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1 **SGLT2 Inhibitors in heart failure with reduced ejection fraction: a meta-analysis**
2 **of the EMPEROR-Reduced and DAPA-HF trials.**

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36

37 **Research in context:**

38 **Evidence before this study:** Large cardiovascular outcome trials in patients with type
39 2 diabetes (T2D) have demonstrated that sodium-glucose cotransporter 2 inhibitors
40 (SGLT2i) improve cardiovascular and renal outcomes, and reduce the risk of heart
41 failure (HF) hospitalisation in patients with and without prior history of HF. These
42 effects on cardiovascular and renal outcomes may not be directly related to glycaemic
43 control, suggesting that the benefits could also extend to patients without diabetes.
44 The Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart
45 Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-HF)
46 was the first outcome trial that was specifically designed to evaluate the effect of
47 SGLT2i in patients with heart failure and a reduced ejection fraction (HFrEF) with or
48 without diabetes. The EMPagliflozin outcomE tRial in Patients With chrOnic heaRt
49 Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trial also studied the
50 same target population, but was enriched for patients with markedly reduced ejection
51 fraction and elevated natriuretic peptide levels. Taken together, the trials enrolled a
52 broader spectrum of severity of HF than either trial alone. In each trial, the SGLT2i
53 reduced the risk of the primary composite endpoint of cardiovascular death or HF
54 hospitalisation.

55 **Added value of this study:** Neither trial was adequately powered to evaluate
56 treatment effects on secondary outcomes such as all-cause mortality, cardiovascular
57 death, serious adverse renal events, or to characterize effects in clinically important
58 subgroups. Using study-level published data from DAPA-HF and patient-level data
59 from EMPEROR-Reduced, we performed a meta-analysis to estimate the effect of
60 SGLT2 inhibition with dapagliflozin and empagliflozin on fatal events, hospitalisation

61 for HF and renal outcomes and in relevant clinical subgroups in a broad spectrum of
62 patients with HFrEF.

63 **Implications of all the available evidence:** Our meta-analysis establishes a solid
64 evidence base confirming an important role of empagliflozin and dapagliflozin primarily
65 to reduce hospitalizations for heart failure, and secondarily, to improve renal outcomes
66 and decrease all-cause and cardiovascular mortality. These benefits are seen
67 regardless of age and sex and irrespective of the presence or absence of diabetes or
68 treatment with a neprilysin inhibitor.

69

70

71

72 **Abstract:**

73 **Background:** Both the DAPA-HF (dapagliflozin) and EMPEROR-Reduced
74 (empagliflozin) trials showed that sodium-glucose cotransporter 2 inhibition reduced
75 the combined risk of cardiovascular death and hospitalisation for heart failure in
76 patients with heart failure and a reduced ejection fraction (HFrEF), with or without
77 diabetes. However, neither trial was powered to evaluate effects on cardiovascular
78 death or all-cause mortality or to characterize effects in clinically important subgroups.

79 **Aims:** Using study-level published data from DAPA-HF and patient-level data from
80 EMPEROR-Reduced, we prospectively estimated the effect of SGLT2 inhibition in
81 patients with HFrEF on fatal and non-fatal heart failure events and renal outcomes in
82 all randomized patients and in relevant subgroups.

83 **Methods:** The primary outcome was all-cause mortality. The effects of treatment in
84 subgroups focused on the combined risk of cardiovascular death or hospitalisation for
85 heart failure.

86 **Findings:** Among 8474 patients combined, the estimated treatment effect gave a 13%
87 reduction in all-cause mortality (pooled HR 0.87, 95%CI 0.77-0.98, P =0.018) and 14%
88 reduction in cardiovascular death (pooled HR 0.86, 95%CI 0.76-0.98, P=0.02).
89 SGLT2 inhibition was accompanied by a 26% relative reduction in the combined risk
90 of cardiovascular death or first HF hospitalisation (pooled HR 0.74, 95%CI 0.68-0.82,
91 P<0.001), and by a 25% decrease in the composite of recurrent hospitalizations for
92 HF or cardiovascular death (pooled HR 0.75, 95%CI 0.68-0.84, P<0.001). The risk of
93 the composite renal endpoint was also reduced (pooled HR 0.62, 95%CI 0.43-0.90,
94 P=0.013). All tests for heterogeneity of effect size between trials were non-significant.
95 The pooled treatment effects showed consistent benefits for subgroups based on age,

96 sex, diabetes, treatment with an ARNI and baseline eGFR, but suggested treatment-
97 by-subgroup interactions for NYHA functional class and race.

98 **Conclusion:** The effects of empagliflozin and dapagliflozin on heart failure
99 hospitalizations were consistent in the two independent trials and suggest that these
100 agents also improve renal outcomes and reduce all-cause and cardiovascular
101 mortality in patients with HFrEF.

102

103 **Key-words:** dapagliflozin; empagliflozin; heart failure; mortality; renal outcomes.

104

105 **Introduction:**

106 Large cardiovascular outcome trials in patients with type 2 diabetes (T2D) have
107 demonstrated that sodium-glucose cotransporter 2 inhibitors (SGLT2i) improve
108 cardiovascular and renal outcomes, and in particular, they reduce the risk of heart
109 failure (HF) hospitalisation¹⁻⁴. The latter was observed in patients with and without prior
110 history of HF⁵⁻⁷. However, patients with known HF comprised only small proportion of
111 the study populations, typically without systematic documentation of left ventricular
112 ejection fraction (LVEF) or natriuretic peptides. Meta-analysis of these cardiovascular
113 outcome trials in patients with T2D showed that these agents reduced the risk of HF
114 hospitalisation and slowed the progression of renal disease^{8, 9}. These effects on
115 cardiovascular and renal outcomes may not be directly related to glycaemic control,
116 suggesting that the benefits could also extend to patients without diabetes¹⁰.

117 The Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening
118 Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (DAPA-
119 HF) was the first published outcome trial specifically designed to evaluate the effect of
120 SGLT2i in patients with heart failure and a reduced ejection fraction (HFrEF) with or
121 without diabetes¹¹. The EMPagliflozin outcomE tRial in Patients With chrOnic heaRt
122 Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trial was
123 simultaneously designed to study the same target population, but was enriched for
124 patients with markedly reduced ejection fraction and elevated natriuretic peptide
125 levels^{11,12}. Taken together, the trials enrolled a broader spectrum of severity of HFrEF
126 than either trial alone. In each trial, the SGLT2i reduced the risk of the composite
127 endpoint of cardiovascular death or HF hospitalisation. Neither trial was adequately
128 powered to evaluate treatment effects on secondary outcomes such as all-cause

129 mortality, cardiovascular death, and serious adverse renal events, or to characterize
130 effects in clinically important subgroups.

131 Because DAPA-HF and EMPEROR-Reduced are the only trials, to date, that
132 included patients with symptomatic HFrEF, elevated natriuretic peptides, with and
133 without type 2 diabetes, we aim to assess the effect of SGLT2 inhibition in this specific
134 population. Other cardiovascular outcome trials using SGLT2 inhibitors included
135 patients with type 2 diabetes among whom a small proportion had investigator
136 reported HF. However, no investigations such as natriuretic peptide measurements or
137 echocardiography were performed to verify or further characterize the HF diagnoses.
138 Using study-level published data from DAPA-HF and patient-level data from
139 EMPEROR-Reduced, we performed a meta-analysis to estimate the effect of SGLT2
140 inhibition with dapagliflozin and empagliflozin on fatal events, hospitalisation for HF
141 and renal outcomes and in relevant clinical subgroups in a broad spectrum of patients
142 with HFrEF.

143

144 **Methods**

145 For this meta-analysis, we used the methods proposed in the Preferred Reporting
146 Items for Systematic Reviews and Meta-Analysis statement¹³. The methodology and
147 outcome measures were pre-specified before unblinding of the data from EMPEROR-
148 Reduced¹¹.

149 We undertook a pre-specified meta-analysis of the two single large-scale
150 cardiovascular outcomes trials published so far that evaluated SGLT2i in patients with
151 HFrEF, with or without diabetes: DAPA-HF (dapagliflozin) and EMPEROR-Reduced
152 (empagliflozin). The patient characteristics and treatment effects overall and in
153 subgroups in individual trials have been previously published^{11, 12}. In brief, both trials

154 included patients with symptomatic heart failure with reduced ejection fraction and
155 elevated natriuretic peptide levels. EMPEROR-Reduced tested empagliflozin 10
156 mg/day p.o. vs. placebo and DAPA-HF tested dapagliflozin 10 mg/day p.o. vs.
157 placebo. The median follow-up time was 16 months in EMPEROR-Reduced and 18
158 months in DAPA-HF. We did not include small trials (<300 patients) of short duration
159 (12 weeks or less), because these provided no meaningful information on major
160 outcomes.

161 EMPEROR-Reduced ClinicalTrials.gov Identifier NCT03057977. DAPA-HF
162 ClinicalTrials.gov Identifier NCT03036124.

163 **Outcomes and subgroups**

164 Time to all-cause mortality was the pre-defined primary endpoint in this meta-analysis.
165 Secondary endpoints assessed were time to cardiovascular death, first hospitalisation
166 for HF or cardiovascular death, first hospitalisation for HF, recurrent hospitalisations
167 for HF or cardiovascular death, and a renal composite defined as $\geq 50\%$ sustained
168 decline in eGFR, end stage renal disease (ESRD) or renal death. Effects in subgroups
169 on the combined risk of cardiovascular death and hospitalisation for heart failure were
170 also evaluated in pre-defined subgroups, relying on published data from DAPA-HF.

171 Because the definition of some endpoints differed slightly between the two
172 trials, we used patient level data from the EMPEROR-Reduced trial to replicate the
173 DAPA-HF definitions for selected endpoints. The primary endpoint was slightly
174 different between the two trials. In DAPA-HF, the primary endpoint was a composite
175 of cardiovascular death or hospitalisation for HF, including urgent visits with
176 intravenous therapy for HF. Since very few patients experienced only an urgent HF
177 visit and the treatment effects on the primary endpoint were nearly identical when such
178 visits were included or excluded, we assumed that the subgroup effects on the DAPA-

179 HF primary endpoint represented the treatment effects on the EMPEROR-Reduced
180 primary endpoint, which did not include urgent care visits.

