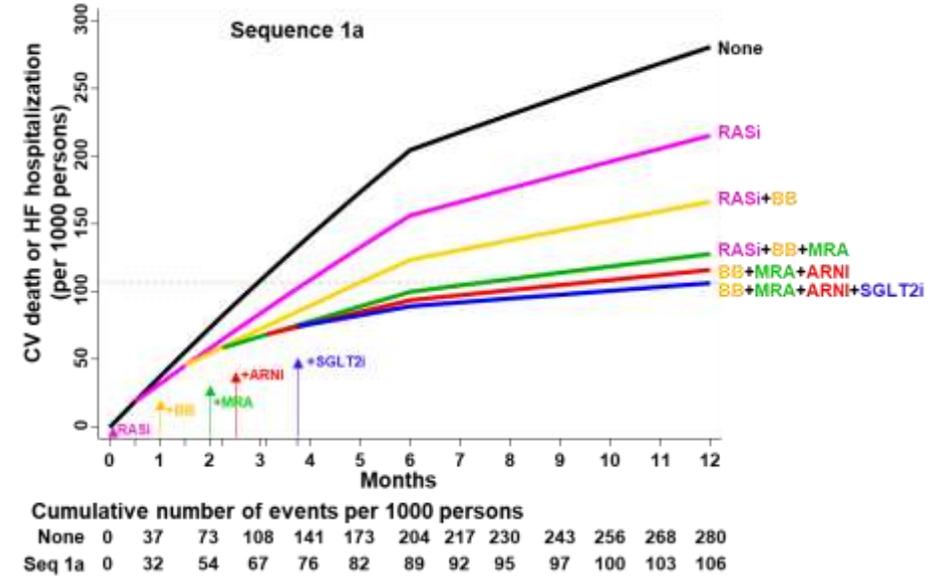
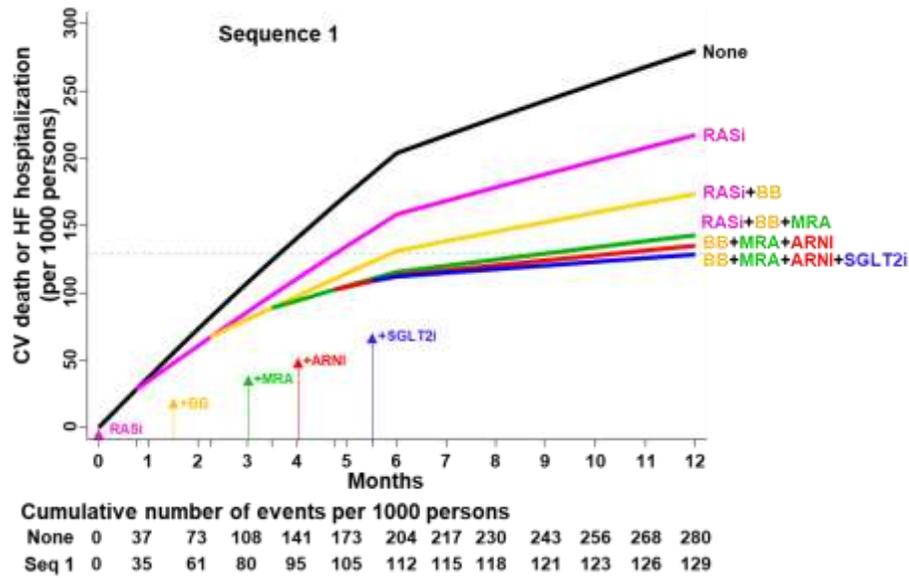


