Semiquantitative urine dipstick protein assessments predict clinical outcomes in patients with heart failure and reduced ejection fraction: Insights from the GALACTIC-HF trial

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BACKGROUND

- The level of urinary protein excretion is an established predictor of kidney and cardiovascular outcomes, but formal laboratory quantification is rarely performed.

- In contrast, dipstick urine testing is often performed, although the results may not be routinely inspected or acted upon.

- We have examined the prognostic value of semiquantitative urine dipstick proteinuria (DP) in patients with heart failure (HF) and reduced ejection fraction (HFrEF).

HYPOTHESIS

- DP predicts clinical outcomes and enables risk stratification in HFrEF.

METHODS

GALACTIC-HF

(Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure)

Key inclusion criteria

- LVEF≤35%
- NYHA functional class II-IV
- Elevated natriuretic peptide level
- Inpatient or outpatient with urgent visit or hospitalization for HF within 1 year

Primary outcome

- Composite of time to a first HF event or cardiovascular death
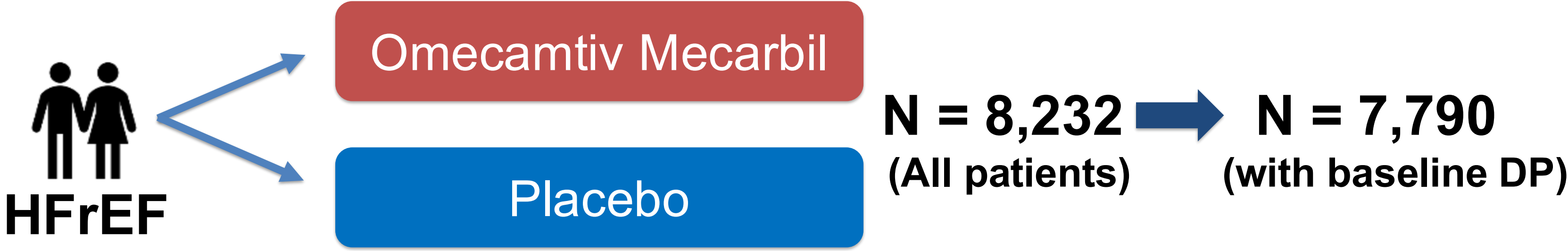
Secondary outcomes

- HF event, cardiovascular death, and all-cause death

Urine dipstick proteinuria (DP) measurements

- Measured in a central laboratory at randomization
- Categorical results: negative, trace, 1+, 2+, 3+, and 4+
  In this study, stratified into three categories:
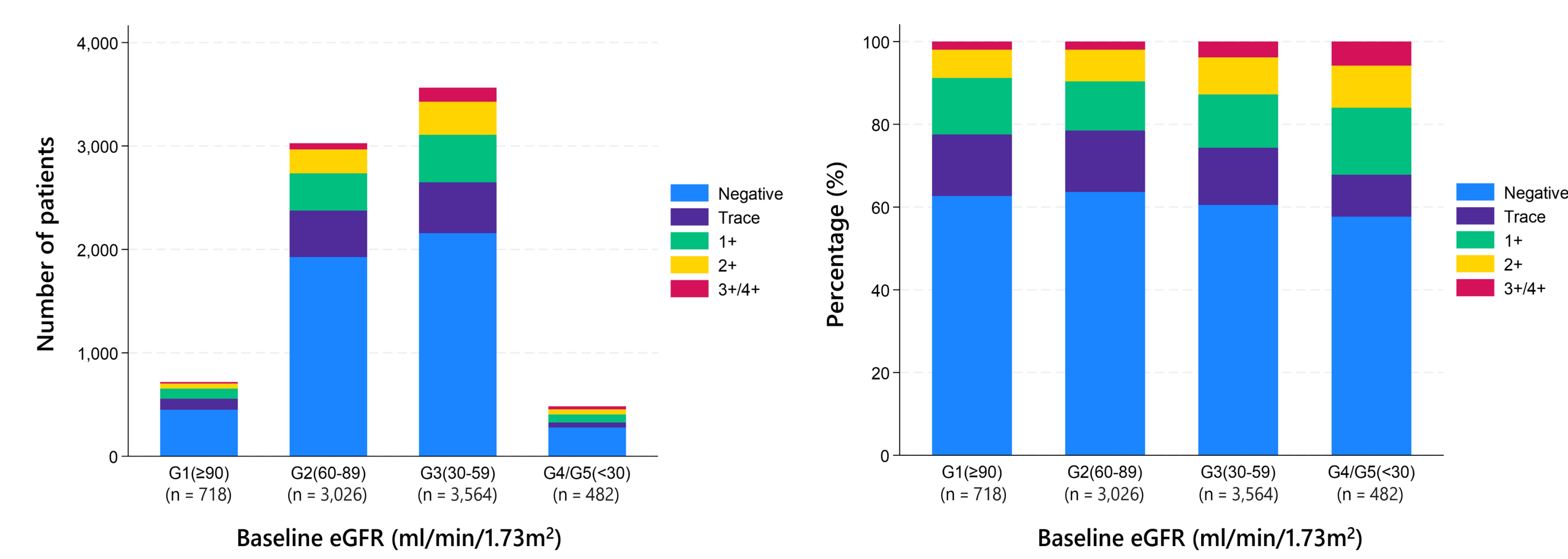 **Negative/Trace, 1+, and ≥2+**