181 Because the definition of the composite renal endpoints assessed in DAPA-HF
182 and EMPEROR-Reduced also differed slightly, we used the definition of the DAPA-
183 HF trial that included a $\geq 50\%$ sustained decline in eGFR, ESRD or renal death, where
184 ESRD was defined as either sustained eGFR < 15 ml/min/1.73m², chronic dialysis or
185 a renal transplant.

186 The pre-defined study subgroups were type 2 diabetes (yes/no), sex, ARNI
187 treatment (yes/no), NYHA class II or III/IV, race (White, Black, Asian), region (North
188 America, Latin America, Europe and Asia), age below or above 65 years (and
189 additionally, < 55 , 55-64, 65-74, and ≥ 75 years), history of HF hospitalisation (yes/no),
190 eGFR below or above 60 ml/min/1.73m², and body mass index (BMI) below or above
191 30 Kg/m². The region subgroup was added post-hoc in order to clarify whether the
192 treatment effects would reflect the results observed on race.

193 Because the definitions of adverse events varied between the two trials, only
194 descriptive data about selected safety endpoints of interest (e.g. for volume depletion,
195 hypoglycaemia, non-traumatic lower limb amputations, fractures, and ketoacidosis)
196 are provided.

197 **Statistical analysis**

198 We used the point estimates and 95% confidence intervals as reported for the
199 individual trials for the meta-analysis, based on an intention-to-treat analysis of all
200 randomized patients. For the time-to-first event endpoints, the meta-analysis is based
201 on hazard ratios derived from Cox proportional hazard models, and the analysis of
202 recurrent events is based on rate ratios derived from the Lin-Wei-Yang-Ying model¹⁴.
203 A fixed effect model with inverse variance weights was used to combine the relative

204 effect measures from both studies on a logarithmic scale. Statistical heterogeneity of
205 the treatment effect from individual studies was descriptively assessed based on the
206 overlap of the confidence intervals and was formally assessed based on the p-value
207 derived from Cochran's Q test. The latter was used to test for treatment-by-subgroup
208 interactions¹⁵.

209 **Role of the funder**

210 Representatives (Martina Brueckmann, Anne Pernille Ofstad, Egon Pfarr, Waheed
211 Jamal) of Boehringer Ingelheim were involved in the design and conduct of the meta-
212 analysis, interpretation of the data, and the preparation, review, and approval of the
213 manuscript. Egon Pfarr and Faiez Zannad had access to all the data. The decision to
214 submit the manuscript for publication was taken by the academic leadership of the
215 steering committee.

216

217 **Results**

218 **DAPA-HF and EMPEROR-Reduced comparison**

219 The characteristics of the DAPA-HF and EMPEROR-Reduced trial populations are
220 depicted in *Table 1*, and the major inclusion and exclusion criteria in the *Supplemental*
221 *Table 1*. Both studies included patients with HFrEF (LVEF≤40%) with and without
222 diabetes. As compared with DAPA-HF, the patients enrolled in the EMPEROR-
223 Reduced trial had a lower ejection fraction (27% vs. 31%), and higher levels of NT-pro
224 BNP and lower eGFR, and were more likely to have been treated with a neprilysin
225 inhibitor at baseline (20% vs. 11%).

226 **Pooled effects on survival and cardiovascular events**

227 Among 8474 patients in the two trials, the treatment effect for mortality was a 13%
228 reduction in all-cause mortality (pooled HR 0.87, 95%CI 0.77-0.98, P =0.018) and 14%

229 reduction in cardiovascular death (pooled HR 0.86, 95%CI 0.76-0.98, P=0.027),
230 Figure 1. SGLT2 inhibition was accompanied by a 26% reduction in the combined risk
231 of cardiovascular death or first HF hospitalisation (pooled HR 0.74, 95%CI 0.68-0.82,
232 P<0.001), by a 25% decrease in the composite of recurrent hospitalisations for HF or
233 cardiovascular death (pooled RR 0.75, 95%CI 0.68-0.84, P<0.001), and by a 31%
234 reduction in the risk of first hospitalisation for HF (pooled HR 0.69, 95%CI 0.62-0.78,
235 P<0.001). There was no statistical evidence for heterogeneity of the treatment effect
236 for any of these endpoints. *Figure 1.*

237 **Pooled effects on renal outcomes**

238 The risk of experiencing the composite renal endpoint (i.e., chronic dialysis or renal
239 transplant or a $\geq 50\%$ sustained reduction of eGFR) was reduced by SGLT2 inhibition
240 (pooled HR 0.62, 95%CI 0.43-0.90, P=0.013). The changes in eGFR over time were
241 similar in both trials; the treatment-related difference in eGFR slopes was 2.1 (1.5-2.7)
242 ml/min/1.73 m² between empagliflozin and placebo in EMPEROR-Reduced and 1.8
243 ml/min/1.73 m² between dapagliflozin and placebo in DAPA-HF, both P<0.001. *Figure*
244 *1.*

245 **Pooled effects in subgroups**

246 The pooled treatment effects for the respective primary endpoint in each trial (time to
247 first HF hospitalisation or cardiovascular death) are shown in *Figure 2* for subgroups
248 according to diabetes, age, sex, treatment with an ARNI, history of HF hospitalisation,
249 eGFR, and BMI. For each of these subgroups, there was no evidence for a treatment-
250 by-subgroup interaction. Nominally significant treatment-by-subgroup interactions
251 were observed for NYHA functional class, race and region, Figure 2. The pooled HR
252 of 0.67 (95%CI 0.59-0.76) in class II patients differed from the pooled HR of 0.87
253 (95%CI 0.75-1.01) in patients in NYHA class III/IV, interaction P=0.009. The pooled

254 HR of 0.83 (95%CI 0.74-0.93) in white patients differed from the pooled HR of 0.53
255 (95%CI 0.37-0.76) in Black patients and the pooled HR of 0.61 (95% CI: 0.49-0.75) in
256 Asian patients, interaction P=0.006. Finally, the pooled HR of 0.88 (95%CI 0.76-0.92)
257 in Europe differed from the pooled HR ratios seen in North America (0.71, 95%CI 0.55-
258 0.92), in Latin America (0.70, 95%CI 0.57-0.84) and in Asia (0.61, 95%CI 0.49-0.76),
259 interaction P=0.037. Despite these observed difference between subgroups, none of
260 the analyses indicates heterogeneity between dapagliflozin and empagliflozin within a
261 subgroup category. *Figure 2.*

262 **Safety**

263 Although absolute numbers of adverse events cannot be validly compared between
264 the two trials due to different AE definitions and observation periods, the safety profile
265 of both SGLT2i indicated no excess in adverse events of interest versus the respective
266 placebo arms. Specifically, the incidence of severe hypoglycemic events was low with
267 no increase in the active treatment groups in both trials (Table 2). The incidence of
268 volume depletion, renal adverse events, bone fractures and lower limb amputations
269 was also balanced between the active arms and respective placebo groups in each
270 trial. There were no cases of ketoacidosis in EMPEROR, and 3(0.1%) patients
271 experienced a diabetic ketoacidosis in DAPA-HF. *Table 2.*

272

273 **Discussion**

274 The present report is the first meta-analysis of the two major outcome trials assessing
275 the effect of SGLT2i in HFrEF with or without diabetes. In 8474 patients with a broad
276 spectrum of severity of HFrEF, SGLT2 inhibition with empagliflozin and dapagliflozin
277 — when added to all appropriate treatments for heart failure — reduced all-cause and
278 cardiovascular mortality, hospitalisations for heart failure, and serious adverse renal

279 outcomes, without heterogeneity between the two trials. No excess in serious adverse
280 effect was seen in either study. Furthermore, no important imbalances for adverse
281 events of interest were raised in either the DAPA-HF or EMPEROR-Reduced trials,
282 and the SGLT2 inhibitors were well-tolerated in both studies.

283 Prior to this meta-analysis, it was known that treatment of patients with type 2
284 diabetes with SGLT2i had major impact to reduce the risk of HF hospitalisations
285 (relative reduction of at least 30%) and to slow the progression of renal disease
286 (relative reduction of at least 40%)⁸. The benefits on HF hospitalisations and on the
287 progression of renal disease were of similar magnitude regardless of the presence of
288 established cardiovascular disease or a history of HF^{8, 9}. The DAPA-HF and
289 EMPEROR-Reduced trials expanded these findings to patients with established
290 HFrEF populations with and without diabetes who were receiving appropriate
291 background treatments for heart failure^{11, 12}. The two trials enrolled overlapping and
292 complementary patient populations, which spanned the broad spectrum of patients
293 with HFrEF seen in clinical practice. This meta-analysis highlights the striking
294 consistency of the findings of cardiovascular and renal benefits with empagliflozin and
295 dapagliflozin in patients with HFrEF across the two trials.

296 The benefit of empagliflozin and dapagliflozin on the primary endpoint of both
297 trials — the combined risk of cardiovascular death and hospitalisation for heart failure
298 — is primarily driven by a ~30% relative reduction in the risk of hospitalisation for heart
299 failure. A benefit on heart failure hospitalisations was observed whether the analysis
300 is confined to first events or to all (first and recurrent) events. When compared with
301 the effect on heart failure hospitalisations, the effect of these drugs on cardiovascular
302 mortality is more modest (a 14% relative reduction) but is statistically significant. The
303 modest size of the cardiovascular mortality benefit may explain why it is observed

304 inconsistently in individual trials. Specifically, the relative reduction in cardiovascular
305 death was 18% (HR 0.82, 95%CI 0.69 to 0.98) in DAPA-HF (with dapagliflozin) and
306 8% (HR 0.92, 95%CI 0.75 to 1.12) in EMPEROR-Reduced (with empagliflozin). In
307 contrast, in trials of patients with type 2 diabetes (with or without heart failure), the
308 reduction in cardiovascular death was 2% (HR 0.98, 95%CI 0.82 to 1.17) in
309 DECLARE-TIMI58 (with dapagliflozin) and 38% (HR 0.62, 95%CI 0.49 to 0.77) in
310 EMPA-REG OUTCOME (with empagliflozin)^{1, 3}. The pattern of inconsistent findings
311 in individual trials and in different disease states may be explicable by the modest,
312 although statistically significant, reduction in cardiovascular death observed in our
313 meta-analysis. In contrast, the 38% reduction in the risk of the renal composite
314 endpoint was clinically important.

