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## **Insulin-like growth factor binding protein-7 concentrations in chronic heart failure: Results from the EMPEROR programme**

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► **To cite this version:**

João Pedro Ferreira, Milton Packer, Naveed Sattar, Javed Butler, Sandra González Maldonado, et al.. Insulin-like growth factor binding protein-7 concentrations in chronic heart failure: Results from the EMPEROR programme. *European Journal of Heart Failure*, 2024, 10.1002/ejhf.3227 . hal-04544325

**HAL Id: hal-04544325**

**<https://hal.univ-lorraine.fr/hal-04544325v1>**

Submitted on 12 Apr 2024

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1 **Insulin-like growth factor binding protein-7 concentrations in Chronic Heart Failure:**

2 **Results from the EMPEROR Program**

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30  
31 **Word count (introduction to conclusion): 3054**

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41 **Abstract**

42 **Aims:** Insulin-like growth factor binding protein-7 (IGFBP7) is a biomarker of tissue  
43 senescence with a role in cardio-renal pathophysiology. The role of IGFBP7 as a prognostic  
44 biomarker across the full ejection fraction (EF) spectrum of heart failure (HF) remains less  
45 well understood. We examined associations between IGFBP7 and risk of cardio-renal  
46 outcomes regardless of EF and the effect of empagliflozin treatment on IGFBP7  
47 concentrations among individuals with HF.

48 **Methods and Results:** IGFBP7 was measured in 1125 study participants from the  
49 EMPEROR-Reduced and EMPEROR-Preserved Trials. Cox regression was used to study  
50 associations with outcomes. Study participants with IGFBP7 levels in the highest tertile had a  
51 higher-risk clinical profile. In Cox proportional hazards models adjusted for clinical  
52 variables, N-terminal pro-B type natriuretic peptide and high-sensitivity cardiac troponin T,  
53 baseline IGFBP7 values in the highest tertile predicted an increased risk of HF hospitalization  
54 or CV death (HR: 2.00 95% CI 1.28-3.10,  $p=0.002$ ,  $p$  for trend  $<0.001$ ) and higher risk of  
55 renal composite endpoint (HR: 4.66, 95% CI: 1.61-13.53,  $p=0.005$ ,  $p$  for trend = 0.001),  
56 regardless of EF. Empagliflozin reduced risk for CV death/HF hospitalization irrespective of  
57 baseline IGFBP7 ( $p$ -trend across IGFBP7 tertiles=0.26). Empagliflozin treatment was not  
58 associated with meaningful change in IGFBP7 at 12 or 52 weeks.

59 **Conclusion:** Across the entire LVEF spectrum in the EMPEROR program, concentrations of  
60 the senescence associated biomarker IGBP7 were associated with higher risk clinical status  
61 and predicted adverse cardio-renal outcomes even in models adjusted for conventional  
62 biomarkers. Empagliflozin did not significantly affect IGFBP7 levels over time.

63 **Trial Registration:** EMPEROR-Reduced (NCT03057977), EMPEROR-Preserved  
64 (NCT03057951)

65 **Keywords:** heart failure, IGFBP7, biomarker, empagliflozin, kidney function,

## 66 **Introduction**

67 The progression of heart failure (HF) includes accelerated aging of the myocardium. Such  
68 myocardial senescence results from permanent cell cycle arrest combined with loss of tissue  
69 renewal. Senescent cells secrete a pool of molecules known as the senescence-associated  
70 secretome that exert autocrine and paracrine to promote the aging process. IGFBP7 (insulin-  
71 like growth factor-binding protein-7) is a prominent member of the senescence-associated  
72 secretome; among the effects of IGFBP7 is to augment cell cycle arrest, while enhancing  
73 oxidative stress, impairing DNA repair and promoting fibrosis. It does so in part by  
74 interfering with the adaptive actions of foxhead box O3a (FOXO3a) to reduce cellular stress  
75 and induce autophagy(1-3). Although originally considered to be a member of the IGFBP  
76 family, IGFBP7 differs from other members of the family in that it binds only weakly to  
77 insulin-like growth factors(4-8).

78 Notably, studies have shown higher blood concentrations of IGFBP7 among patients  
79 with acute or chronic HF syndromes are associated with abnormalities of diastolic filling and  
80 increases in left atrial volume(9, 10). Furthermore, high concentrations of IGFBP7 may be  
81 additive to those of N-terminal pro-B type natriuretic peptide (NT-proBNP) for diagnostic  
82 accuracy in HF and in predicting an adverse prognosis in acute and chronic HF(11, 12).  
83 However, the true additive value of IGFBP7 for prognostication relative to conventional  
84 biomarkers such as NT-proBNP or high sensitivity cardiac troponin (hs-cTn) has not been  
85 explored across the entire range of left ventricular ejection fraction (LVEF). Furthermore, the  
86 effect of empagliflozin on concentrations of IGFBP7 is not described. We therefore sought to  
87 more thoroughly evaluate this question among study participants in the Empagliflozin  
88 Outcome Trial in Patients with Chronic Heart Failure (EMPEROR) program.

## 89 **Methods**

90 *Study sample*

91 The design and results of EMPEROR-Reduced and EMPEROR-Preserved trials have been  
92 published(13, 14). This study consists of 9718 individuals who were initially enrolled in the  
93 EMPEROR-Reduced (n = 3730) and EMPEROR-Preserved (n = 5988) trials. In brief, the  
94 trials included individuals with class II-IV HF and elevated levels of natriuretic peptides  
95 across a broad spectrum of LVEF. Written informed consent was obtained from all patients  
96 and the study protocols were approved by the ethics committees of all participating  
97 institutions.

98         Apart from their usual treatment for HF, patients who met the eligibility criteria were  
99 randomly assigned in a double-blind manner, with a 1:1 ratio, to receive either a placebo or  
100 empagliflozin at a 10 mg dose per day. During study visits, outcomes related to HF were  
101 assessed. In both trials, the primary outcome was a combination of cardiovascular death or  
102 hospitalization due to HF. The primary renal outcome was the combined risk of an estimated  
103 glomerular filtration rate (eGFR) decrease of at least 40% over time, an eGFR decline to <10  
104 or <15 ml/min/1.73m<sup>2</sup> (for patients with baseline eGFR < or ≥ 30 ml/min/1.73m<sup>2</sup>,  
105 respectively), chronic dialysis, or renal replacement therapy.

