

Accelerated Article Preview

Lifetime Benefits of Comprehensive Medical Therapy in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

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1 **Editor summary:**
2 In a cross-trial analysis, combined treatment with medications that have individually shown to
3 improve cardiovascular outcomes in heart failure with mildly reduced or preserved ejection
4 fraction demonstrates substantial benefit, including for event-free survival.

5

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13 **1. Extended Data**

14

Figure or Table # Please group Extended Data items by type, in sequential order. Total number of items (Figs. + Tables) must not exceed 10.	Figure/Table title One sentence only	Filename Whole original file name including extension. i.e.; Smith_ED_Fig1.jpg	Figure/Table Legend If you are citing a reference for the first time in these legends, please include all new references in the main text Methods References section, and carry on the numbering from the main References section of the paper. If your paper does not have a Methods section, include all new references at the end of the main Reference list.
Extended Data Table. 1	Baseline Characteristics of Base Population from the DELIVER Trial	Solomon_ED_Table1.pdf	
Extended Data Table. 2	Sensitivity Analysis Assuming Subadditive Effects of Comprehensive Medical Therapy	Solomon_ED_Table2.pdf	
Extended Data Table. 3	Sensitivity Analysis Assuming Declining Efficacy of Comprehensive Medical Therapy Over Time	Solomon_ED_Table3.pdf	

Extended Data Table. 4	Risk of Bias Assessment Using the Revised Tool to Assess Risk of Bias in Randomized Trials (RoB 2.0)	Solomon_ED_Table4.pdf	
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17 **1. Supplementary Information:**

18 **A. PDF Files**

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Item	Present?	Filename Whole original file name including extension. i.e.: Smith_SI.pdf. The extension must be .pdf	A brief, numerical description of file contents. i.e.: <i>Supplementary Figures 1-4, Supplementary Discussion, and Supplementary Tables 1-4.</i>
Supplementary Information	No		
Reporting Summary	Yes	Solomon_SI_ReportngSummary.pdf	
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21

22 **Lifetime Benefits of Comprehensive Medical Therapy in Heart Failure with Mildly
23 Reduced or Preserved Ejection Fraction**

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45
46 **Abstract**
47 Sodium glucose co-transporter-2 inhibitors (SGLT2i) and the non-steroidal mineralocorticoid
48 receptor antagonist (nsMRA) finerenone have each been shown to individually improve heart
49 failure events among patients with heart failure and mildly reduced or preserved ejection fraction
50 (HFmrEF/HFpEF). Moreover, the angiotensin receptor neprilysin inhibitor (ARNI)
51 sacubitril/valsartan has been shown to improve outcomes in patients with HFmrEF/HFpEF with
52 a left ventricular ejection fraction (LVEF) below normal (<60%). However, the expected benefits
53 of the combined use of these agents with long-term administration are not well defined. In this
54 cross-trial analysis of DELIVER, FINEARTS-HF, and PARAGON-HF, combined use of
55 SGLT2i and nsMRA therapies was estimated to reduce the risk of cardiovascular death or first
56 worsening HF event by 31% in the overall population (HR 0.69; 95% CI 0.59 to 0.81), while
57 combined use of SGLT2i, nsMRA, and ARNI therapies was estimated to reduce risk by 39% in
58 patients with HFmrEF/HFpEF and an LVEF<60% (HR 0.61; 95% CI 0.48 to 0.77). With long-
59 term use, combined SGLT2i and nsMRA therapies in a 65-year-old patient with
60 HFmrEF/HFpEF, or combined SGLT2i, nsMRA, and ARNI therapies in a 65-year-old patient
61 with an LVEF<60%, were projected to afford 3.6 (2.0 to 5.2) or 4.9 (2.6 to 7.3) additional years
62 free from cardiovascular death or a HF event, respectively. Combined therapy was estimated to
63 result in meaningful gains in event-free survival across a broad age range from 55 to 85 years.
64 Among patients with HFmrEF and HFpEF, the potential aggregated long-term treatment effects

of early combination medical therapy with SGLT2i and nsMRA (and ARNI in selected individuals) are projected to be substantial.

Patients with heart failure with preserved ejection fraction (HFpEF) experience life expectancies that are considerably shorter than their peers of similar ages.¹ Until recently, the management of HFpEF was largely empirical and limited to diuretics, blood pressure control, and comorbidity management. Indeed, before 2023, major clinical practical guidelines offered no class I (strong) recommendation for any specific pharmacotherapy (beyond diuretics) in the treatment of HFpEF. However, since then, the sodium glucose co-transporter-2 inhibitors (SGLT2i) have been shown to improve cardiovascular outcomes and are strongly recommended in patients with heart failure and mildly reduced or preserved ejection fraction (HFmrEF/HFpEF), i.e. a left ventricular ejection fraction (LVEF) >40%.^{2,3} A trial of the non-steroidal mineralocorticoid receptor antagonist (nsMRA) finerenone demonstrated its efficacy and safety in this same population which supported its recent regulatory approval by the US Food and Drug Administration.⁴ In addition, a trial of the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan, while narrowly missing its primary endpoint,⁵ suggested efficacy in patients with a LVEF below normal (<60%).⁶ Smaller trials with shorter duration follow-up periods have suggested potential early efficacy with incretin-based therapies, but long-term outcomes trials are awaited. As randomized clinical trials tested these therapies individually in trials conducted over an average follow-up of 2 to 3 years on the background of varying medical therapy regimens, the expected benefits of their combined use when administered long-term are not well defined.

Multiple stakeholders (patients, clinicians, health systems, payors) may be interested in the therapeutic potential of these therapies when used together in the management of this growing population. As such, we first estimated the aggregate *relative* benefits of SGLT2i and nsMRA in all patients with HFmrEF/HFpEF and the combination of SGLT2i, nsMRA, and ARNI in those with HFmrEF/HFpEF and a LVEF <60%. We then projected the potential *absolute* long-term gains in event-free survival with comprehensive medical therapy.

Results

Relative Treatment Effects of Comprehensive Medical Therapy. For the main analysis, we derived treatment estimates from 6,263 participants in DELIVER and 6,001 participants in FINEARTS-HF (**Table 1**). In the subgroup of individuals with LVEF below normal (<60%), we

estimated treatment effects from 4,372 participants in DELIVER, 4,846 in FINEARTS-HF, and 2,070 in PARAGON-HF. These trials evaluated older participants with HF (mean ages 72 to 73 years), with balanced sex distribution (44% to 52% women), and a high rate of comorbidities. Background MRA use was 26% in PARAGON-HF and 43% in DELIVER. Background ARNI use was 5% in DELIVER and 9% in FINEARTS-HF. Background SGLT2i use was 1% in PARAGON-HF and 14% in FINEARTS-HF (**Table 2**). Within each of the trials, serious adverse events were reported at similar frequencies between the study arms. Hypotension (systolic blood pressure<100mmHg) was more common with finerenone (vs. placebo) and ARNI (vs. valsartan), and elevated serum potassium >5.5mmol/L was more common with finerenone (vs. placebo);

Table 3.

Combination use of SGLT2i and nsMRA was estimated to reduce the risk of the primary endpoint of cardiovascular death or first worsening HF event by 31% in the overall HFmEF/HFpEF population (HR 0.69; 95% CI 0.59 to 0.81). In individuals with an LVEF below normal (<60%), the combined use of SGLT2i, nsMRA, and ARNI was estimated to reduce risk by 39% (HR 0.61; 95% CI 0.48 to 0.77); **Figure 1**. When considering the effects of ARNI (against a putative placebo), the combination use of SGLT2i, nsMRA, and ARNI (vs. putative placebo) was estimated to reduce risk by 47% (HR 0.53; 95% CI 0.39 to 0.71). In the overall population, results were consistent in a sensitivity analysis examining SGLT2i as a class (based on meta-analysis of DELIVER and EMPEROR-Preserved) and MRAs as a class (based on meta-analysis of FINEARTS-HF and TOPCAT) (aggregate HR 0.70; 95% CI 0.61 to 0.79). In sensitivity analyses, aggregate relative treatment effects remained robust for the composite of all-cause death or worsening HF event (HR 0.76; 95% CI 0.66 to 0.87) to account for competing risks of mortality and when evaluating the composite of cardiovascular death or HF hospitalization (not considering urgent HF visits) (HR 0.71; 95% CI 0.60 to 0.84).

Applying guideline-concordant LVEF designations, comprehensive medical therapy was estimated to reduce the primary endpoint by 32% (HR 0.68; 95% CI 0.56 to 0.83) in those with HFpEF (LVEF≥50%) with SGLT2i and nsMRA and by 42% (HR 0.58; 95% CI 0.40 to 0.85) in those with HFmrEF (LVEF 40 to 50%) with SGLT2i, nsMRA, and ARNI.

3-Year Absolute Risk Reductions and NNT. We estimated event-free survival in 1,754 participants with HFmrEF/HFpEF in the control arm of the DELIVER trial (main analysis) and

127 in the subset of 1,123 participants with HFmrEF/HFpEF and an LVEF below normal (<60%).
128 Mean age was 72.5 ± 9.0 years, and 818 (46.6%) were women (**Extended Data Table 1**).

129 In the overall HFmrEF/HFpEF population, over a median within-trial follow-up of 2.2
130 years (25th-75th percentiles 1.5 to 2.7 years), 330 primary events were observed with a
131 corresponding event rate of 9.1 (95% CI 8.1 to 10.1) per 100 patient-years. Based on this
132 observed annualized event rate in the control group of DELIVER, the range of aggregate
133 absolute risk reductions were estimated to be 4% to 9% with 3 years of comprehensive medical
134 therapy, with a corresponding number-needed-to-treat of 11 to 25 in the prevention of a primary
135 endpoint.

136 In the LVEF below normal subpopulation, over a median within-trial follow-up of 2.3
137 years (25th-75th percentiles 1.5 to 2.8 years), 211 primary events were observed with a
138 corresponding event rate of 9.1 (95% CI 7.9 to 10.4). With 3 years of comprehensive medical
139 therapy, the absolute risk reductions would range from 5% to 12% with a corresponding number-
140 needed-to-treat of 9 to 20 in the prevention of a primary endpoint.