315 The effect on the combined risk of cardiovascular death or hospitalisation for
316 heart failure was consistent across most subgroups, including those based on age and
317 sex, regardless of the presence or absence of diabetes, and impaired renal function.
318 Of note, the consistent effect of dapagliflozin and empagliflozin in patients with an
319 estimated glomerular filtration rate of less than 60 ml/min/1.73m² provides evidence of
320 an important reduction of cardiovascular death or hospitalisation for heart failure in this
321 high-risk subgroup. However, nominally significant treatment-by-subgroup interactions
322 were observed for NYHA functional class, race, and geographical region, raising the
323 possibility of an attenuated, although still meaningful, effect in patients with class III/IV
324 symptoms, in white patients and in patients enrolled in Europe.

325 The exact mechanisms by which SGLT2i exerted their benefits in these
326 populations are not completely established, but they may not be directly related to
327 glucose control and appear to be due to direct cardioprotective and nephroprotective

328 effects, which may be related to actions on sodium balance, energy homeostasis, and
329 to their actions to mitigate cellular stress^{10, 16, 17}.

330 **Limitations**

331 Several limitations should be highlighted in this meta-analysis. We did not have access
332 to the individual patient data from DAPA-HF; therefore, we could only evaluate the
333 endpoints and subgroups that were publicly available from DAPA-HF. No correction
334 for multiplicity of subgroup testing was performed, hence, subgroup findings should be
335 regarded as hypothesis generating. In general, subgroup effects and interaction P
336 values should be interpreted cautiously because they are subject to the play of chance.
337 Additionally, it is understood that statistical heterogeneity cannot be reliably discerned
338 if an analysis is based on only two studies; however, the point estimates for the
339 treatment effect for all endpoints are remarkably consistent.

340

341 **Conclusion**

342 Our meta-analysis establishes a solid evidence base confirming an important role of
343 empagliflozin and dapagliflozin to reduce heart failure hospitalizations in HFrEF and
344 suggest that these agents also reduce all-cause and cardiovascular mortality and
345 improve renal outcomes. These benefits are seen whether patients have diabetes or
346 not, are women or men, younger or older, and are receiving or not neprilysin inhibitors.
347 Such a combination of benefits is unique among currently available drugs for heart
348 failure.

349

350 **Authors` contribution**

351 The statistical analysis was performed by Egon Pfarr who is an employee of
352 Boehringer Ingelheim and a named author of this manuscript, working closely with

353 Stuart Pocock, who is not an employee of the sponsor and is also a named author.
354 Faiez Zannad and João Pedro Ferreira, who are not employees of the sponsor, drafted
355 the first version of the manuscript and subsequent revisions. All the other authors read
356 and edited the manuscript. All the authors approved the final version and the decision
357 to submit the manuscript.

358

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363 was provided by Mathew Smith of Elevate Scientific Solutions.

364

365 **Declaration of interest**

366 FZ reports personal fees from Boehringer Ingelheim during the conduct of the study;
367 personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, other from
368 cardiorenal, personal fees from AstraZeneca, Vifor Fresenius, Cardior, Cereno
369 pharmaceutical , Applied Therapeutics , Merck, other from CVCT , personal fees
370 from BAYER and Cellprothera, outside the submitted work; JPF reports consulting
371 fees from Boehringer Ingelheim during the conduct of the study; SP reports personal
372 fees from Boehringer Ingelheim during the conduct of the study; SDA reports grants
373 from Vifor Int, personal fees from Vifor Int, Bayer, Boehringer Ingelheim, Novartis,
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379 G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold,
380 Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana
381 Medical, V-Wave Limited, and from Vifor, outside the submitted work; GF reports to
382 have received payment other from Boehringer Ingelheim for being a trial committee
383 member during the conduct of the study; and from Medtronic, Vifor, Servier and
384 Novartis for being a trial committee member, outside the submitted work; MB, APO,
385 EP and WJ are employees of Boehringer Ingelheim; MP reports personal fees from
386 Boehringer Ingelheim, during the conduct of the study; personal fees from Abbvie,
387 personal fees from Akcea, personal fees from Amarin, personal fees from
388 AstraZeneca, personal fees from Amgen, personal fees from Boehringer Ingelheim,
389 personal fees from Cardioentis, personal fees from Daiichi Sankyo, personal fees
390 from Johnson & Johnson, personal fees from Lilly, personal fees from Novartis,
391 personal fees from Pfizer, personal fees from Relypsa, personal fees from Sanofi,
392 personal fees from Synthetic Biologics, personal fees from Theravance, personal
393 fees from NovoNordisk, outside the submitted work.

394

395 **Data sharing statement**

396 The study protocol and statistical analysis plan are available upon request to the
397 corresponding author. Stuart Pocock at the London School of Hygiene served as
398 external statistician and approved all the data.

399

400

401 **Figure legends**

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426 Figure 1: Meta-analysis of EMPEROR-Reduced and DAPA-HF: Overall treatment
427 effects on, a) all-cause mortality, b) cardiovascular death, c) first hospitalization for
428 heart failure or CV death d) first hospitalization for heart failure, e) first kidney
429 composite*, and f) all (first and recurrent) hospitalization for HF or cardiovascular
430 death

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432 * Defined as time to first occurrence of any of the components of $\geq 50\%$ sustained
433 decline in eGFR, ESRD or renal death. ESRD was defined as either sustained eGFR
434 < 15 ml/min/1.73m², chronic dialysis treatment or receiving a renal transplant. For
435 patients with eGFR < 30 ml/min/1.73 m² in EMPEROR (these were excluded from
436 DAPA-HF), ESRD was defined as sustained eGFR < 10 ml/min/1.73m², chronic
437 dialysis treatment or receiving a renal transplant.

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451 Figure 2: Pooled treatment effects of empagliflozin and dapagliflozin on the composite
452 of first hospitalisation for heart failure or CV death in relevant subgroups: a) by
453 diabetes status, b) by sex, c) by use of ARNI, d) by age* (≤ 65 and > 65 years), and e)
454 (< 55 , 55 to 64, 65 to 74, and ≥ 75 years), f) by history of a hospitalisation for heart
455 failure**, g) by eGFR, h) by NYHA functional class, i) by race, j) by region, and k) by
456 BMI.

457

458 * For EMPEROR-Reduced, the age subgroups were < 65 and ≥ 65 years, and < 50 , 50
459 to 64, 65 to 74, and ≥ 74 years

460 ** In EMPEROR-Reduced: a history of a hospitalization for heart failure the last 12
461 months

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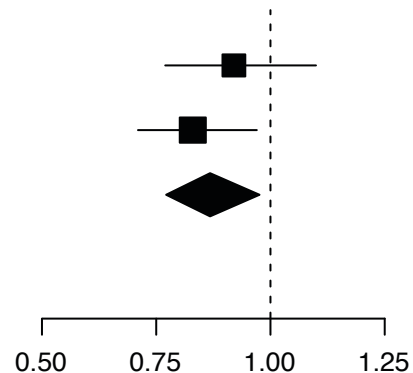
Figure 1

a) All-cause mortality

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
EMPEROR-Reduced	249/1863 (13.4)	266/1867 (14.2)	0.92 (0.77, 1.10)
DAPA-HF	276/2373 (11.6)	329/2371 (13.9)	0.83 (0.71, 0.97)
Total			0.87 (0.77, 0.98)

Test for overall treatment effect, $p=0.018$

Test for heterogeneity of effect, $p=0.39$

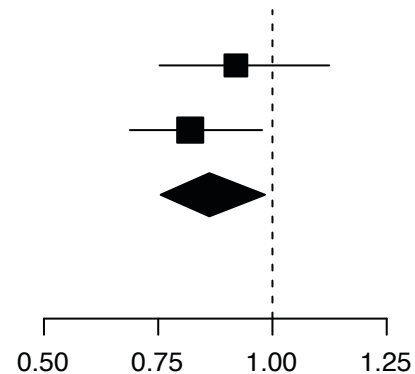


b) Cardiovascular death

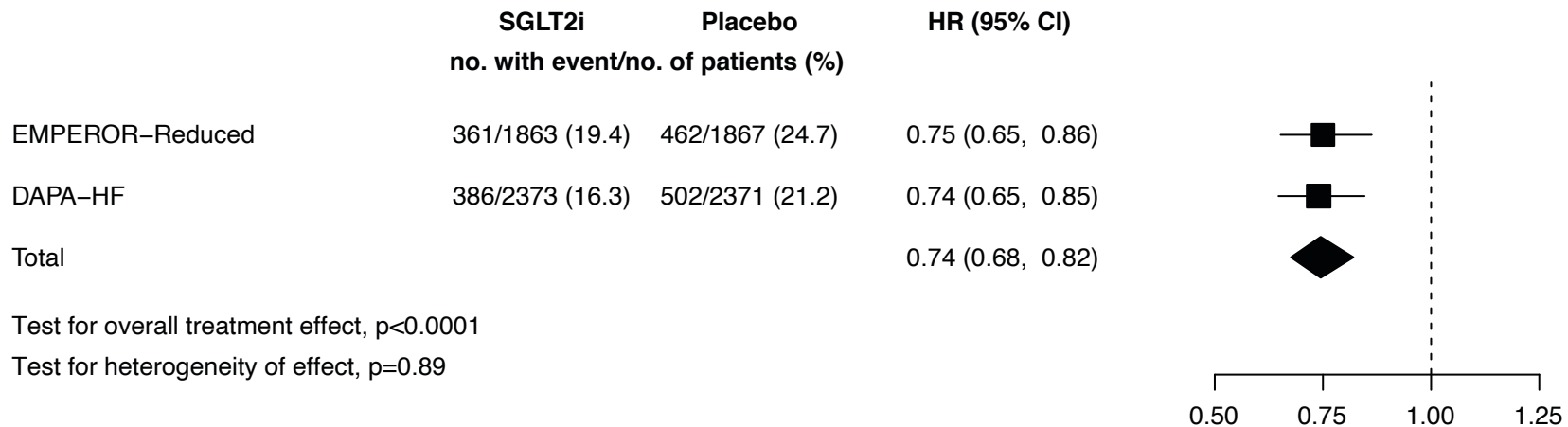
	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
EMPEROR-Reduced	187/1863 (10.0)	202/1867 (10.8)	0.92 (0.75, 1.12)
DAPA-HF	227/2373 (9.6)	273/2371 (11.5)	0.82 (0.69, 0.98)
Total			0.86 (0.76, 0.98)

