

## Supplemental Material

Supplemental Table 1. Simple integer risk model for cardiovascular death or hospitalization for heart failure

Variable	HR (95%CI)	Coef.	Points	p-value
History of CV disease	2.85 (2.43-3.34)	1.05	+3	<0.001
UACR >30 mg/g	2.36 (2.02-2.74)	0.86	+2	<0.001
Age >65 years	1.65 (1.40-1.93)	0.50	+2	<0.001
eGFR <90 ml/min/1.73m <sup>2</sup>	1.38 (1.16-1.63)	0.32	+1	<0.001
HBA1C >8%	1.36 (1.16-1.59)	0.31	+1	<0.001
Waist circumference (high)	1.34 (1.11-1.60)	0.29	+1	0.002
Men	1.19 (1.01-1.41)	0.17	+1	0.049

Legend: CV, cardiovascular disease including prior hospitalization for heart failure; High waist circumference, >88 cm for women and >102 cm for men; BP, blood pressure; HBA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

Model adjusted on the randomized treatment (intensive vs. standard glucose lowering treatment).

Model C-index for cardiovascular death or hospitalization for heart failure =0.73.

Model C-index for cardiovascular death =0.72.

Total integer score =11 points (n =10251). Risk tertiles: ≤3 points =low risk (n =3453); 4-6 points =medium risk (n =4217); 7-11 points =high risk (n =2581).

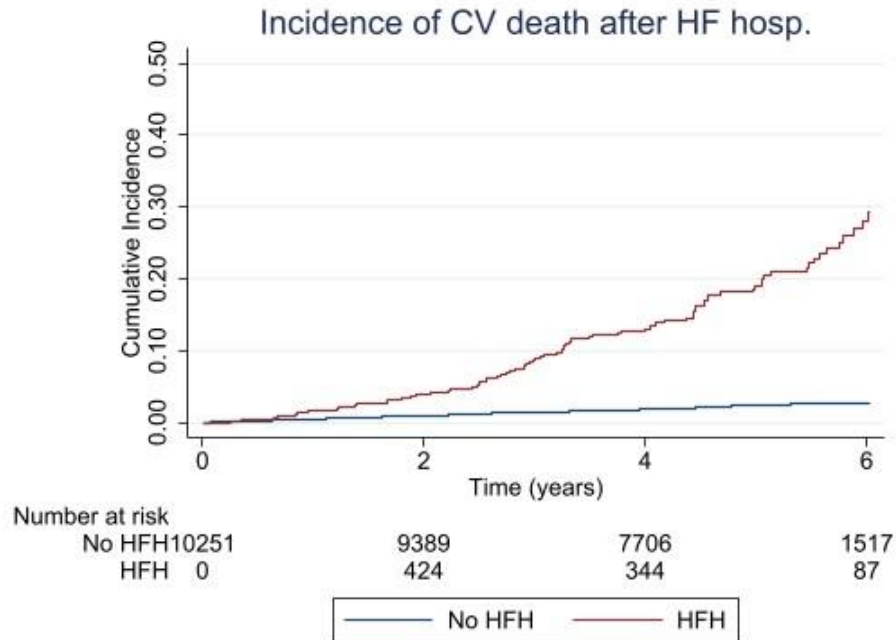
Supplemental Table 2. Associations between “sustained” WKF and subsequent cardiovascular mortality

WKF	CV death			
	Event (n =331)	No Event (n =9917)	Adjusted HR (95%CI)*	P-value*
>30% eGFR drop	141 (42.6%)	4198 (42.3%)	1.46 (0.94-2.25)	0.085
>40% eGFR drop	88 (26.6%)	2280 (23.0%)	1.96 (1.18-3.24)	0.009
>50% eGFR drop	44 (13.3%)	1047 (10.6%)	2.67 (1.42-5.02)	0.002

Legend: CV, cardiovascular; WKF, worsening kidney function; eGFR, estimated glomerular filtration rate.

“Sustained” WKF was defined by an eGFR drop >30%, 40% or 50% in at least 2 consecutive visits separated by a minimum of 3 months.

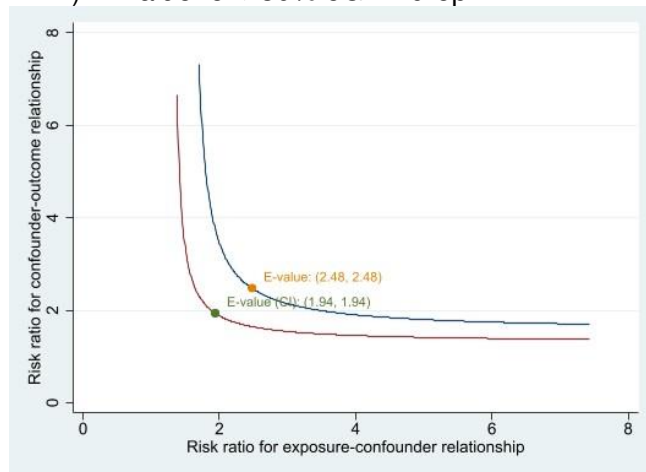
Supplemental Figure 1. Incidence of cardiovascular death after a hospitalization for heart failure