106         Participation in the trials was not contingent on submitting samples of plasma, serum,  
107 DNA, or urine for biobanking. Bio-samples were only obtained once a separate informed  
108 consent was provided in compliance with local ethical and regulatory regulations. The  
109 concepts and technique of sample collection for biobanking in the EMPEROR trials and the  
110 list of nations that took part in the biobanking for biomarker sub-study have been published  
111 elsewhere(15). **Figure 1** details the study flow for the present analysis; for the purposes of  
112 this analysis, 594 study participants were included from EMPEROR-Reduced (LVEF <40%),  
113 while 531 study participants were included from EMPEROR-Preserved (LVEF ≥40%).

114 *Biomarker measurement*

115 Biomarkers were measured in serum samples in the placebo and empagliflozin arms at  
116 baseline (N= 561, 564), 12 weeks (N=558, 557) and 52 weeks (N=355, 358). The  
117 measurements of IGFBP7, as well as hs-cTnT, carbohydrate antigen 125 (CA-125), growth  
118 differentiation factor-15 (GDF-15), angiopoietin 2 (ANGPT-2), fatty acid-binding protein-3  
119 (FABP-3) and bone morphogenetic protein 10 (BMP-10), were performed within the  
120 Biomarker Research Agreement of Boehringer Ingelheim, the sponsor of the EMPEROR  
121 trials and Roche Diagnostics International Ltd. These measurements were made using an  
122 electrochemiluminescence immunoassay (Elecsys®, Roche Diagnostics). NT-proBNP was  
123 previously measured using similar methodology(16). Additionally, plasma samples from the  
124 same study participants were included in a plasma proteomics study using the Olink®  
125 Explore 1536 platform previously reported(17).

126 *Statistical analysis*

127 Mean (standard deviation), median (interquartile range), and count (frequency) were used to  
128 describe the distribution of continuous and categorical variables as appropriate. Cox  
129 proportional hazard regression models and negative binomial models were used to analyze  
130 the associations between baseline IGFBP7 and major HF outcomes, as appropriate.  
131 Multivariable models included age, sex, geographical region, diabetes, LVEF, eGFR, and trial  
132 (EMPEROR-Reduced or EMPEROR-Preserved) as covariates, and were additionally  
133 adjusted for log-transformed baseline hs-cTnT and NT-proBNP, the most important  
134 biomarker predictors of the primary outcome in the EMPEROR studies(18-21). Additional  
135 adjustment was performed on GDF-15, another important prognostic marker in the  
136 EMPEROR-Program (22). Week 12 landmark analysis were performed to study the  
137 associations between IGFBP7 changes and the subsequent occurrence of the primary

138 outcome. Heterogeneity of treatment effect on major HF outcomes across the groups defined  
139 by the tertiles of GDF-15 was investigated by fitting Cox regression and negative binomial  
140 models, as appropriate, adjusted by the prespecified covariates except for hs-cTnT and NT-  
141 proBNP and including a IGFBP7-group by treatment interaction. With the mentioned  
142 baseline covariates and baseline IGFBP7 levels considered, changes in IGFBP7 levels over  
143 time were examined using mixed models for repeated measurements adjusted with same  
144 covariates as multivariable models, excluding hs-cTnT and NT-proBNP. These models  
145 compared the change in plasma concentrations for each protein from baseline to weeks 12  
146 and 52 between treatment groups (empagliflozin vs. placebo). Correlation between IGFBP7  
147 and proteins measured by Olink® Explore 1536 platform and the remaining proteins  
148 measured by Roche Diagnostics were assessed by calculating Spearman correlation  
149 coefficients. Statistical analyses were performed using the SAS software, version 9.4 (SAS  
150 Institute, Inc.; Cary, NC). All tests were two-sided, and p-values < 0.05 were considered  
151 statistically significant.

## 152 **Results**

153 Of 1125 people with HF included in this study, 361 (32%) were female. The mean (standard  
154 deviation) age of study participants was 70±10 years. Most study participants were White  
155 (n=948, 84%) and reside in Europe (n=632, 56%). Baseline characteristics of the study  
156 population stratified by thirds of IGFBP7 levels are detailed in **Table 1**. Study participants  
157 with the highest IGFBP7 concentrations were older, more likely to be male, had a higher  
158 prevalence of diabetes mellitus, atrial fibrillation, valvular heart disease, lower eGFR, and  
159 higher albumin/creatinine ratio, NT-proBNP and hs-cTnT compared to other tertiles.

160 The results of the Cox regression analysis are detailed in **Figure 2**. In multivariable  
161 model, considering study participants with IGFBP7 concentrations in tertile 1 as a reference,

162 participants with IGFBP7 concentrations in the highest tertile were at significantly higher risk  
163 for the primary endpoint of the EMPEROR Trial, HF hospitalization/CV death (hazard ratio  
164 [HR]: 2.00 [95% confidence interval (CI): 1.28-3.10], p-value <0.001). **Figure 3** depicts the  
165 cumulative incidence function of the primary endpoint of the EMPEROR Trials for each  
166 IGFBP7 tertile. Patients with IGFBP7 concentrations in the highest tertile had a significantly  
167 higher rate of HF hospitalization/CV death compared to others (Log rank p-value <0.001).  
168 Associations remained similar with additional adjustment on baseline GDF-15 levels:  
169 EMPEROR-Pooled tertile 3 vs tertile 1 primary outcome HR 1.66, 95%CI 1.03-2.67, P  
170 =0.03.

171 Associations for spline-transformed continuous IGFBP7 levels are presented in the  
172 **Supplementary Figure 1.**

173 In week 12 landmark analysis, IGFBP7 changes (from baseline to week 12) were  
174 strongly associated with the primary outcome: adjusted HR 2.67 for a fold-change in IGFBP7  
175 from baseline to week 12 (HR 4.12, 95% CI 2.21-7.69 in the log-scale, P <0.0001), adjusting  
176 on the “extended model” plus baseline IGFBP7 levels.

177 As also shown in **Figure 2**, higher tertiles of IGFBP7 were associated with an array of  
178 other cardio-renal events, including significant adjusted risk for first HF event (HR 2.20  
179 [95% CI 1.19-3.82]; p = 0.002), total HF events (adjusted event rate ratio: 2.13 [95% CI:  
180 1.19-3.82], p-value = 0.004), CV death (HR: 1.84 [95% CI: 1.00-3.41]; p =0.04) as well as  
181 sustained eGFR reduction  $\geq 40\%$  or ESRD (HR: 4.66 [95%CI: 1.61-13.53], p-value = 0.001).

182 **Supplemental Table 1 and 2** show the association between IGFBP-7 tertiles and  
183 clinical outcomes among individuals with HF<sub>r</sub>EF and HF<sub>p</sub>EF respectively. No significant  
184 interaction was found between LVEF levels (<40% or  $\geq 40\%$  according to populations of

185 EMPEROR-Reduced and EMPEROR-preserved trials) and IGFBP-7 concentrations for  
186 prediction of clinical outcomes (p for interactions by study >0.1).