141
142 **Long-Term Projections of Event-Free Survival Gains.** In the overall population, forecasted
143 long-term survival free from the primary endpoint (cardiovascular death or worsening HF event)
144 was estimated to be 10.7 years (95% CI 9.3 to 12.1) in placebo-treated participants on standard
145 therapy and 14.3 years (95% CI 12.7 to 15.9) with comprehensive treatment with SGLT2i and
146 nsMRA. We estimated comprehensive medical therapy to provide 3.6 (2.0 to 5.2) additional
147 years free from cardiovascular death or HF event in a 65-year-old participant (**Figure 2**). Event-
148 free survival gains remained substantial in sensitivity analyses assuming subadditive treatment
149 effects of therapies (**Extended Data Table 2**) and waning efficacy of comprehensive medical
150 therapy over time (**Extended Data Table 3**). Meaningful gains in event-free survival were
151 observed across a broad age range (**Figure 3**) from 1.5 (0.9 to 2.1) additional years in an 85-
152 year-old to 4.1 (2.2 to 6.1) additional years in a 55-year-old. In a 65-year-old HFmrEF/HFpEF
153 patient with LVEF below normal (<60%), comprehensive treatment with SGLT2i, nsMRA, and
154 ARNI was estimated to afford 4.9 (2.6 to 7.3) years free from cardiovascular death or HF event.
155

156 **Discussion**

157 The population of HFpEF is projected to continue to rise globally,¹⁸ and individuals living with
158 the disease have a guarded prognosis and face a high burden of hospitalizations and healthcare
159 encounters.¹ As such, extending event-free survival represents a core treatment goal in this high-
160 risk population. In the adjacent population of HF with reduced ejection fraction, we previously
161 estimated that comprehensive medical therapy with 4 therapies (targeting 5 distinct pathways)
162 with ARNI, β-blocker, MRA, and SGLT2i could afford over 6 years of additional event-free
163 survival in a 65-year-old compared with conventional medical therapy (consisting of an ACE
164 inhibitor or angiotensin receptor blocker and β blocker).¹⁹ This “pillar-based” comprehensive
165 medical therapy approach has now been embraced by contemporary clinical practice guidelines
166 and represents the new standard of care globally for HFrEF.^{9,10}

167 HFpEF is recognized to be a systemic syndrome with both myocardial dysfunction and
168 peripheral abnormalities that contribute to disease progression.²⁰ Similar to HFrEF, combining
169 multiple therapies targeting distinct pathophysiologic mechanisms may most comprehensively
170 attenuate risks of morbidity and mortality. The SGLT2i represented the first class of therapies
171 (beyond diuretics) that have been strongly recommended as a class I guideline recommendation
172 across the full spectrum of LVEF, including in HFpEF.⁹ The recent FINEARTS-HF trial⁴
173 demonstrated that a second therapy, the nsMRA finerenone, is beneficial in improving outcomes
174 in patients with HFmrEF/HFpEF, including among those already treated with an SGLT2i. The
175 US Food and Drug Administration has since approved finerenone for the management of patients
176 with HF and an LVEF $\geq 40\%$. The ARNI sacubitril/valsartan, which targets both the renin-
177 angiotensin system and the natriuretic peptide axis, appears to be most beneficial in those with
178 LVEF below normal,^{5,6} and is now approved for use in many countries worldwide for this
179 indication.

180 Compared with standard care (which encompassed management of congestion and
181 comorbidities such as hypertension), comprehensive medical therapy inclusive of SGLT2i and
182 nsMRA were estimated to reduce risks of cardiovascular death or worsening HF events by over
183 30% and the further addition of ARNI among individuals with an LVEF below normal was
184 estimated to reduce risks of clinical events by nearly 40%. Previous cross-trial analyses were
185 limited to estimating the relative treatment benefits with comprehensive medical therapy without
186 offering perspective on potential absolute treatment gains, especially over a long-term horizon.²¹
187 Over 3 years, the estimated absolute risk reduction ranged from 4% to 9%, corresponding to a

number-needed-to-treat of 11 to 25 to prevent a clinical event. Over a lifetime horizon, we estimated that comprehensive medical therapy would substantially extend event-free survival in the overall population and in those with LVEF below normal. As younger individuals with HF have longer disease duration and expected residual lifespan, estimated gains in event-free survival with comprehensive medical therapy were greatest in this population. However, across a broad age range, including among people aged 85 years and older, we forecasted meaningful absolute gains in event-free survival. Taken together, these cross-trial data analyses summarize important therapeutic advances in recent years and serve as a reference for relative and absolute gains that might be expected with comprehensive medical therapy.

The first central assumption in our study was that each individual therapy provides additive benefits in patients with HFmrEF/HFpEF. Several lines of evidence suggest that this is an acceptable analytic assumption. First, each of the therapies evaluated has a distinct mechanism of action with no known pharmacological interactions. Second, subgroup analyses from pivotal randomized clinical trials have shown that the benefits of one therapy do not appear attenuated based on background treatment regimens,²²⁻²⁴ suggesting complementary protection against clinical events. However, we acknowledge that background use of these therapies was incomplete potentially limiting the power to detect heterogeneity if indeed it was present. Third, recent trials have directly tested the combined use of SGLT2i and MRAs in patients with HFpEF and separately in individuals with chronic kidney disease, and shown that combination therapy affords incremental and additive effects on markers of cardiovascular and kidney health.^{25,26} Reassuringly, even when assuming subadditive benefits of these therapies, the long-term gains in event-free survival are projected to be substantial.

The second central assumption was that the therapeutic effects observed during each trial would be sustained during lifetime use of therapies. Clinical trials of HF therapies are often conducted with average follow-up durations of 2 to 3 years; however, guidelines recommend the long-term continuation of these therapies for much longer treatment horizons, often indefinitely. We developed and validated a methodology to project within-trial observations to estimate long-term disease trajectories, assuming stable treatment effects over time.^{11,12} However, adherence in real-world clinical care settings is known to be lower than during the conduct of clinical trials. The clinical benefits of both SGLT2i and nsMRA have been shown to attenuate even after short-term drug interruption (within 30 days).^{27,28} However, clinically relevant gains in long-term

event-free survival are expected even when assuming waning efficacy of comprehensive medical therapy over time. We did not however consider other critical issues regarding the long-term use of therapies, including costs, ongoing access, treatment complexity, and polypharmacy. These factors should be considered in the overall assessment of the risks and benefits of comprehensive medical therapy when applying these summary efficacy data to clinical practice.

The final central assumption is that the long-term benefits projected in this cross-trial analysis would translate to clinically relevant benefits when implemented in “real world” settings. Participants were carefully selected according to specific eligibility criteria in each trial, and in PARAGON-HF, patients were required to tolerate half-target doses of each of the study drugs prior to randomization.⁵ We considered treatment effects derived from the overall trial populations (aside from the subpopulation with LVEF below normal) as clinical trials have not consistently demonstrated heterogeneity by individual subgroups, but effectiveness of these therapies may still vary in individual patients when applied in usual clinical care settings. Unlike the previous cross-trial analysis in HFrEF,¹⁹ we projected long-term event-free survival gains with comprehensive medical therapy in HFmrEF/HFpEF but did not consider additive effects on mortality outcomes as none of the individual trials demonstrated significant benefits on overall or cardiovascular mortality. In light of these considerations, we intentionally made conservative analytic choices in our long-term projections and subjected our findings to a range of sensitivity analyses to support their robustness.

While we focused on the aggregate benefits that may be realized with complete implementation of these therapies, safety and tolerability cannot be ignored when considering multi-drug regimens in older individuals with HFpEF. Data from pivotal trials support the safety of these therapies when initiated on the background of varying medical regimens.³⁻⁵ In routine clinical practice, however, similar follow-up protocols with close monitoring and frequent study visits may be challenging to replicate. All 3 classes of therapies are hemodynamically active with potentially additive blood pressure lowering when initiated together.^{25,26} Simultaneous initiation of MRAs and SGLT2i is also known to induce potentially additive acute reductions in kidney function^{25,26} that appear entirely hemodynamically mediated and not associated with tubular injury or long-term adverse prognosis. MRAs such as finerenone are known to increase serum potassium levels, but early combination with either an SGLT2i²⁹ or ARNI³⁰ (when switched from a renin angiotensin system inhibitor) may attenuate risks of hyperkalemia, suggesting that

250 these combinations may in fact be safer. It is reassuring that upon drug cessation, the early
251 changes in hemodynamics, kidney function, and potassium are fully reversible.^{26,28} Although
252 initial data from implementation trials³¹ suggest overall safety of an approach of rapid sequence
253 implementation of multi-drug regimens, a more sequenced approach to initiation of therapies
254 may be needed for patients who are predicted to have poorer tolerability (such as those who are
255 frail or clinically tenuous).

256 The therapeutic landscape of HFpEF continues to rapidly evolve. We attempted to
257 consider the totality of available evidence, including major positive trials powered for clinical
258 outcomes in broad populations of HFpEF, that have supported regulatory approvals for the
259 management of this condition. There has been considerable interest in the potential role of
260 obesity-targeted therapies, such as the glucagon-like peptide-1 receptor agonists and related
261 compounds, in the management of HFpEF. In fact, 3 recent trials with sample sizes of ~500 to
262 750 participants have demonstrated clinical benefits.³²⁻³⁴ However, while awaiting larger trials
263 (such as NCT07037459), we have not considered these therapies in the cross-trial analysis given
264 the exclusive focus on a specific phenotype of HFpEF (with a body mass index $\geq 30\text{kg/m}^2$),
265 limited number of clinical events (<100 events in each of the trials completed thus far), and
266 relatively short duration of follow-up (1 to 2 years). Similarly, we did not consider use of renin
267 angiotensin system inhibitors alone, despite their common use in this population for the
268 management of comorbidities (such as hypertension, diabetes, coronary artery disease, and
269 chronic kidney disease), as primary trials did not meet their primary endpoints^{8,35} and these
270 therapies are not approved for this indication.

