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# Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials

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1 **Estimating Lifetime Benefits of Comprehensive Disease-Modifying Pharmacologic**  
2 **Therapies in Heart Failure with Reduced Ejection Fraction**

3  
4 **Running Title:** Comprehensive Disease-Modifying Therapies in HFrEF

5  
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24  
25 **Key Words:** combination; guideline-directed medical therapy; heart failure; treatment

26  
27 **Clinical Trial Registration:**

28 EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart  
29 Failure): NCT00232180

30 PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin  
31 Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on  
32 Global Mortality and Morbidity in Heart Failure Trial): NCT01035255

33 DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure):  
34 NCT03036124

35  
36 **Word Count:** 3,228; **References:** 30

37  
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41 **Research in Context**

42

43 *Evidence before this study*

44 Patients with heart failure with reduced ejection (HFrEF) experience substantially shorter life  
45 expectancies compared with persons in the general population of similar age. Multiple therapies  
46 are now known to individually extend survival in chronic HFrEF. While most patients are  
47 currently treated with renin-angiotensin-system inhibitors (RASi) and  $\beta$ -blockers, three drug  
48 classes (ARNI, MRA, SGLT2i) have additionally been shown to reduce mortality in HFrEF  
49 beyond these previously established core elements. Real-world data have highlighted incomplete  
50 use of these more recent additions to the therapeutic armamentarium.

51

52 *Added value of this study*

53 Leveraging data from 3 contemporary randomized clinical trials in chronic HFrEF, we estimate  
54 that comprehensive disease-modifying pharmacologic therapy (ARNI+ $\beta$ -  
55 blocker+MRA+SGLT2i) reduces the hazard of cardiovascular death or HF hospitalization by  
56 62% (HR 0.38; 95% CI 0.30-0.47) compared with limited conventional therapy (ACEi/ARB+  $\beta$ -  
57 blocker). Depending on the age of therapeutic optimization, treatment with comprehensive  
58 disease-modifying pharmacologic therapy was estimated to afford 1.4 to 6.3 additional years  
59 alive and 2.7 to 8.3 additional years free from cardiovascular death or HF hospitalization  
60 compared with treatment with ACEi/ARB +  $\beta$ -blocker alone.

61

62 *Implications of all the available evidence*

63 Compared with limited conventional neurohormonal medical therapies commonly used in  
64 clinical practice, these data support the central role of comprehensive disease-modifying  
65 pharmacologic therapy to halt or delay clinical progression and extend survival in HFrEF. Given  
66 incomplete uptake of well-established and novel therapies, innovative and disruptive  
67 implementation strategies are urgently needed to facilitate use of combination multi-drug  
68 regimens in appropriately selected patients with HFrEF. The survival benefits estimated with  
69 comprehensive disease-modifying pharmacologic therapy may be important in shared  
70 therapeutic decision-making and future health system valuation.

71 **Summary**

72

73 **Background**

74 Three drug classes (mineralocorticoid receptor antagonists [MRA], angiotensin receptor-  
75 neprilysin inhibitors [ARNI], and sodium glucose cotransporter-2 inhibitors [SGLT2i]) have  
76 been shown to reduce mortality in heart failure with reduced ejection fraction [HFrEF] beyond  
77 angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [ACEi/ARB] and  $\beta$ -  
78 blockers. However, each class was studied with variable background therapy and the expected  
79 treatment benefits with their combined use are not known.

80

81 **Methods**

82 We estimated treatment effects of comprehensive disease-modifying pharmacologic therapy  
83 (ARNI+ $\beta$ -blocker+MRA+SGLT2i) vs. limited conventional therapy (ACEi/ARB+  $\beta$ -blocker) in  
84 chronic HFrEF by making indirect comparisons of pivotal trials. Treatment estimates were  
85 derived from EMPHASIS-HF (n=2,737), PARADIGM-HF (n=8,399), and DAPA-HF (n=4,744).  
86 Assuming these relative treatment effects are consistent over time, we then projected potential  
87 incremental long-term survival gains with comprehensive disease-modifying therapy in the  
88 control arm of the EMPHASIS-HF trial (which required use of ACEi/ARB +  $\beta$ -blocker, unless  
89 contraindicated).

90

91 **Findings**

92 The imputed aggregate treatment effects of comprehensive disease-modifying therapy vs.  
93 ACEi/ARB+  $\beta$ -blocker on cardiovascular death or HF hospitalization was 62% (HR 0.38; 95%  
94 CI 0.30-0.47). Reductions in hazard of cardiovascular death alone, HF hospitalization alone, and  
95 all-cause mortality were 50% (HR 0.50; 95% CI 0.37-0.67), 68% (HR 0.32; 95% CI 0.24-0.43),  
96 and 47% (HR 0.53; 95% CI 0.40-0.70), respectively. Based on the 16% annualized event rate of  
97 cardiovascular death or HF hospitalization in the control arm of EMPHASIS-HF, the range of  
98 aggregate treatment effects would translate to an estimated absolute risk reduction with  
99 comprehensive disease-modifying therapy of 18-25% over 3 years with a corresponding number-  
100 needed-to-treat of 4 to 6. Treatment with comprehensive disease-modifying pharmacologic  
101 therapy was estimated to afford 2.7 additional years (for an 80-year old) to 8.3 (for a 55 year-old)  
102 additional years free from cardiovascular death or HF hospitalization and 1.4 additional years  
103 (for an 80-year old) to 6.3 (for a 55 year-old) additional years alive compared with limited  
104 conventional medical therapy with ACEi/ARB+ $\beta$ -blocker alone.

105

106 **Interpretation**

107 Among patients with HFrEF, the anticipated aggregate treatment effects of early comprehensive  
108 disease-modifying pharmacologic therapy are substantial and may extend survival and event-free  
109 survival by up to 6 years and 8 years, respectively.

110

111 **Funding**

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113 was funded by AstraZeneca.

