

Supplementary Online Content

Krim SR, Anand S, Greene SJ, et al. Torsemide vs furosemide among patients with new-onset vs worsening chronic heart failure: a substudy of the TRANSFORM-HF randomized clinical trial. *JAMA Cardiol*. Published online November 13, 2023. doi:10.1001/jamacardio.2023.4776

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Baseline characteristics of study participants (Demographics, Laboratory, and Vital Signs, Heart Failure Characteristics and Medical History) by HF type, for patients with ≤40% EF

	All Patients N=1,835	De novo N=558	WHF N=1,277	P-value
Demographics				
Age, years				<.001
N	1835	558	1277	
Mean (SD)	61.7 (13.8)	57.7 (13.7)	63.5 (13.4)	
Median (25 th , 75 th)	63.0 (53, 72)	58.0 (50, 67)	65.0 (56, 73)	
Female sex	567 (30.9%)	187 (33.5%)	380 (29.8%)	0.11
Race				<.001
American Indian or Alaska Native	10 (0.5%)	3 (0.5%)	7 (0.5%)	
Asian	47 (2.6%)	23 (4.1%)	24 (1.9%)	
Black or African American	667 (36.4%)	163 (29.3%)	504 (39.5%)	
Native Hawaiian or Other Pacific Islander	19 (1.0%)	6 (1.1%)	13 (1.0%)	
White	998 (54.5%)	324 (58.2%)	674 (52.9%)	
Other	67 (3.7%)	31 (5.6%)	36 (2.8%)	
Multiple	24 (1.3%)	7 (1.3%)	17 (1.3%)	
Hispanic or Latino	104 (5.7%)	34 (6.1%)	70 (5.5%)	0.59
Laboratory values				
Sodium, mEq/L				0.58
Mean (SD)	137.5 (3.6)	137.6 (3.5)	137.4 (3.6)	
Potassium, mEq/L				0.07
Mean (SD)	4.05 (0.45)	4.02 (0.44)	4.06 (0.45)	
Blood urea nitrogen, mg/dL				<.001
Mean (SD)	31.3 (37.0)	29.7 (53.6)	32.0 (26.7)	
Creatinine, mg/dL				<.001
Mean (SD)	1.379 (0.596)	1.232 (0.576)	1.443 (0.594)	
Estimated Glomerular filtration rate, mL/min/1.73 m ²				<.001
Mean (SD)	62.6 (24.4)	71.2 (24.1)	58.9 (23.6)	
N-Terminal pro B-type natriuretic peptide, pg/mL				0.004
N	871	264	607	
Median (25 th , 75 th)	4554.0 (2368.0, 9620.0)	4015.5 (2179.0, 8257.5)	4921.0 (2451.0, 10290.0)	
B-type natriuretic peptide (BNP), pg/mL				0.004

	All Patients N=1,835	De novo N=558	WHF N=1,277	P-value
N	860	259	601	
Median (25 th , 75 th)	1265.0 (643.7, 2258.5)	1111.3 (607.0, 1850.0)	1345.0 (665.0, 2384.0)	
Hemoglobin, g/L				<.001
Mean (SD)	12.50 (3.71)	13.06 (2.39)	12.26 (4.14)	
Vital signs				
Systolic blood pressure, mmHg				0.135
Mean (SD)	114.4 (17.9)	115.2 (17.4)	114.0 (18.1)	
Diastolic blood pressure, mmHg				<.001
Mean (SD)	70.6 (13.2)	72.5 (13.0)	69.8 (13.2)	
Heart rate, BPM				<.001
Mean (SD)	82.8 (15.8)	86.3 (15.5)	81.3 (15.6)	
BMI, kg/m ²				0.01
Mean (SD)	31.32 (9.02)	31.97 (8.71)	31.03 (9.14)	
Heart Failure Characteristics				
Duration of diagnosis prior to hospitalization:				
≤ 30 days Duration	78 (6.1%)	0	78 (6.1%)	
> 30 days and ≤ 12 months Duration	229 (17.9%)	0	229 (17.9%)	
> 12 months Duration	864 (67.7%)	0	864 (67.7%)	
Unknown	106 (8.3%)	0	106 (8.3%)	
New York Heart Association class at hospital admission				0.003
I	25 (1.4%)	5 (0.9%)	20 (1.6%)	
II	196 (10.7%)	56 (10.1%)	140 (11.0%)	
III	788 (43.0%)	220 (39.6%)	568 (44.5%)	
IV	289 (15.8%)	78 (14.0%)	211 (16.5%)	
Unknown	533 (29.1%)	197 (35.4%)	336 (26.4%)	
New York Heart Association class at randomization				0.005
I	49 (2.7%)	10 (1.8%)	39 (3.1%)	
II	432 (23.5%)	137 (24.6%)	295 (23.1%)	
III	652 (35.5%)	170 (30.5%)	482 (37.7%)	
IV	155 (8.4%)	47 (8.4%)	108 (8.5%)	
Unknown	547 (29.8%)	194 (34.8%)	353 (27.6%)	
KCCQ Baseline Clinical Summary Score				0.01

	All Patients N=1,835	De novo N=558	WHF N=1,277	P-value
Mean (SD)	44.59 (23.17)	46.85 (23.40)	43.60 (23.01)	
Median (25 th , 75 th)	42.7 (27.1, 60.9)	46.4 (29.7, 64.1)	41.7 (26.0, 60.3)	
Ischemic etiology	586 (31.9%)	118 (21.1%)	468 (36.6%)	<.001
Chronic kidney disease	588 (32.0%)	71 (12.7%)	517 (40.5%)	<.001
Diabetes mellitus	842 (45.9%)	187 (33.5%)	655 (51.3%)	<.001
Hypertension	1424 (77.8%)	373 (67.2%)	1051 (82.4%)	<.001
Atrial fibrillation or atrial flutter	739 (40.6%)	146 (26.4%)	593 (46.8%)	<.001
Chronic lung disease (including COPD)	386 (21.1%)	70 (12.6%)	316 (24.8%)	<.001
Loop diuretics				
Oral loop diuretic <u>prior</u> to index hospital admission (most recent)				<.001
No	658 (35.9%)	462 (82.8%)	196 (15.3%)	
Yes	1177 (64.1%)	96 (17.2%)	1081 (84.7%)	
Total daily dose prescribed (furosemide equivalents), mg				<.001
Mean (SD)	67.4 (62.5)	44.1 (27.3)	69.5 (64.3)	
Specific Loop Diuretic Prior to Index Admission (among those on a loop diuretic)¹				
Furosemide	928 (78.8%)	86 (89.6%)	842 (77.9%)	
Torsemide	163 (13.8%)	6 (6.3%)	157 (14.5%)	
Bumetanide	86 (7.3%)	4 (4.2%)	82 (7.6%)	
Ethacrynic acid	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Discharge				
Prescribed <u>assigned</u> loop diuretic ²	1598 (90.5%)	495 (92.4%)	1103 (89.7%)	0.02
Total daily dose prescribed (furosemide equivalents) ¹ , mg				<.001
Mean (SD)	81.3 (66.5)	67.4 (55.3)	87.6 (70.2)	
Total daily dose prescribed (reported), mg				<.001
Mean (SD)	61.2 (53.3)	52.0 (48.2)	65.4 (54.9)	
Baseline medications taken at the time of randomization				
ACE or ARB	821 (44.7%)	277 (49.6%)	544 (42.6%)	0.005
Angiotensin receptor-neprilysin inhibitor (ARNi) ³	463 (25.2%)	132 (23.7%)	331 (25.9%)	0.30
ACE or ARB or ARNi	1240 (67.6%)	393 (70.4%)	847 (66.3%)	0.08

	All Patients N=1,835	De novo N=558	WHF N=1,277	P-value
Aldosterone antagonist / mineralocorticoid receptor antagonist (MRA)	813 (44.3%)	241 (43.2%)	572 (44.8%)	0.52
Beta blocker	1496 (81.5%)	423 (75.8%)	1073 (84.0%)	<.001
SGLT-2 inhibitor	139 (7.8%)	38 (7.0%)	101 (8.2%)	0.38
Long-acting nitrate	266 (14.5%)	57 (10.2%)	209 (16.4%)	<.001
Thiazide diuretic	65 (3.6%)	16 (2.9%)	49 (3.9%)	0.30
Digoxin	125 (6.8%)	23 (4.1%)	102 (8.0%)	0.002
Hydralazine	263 (14.3%)	69 (12.4%)	194 (15.2%)	0.11
Ivabradine	7 (0.4%)	1 (0.2%)	6 (0.5%)	0.68

¹ Loop diuretic doses were converted to Furosemide equivalents with 1mg Bumetanide = 20mg Torsemide = 50mg Ethacrynic acid = 40mg Furosemide for oral diuretics; and 1mg Bumetanide = 50mg Ethacrynic acid = 20mg Furosemide for intravenous diuretics.

² Denominator is the patients with known prescription status of the assigned loop diuretic at each visit (i.e., excludes patients who died by the time of the visit or who had unknown prescription status at the visit).