271 Among patients with HFmrEF and HFpEF, the anticipated aggregate long-term treatment
272 effects of early comprehensive medical therapy with SGLT2i and nsMRA (and ARNI in selected
273 individuals) are projected to be substantial. These data underscore the urgent need to bolster
274 global implementation efforts to improve the use of medical therapies in HFmrEF/HFpEF, a
275 population with previously limited therapeutic options.

276
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286

287 **Competing Interests Statement:**

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340 Cardiorenal, Eshmoun Clinical research and being the founder of Cardiovascular Clinical
341 Trialists. **Dr. Docherty** reports that his employer, the University of Glasgow, has been
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343 and he has received speaker fees from AstraZeneca, Boehringer Ingelheim, Pharmacosomos, and
344 Translational Medicine Academy; has served on advisory boards or performed consultancy for
345 FIRE-1, Us2.ai, and Bayer AG; holds stock in Us2.ai; has served on a Clinical Endpoint
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Table 1. Key Trial Design Features

	DELIVER (n=6,263)	FINEARTS-HF (n=6,001)	PARAGON-HF (n=4,796)
Comparison	Dapagliflozin vs. Placebo	Finerenone vs. Placebo	Sacubitril/valsartan vs. Valsartan
Study Type	Randomized, double-blind, clinical trial	Randomized, double-blind, clinical trial	Randomized, double-blind, clinical trial
Enrollment Period	2018-2021	2020-2023	2014-2016
Global Enrollment	350 sites in 20 countries	654 sites in 37 countries	848 sites in 43 countries
Median Follow-up (years)	2.3	2.7	2.9
Patient Population	Patients ≥ 40 years with HF with NYHA class II-IV functional class symptoms	Patients ≥ 40 years with HF with NYHA class II-IV functional class symptoms	Patients ≥ 18 years with HF with NYHA class II-IV functional class symptoms
Setting of Enrollment	Patients could be randomized across ambulatory and hospitalized populations	Patients could be randomized across ambulatory and hospitalized populations	Patients could be screened, but not randomized during hospitalization for HF
LVEF	$>40\%$	$\geq 40\%$	$\geq 45\%$
Cardiac Structure and Function	Evidence of structural heart disease (i.e. left ventricular hypertrophy or left atrial enlargement)	Evidence of structural heart disease (i.e. left ventricular hypertrophy or left atrial enlargement)	Evidence of structural heart disease (i.e. left ventricular hypertrophy or left atrial enlargement)
Natriuretic Peptides	NT-proBNP ≥ 600 pg/mL (in AF) or NT-proBNP ≥ 300 pg/mL (if not in AF)	NT-proBNP ≥ 300 pg/ml (or BNP ≥ 100 pg/ml) within 30 days (in those without a recent worsening HF event) or within 90 days (in those with a recent worsening HF event). Qualifying levels of NT-proBNP or BNP were tripled in AF	NT-proBNP >900 pg/mL (in AF) or NT-proBNP >300 pg/mL (if not in AF) If recently hospitalized for HF within 9 months, NT-proBNP >600 pg/mL (in AF) or

			NT-proBNP>200pg/mL (if not in AF)
Body Mass Index	$\leq 50\text{kg}/\text{m}^2$	$\leq 50\text{kg}/\text{m}^2$	$\leq 40\text{kg}/\text{m}^2$
Systolic Blood Pressure	$\geq 95\text{ mmHg}$ at screening and at randomization	$\geq 90\text{ mmHg}$ at screening and at randomization	$\geq 110\text{ mmHg}$ at screening and $\geq 100\text{ mmHg}$ at randomization
Potassium	--	$\leq 5.0\text{ mmol/L}$ at screening and at randomization	$\leq 5.2\text{ mEq/L}$ at screening and $\leq 5.4\text{ mEq/L}$ at randomization
Estimated Glomerular Filtration Rate	$\geq 25\text{ mL/min}/1.73\text{ m}^2$ at screening	$\geq 25\text{ mL/min}/1.73\text{ m}^2$ at screening and at randomization	$\geq 30\text{ mL/min}/1.73\text{ m}^2$ at screening and $\geq 25\text{ mL/min}/1.73\text{ m}^2$ at randomization and without greater than a 35% reduction in eGFR during either run-in period
Run-In Period	None	None	Single-blind run-in phase with half-target doses of both study drugs
Primary Endpoint	Cardiovascular death or <u>first</u> worsening HF event	Cardiovascular and <u>total</u> worsening HF events	Cardiovascular death and <u>total</u> HF hospitalizations

369

370 Abbreviations: BNP = B-type natriuretic peptide; eGFR = estimated glomerular filtration rate;

371 HF = heart failure; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; NYHA

372 = New York Heart Association

373

374 **Table 2. Selected Baseline Characteristics**

	DELIVER (n=6,263)	FINEARTS-HF (n=6,001)	PARAGON-HF (n=4,796)
Age (years)	72 ± 10	72 ± 9	73 ± 8
Women	2,747 (44%)	2,732 (46%)	2,479 (52%)
Body mass index, kg/m² mean±SD	30 ± 6	30 ± 6	30 ± 5
Systolic blood pressure (mmHg), mean±SD	128 ± 15	129 ± 15	131 ± 16
Left ventricular ejection fraction (%), mean±SD	54 ± 9	53 ± 8	58 ± 8
New York Heart Association class III or IV	1,549 (25%)	1,854 (31%)	951 (20%)
Atrial fibrillation	3,552 (57%)	3,273 (55%)	2,521 (53%)
Diabetes mellitus	2,806 (45%)	2439 (41%)	2,062 (43%)
Loop diuretics	4,811 (77%)	5239 (87%)	3,757 (78%)
ARNI	301 (5%)	513 (9%)	--
SGLT2 inhibitor	--	817 (14%)	28 (0.6%)
MRA	2,667 (43%)	--	1,239 (26%)
β-blockers	5,167 (83%)	5,095 (85%)	3,821 (80%)

375

376 Data are presented as n (%) or mean (SD), unless otherwise stated.

377

378 Abbreviations: ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid
379 receptor antagonist; SD = standard deviation; SGLT2 = sodium-glucose co-transporter-2

380

381 **Table 3. Selected Adverse Events**

Safety Event	DELIVER		FINEARTS-HF		PARAGON-HF	
	Dapagliflozin	Placebo	Finerenone	Placebo	Sacubitril/ Valsartan	Valsartan
Any serious adverse event	1361/3126 (43.5)	1423/3127 (45.5)	1157/2993 (38.7)	1213/2993 (40.5)	1424/2419 (58.9)	1416/2402 (59.0)
Renal impairment	10/3126 (0.3)	7/3127 (0.2)	57/2897 (2.0)	34/2888 (1.2)	38/2407 (1.6)	40/2389 (1.7)
Hypotension	6/3126 (0.2)	1/3127 (0.0)	538/2911 (18.5)	361/2904 (12.4)	380/2407 (15.8)	257/2389 (10.8)
Elevated serum potassium >5.5mmol/L	--	--	413/2898 (14.3)	199/2889 (6.9)	316/2386 (13.2)	361/2367 (15.3)

382

383 Adverse events were defined differently across trials and were collected in the safety analytic
 384 sets. Renal impairment was defined as events leading to permanent study drug discontinuation
 385 (in DELIVER) and as serum creatinine levels $\geq 3.0\text{mg/dL}$ (in FINEARTS-HF and PARAGON-
 386 HF). Hypotension was defined as events leading to permanent study drug discontinuation (in
 387 DELIVER), any visit systolic blood pressure $<100\text{mmHg}$ (in FINEARTS-HF), and investigator-
 388 reported hypotension with systolic blood pressure $<100\text{mmHg}$ (in PARAGON-HF). Serum
 389 potassium levels after randomization were not collected in the DELIVER trial.

390

391

392 **Figure Legends**

393 **Figure 1. Aggregate Relative Risk Reduction on Cardiovascular Death or Worsening HF**
394 **Event with Comprehensive Medical Therapy.** Aggregate relative benefits of SGLT2i and
395 nsMRA in the overall population (left) and the combination of SGLT2i, nsMRA, and ARNI in
396 individuals with a left ventricular ejection fraction (LVEF) below normal <60% (right).
397 Treatment estimates for individual therapies and their combination are summarized as hazard
398 ratios (HR) and 95% confidence intervals (CI). “Standard treatment” in the comparator
399 populations constituted treatment according to the standard of care based on local guidelines, but
400 did not mandate any specific pharmacotherapy. For the main analysis, we derived treatment
401 estimates from 6,263 participants in DELIVER and 6,001 participants in FINEARTS-HF. In the
402 subgroup of individuals with LVEF below normal (<60%), we estimated treatment effects from
403 4,372 participants in DELIVER, 4,846 in FINEARTS-HF, and 2,070 in PARAGON-HF.
404 Abbreviations: ARNI = angiotensin receptor neprilysin inhibitor; HFmrEF = heart failure with
405 mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; nsMRA
406 = non-steroidal mineralocorticoid receptor antagonist; SGLT2i = sodium glucose co-transporter-
407 2 inhibitor.

408 **Figure 2. Estimated Absolute Event-Free Survival Gains with Comprehensive Medical**
409 **Therapy.** Kaplan-Meier estimated curves for patients starting at 65 years of age for survival free
410 from the primary endpoint (cardiovascular death or worsening HF event) in the overall
411 HFmrEF/HFpEF population (left) and in individuals with HFmrEF/HFpEF with a LVEF below
412 normal <60% (right). Residual event-free lifespan was estimated using the area under the
413 survival curve up to a maximum of 100 years of age. Abbreviations are as in Figure 1.

