Effect of Aliskiren on Post-discharge Mortality and Heart Failure Readmissions Among Patients Hospitalized for Heart Failure: AliSkiren TRial ON Acute heart failure oUTcomes (ASTRONAUT)

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Study Organization

Study Executive Committee:

- Mihai Gheorghiade, MD; Chair
- Aldo P. Maggioni, MD; Co-Chair
- Michael Böhm, MD
- Gregg C. Fonarow, MD
- Faiez Zannad, MD, PhD

Study Data Monitoring Committee:

- Karl Swedberg, MD, PhD; Chair
- Jeffrey S. Borer, MD
- Bertram Pitt, MD
- Stuart Pocock, PhD
- Jean Rouleau, MD

Central Endpoint Committee:

- Scott D. Solomon, MD; Chair
- Eldrin F. Lewis, MD; Co-Chair
- Peter Finn, MD
- Larry Weinrauch, MD
- Ebrahim Barkoudah, MD
- Kayode Odutayo, MD

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Background and rationale

- Post-discharge mortality and re-hospitalization rates remain high in patients hospitalized for HF, despite the use of evidence-based therapies[1–4]
- Inhibition of the RAAS with ACEIs, ARBs and aldosterone antagonists is beneficial in patients with HF and reduced ejection fraction[5,6], but induces compensatory increases in renin and downstream RAAS intermediaries[7]
- The direct renin inhibitor aliskiren represents a distinct mechanism for RAAS blockade with the theoretical benefit of upstream RAAS inhibition at the point of pathway activation[7]
- ASTRONAUT tested the hypothesis that neurohormonal modulation with aliskiren in addition to standard therapy during the early post-discharge period, sometimes referred to as the 'vulnerable phase',[3] may improve long-term outcomes[7]

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; HF=heart failure; RAAS=renin-angiotensin-aldosterone system

1. Gheorghiade M, et al. JAMA 2006;296: 2217–26; 2. Blair JE, et al. J Am Coll Cardiol 2008;52:1640–48; 3. Gheorghiade M, et al. J Am Coll Cardiol 2013;61:391–403; 4. Bueno H, et al. JAMA 2010;303:2141–7; 5. Hunt SA, et al. Circulation 2009;119:e391–e479; 6. McMurray JJ, et al. Eur Heart J 2012;33:1787–1847; 7. Gheorghiade M, et al. Eur J Heart Fail 2011;13:100–6

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ASTRONAUT: Study Objectives

Primary:

- CV death or HF re-hospitalization within 6 months

Key Secondary:

- CV death or HF re-hospitalization within 12 months

Secondary:

- First CV event within 12 months (i.e., CV death, HF hospitalization, non-fatal MI, non-fatal stroke, sudden death with resuscitation)
- All-cause mortality within 6 and 12 months
- Change from baseline in NT-proBNP at 1, 6, and 12 months of follow-up

CV=cardiovascular; HF=heart failure; MI=myocardial infarction
NT-proBNP=N-terminal pro-B-type natriuretic peptide

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Selection Criteria

Selected inclusion criteria:

- Patients with chronic HF after a period of acute decompensation
- LVEF ≤40% **and** BNP ≥400 pg/mL or NT-proBNP ≥1,600 pg/mL
- Hemodynamically/clinically stable, defined as SBP ≥110 mmHg for at least 6 hours and no use of IV vasodilators (except nitrates), and/or any IV inotropic therapy from the time of hospital presentation to randomization

Selected exclusion criteria:

- MI, cardiac surgery or stroke within 3 months prior to enrollment
- eGFR <40 mL/min/1.73 m^2 or potassium >5.0 mEq/L
- Severe hyponatremia <130 mEq/L

BNP=B-type natriuretic peptide; eGFR=estimated glomerular filtration rate; HF=heart failure; IV=intravenous; LVEF=left ventricular ejection fraction; MI=myocardial infarction; NT-proBNP=N-terminal pro-B-type natriuretic peptide; SBP=systolic blood pressure

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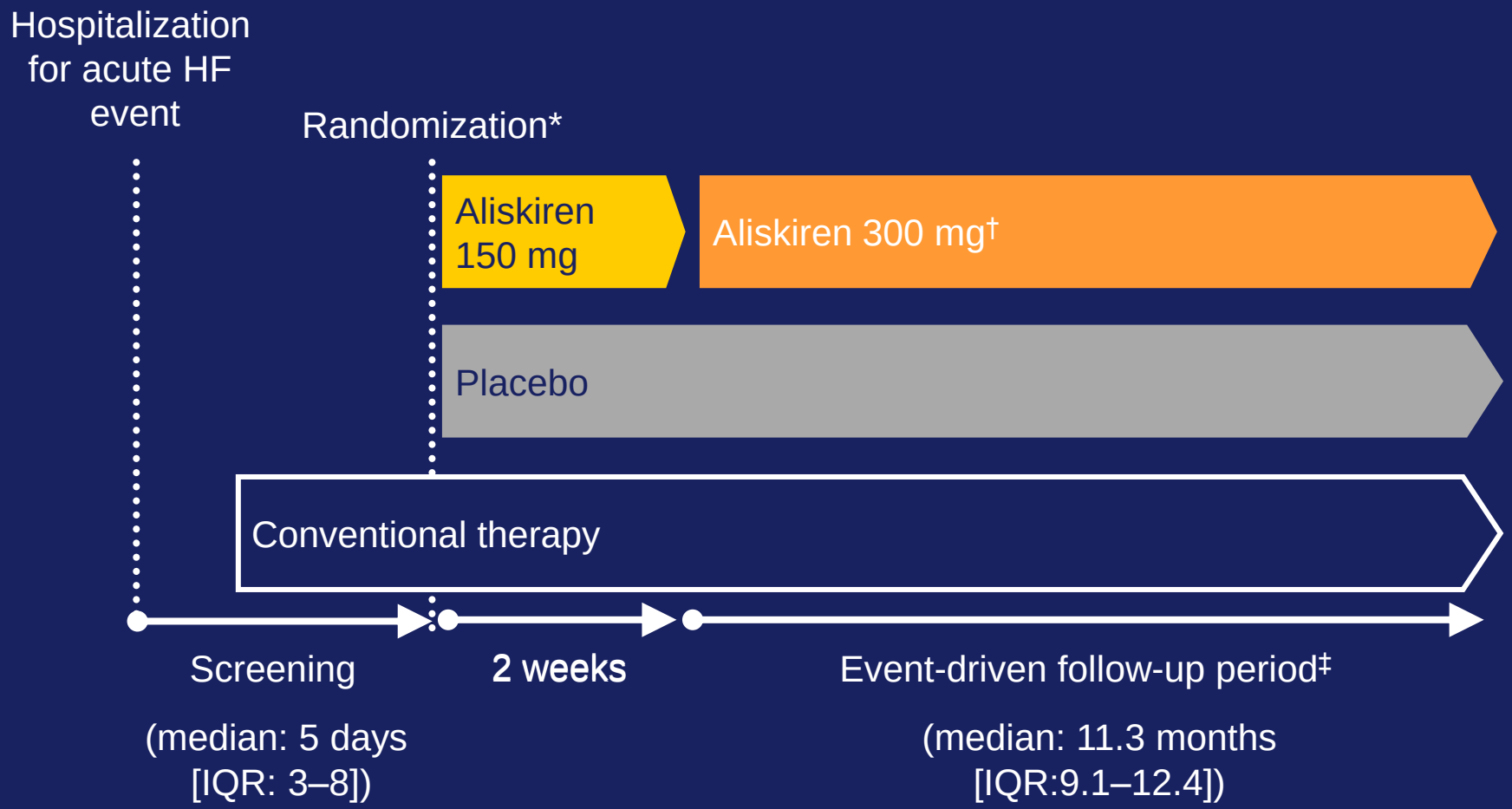
Study Design