HFrEF → Omecamtiv Mecarbil / Placebo
N = 8,232 (All patients) → N = 7,790 (with baseline DP)

RESULTS

Table 1. Patient characteristics according to urine DP category

	Negative/Trace (n = 5,910)	1+ (n = 995)	≥2+ (n = 885)	P for trend
Age (years)	65 ± 11	65 ± 12	62 ± 11	<0.001
Male -no(%)	4,635 (78.4)	799 (80.3)	717 (81.0)	0.041
NYHA classification III/IV -no(%)	2,683 (45)	502 (50)	466 (53)	<0.001
Inpatient	1,482 (25.1)	247 (24.8)	193 (21.8)	0.056
Body mass index (kg/m²)	28 ± 6	29 ± 7	30 ± 7	<0.001
Heart Rate (beats/min)	72 ± 12	74 ± 12	75 ± 12	<0.001
Systolic Blood Pressure (mmHg)	115 ± 15	118 ± 16	123 ± 16	<0.001
Left ventricular ejection fraction (%)	27 ± 6	27 ± 7	27 ± 6	0.002
NT-proBNP (pg/mL)	1,763 (898-3,475)	2,558 (1,310-5,284)	3,390 (1,667-6,719)	<0.001
Troponin-I (ng/L)	24 (12-48)	30 (17-59)	36 (20-67)	<0.001
Serum creatinine (µmol/L)	103 (86-129)	108 (88-140)	115 (94-145)	<0.001
eGFR (mL/min/1.73m²)	60 (46-75)	58 (42-74)	54 (41-69)	<0.001
Type 2 diabetes mellitus	2,169 (37)	459 (46)	512 (58)	<0.001
Hypertension	4,027 (68)	742 (75)	703 (79)	<0.001
Myocardial infarction	2,468 (42)	445 (45)	346 (39)	0.50
Atrial fibrillation or flutter	1,552 (26)	318 (32)	251 (28)	0.011
ACEi, ARB, or ARNI	5,165 (87)	853 (86)	771 (87)	0.46
Beta-blocker	5,572 (94)	936 (94)	849 (96)	0.097
SGLT2 inhibitor	162 (3)	29 (3)	17 (2)	0.26
MRAs	4,694 (79)	746 (75)	632 (71)	<0.001
Diuretics	5,283 (89)	900 (91)	798 (90)	0.32
Cardiac-resynchronization therapy	905 (15)	121 (12)	63 (7)	<0.001
Implantable cardioverter-defibrillator	1,944 (33)	309 (31)	199 (23)	<0.001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and SGLT2, sodium–glucose cotransporter 2. Values are mean ± standard deviation, n (%), or median (interquartile range).