414 **Figure 3. Event-Free Survival Gains with Comprehensive Medical Therapy across the Age**
415 **Spectrum.** **(A)** Estimated mean survival free from the primary endpoint in the DELIVER control
416 group and the simulated comprehensive medical therapy group for every age between 55 and 85
417 years in the overall population with HFmrEF/HFpEF (left) or patients with HFmrEF/HFpEF and
418 LVEF below normal (<60%) (right). **(B)** Treatment differences (data points), smoothed estimates
419 (solid lines), and 95% confidence interval (CI) of the smoothed estimates (dashed lines) are
420 displayed for mean event-free survival with comprehensive medical therapy after application of a
421 locally weighted scatterplot smoothing procedure. Data are shown for the overall population with
422 HFmrEF/HFpEF (left) or patients with HFmrEF/HFpEF and LVEF below normal (<60%)
423 (right). Abbreviations are as in Figure 1.

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652

653 **Methods**

654 In this cross-trial analysis, we identified pivotal trials that supported the regulatory evaluation of
655 therapies approved by the US Food and Drug Administration (as of August 2025) for the
656 management of HFmrEF/HFpEF. We leveraged individual participant-level data which we had
657 direct access to to represent each class of therapies: SGLT2i (dapagliflozin in DELIVER),
658 nsMRA (finerenone in FINEARTS-HF), and ARNI (sacubitril/valsartan in PARAGON-HF).
659 **Table 1** summarizes key design features of each trial. All trials were assessed as high quality
660 with a low risk of bias (**Extended Data Table 4**). The primary results of each trial have been
661 previously published and the study protocols and statistical analysis plans are publicly
662 available.³⁻⁵ All participants provided informed consent, and trial protocols were approved by
663 local institutional review boards or ethics committees.

664

665 **DELIVER.** From 2018 to 2021, the DELIVER (Dapagliflozin Evaluation to Improve the LIVES
666 of Patients with Preserved Ejection Fraction Heart Failure; ClinicalTrials.gov Identifier:
667 NCT03619213) trial³ randomly assigned 6,263 adults ≥ 40 years with symptomatic HF and an
668 LVEF $>40\%$ to dapagliflozin 10mg once daily or matching placebo. All participants were
669 required to have evidence of structural heart disease and elevated natriuretic peptide levels.
670 Median follow-up was 2.3 years.

671

672 **FINEARTS-HF.** From 2020 to 2023, the FINEARTS-HF (FINererenone trial to investigate
673 Efficacy and sAfety superioR to placebo in paTientS with Heart Failure; ClinicalTrials.gov
674 Identifier: NCT04435626) trial⁴ randomly assigned 6,001 adults ≥ 40 years with symptomatic HF
675 and an LVEF $\geq 40\%$ to finerenone or matching placebo titrated to target doses of 20mg or 40mg
676 (depending on baseline estimated glomerular filtration rate). All participants were required to
677 have evidence of structural heart disease and elevated natriuretic peptide levels. Median follow-
678 up was 2.7 years.

679

680 **PARAGON-HF.** From 2014 to 2016, the PARAGON-HF (Prospective Comparison of ARNI
681 [angiotensin receptor–neprilysin inhibitor] with ARB Global Outcomes in HF with Preserved
682 Ejection Fraction; ClinicalTrials.gov Identifier: NCT01920711) trial⁵ randomly assigned 4,796
683 adults ≥ 18 years with symptomatic HF and an LVEF $\geq 45\%$ to the ARNI sacubitril/valsartan
684 (target dose, 97mg of sacubitril with 103mg of valsartan twice daily) versus the angiotensin
685 receptor blocker valsartan (target dose, 160mg twice daily). Only participants who tolerated half
686 target doses of both study medications during a single-blind run-in phase were randomized. All
687 participants were required to have evidence of structural heart disease and elevated natriuretic
688 peptide levels. Median follow-up was 2.9 years.

689

690 **Clinical Outcomes.** Our primary endpoint was a composite of cardiovascular death or
691 worsening HF event (which included both a hospitalization for HF and an urgent ambulatory
692 encounter for HF requiring intravenous HF therapies). All potential HF events and deaths were
693 prospectively collected and adjudicated by blinded clinical endpoints committees.

694

695 **Statistical Analysis.** We first estimated the aggregate relative effects of comprehensive medical
696 therapy based on individual treatment effects observed in each component trial. We used
697 established methods of indirect comparisons, which are commonly applied in putative placebo
698 assessments.⁷ The accompanying 95% confidence interval was estimated by the square root of
699 the sum of the squared standard errors of the logarithmic hazard ratios (HR) of the individual
700 trial treatment effects. Cox proportional hazards models were used to estimate all time-to-first
701 composite endpoints with trial-specific stratification terms as prespecified in each trial protocol:

702 DELIVER (diabetes status),³ FINEARTS-HF (geographic region and LVEF<60% or ≥60%),⁴
703 and PARAGON-HF (geographic region).⁵ No covariate adjustment was made.

704 We considered comprehensive medical therapy as the combined use of SGLT2i and
705 nsMRA for the overall population. As ARNI is indicated in many countries worldwide
706 specifically for the treatment of patients with HF and LVEF below normal, we considered
707 comprehensive medical therapy as the combined use of SGLT2i, nsMRA, and ARNI for patients
708 with an LVEF<60%. As PARAGON-HF was an active-controlled trial, we employed the same
709 methods of indirect comparisons to estimate the treatment effects of ARNI if it was instead
710 compared against a putative placebo.⁷ To do so, participant-level data were accessed from the
711 CHARM-Preserved (Candesartan Cilexetil in Heart Failure Assessment of Reduction in
712 Mortality and Morbidity) trial, which tested the angiotensin receptor blocker, candesartan (target
713 dose 32mg once daily) against placebo among 3,023 patients with symptomatic HF and
714 LVEF>40%.⁸ As urgent HF visits were not collected or adjudicated in CHARM-Preserved, the
715 endpoint of cardiovascular death or HF hospitalization was considered instead. We additionally
716 conducted alternative segmenting aligned with contemporary guideline designations of LVEF^{9,10}
717 and separately evaluated HFmrEF (LVEF between 40 and 50%) and HFpEF (LVEF of 50% or
718 greater). The comparator populations were individuals treated according to the standard of care
719 based on local guidelines, but did not mandate any specific pharmacotherapy.

720 We then projected the long-term absolute event-free survival gains by applying the
721 imputed treatment effects of comprehensive medical therapy to the control group of the
722 DELIVER trial. To consider individuals untreated with these therapies, we excluded individuals
723 already treated with an ARNI or an MRA at baseline (n=1,378). We leveraged validated actuarial
724 (age-based) methods^{11,12} that reshape the follow-up horizon from considering time since
725 randomization to evaluating age instead. At every age between 55 years and 85 years, we
726 calculated nonparametric Kaplan-Meier estimates of residual survival free from the primary
727 endpoint. Projected event-free survival was then estimated as the area under the survival curve
728 (up to a maximum of 100 years). We separately estimated long-term event-free survival as
729 observed in individuals in the DELIVER control arm (comparator group) and simulated if treated
730 with comprehensive medical therapy. As there were no observed age-by-treatment interactions in
731 any of the component trials,¹³⁻¹⁷ the difference in areas under the survival curves represented the
732 gains in event-free survival with comprehensive medical therapy at any given age of starting

733 therapy. We additionally applied the lower and upper bounds of the 95% CI around the relative
734 treatment effects to the DELIVER control group to provide a range of uncertainty of our
735 estimates. For display purposes, event-free survival gains across the age range were smoothed
736 after application of a locally weighted scatterplot smoothing procedure.

737

738 **Sensitivity Analyses**

739 We conducted a series of sensitivity and supplemental analyses to test the robustness of our
740 cross-trial analysis. First, instead of considering DELIVER data alone, data from a meta-analysis
741 of the 2 large SGLT2i outcomes trials in HFmrEF/HFpEF were used instead to summarize
742 treatment effects of SGLT2i.¹⁴ Similarly, instead of using FINEARTS-HF alone, data from a
743 meta-analysis of FINEARTS-HF and a previous large HFmrEF/HFpEF outcomes trial of the
744 steroidal MRA spironolactone were used instead to summarize treatment effects of MRA.¹⁵
745 Second, we estimated the treatment effects of comprehensive medical therapy without making
746 the assumption that two therapies when used together would provide fully additive effects. To do
747 so, we assumed that the treatment effects of nsMRA may be 50%, 75%, and 90% of its full
748 efficacy when added to an SGLT2i. In each scenario, we multiplied the beta coefficient of the
749 hazard ratio for nsMRA by the percentage of subadditive assumed effect; the resulting estimates
750 were then inputted into the indirect comparison calculations to derive the treatment effects of
751 comprehensive therapy. Third, we evaluated the long-term event-free survival gains of
752 comprehensive medical therapy assuming declining or waning efficacy over time. Specifically,
753 we assumed a yearly decline of 2%, 5%, and 10% (compared with the previous year) in the
754 efficacy of comprehensive medical therapy. Fourth, to account for potential competing risks of
755 mortality, we evaluated comprehensive treatment effects on the composite endpoint of all-cause
756 death or worsening HF event. Finally, to address concerns that urgent HF visits may not be
757 clinically meaningful as the other elements of the composite endpoint, we evaluated the
758 composite of cardiovascular death or hospitalization for HF (not considering urgent HF visits).

759 Statistical analyses were performed using STATA, and p-values less than 0.05 were
760 considered statistically significant.