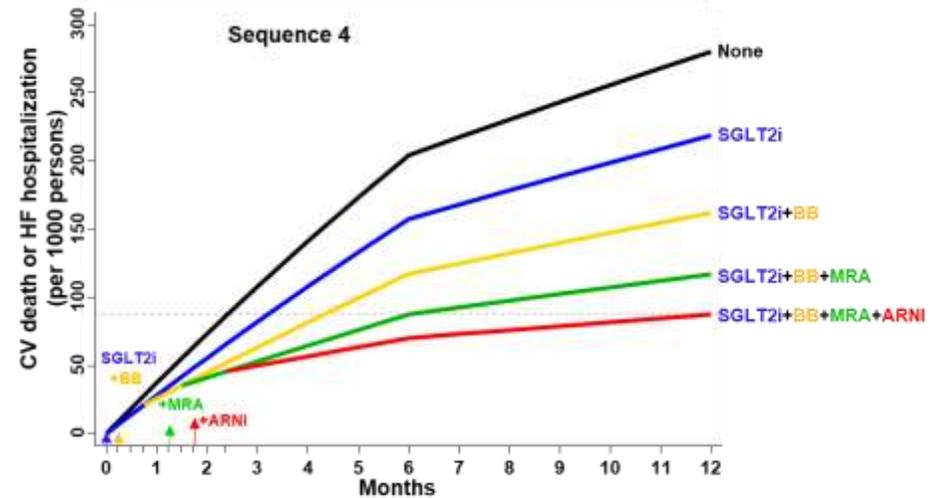
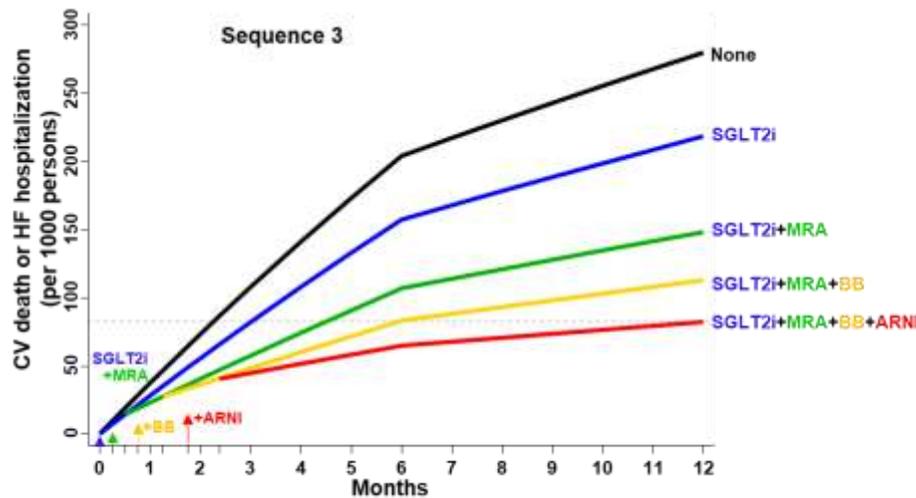
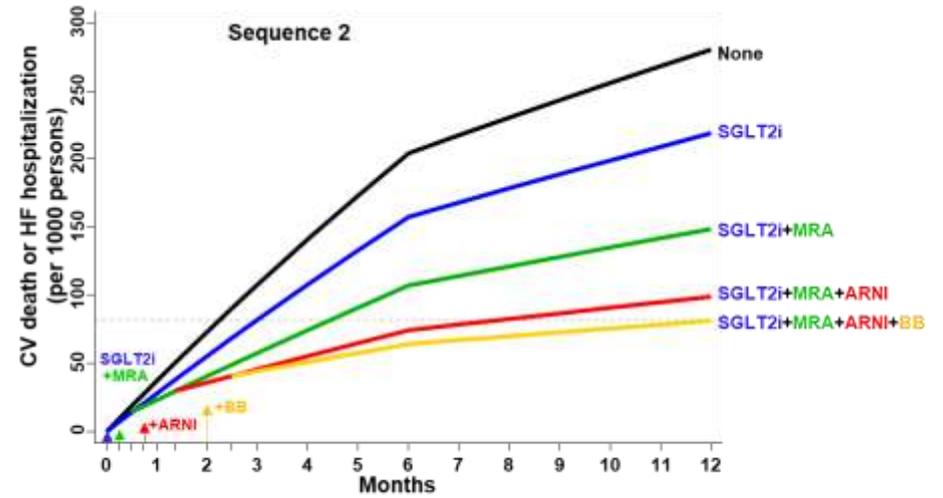
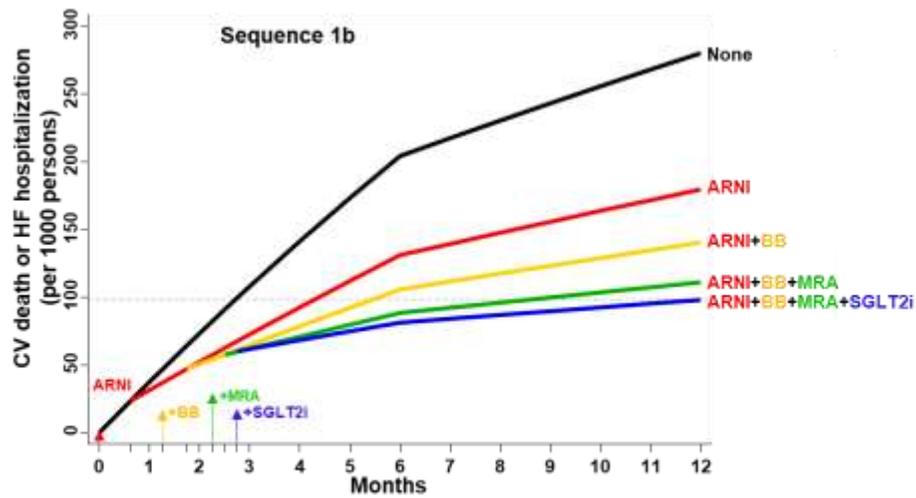


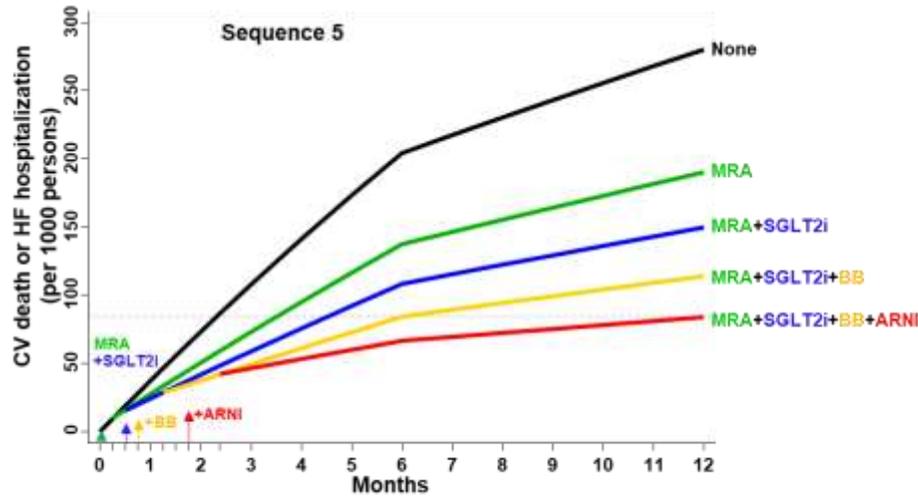
The colours of boxes indicate different medications, i.e., pink for RASi, orange for BB, green for MRA, red for ARNI and blue for SGLT2i.