114

115 **Introduction**

116 Patients with heart failure with reduced ejection (HFrEF) experience substantially shorter life  
117 expectancies compared with persons in the general population of similar age.<sup>1,2</sup> Over the last 3  
118 decades, there have been stepwise advancements in pharmacotherapy for patients with HFrEF.  
119 While most patients are currently treated with renin-angiotensin-system inhibitors (RASi) and  $\beta$ -  
120 blockers,<sup>3-5</sup> three drug classes have additionally been shown to reduce mortality in HFrEF  
121 beyond these previously established core elements. Trials have demonstrated clinical superiority  
122 of mineralocorticoid receptor antagonists (MRA)<sup>6,7</sup> and sodium-glucose cotransporter-2  
123 inhibitors (SGLT2i)<sup>8</sup> when each was tested against a placebo control in addition to standard care  
124 inclusive of RASi and  $\beta$ -blockers (as tolerated). In addition, the angiotensin receptor-neprilysin  
125 inhibitor (ARNI), sacubitril/valsartan, has been shown to be superior when directly tested against  
126 an angiotensin-converting enzyme inhibitor (ACEi) in improving clinical outcomes.<sup>9</sup> Real-world  
127 data have highlighted incomplete use of these more recent additions to the therapeutic  
128 armamentarium, even among patients deemed clinically eligible without apparent  
129 contraindication or documented intolerance. For instance, despite class I guideline  
130 recommendations, use of MRAs (33.7% to 35.7%) and ARNI (13.6% to 19.8%) in eligible  
131 patients remains suboptimal. Similarly, although it has been over 4 years since clinical trials have  
132 demonstrated benefits of SGLT2i in high-risk patients with type 2 diabetes, only 2% of HFrEF  
133 patients with comorbid diabetes are currently being treated with SGLT2i in clinical practice.<sup>3-  
134 5,10,11</sup> These gaps in evidence-based medical therapies have been implicated in relatively stagnant  
135 mortality trajectories of patients living with HFrEF.<sup>12</sup>

136  
137 Communication of the estimated treatment benefits of comprehensive disease-modifying  
138 pharmacologic therapy (ARNI,  $\beta$ -blocker, MRA, & SGLT2i) on clinical outcomes, especially if  
139 used over a lifetime, may facilitate decision-making by patients, clinicians, health systems, and  
140 payers. We first estimated anticipated *relative* treatment effects of comprehensive disease-  
141 modifying pharmacologic therapy vs. limited conventional therapy (ACEi/angiotensin receptor  
142 blocker (ARB)+  $\beta$ -blocker) in chronic HFrEF by making indirect comparisons of pivotal  
143 randomized clinical trials.<sup>6,8,13</sup> Using validated actuarial methods and assuming consistent  
144 treatment effects over time, we then project *absolute* survival gains with comprehensive disease-

145 modifying pharmacologic therapy if applied long-term, when compared with limited  
146 conventional therapies.

147

## 148 **Methods**

149 **Relative Treatment Effects of Comprehensive Disease-Modifying Therapy.** To estimate the  
150 effect of comprehensive disease-modifying pharmacologic therapy against previously established  
151 conventional therapy (ACEi/ARB+  $\beta$ -blocker), we leveraged overall trial-level estimates from  
152 pivotal randomized clinical trials demonstrating the efficacy and safety of MRA,<sup>6</sup> ARNI,<sup>13</sup> &  
153 SGLT2i.<sup>8</sup> Using established methods of indirect comparisons (commonly applied to assess  
154 treatment effects if a placebo was selected in an active-controlled trial),<sup>14-17</sup> we estimated  
155 combination effects of comprehensive disease-modifying therapy based on the product of  
156 treatment effects derived from each trial (**Supplemental Figure 1**). The 95% confidence interval  
157 (CI) was derived from square root of the sum of squared standard errors of the logarithmic  
158 hazard ratios (HR) across all 3 comparisons. All trials required background therapy (as tolerated)  
159 with RASi+  $\beta$ -blocker. As the use of MRA and ARNI was variable in these trials, we derived  
160 *conservative* estimates of the aggregate treatment effects by additionally assessing treatment  
161 effects in key subgroups treated with these therapies at baseline.

162

163 **EMPHASIS-HF.** From 2006 to 2010, EMPHASIS-HF (Eplerenone in Mild Patients  
164 Hospitalization and Survival Study in Heart Failure)<sup>6</sup> randomized 2,737 patients over the age of  
165 55 years with chronic HFrEF ( $\leq 30\%$  or  $\leq 35\%$  with prolonged QRS duration) with New York  
166 Heart Association (NYHA) class II symptoms to eplerenone 25-50mg once daily or matching  
167 placebo. All patients were required to be on maximally tolerated ACEi/ARB and a  $\beta$ -blocker at  
168 baseline. Median duration follow-up was 21 months.

169

170 **PARADIGM-HF.** From 2009 to 2012, PARADIGM-HF (Prospective Comparison of ARNI  
171 with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial)<sup>13</sup>  
172 enrolled 10,521 patients at least 18 years of age with HFrEF ( $\leq 40\%$ ; changed to  $\leq 35\%$  by  
173 protocol amendment) and NYHA functional class II-IV. Patients tolerating sequential single-  
174 blind run-in phases with target doses of enalapril and sacubitril/valsartan (n=8,399) were  
175 randomized to enalapril 10mg twice daily or sacubitril/valsartan 200mg twice daily. Treatment

176 with stable doses of ACEi/ARB+ $\beta$ -blocker for at least 4 weeks was required by trial protocol.  
177 Median follow-up was 27 months.

178  
179 **DAPA-HF.** From 2017 to 2018, DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes  
180 in Heart Failure)<sup>8</sup> randomized 4,744 patients who were age  $\geq 18$  years with chronic HFrEF  
181 ( $\leq 40\%$ ) and NYHA class II-IV symptoms to dapagliflozin 10mg once daily or matching placebo.  
182 Patients with and without diabetes mellitus were evaluated. In sensitivity analysis, we evaluated  
183 the effects of SGLT2i when used in a combination regimen by leveraging subgroup data from  
184 patients at baseline who were treated with ARNI (n=508; 11%). Median follow-up was 18  
185 months.

186  
187 **Clinical Outcomes.** The primary endpoint for the current analysis was composite of  
188 cardiovascular death or first HF hospitalization. Additional endpoints of interest included each of  
189 the components of this composite and all-cause mortality.

190  
191 **Estimating Gains in Event-Free Survival and Overall Survival.** We then simulated event-free  
192 survival and overall survival by applying the treatment effects of comprehensive disease-  
193 modifying pharmacologic therapy (as estimated above) to the control arm of the EMPHASIS-HF  
194 trial. We used previously validated actuarial (age-based) methods<sup>18</sup> to calculate non-parametric  
195 Kaplan-Meier estimates of survival free from a primary endpoint and overall life expectancy at  
196 every year of age among patients in control arm of the EMPHASIS-HF trial.<sup>19</sup> This method uses  
197 age (at baseline and at the time of an event or death) as the time horizon rather than time from  
198 randomization. The area under the survival curve (up to a maximum of 90 years) reflected  
199 projected event-free survival and overall survival. Since age-treatment interactions have not been  
200 observed in each of the pivotal trials,<sup>20-22</sup> differences in survival curves reflect projected event-  
201 free survival and residual survival. For every age between 55 years (entry criteria for  
202 EMPHASIS-HF) and 80 years, we compared survival estimates of patients in the EMPHASIS-  
203 HF control arm as observed in the trial and as simulated if treated with comprehensive disease-  
204 modifying pharmacologic therapy. To estimate uncertainty around these survival gains, we  
205 additionally simulated survival under comprehensive medical therapy if the upper and lower  
206 bounds of the relative treatment effect were applied to the EMPHASIS-HF control arm.