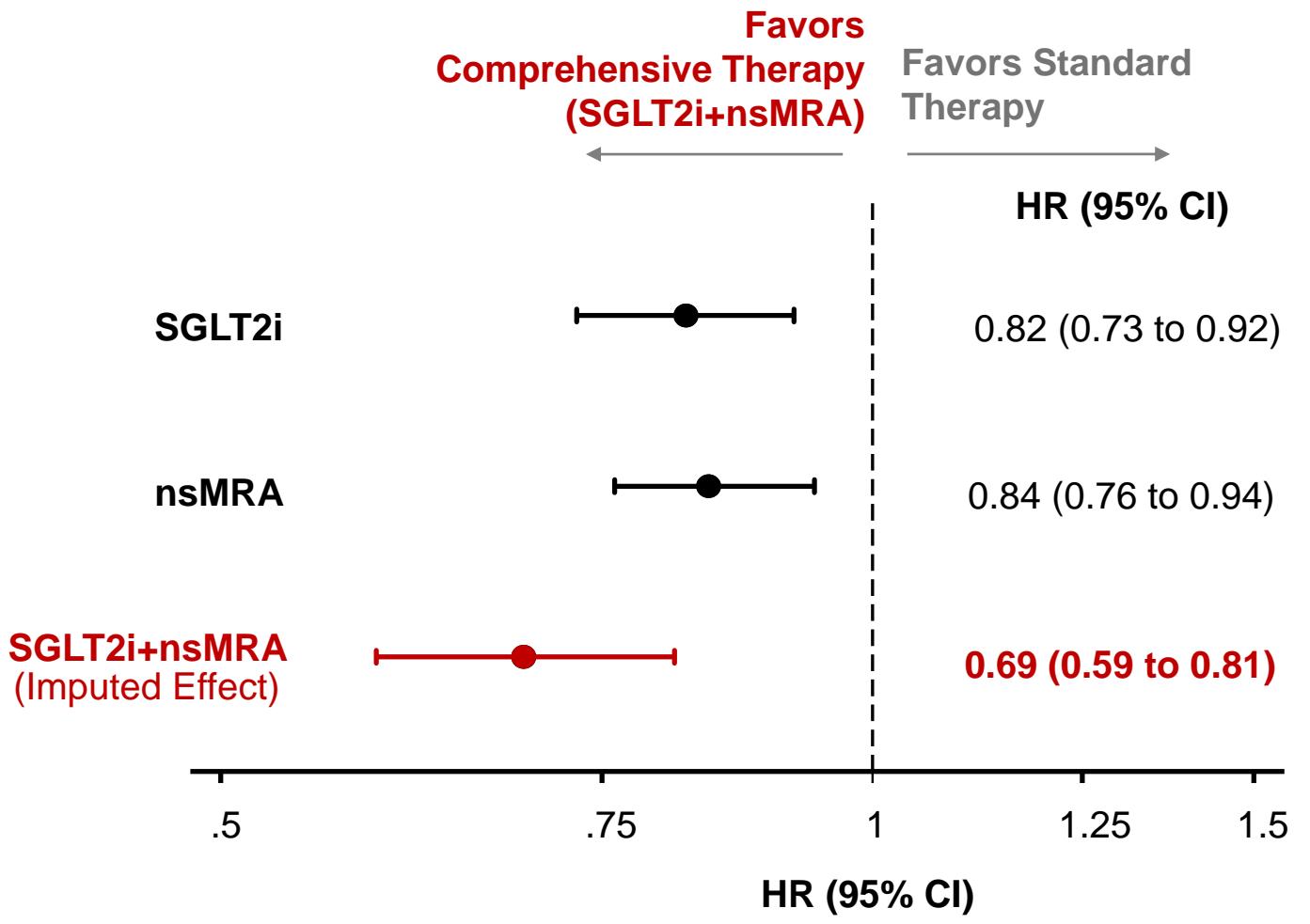
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762 **Data Availability:** All trial funders are committed to sharing access to patient-level data

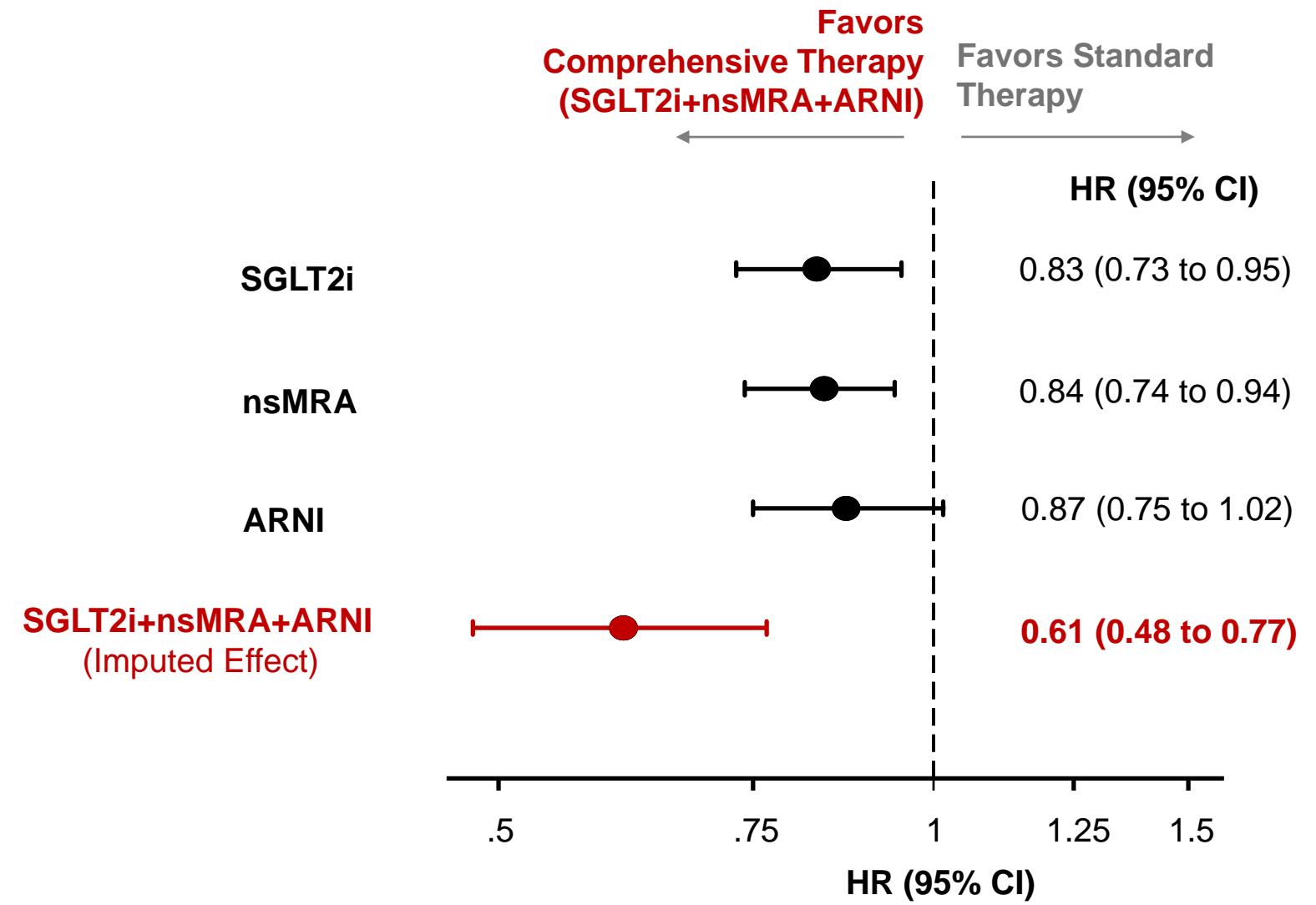
763 and supporting clinical documents from eligible studies. The trial data availability is according to
764 the separate criteria and processes for AstraZeneca
765 (<https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>), Bayer
766 (<https://vivli.org/ourmember/bayer/>), and Novartis
767 (https://www.novartis.com/sites/novartis_com/files/clinical-trial-data-transparency.pdf)

