

**IGFBP7 Concentrations in Chronic Heart Failure:  
Results from the EMPEROR Program**

	Page
Table of content	
<b>Supplemental Figure 1.</b> Cox regression for time to first event of HHF or CV death by IGFBP-7 at baseline (continuous spline)	2-3
<b>Supplemental Table 1.</b> Cox and negative binomial regression results by thirds of IGFBP-7 levels at baseline among individuals with HFrEF	4
<b>Supplemental Table 2.</b> Cox and negative binomial regression results by thirds of IGFBP-7 levels at baseline among individuals with HFpEF	5
<b>Supplemental Table 3.</b> Top 30 correlations with IGFBP7. Source of data indicated for each.	6

**Supplemental Figure 1.** Cox regression for time to first event of HHF or CV death by IGFBP-7 at baseline (continuous spline) A) pooled data, B) rEF, C) pEF

A)

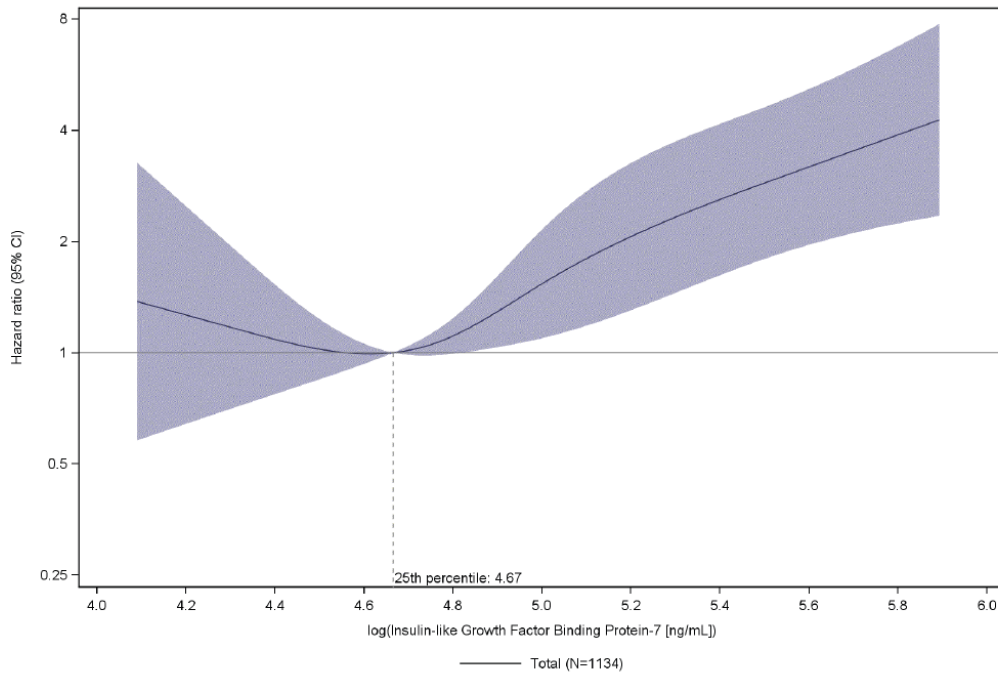


Figure 14.3.1.4 Cox regr. for time to first event of adjudicated HHF or CV death by IGFBP-7 at baseline (cont - spline) - BM-B.121 and .110 pooled  
Knot 1: 5th percentile: 4.32, knot 2: 35th percentile: 4.76, knot 3: 65th percentile: 5.00, knot 4: 95th percentile: 5.56

B)