³ Angiotensin receptor-neprilysin inhibitor (ARNi) was reported as being taken (Y) or missing. For calculating the percent of patients on this medication at baseline, if it was not reported as Yes, it was assumed to be No.

eTable 2. Baseline characteristics of study participants (Demographics, Laboratory, and Vital Signs, Heart Failure Characteristics and Medical History) by HF type, for patients with >40% EF

	All Patients N=799	De novo N=227	WHF N=572	P-value
Demographics				
Age, years				<.001
N	799	227	572	
Mean (SD)	69.5 (12.8)	66.3 (13.5)	70.8 (12.3)	
Median (25 th , 75 th)	71.0 (62, 78)	68.0 (58, 77)	73.0 (64, 80)	
Female sex	385 (48.2%)	96 (42.3%)	289 (50.5%)	0.04
Race				0.9
American Indian or Alaska Native	2 (0.3%)	0 (0.0%)	2 (0.4%)	
Asian	13 (1.6%)	4 (1.8%)	9 (1.6%)	
Black or African American	221 (27.7%)	59 (26.0%)	162 (28.4%)	
Native Hawaiian or Other Pacific Islander	1 (0.1%)	0 (0.0%)	1 (0.2%)	
White	535 (67.1%)	158 (69.6%)	377 (66.1%)	
Other	9 (1.1%)	3 (1.3%)	6 (1.1%)	
Multiple	16 (2.0%)	3 (1.3%)	13 (2.3%)	
Hispanic or Latino	37 (4.6%)	10 (4.4%)	27 (4.7%)	0.85
Laboratory values				
Sodium, mEq/L				0.91
Mean (SD)	138.3 (3.7)	138.3 (3.6)	138.3 (3.7)	
Potassium, mEq/L				0.01
Mean (SD)	4.02 (0.47)	3.96 (0.46)	4.04 (0.47)	
Blood urea nitrogen, mg/dL				<.001
Mean (SD)	35.8 (40.5)	28.1 (26.1)	38.9 (44.6)	
Creatinine, mg/dL				<.001
Mean (SD)	1.442 (0.684)	1.292 (0.646)	1.502 (0.690)	
Estimated Glomerular filtration rate, mL/min/1.73 m ²				<.001
Mean (SD)	56.1 (24.9)	64.0 (24.5)	53.0 (24.3)	
N-Terminal pro B-type natriuretic peptide, pg/mL				0.33
N	442	113	329	
Median (25 th , 75 th)	2855.0 (1341.0, 5723.0)	2565.0 (1567.0, 4555.0)	2988.0 (1335.0, 6326.0)	
B-type natriuretic peptide (BNP), pg/mL				0.05

	All Patients N=799	De novo N=227	WHF N=572	P-value
N	359	115	244	
Median (25 th , 75 th)	558.0 (335.0, 1041.0)	508.0 (313.9, 886.0)	626.5 (341.0, 1152.0)	
Hemoglobin, g/L				<.001
Mean (SD)	11.39 (6.76)	11.66 (2.45)	11.28 (7.84)	
Vital signs				
Systolic blood pressure, mmHg				0.26
Mean (SD)	127.9 (20.0)	129.3 (20.5)	127.3 (19.8)	
Diastolic blood pressure, mmHg				0.003
Mean (SD)	68.2 (12.5)	70.4 (13.0)	67.3 (12.2)	
Heart rate, BPM				0.03
Mean (SD)	76.6 (15.2)	78.5 (15.9)	75.9 (14.8)	
BMI, kg/m ²				0.8
Mean (SD)	34.20 (10.18)	34.02 (9.90)	34.27 (10.30)	
Heart Failure Characteristics				
Duration of diagnosis prior to hospitalization:				
≤ 30 days Duration	32 (5.6%)	0	32 (5.6%)	
> 30 days and ≤ 12 months Duration	98 (17.1%)	0	98 (17.1%)	
> 12 months Duration	373 (65.2%)	0	373 (65.2%)	
Unknown	69 (12.1%)	0	69 (12.1%)	
New York Heart Association class at hospital admission				0.021
I	9 (1.1%)	2 (0.9%)	7 (1.2%)	
II	77 (9.7%)	27 (11.9%)	50 (8.8%)	
III	333 (41.8%)	82 (36.1%)	251 (44.0%)	
IV	93 (11.7%)	19 (8.4%)	74 (13.0%)	
Unknown	285 (35.8%)	97 (42.7%)	188 (33.0%)	
New York Heart Association class at randomization				0.03
I	18 (2.3%)	5 (2.2%)	13 (2.3%)	
II	189 (23.7%)	60 (26.4%)	129 (22.6%)	
III	263 (32.9%)	63 (27.8%)	200 (35.0%)	
IV	31 (3.9%)	3 (1.3%)	28 (4.9%)	
Unknown	298 (37.3%)	96 (42.3%)	202 (35.3%)	
KCCQ Baseline Clinical Summary Score				0.002
Mean (SD)	41.07 (22.99)	45.14 (23.52)	39.49 (22.60)	

	All Patients N=799	De novo N=227	WHF N=572	P-value
Median (25 th , 75 th)	37.5 (22.9, 57.5)	42.7 (26.6, 60.4)	36.1 (21.9, 55.2)	
Ischemic etiology	170 (21.3%)	37 (16.3%)	133 (23.3%)	0.02
Chronic kidney disease	330 (41.3%)	55 (24.2%)	275 (48.1%)	<.001
Diabetes mellitus	420 (52.6%)	108 (47.6%)	312 (54.5%)	0.07
Hypertension	711 (89.1%)	193 (85.0%)	518 (90.7%)	0.02
Atrial fibrillation or atrial flutter	427 (53.5%)	93 (41.2%)	334 (58.4%)	<.001
Chronic lung disease (including COPD)	238 (30.2%)	34 (15.2%)	204 (36.1%)	<.001
Loop diuretics				
Oral loop diuretic <u>prior</u> to index hospital admission (most recent)				<.001
No	218 (27.3%)	149 (65.6%)	69 (12.1%)	
Yes	581 (72.7%)	78 (34.4%)	503 (87.9%)	
Total daily dose prescribed (furosemide equivalents), mg				<.001
Mean (SD)	63.6 (61.6)	43.7 (31.7)	66.6 (64.4)	
Specific Loop Diuretic Prior to Index Admission (among those on a loop diuretic)¹				
Furosemide	470 (80.9%)	73 (93.6%)	397 (78.9%)	
Torsemide	77 (13.3%)	3 (3.8%)	74 (14.7%)	
Bumetanide	34 (5.9%)	2 (2.6%)	32 (6.4%)	
Ethacrynic acid	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Discharge				
Prescribed <u>assigned</u> loop diuretic ²	707 (90.8%)	197 (90.0%)	510 (91.1%)	0.9
Total daily dose prescribed (furosemide equivalents) ¹ , mg				<.001
N	678	183	495	
Mean (SD)	77.3 (58.7)	59.5 (44.5)	83.9 (61.9)	
Median (25 th , 75 th)	80 (40, 80)	40 (40, 80)	80 (40, 120)	
Total daily dose prescribed (reported), mg				<.001
N	678	183	495	
Mean (SD)	57.6 (47.0)	45.9 (42.6)	61.9 (47.8)	
Median (25 th , 75 th)	40 (20, 80)	40 (20, 40)	40 (20, 80)	
Baseline medications taken at the time of randomization				
ACE or ARB	319 (39.9%)	107 (47.1%)	212 (37.1%)	0.01
Angiotensin receptor-neprilysin inhibitor (ARNi) ³	48 (6.0%)	7 (3.1%)	41 (7.2%)	0.03
ACE or ARB or ARNi	360 (45.1%)	112 (49.3%)	248 / 572 (43.4%)	0.12
Aldosterone antagonist / mineralocorticoid receptor antagonist (MRA)	158 (19.8%)	29 (12.8%)	129 / 572 (22.6%)	0.002

	All Patients N=799	De novo N=227	WHF N=572	P-value
Beta blocker	592 (74.1%)	159 (70.0%)	433 (75.7%)	0.10
SGLT-2 inhibitor	22 (2.9%)	6 (2.7%)	16 (2.9%)	0.86
Long-acting nitrate	103 (12.9%)	19 (8.4%)	84 (14.8%)	0.01
Thiazide diuretic	50 (6.3%)	16 (7.1%)	34 (6.0%)	0.6
Digoxin	31 (3.9%)	8 (3.5%)	23 (4.0%)	0.7
Hydralazine	130 (16.3%)	28 (12.3%)	102 (17.8%)	0.1
Ivabradine	0 (0.0%)	0 (0.0%)	0 (0.0%)	

¹ Loop diuretic doses were converted to Furosemide equivalents with 1mg Bumetanide = 20mg Torsemide = 50mg Ethacrynic acid = 40mg Furosemide for oral diuretics; and 1mg Bumetanide = 50mg Ethacrynic acid = 20mg Furosemide for intravenous diuretics.

² Denominator is the patients with known prescription status of the assigned loop diuretic at each visit (i.e., excludes patients who died by the time of the visit or who had unknown prescription status at the visit).