ARNI denotes angiotensin receptor neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Figure 2a. Cumulative incidence of the composite of HF hospitalization or CV 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**)







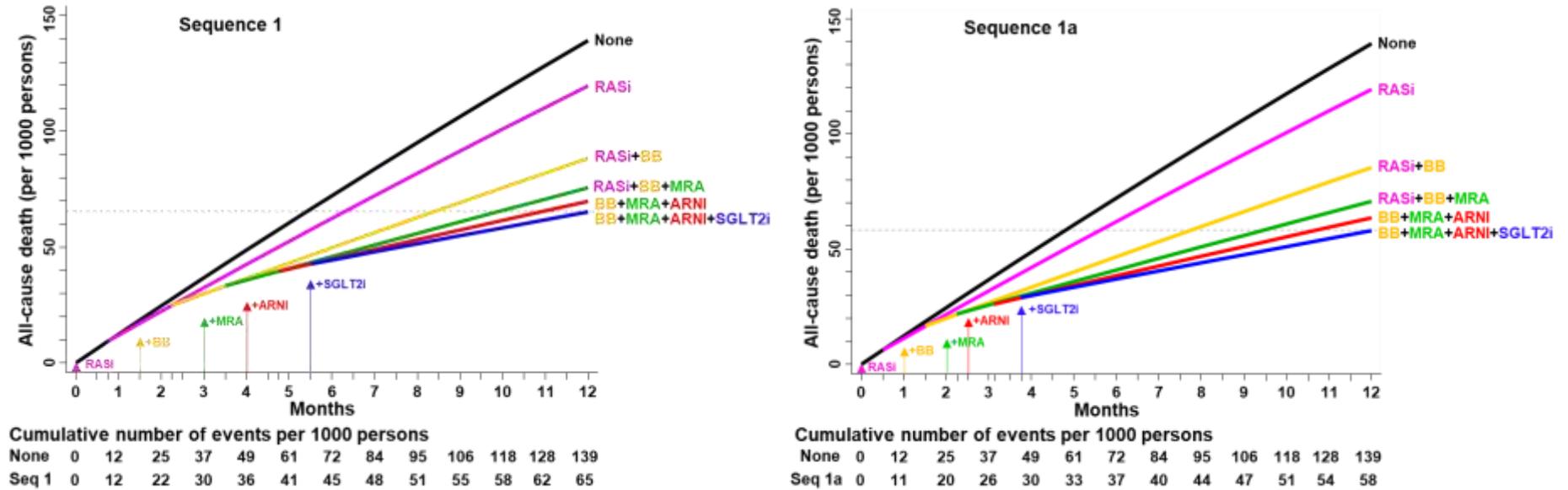
Cumulative number of events per 1000 persons	
None	0 37 73 108 141 173 204 217 230 243 256 268 280
Seq 5	0 24 38 46 53 60 66 69 72 75 78 81 84

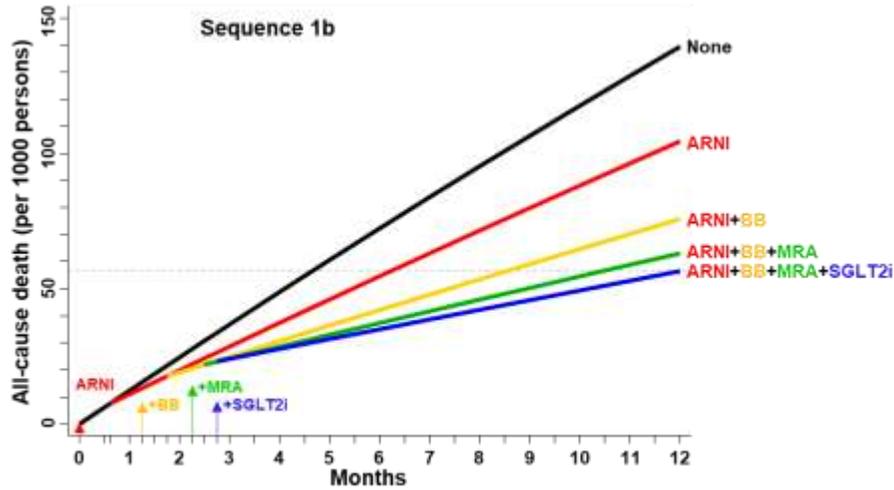
The rates of clinical outcomes in treatment-naïve patients were based on the rates among patients who were randomized in the placebo arm in SOLVD-Treatment and who were in the placebo arm of CHARM-alternative and not treated with a beta-blocker or an MRA. The rate for the composite of HF hospitalization or CV 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 RASi, orange for BB, green for MRA, red for ARNI and blue for SGLT2i. The grey dashed horizontal line denotes the probability of the clinical outcome at 12 months.

ARNI denotes 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.