187 **Table 2** details effect of empagliflozin on endpoints in the EMPEROR Trials as a  
188 function of baseline IGFBP7. Two observations may be made: firstly, higher concentrations  
189 of IGFBP7 were routinely associated with higher event rates regardless of treatment  
190 assignment; second, in most cases, no interaction of treatment effect of empagliflozin by  
191 baseline IGFBP7 was detected, however effect of empagliflozin to improve time to first HF  
192 hospitalization may have been attenuated among those in the lowest IGFBP7 tertile. In **Table**  
193 **3**, eGFR slope across IGFBP7 tertiles is detailed as is treatment effect of empagliflozin.  
194 Similar to clinical events, decay of renal function (reflected in a more negative eGFR slope)  
195 was generally worse in those with higher IGFBP7 concentrations. Empagliflozin had  
196 generally similar effects on eGFR slope across tertiles of IGFBP7.

197 **Supplemental Table 3** displays the top correlations between baseline IGFBP7 and  
198 proteins measured through Olink proteomics or other automated immunoassays. At baseline,  
199 most correlations were modest. The highest correlations of IGFBP7 (Spearman correlation >  
200 0.60) were found with bone morphogenic protein-10, fatty acid binding protein-3, and growth  
201 differentiation factor-15.

202 **Table 4** shows the concentration of IGFBP7 among empagliflozin compared to  
203 placebo groups at baseline and follow-up visits. Treatment with empagliflozin was associated  
204 with a 3% greater reduction of IGFBP7 level versus placebo to week 12 (adjusted geometric  
205 mean ratio: 0.97; 95% confidence interval [CI], 0.94-1.00, p=0.05) but not to week 52  
206 (adjusted geometric mean ratio: 1.02, 95% CI 0.98-1.06; p=0.35) (**Figure 4**).

207 **Discussion**

208 Prior studies have suggested IGFBP7 measurement may inform cardio-renal risk in both  
209 acute and chronic HF states(12, 23, 24) but the value of the marker across the wide range of  
210 LVEF remained unclear, the meaning of IGFBP7 to prognosticate cardiac and renal outcomes  
211 even in presence of other biomarkers required further analyses, and the impact of SGLT2  
212 inhibition on IGFBP7 was uncertain. In this study from the EMPEROR program, we showed  
213 that elevated IGFBP7 levels were associated with more advanced age, a higher prevalence of  
214 dysglycemia, and a greater burden of cardiac and kidney dysfunction. Higher concentrations  
215 of IGFBP7 or change in IGFBP7 were predictive of increased risk of HF hospitalization,  
216 cardiovascular mortality, and progression of kidney disease even when adjusted for other  
217 relevant biomarkers, including NT-proBNP and hs-cTnT, the strongest overall prognostic  
218 measures in the EMPEROR program (20, 21); similar findings were present when further  
219 adjusting for GDF-15. IGFBP7 was a robust predictor of risk across the wide LVEF range in  
220 the EMPEROR Trials and in most cases no interaction by baseline LVEF was present  
221 regarding both the ability of IGFBP7 to prognosticate outcomes or predict effect of  
222 empagliflozin although effect of empagliflozin to improve time to first HF hospitalization  
223 may have been attenuated among those in the lowest IGFBP7 tertile. Concentrations of  
224 IGFBP7 were not meaningfully lowered by treatment with empagliflozin. In aggregate, these  
225 results demonstrate that IGFBP7 is an important cardiorenal risk marker across the spectrum  
226 of LVEF in persons with HF and add considerably to available knowledge regarding the  
227 biomarker in those treated with SGLT2 inhibitors(25).

228 A potential role for IGFBP7 in HF was originally identified in a proteomics screen in  
229 an animal model of cardiomyopathy(26), and numerous studies have since linked  
230 concentrations of IGFBP7 to worse systolic and diastolic function in patients with HF(12, 23,  
231 24). As part of the senescence-associated secretome, IGFBP7 has a broad range of effects  
232 including induction of cell cycle arrest, interference with DNA repair and detoxification of

233 reactive oxygen species, and promotion of fibrosis, potentially mediated by an action to  
234 suppress FOXO3a signaling(27, 28). Gene knock-out of IGFBP7 in HF models is associated  
235 with a reduction in proinflammatory and profibrotic pathways, resulting in preservation of  
236 cardiac function(9). Furthermore, RNA-mediated silencing of IGFBP7 or neutralization with  
237 monoclonal antibodies blocked the actions of IGFBP7 on FOXO3a signaling and mitigated  
238 pressure-overload induced HF(29). A similar role has been identified for IGFBP7 in the  
239 kidney, where it acts as a marker of renal stress and a potential mediator of the progression of  
240 chronic kidney disease(30). These results implicate IGFBP7 as a potential target for future  
241 therapies to slow the progression of HF and nephropathy.

242 Notably, baseline IGFBP7 concentrations or changes in IGFBP7 were strongly  
243 prognostic for major cardio-renal outcomes in EMPEROR, adding strong prognostic value  
244 across the entire LVEF spectrum. The fact that IGFBP7 remained a robust predictor of  
245 outcomes in the trial even when adjusted for NT-proBNP and hs-cTnT results is noteworthy:  
246 these two biomarkers have been found to be dominant for predicting outcomes in the trial  
247 program, almost routinely superseding other biomarkers, so the finding of prognostic  
248 meaning with IGFBP7 in this study is quite meaningful. Given the primacy of NT-  
249 proBNP(16) and hs-cTnT(19) for prognosis in the EMPEROR program(21), the results of  
250 this study further solidify the robustness of IGFBP7 for prognostic assessment. We extend the  
251 results to also show IGFBP7 remains strongly prognostic when further adjusted for GDF-15  
252 concentrations in addition to NT-proBNP and hs-cTnT. As few biomarkers substantially add  
253 to information from NT-proBNP and hs-cTnT, the results are important and suggest that  
254 IGFBP7 adds orthogonal biologic information to measures of myocardial wall stress and  
255 cardiomyocyte necrosis. It is reasonable to consider the paradigm of wall stress (NT-proBNP)  
256 triggering a cascade of senescence signaling (IGFBP7), culminating in necrosis (hs-cTnT).

257 Further translational research is needed to understand links between IGFBP7, related  
258 biomarkers, and clinical outcomes in HF.