*Patients were hemodynamically/clinically stable and randomized prior to discharge; †Patients not tolerating the 300 mg study medication dose could be down titrated to the 150 mg dose at the investigators discretion at any time during the study; ‡Study visits scheduled at 2, 3, 6, 9, and 12 months with electrolyte levels (i.e., potassium and sodium) and renal function (i.e., GFR) measured at every visit

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Statistical Analysis

- 1,782 patients were required to reach 381 primary events (80% power to reject null hypothesis at 0.05 level)
- A re-assessment of the sample size was conducted following the results of the ALTITUDE trial;[1] it was determined that the required number of primary events would be achieved with the 1,639 patients already randomized and therefore enrollment was stopped

ALTITUDE=Aliskiren Trial In Type 2 diabetes Using cardio-renal Disease Endpoints

1. Parving H-H, et al. N Engl J Med 2012;367:2204–13

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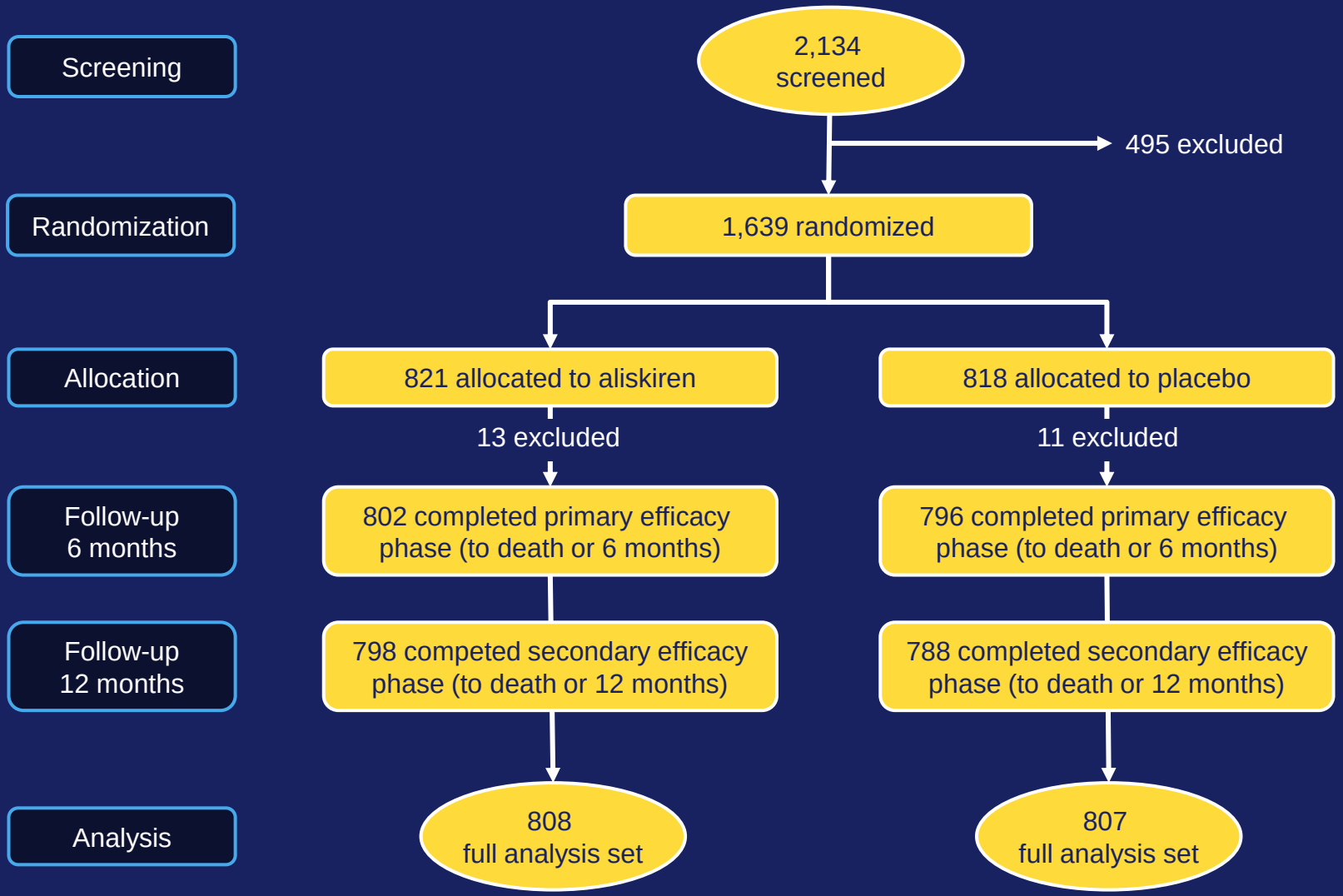
Patient Flow