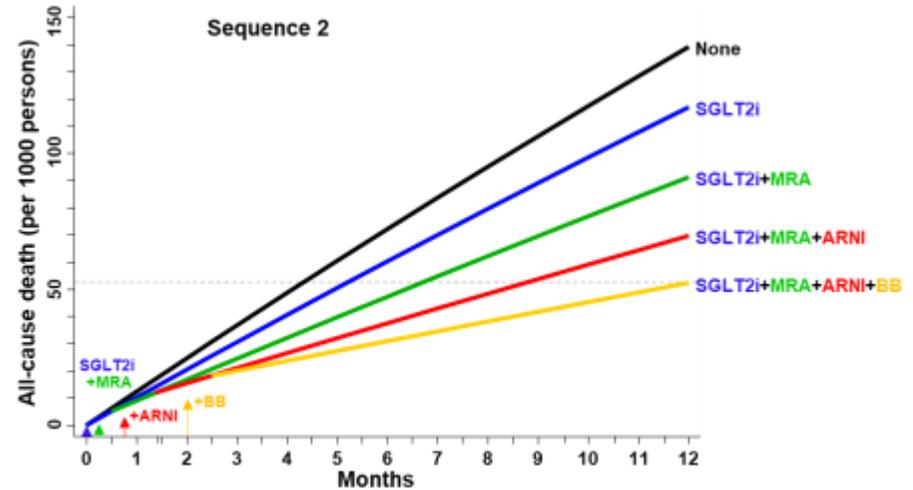
Figure 2b. Cumulative incidence of **all-cause death**, after cumulative introduction of disease-modifying medications, assuming the effect of treatment starts **midway** through the up-titration period for each medication (**Sequences 1, 1a, 1b, 2-5**)





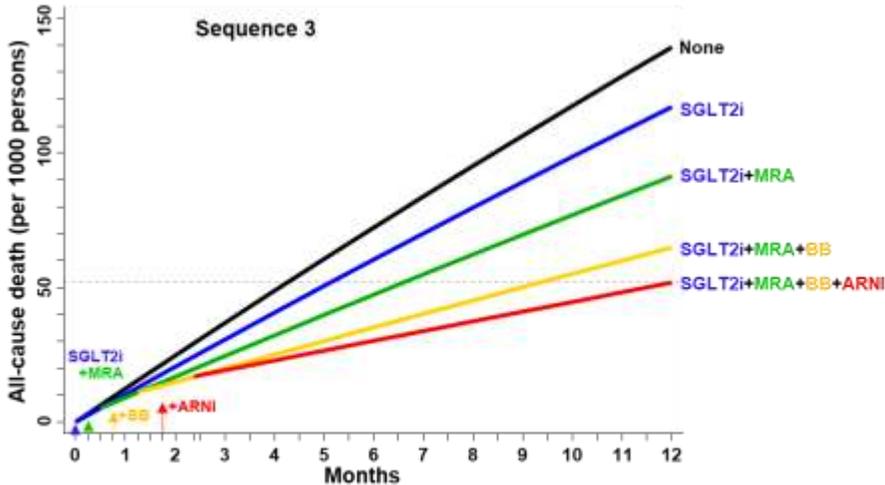
Cumulative number of events per 1000 persons

None	0	12	25	37	49	61	72	84	95	106	118	128	139
Seq 1b	0	11	19	24	28	31	35	39	42	46	49	53	57



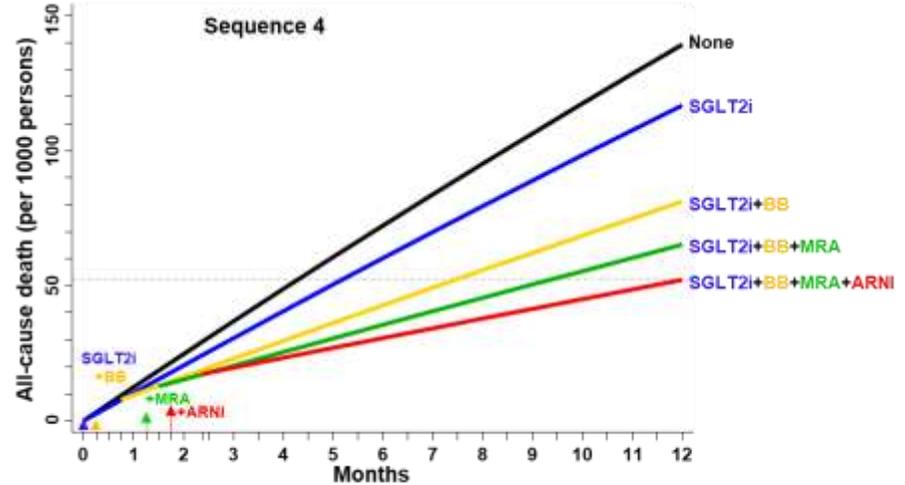
Cumulative number of events per 1000 persons

None	0	12	25	37	49	61	72	84	95	106	118	128	139
Seq 2	0	9	16	20	24	27	31	35	38	42	46	49	53



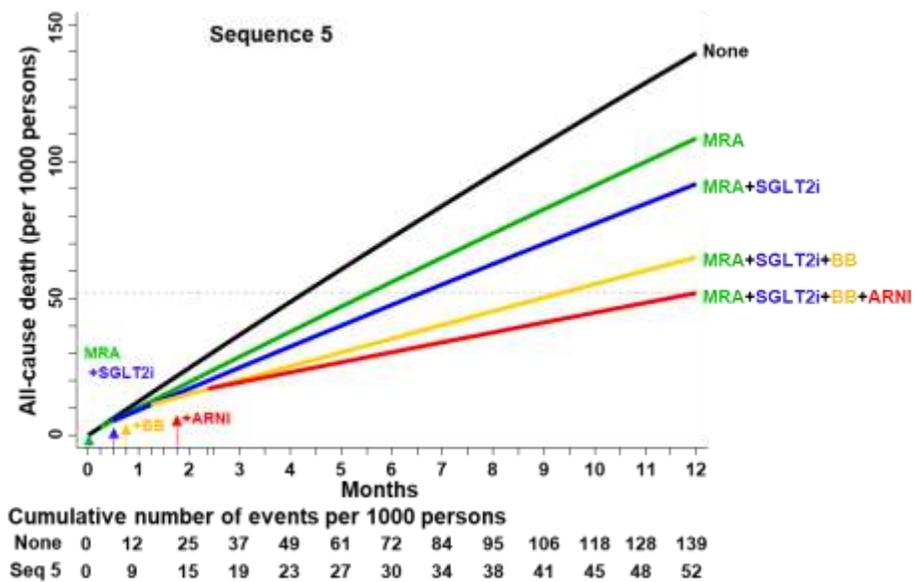
Cumulative number of events per 1000 persons