³ Angiotensin receptor-neprilysin inhibitor (ARNi) was reported as being taken (Y) or missing. For calculating the percent of patients on this medication at baseline, if it was not reported as Yes, it was assumed to be N

eTable 3: Time-to-event outcome comparison between de-novo and WHF for overall patients and stratified by ejection fraction

Outcomes	De Novo HF ¹ N=838 events (rate per 100 patient-years)	WHF ¹ N=2,020 events (rate per 100 patient-years)	Unadjusted		Adjusted		Interaction P- Value ³
			HR (95% CI) ²	P-value ²	HR (95% CI) ²	P-value ²	
All-Cause Mortality over 12 Months							
Overall	65 (9.1)	408 (25.4)	0.36 (0.28, 0.47)	<0.001	0.50 (0.38, 0.66)	<0.001	
EF Level							0.28
≤40%	38 (8.0)	262 (26.0)	0.31 (0.22, 0.44)	<0.001	0.55 (0.38, 0.78)	<0.001	
>40%	19 (9.5)	109 (23.3)	0.41 (0.25, 0.67)	<0.001	0.76 (0.46, 1.25)	0.28	
All-Cause Mortality or Re-hospitalization over 12 Months							
Overall	293 (67.1)	1080 (118.3)	0.58 (0.51, 0.66)	<0.001	0.67 (0.61, 0.80)	<0.001	
EF Level							0.22
≤40%	173 (58.0)	678 (118.6)	0.50 (0.43, 0.60)	<0.001	0.72 (0.60, 0.85)	<0.001	
>40%	95 (84.4)	311 (117.4)	0.73 (0.58, 0.92)	0.01	0.86 (0.68, 1.08)	0.12	
All-Cause First Re-hospitalization over 12 Months							
Overall	253 (59.2)	853 (99.1)	0.62 (0.54, 0.71)	<0.001	0.71 (0.61, 0.83)	<0.001	
EF Level							0.22
≤40%	146 (50.0)	531 (98.4)	0.53 (0.44, 0.63)	<0.001	0.72 (0.59, 0.87)	<0.001	
>40%	85 (77.5)	252 (100.9)	0.78 (0.61, 1.00)	0.05	0.87 (0.68, 1.12)	0.28	

1 For each cell, for all-cause mortality and all-cause mortality or re-hospitalization over 12 months, the numbers displayed are number of events (Kaplan-Meier failure rate %) event rate per 100 patient-years of follow-up. For all-cause first re-hospitalization, the numbers displayed are number of events (cumulative incidence rate %) event rate per 100 patient-years of follow-up.

2 For all-cause mortality and all-cause mortality/re-hospitalization over 12 months, hazard ratio (HR), 95% confidence interval (CI) and p-value are based on a Cox proportional hazards regression model. For all-cause first primary re-hospitalization over 12 months, hazard ratio (HR), 95% confidence interval (CI) and p-value is based on a Cox proportional hazards model where death is considered as competing risk and is censored at time of death. Unadjusted models will only contain main effect HF type (De Novo, worsening HF) as covariate. All adjusted models for overall patients contain main effect HF type (De Novo, worsening HF), age, sex, race, baseline ejection fraction categories (≤40%, 41-49%, ≥50% and unknown), systolic blood pressure, eGFR, hemoglobin, body mass index (BMI), diabetes, atrial fibrillation/flutter, ischemic etiology, chronic lung disease. For adjusted model in the stratified analyses by EF levels (≤40, >40), the same covariates are used, except that baseline ejection fraction will be continuous.

3 The interaction p-value for HF type and baseline EF levels (≤40%, >40%) are derived from adjusted model for patients with known EF levels. The covariates are HF type (De Novo, worsening HF), age, sex, race, baseline ejection fraction levels (≤40%, >40%), systolic blood pressure, eGFR, hemoglobin, body mass index (BMI), diabetes, atrial fibrillation/flutter, ischemic etiology, chronic lung disease and the interaction term.

eTable 4. Effect of HF type on total re-hospitalizations through Month 12 for overall patients and stratified by ejection fraction

Outcomes	De Novo HF N=838	WHF N=2,020	All Patients N=2,858	Unadjusted NBR		Adjusted NRB		Interaction P-Value ³
				RR (95% CI) ²	P- Value ²	RR (95% CI) ²	P- Value ²	
Overall				0.57 (0.49, 0.65)	<0.001	0.64 (0.56, 0.75)	<0.001	
Patients with a re-hospitalization event ¹	253 (30.2%)	853 (42.2%)	1106 (38.7%)					
First event rate per 100 pt-years	59.2	99.1	85.9					
Total number of events	394	1514	1908					
Total event rate per 100 pt-years	71.5	123.2	107.2					
EF Level								0.01
≤40%				0.46 (0.38, 0.55)	<0.001	0.53 (0.44, 0.64)	<0.001	
Patients with a re-hospitalization event ¹	146 (26.2%)	531 (41.6%)	677 (36.9%)					
First event rate per 100 pt-years	50.0	98.4	81.4					
Total number of events	211	964	1175					
Total event rate per 100 pt-years	58.1	125.5	103.9					
>40%				0.74 (0.58, 0.95)	0.02	0.82 (0.64, 1.05)	0.11	
Patients with a re-hospitalization event ¹	85 (37.4%)	252 (44.1%)	337 (42.2%)					
First event rate per 100 pt-years	77.5	100.9	93.7					
Total number of events	148	447	595					
Total event rate per 100 pt-years	96.2	123.3	115.2					

¹ Re-hospitalization defined as at least a 24-hour stay (or a change in calendar date if the time of admission/discharge is not available) or reported as an in-patient admission by the patient/proxy with an admission date and no discharge date. The numbers displayed are number of events (% of patients with events).

² Relative risk (RR), 95% confidence interval (CI) and p-value are from a negative binomial regression (NBR) of the frequency of re-hospitalizations with an offset term of the log of each subject's months to last rehospitalization assessment through month 12. Unadjusted models contain only main effect HF type (De Novo, worsening HF) as covariate. All adjusted models contain main effect HF type (De Novo, worsening HF), age, sex, race, baseline ejection fraction categories (≤40, 41-49, ≥50, unknown), systolic blood pressure, eGFR, hemoglobin, body mass index (BMI), diabetes, atrial fibrillation/flutter, ischemic etiology, chronic lung disease. For adjusted model in the analyses stratified by EF levels (≤40, >40), the same covariates are used, except that continuous baseline ejection fraction will be used as covariate.

³ The interaction p-value for HF type and baseline EF levels (≤40%, >40%) are derived from adjusted model for patients with known EF levels. The covariates are HF type (De Novo, worsening HF), age, sex, race, baseline ejection fraction levels (≤40%, >40%), systolic blood pressure, eGFR, hemoglobin, body mass index (BMI), diabetes, atrial fibrillation/flutter, ischemic etiology, chronic lung disease and the interaction term.

eTable 5. Comparison of KCCQ Clinical Summary Score by HF Type for overall patients and by EF levels – Least Square Mean by Visit

	Unadjusted				Adjusted				Interaction P-value ²
	Least Square Means		Estimated Difference in Means (95% CI) (De novo – WHF) ¹	P-value ²	Least Square Means		Estimated Difference in Means (95% CI) (De novo – WHF) ¹	P-value ²	
	De Novo HF N=838	WHF N=2,020				De Novo HF N=838			WHF N=2,020
Month 1 Change from Baseline (95% CI)									
Overall	35.45 (33.65, 37.25)	26.34 (25.14, 27.55)	9.11 (6.94, 11.27)	<0.001	29.83 (27.40, 32.26)	22.21 (20.30, 24.11)	7.63 (5.37, 9.89)	<0.001	
EF Levels									0.63
EF≤40%	36.83 (34.67, 39.00)	27.76 (26.26, 29.25)	9.08 (6.44, 11.71)	<0.001	32.80 (30.27, 35.34)	24.84 (22.94, 26.74)	7.96 (5.23, 10.70)	<0.001	
EF>40%	31.73 (28.29, 35.18)	23.28 (21.06, 25.50)	8.46 (4.36, 12.55)	<0.001	27.27 (23.57, 30.97)	20.50 (17.95, 23.04)	6.78 (2.67, 10.88)	0.001	
Month 6 Change from Baseline (95% CI)									
Overall	35.57 (33.65, 37.49)	28.89 (27.58, 30.21)	6.68 (4.35, 9.01)	<0.001	30.03 (27.52, 32.54)	24.89 (22.91, 26.87)	5.14 (2.74, 7.55)	<0.001	
EF Levels									0.64
EF≤40%	37.34 (35.01, 39.67)	30.32 (28.67, 31.97)	7.01 (4.16, 9.87)	<0.001	33.31 (30.65, 35.98)	27.58 (25.56, 29.60)	5.73 (2.79, 8.68)	<0.001	
EF>40%	30.99 (27.37, 34.61)	24.87 (22.44, 27.30)	6.12 (1.76, 10.48)	0.01	26.61 (22.76, 30.47)	22.12 (19.39, 24.85)	4.49 (0.14, 8.84)	0.04	
Month 12 Change from Baseline (95% CI)									
Overall	35.50 (33.48, 37.52)	27.70 (26.27, 29.14)	7.79 (5.31, 10.27)	<0.001	29.94 (27.35, 32.54)	23.68 (21.62, 25.74)	6.26 (3.72, 8.81)	<0.001	
EF Levels									0.77