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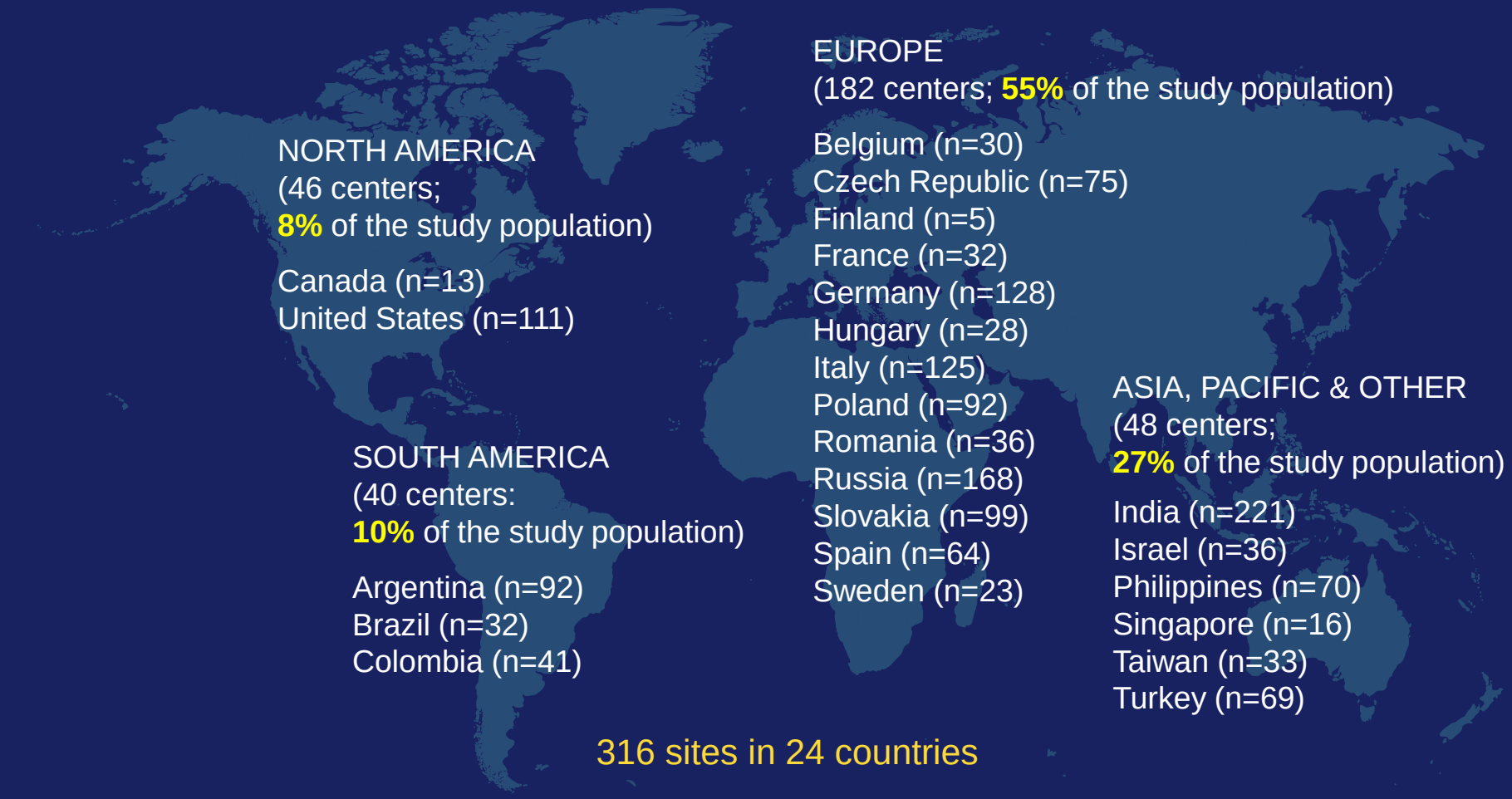
Geographic Distribution of Patients in ASTRONAUT



NORTH AMERICA
(46 centers;
8% of the study population)

Canada (n=13)
United States (n=111)

SOUTH AMERICA
(40 centers:
10% of the study population)

Argentina (n=92)
Brazil (n=32)
Colombia (n=41)

EUROPE
(182 centers; **55%** of the study population)

Belgium (n=30)
Czech Republic (n=75)
Finland (n=5)
France (n=32)
Germany (n=128)
Hungary (n=28)
Italy (n=125)
Poland (n=92)
Romania (n=36)
Russia (n=168)
Slovakia (n=99)
Spain (n=64)
Sweden (n=23)

ASIA, PACIFIC & OTHER
(48 centers;
27% of the study population)

India (n=221)
Israel (n=36)
Philippines (n=70)
Singapore (n=16)
Taiwan (n=33)
Turkey (n=69)

316 sites in 24 countries

2,134 patients were screened between May 2009 and July 2012; 1,639 patients were randomized

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Baseline Characteristics

Baseline characteristic*	Aliskiren (n=808)	Placebo (n=807)	Total (n=1,615)
Age, mean (SD), years	64.7 (12.44)	64.5 (11.88)	64.6 (12.16)
Male, n (%)	637 (78.8)	610 (75.6)	1,247 (77.2)
Ischemic heart failure etiology, n (%)	520 (64.4)	507 (62.8)	1,027 (63.6)
LVEF, mean (SD), %	27.9 (7.3)	27.8 (7.2)	27.9 (7.3)
SBP, mean (SD), mmHg	123 (13)	123 (13)	123 (13)
Heart rate, mean (SD), bpm	78 (16)	78 (16)	78 (16)
eGFR, mean (SD), mL/min/1.73 m^2	**67 (20)**	**66 (20)**	**67 (20)**
NT-proBNP at admission, median (IQR), pg/mL	**4,278 (2,755–7,755)**	**4,184 (2,706–7,921)**	**4,239 (2,710–7,886)**
NT-proBNP at randomization, median (IQR), pg/mL	**2,838 (1,516–5,235)**	**2,674 (1,551–5,233)**	**2,718 (1,531–5,235)**

*Data collected at time of randomization unless specified otherwise in the protocol
eGFR=estimated glomerular filtration rate; IQR=interquartile range; LVEF=left ventricular ejection fraction; NT-proBNP=N-terminal pro-B-type natriuretic peptide; SD=standard deviation

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Cardiac and Non-cardiac Comorbidities

Baseline characteristic	Aliskiren N=808 n (%)	Placebo N=807 n (%)	Total N=1,615 n (%)
Hypertension	612 (75.7)	613 (76.0)	1,225 (75.9)
Coronary artery disease	443 (54.8)	438 (54.3)	881 (54.6)
Atrial fibrillation	337 (41.7)	339 (42.0)	676 (41.9)
Diabetes mellitus	319 (39.5)	343 (42.5)	662 (41.0)
Renal insufficiency	160 (19.8)	172 (21.3)	332 (20.6)
COPD	168 (20.8)	154 (19.1)	322 (19.9)

COPD=chronic obstructive pulmonary disease

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Background Therapies

Baseline characteristic*	Aliskiren N=808 n (%)	Placebo N=807 n (%)	Total N=1,615 n (%)
Diuretic	775 (95.9)	773 (95.8)	1,548 (95.9)
ACEI/ARB	686 (84.9)	674 (83.6)	1,360 (84.2)
β-blocker	660 (81.7)	673 (83.4)	1,333 (82.5)
Mineralocorticoid receptor antagonist	448 (55.4)	473 (58.6)	921 (57.0)
Digoxin	319 (39.5)	309 (38.3)	628 (38.9)
Antiplatelet therapy	528 (65.3)	513 (63.6)	1,041 (64.5)
Implantable cardioverter-defibrillator	126 (15.6)	127 (15.7)	253 (15.7)
Permanent pacemaker (including CRT)	95 (11.8)	86 (10.7)	181 (11.2)