259 In EMPEROR, across nearly all outcomes evaluated, treatment with empagliflozin  
260 was associated with generally similar event reductions regardless of baseline IGFBP7  
261 concentration; effect of empagliflozin on time to first HF hospitalization might have been  
262 attenuated in the lowest IGFBP7 tertile. Taken in aggregate, these results suggest that  
263 IGFBP7 measurement should not be used to decide on whether to utilize an SGLT2 inhibitor  
264 in HF, although those with highest IGFBP7 values had large absolute risk reduction. In  
265 contrast to treatment of HF with sildenafil(31), sacubitril/valsartan(12) or heart  
266 transplantation(32), where such treatments may lower concentrations of IGFBP7, in this  
267 study, treatment with empagliflozin did not meaningfully reduce concentrations of the  
268 biomarker during the duration of study, similar to results from analyses of canagliflozin in  
269 persons with type 2 diabetes(16, 33). This implies factors leading to rise of IGFBP7 may be  
270 independent of effects of SGLT2 inhibition.

271 It is noteworthy that despite the multiple cardioprotective effects of SGLT2 inhibitors  
272 (34), concentrations of the prognostic IGFBP7 were reduced by 3% at week 12, but not at  
273 week 52 of the study. These results are consistent with prior evidence suggesting  
274 canagliflozin did not reduce IGFBP7 concentrations in those with diabetes and CV risk  
275 treated for a year (30). In contrast, another study of individuals with diabetic kidney disease  
276 suggested canagliflozin reduced IGFBP7 by approximately 2% over a similar time course of  
277 treatment (35). More in-depth understanding regarding how biomarkers like IGFBP7 might  
278 reflect benefit of therapeutics including SGLT2 inhibitors is needed.

279 A particular strength of the EMPEROR Trial is the depth of biomarker data available  
280 for cross-correlation. Our study reveals correlations between the level of IGFBP7 and certain

281 plasma proteins that are linked to key processes in cardiovascular disease. Whereas most of  
282 the correlations were modest in nature, several proteins with links with myocardial disease  
283 processes, including cardiac remodeling showed at least moderate correlation with  
284 IGFBP7.(36) (37). The top correlations with IGFBP7 ( $Rho >0.6$ ) are Bone Morphogenic  
285 Protein (BMP)-10, Fatty Acid Binding Protein (FABP)-3, and GDF-15. In experimental  
286 models BMP10 stimulated cardiomyocyte proliferation and repaired cardiac function after  
287 heart injury(37), BMP10 has also been described as a marker of adverse atrial remodelling  
288 (38). FABP3, is a small protein found intracellularly within cardiac or skeletal muscles that  
289 become released into circulation and excreted into the urinary system following injury to  
290 skeletal muscle, which may occur secondary to PAD-related tissue ischemia. FABP3 has been  
291 implicated in metabolic syndrome and mitochondrial dysfunction (39, 40). The implication of  
292 GDF-15 in the EMPEROR program has been thoroughly discussed (22), however the  
293 correlation with IGFBP7 and additive value for prognosis of these two biomarkers is  
294 noteworthy. The investigation into the relationship between IGFBP7 and myocardial disease  
295 processes requires additional research.

296         There are several study limitations that should be considered when interpreting our  
297 findings. Prior studies have implicated IGFBP7 as a cardio-renal prognostic biomarker; this  
298 study considerably extends the understanding of this biomarker in numerous ways: first, we  
299 evaluate its prognostic meaning across the wide EF range in the EMPEROR program,  
300 thoroughly evaluating it relative to both NT-proBNP and hs-cTnT; second, we evaluated  
301 impact of empagliflozin on IGFBP7 concentrations; lastly, we provide cross-correlations with  
302 other markers identified in a proteomics screen. A second limitation is that IGFBP7 is not  
303 cardiac specific and may be expressed in multiple tissues. For example, recent studies have  
304 implicated expression of the peptide in renal tubular epithelium and concentrations of the  
305 biomarker are strongly prognostic for renal outcomes in chronic diabetes mellitus(16, 33).

306 Our study involved the measurement of IGFBP7 levels in blood. The concentration of  
307 IGFBP7 in the heart may not be directly related to its level in the bloodstream. Furthermore,  
308 most of the study population were white males. Future research might explore the comparison  
309 of IGFBP7 levels among various races and ethnicities. This post hoc analysis included  
310 analyses without adjusting for multiple comparisons. Finally, the study participants were only  
311 monitored for 3 years. As a result, additional research is needed to determine the long-term  
312 effects of IGFBP7 levels on HF prognosis.

313 In conclusion, this study provides evidence regarding the importance of IGFBP7  
314 among patients with HF. More elevated baseline IGFBP7 concentrations were associated with  
315 a higher risk phenotype and were correlated with key biomarkers associated with myocardial  
316 processes pivotal in HF. Elevated values of IGFBP7 were linked to heightened adjusted risk  
317 of HF hospitalization, diminished survival, and higher risk of kidney failure across the entire  
318 LVEF range in HF. IGFBP7 remained a robust predictor of risk regardless of adjustment with  
319 NT-proBNP or hs-cTnT. Lastly, concentrations of IGFBP7 were not meaningfully affected by  
320 therapy with empagliflozin. Our results, demonstrated across the wide LVEF range in the  
321 EMPEROR program, further emphasize IGFBP7 as an important biomarker in HF.

322 **Funding:** Dr. Januzzi is supported in part by the Hutter Family Professorship.