	Unadjusted				Adjusted				
	Least Square Means		Estimated Difference in Means (95% CI) (De novo – WHF) ¹	P-value ²	Least Square Means		Estimated Difference in Means (95% CI) (De novo – WHF) ¹	P-value ²	Interaction P-value ²
De Novo HF N=838	WHF N=2,020	De Novo HF N=838			WHF N=2,020				
EF≤40%	37.08 (34.63, 39.53)	29.43 (27.64, 31.22)	7.65 (4.62, 10.69)	<0.001	33.04 (30.26, 35.82)	26.63 (24.49, 28.77)	6.41 (3.29, 9.53)	<0.001	
EF>40%	31.81 (28.02, 35.60)	22.89 (20.27, 25.51)	8.91 (4.30, 13.52)	<0.001	27.33 (23.31, 31.35)	20.11 (17.21, 23.02)	7.21 (2.61, 11.82)	0.002	

¹ Estimated difference in means, 95% confidence interval (CI) and p-value are from a linear mixed model with repeated measures on KCCQ-CSS score change from baseline in Month 12. Unadjusted models will include terms for HF type, time (i.e., visit) and HF type by time interaction as fixed effects, and the baseline score. Adjusted models for overall patients will include additional covariates for age, sex, race, baseline ejection fraction categories (<=40, 41-49, >= 50, unknown), systolic blood pressure, eGFR, hemoglobin, body mass index (BMI), diabetes, atrial fibrillation/flutter, ischemic etiology and chronic lung disease. For adjusted model in the stratified analyses by EF levels (<=40, >40), the same covariates are used, except that baseline ejection fraction will be continuous.

² The interaction p-value for HF type and baseline EF levels (<=40%, >40%) are derived from adjusted model for patients with known EF levels with additional covariates for age, sex, race, baseline ejection fraction categories (<=40, >40), systolic blood pressure, eGFR, hemoglobin, body mass index (BMI), diabetes, atrial fibrillation/flutter, ischemic etiology and chronic lung disease.

eTable 6. Treatment Effect on total re-hospitalizations through Month 12 by HF type for overall patients and stratified by EF levels

Outcomes	De Novo HF			WHF			Interaction P-Value ³
	Torsemide	Furosemide	NBR RR (95% CI) ²	Torsemide	Furosemide	NBR RR (95% CI) ²	
Overall			0.83 (0.65, 1.07)			0.98 (0.85, 1.12)	0.28
Patients with a re-hospitalization event ¹	121 (28.3%)	132 (32.2%)		411 (41.0%)	442 (43.4%)		
First event rate per 100 pt-years	54.8	63.9		94.5	103.9		
Total number of events	184	210		746	768		
Total event rate per 100 pt-years	65.7	77.5		122.1	124.2		
EF Level							
≤40%			0.82 (0.60, 1.13)			1.03 (0.86, 1.22)	0.23
Patients with a re-hospitalization event ¹	74 (26.0%)	72 (26.4%)		264 (40.7%)	267 (42.5%)		
First event rate per 100 pt-years	49.0	51.0		95.0	102.1		
Total number of events	103	108		496	468		
Total event rate per 100 pt-years	54.4	62.2		127.7	123.2		
>40%			0.906 (0.602, 1.364)			0.87 (0.68, 1.11)	0.87
Patients with a re-hospitalization event ¹	39 (32.8%)	46 (42.6%)		118 (42.1%)	134 (45.9%)		
First event rate per 100 pt-years	67.6	88.4		92.0	110.2		
Total number of events	70	78		213	234		
Total event rate per 100 pt-years	91.5	100.8		116.7	129.9		

¹ Re-hospitalization defined as at least a 24-hour stay (or a change in calendar date if the time of admission/discharge is not available) or reported as an in-patient admission by the patient/proxy with an admission date and no discharge date. The numbers displayed are number of events (% of patients with events).

² Relative risk (RR), 95% confidence interval (CI) and p-value are from a negative binomial regression (NBR) of the frequency of re-hospitalizations with an offset term of the log of each subject's months to last rehospitalization assessment through month 12. For the overall patient model, the covariates are diuretic treatment (torsemide, furosemide), HF type, age, sex, baseline EF categories (<=40, 41-49, >= 50, unknown). For each stratified analysis by EF level, the covariates are diuretic treatment, HF type, age, sex and continuous baseline EF.

³ The interaction p-values are between diuretic treatment and HF type for overall patients and each EF level.

eTable 7. Comparison of KCCQ Clinical Summary Score between treatment diuretics groups by HF types – Least Square Mean by Visit for overall patients and stratified by EF levels

	De Novo HF				WHF				
	Furosemide N=410	Torsemide N=428	Estimated Difference in Means (T vs F)	Estimated Difference P-value	Furosemide N=1,018	Torsemide N=1,002	Estimated Difference in Means (T vs F)	Estimated Difference P-value	Interaction P-value
Month 1 Change from Baseline (95% CI)									
Overall	28.6 (25.6,31.7)	31.0 (28.0,34.0)	2.3 (-1.2, 5.9)	0.20	21.7 (19.4,23.9)	22.7 (20.5,24.9)	1.0 (-1.3, 3.4)	0.4	0.5
EF≤40%	30.4 (26.9,33.9)	32.6 (29.3,35.9)	2.2 (-2.03, 6.5)	0.30	23.6 (21.1,26.1)	25.1 (22.6,27.6)	1.5 (-1.4, 4.4)	0.3	0.8
EF>40%	29.6 (23.9,35.2)	31.6 (25.9,37.3)	2.02 (-5.0, 9.03)	0.57	22.6 (18.5,26.7)	22.6 (18.6,26.6)	-0.1 (-4.6, 4.4)	0.9	0.6
Month 6 Change from Baseline (95% CI)									
Overall	29.5 (26.3,32.6)	30.6 (27.4,33.7)	1.1 (-2.7, 4.9)	0.6	25.3 (23.0,27.7)	24.4 (22.0,26.7)	-1.0 (-3.6, 1.6)	0.5	0.4
EF≤40%	32.2 (28.5,35.9)	32.0 (28.4,35.4)	-0.3 (-4.9, 4.3)	0.9	26.9 (24.3,29.6)	27.3 (24.6,30.0)	0.4 (-2.9, 3.6)	0.8	0.8
EF>40%	28.3 (22.7,34.0)	31.5 (25.6,37.4)	3.1 (-4.0,10.3)	0.4	27.1 (22.8,31.4)	21.8 (17.7,26.0)	5.3 (-10.1,-0.5)	0.03	0.05
Month 12 Change from Baseline (95% CI)									
Overall	29.0 (25.7,32.3)	30.8 (27.6,34.1)	1.8 (-2.1, 5.8)	0.4	24.0 (21.5,26.5)	23.3 (20.8,25.8)	-0.7 (-3.6, 2.1)	0.6	0.3
EF≤40%	31.8 (28.1,35.5)	31.8 (28.2,35.4)	-0.0 (-4.7, 4.7)	1.0	26.1 (23.3,28.8)	26.3 (23.5,29.1)	0.2 (-3.2, 3.6)	0.9	0.9
EF>40%	28.7 (22.5,34.9)	32.8 (26.3,39.3)	4.1 (-4.0,12.1)	0.3	24.0 (19.2,28.8)	20.6 (16.0,25.1)	-3.4 (-9.0, 2.2)	0.2	0.1