Figure 1. KDIGO classification and urine dipstick protein (DP) category

G1: eGFR is ≥90 mL/min/1.73 m², G2: eGFR is 60-89 mL/min/1.73 m² , G3a: eGFR is 30-59 mL/min/1.73 m², G4/5: eGFR is <30 mL/min/1.73 m²
Abbreviations: eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease, Improving Global Outcomes

Table 2. Clinical outcomes according to baseline urine DP category

	Negative/Trace	1+	≥2+
N(%)	5,910 (75.9)	995 (12.8)	885 (11.4)
HF event or CV death			
Event rate (95% CI)	21.8 (20.8-22.7)	34.8 (31.8-38.0)	38.1 (34.7-41.9)
HR (95% CI)*	Reference	1.54 (1.40-1.71)	1.73 (1.56-1.92)
Adjusted HR (95% CI)**	Reference	1.26 (1.14-1.40)	1.28 (1.14-1.44)
HF event			
Event rate (95% CI)	16.6 (15.8-17.5)	27.2 (24.6-30.2)	29.7 (26.7-33.0)
HR (95% CI)*	Reference	1.57 (1.40-1.77)	1.78 (1.58-2.00)
Adjusted HR (95% CI)**	Reference	1.31 (1.16-1.47)	1.35 (1.18-1.54)
CV death			
Event rate (95% CI)	9.7 (9.1-10.3)	13.3 (11.7-15.1)	15.1 (13.2-17.2)
HR (95% CI)*	Reference	1.37 (1.19-1.58)	1.56 (1.35-1.81)
Adjusted HR (95% CI)**	Reference	1.10 (0.95-1.28)	1.15 (0.98-1.35)
All-cause death			
Event rate (95% CI)	12.8 (12.1-13.5)	17.6 (15.7-19.7)	20.3 (18.1-22.7)
HR (95% CI)*	Reference	1.38 (1.22-1.56)	1.60 (1.41-1.81)
Adjusted HR (95% CI)**	Reference	1.11 (0.97-1.26)	1.17 (1.01-1.34)

Abbreviations: CI, confidence interval; CV, cardiovascular; HF, heart failure; and HR, hazard ratio
Event rate is the number of events per 100 person-years.
* Models were stratified by region and randomization setting (inpatient or outpatient) and adjusted for treatment assignment.
**Models were stratified by region and randomization setting (inpatient or outpatient), and adjusted for treatment assignment, age, sex, race, systolic blood pressure, body mass index, NYHA functional class III/IV, left ventricular ejection fraction, NT-proBNP (log-transformed), hemoglobin, atrial fibrillation/flutter at screening, history of myocardial infarction, diabetes mellitus, serum creatinine, and troponin I.