323 **Disclosures:** Dr. Packer reports consulting to 89bio, Abbvie, Altimmune, Alnylam, Amarin,  
324 Amgen, Ardelyx, AstraZeneca, Boehringer Ingelheim, Caladrius, Casana, CSL Behring,  
325 Cytokinetics, Imara, Lilly, Medtronic, Moderna, Novartis, Reata, Relypsa, and Salamandra;  
326 Dr. Sattar has consulted for and/or received speaker fees from Abbott Laboratories, Amgen,  
327 AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Merck Sharp &  
328 Dohme, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Sanofi; and received grant  
329 support paid to his University from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche  
330 Diagnostics outside the submitted work; Dr. Butler has received consulting income from  
331 Abbott, American Regent, Amgen, Applied Therapeutic, AstraZeneca, Bayer, Boehringer  
332 Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CVRx, Cytokinetics,  
333 Edwards, Element Science, Innolife, Impulse Dynamics, Imbria, Inventiva, Lexicon, Lilly,  
334 LivaNova, Janssen, Medtronics, Merck, Occlutech, Novartis, Novo Nordisk, Pfizer,  
335 Pharmacosmos, Pharmain, Roche, Sequana, SQ Innovation, and Vifor; Dr Ferreira has  
336 received research support from Boehringer-Ingelheim, Novartis, and AstraZeneca through his  
337 institution the University of Porto; Drs. González Maldonado, Panova-Noeva, and Sumin are  
338 employees of Boehringer-Ingelheim; Dr. Masson is an employee of Roche diagnostics; Dr.  
339 Pocock is a consultant with Boehringer Ingelheim; Dr. Anker reports Grants and personal fees  
340 from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work  
341 and/or lectures from Actimed, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim,  
342 Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards,  
343 Farraday Pharmaceuticals, GSK, HeartKinetics, Impulse Dynamics, Novartis, Occlutech,  
344 Pfizer, Repairon, Sensible Medical, Servier, Vectorious, and V-Wave. Named co-inventor of  
345 two patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367),  
346 but he does not benefit personally from the related issued patents; Dr. Zannad reports  
347 personal fees from 89bio, Applied Therapeutics, Bayer, Biopeutics, Boehringer, BMS, CVRx,  
348 Cardior, Cambrian, Cereno pharmaceutical, Cellprothera, CEVA, Merck, Novartis,  
349 NovoNordisk, Otsuka, Owkin, Servier, having stock options at G3Pharmaceutical and  
350 equities at Cereno pharmaceutical, Cardiorenal, Eshmoun Clinical research and being the  
351 founder of Cardiovascular Clinical Trialists (CVCT).; Dr. Januzzi is a Trustee of the  
352 American College of Cardiology, has received grant support from Abbott, Applied  
353 Therapeutics, HeartFlow Inc, Innolife and Roche Diagnostics, consulting income from  
354 Abbott, AstraZeneca, Bayer, Beckman, Boehringer-Ingelheim, Janssen, Novartis, Merck, and  
355 Roche Diagnostics, and participates in clinical endpoint committees/data safety monitoring  
356 boards for Abbott, AbbVie, Bayer, CVRx, Intercept, Pfizer and Takeda. The rest of the  
357 authors report no disclosures.

358

359

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474 **Figure legends**

475 **Figure 1:** Study flowchart

476 **Figure 2:** Cox regression and negative binomial regression results by tertile of IGFBP7 at  
477 baseline. Multivariable models adjusted for age, sex, baseline eGFR, baseline LVEF, log  
478 (NT-proBNP), log (HS Troponin T), region, diabetes, treatment arm (empagliflozin vs.  
479 placebo), study (EMPEROR-Reduced vs. EMPEROR-Preserved). Results for total HHF are  
480 reported as adjusted rate ratios from a negative binomial model with the addition of log(days  
481 at risk) as an offset. Abbreviations: CV: cardiovascular, HF: heart failure, ESRD: end-stage  
482 renal disease, HHF: hospitalization for heart failure, IGFBP7: insulin growth factor binding  
483 protein 7.

484 **Figure 3:** Cumulative incidence function of HF hospitalization/CV death according to  
485 IGFBP7 Tertile group. T denotes: tertile.

486 **Figure 4:** IGFBP7 concentration across study visits stratified by treatment arm

487 **Table 1.** Baseline characteristics of study population stratified by tertile of IGFBP7  
 488 concentration.

	<b>Tertile 1 N=375</b>	<b>Tertile 2 N=375</b>	<b>Tertile 3 N=375</b>
<b>Age, year</b>	67.1 (10.2)	71.2 (9.1)	71.7 (10.1)
<b>Sex</b>			
Male	239 (63.7)	262 (69.9)	263 (70.1)
Female	136 (36.3)	113 (30.1)	112 (29.9)
<b>Race</b>			
White	310 (82.7)	318 (84.8)	320 (85.3)
Black	9 (2.4)	9 (2.4)	7 (1.9)
Asian	28 (7.5)	35 (9.3)	33 (8.8)
Other	24 (6.4)	10 (2.7)	11 (2.9)
<b>Ethnicity</b>			
Not Hispanic / Latino	285 (76.0)	296 (78.9)	273 (72.8)
Hispanic / Latino	75 (20.0)	68 (18.1)	95 (25.3)
<b>Region</b>			
North America	46 (12.3)	39 (10.4)	71 (18.9)
Latin America	72 (19.2)	62 (16.5)	83 (22.1)
Europe	221 (58.9)	233 (62.1)	178 (47.5)
Asia	25 (6.7)	30 (8.0)	31 (8.3)
Other	11 (2.9)	11 (2.9)	12 (3.2)
<b>Smoking status</b>			
Never smoked	167 (44.5)	165 (44.0)	166 (44.3)
Ex-smoker	154 (41.1)	168 (44.8)	179 (47.7)
Currently smokes	43 (11.5)	33 (8.8)	26 (6.9)
<b>Drinking alcohol</b>			
Does not drink alcohol	218 (58.1)	228 (60.8)	223 (59.5)
Drinks alcohol	143 (38.1)	137 (36.5)	144 (38.4)
<b>Changes in NYHA during 3m</b>			
Improved	49 (13.1)	43 (11.5)	43 (11.5)
No change	310 (82.7)	314 (83.7)	295 (78.7)
Unstable	2 (0.5)	0	6 (1.6)
Worsened	14 (3.7)	18 (4.8)	31 (8.3)
<b>Time since HF diagnosis, y</b>	4.6 (5.2)	4.8 (5.2)	5.5 (5.9)
<b>HF hospitalization within 1 year</b>	108 (28.8)	92 (24.5)	108 (28.8)
<b>Diabetes status</b>			
Diabetic	164 (43.7)	182 (48.5)	195 (52.0)
Non-diabetic	211 (56.3)	193 (51.5)	180 (48.0)
<b>LVEF, %</b>	39.5 (14.8)	40.7 (14.8)	40.2 (15.4)
<b>LVEF</b>			
<50 %	263 (70.1)	252 (67.2)	257 (68.5)
50 to <60%	53 (14.1)	65 (17.3)	62 (16.5)
≥ 60%	59 (15.7)	58 (15.5)	56 (14.9)
<b>SBP, mmHg</b>	128.2 (16.2)	128.2 (15.8)	127.3 (15.4)
<b>DBP, mmHg</b>	75.0 (10.7)	74.6 (10.6)	74.4 (10.4)
<b>Heart rate, bpm</b>	69.5 (11.8)	71.2 (12.3)	70.7 (11.3)
<b>BMI, kg/m<sup>2</sup></b>	29.35 (5.47)	29.06 (5.73)	29.60 (5.77)
<b>eGFR, mL/min/1.73 m<sup>2</sup></b>	70.9 (18.7)	60.1 (18.8)	50.3 (18.4)