*Data collected at time of randomization
ACEI=angiotensin-converting enzyme inhibitor;
ARB=angiotensin receptor blocker; CRT=cardiac resynchronization therapy

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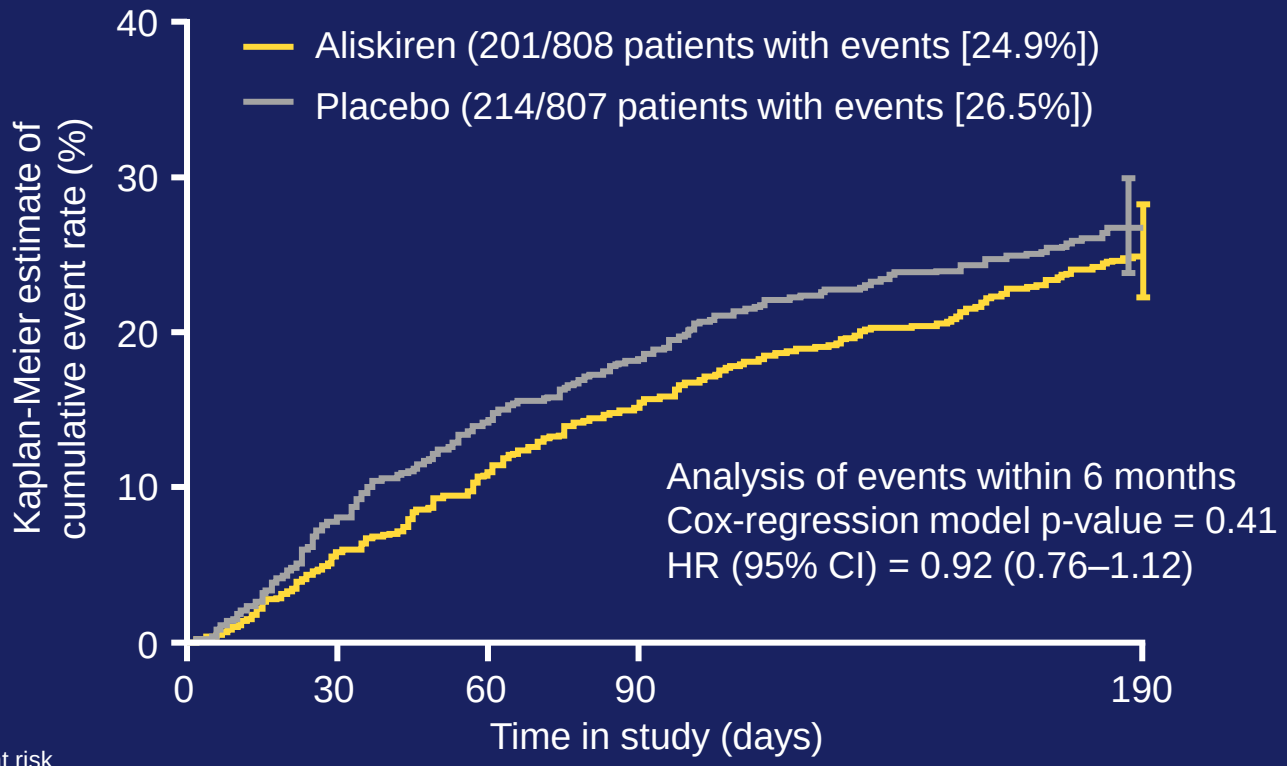
Primary Endpoint:
CV Death or HF Re-hospitalization Within 6 Months



	Aliskiren N=808 n (%)	Placebo N=807 n (%)	HR (95% CI)	p-value (two sided)
CV death	77 (9.5)	85 (10.5)	0.92 (0.68–1.26)	0.60
HF re-hospitalization	153 (18.9)	166 (20.6)	0.90 (0.72–1.12)	0.35

CI=confidence interval; CV=cardiovascular; HF=heart failure; HR=hazard ratio

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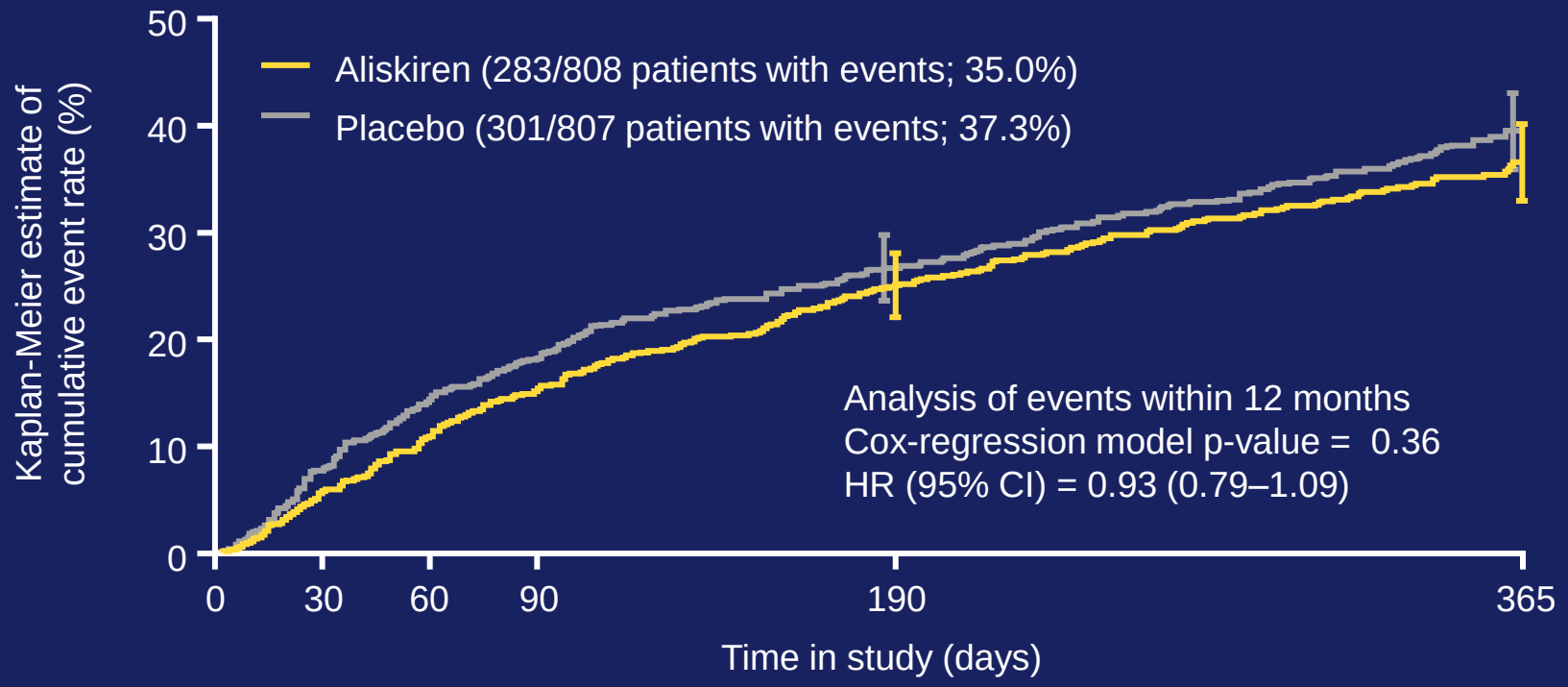
Key Secondary Endpoint:
CV Death or HF Re-hospitalization Within 12 Months