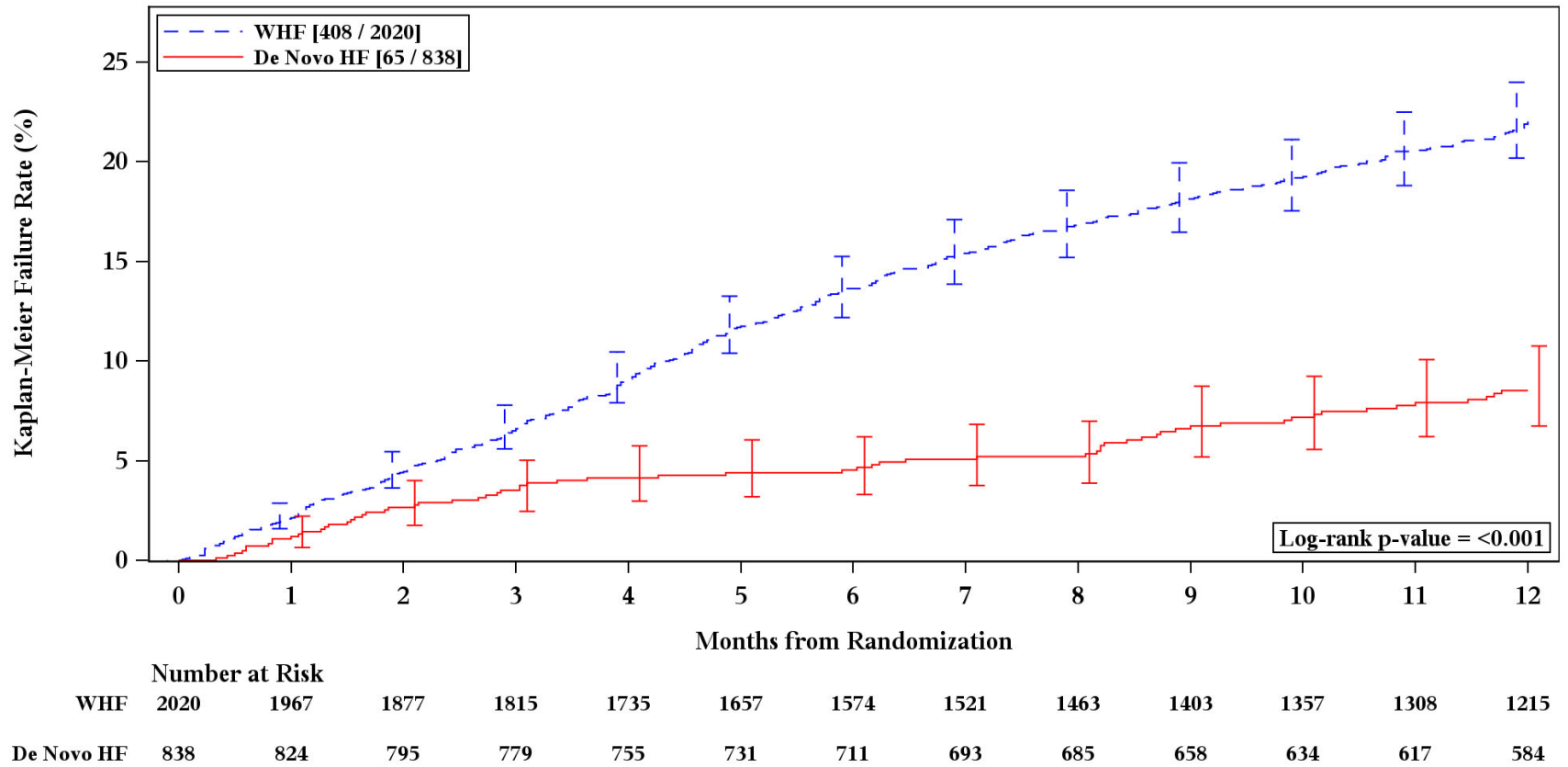
eTable 8. Diuretic dose adherence at Discharge, month 1, 6 and 12 by heart failure type and diuretic treatment

Timepoint	De Novo		WHF		All Patients N=2,786
	Torsemide (N=413)	Furosemide (N=403)	Torsemide (N=976)	Furosemide (N=994)	
Discharge					
Patients with known loop diuretic status at discharge*	391 (94.7%)	394 (97.8%)	939 (96.2%)	962 (96.8%)	2686 (96.4%)
Prescribed <u>assigned</u> loop diuretic ¹	349 (89.3%)	368 (93.4%)	838 (89.2%)	874 (90.9%)	2429 (90.4%)
Total daily dose prescribed (furosemide equivalents) ² , mg	59.2 (50.4)	70.5 (52.6)	88.3 (75.3)	82.6 (57.9)	79.4 (63.6)
Total daily dose prescribed (reported) ² , mg	29.6 (25.2)	70.5 (52.6)	44.1 (37.6)	82.6 (57.9)	59.9 (51.2)
Prescribed a different loop diuretic ¹	28 (7.2%)	13 (3.3%)	80 (8.5%)	60 (6.2%)	181 (6.7%)
Crossover (between arms) ¹	25 (6.4%)	8 (2.0%)	68 (7.2%)	43 (4.5%)	144 (5.4%)
No loop diuretic currently prescribed ¹	14 (3.6%)	13 (3.3%)	21 (2.2%)	28 (2.9%)	76 (2.8%)
Month 1					
Patients with known loop diuretic status at Month 1*	295 (98.0%)	293 (98.0%)	639 (98.3%)	660 (97.5%)	1887 (97.9%)
Prescribed <u>assigned</u> loop diuretic ¹	247 (83.7%)	249 (85.0%)	540 (84.5%)	556 (84.2%)	1592 (84.4%)
Total daily dose prescribed (furosemide equivalents) ² , mg	55.5 (46.3)	58.8 (42.5)	86.1 (82.1)	72.3 (53.2)	72.1 (63.2)
Total daily dose prescribed (reported) ² , mg	27.8 (23.1)	58.8 (42.5)	43.0 (41.0)	72.3 (53.2)	53.4 (46.8)
Prescribed a different loop diuretic ¹	19 (6.4%)	17 (5.8%)	61 (9.5%)	75 (11.4%)	172 (9.1%)
Crossover (between arms) ¹	18 (6.1%)	7 (2.4%)	52 (8.1%)	44 (6.7%)	121 (6.4%)
No loop diuretic currently prescribed ¹	29 (9.8%)	27 (9.2%)	38 (5.9%)	29 (4.4%)	123 (6.5%)
Month 6					
Patients with known loop diuretic status at Month 6*	251 (98.0%)	257 (98.8%)	512 (98.5%)	540 (98.5%)	1560 (98.5%)
Prescribed <u>assigned</u> loop diuretic ¹	196 (78.1%)	197 (76.7%)	428 (83.6%)	397 (73.5%)	1218 (78.1%)
Total daily dose prescribed (furosemide equivalents) ² , mg	60.2 (70.3)	56.4 (40.5)	86.0 (88.0)	70.3 (56.1)	72.1 (70.2)
Total daily dose prescribed (reported) ² , mg	30.1 (35.1)	56.4 (40.5)	43.0 (44.0)	70.3 (56.1)	52.4 (49.0)
Prescribed a different loop diuretic ¹	19 (7.6%)	25 (9.7%)	61 (11.9%)	95 (17.6%)	200 (12.8%)
Crossover (between arms) ¹	18 (7.2%)	16 (6.2%)	49 (9.6%)	61 (11.3%)	144 (9.2%)
No loop diuretic currently prescribed ¹	36 (14.3%)	35 (13.6%)	23 (4.5%)	48 (8.9%)	142 (9.1%)

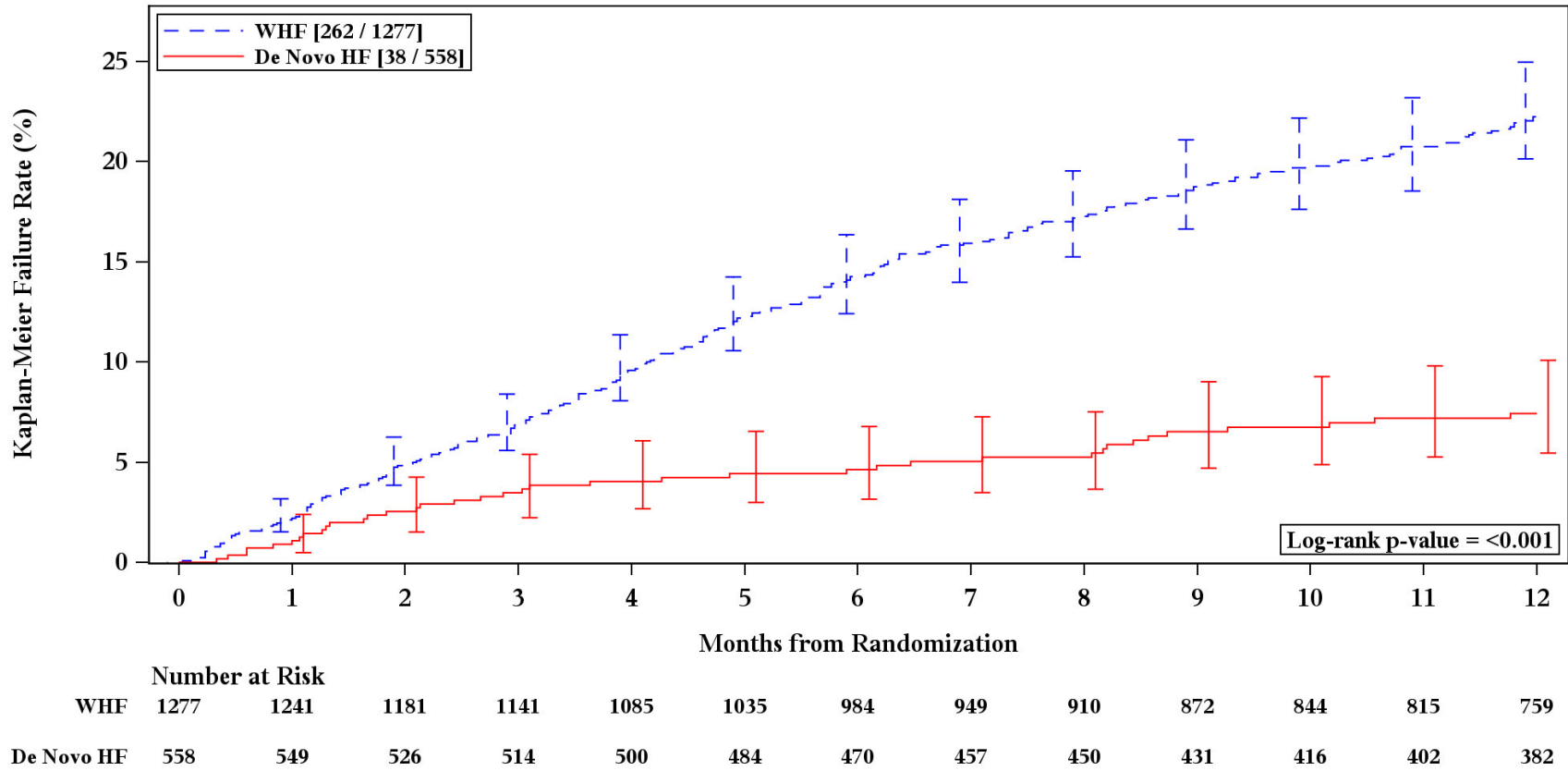
Timepoint	De Novo		WHF		All Patients N=2,786
	Torsemide (N=413)	Furosemide (N=403)	Torsemide (N=976)	Furosemide (N=994)	
Month 12					
Patients with known loop diuretic status at Month 12*	219 (99.5%)	222 (99.6%)	416 / 423 (98.3%)	415 (98.6%)	1272 (98.8%)
Prescribed <u>assigned</u> loop diuretic ¹	147 (67.1%)	169 (76.1%)	326 (78.4%)	288 (69.4%)	930 (73.1%)
Total daily dose prescribed (furosemide equivalents) ² , mg	71.4 (113.1)	54.7 (41.6)	87.2 (83.8)	65.4 (47.4)	72.2 (74.4)
Total daily dose prescribed (reported) ² , mg	35.7 (56.6)	54.7 (41.6)	43.6 (41.9)	65.4 (47.4)	51.2 (47.1)
Prescribed a different loop diuretic ¹	20 (9.1%)	17 (7.7%)	61 (14.7%)	80 (19.3%)	178 (14.0%)
Crossover (between arms) ¹	14 (6.4%)	11 (5.0%)	45 (10.8%)	56 (13.5%)	126 (9.9%)
No loop diuretic currently prescribed ¹	52 (23.7%)	36 (16.2%)	29 (7.0%)	47 (11.3%)	164 (12.9%)