<b>Albumin/Cr ratio*</b> , mg/g	10.61 (5.30-30.00)	15.03 (7.07-48.62)	35.18 (9.72-131.00)
Atrial fibrillation/flutter	129 (34.4)	189 (50.4)	231 (61.6)
Atrial fibrillation	122 (32.5)	180 (48.0)	226 (60.3)
Hypertension	302 (80.5)	307 (81.9)	323 (86.1)
Hypercholesterolemia	257 (68.5)	252 (67.2)	274 (73.1)
ACS within 6 months	19 (5.1)	22 (5.9)	18 (4.8)
MI	146 (38.9)	130 (34.7)	140 (37.3)
CAD	152 (40.5)	150 (40.0)	159 (42.4)
CABG or PCI	146 (38.9)	134 (35.7)	151 (40.3)
Valvular heart disease	57 (15.2)	53 (14.1)	73 (19.5)
Invasive EP procedure	37 (9.9)	26 (6.9)	33 (8.8)
Left Bundle Branch Block	49 (13.1)	45 (12.0)	38 (10.1)
Cardiac Biomarker			
NT-proBNP, pg/mL	1048 (582-1746)	1268 (725-2239)	1968 (1050-3410)
hs-cTnT, ng/L	15.50 (10.80-22.40)	17.80 (12.50-27.35)	25.95 (17.50-37.50)

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489 Abbreviations: ACS: acute coronary syndrome, BMI: body mass index, CABG: coronary  
490 artery bypass graft, CAD: coronary artery disease, DBP: diastolic blood pressure, eGFR:  
491 estimated glomerular filtration rate, EP electrophysiology, HF: heart failure, hs-cTnT: high  
492 sensitive cardiac troponin T, LVEF: left ventricular ejection fraction, MI: myocardial  
493 infarction, NYHA: New York heart association, NT-proBNP: N terminal pro b type  
494 natriuretic peptides, PCI: percutaneous coronary intervention, SBP: systolic blood pressure.

**Table 2:** Effect of empagliflozin on endpoints in the EMPEROR Trials as a function of baseline IGFBP7. In most cases, no interaction by baseline IGFBP7 was detected, however effect of empagliflozin to improve time to first HF hospitalization may have been attenuated among those in the lowest IGFBP7 tertile.

	<b>Placebo incidence rate (Events per 100 patient years; 95% CI)</b>	<b>Empagliflozin 10 mg incidence rate (Events per 100 patient years; 95% CI)</b>	<b>Hazard ratio (95% CI)</b>	<b>Interaction trend p-value</b>
<b>CV death/HF hospitalization</b>				
Tertile 1	5.67 (3.36-8.57)	6.65 (4.06-9.87)	1.15 (0.61-2.19)	0.26
Tertile 2	8.81 (5.76-12.51)	5.16 (3.00-7.88)	0.58 (0.31-1.08)	
Tertile 3	19.51 (14.62-25.10)	14.67 (10.58-19.43)	0.69 (0.45-1.04)	
<b>First HF hospitalization</b>				
Tertile 1	2.52 (1.09-4.54)	4.99 (2.79-7.81)	1.95 (0.83-4.62)	0.07
Tertile 2	6.10 (3.62-9.23)	3.64 (1.88-5.97)	0.57 (0.27-1.19)	
Tertile 3	15.09 (10.83-20.05)	11.53 (7.94-15.78)	0.68 (0.42-1.08)	
<b>CV death</b>				
Tertile 1	3.73 (1.93-6.12)	2.86 (1.31-5.00)	0.77 (0.32-1.83)	0.76
Tertile 2	4.16 (2.21-6.70)	2.04 (0.82-3.81)	0.55 (0.22-1.38)	
Tertile 3	7.06 (4.43-10.31)	6.09 (3.67-9.12)	0.84 (0.45-1.56)	
<b>Total HF hospitalizations*</b>				
Tertile 1	3.73	7.03	1.78 (0.75, 4.22)	0.17
Tertile 2	8.95	5.57	0.68 (0.31, 1.50)	
Tertile 3	24.16	18.62	0.80 (0.43, 1.47)	
<b>First intensification of diuretic</b>				
Tertile 1	8.76 (5.72-12.44)	7.50 (4.70-10.94)	0.79 (0.44-1.40)	0.51
Tertile 2	12.38 (8.58-16.88)	7.96 (5.15-11.37)	0.63 (0.38-1.06)	
Tertile 3	18.32 (13.55-23.79)	12.46 (8.68-16.92)	0.61 (0.39-0.95)	

CV denotes: cardiovascular; HF denotes: heart failure; CI denotes: confidence intervals; hazard ratios based on Cox regression models and \*adjusted event rate ratio based on negative binomial regression with terms for age, baseline eGFR (CKD-EPI), baseline LVEF, region, diabetes at baseline, sex, study, treatment assignment, tertiles of IGFBP7 at baseline and treatment by tertiles of IGFBP7 at baseline interaction.

Additionally, the negative binomial regression model included log(days at risk) as an offset. Too few events were present to analyze sustained eGFR reduction  $\geq 40\%$  or ESRD in this analysis.

**Table 3:** Adjusted eGFR change slope from baseline by tertiles of IGFBP7 at baseline in A) all study participants and B) by treatment assignment.

**A)**

	$\beta$	95 % CI	p-value
Lowest tertile slope* [/year]	-1.771	(-2.545 - -0.997)	<0.001
Middle tertile slope* [/year]	-1.044	(-1.784 - -0.303)	0.006
Highest tertile slope* [/year]	-2.179	(-2.977 - -1.382)	<0.001
Middle vs Low	0.727	(-0.346 - 1.800)	0.18
High vs Low	-0.409	(-1.567 - 0.750)	0.49

**B)**

Category	Placebo slope (/year)	Empagliflozin 10 mg slope (/year)	Treatment by time interaction p-value	Subgroup interaction trend p-value
Tertile 1	-2.551 (-3.590 - -1.512)	-1.609 (-2.672 - -0.545)	0.21	0.93
Tertile 2	-2.462 (03.514 - -1.411)	-0.036 (-1.037 - 0.966)	0.001	
Tertile 3	-2.152 (-3.233 - -1.070)	-1.312 (-2.374 - -0.250)	0.28	

Model includes baseline eGFR (CKD-EPI), age, baseline LVEF, log (NT-proBNP) [pg/mL] at baseline, log (hs-cTnT) [ng/L] at baseline as linear covariate(s) and region, diabetes at baseline, sex, treatment, study, baseline eGFR (CKD-EPI) by Time interaction, Time by tertiles of IGFBP7 at baseline interaction, tertiles of IGFBP7 at baseline as fixed effect(s). Intercept and slope allowed to vary randomly between patients.

\* Slope measured at baseline eGFR (CKD-EPI) = 60.45.