Test for overall treatment effect, $p=0.027$

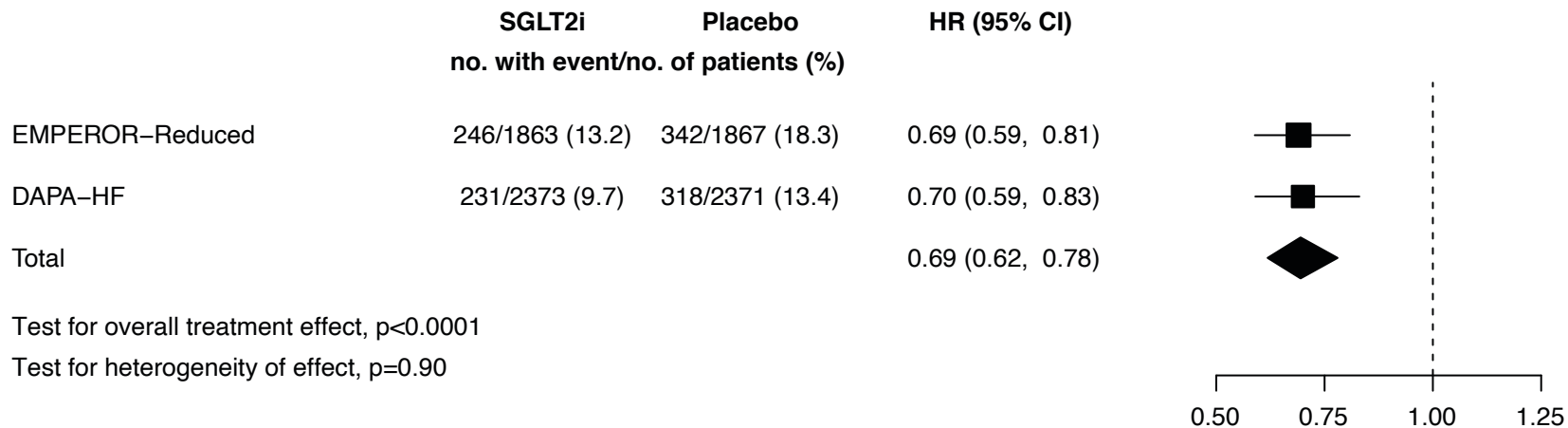
Test for heterogeneity of effect, $p=0.40$



c) First hospitalisation for heart failure or cardiovascular death



d) First hospitalisation for heart failure

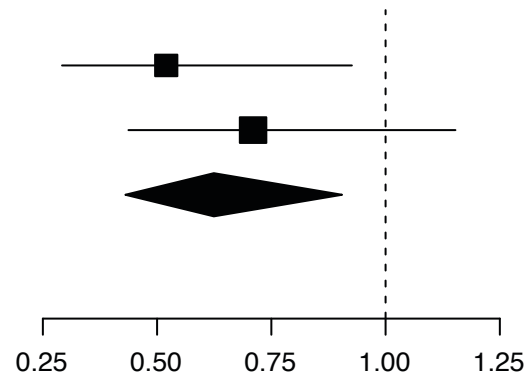


e) First kidney composite*

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		
EMPEROR-Reduced	18/1863 (1.0)	33/1867 (1.8)	0.52 (0.29, 0.92)
DAPA-HF	28/2373 (1.2)	39/2371 (1.6)	0.71 (0.44, 1.16)
Total			0.62 (0.43, 0.90)

Test for overall treatment effect, $p=0.0128$

Test for heterogeneity of effect, $p=0.42$



f) All (first and recurrent) hospitalisation for heart failure or cardiovascular death

	SGLT2i	Placebo	RR (95% CI)
	no. of events/no. of patients (% rate)		
EMPEROR-Reduced	575/1863 (30.9)	753/1867 (40.3)	0.76 (0.65, 0.89)
DAPA-HF	567/2373 (23.9)	742/2371 (31.3)	0.75 (0.65, 0.88)
Total			0.75 (0.68, 0.84)

Test for overall treatment effect, $p < 0.0001$

Test for heterogeneity of effect, $p = 0.91$

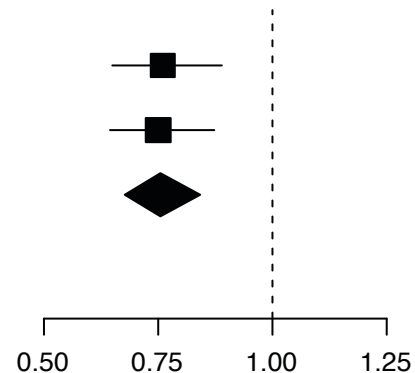
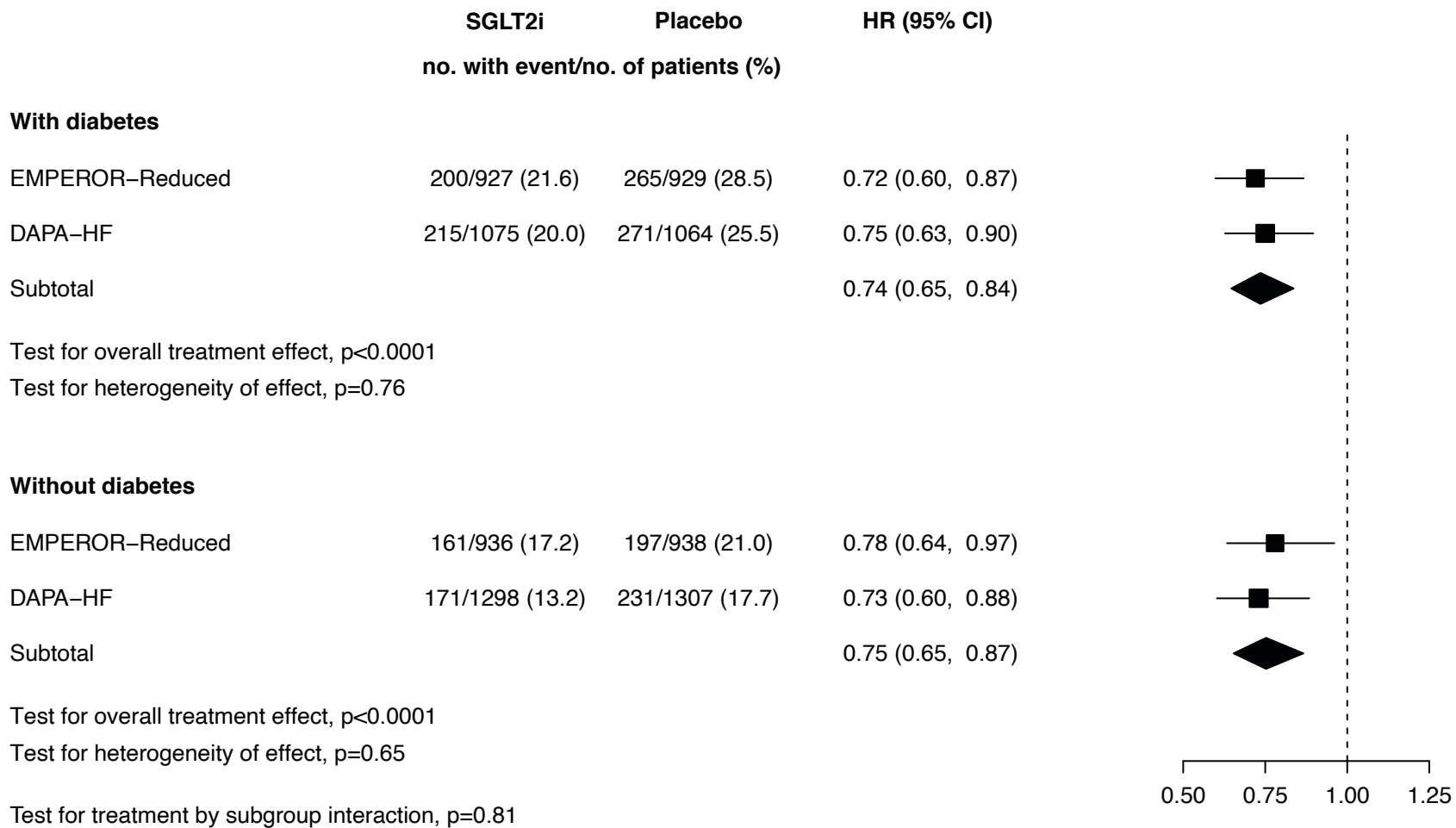
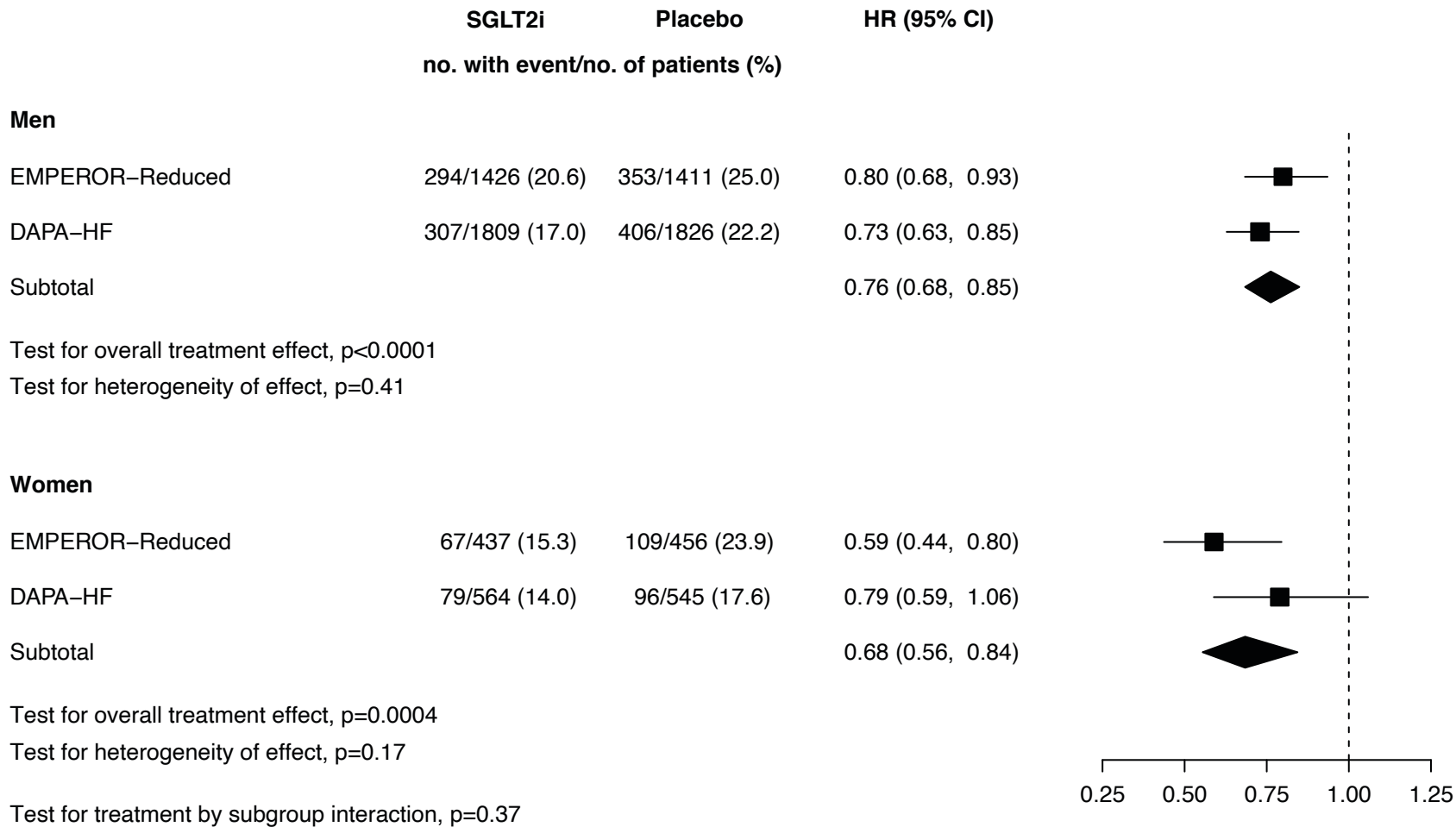