Patients at risk						
Aliskiren	808	762	716	679	597	204
Placebo	807	743	690	655	578	196

	Aliskiren N=808 n (%)	Placebo N=807 n (%)	HR (95% CI)	p-value (two sided)
CV death	126 (15.6)	137 (17.0)	0.94 (0.73–1.19)	0.60
HF re-hospitalization	212 (26.2)	224 (27.8)	0.93 (0.77–1.12)	0.44

CI=confidence interval; CV=cardiovascular; HF=heart failure; HR=hazard ratio

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Secondary Endpoints (12 Months)

Endpoint	Aliskiren N=808 n (%)	Placebo N=807 n (%)	HR (95% CI)	p-value (two sided)
All-cause death	144 (17.8)	148 (18.3)	0.99 (0.78–1.24)	0.92
First CV Event	**293 (36.3)**	**321 (39.8)**	**0.88 (0.75–1.03)**	**0.12**
CV death	126 (15.6)	137 (17.0)	0.94 (0.73–1.19)	0.60
HF re-hospitalization	212 (26.2)	224 (27.8)	0.93 (0.77–1.12)	0.44
Fatal or non-fatal MI	18 (2.2)	38 (4.7)	0.47 (0.27–0.83)	<0.01
Fatal or non-fatal stroke	18 (2.2)	27 (3.3)	0.63 (0.34–1.14)	0.13
Resuscitated sudden death	5 (0.6)	10 (1.2)	0.52 (0.18–1.52)	0.23
Patients re-hospitalized for any cause	389 (48.1)	396 (49.1)	—	0.73‡

Data analyzed using Cox-regression model unless otherwise stated; ‡Fisher's Exact Test
CI=confidence interval; CV=cardiovascular; HF=heart failure; HR=hazard ratio; MI=myocardial infarction

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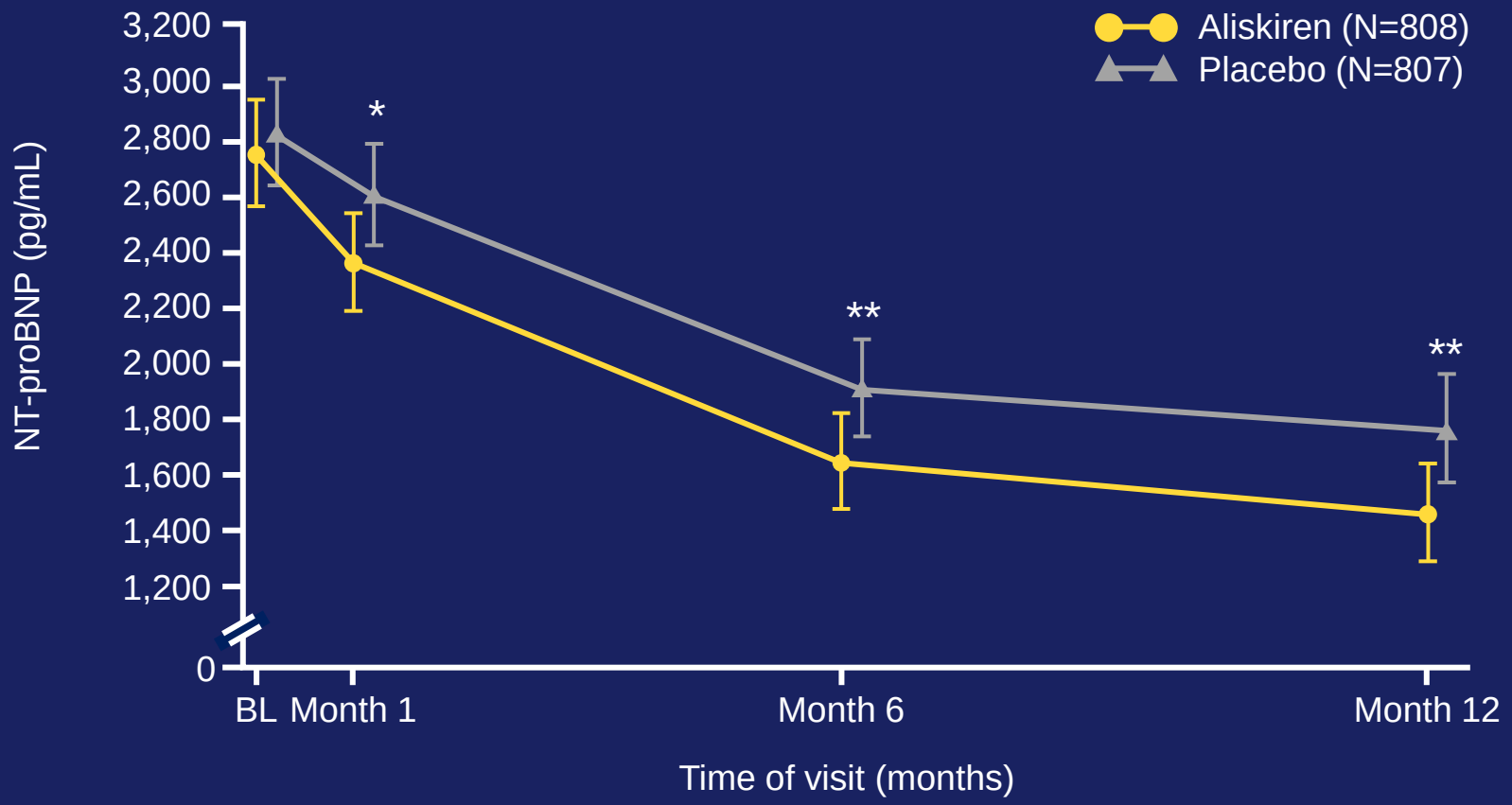
Change in NT-proBNP With Time



Number of subjects				
Aliskiren	778	673	573	451
Placebo	776	678	562	430

*p=0.01, **p<0.01 between treatment comparison
Data presented as geometric mean +/– 95% confidence interval
BL=baseline; NT-proBNP=N-terminal pro-B-type natriuretic peptide