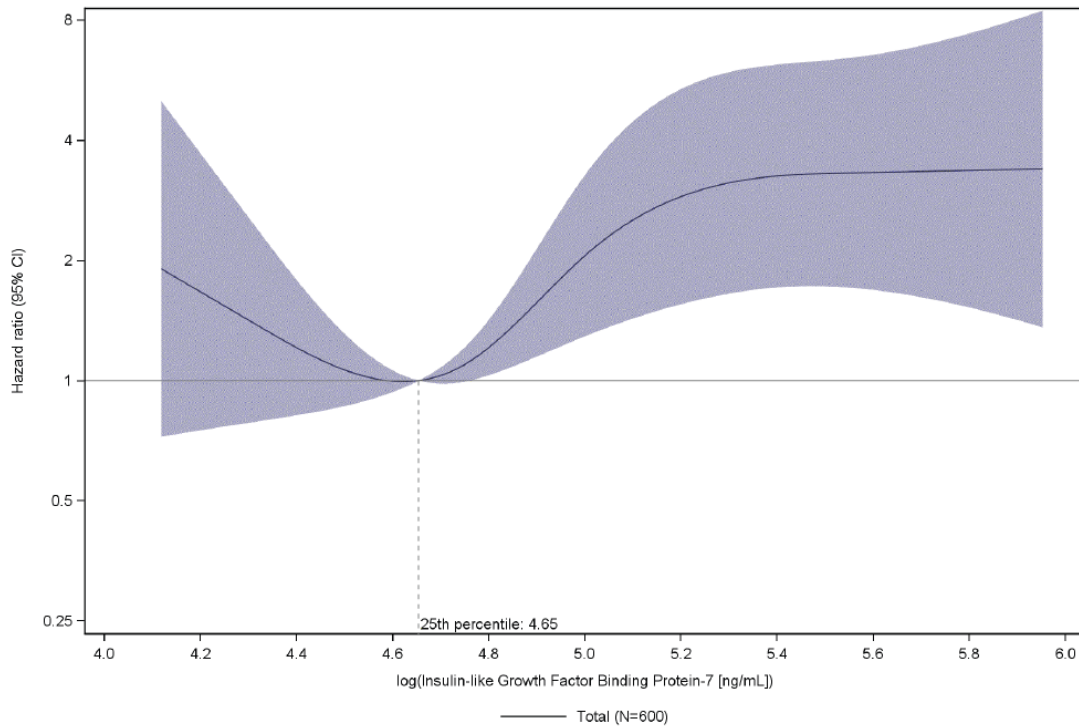


Figure 14.1.1.4 Cox regr. for time to first event of adjudicated HHF or CV death by IGFBP-7 at baseline (cont - spline) - BM-B.121  
Knot 1: 5th percentile: 4.31, knot 2: 35th percentile: 4.75, knot 3: 65th percentile: 5.01, knot 4: 95th percentile: 5.56

C)

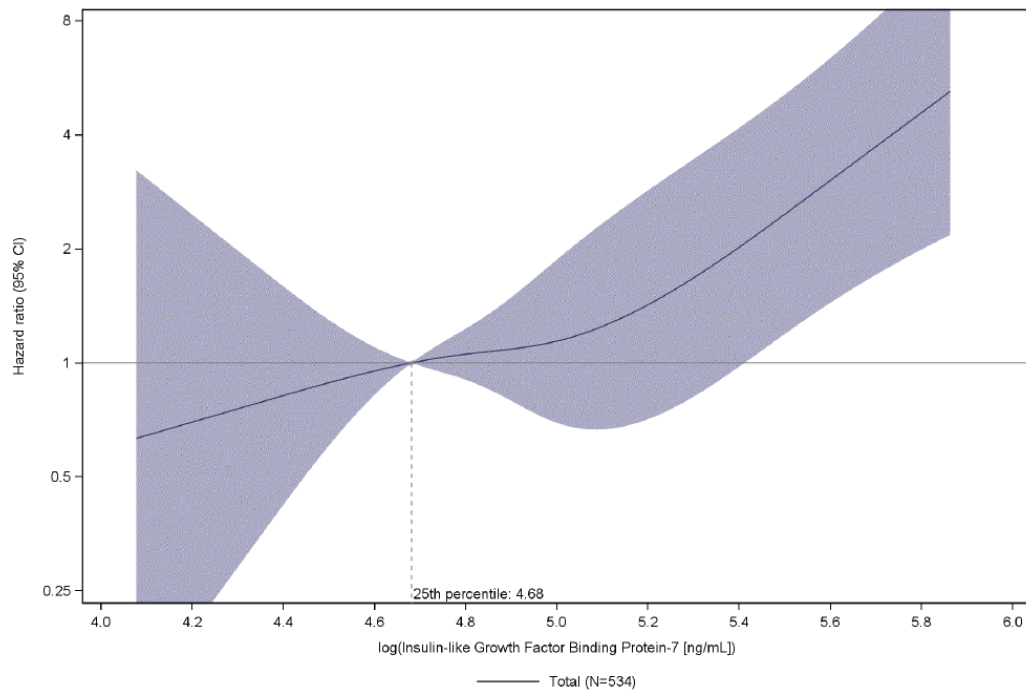


Figure 14.2.1.4 Cox regr. for time to first event of adjudicated HHF or CV death by IGFBP-7 at baseline (cont - spline) - BM-B.110  
Knot 1: 5th percentile: 4.36, knot 2: 35th percentile: 4.78, knot 3: 65th percentile: 5.00, knot 4: 95th percentile: 5.56

**Supplemental Table 1.** Cox and negative binomial regression results by thirds of IGFBP-7 levels at baseline among individuals with HFrEF

	<b>Tertile 1 N=198</b>	<b>Tertile 2 N=198</b>	<b>Tertile 3 N=198</b>
<b>HHF or CV death</b>			
Incidence rate [patients with events per 100 patient-years at risk] (95% CI)	8.16 (4.98-12.10)	10.14 (6.50-14.58)	25.83 (19.51-33.02)
Hazard ratio* (95% CI)	Referent	1.29 (0.69-2.38)	2.60 (1.41-4.79)
p-value	--	0.43	0.002
P for trend	--	0.001	--
<b>First event of adjudicated HHF</b>			
Incidence rate [patients with events per 100 patient-years at risk] (95% CI)	6.12 (3.42-9.58)	7.18 (4.18-10.98)	21.21 (15.53-27.77)
Hazard ratio* (95% CI)	Referent	1.20 (0.58-2.46)	2.60 (1.29-5.25)
p-value	--	0.62	0.008
P for trend	--	0.005	--
<b>CV death</b>			
Incidence rate [patients with events per 100 patient-years at risk] (95% CI)	3.50 (1.60-6.14)	4.80 (2.48-7.88)	7.41 (4.46-11.09)
Hazard ratio* (95% CI)	Referent	1.33 (0.53-3.29)	1.79 (0.69-4.65)
p-value	--	0.54	0.23
P for trend	--	0.23	--
<b>Total HHF (first and recurrent)</b>			
Unadjusted event rate [events per 100 patient-years at risk]	9.38	11.20	33.27
Adjusted event rate ratio (95% CI)	Referent	1.01 (0.48-2.14)	2.24 (1.01-4.95)
p-value	--	0.98	0.05
P for trend	--	0.03	--
<b>Sustained eGFR reduction <math>\geq</math>40% or ESRD</b>			
Incidence rate [patients with events per 100 patient-years at risk] (95% CI)	1.46 (0.30-3.52)	1.02 (0.12-2.83)	4.95 (2.37-8.45)
Hazard ratio* (95% CI)	Referent	NA	NA
p-value	--	NA	NA
P for trend	--	NA	--

\*Multivariable model adjusted for age, sex, baseline eGFR, baseline LVEF, log (NT-proBNP), log (hs-cTnT), region, diabetes, treatment arm (empagliflozin vs placebo)

NA: not applicable due to low statistical power.

**Supplemental Table 2.** Cox and negative binomial regression results by thirds of IGFBP-7 levels at baseline among individuals with HFpEF.

	<b>Tertile 1</b> <b>N=177</b>	<b>Tertile 2</b> <b>N=177</b>	<b>Tertile 3</b> <b>N=177</b>
<b>HHF or CV death</b>			
Incidence rate [patients with events per 100 patient-years at risk] (95% CI)	4.51 (2.62-6.89)	4.85 (2.87-7.33)	11.34 (8.02-15.22)
Hazard ratio* (95% CI)	Referent	0.90 (0.46-1.77)	1.58 (0.82-3.04)
p-value	--	0.76	0.17
P for trend	--	0.13	--
<b>First event of adjudicated HHF</b>			
Incidence rate [patients with events per 100 patient-years at risk] (95% CI)	2.39 (1.09-4.18)	2.96 (1.48-4.95)	8.06 (5.31-11.37)
Hazard ratio* (95% CI)	Referent	0.95 (0.39-2.33)	1.60 (0.69-3.75)
p-value	--	0.91	0.27
P for trend	--	0.21	--
<b>CV death</b>			
Incidence rate [patients with events per 100 patient-years at risk] (95% CI)	2.60 (1.25-4.44)	2.33 (1.07-4.08)	5.84 (3.61-8.58)
Hazard ratio* (95% CI)	Referent	0.82 (0.33-2.06)	2.22 (0.94-5.25)
p-value	--	0.68	0.07
P for trend	--	0.05	--
<b>Total HHF (first and recurrent)</b>			
Unadjusted event rate [events per 100 patient-years at risk]	2.87	4.16	12.80
Hazard ratio (95% CI)	Referent	0.96 (0.36-2.57)	2.62 (1.06-6.52)
p-value	--	0.93	0.04
P for trend	--	0.02	--
<b>Sustained eGFR reduction <math>\geq</math>40% or ESRD</b>			
Incidence rate [patients with events per 100 patient-years at risk] (95% CI)	0.62 (0.08-1.73)	1.22 (0.33-2.67)	5.41 (3.09-8.37)
Hazard ratio* (95% CI)	Referent	2.65 (0.46-15.35)	18.50 (3.63-94.27)
p-value	--	0.28	<0.001
P for trend	--	<0.0001	--

\*Multivariable model adjusted for age, sex, baseline eGFR, baseline LVEF, log (NT-proBNP), log (hs-cTnT), region, diabetes, treatment arm (empagliflozin vs placebo).

<b>Supplemental Table 3.</b> Top 30 correlations with IGFBP7. Source of data indicated for each.	<b>Spearman correlation</b>
Immunoassay: Bone Morphogenic Protein-10	0.68
Immunoassay: Fatty Acid Binding Protein-3	0.66
Immunoassay: Growth Differentiation Factor-15	0.64
OLINK: Insulin-like growth factor-binding protein 7	0.57
Immunoassay: Angiopoietin-2	0.54
OLINK: CCN family member 4	0.53
OLINK: Layilin	0.52
OLINK: Follistatin-related protein 3	0.52
OLINK: Phosphoinositide-3-kinase-interacting protein 1	0.51
OLINK: Lysosome membrane protein 2	0.51
OLINK: Insulin-like growth factor-binding protein 4	0.51
OLINK: Tumor necrosis factor receptor superfamily member 1A	0.5
OLINK: Scavenger receptor class F member 2	0.5
OLINK: Junctional adhesion molecule B	0.5
OLINK: Tumor necrosis factor receptor superfamily member 19	0.5
OLINK: UL16-binding protein 2	0.5
OLINK: Collagen alpha-3	0.49
OLINK: Collectin-12	0.49
OLINK: Actin, aortic smooth muscle	0.49
OLINK: Basement membrane-specific heparan sulfate proteoglycan core protein	0.49
OLINK: Tumor necrosis factor receptor superfamily member 27	0.49
OLINK: Metalloproteinase inhibitor 1	0.49
OLINK: C-type lectin domain family 14 member A	0.49
OLINK: Tumor necrosis factor receptor superfamily member 19L	0.49
OLINK: B-cell antigen receptor complex-associated protein beta chain	0.49
OLINK: Ephrin type-A receptor 2	0.49
OLINK: CD302 antigen	0.48
OLINK: Tumor necrosis factor receptor superfamily member 3	0.48
OLINK: Cytoskeleton-associated protein 4	0.48
OLINK: TGF-beta receptor type-2	0.47