Footnote: Denominators: * = patients with available KCCQ-CSS data at the associated study visit; ¹ = patients with a known loop diuretic status; ² = data available for 2318, 1260, 892, 676 patients at Discharge, 1 month, 6 months, and 12 months, respectively.

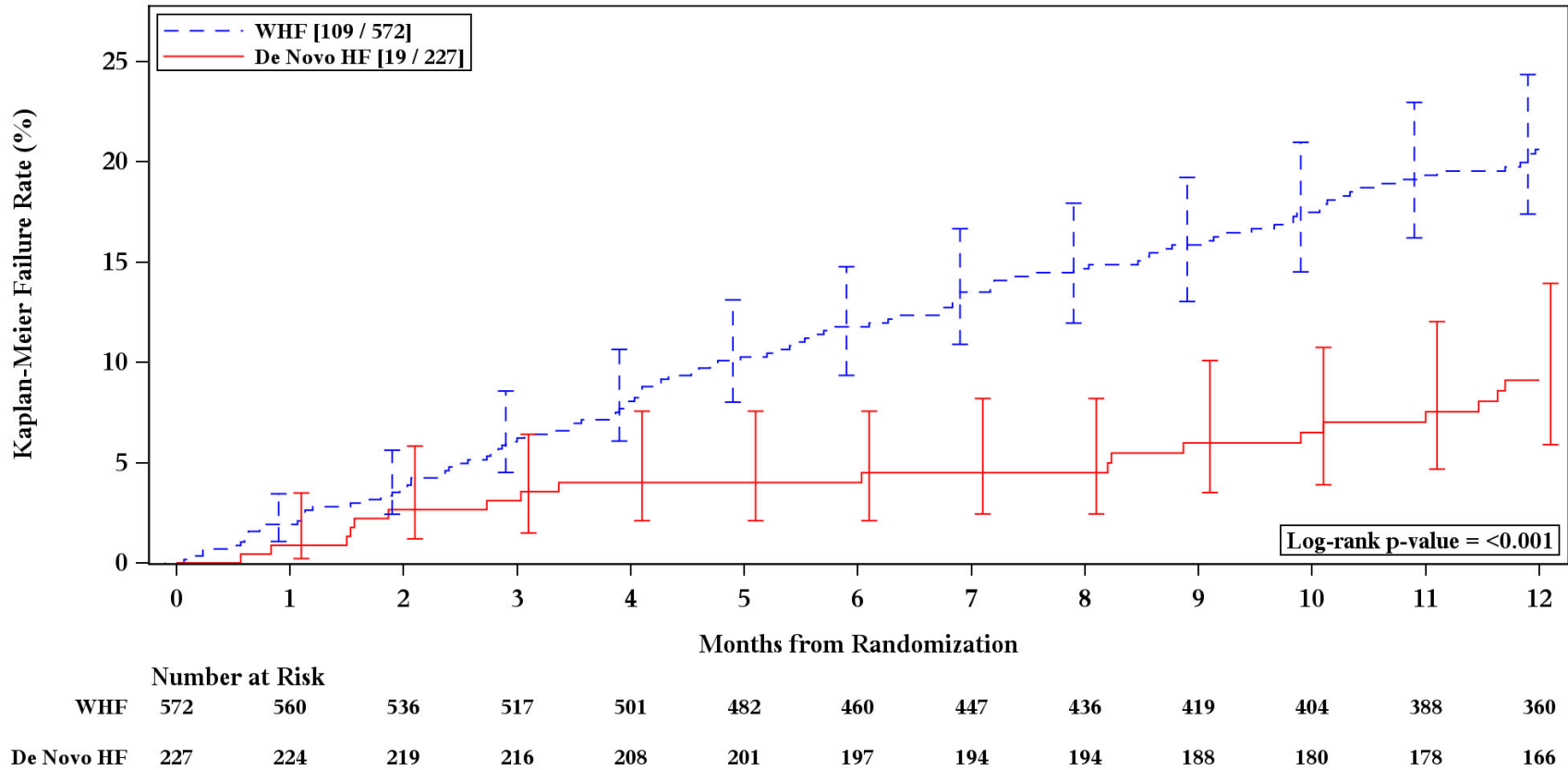
eFigure 1: Unadjusted Kaplan-Meier curves for time to all-cause mortality comparing De novo and worsening HF for overall patients over 12 months



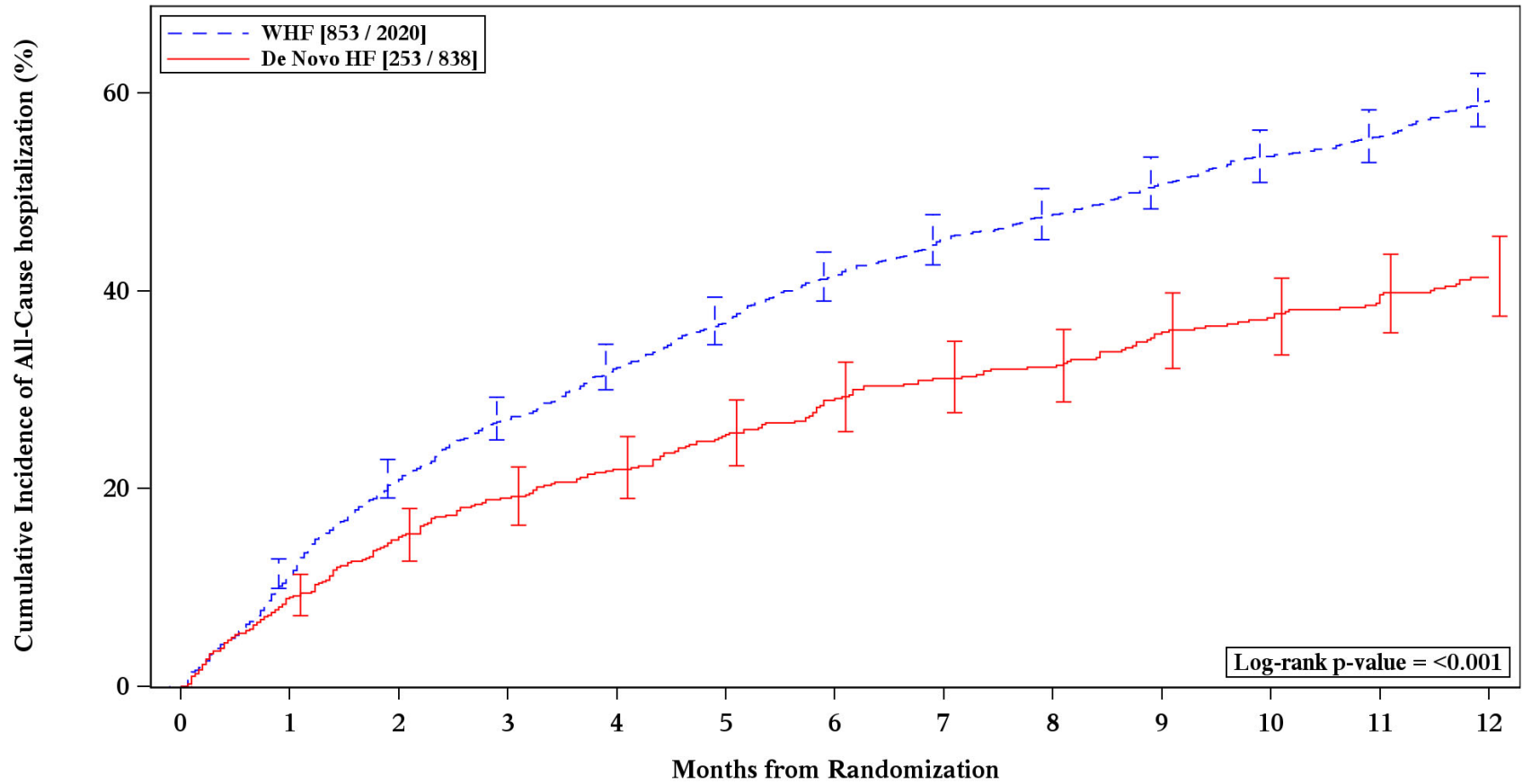
eFigure 2: Unadjusted Kaplan-Meier curves for time to all-cause mortality comparing De novo and WHF for patients with EF level $\leq 40\%$ over 12 months



eFigure 3: Unadjusted Kaplan-Meier curves for time to all-cause mortality comparing De novo and WHF for patients with EF level >40% over 12 months