207 Estimates of survival gains were smoothed with a locally weighted scatterplot smoothing  
208 (LOWESS) procedure.

209  
210 **Comparator Group of ACEi/ARB+ $\beta$ -blocker+MRA.** We finally estimated the incremental  
211 effects of comprehensive pharmacological medical therapy (ARNI,  $\beta$ -blocker, MRA, & SGLT2i)  
212 if patients were already treated with ACEi/ARB+ $\beta$ -blocker+MRA. As a reference population, we  
213 used the eplerenone treatment arm of the EMPHASIS-HF trial (in which baseline use of  
214 ACEi/ARB+ $\beta$ -blocker as tolerated was protocol-specified and patients were randomly assigned  
215 to receive the MRA, eplerenone). To estimate the incremental effects of switching to ARNI and  
216 adding SGLT2i, we applied treatment estimates from subgroup data of those who were treated  
217 with an MRA at baseline in PARADIGM-HF (n=4,671; 56%) and DAPA-HF (n=3,370; 71%).

218  
219 All participants provided written consent and the study protocol of each pivotal trial was  
220 approved by the institutional review board at each participating site. All analyses were performed  
221 using STATA, version 14.1 (StataCorp, College Station, TX). P-values<0.05 were considered  
222 statistically significant.

223  
224 **Role of the Funding Source.** The trial sponsors had no role in the design, analysis, interpretation,  
225 writing of the manuscript, or decision to submit this post hoc analysis. The first author and the  
226 corresponding author were responsible for the decision to submit the manuscript.

227

## 228 **Results**

229 **Relative Treatment Effects of Comprehensive Disease-Modifying Therapy.** For the primary  
230 analysis, we analyzed trial-level estimates from EMPHASIS-HF (n=2,737), PARADIGM-HF  
231 (n=8,399), and DAPA-HF (n=4,744); **Table 1.** The imputed treatment effect of comprehensive  
232 disease-modifying pharmacologic therapy (with ARNI,  $\beta$ -blocker, MRA, & SGLT2i) vs. limited  
233 conventional therapy (with ACEi/ARB +  $\beta$ -blocker) on the primary endpoint of cardiovascular  
234 death or first HF hospitalization was 62% (HR 0.38; 95% CI 0.30-0.47); **Figure 1.** Reductions in  
235 hazard of cardiovascular death alone, HF hospitalization alone, and all-cause mortality were 50%  
236 (HR 0.50; 95% CI 0.37-0.67), 68% (HR 0.32; 95% CI 0.24-0.43), and 47% (HR 0.53; 95% CI  
237 0.40-0.70), respectively (**Supplemental Figure 1**).



238 In sensitivity analysis, we substituted DAPA-HF overall treatment estimates with that  
239 derived from the subset of patients at baseline treated with ARNI (n=508; 11%). The estimated  
240 treatment effects of comprehensive disease-modifying pharmacologic therapy on the primary  
241 endpoint was similar: HR 0.39; 95% CI 0.25-0.61.

242  
243 **Absolute Event-Free and Total Survival Gains with Quadruple Therapy.** We estimated  
244 survival in 1,373 patients in the placebo arm of EMPHASIS-HF. At baseline, an ACEi and/or  
245 ARB was used in 93% of patients and a  $\beta$ -blocker in 87%. Mean age was  $68.6 \pm 7.6$  years; 78%  
246 were men and 83% were white. Mean left ventricular ejection fraction (LVEF) was  $26.1 \pm 4.7\%$   
247 and 53% had a prior history of HF hospitalization.

248 Over median follow-up of 20.5 (9.5-32.5) months, 356 primary endpoints (25.9%;  
249 16.4[14.8-18.2] per 100 patient-years) and 213 deaths (15.5%; 8.9[7.8-10.2] per 100 patient-  
250 years) occurred in the control arm of EMPHASIS-HF. Based on the annualized event rate of  
251 cardiovascular death or HF hospitalization in the control arm of EMPHASIS-HF, the range of  
252 aggregate treatment effects would translate to an estimated absolute risk reduction with  
253 comprehensive disease-modifying pharmacologic therapy of 18-25% over 3 years with a  
254 corresponding number-needed-to-treat of 4 to 6 in the prevention of a primary endpoint. With  
255 respect to mortality, absolute risk reductions were estimated to range between 6-13% over 3  
256 years with a number-needed-to-treat of 8 to 16 in the prevention of 1 death.

257 At age 55, the estimated survival free from a primary endpoint was 14.7 years with  
258 comprehensive disease-modifying pharmacologic therapy and 6.4 years with ACEi/ARB+ $\beta$ -  
259 blocker (difference: 8.3 years; 95% CI 6.2-10.7 years); **Figure 2**. At age 55, the estimated overall  
260 residual survival was 17.7 years with comprehensive disease-modifying pharmacologic therapy  
261 and 11.4 years with ACEi/ARB+ $\beta$ -blocker (difference: 6.3 years; 95% CI 3.4-9.1 years); **Figure**  
262 **3**. Given that baseline life expectancies varied by age, we further estimated absolute survival  
263 gains across a broad range of ages (55 to 80 years); **Figure 4**. Treatment with comprehensive  
264 disease-modifying pharmacologic therapy was estimated to afford 2.7 additional years (for an  
265 80-year old) to 8.3 (for a 55 year-old) additional years free from a primary endpoint and 1.4  
266 additional years (for an 80-year old) to 6.3 (for a 55 year-old) additional years alive compared  
267 with limited conventional medical therapy with ACEi/ARB+ $\beta$ -blocker alone.

268

269 **Comparator Group of ACEi/ARB+ $\beta$ -blocker+MRA.** If ACEi/ARB+ $\beta$ -blocker+MRA was  
270 selected as the comparator, further therapeutic optimization by switching to ARNI & adding  
271 SGLT2i would be expected to reduce the hazard of the primary endpoint by 36% (HR 0.64; 95%  
272 CI 0.52-0.78). Comprehensive disease-modifying therapy would be estimated to yield 1.2 to 4.1  
273 additional years free from the primary endpoint and 0.8 to 3.1 years alive compared with  
274 treatment with ACEi/ARB+ $\beta$ -blocker+MRA.