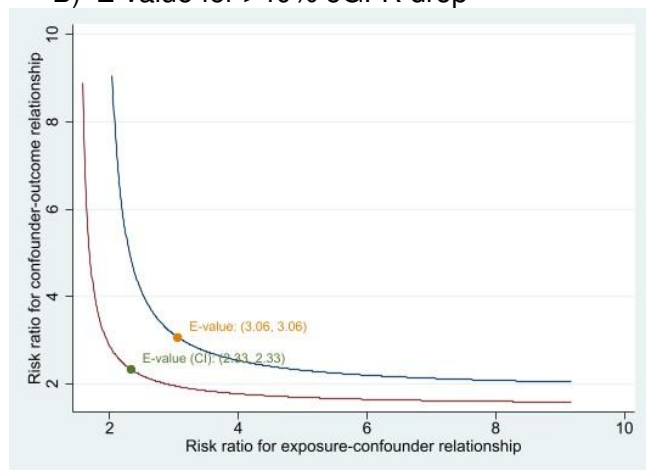
Legend: CV, cardiovascular; HF, heart failure; HFH, heart failure hospitalization. Adjusted HR (95%CI) for the composite of cardiovascular death or heart failure hospitalization after a HHH = 5.17 (3.91-6.83),  $p < 0.001$  (see also the Table 2).

Supplemental Figure 2. E-value analysis to assess the robustness of the associations of an eGFR drop of 30%, 40% and 50% with the outcome of cardiovascular death

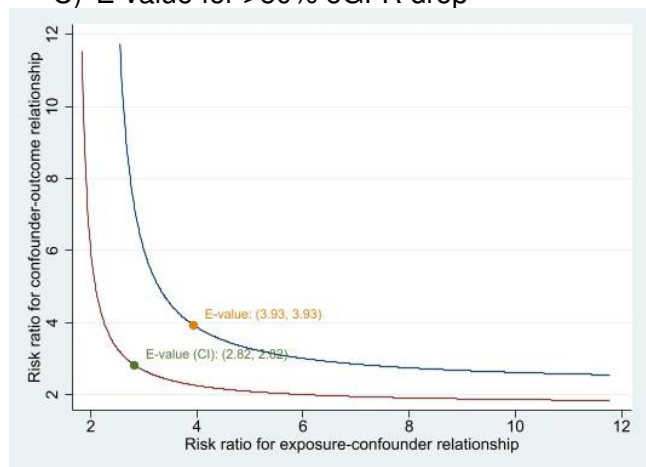
A) E-value for >30% eGFR drop



B) E-value for >40% eGFR drop

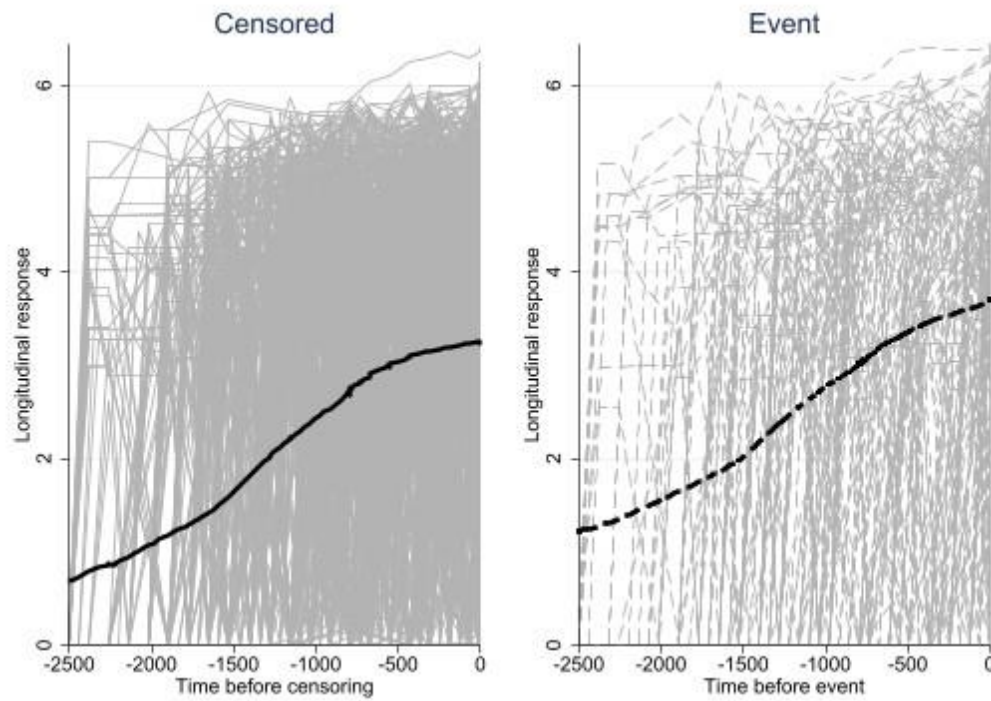


C) E-value for >50% eGFR drop



Legend: An eGFR >30% has an E-value of 2.48 which is very close to the hazard ratio observed for urinary albumin-to-creatinine (HR =2.36) ratio and history of cardiovascular disease (HR =2.85), meaning that another (or multiple) covariate(s) with such association(s) could offset the association of an eGFR >30% back to null (HR =1). The E-values for eGFR >40% and >50% are greater than 3, suggesting that it would be unlikely for a covariate to offset these associations back to the null.

Supplemental Figure 3. Joint model for eGFR change throughout the follow-up in patients with and without a cardiovascular death or hospitalization for heart failure composite event



Legend: Event, cardiovascular death or hospitalization for heart failure; eGFR, estimated glomerular filtration rate (log transformed).

Joint-model association of continuous log eGFR change with the composite of cardiovascular death or hospitalization for heart failure: Coef. (95%CI) =0.46 (0.39-0.52),  $p < 0.001$ .

Joint-model association of >40% eGFR drop with the composite of cardiovascular death or hospitalization for heart failure: Coef. (95%CI) =1.85 (1.60-2.11),  $p < 0.001$ .