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Safety: Adverse and Serious Adverse Events

Endpoint	Aliskiren N=808 n (%)	Placebo N=810 n (%)	Total N=1,618 n (%)	p-value
Patients with ≥1 AE	670 (82.9)	667 (82.3)	1,337 (82.6)	0.79
Patients with ≥1 SAE	421 (52.1)	435 (53.7)	856 52.9)	0.55
Patients who discontinued study drug due to any AEs	171 (21.2)	163 (20.1)	334 (20.6)	0.62
Patients who discontinued study drug due to any SAEs	79 (9.8)	108 (13.3)	187 (11.6)	0.03
Patients who discontinued study drug due to non-serious AEs	95 (11.8)	60 (7.4)	155 (9.6)	<0.01

AE=adverse event; SA=serious adverse event

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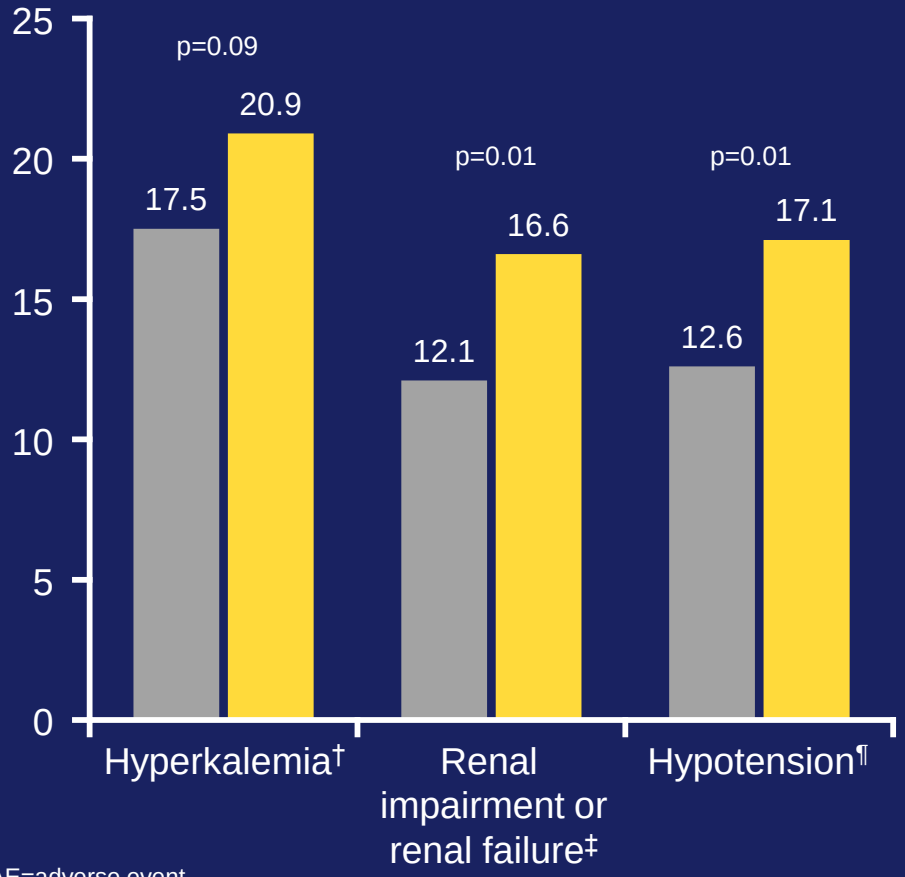
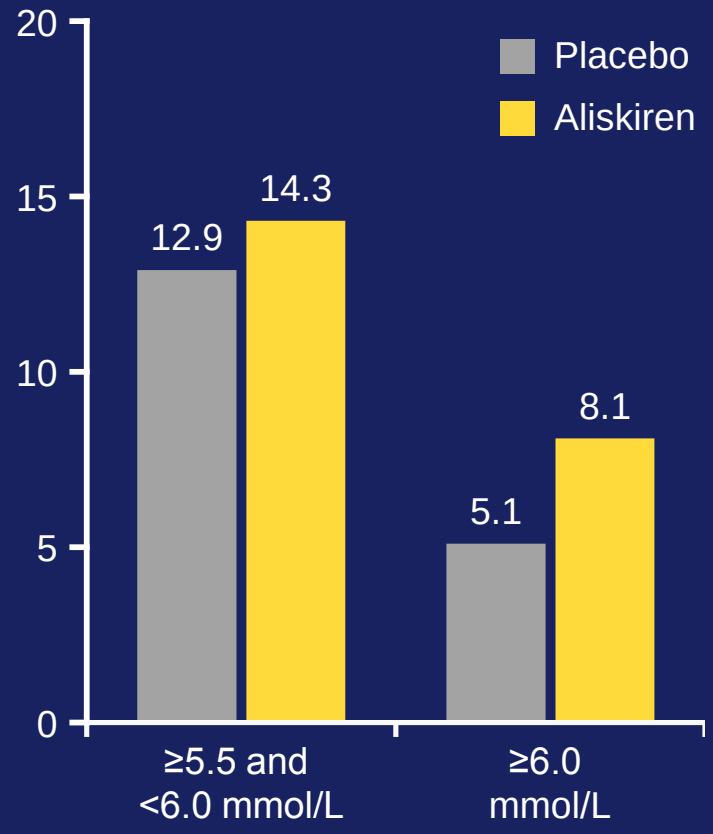
Safety: Hyperkalemia, Renal Dysfunction and Hypotension

Proportion of patients experiencing stated AE (%)



Proportion of patients with elevated serum potassium levels (%)



AE=adverse event
†Includes hyperkalemia and increased blood potassium level
‡Includes abnormal renal function test, acute renal failure, decreased urine output , increased blood creatinine, acute pre-renal failure, renal impairment, renal failure, decreased glomerular filtration rate and increased blood urea
¶Includes decreased blood pressure, postural dizziness, hypotension, orthostatic hypotension and procedural hypotension