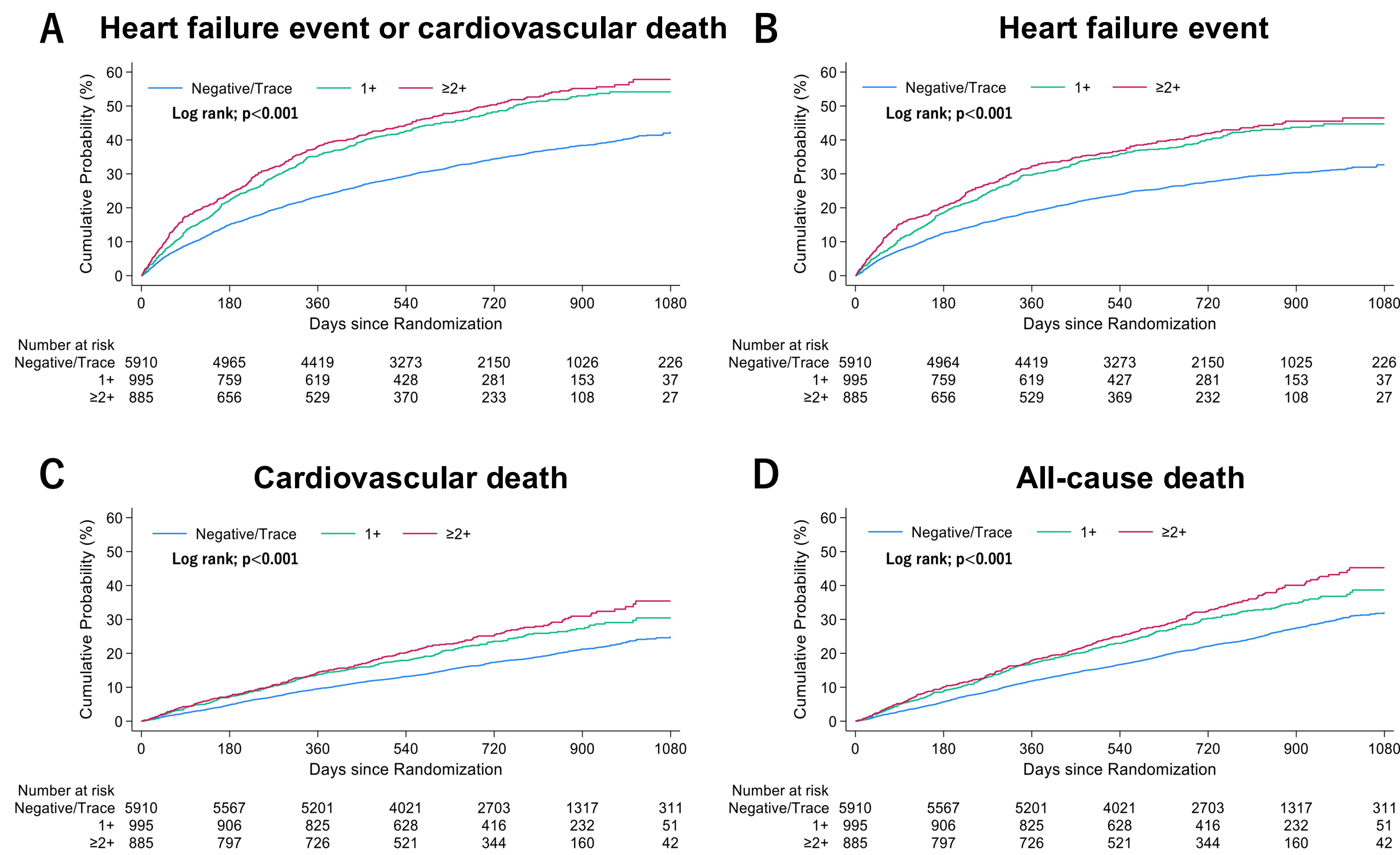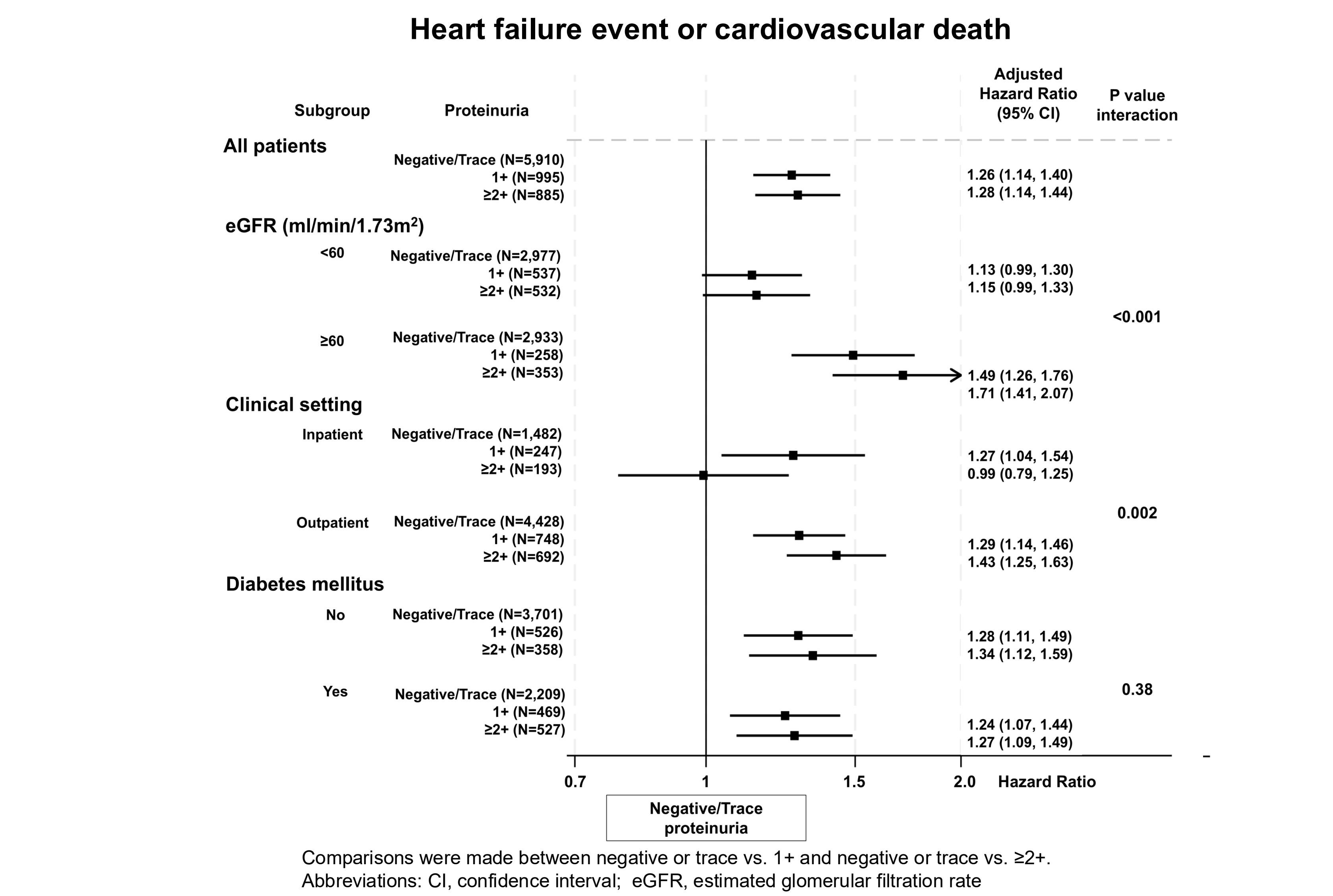### Figure 2. Clinical outcomes according to baseline urine DP category