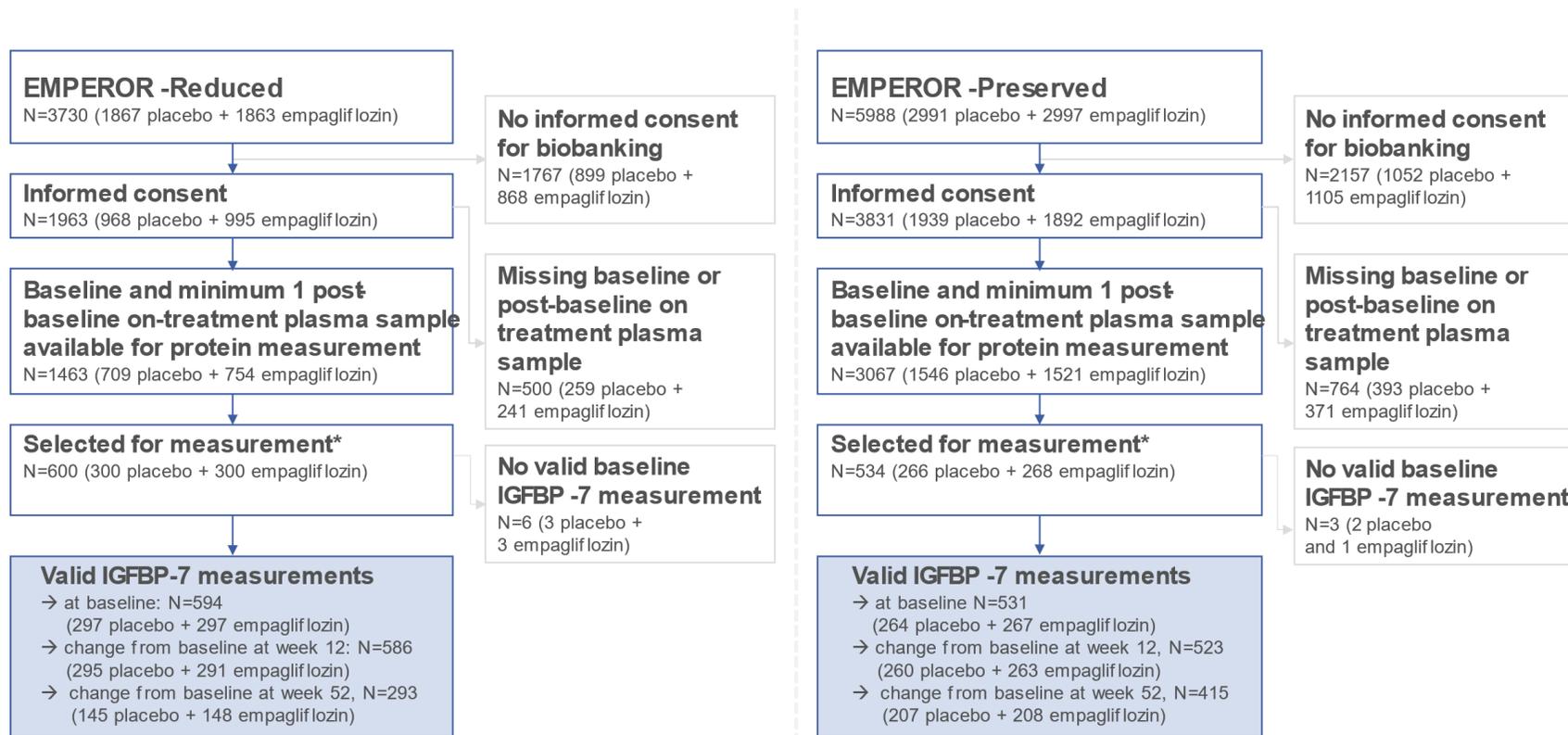
**Table 4:** IGFBP7 concentration (ng/mL) among placebo and empagliflozin arms across study visits

<b>Statistic</b>	<b>Placebo</b>	<b>Empagliflozin 10mg</b>
<b>Baseline</b>		
Values at visit		
Number of patients	558	561
gMean (gCV [%])	133.7 (37.3)	135.2 (38.2)
<b>Week 12</b>		
Values at visit		
Number of patients	555	554
gMean (gCV [%])	137.2 (37.5)	134.5 (37.5)
Adjusted* gMean	137.5	133.1
95% confidence interval	(134.4, 140.6)	(130.2, 136.2)
Relative change from baseline		
gMean ratio (gCV [%])	1.02 (32.81)	0.99 (29.54)
Adjusted* gMean ratio	1.03	0.99
95% confidence interval	(1.00, 1.05)	(0.97, 1.02)
Comparison vs Placebo (ratio of relative change)		
Adjusted* gMean ratio	referent	0.97
95% confidence interval	---	(0.94, 1.00)
p-value	---	0.05
<b>Week 52</b>		
Values at visit		
Number of patients	352	356
gMean (gCV [%])	135.2 (37.4)	138.0 (36.7)
Adjusted* gMean	136.6	139.3
95% confidence interval	(132.6, 140.7)	(135.3, 143.5)
Relative change from baseline		
gMean ratio (gCV [%])	1.01 (33.6)	1.04 (34.6)
Adjusted* gMean ratio	1.02	1.04
95% confidence interval	(0.99, 1.05)	(1.01, 1.07)
Comparison vs Placebo (ratio of relative change)		
Adjusted* gMean ratio	referent	1.02
95% confidence interval	---	(0.98, 1.06)
p-value	---	0.35

\* Model includes age, baseline eGFR (CKD-EPI), baseline LVEF as linear covariates and study, region, baseline diabetes status, sex, treatment by visit interaction, log(baseline IGFBP7) by visit interaction as fixed effects.

Figure 1:

## Sampling for biobanking and IGFBP -7 measurements



\*Random sampling stratified by treatment and availability of data, originally selected for OLINK measurement, same patients used for IGFBP -7 measurement.