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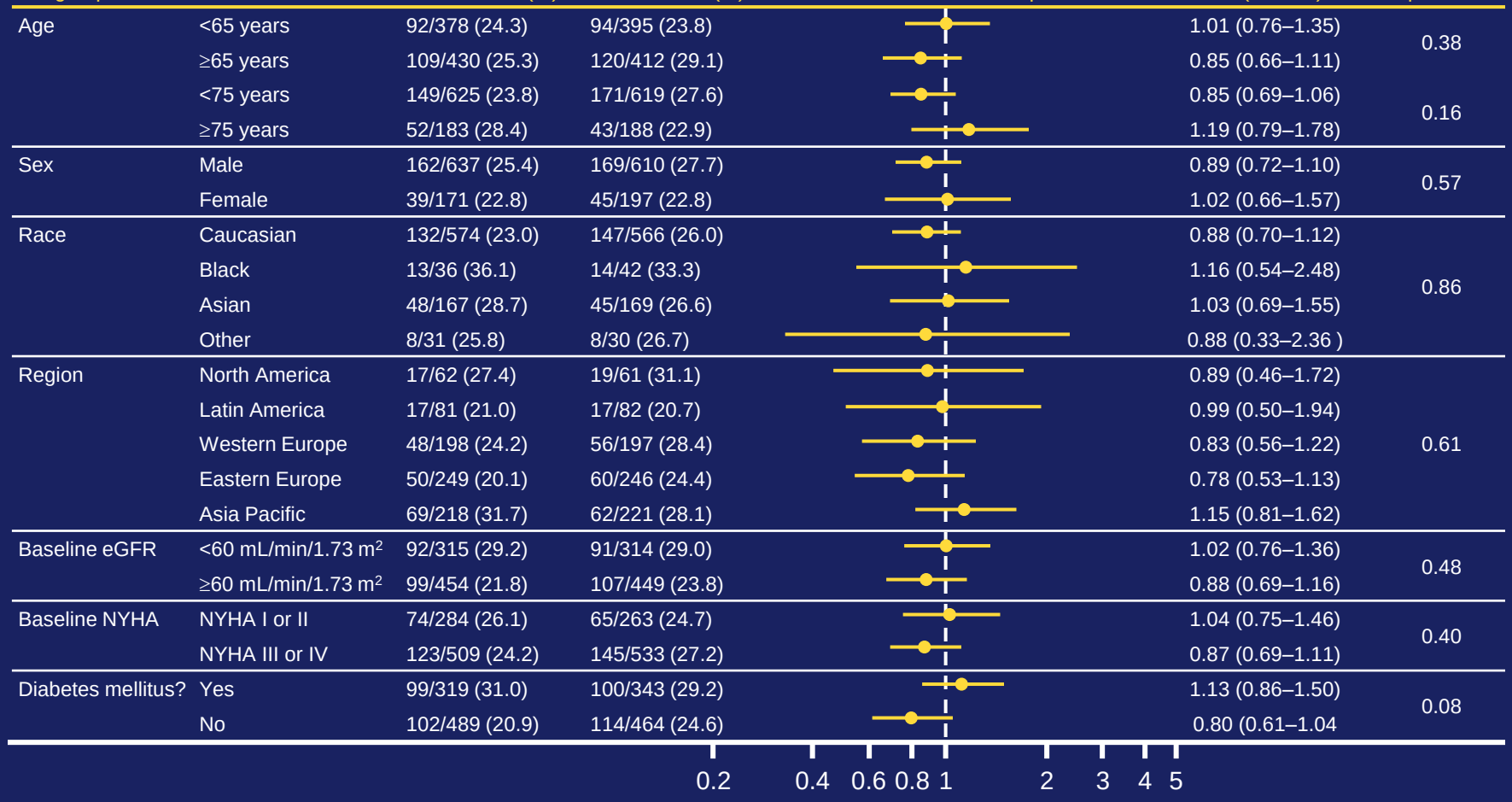
Sub-group Analysis for Primary Endpoint of CV Death or HF Re-hospitalization Within 6 months

Subgroup variable		Aliskiren n/N (%)	Placebo n/N (%)	HR (95% CI)	Interaction p-value
Age	<65 years	92/378 (24.3)	94/395 (23.8)	1.01 (0.76–1.35)	0.38
	≥65 years	109/430 (25.3)	120/412 (29.1)	0.85 (0.66–1.11)	
	<75 years	149/625 (23.8)	171/619 (27.6)	0.85 (0.69–1.06)	0.16
	≥75 years	52/183 (28.4)	43/188 (22.9)	1.19 (0.79–1.78)	
Sex	Male	162/637 (25.4)	169/610 (27.7)	0.89 (0.72–1.10)	0.57
	Female	39/171 (22.8)	45/197 (22.8)	1.02 (0.66–1.57)	
Race	Caucasian	132/574 (23.0)	147/566 (26.0)	0.88 (0.70–1.12)	0.86
	Black	13/36 (36.1)	14/42 (33.3)	1.16 (0.54–2.48)	
	Asian	48/167 (28.7)	45/169 (26.6)	1.03 (0.69–1.55)	
	Other	8/31 (25.8)	8/30 (26.7)	0.88 (0.33–2.36)	
Region	North America	17/62 (27.4)	19/61 (31.1)	0.89 (0.46–1.72)	0.61
	Latin America	17/81 (21.0)	17/82 (20.7)	0.99 (0.50–1.94)	
	Western Europe	48/198 (24.2)	56/197 (28.4)	0.83 (0.56–1.22)	
	Eastern Europe	50/249 (20.1)	60/246 (24.4)	0.78 (0.53–1.13)	
	Asia Pacific	69/218 (31.7)	62/221 (28.1)	1.15 (0.81–1.62)	
Baseline eGFR	<60 mL/min/1.73 m^2	92/315 (29.2)	91/314 (29.0)	1.02 (0.76–1.36)	0.48
	≥60 mL/min/1.73 m^2	99/454 (21.8)	107/449 (23.8)	0.88 (0.69–1.16)	
Baseline NYHA	NYHA I or II	74/284 (26.1)	65/263 (24.7)	1.04 (0.75–1.46)	0.40
	NYHA III or IV	123/509 (24.2)	145/533 (27.2)	0.87 (0.69–1.11)	
Diabetes mellitus?	Yes	99/319 (31.0)	100/343 (29.2)	1.13 (0.86–1.50)	0.08
	No	102/489 (20.9)	114/464 (24.6)	0.80 (0.61–1.04	



CI=confidence interval; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; HR=hazard ratio; NYHA=New York Heart Association