A. Heart failure event or cardiovascular death
B. Heart failure event
C. Cardiovascular death
D. All-cause death

Figure 3. Primary outcome by urine DP category in key subgroups

Heart failure event or cardiovascular death

Subgroup	Proteinuria	Adjusted Hazard Ratio (95% CI)	P value interaction
All patients	Negative/Trace (N=5,910)		
	1+ (N=995)	1.26 (1.14, 1.40)	
	≥2+ (N=885)	1.28 (1.14, 1.44)	
eGFR (ml/min/1.73m²)			
<60	Negative/Trace (N=2,977)		
	1+ (N=537)	1.13 (0.99, 1.30)	
	≥2+ (N=532)	1.15 (0.99, 1.33)	<0.001
≥60	Negative/Trace (N=2,933)		
	1+ (N=258)	1.49 (1.26, 1.76)	
	≥2+ (N=353)	1.71 (1.41, 2.07)	
Clinical setting			
Inpatient	Negative/Trace (N=1,482)		
	1+ (N=247)	1.27 (1.04, 1.54)	
	≥2+ (N=193)	0.99 (0.79, 1.25)	0.002
Outpatient	Negative/Trace (N=4,428)		
	1+ (N=748)	1.29 (1.14, 1.46)	
	≥2+ (N=692)	1.43 (1.25, 1.63)	
Diabetes mellitus			
No	Negative/Trace (N=3,701)		
	1+ (N=526)	1.28 (1.11, 1.49)	
	≥2+ (N=358)	1.34 (1.12, 1.59)	0.38
Yes	Negative/Trace (N=2,209)		
	1+ (N=469)	1.24 (1.07, 1.44)	
	≥2+ (N=527)	1.27 (1.09, 1.49)	

Comparisons were made between negative or trace vs. 1+ and negative or trace vs. ≥2+.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate

CONCLUSIONS

- In GALACTIC-HF, higher urine DP levels were independently associated with a higher risk of adverse clinical outcomes.

- Urine DP is a simple and inexpensive test with prognostic value in HFrEF.