ACCELERATED ARTICLE PREVIEW

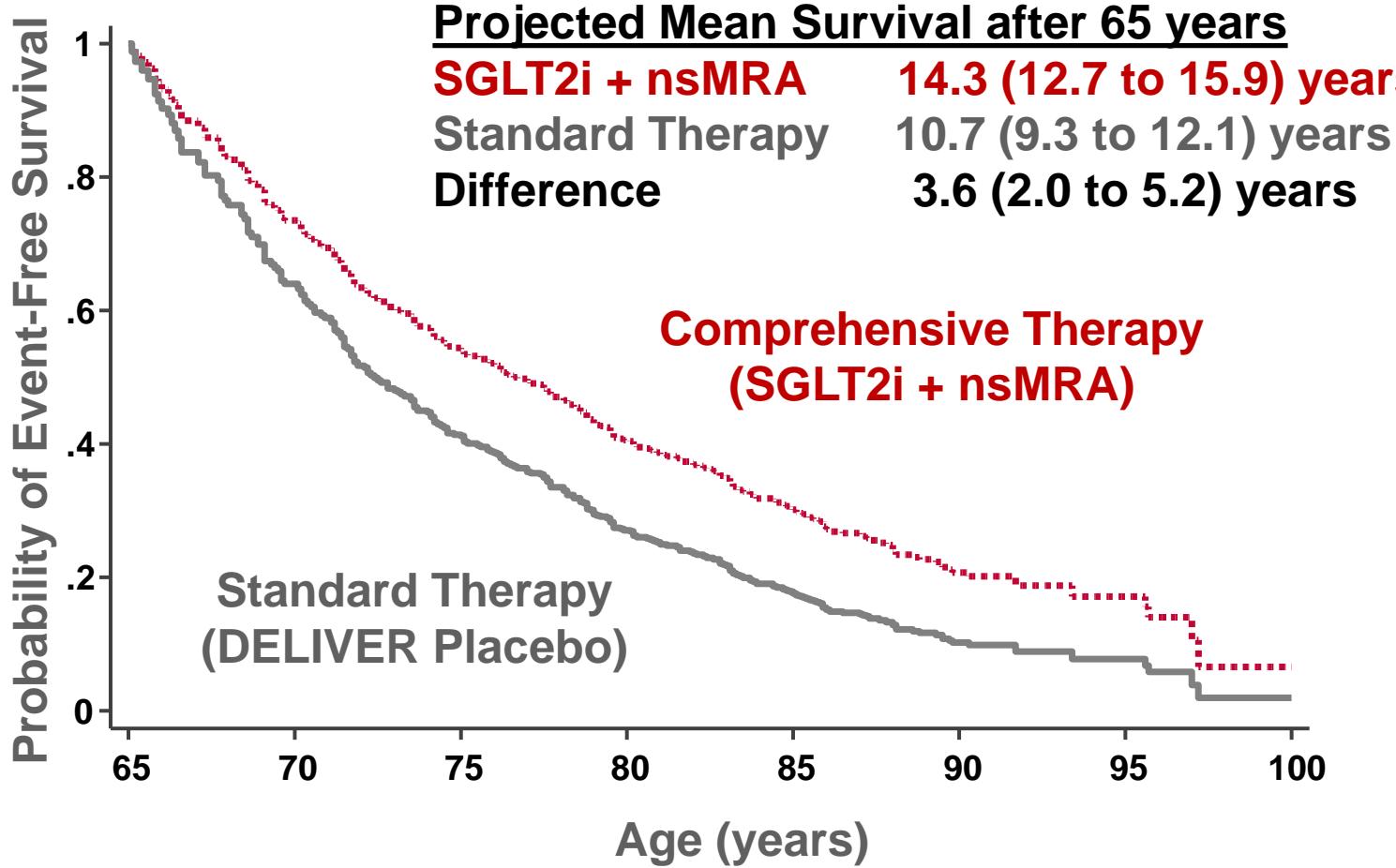
Overall Population with HFmrEF/HFpEF



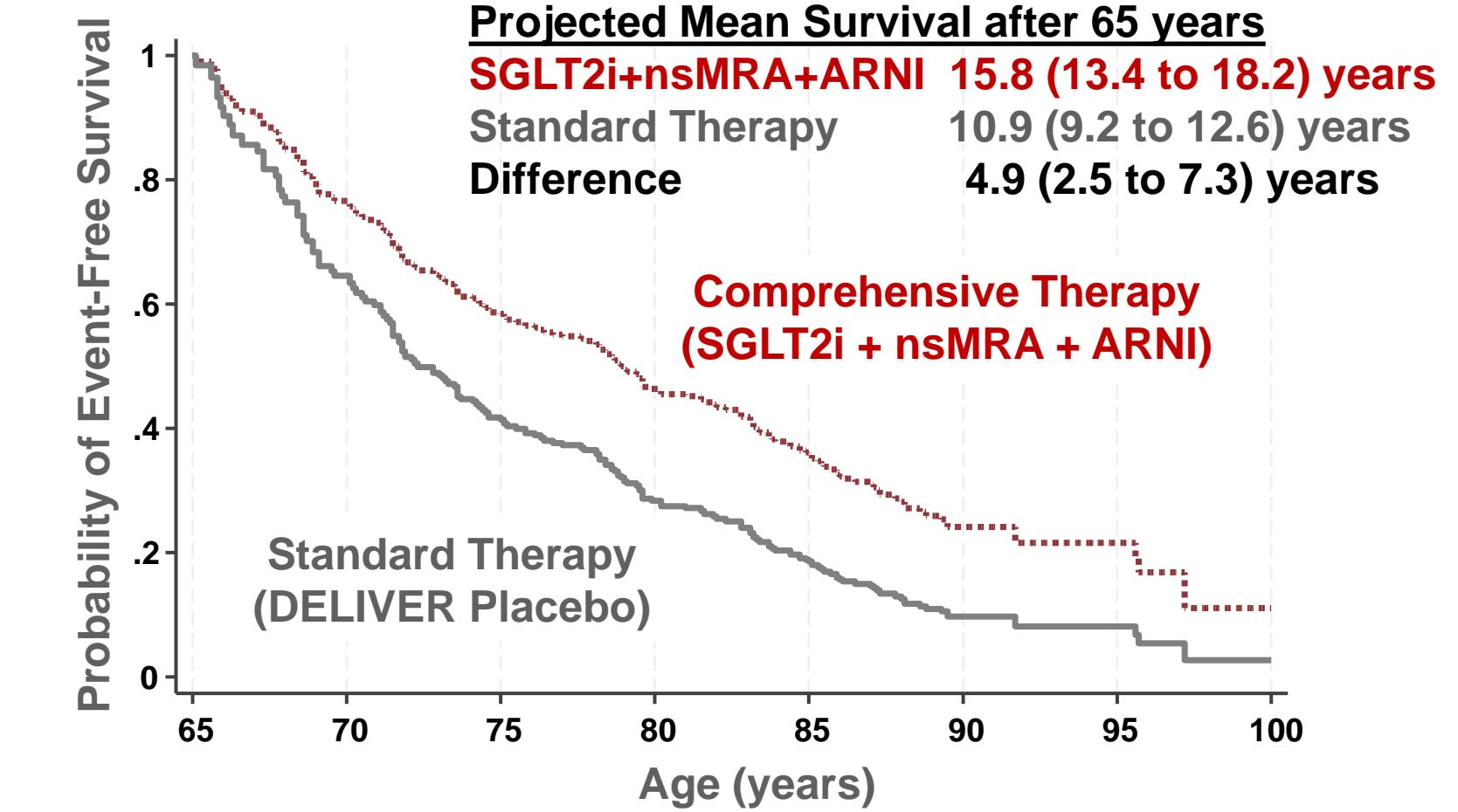
Patients with HFmrEF/HFpEF & LVEF Below Normal (<60%)