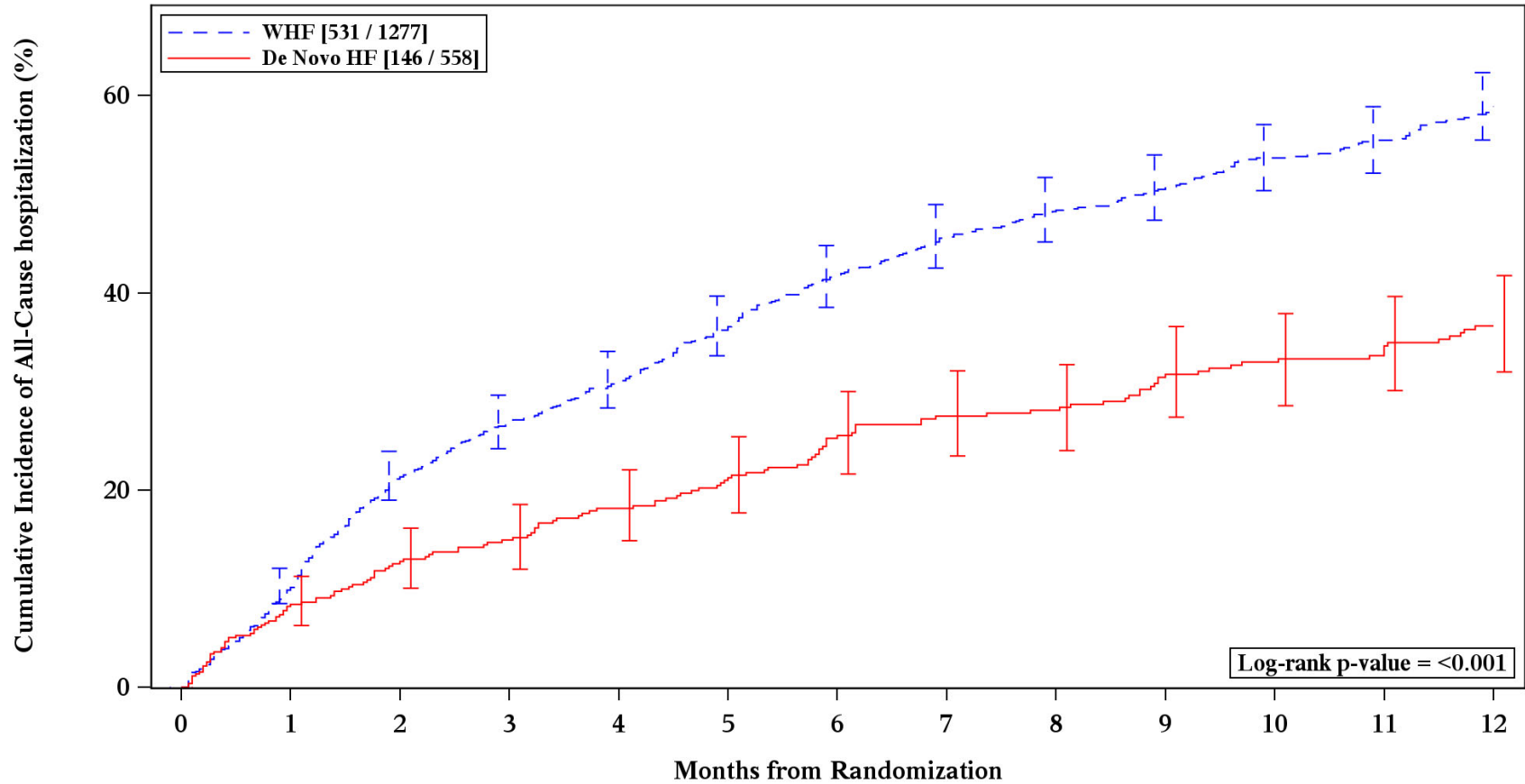
eFigure 4: Unadjusted cumulative incidence curves for all-cause hospitalization over 12 months comparing de novo and Worsening HF



	Number at Risk												
	0	1	2	3	4	5	6	7	8	9	10	11	12
WHF	2020	1517	1221	1087	974	887	766	675	610	556	511	474	312
De Novo HF	838	649	548	508	474	441	398	366	349	322	300	286	192

Note: Patients who died were censored at time of death.

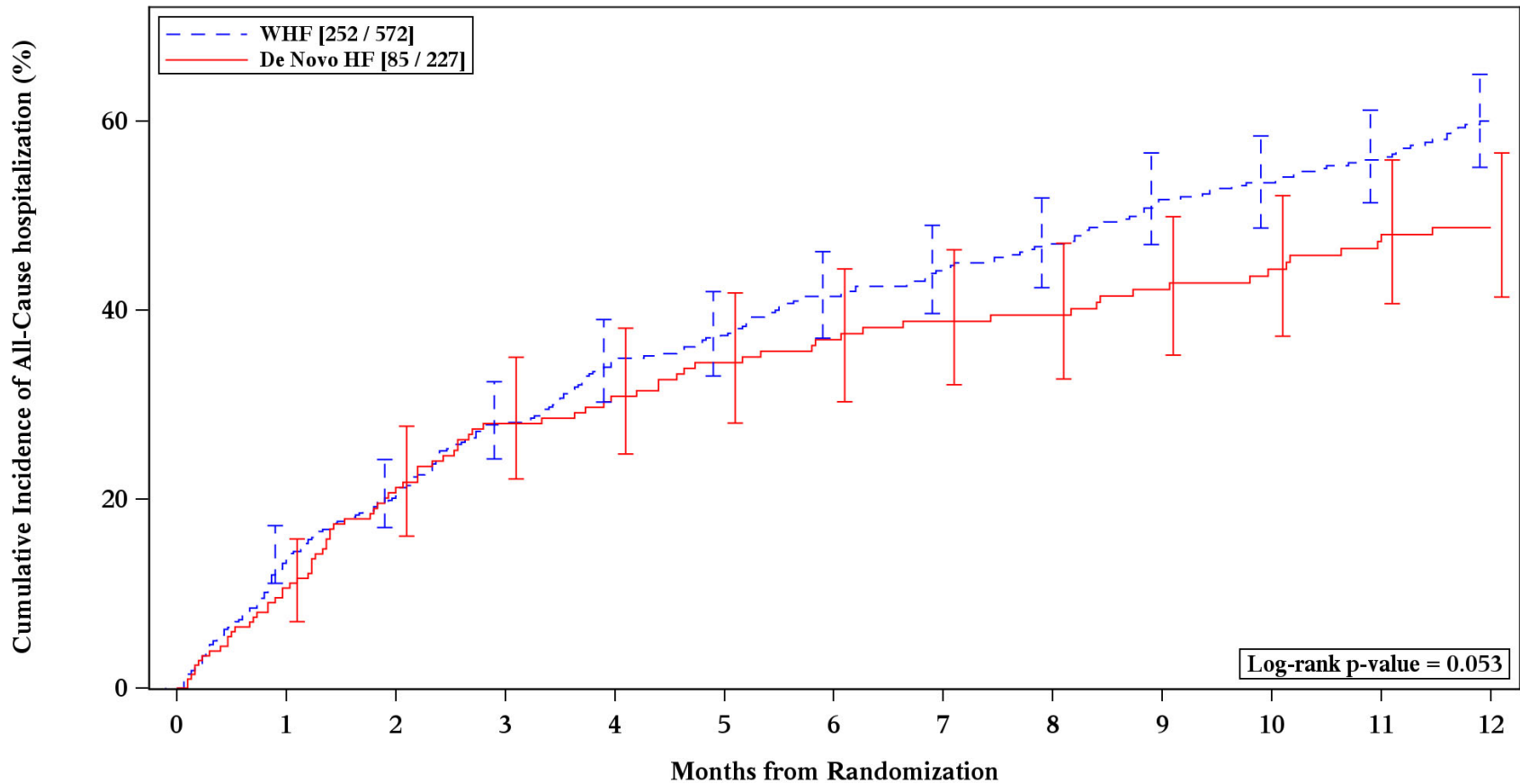
eFigure 5: Unadjusted cumulative incidence curves for all-cause hospitalization over 12 months comparing De novo and WHF for patients with EF level $\leq 40\%$



	Number at Risk												
	0	1	2	3	4	5	6	7	8	9	10	11	12
WHF	1277	970	764	684	615	555	477	414	373	347	317	293	200
De Novo HF	558	435	368	347	322	303	272	251	241	224	210	201	144

Note: Patients who died were censored at time of death.