Figure 2

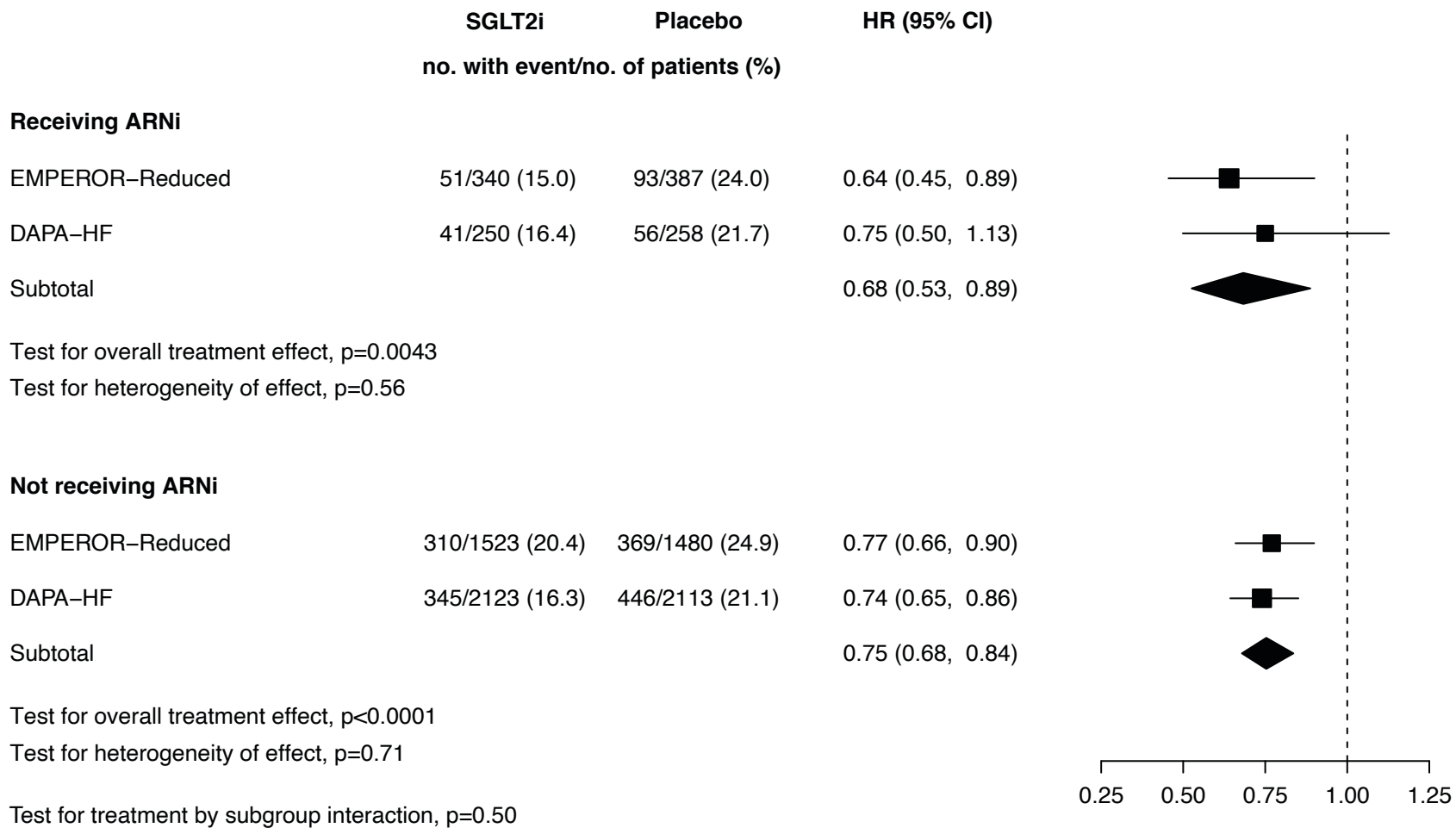
a) Diabetes status



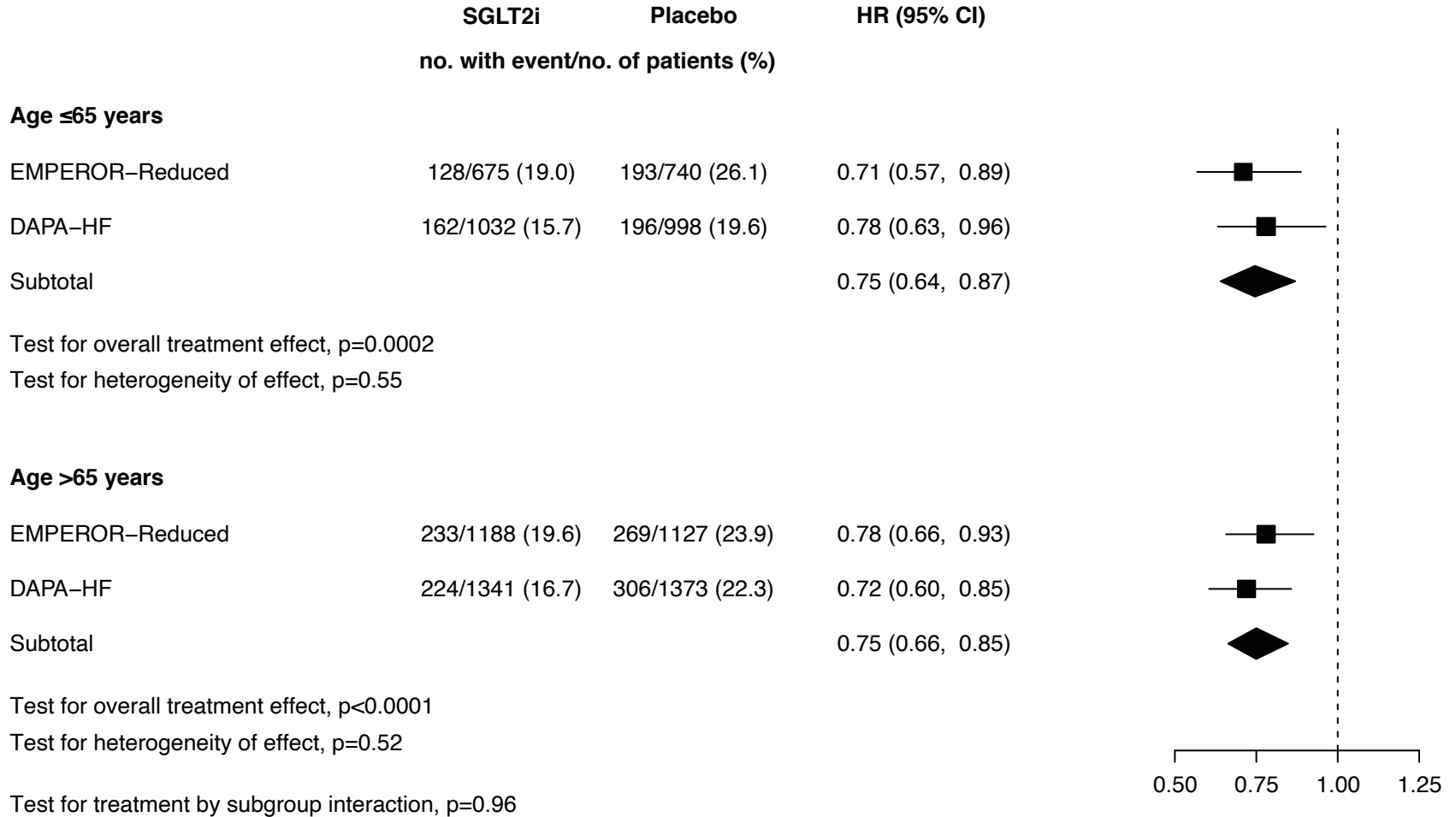
b) Sex