None	0	12	25	37	49	61	72	84	95	106	118	128	139
Seq 3	0	9	15	19	23	26	30	34	37	41	45	48	52



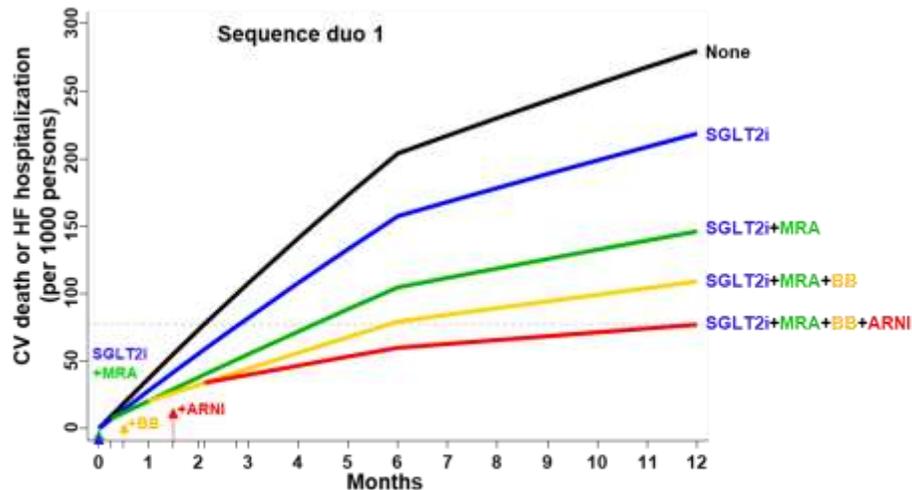
Cumulative number of events per 1000 persons

None	0	12	25	37	49	61	72	84	95	106	118	128	139
Seq 4	0	9	15	20	23	27	31	34	38	41	45	49	52

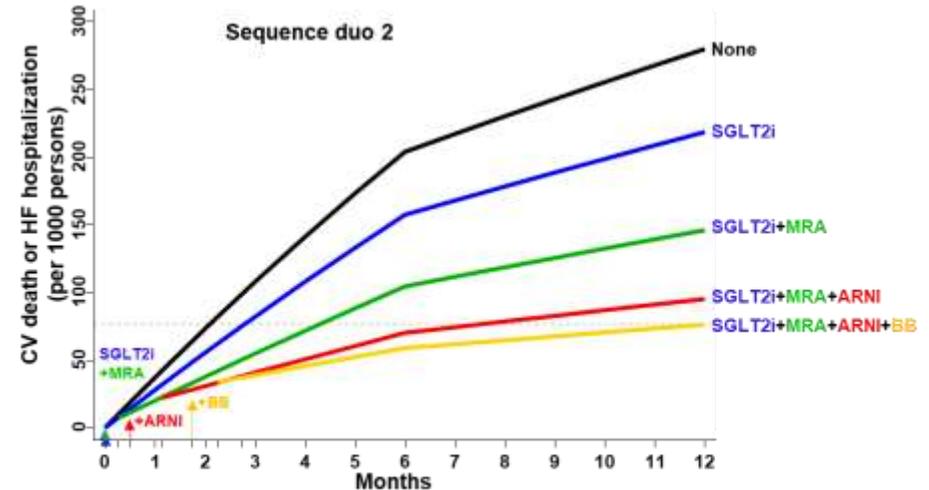


The rate for all-cause mortality was 150 per 1000 person-years throughout. Other figure legends are the same as those in Figure 2a.

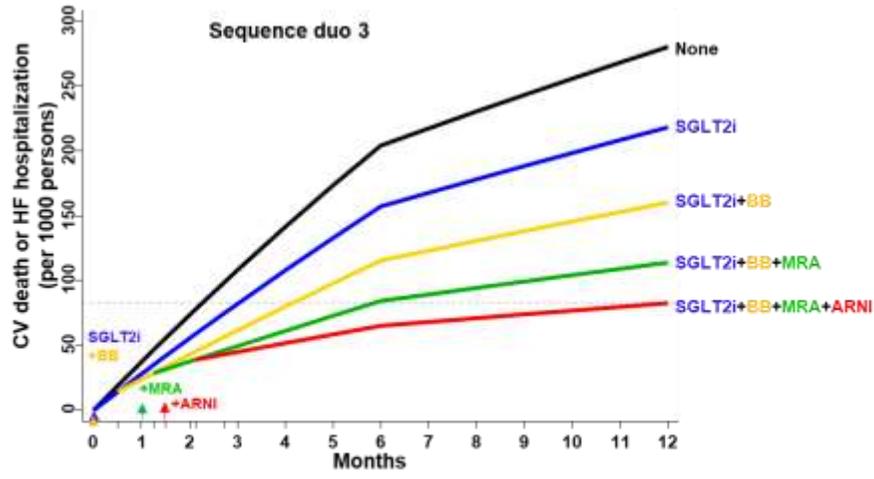
Figure 3a. Cumulative incidence of the composite of HF hospitalization or CV death, after cumulative introduction of disease modifying medications, assuming the effect of treatment starts midway through the up-titration period for each medication (Sequences using duos 1-6)