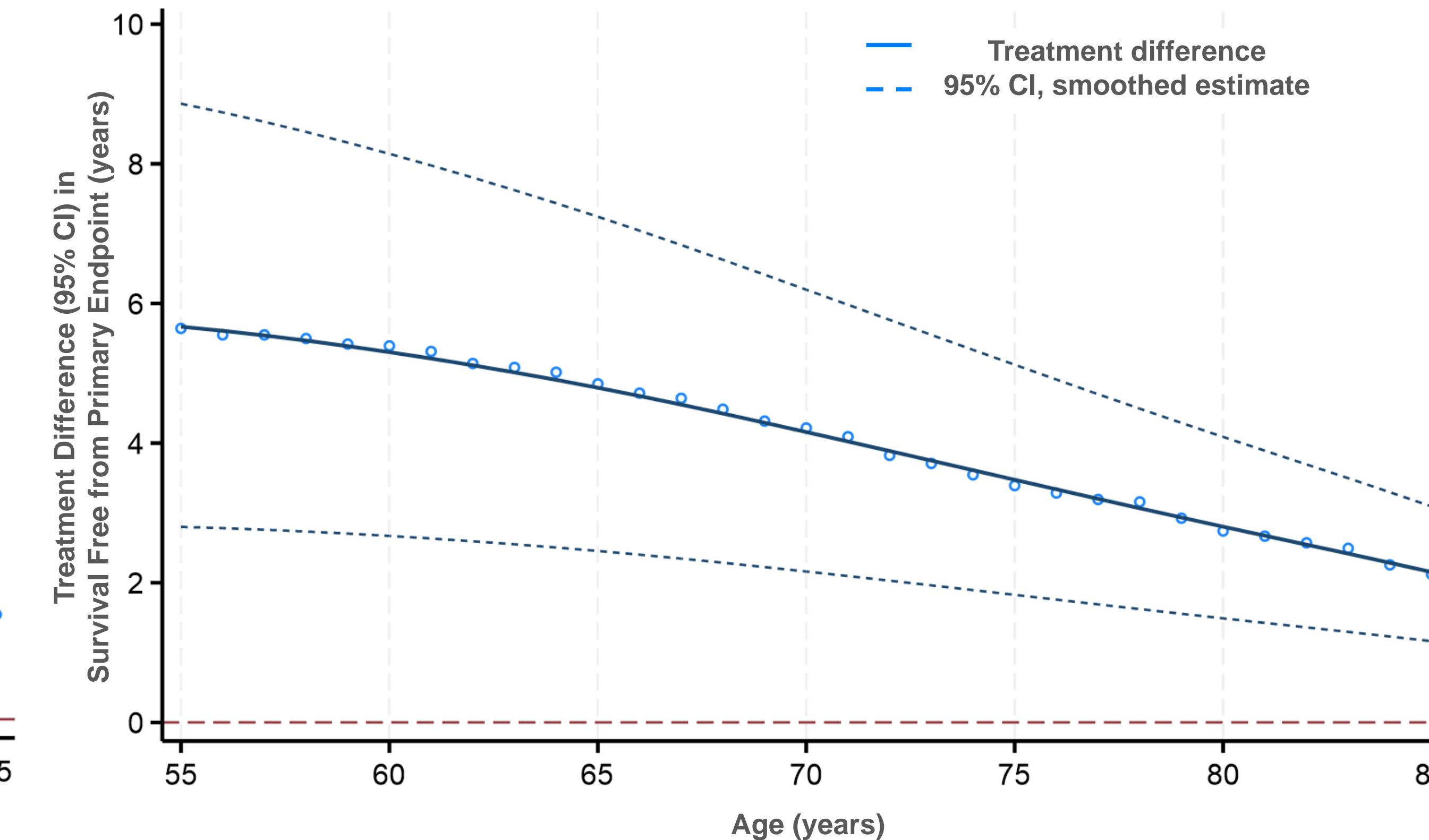
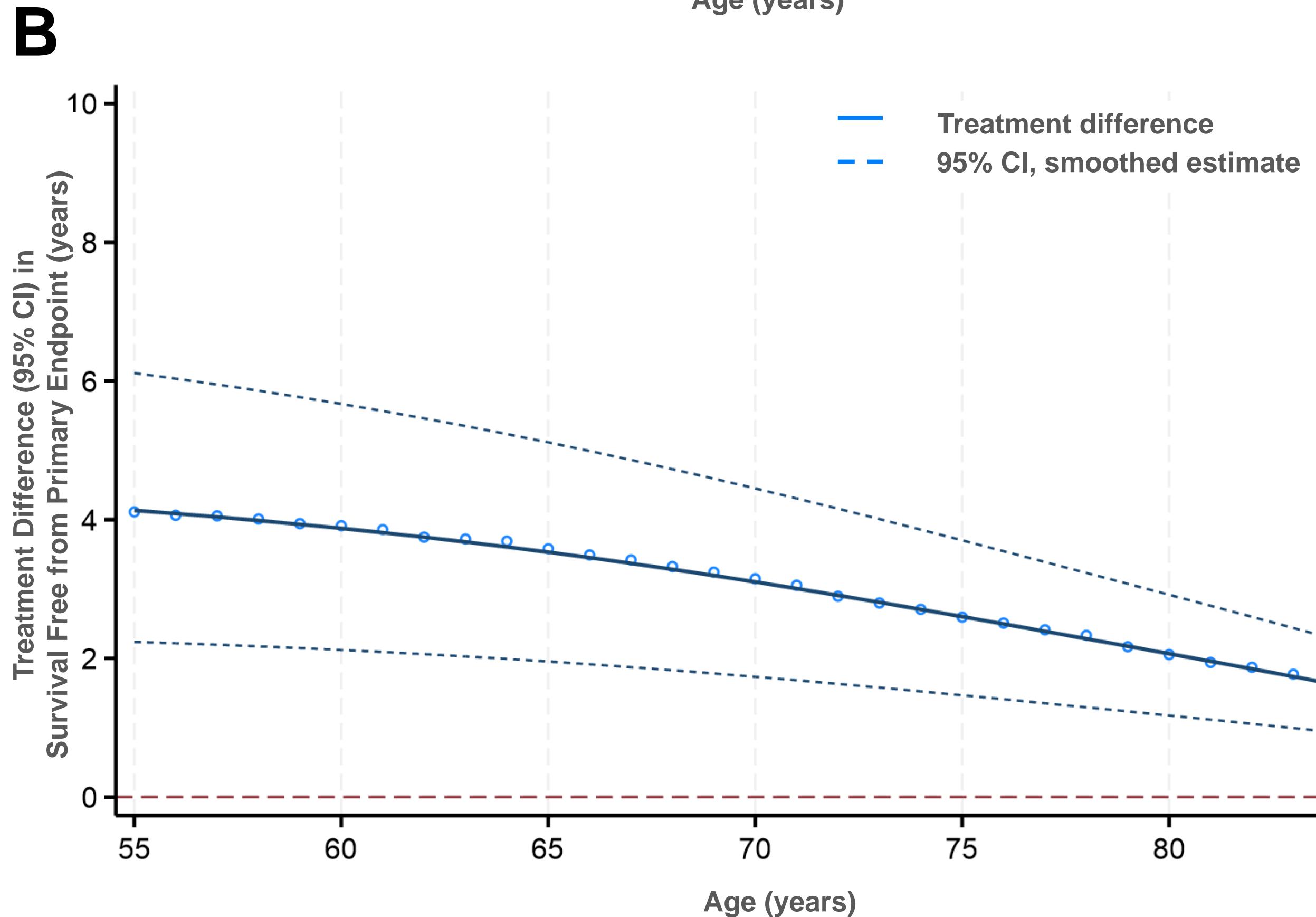
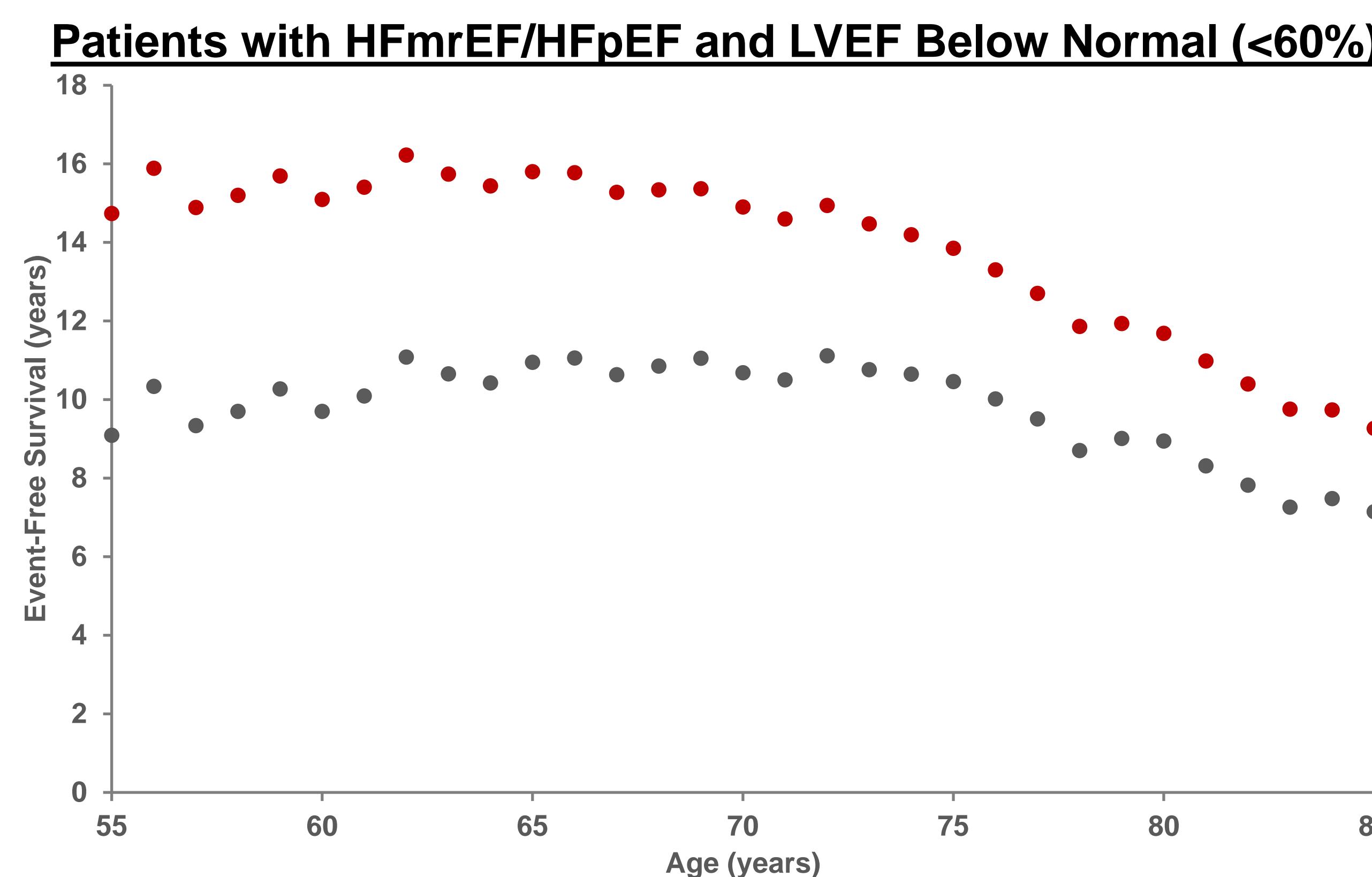
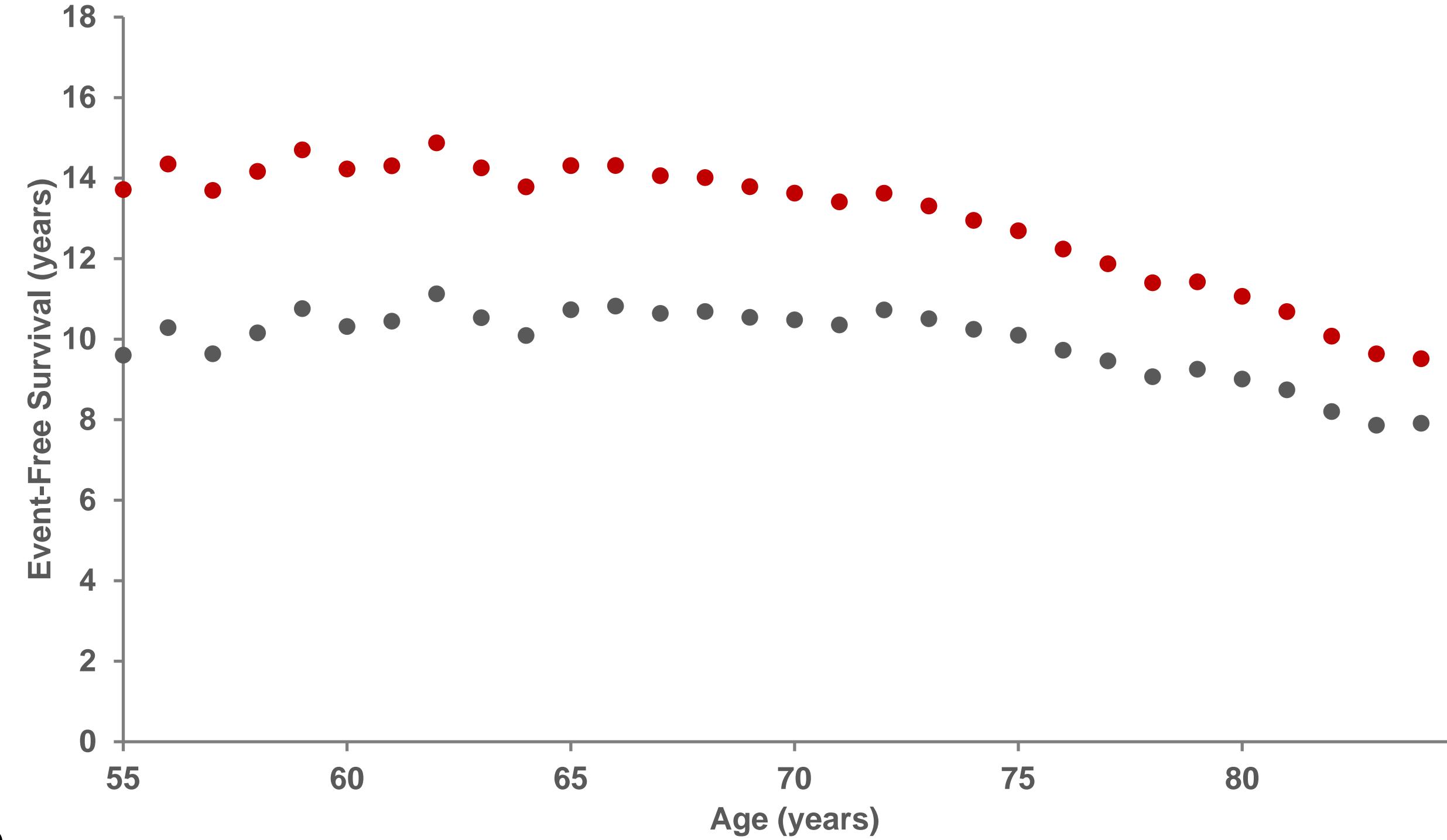