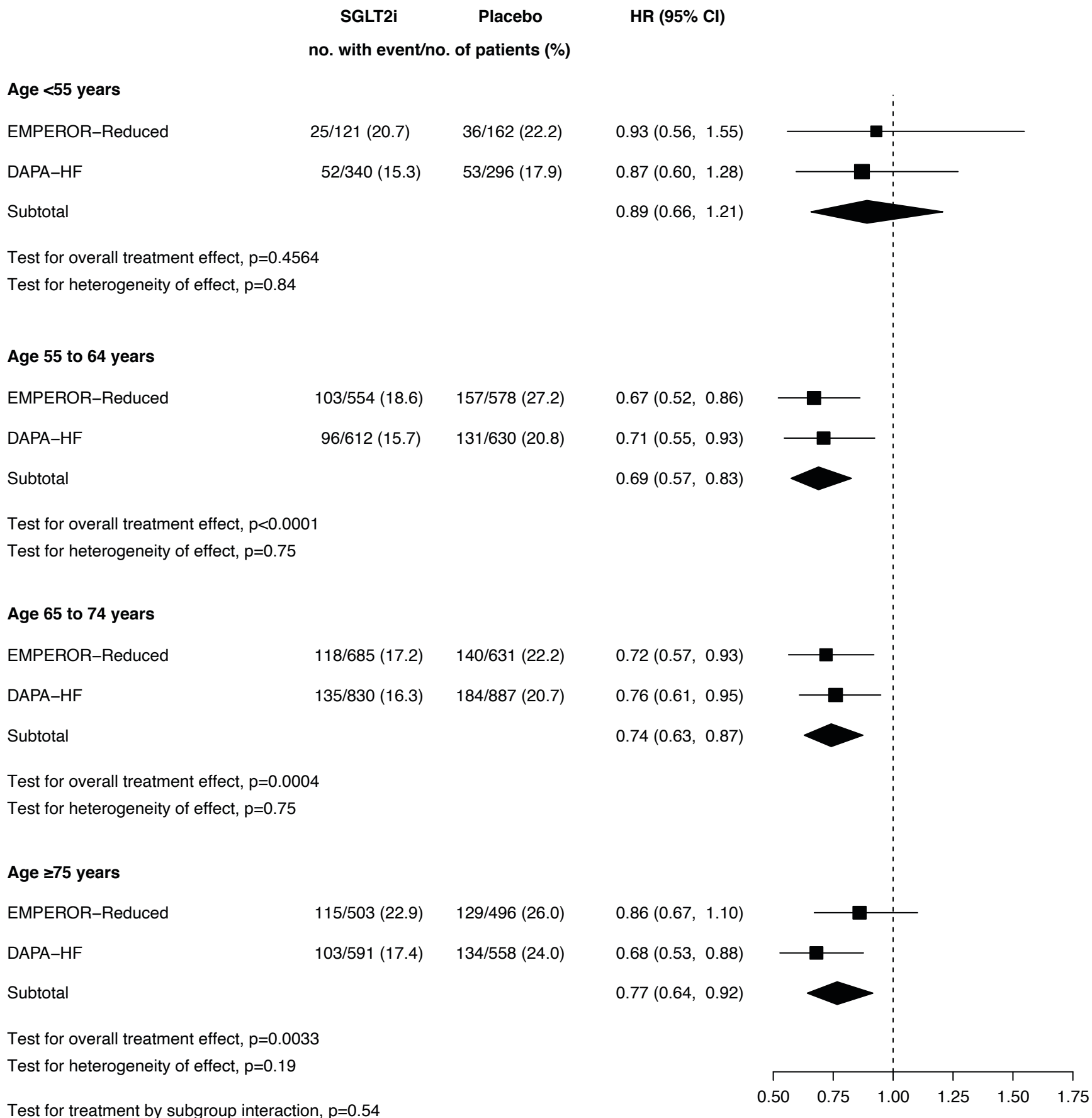
c) Use of ARNi



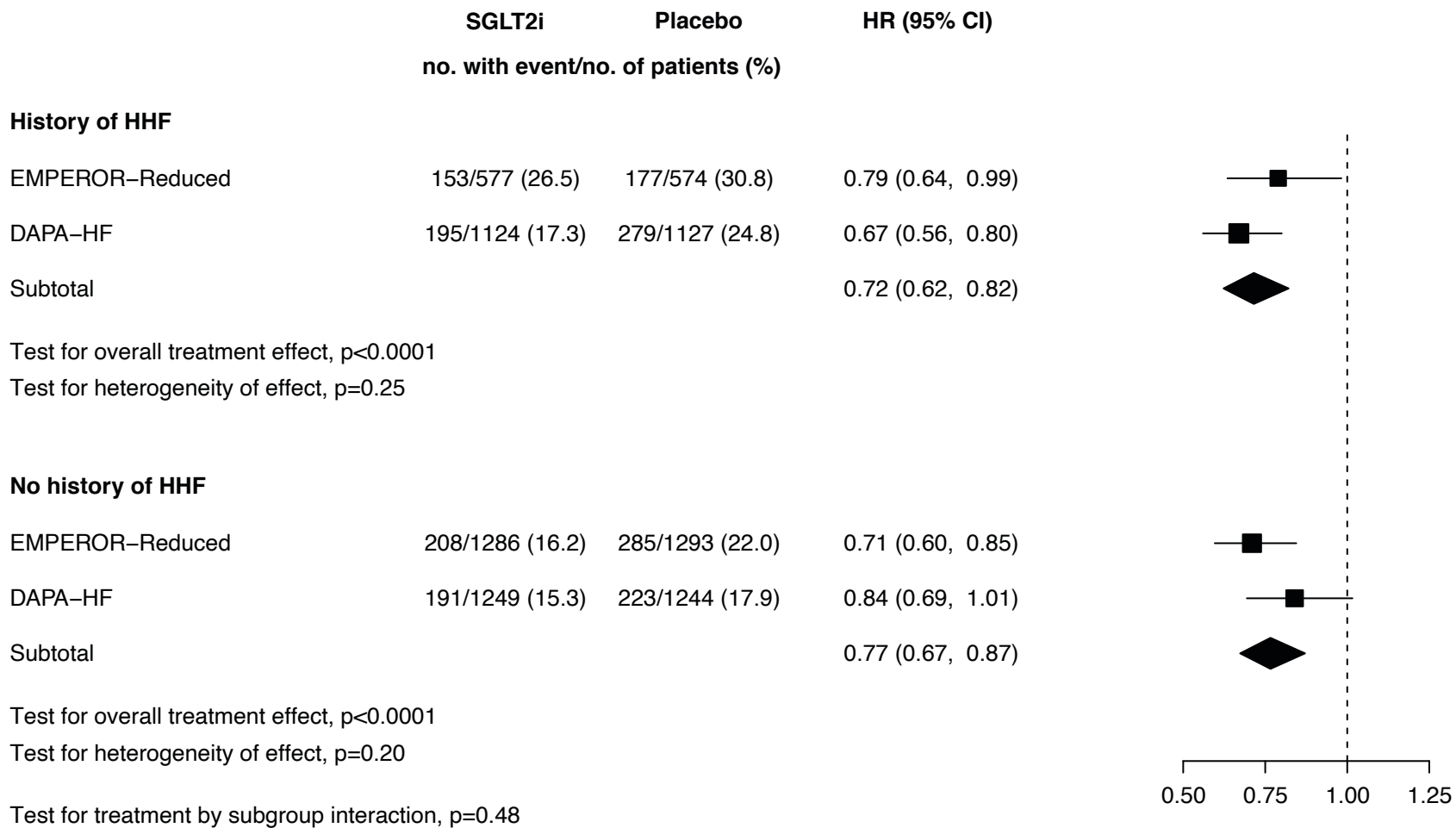
d) Age (≤ 65 and >65 years)