275

## 276 **Discussion**

277 A central goal of HF therapeutics is to safely prevent or postpone morbidity-free survival. In  
278 HFrEF, multiple therapeutic advances have offered promise in delaying clinical progression and  
279 extending disease-free survival. Combination therapy with ARNI,  $\beta$ -blocker, and MRA  
280 represents the current guideline-recommended therapeutic standard in HFrEF. In light of robust  
281 and favorable clinical trial data, the addition of SGLT2i in a comprehensive regimen is poised to  
282 be adopted in clinical practice guidelines. Comprehensive disease-modifying pharmacologic  
283 therapies (inclusive of 4 pills, but 5 distinct drugs) now target multiple mechanistic pathways  
284 beyond conventional neurohormonal therapies (ACEi/ARB+ $\beta$ -blocker). While these therapies  
285 have been individually investigated in rigorously conducted randomized clinical trials, the  
286 aggregate effects on clinical outcomes of their combined use had not been directly defined.

287

288 Adequately powered trials evaluating the long-term clinical effects of various therapeutic  
289 combinations may be challenging to conduct with traditional approaches. As such, we applied  
290 established methods available to first estimate the relative treatment effects of comprehensive  
291 disease-modifying pharmacologic therapy and then to forecast these benefits on long-term  
292 survival. ACEi/ARB+ $\beta$ -blocker therapy alone has been previously estimated to lower hazards of  
293 death by 43-53% vs. placebo in historical randomized clinical trials.<sup>23</sup> When compared with this  
294 previously established treatment regimen widely administered in clinical practice,<sup>3-5</sup> we estimate  
295 that optimization with comprehensive disease-modifying pharmacologic therapy would be  
296 expected to further lower cardiovascular death or HF hospitalization by over 60%. Over 3 years,  
297 the estimated absolute risk reduction was 18-25% with a number-needed-to-treat to prevent 1  
298 event of only 4 to 6. With lifetime use, assuming consistent treatment benefits, these exploratory  
299 actuarial analyses suggest potential event-free survival gains of up to 8 years and absolute

300 survival gains of up to 6 years. Even among patients who are already treated with ACEi/ARB+β-  
301 blocker+MRA therapy (an evidence-based, guideline-supported strategy that remains  
302 underutilized), we estimate substantial survival benefits with further optimization with switching  
303 to an ARNI and adding an SGLT2i. Younger patients with HFrEF, who would be anticipated to  
304 have longer projected survival and treatment duration, stand to benefit the most from survival  
305 gains related to comprehensive disease-modifying pharmacologic therapy. Yet, for all age groups  
306 analyzed meaningful gains in life-years were projected. These summary data serve as a testament  
307 to the tremendous progress in understanding optimal treatment approaches to chronic HFrEF  
308 garnered from clinical trials conducted over the last 3 decades.

309

310 Each pivotal randomized clinical trial of medical therapy for HFrEF was conducted sequentially  
311 during different eras and as such we evaluated the best available data (including subgroups fully  
312 treated on background therapies). While these data do suggest substantial benefits with early  
313 combination therapy, these do not inform a specific therapeutic sequence or pathway for  
314 prioritizing initiation. For instance, although EMPHASIS-HF was conducted prior to  
315 PARADIGM-HF, early switching of ACEi/ARB to ARNI may facilitate subsequent integration  
316 of MRA, due to lower attendant risks of hyperkalemia.<sup>24</sup> Conversely, blood pressure lowering  
317 with upstream integration of ARNI may preclude subsequent dose titration or initiation of other  
318 disease-modifying therapies. Similarly, while DAPA-HF mostly recently demonstrated the  
319 therapeutic potential of SGLT2i in HFrEF, earlier use of SGLT2i in therapeutic pathways, prior  
320 to ARNI or MRA, may still be safe and effective. The largely non-overlapping posited  
321 mechanisms of benefit, routes of metabolism, and adverse event profiles argue that both ARNI  
322 and SGLT2i should be rapidly integrated into clinical care of HFrEF, irrespective of specific  
323 order of initiation.

324

325 Accumulating data have suggested that clustered or near-simultaneous initiation and rapid  
326 uptitration of guideline-directed medical therapies are feasible and safe, either under the  
327 guidance of structured ambulatory programs or in hospitalized settings.<sup>25</sup> Once these therapies  
328 become broadly available and generic, a polypill of comprehensive disease-modifying therapy  
329 may be feasibly implemented to promote effective and equitable therapy at the population  
330 level.<sup>26</sup> While these analyses support the aggregate efficacy of combination, comprehensive

331 disease-modifying pharmacologic therapy, these data do not inform other practical aspects that  
332 may influence decision-making around its implementation. Multi-drug regimens increase the  
333 potential for non-adherence, partially related to incremental out-of-pocket expenditures and  
334 therapeutic complexity. These analyses also do not dissect potential safety issues related to  
335 comprehensive therapy. However, data from pivotal clinical trials have added reassurance that  
336 optimizing therapeutic regimens can be done safely with appropriate follow-up and monitoring.  
337 For instance, in PARADIGM-HF, sacubitril/valsartan resulted in less hyperkalemia and renal  
338 insufficiency compared with enalapril when added to background MRA therapy.<sup>24</sup> Similarly,  
339 there were low rates of drug discontinuation or serious adverse events with addition of  
340 dapagliflozin to excellent background medical therapy in DAPA-HF, and these risks were  
341 comparable to those observed with placebo.<sup>8</sup> However, understanding tolerability and safety of  
342 comprehensive disease-modifying therapy with real-world use is of high priority. Parallel efforts  
343 to advance implementation science are needed to complement clinical trial evidence to promote  
344 optimal use of therapies at target doses among patients with HFrEF.

345  
346 Traditional reporting of treatment effects in clinical trials (such as a HR) is often challenging to  
347 communicate to patients and clinicians. Reductions in potential future events may be difficult to  
348 conceptualize given the lack of a reference.<sup>27</sup> Given the chronicity of HF and since trials are  
349 typically conducted over a time course shorter than the life expectancy of a patient, projections  
350 of lifetime application of a given therapy beyond the duration of the trial may better frame its  
351 anticipated long-term benefits. We developed and validated actuarial methods using clinical trial  
352 data to estimate residual lifespan.<sup>18</sup> Our estimates of average survival are congruent with  
353 previously published age-specific life expectancy in HF. We estimated that a 55-year old in  
354 EMPHASIS-HF would live on average for 11.4 years; a previous population-based cohort study  
355 from Canada similarly estimated average survival of patients with HFrEF aged 50-60 years to be  
356  $11.3 \pm 3.3$  years.<sup>2</sup> Estimation of life expectancy and quantification of potential survival gains with  
357 a given intervention may facilitate medical decision-making. Communication of the substantial  
358 survival gains free from clinical events may encourage initiation and adherence to combination,  
359 comprehensive disease-modifying pharmacologic medical therapy.