Cumulative number of events per 1000 persons	
None	0 37 73 108 141 173 204 217 230 243 256 268 280
Seq duo 1	0 20 33 40 47 53 60 63 66 69 72 75 78

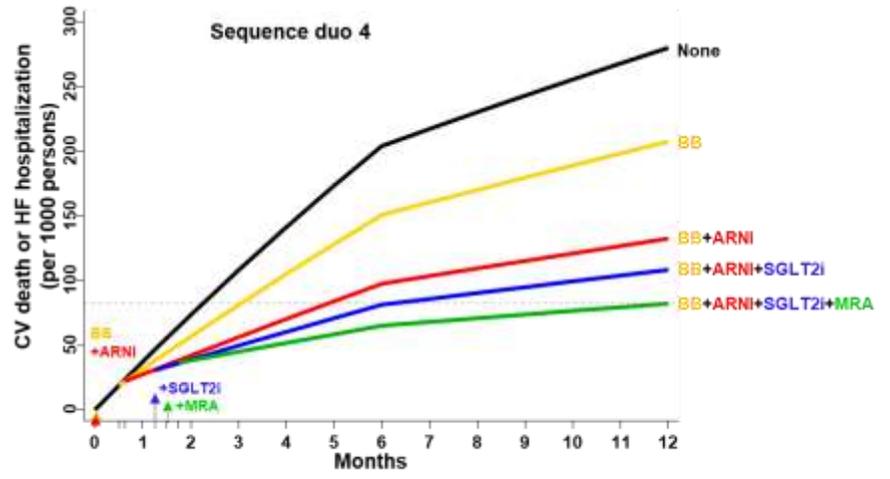


Cumulative number of events per 1000 persons	
None	0 37 73 108 141 173 204 217 230 243 256 268 280
Seq duo 2	0 20 31 39 46 52 59 62 65 68 71 74 77



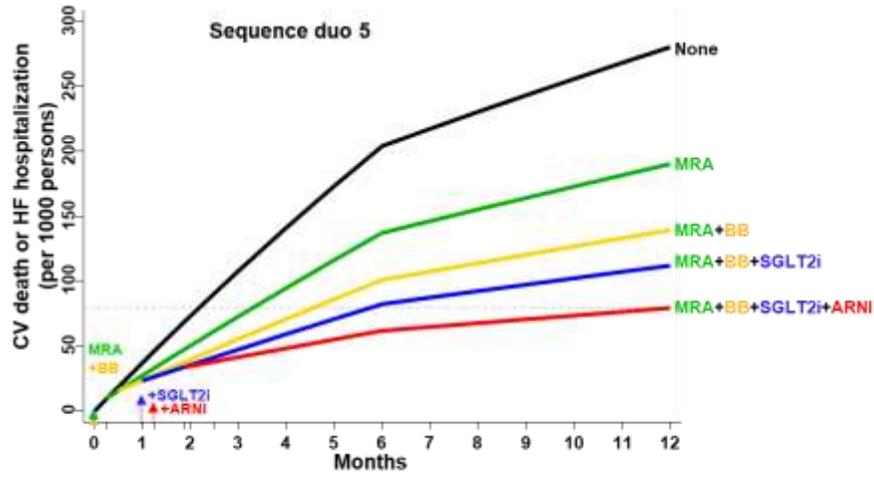
Cumulative number of events per 1000 persons

	0	37	73	108	141	173	204	217	230	243	256	268	280
None	0	37	73	108	141	173	204	217	230	243	256	268	280
Seq duo 3	0	24	38	45	52	58	65	68	71	74	77	80	82



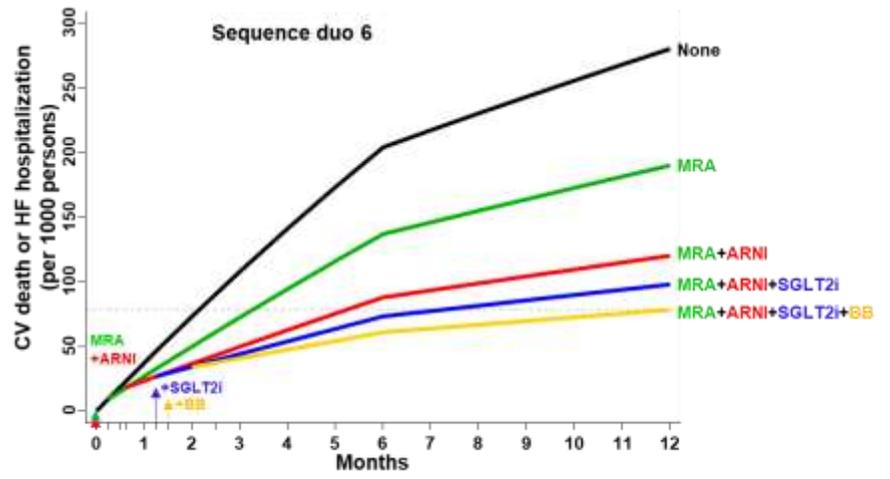
Cumulative number of events per 1000 persons