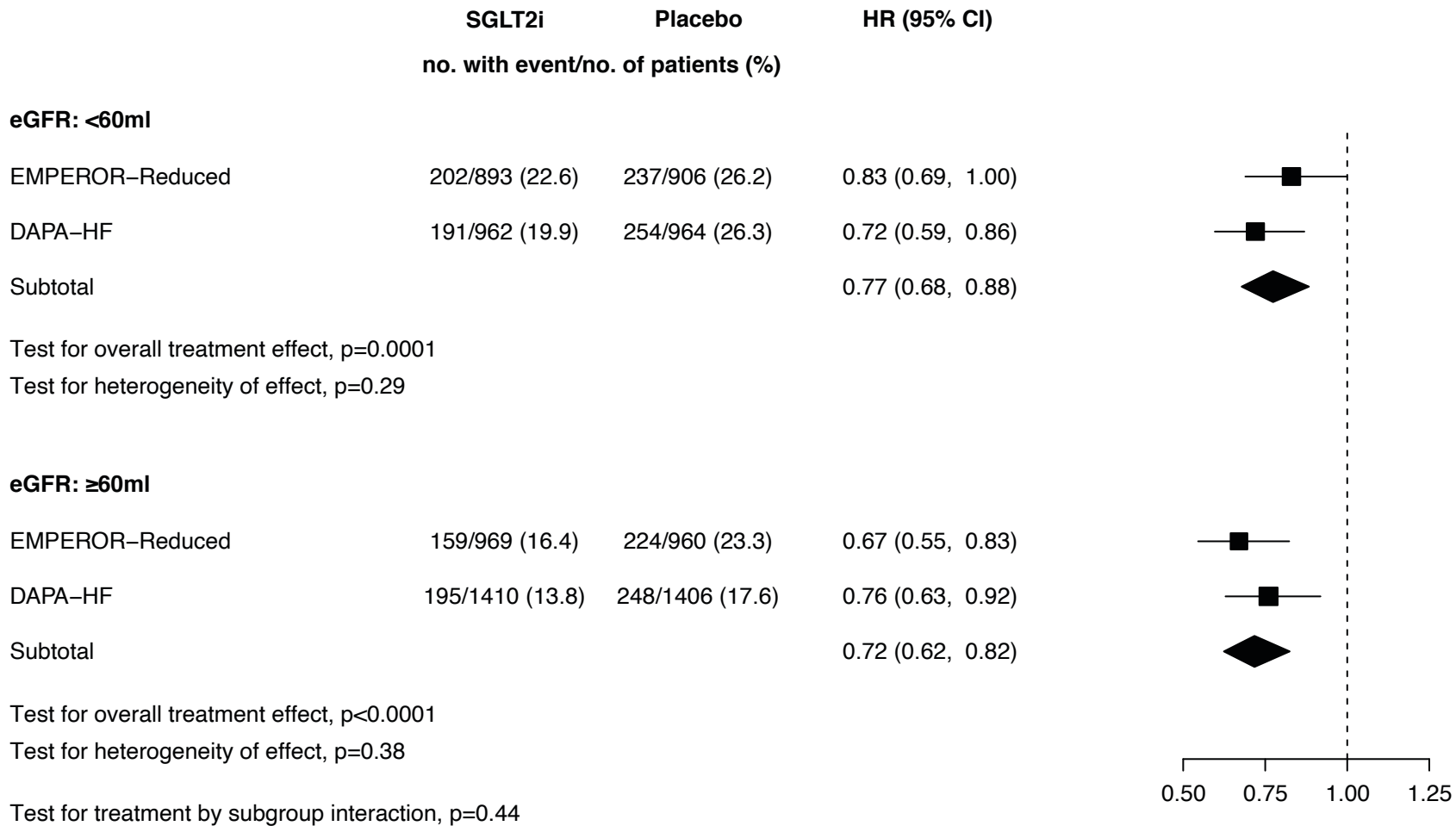
e) Age (<55, 55 to 64, 65 to 74, and ≥75 years)



f) History of hospitalisation for heart failure



g) eGFR



h) NYHA functional class

	SGLT2i	Placebo	HR (95% CI)
	no. with event/no. of patients (%)		

NYHA class: II

EMPEROR-Reduced	220/1399 (15.7)	299/1401 (21.3)	0.71 (0.59, 0.84)
DAPA-HF	190/1606 (11.8)	289/1597 (18.1)	0.63 (0.52, 0.75)
Subtotal			0.67 (0.59, 0.76)

Test for overall treatment effect, $p < 0.0001$

Test for heterogeneity of effect, $p = 0.36$

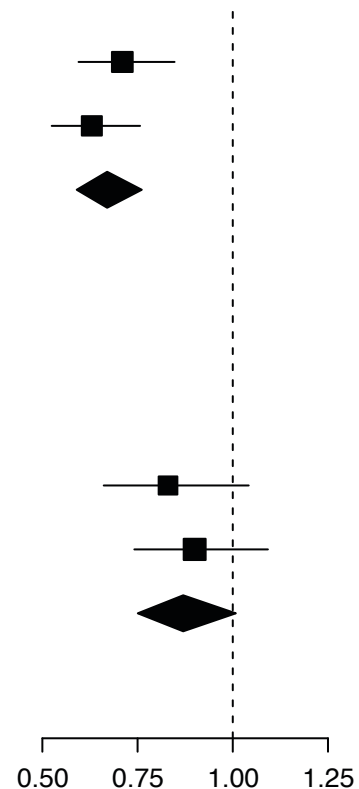
NYHA class: III-IV

EMPEROR-Reduced	141/464 (30.4)	163/466 (35.0)	0.83 (0.66, 1.04)
DAPA-HF	196/767 (25.6)	213/774 (27.5)	0.90 (0.74, 1.09)
Subtotal			0.87 (0.75, 1.01)

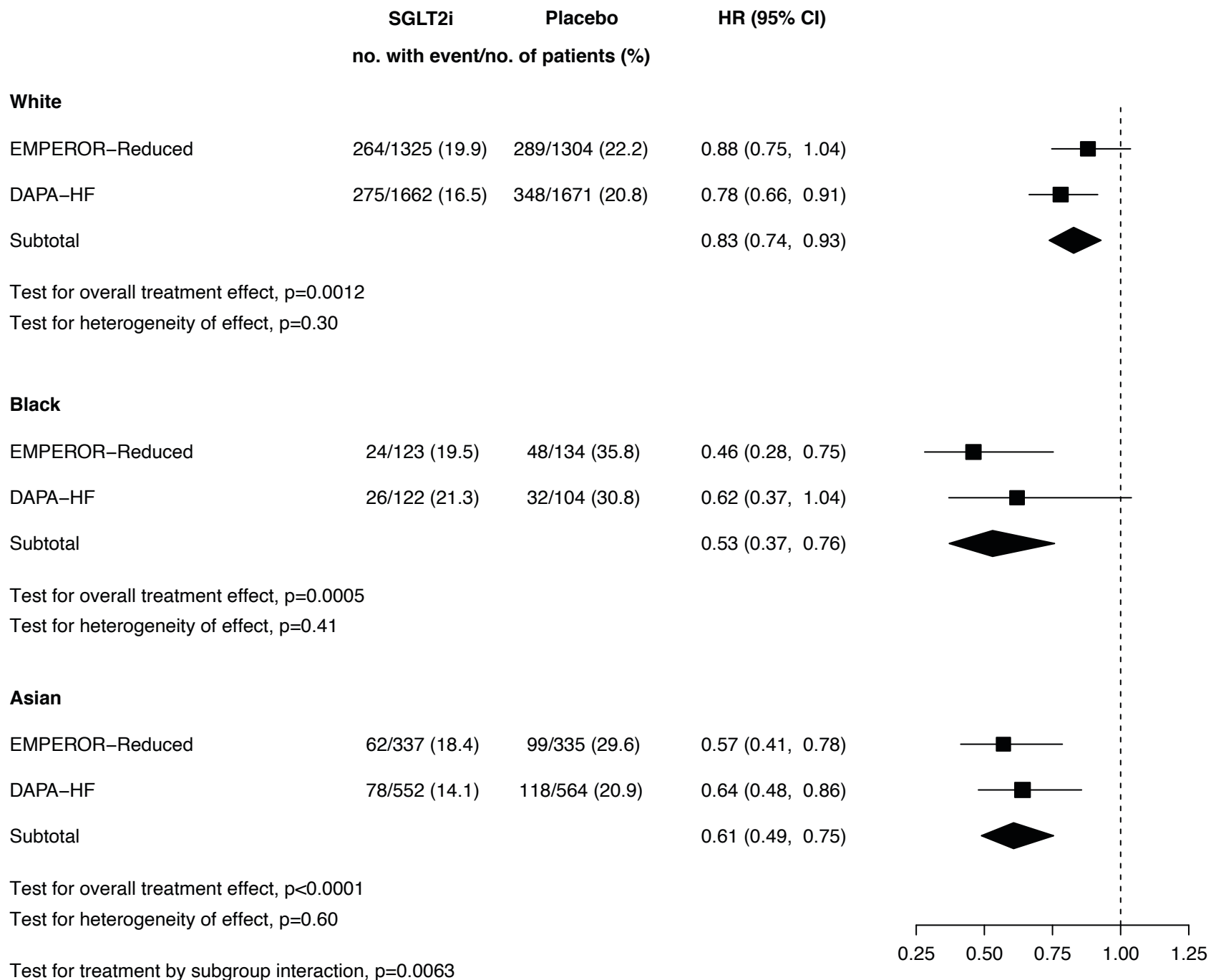
Test for overall treatment effect, $p = 0.0638$