360

361 The analytic methods employed have important assumptions and limitations. First, we assume  
362 that adherence to therapies and treatment benefits observed during short duration trial follow-up  
363 would be expected to persist long-term. However, greater nonadherence, especially considering  
364 use of multiple therapies, may be expected in usual care settings, which would in turn attenuate  
365 these projected survival gains. Furthermore, it is uncertain whether clinical benefits of these  
366 therapies continue to accrue over lifetime exposure. Second, these methods may overestimate the  
367 expected aggregate effects as we assume additive benefits. It is plausible that the composite  
368 benefits of combination regimens may be partially attenuated due to overlapping mechanistic  
369 pathways. To address this, we conducted sensitivity analyses using subgroup data of patients  
370 treated with various background therapies which yielded consistent findings. Third, the trials  
371 analyzed in this study were conducted over different time frames with variable populations,  
372 clinical risk, and background therapies. However, as we strictly only considered treatment effect  
373 estimates derived from randomized comparisons *within* trials, these factors were assumed to be  
374 balanced between treatment arms (as a function of randomization). Furthermore, we only  
375 considered relative (rather than absolute) treatment effects as these may be more comparable  
376 across trials. Fourth, our survival estimates may not be generalizable beyond the scope of these  
377 clinical trial populations. In this analysis, we attempted to provide population-level estimates of  
378 anticipated treatment effects. We did not evaluate variation in survival benefits by specific  
379 patient characteristics (such as race) due to small sample sizes which may produce unstable  
380 estimates and as primary trials detected limited treatment heterogeneity across key subgroups.  
381 However, individual patient factors are important to consider as comprehensive disease-  
382 modifying therapies are broadly applied. Fifth, we only included pharmacological therapies that  
383 have been shown to definitively improve survival in general cohorts of patients with HFrEF. We  
384 did not consider therapies that predominantly influence non-fatal HF events (such as digoxin and  
385 ivabradine), therapies that reduce mortality in specific subgroups (such as fixed-dose  
386 combination of isosorbide dinitrate plus hydralazine), and non-pharmacological therapies,  
387 including devices. Sixth, DAPA-HF was the first HF outcomes trial of SGLT2i to report;  
388 ongoing parallel investigations (NCT03057977) will further hone the effect estimates of SGLT2i  
389 as a class in HFrEF. Finally, our analyses focused on therapeutic benefits on key cardiovascular  
390 endpoints, including mortality, and did not account for potential adverse events or costs  
391 associated with use of comprehensive therapy. Despite these limitations, given that long-term

392 trials of comprehensive disease-modifying pharmacologic therapy are not available, these novel  
393 analyses from pivotal trials provide the best estimates of their potential combined therapeutic  
394 effects.

395  
396 Compared with limited conventional neurohormonal medical therapies commonly used in  
397 clinical practice, these data support the central role of comprehensive disease-modifying  
398 pharmacologic therapy to halt or delay clinical progression and extend survival in HFrEF. Given  
399 incomplete uptake of well-established and novel therapies, innovative and disruptive  
400 implementation strategies are urgently needed to facilitate use of combination multi-drug  
401 regimens in appropriately selected patients with HFrEF. The survival benefits estimated with  
402 comprehensive disease-modifying pharmacologic therapy may be important in shared  
403 therapeutic decision-making and future health system valuation.

404

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488

#### 489 **Contributors**

490 MV, BLC, & SDS conceived of and designed the study. MV, BLC, & JPF did the analysis. MV  
491 drafted the manuscript. All authors contributed to data interpretation and writing of the final  
492 version of the manuscript.

493

#### 494 **Declaration of Interests**

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525 Ironwood, Merck, Novartis, Pfizer, Takeda, and Theracos.

526 All other authors report no disclosures relevant to this work.

527

### 528 **Data Sharing**

529 All trial sponsors are committed to sharing access to patient-level data and supporting clinical  
530 documents from eligible studies. The trial data availability is according to the criteria and  
531 processes described.<sup>28-30</sup>

532

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534 None

535 **Figure Legends**

536 **Figure 1. Estimation of Relative Treatment Effects of Comprehensive Disease-Modifying**  
537 **Pharmacologic Therapy on Key Cardiovascular Events**

538 This putative analysis estimates the treatment effects of comprehensive disease-modifying  
539 pharmacologic therapy compared with angiotensin-converting enzyme inhibitor  
540 (ACEi)/angiotensin receptor blocker (ARB)+  $\beta$ -blocker by making indirect comparisons of  
541 pivotal trials in heart failure (HF).

542

543 Abbreviations = ARNI = angiotensin receptor neprilysin inhibitor; CI = confidence interval; CV  
544 = cardiovascular; HR = hazard ratio; MRA = mineralocorticoid receptor antagonist; SGLT2i =  
545 sodium-glucose cotransporter-2 inhibitor.

546

547 **Figure 2. Event-Free Survival with Comprehensive Disease-Modifying Therapy (ARNI+ $\beta$ -**  
548 **blocker+MRA+SGLT2i) vs. Limited Conventional Therapy (ACEi/ARB +  $\beta$ -blocker)**

549 Age-based Kaplan–Meier estimated curves are displayed for patients at age 55 years (**A**) and 65  
550 years (**B**) for survival free from the primary endpoint, cardiovascular death or heart failure  
551 hospitalization. The control arm of the EMPHASIS-HF (Eplerenone in Mild Patients  
552 Hospitalization and Survival Study in Heart Failure) who were required to be on maximally  
553 tolerated ACEi/ARB+  $\beta$ -blocker therapy served as the reference group (red). The comparator  
554 was a simulated group by applying the estimated treatment effects of comprehensive therapy to  
555 the control arm of the EMPHASIS-HF trial (grey). Residual event-free survival was estimated  
556 using the area under the survival curve up to a maximum of 90 years.

557

558 Abbreviations = ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor  
559 blocker; ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid receptor  
560 antagonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

561

562 **Figure 3. Long-Term Survival with Comprehensive Disease-Modifying Therapy (ARNI+ $\beta$ -**  
563 **blocker+MRA+SGLT2i) vs. Limited Conventional Therapy (ACEi/ARB +  $\beta$ -blocker)**

564 Age-based Kaplan–Meier estimated curves are displayed for patients at age 55 years (**A**) and 65  
565 years (**B**) for survival. Residual lifespan was estimated using the area under the survival curve up  
566 to a maximum of 90 years. Methods and abbreviations as per Figure 2.

567

568 **Figure 4. Treatment Benefits on Overall Survival and Event-Free Survival with**  
569 **Comprehensive Disease-Modifying Therapy (ARNI+ $\beta$ -blocker+MRA+SGLT2i) vs. Limited**  
570 **Conventional Therapy (ACEi/ARB +  $\beta$ -blocker)**

571 Estimated mean event-free survival times (**A**) and overall survival times (**B**) in the EMPHASIS-  
572 HF control arm and the simulated comprehensive therapy group for every age between 55 and 80  
573 years. Treatment differences and 95% confidence intervals (CI) are estimated for mean event-  
574 free survival (**C**) and overall survival (**D**) after application of a locally weighted scatterplot  
575 smoothing procedure. The dashed lines represent survival gains if the upper and lower bounds of  
576 the relative treatment effect are applied as the simulated comprehensive therapy group.