	0	37	73	108	141	173	204	217	230	243	256	268	280
None	0	37	73	108	141	173	204	217	230	243	256	268	280
Seq duo 4	0	28	38	45	52	59	65	68	71	74	77	80	82



Cumulative number of events per 1000 persons

	0	37	73	108	141	173	204	217	230	243	256	268	280
None	0	37	73	108	141	173	204	217	230	243	256	268	280
Seq duo 5	0	24	35	42	48	55	62	65	68	71	73	76	79

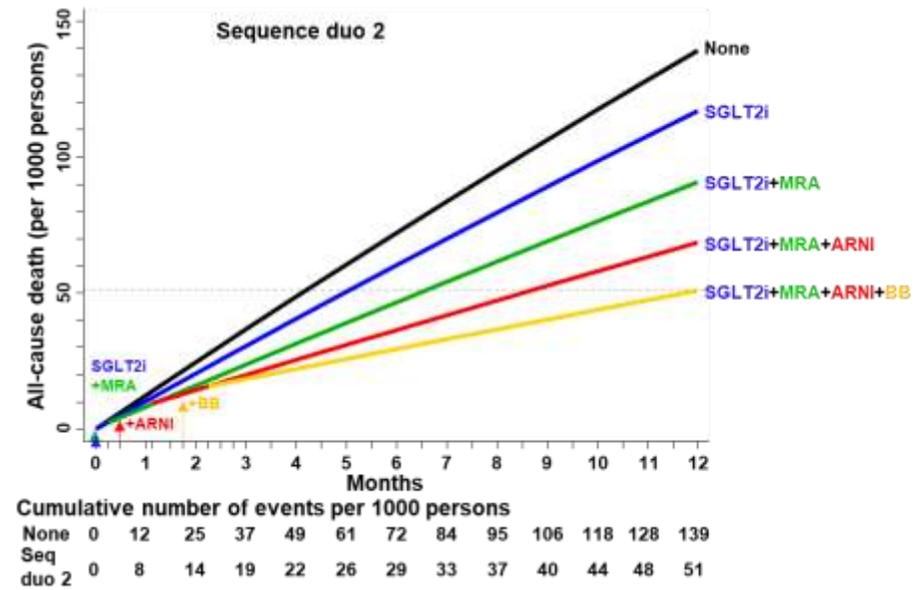
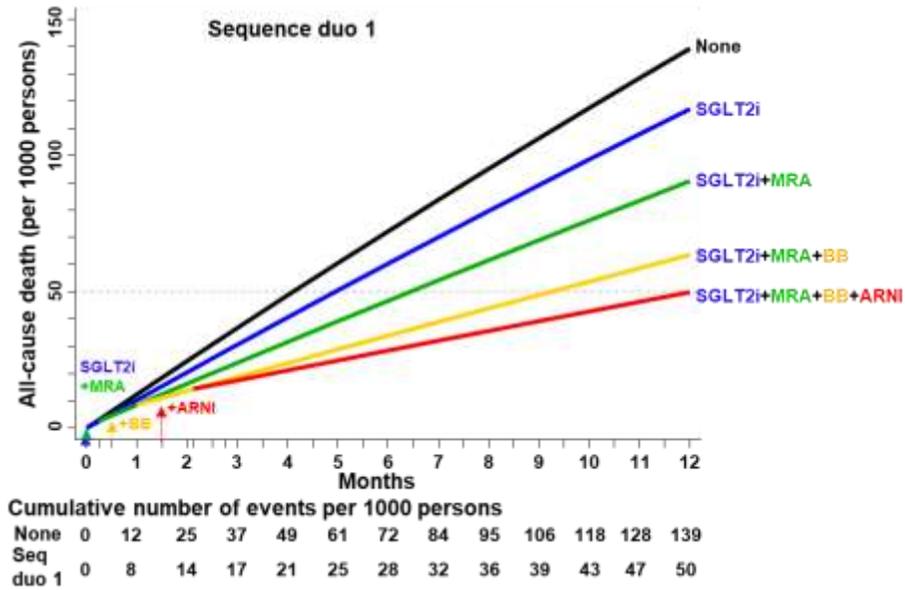


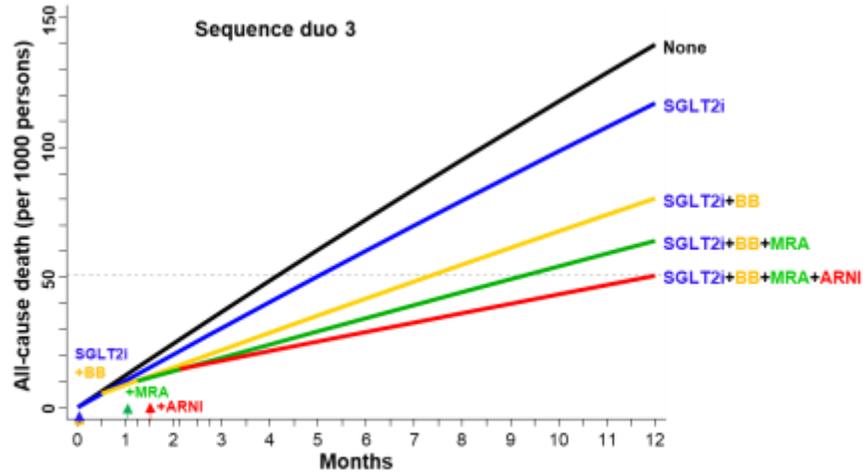
Cumulative number of events per 1000 persons

	0	37	73	108	141	173	204	217	230	243	256	268	280
None	0	37	73	108	141	173	204	217	230	243	256	268	280
Seq duo 6	0	23	34	41	48	54	61	64	67	70	73	76	78

Figure legends are the same as those in Figure 2a.

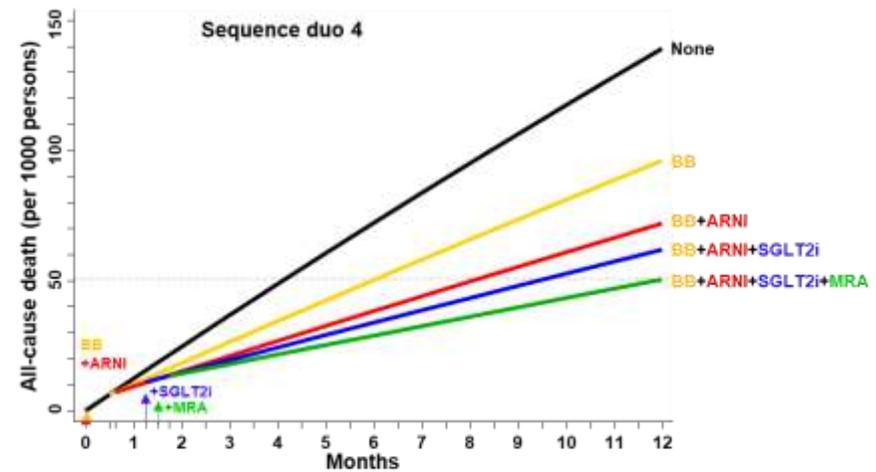
Figure 3b. Cumulative incidence of all-cause death, after cumulative introduction of disease modifying medications, assuming the effect of treatment starts midway through the up-titration period for each medication (Sequences using duos 1-6)





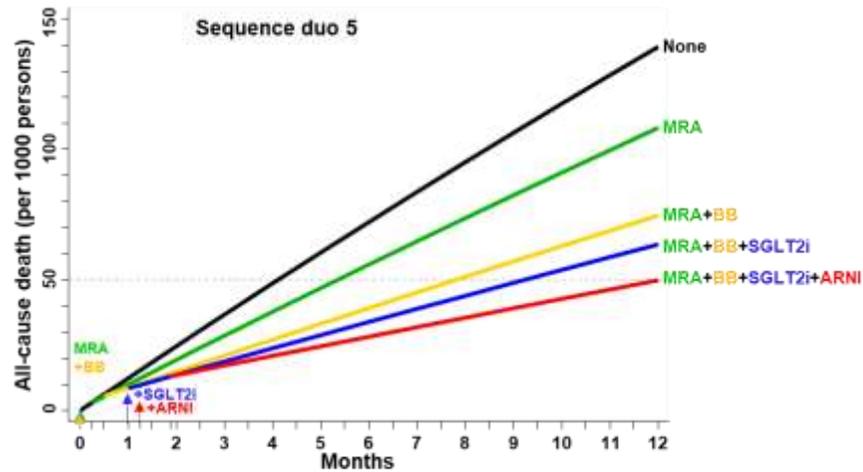
Cumulative number of events per 1000 persons

None	0	12	25	37	49	61	72	84	95	106	118	128	139
Seq	0	9	14	18	22	25	29	33	36	40	43	47	51
duo 3													



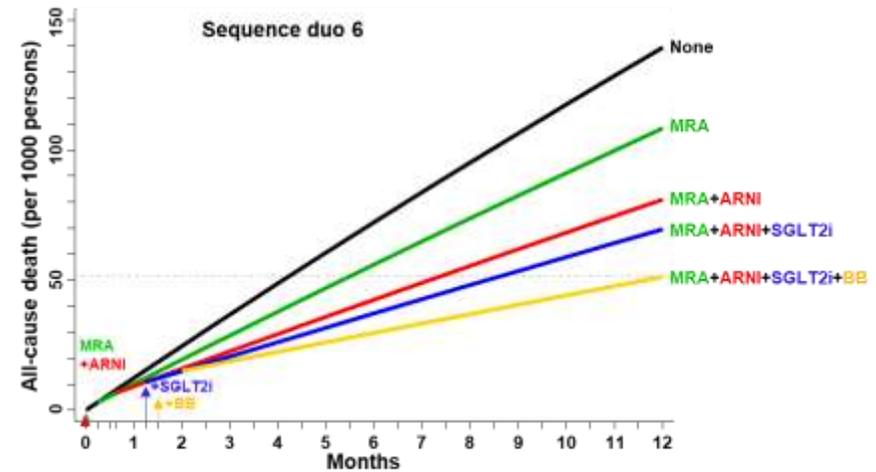
Cumulative number of events per 1000 persons

None	0	12	25	37	49	61	72	84	95	106	118	128	139
Seq	0	9	14	18	22	25	29	33	36	40	43	47	51
duo 4													



Cumulative number of events per 1000 persons

None	0	12	25	37	49	61	72	84	95	106	118	128	139
Seq	0	9	14	17	21	25	28	32	35	39	43	46	50
duo 5													



Cumulative number of events per 1000 persons

None	0	12	25	37	49	61	72	84	95	106	118	128	139
Seq	0	9	15	19	22	26	30	33	37	41	44	48	51
duo 6													

Figure legends are the same as those in Figure 2b.