Figure 2:

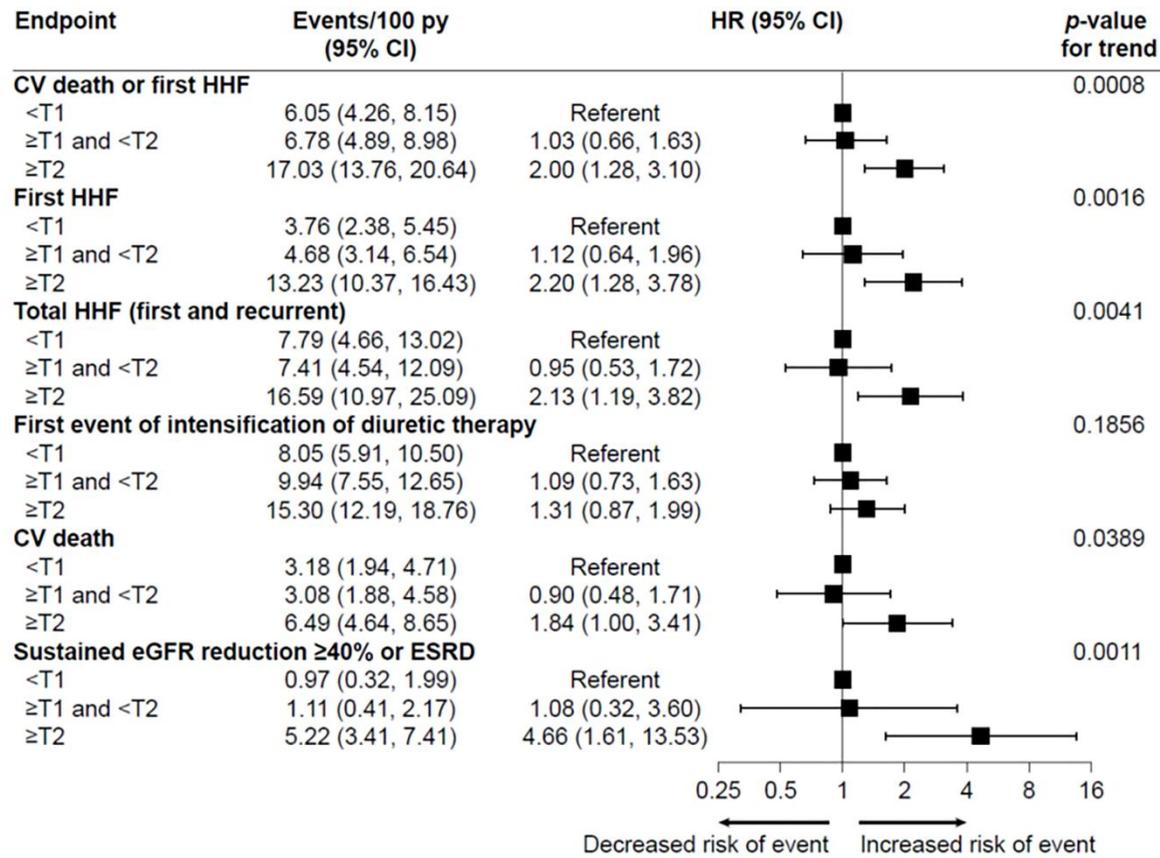
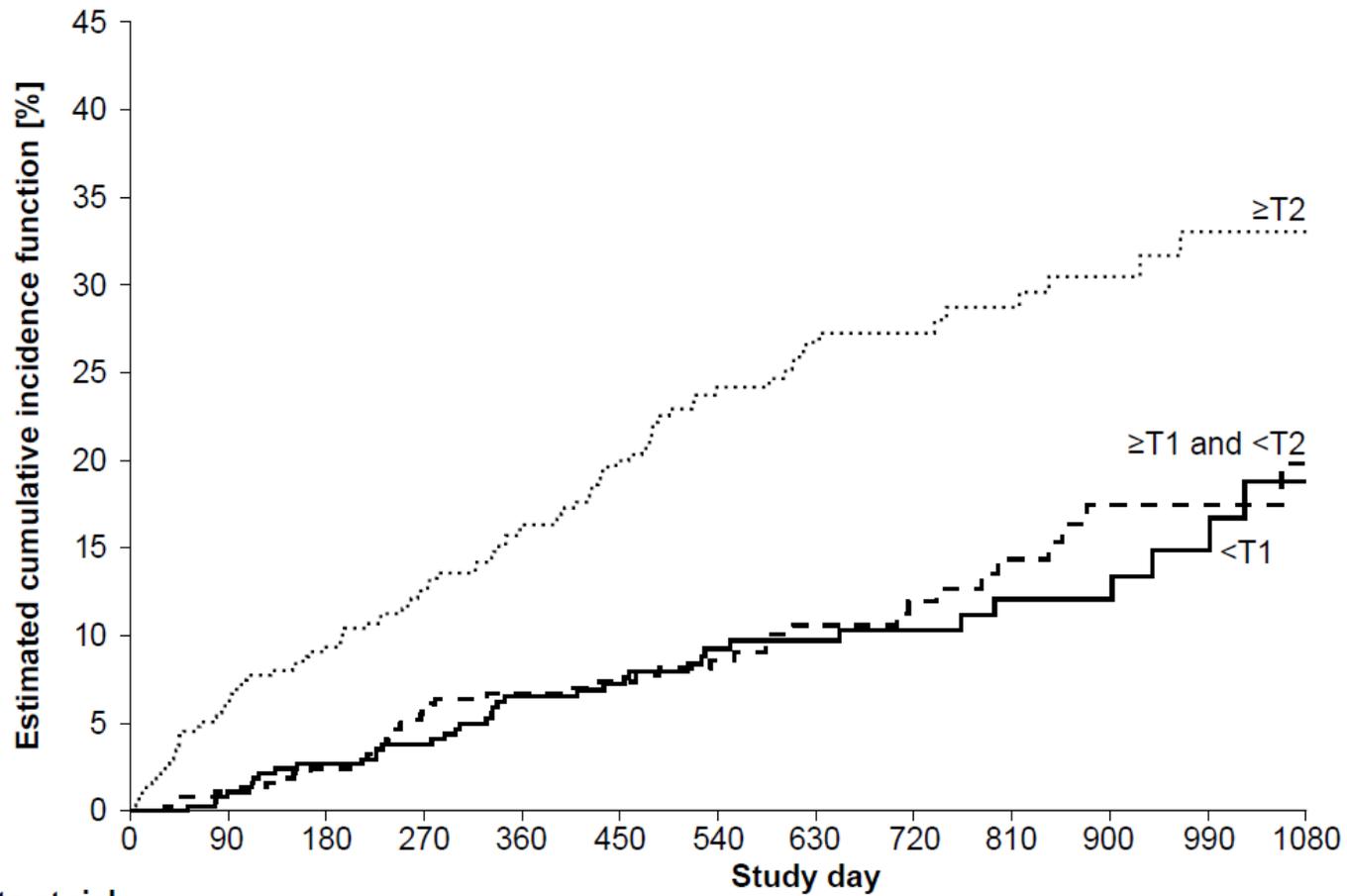


Figure 3:



**Patients at risk**

<math>< T1</math>	375	371	364	331	287	253	194	160	113	95	66	46	27
<math>\ge T1</math> and <math>< T2</math>	375	371	364	320	292	255	199	155	121	95	69	51	33
<math>\ge T2</math>	375	352	338	297	263	221	163	128	97	79	56	42	20

Figure 4:

