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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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39 Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail ssolomon@bwh.harvard.edu

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 β -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+ β -
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+ β -
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 + β -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 β -
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+ β -blocker+MRA+SGLT2i) vs. limited conventional therapy (ACEi/ARB+ β -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 + β -blocker, unless
89 contraindicated).

90

91 **Findings**

92 The imputed aggregate treatment effects of comprehensive disease-modifying therapy vs.
93 ACEi/ARB+ β -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+ β -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.^{1,2} 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 β -
120 blockers,³⁻⁵ 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)^{6,7} and sodium-glucose cotransporter-2
123 inhibitors (SGLT2i)⁸ when each was tested against a placebo control in addition to standard care
124 inclusive of RASi and β -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.⁹ 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.¹²

136
137 Communication of the estimated treatment benefits of comprehensive disease-modifying
138 pharmacologic therapy (ARNI, β -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)+ β -blocker) in chronic HFrEF by making indirect comparisons of pivotal
143 randomized clinical trials.^{6,8,13} 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+ β -blocker), we leveraged overall trial-level estimates from
152 pivotal randomized clinical trials demonstrating the efficacy and safety of MRA,⁶ ARNI,¹³ &
153 SGLT2i.⁸ Using established methods of indirect comparisons (commonly applied to assess
154 treatment effects if a placebo was selected in an active-controlled trial),¹⁴⁻¹⁷ 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+ β -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)⁶ 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 β -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)¹³
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+ β -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)⁸ randomized 4,744 patients who were age ≥ 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) methods¹⁸ 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.¹⁹ 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,²⁰⁻²² 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+ β -blocker+MRA.** We finally estimated the incremental
211 effects of comprehensive pharmacological medical therapy (ARNI, β -blocker, MRA, & SGLT2i)
212 if patients were already treated with ACEi/ARB+ β -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+ β -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, β -blocker, MRA, & SGLT2i) vs. limited
233 conventional therapy (with ACEi/ARB + β -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 β -blocker in 87%. Mean age was 68.6 ± 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+ β -
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+ β -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+ β -blocker alone.

268

269 **Comparator Group of ACEi/ARB+β-blocker+MRA.** If ACEi/ARB+β-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+β-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, β-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+β-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+β-blocker therapy alone has been previously estimated to lower hazards of
293 death by 43-53% vs. placebo in historical randomized clinical trials.²³ When compared with this
294 previously established treatment regimen widely administered in clinical practice,³⁻⁵ 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.²⁴ 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.²⁵ 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.²⁶ 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.²⁴ 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.⁸ 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.²⁷ 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.¹⁸ 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 ± 3.3 years.² 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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527

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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.²⁸⁻³⁰

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)+ β -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+ β -**
548 **blocker+MRA+SGLT2i) vs. Limited Conventional Therapy (ACEi/ARB + β -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+ β -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+ β -**
563 **blocker+MRA+SGLT2i) vs. Limited Conventional Therapy (ACEi/ARB + β -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+ β -blocker+MRA+SGLT2i) vs. Limited**
570 **Conventional Therapy (ACEi/ARB + β -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

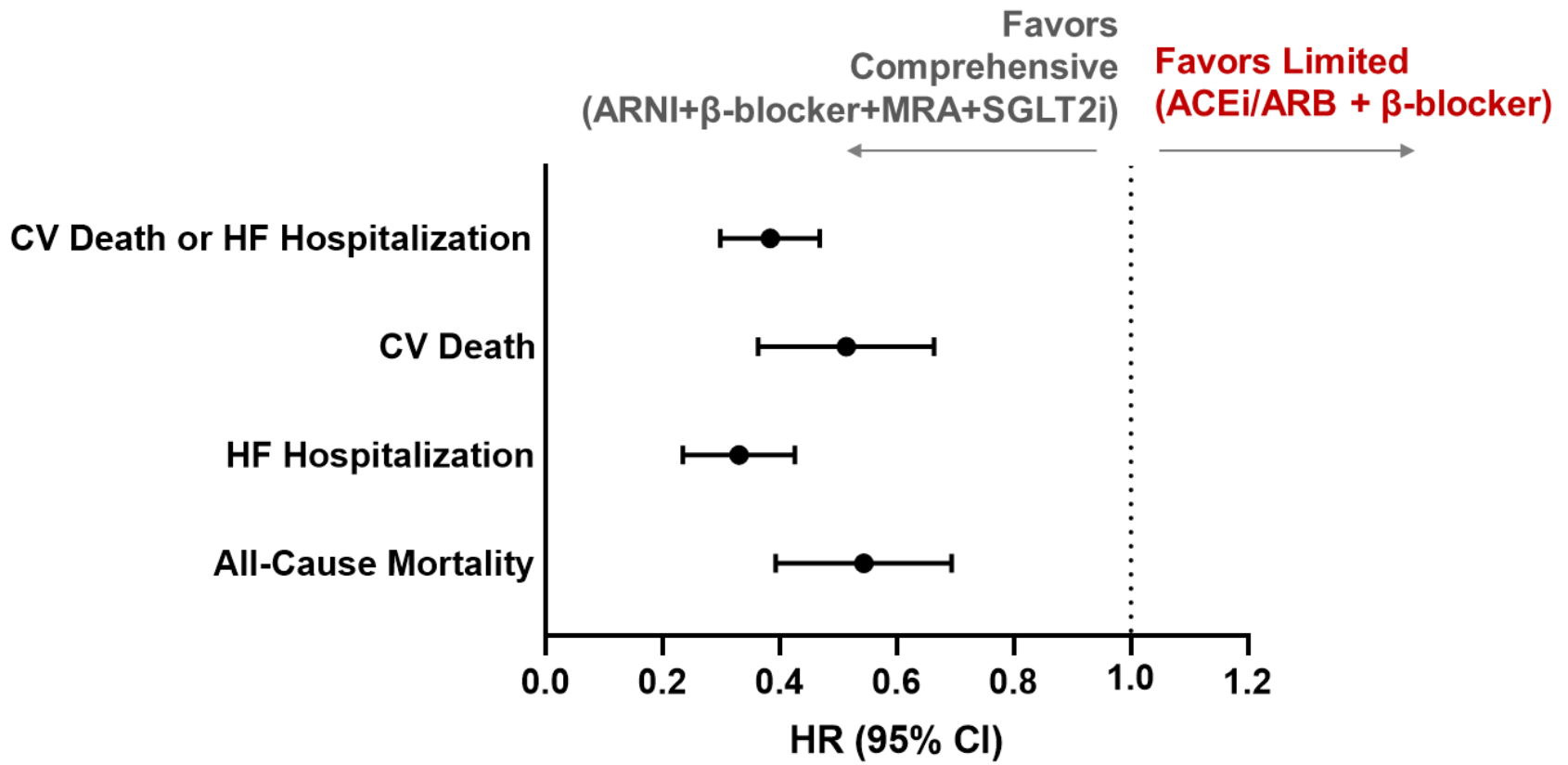
	EMPHASIS-HF (n=2,737)	PARADIGM-HF (n=8,399)	DAPA-HF (n=4,744)	
Comparison	Eplerenone vs. Placebo	Sacubitril/Valsartan vs. Enalapril	Dapagliflozin vs. Placebo	
Enrollment Period	2006-2010	2009-2012	2017-2018	
Median Follow-up (months)	21	27	18	
Age (years)	69 ± 8	64 ± 11	66 ± 11	
Women	610 (22%)	1832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

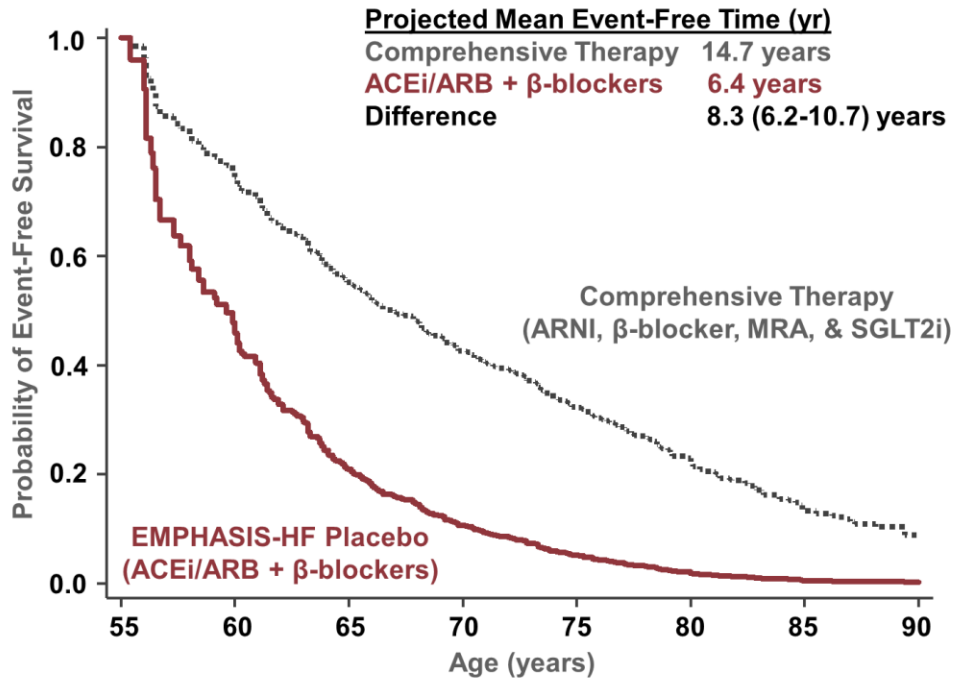
584 **Figure 1.**
585



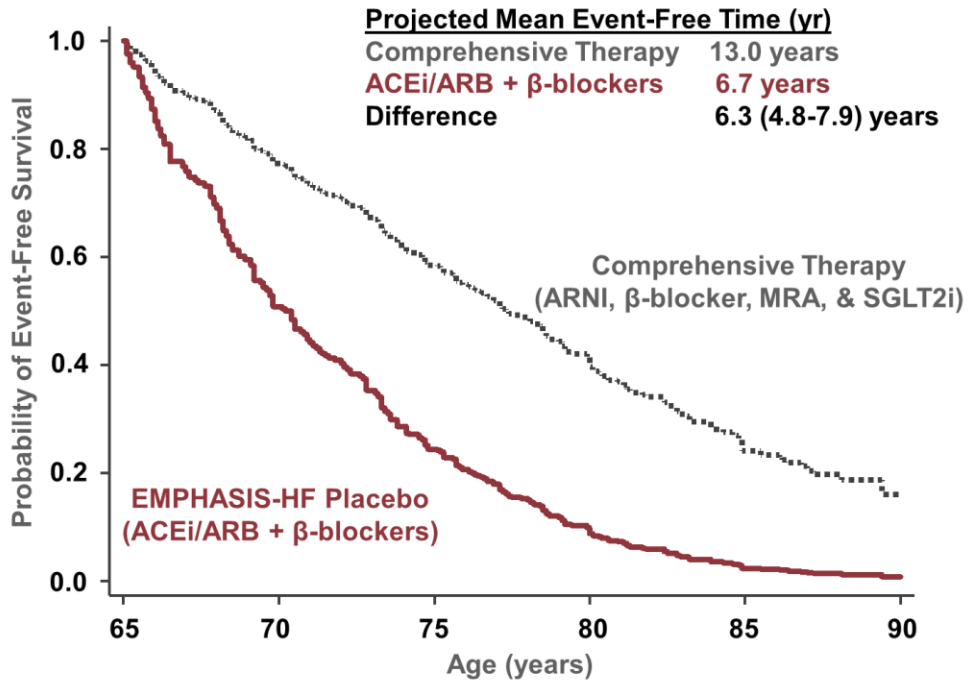
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Figure 2.

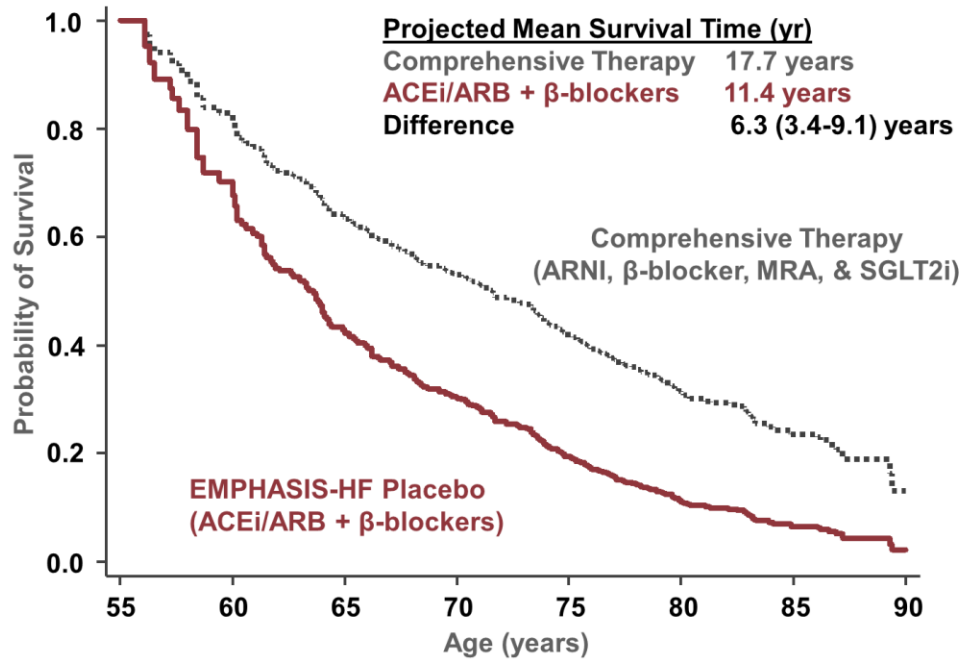
A. Projected Event-Free Survival after 55 Years



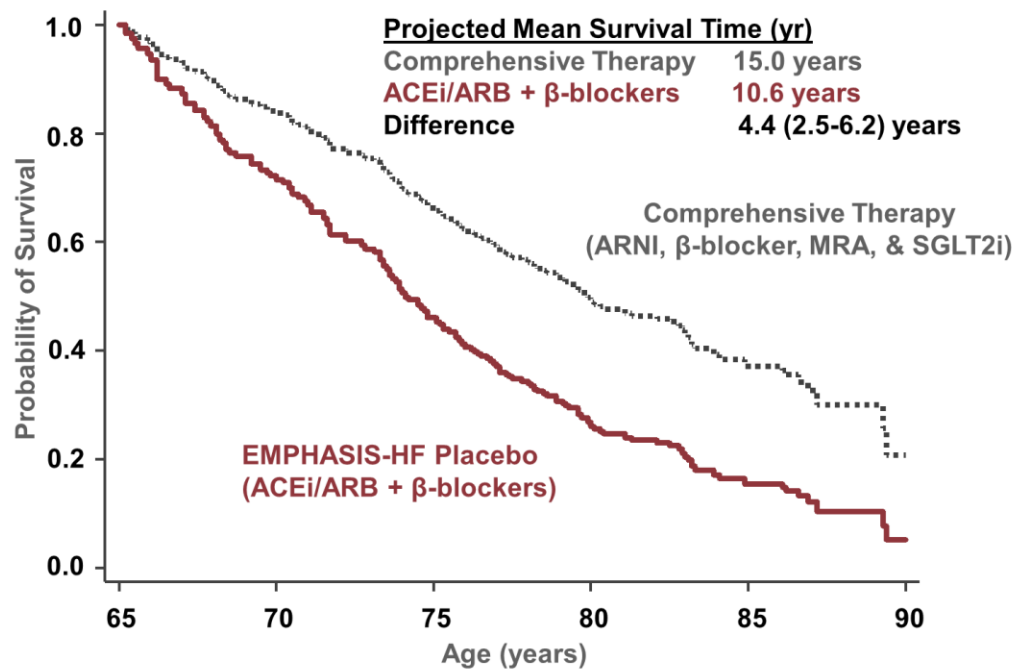
B. Projected Event-Free Survival after 65 Years



A. Projected Survival after 55 Years

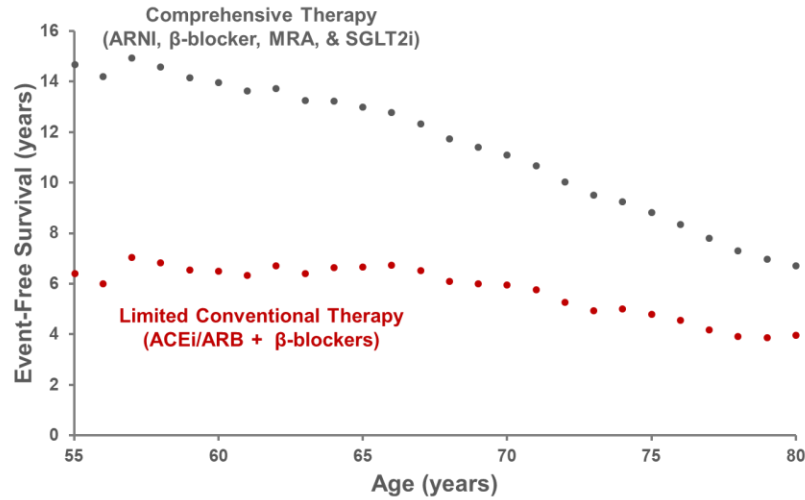


B. Projected Survival after 65 Years

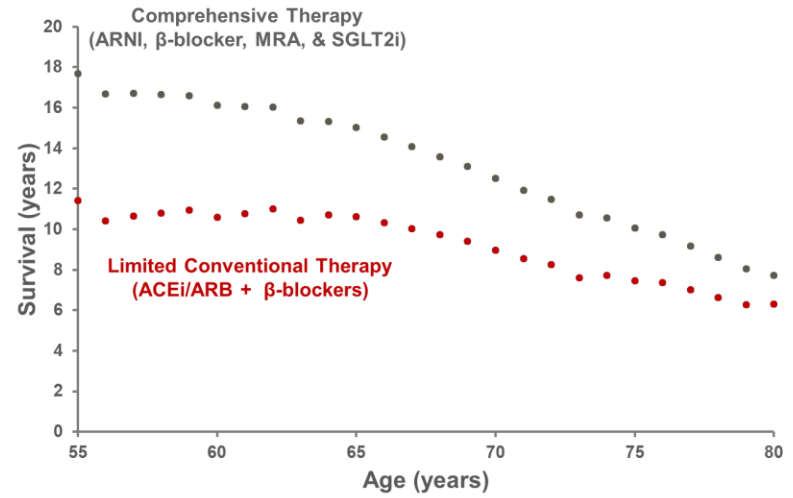


589 **Figure 4.**

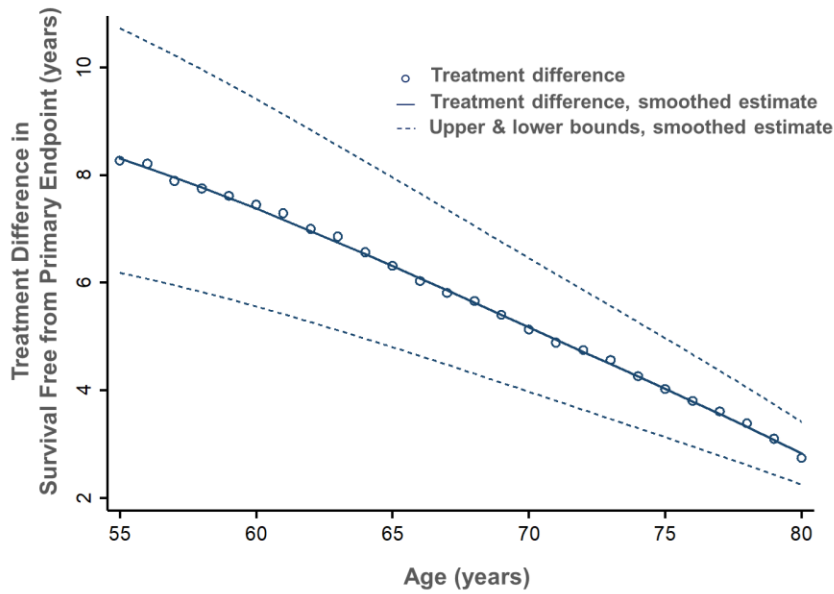
590 **A. Estimated Survival Free from Primary Endpoint**



B. Estimated Residual Survival



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



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