Overall Population with HFmrEF/HFpEF



Patients with HFmrEF/HFpEF and LVEF Below Normal (<60%)



A
Overall Population with HFmrEF/HFpEF

Extended Data Table 1. Baseline Characteristics of Base Population from the DELIVER Trial

	Overall HFmrEF/HFpEF Population (n=1,754)	Patients with HFmrEF/HFpEF and a LVEF <60% (n=1,123)
Age (years)	72.5 ± 9.0	71.9 ± 9.3
Women	818 (46.6%)	475 (42.3%)
Body mass index (kg/m²)	30.1 ± 6.1	30.0 ± 6.0
Systolic blood pressure (mmHg)	130.7 ± 15.1	130.4 ± 15.1
Region		
Europe/Saudi Arabia	854 (48.7%)	607 (54.1%)
Asia	289 (16.5%)	164 (14.6%)
Latin America	335 (19.1%)	189 (16.8%)
North America	276 (15.7%)	163 (14.5%)
Left ventricular ejection fraction (%)	55.7 ± 8.8	50.3 ± 5.1
NYHA class III or IV	378 (21.6%)	268 (23.9%)
History of Diabetes	842 (48.0%)	537 (47.8%)
History of AF/AFL	995 (56.7%)	644 (57.3%)
eGFR (mL/min/1.73m²)	60.2 ± 19.3	60.8 ± 19.3
eGFR <60mL/min/1.73m²	891 (50.8%)	550 (49.0%)
NT-proBNP (pg/mL), median [25th-75th percentile]	973.5 [581-1688]	1056 [629-1854]
ACEi/ARB	1325 (75.5%)	848 (75.5%)
β-blocker	1408 (80.3%)	918 (81.7%)
Loop diuretic	1390 (79.2%)	916 (81.6%)

Data are presented as n (%) or mean (SD), unless otherwise stated.

The base population for this analysis included participants in the DELIVER trial assigned to the placebo arm who were not treated with an angiotensin receptor neprilysin inhibitor or mineralocorticoid receptor antagonist at baseline.

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; AF/AFL = atrial fibrillation/flutter; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; NYHA = New York Heart Association.

Extended Data Table 2. Sensitivity Analysis Assuming Subadditive Effects of Comprehensive Medical Therapy

Additivity of Treatment Benefits	Assumed Estimated Treatment Effect Hazard Ratio (95% Confidence Interval)	Long-Term Event-Free Survival Gains
Second Therapy Completely Additive	0.69 (0.59 to 0.81)	3.6 (2.0 to 5.2)
Second Therapy 90% Effective when Added to the First	0.70 (0.60 to 0.82)	3.4 (1.9 to 5.0)
Second Therapy 75% Effective when Added to the First	0.72 (0.61 to 0.84)	3.2 (1.6 to 4.8)
Second Therapy 50% Effective when Added to the First	0.75 (0.64 to 0.88)	2.7 (1.2 to 4.3)

We assumed that the treatment effects of nsMRA may be 50%, 75%, and 90% of its full efficacy when added to an SGLT2i. In each scenario, we multiplied the beta coefficient of the hazard ratio for nsMRA by the percentage of subadditive assumed effect; the resulting estimates were then inputted into the indirect comparison calculations to derive the treatment effects of comprehensive therapy.

Extended Data Table 3. Sensitivity Analysis Assuming Declining Efficacy of Comprehensive Medical Therapy Over Time

Consistency of Treatment Effect over Time	Assumed Starting Estimated HR at Age 65	Assumed Ending Estimated HR at Age 100	Event-Free Survival Gains
Consistent Treatment Effect Over Time	0.69	0.69	3.6 (2.0 to 5.2)
2% Decline per Year	0.69	0.83	3.0 (1.7 to 4.3)
5% Decline per Year	0.69	0.94	2.4 (1.3 to 3.4)
10% Decline per Year	0.69	0.99	1.7 (1.0 to 2.4)

We evaluated the long-term event-free survival gains of comprehensive medical therapy assuming declining or waning efficacy over time. Specifically, we assumed a yearly decline of 2%, 5%, and 10% (compared with the previous year) in the efficacy of comprehensive medical therapy. Hazard ratio (HR) of comprehensive medical therapy is presented at age 65 years (without discounting) and with various scenarios of declining efficacy over time through the end of forecasted follow-up age of 100 years.

Extended Data Table 4. Risk of Bias Assessment Using the Revised Tool to Assess Risk of Bias in Randomized Trials (RoB 2.0)

Study Name	Year	Randomization Bias	Intervention Deviation	Missing Outcome Data	Measurement of Outcome	Reporting of Outcome	Overall Risk
PARAGON-HF	2019	Low	Low	Low	Low	Low	Low
DELIVER	2022	Low	Low	Low	Low	Low	Low
FINEARTS-HF	2024	Low	Low	Low	Low	Low	Low

Reporting Summary

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- A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
Give P values as exact values whenever suitable.
- For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection No specific additional software was used for data collection for this cross-trial analysis.

Data analysis Statistical analyses were conducted using STATA version 18.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

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Individual participant data from the 3 completed trials were accessed. Categorical variables were harmonised and all variables computed to the same scale or units of measurement. Variable names were standardized across individual trial datasets. The baseline characteristics of trial participants were extracted and relevant subgroup variables extracted. Time to event (harmonized to days since randomization) and censoring variables for each of the outcomes listed were also extracted.

For each of the 3 clinical trials (DELIVER, FINEARTS-HF, and PARAGON-HF), the trial funders are committed to sharing access to patient-level data and supporting clinical documents from eligible studies. The trial data availability is according to the separate criteria and processes for AstraZeneca (<https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure>), Bayer (<https://vivli.org/ourmember/bayer/>), and Novartis (https://www.novartis.com/sites/novartis_com/files/clinical-trial-data-transparency.pdf).

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender

The n (%) of women was described by trial population (DELIVER, FINEARTS-HF, and PARAGON-HF).

Reporting on race, ethnicity, or other socially relevant groupings

This report does not contain any specific race, ethnicity, or socially relevant group data.

Population characteristics

Patients with heart failure with mildly reduced or preserved ejection fraction

Recruitment

All participants randomized in each of the 3 trials were considered for this cross-trial analysis with only patients with critical Good Clinical Practice violations excluded.

Ethics oversight

The trial protocols were approved by ethics committees or institutional review boards at all participating sites and all patients provided explicit written informed consent.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

Life sciences

Behavioural & social sciences Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

For the main analysis, we derived treatment estimates from 6,263 participants in DELIVER and 6,001 participants in FINEARTS-HF. In the subgroup of individuals with LVEF below normal (<60%), we estimated treatment effects from 4,372 participants in DELIVER, 4,846 in FINEARTS-HF, and 2,070 in PARAGON-HF. As this was a cross-trial analysis of completed randomized clinical trials, we considered all randomized participants under intention-to-treat principles. These samples represent the largest trials evaluating each individual drug therapy in this target population and thus are felt to sufficient to provide stable estimates of treatment effects on clinical outcomes.

Data exclusions

Only patients with critical Good Clinical Practice violations were excluded.

Replication

As randomized assessments of comprehensive therapy have not been conducted to date in this target population, replication of our cross-trial analysis was not feasible.

Randomization

In the DELIVER trial, 6,263 adults ≥40 years with symptomatic HF and an LVEF>40% were randomly assigned 1:1 to dapagliflozin 10mg once daily or matching placebo. In the FINEARTS-HF trial, 6,001 adults ≥40 years with symptomatic HF and an LVEF ≥40% were randomly assigned 1:1 to finerenone or matching placebo titrated to target doses of 20mg or 40mg (depending on baseline estimated glomerular filtration rate). In PARAGON-HF, 4,796 adults ≥18 years with symptomatic HF and an LVEF ≥45% were randomly assigned to the ARNI sacubitril/valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) versus the angiotensin receptor blocker valsartan (target dose, 160 mg twice daily). Only participants who tolerated half target doses of both study medications during a single-blind run-in phase were randomized.

Blinding

All 3 trials were double-blind randomized clinical trials. Specifically, all investigators and participants remained strictly blinded to treatment arm allocation during the randomized period.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
<input checked="" type="checkbox"/>	Antibodies
<input checked="" type="checkbox"/>	Eukaryotic cell lines
<input checked="" type="checkbox"/>	Palaeontology and archaeology
<input checked="" type="checkbox"/>	Animals and other organisms
<input type="checkbox"/>	Clinical data
<input checked="" type="checkbox"/>	Dual use research of concern
<input checked="" type="checkbox"/>	Plants

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	ChIP-seq
<input checked="" type="checkbox"/>	Flow cytometry
<input checked="" type="checkbox"/>	MRI-based neuroimaging

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration

DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; ClinicalTrials.gov Identifier: NCT03619213); FINEARTS-HF (FINerenone trial to investigate Efficacy and safety superior to placebo in patients with Heart Failure; ClinicalTrials.gov Identifier: NCT04435626), PARAGON-HF (Prospective Comparison of ARNI [angiotensin receptor-neprilysin inhibitor] with ARB Global Outcomes in HF with Preserved Ejection Fraction; ClinicalTrials.gov Identifier: NCT01920711)

Study protocol

The study protocols and the statistical analysis plans for each of the included trials are published and publicly available for review

Data collection

Participants in DELIVER were enrolled from 2018 to 2021 across 20 countries. Participants in FINEARTS-HF were enrolled from 2020 through 2023 across 37 countries. Participants in PARAGON-HF were enrolled from 2014 to 2016 across 43 countries. All 3 trials were global clinical trials with enrollment from academic/hospital-based or community health care facilities.

Outcomes

The primary endpoint was a composite of cardiovascular death or worsening HF event (which included both hospitalizations for HF and urgent ambulatory encounters for HF requiring intravenous HF therapies). All potential HF events and deaths were prospectively collected and adjudicated by blinded clinical endpoints committees.

Plants

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.