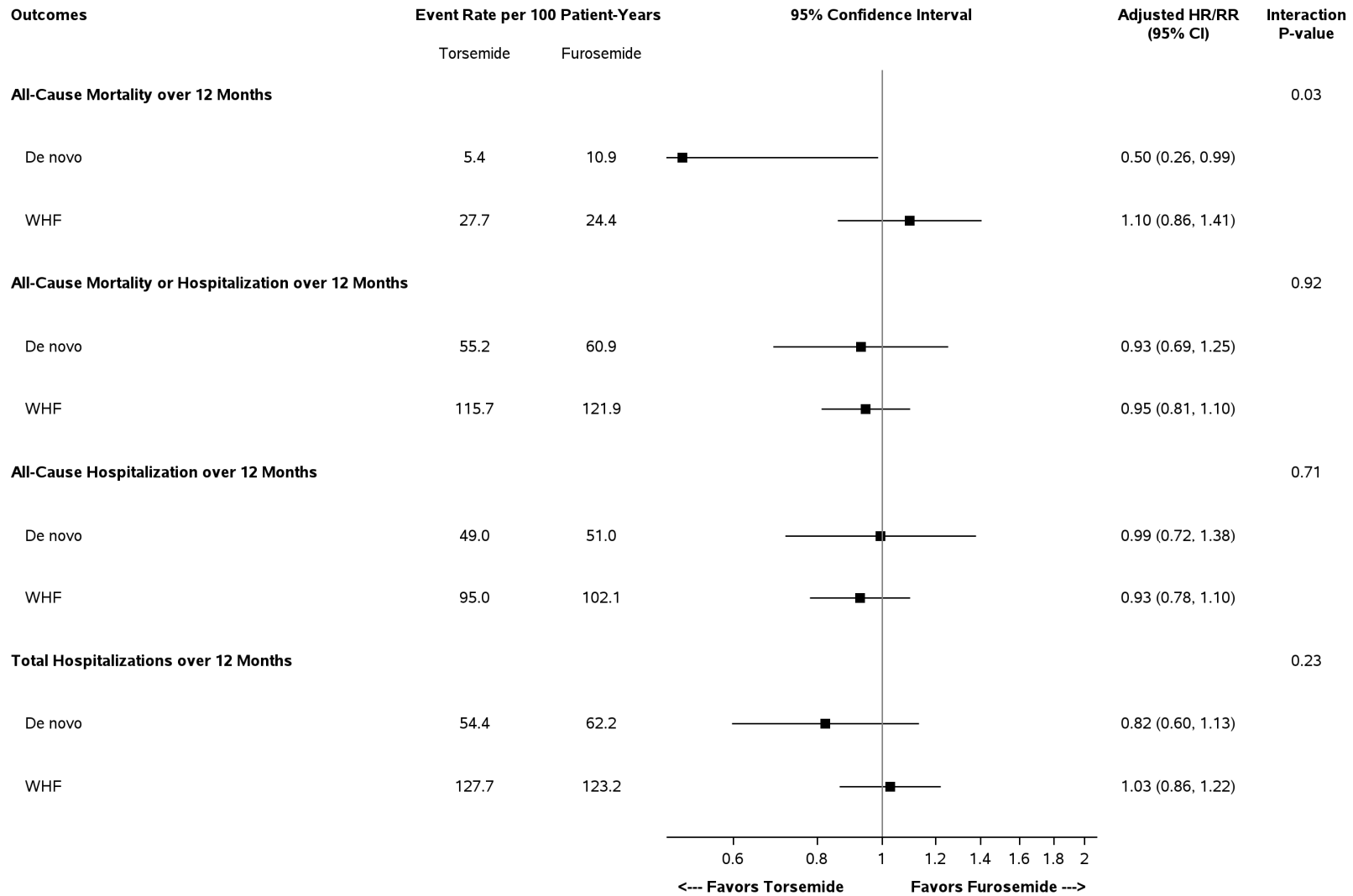
eFigure 6: Unadjusted cumulative incidence curves for all-cause hospitalization over 12 months comparing De novo and WHF for patients with EF level >40%



Number at Risk		0	1	2	3	4	5	6	7	8	9	10	11	12
WHF	572	421	356	310	277	259	224	202	185	163	155	144	144	92
De Novo HF	227	174	142	127	118	109	101	93	90	84	76	72	72	43

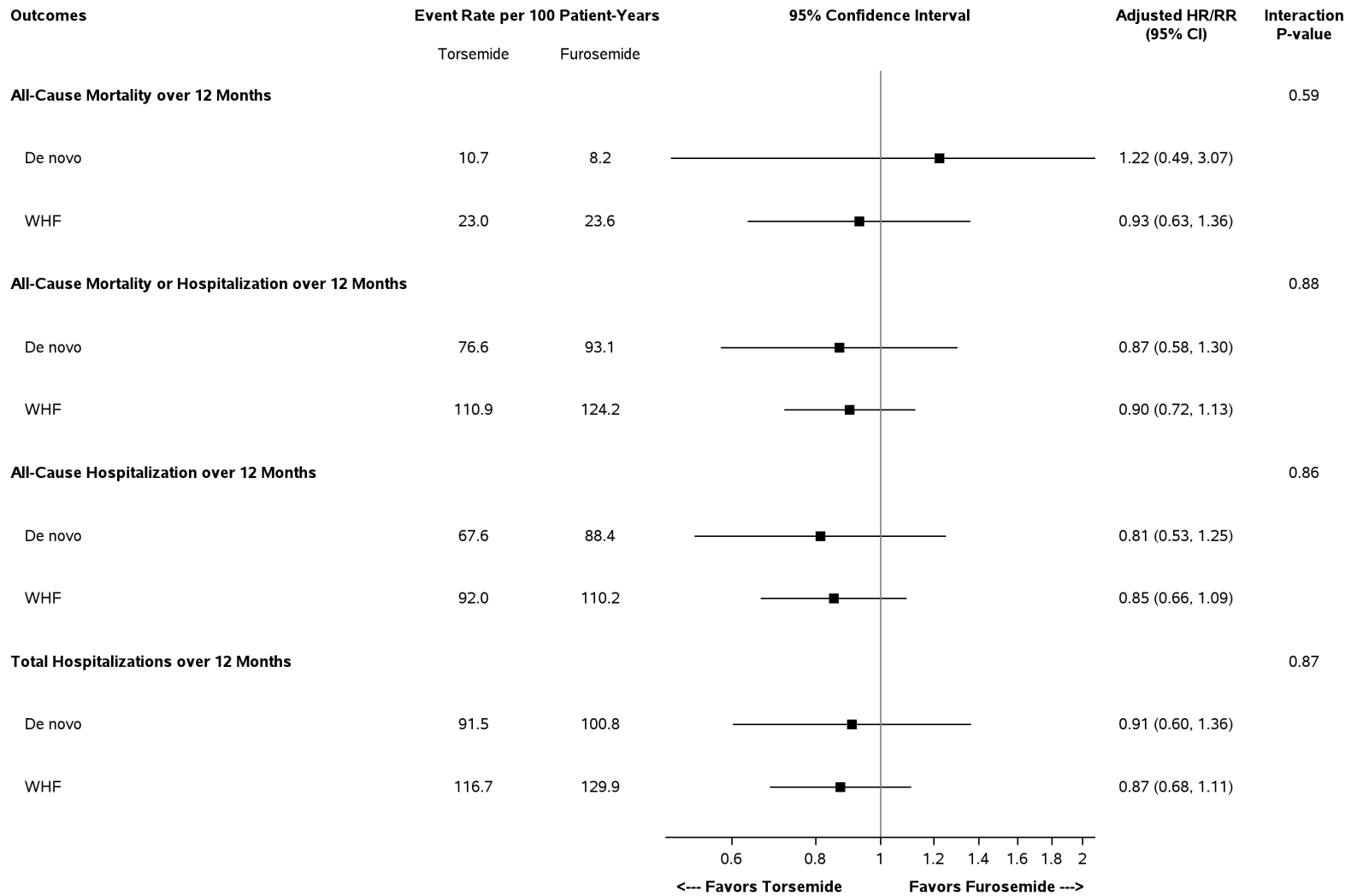
Note: Patients who died were censored at time of death.

eFigure 7: Forest plot of HR/RR comparing randomized diuretic treatments (Torsemide vs Furosemide) for overall patients and patients for all endpoints among patient with EF level $\leq 40\%$



Note: First event rates per 100 patient-years are reported for all-cause mortality, all-cause mortality or hospitalization and all-cause hospitalization. For total hospitalizations, the total event rates per 100 patient-years are reported. HR=Hazard Ratio RR=Rate Ratio

eFigure 8: Forest plot of HR/RR comparing randomized diuretic treatments (Torsemide vs Furosemide) for overall patients and patients for all endpoints among patient with EF level >40%



Note: First event rates per 100 patient-years are reported for all-cause mortality, all-cause mortality or hospitalization and all-cause hospitalization. For total hospitalizations, the total event rates per 100 patient-years are reported.
 HR=Hazard Ratio RR=Rate Ratio