577 Abbreviations as per Figure 1.

578 **Table 1. Key Baseline Characteristics & Background Medical Therapy**

579

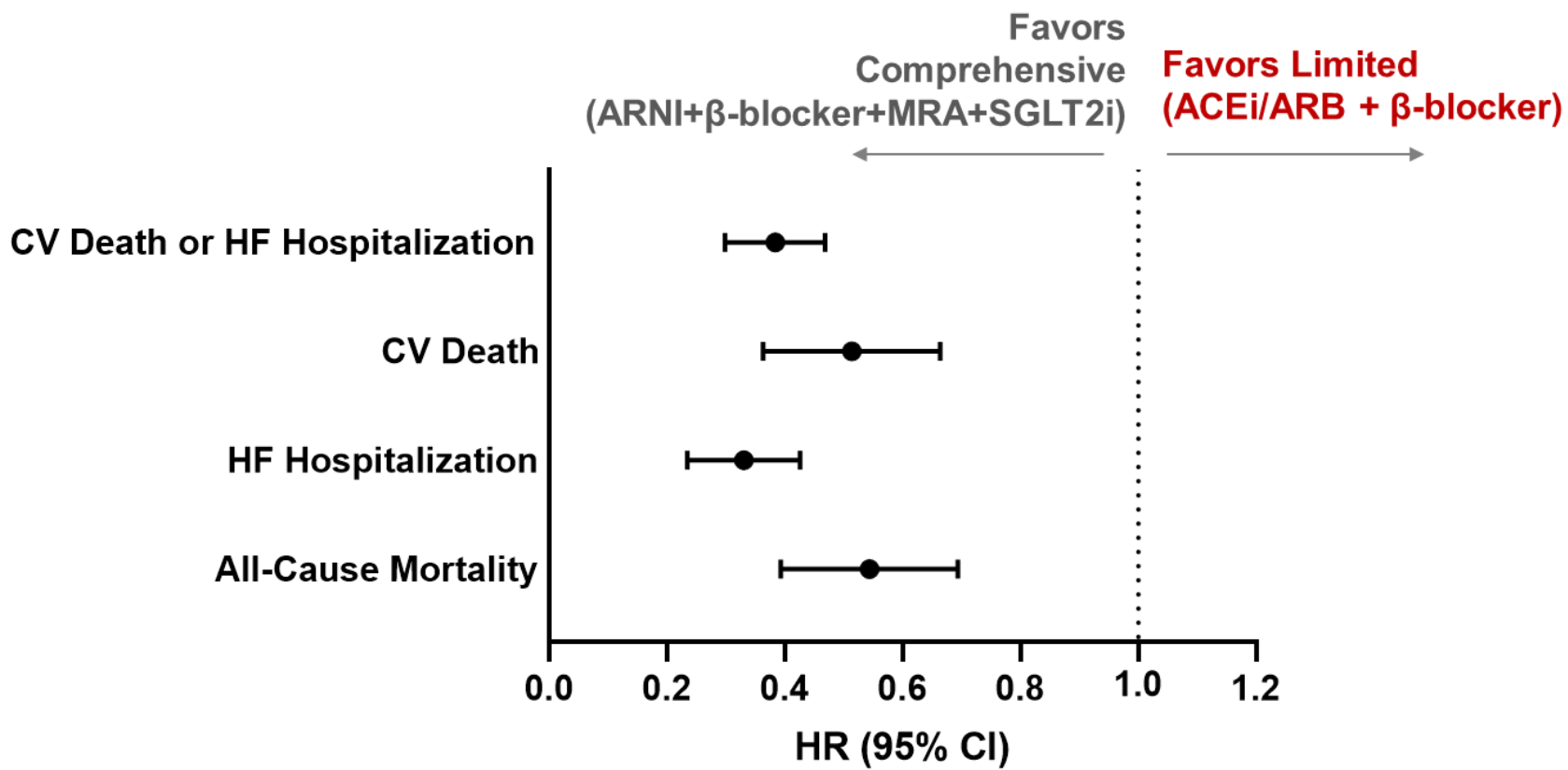
	<b>EMPHASIS-HF (n=2,737)</b>	<b>PARADIGM-HF (n=8,399)</b>	<b>DAPA-HF (n=4,744)</b>	
<b>Comparison</b>	Eplerenone vs. Placebo	Sacubitril/Valsartan vs. Enalapril	Dapagliflozin vs. Placebo	
<b>Enrollment Period</b>	2006-2010	2009-2012	2017-2018	
<b>Median Follow-up (months)</b>	21	27	18	
<b>Age (years)</b>	69 ± 8	64 ± 11	66 ± 11	
<b>Women</b>	610 (22%)	1832 (22%)	1109 (23%)	
<b>Systolic blood pressure (mmHg), mean±SD</b>	124±17	121 ± 15	122 ± 16	
<b>Heart rate (bpm), mean±SD</b>	72±13	72 ± 12	72 ± 12	
<b>Left ventricular ejection fraction (%), mean±SD</b>	26 ± 5	30 ± 6	31 ± 7	
<b>New York Heart Association Class</b>				
	<b>1</b>	0 (0%)	389 (5%)	0 (0%)
	<b>2</b>	2737 (100%)	5919 (71%)	3203 (68%)
	<b>3</b>	0 (0%)	2018 (24%)	1498 (32%)
	<b>4</b>	0 (0%)	60 (1%)	43 (1%)
<b>Atrial fibrillation</b>	844 (31%)	3091 (37%)	1818 (38%)	
<b>Diabetes mellitus</b>	859 (31%)	2907 (35%)	1983 (42%)	
<b>Prior hospitalization for HF</b>	1440 (53%)	5274 (63%)	2251 (47%)	
<b>Diuretics</b>	2326 (85%)	6738 (80%)	4433 (93%)	
<b>ACEi/ARB/ARNI*</b>	2557 (93%)	8379 (100%)	xxx (94%)	
<b>β-blocker</b>	2374 (87%)	7811 (93%)	4558 (96%)	
<b>MRA</b>	--	4671 (56%)	3370 (71%)	

580 \* DAPA-HF is the only trial that enrolled patients on background ARNI (n=508)