Test for heterogeneity of effect, $p = 0.60$

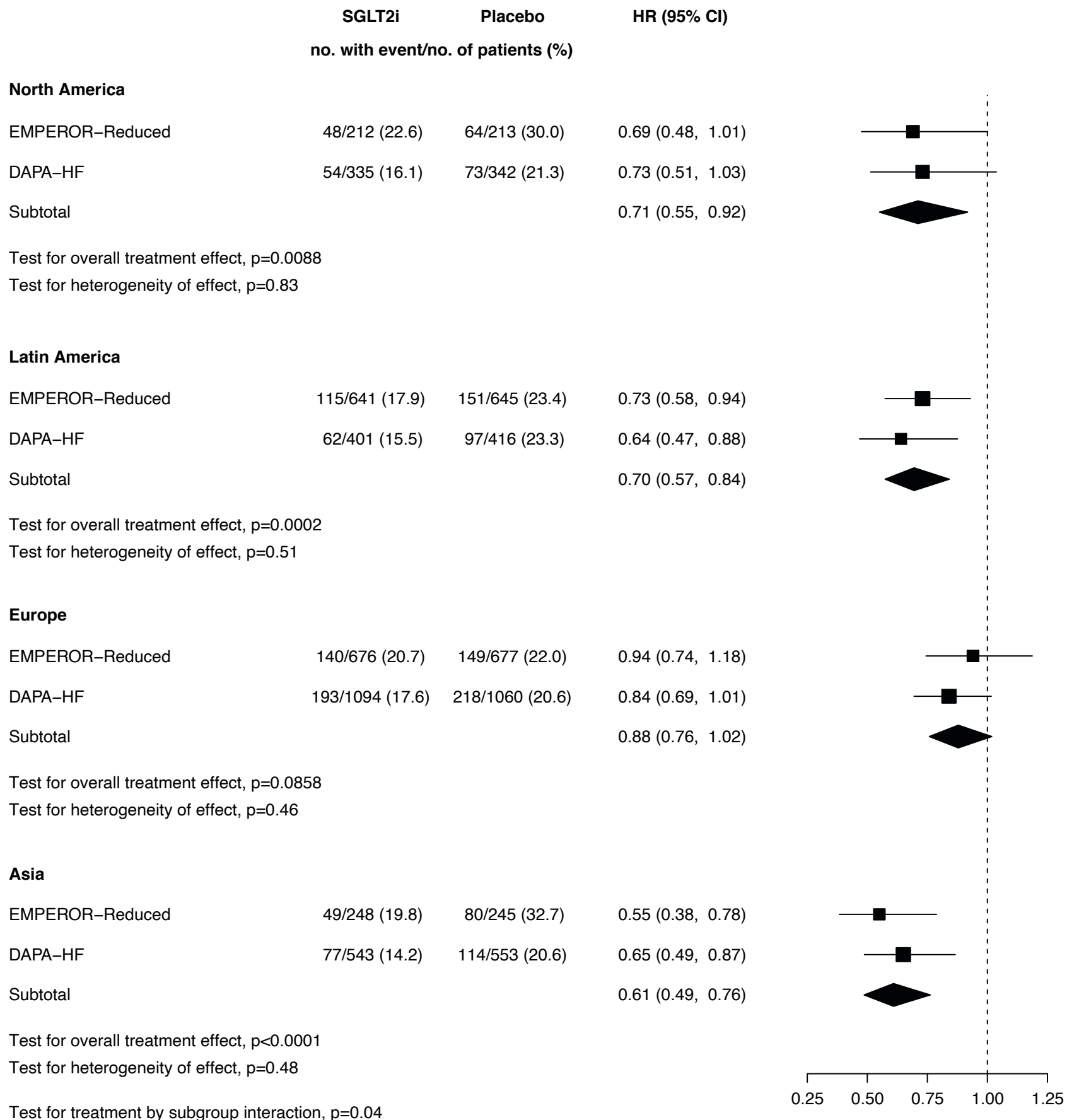
Test for treatment by subgroup interaction, $p = 0.0087$



i) Race



j) Region



k) BMI

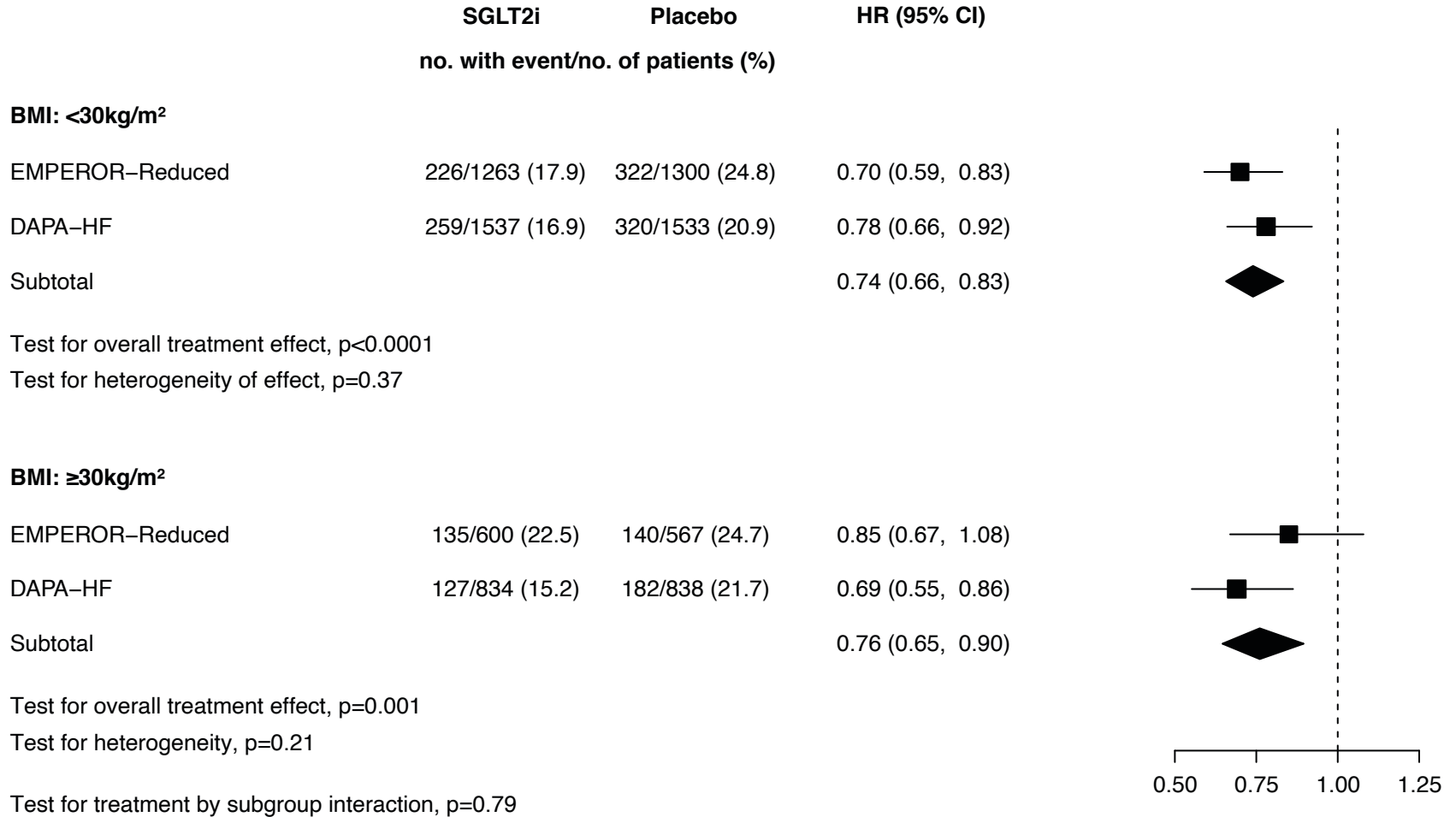


Table 1. Overview of main characteristics of the two trial populations at baseline

	EMPEROR-reduced		DAPA-HF	
	Empagliflozin	Placebo	Dapagliflozin	Placebo
Number of participants	1863	1867	2373	2371
Mean±SD age, years	67.2 ± 10.8	66.5 ± 11.2	66.2 ± 11.0	66.5 ± 10.8
Females	437 (23.5%)	456 (24.4%)	564 (23.8%)	545 (23.0%)
NYHA functional classification				
II	1399 (75.1%)	1401 (75.0%)	1606 (67.7%)	1597 (67.4%)
III	455 (24.4%)	455 (24.4%)	747 (31.5%)	751 (31.7%)
IV	9 (0.5%)	11 (0.6%)	20 (0.8%)	23 (1.0%)
Mean LVEF (%), mean ± SD	27.7 ± 6.0	27.2 ± 6.1	31.2 ± 6.7	30.9 ± 6.9
NT-pro BNP, pg/ml, median (Q1-Q3)	1887 (1077-3429)	1926 (1153-3525)	1428 (857-2655)	1446 (857-2641)
Medical history				
Hospitalisation for HF*	577 (31.0%)	574 (30.7%)	1124 (47.4%)	1127 (47.5%)
Diabetes**	927 (49.8%)	929 (49.8%)	1075 (45.3%)	1064 (44.9%)
Mean ± SD eGFR, ml/min/1.73 m² ***	61.8 ± 21.7	62.2 ± 21.5	66.0 ± 19.6	65.5 ± 19.3
Heart failure medications				
ACE inhibitor	867 (46.5%)	836 (44.8%)	1332 (56.1%)	1329 (56.1%)
ARB	451 (24.2%)	457 (24.5%)	675 (28.4%)	632 (26.7%)
Mineralocorticoid receptor antagonist	1306 (70.1%)	1355 (72.6%)	1696 (71.5%)	1674 (70.6%)
ARNI	340 (18.3%)	387 (20.7%)	250 (10.5%)	258 (10.9%)
Device therapy				
ICD or CRT-D	578 (31.0%)	593 (31.8%)	622 (26.2%)	620 (26.1%)
CRT-D or CRT-P	220 (11.8%)	222 (11.9%)	190 (8.0%)	164 (6.9%)

Data are n (%), unless otherwise specified.

* For EMPEROR-Reduced: last 12 months

** determined by a combination of medical history and pre-treatment HbA1c

*** *CKD-EPI formula

Legend: LVEF, left ventricular ejection fraction; CV, cardiovascular; HF, heart failure; SD, standard deviation; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; ICD, implantable cardiac defibrillator; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker.

Table 2. Relevant adverse events reported in the two trials.

	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin (n=1863) N (%)	Placebo (n=1863) N (%)	Dapagliflozin (n=2373) N (%)	Placebo (n=2371) N (%)
Serious AEs*	772 (41.4)	896 (48.1)	846 (35.7)	951 (40.2)
Any renal AE	175 (9.4)	192 (10.3)	141 (6.0)	158 (6.7)
Volume depletion	197 (10.6)	184 (9.9)	170 (7.2)	153 (6.5)
Ketoacidosis	0 (0.0)	0 (0.0)	3 (0.1)	0
Severe hypoglycaemic events	6 (0.3)	7 (0.4)	4 (0.2)	4 (0.2)
Bone fractures	45 (2.4)	42 (2.3)	48 (2.0)	47 (2.0)
Lower limb amputation	13 (0.7)	10 (0.5)	13 (0.5)	12 (0.5)
Fournier's Gangrene	1 (0.1)	0	0	1 (0.1)

* Definitions of medical concepts describing adverse events of interest were not exactly the same across the two trials. The absolute numbers of events cannot be compared across the two trials due to different definitions and observation periods. For EMPEROR-Reduced: Shown are adverse events up to 7 days following discontinuation of study medication, for lower limb amputations up to the end of the trial. For DAPA-HF: On treatment (SAS) analysis set for all AEs, except for lower limb amputation shown on and off treatment.

See supplemental table 3 for further details on adverse event definitions.

Legend: AE, adverse events.