581

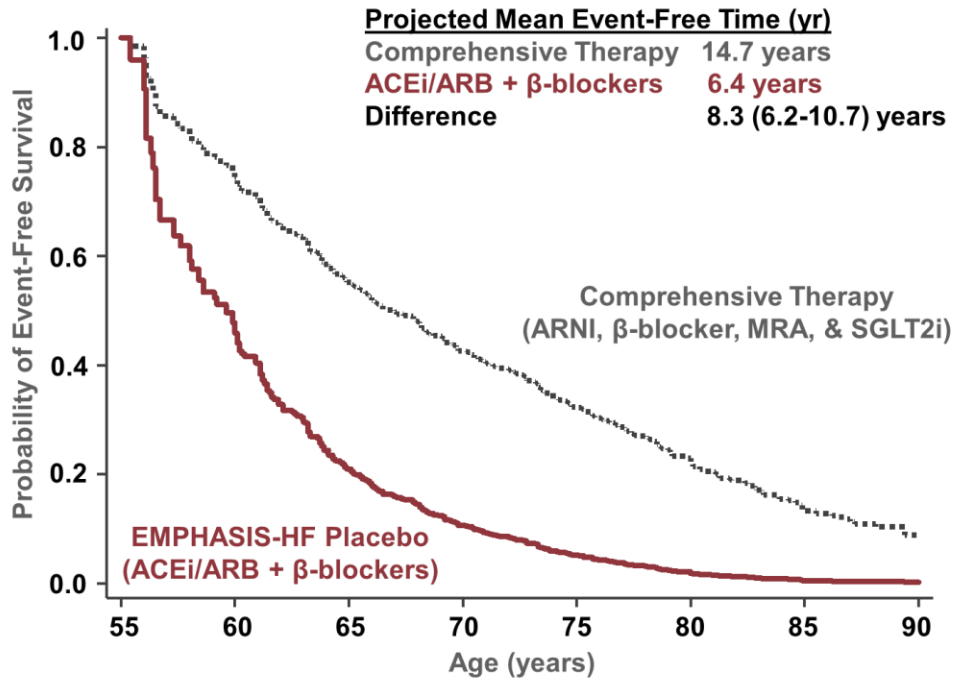
582 Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-  
583 neprilysin inhibitor; HF = heart failure; MRA = mineralocorticoid receptor antagonist; SD = standard deviation

584 **Figure 1.**  
585

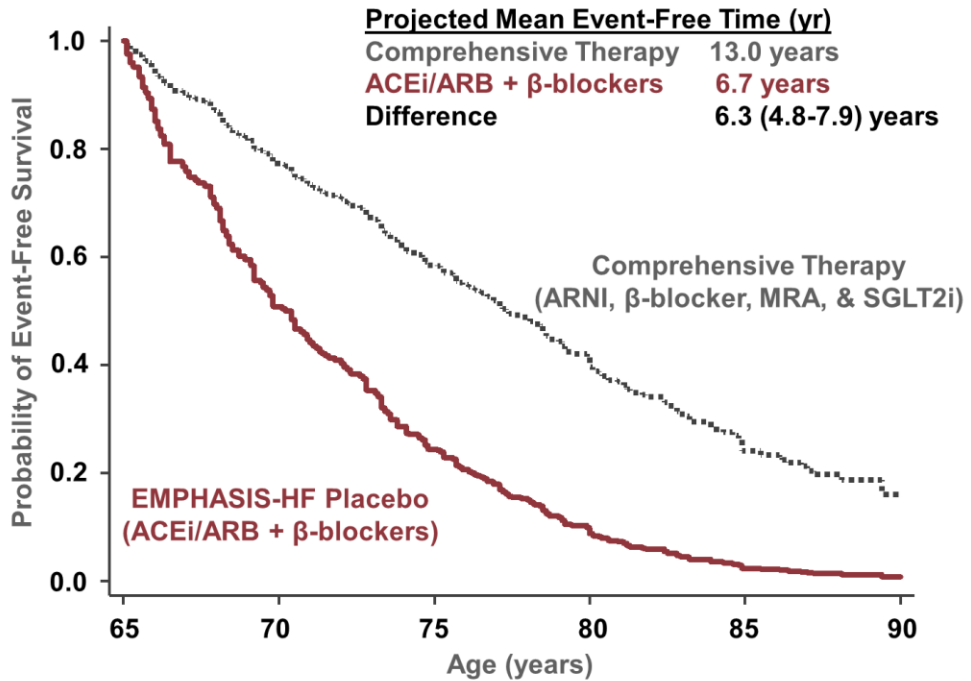


586 Figure 2.  
587

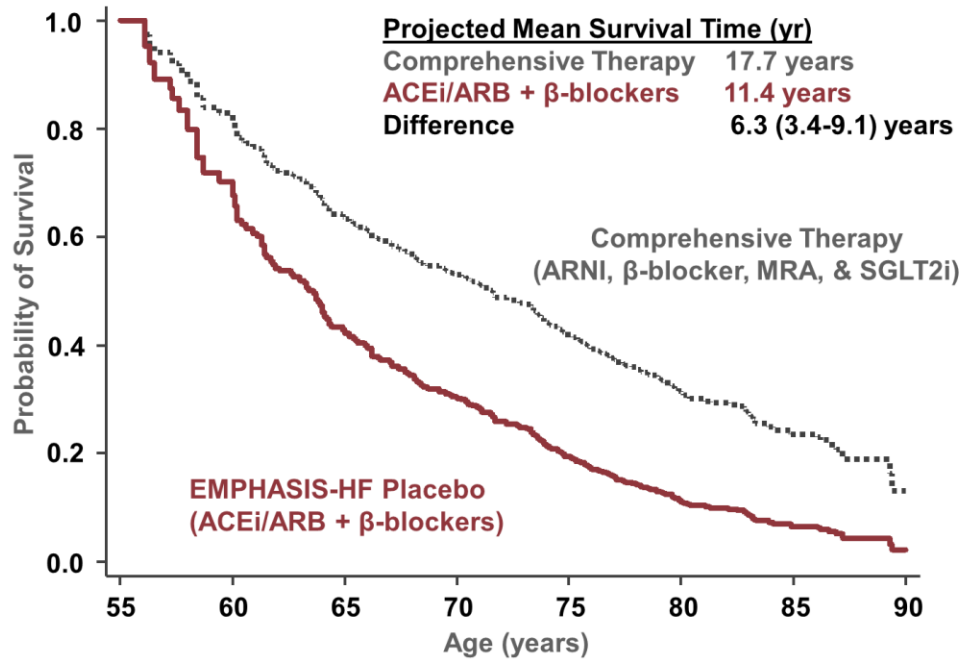
**A. Projected Event-Free Survival after 55 Years**



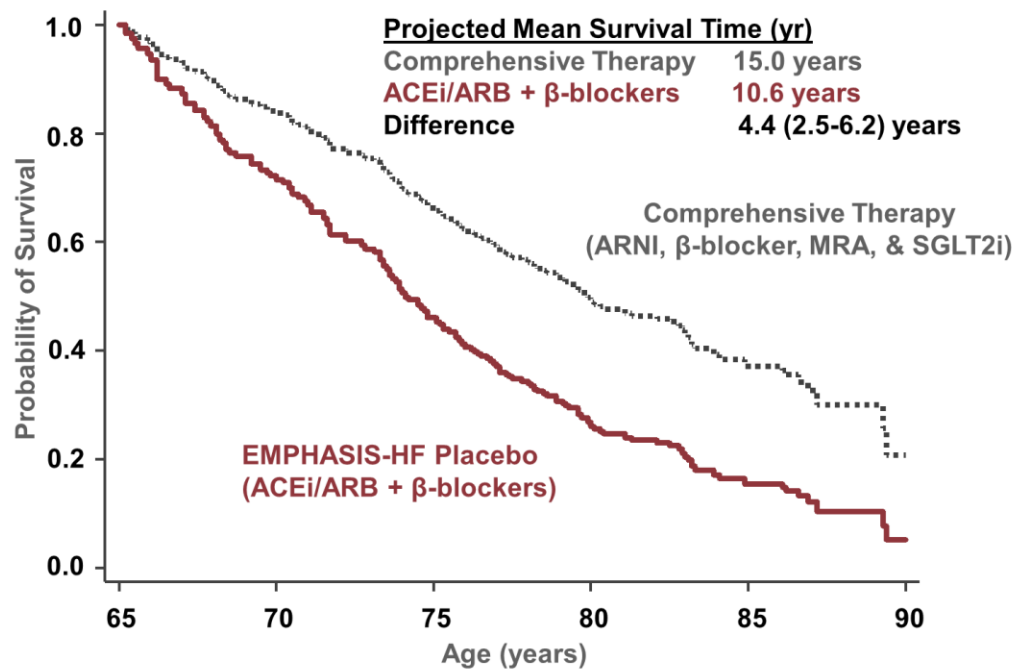
**B. Projected Event-Free Survival after 65 Years**



**A. Projected Survival after 55 Years**



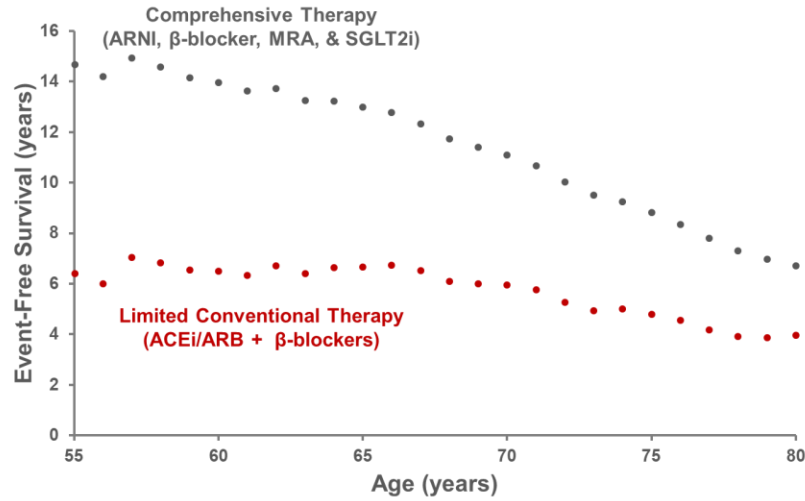
**B. Projected Survival after 65 Years**



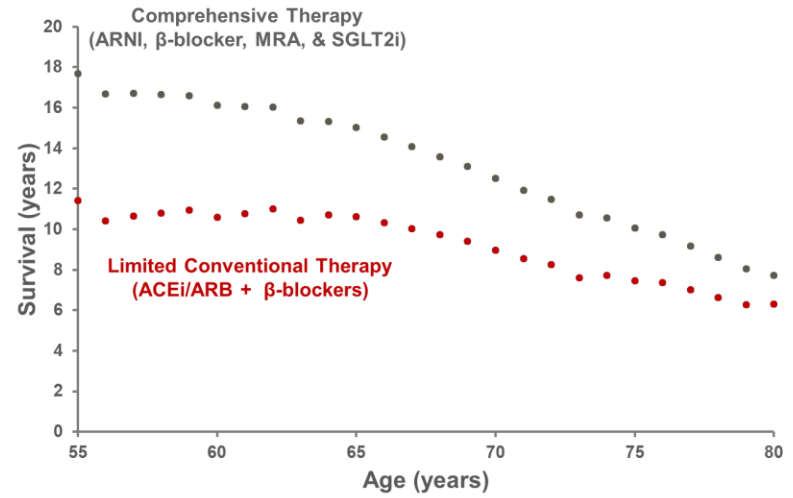


589 **Figure 4.**

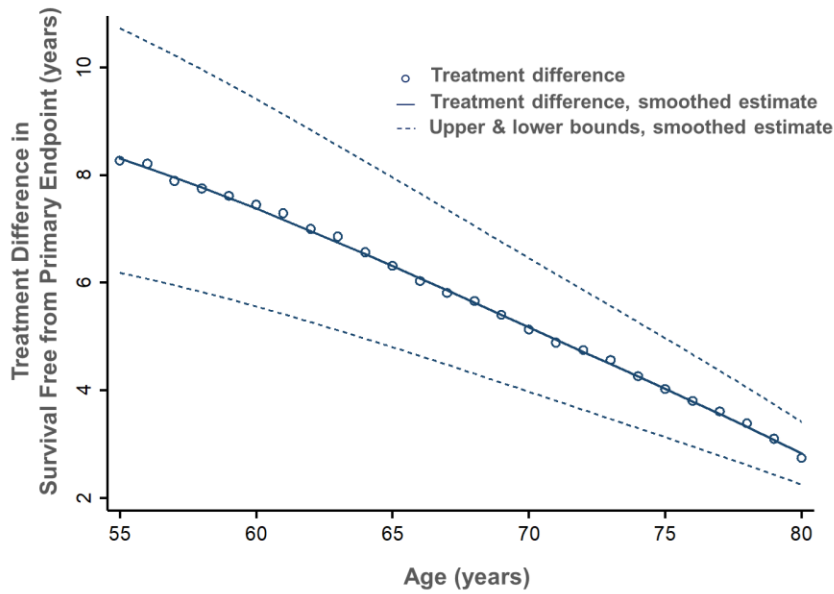
590 **A. Estimated Survival Free from Primary Endpoint**



**B. Estimated Residual Survival**



**C. Imputed Effect of Comprehensive Therapy on Event-Free Survival**



**D. Imputed Effect of Comprehensive Therapy on Long-Term Survival**