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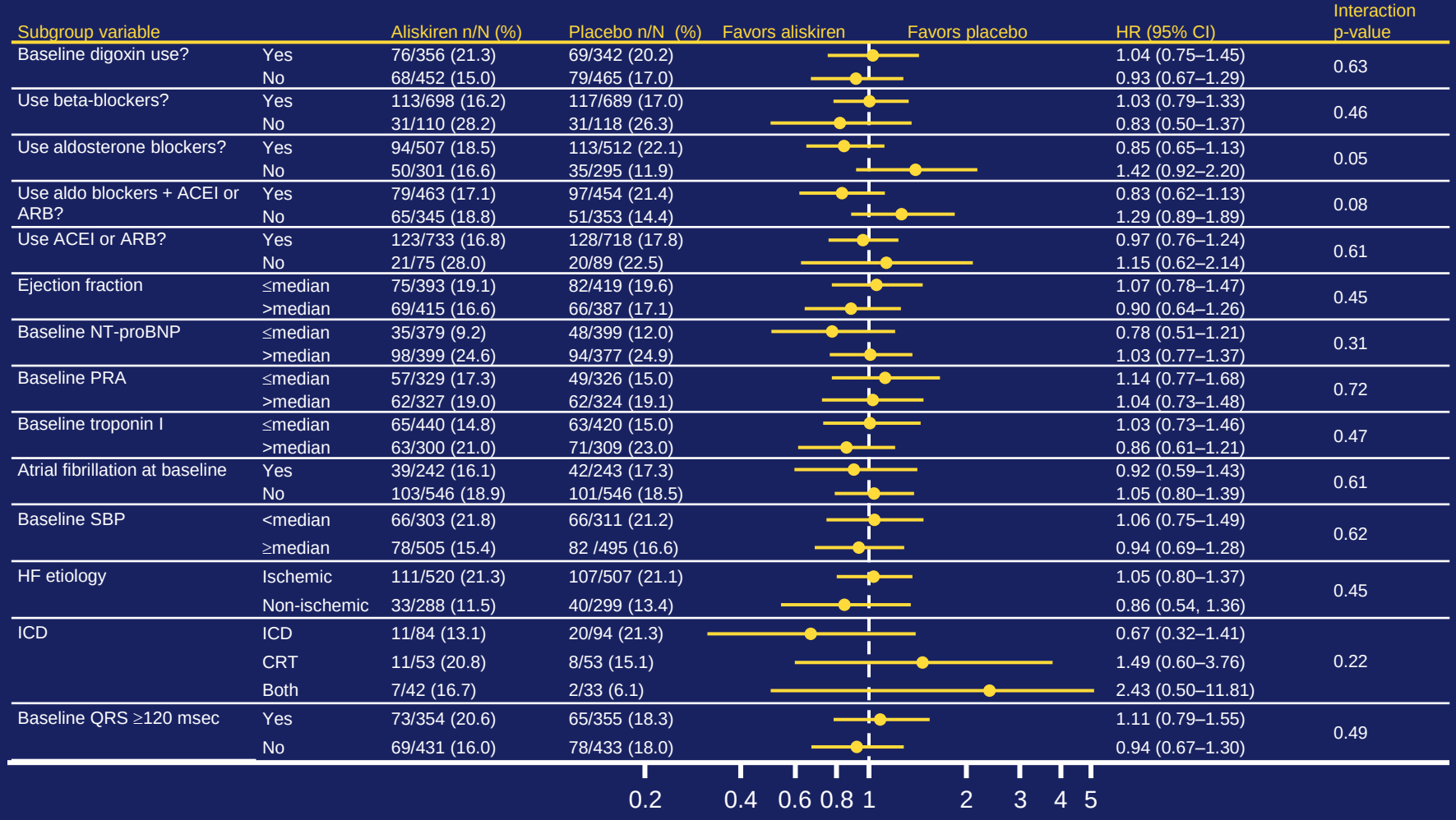
Sub-group Analysis for Primary Endpoint of CV Death or HF Re-hospitalization Within 6 months

Subgroup variable		Aliskiren n/N (%)	Placebo n/N (%)	HR (95% CI)	Interaction p-value
Baseline digoxin use?	Yes	76/356 (21.3)	69/342 (20.2)	1.04 (0.75–1.45)	0.63
	No	68/452 (15.0)	79/465 (17.0)	0.93 (0.67–1.29)	
Use beta-blockers?	Yes	113/698 (16.2)	117/689 (17.0)	1.03 (0.79–1.33)	0.46
	No	31/110 (28.2)	31/118 (26.3)	0.83 (0.50–1.37)	
Use aldosterone blockers?	Yes	94/507 (18.5)	113/512 (22.1)	0.85 (0.65–1.13)	0.05
	No	50/301 (16.6)	35/295 (11.9)	1.42 (0.92–2.20)	
Use aldo blockers + ACEI or ARB?	Yes	79/463 (17.1)	97/454 (21.4)	0.83 (0.62–1.13)	0.08
	No	65/345 (18.8)	51/353 (14.4)	1.29 (0.89–1.89)	
Use ACEI or ARB?	Yes	123/733 (16.8)	128/718 (17.8)	0.97 (0.76–1.24)	0.61
	No	21/75 (28.0)	20/89 (22.5)	1.15 (0.62–2.14)	
Ejection fraction	≤median	75/393 (19.1)	82/419 (19.6)	1.07 (0.78–1.47)	0.45
	>median	69/415 (16.6)	66/387 (17.1)	0.90 (0.64–1.26)	
Baseline NT-proBNP	≤median	35/379 (9.2)	48/399 (12.0)	0.78 (0.51–1.21)	0.31
	>median	98/399 (24.6)	94/377 (24.9)	1.03 (0.77–1.37)	
Baseline PRA	≤median	57/329 (17.3)	49/326 (15.0)	1.14 (0.77–1.68)	0.72
	>median	62/327 (19.0)	62/324 (19.1)	1.04 (0.73–1.48)	
Baseline troponin I	≤median	65/440 (14.8)	63/420 (15.0)	1.03 (0.73–1.46)	0.47
	>median	63/300 (21.0)	71/309 (23.0)	0.86 (0.61–1.21)	
Atrial fibrillation at baseline	Yes	39/242 (16.1)	42/243 (17.3)	0.92 (0.59–1.43)	0.61
	No	103/546 (18.9)	101/546 (18.5)	1.05 (0.80–1.39)	
Baseline SBP	<median	66/303 (21.8)	66/311 (21.2)	1.06 (0.75–1.49)	0.62
	≥median	78/505 (15.4)	82 /495 (16.6)	0.94 (0.69–1.28)	
HF etiology	Ischemic	111/520 (21.3)	107/507 (21.1)	1.05 (0.80–1.37)	0.45
	Non-ischemic	33/288 (11.5)	40/299 (13.4)	0.86 (0.54, 1.36)	
ICD	ICD	11/84 (13.1)	20/94 (21.3)	0.67 (0.32–1.41)	
	CRT	11/53 (20.8)	8/53 (15.1)	1.49 (0.60–3.76)	0.22
	Both	7/42 (16.7)	2/33 (6.1)	2.43 (0.50–11.81)	
Baseline QRS ≥120 msec	Yes	73/354 (20.6)	65/355 (18.3)	1.11 (0.79–1.55)	0.49
	No	69/431 (16.0)	78/433 (18.0)	0.94 (0.67–1.30)	



ACEI=angiotensin-converting enzyme inhibitor; Aldo=aldosterone; ARB=angiotensin receptor blocker; CI=confidence interval; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HF=heart failure; HR=hazard ratio; ICD=implantable cardioverter-defibrillator; NT-proBNP=N-terminal pro-B-type natriuretic peptide; PRA=plasma renin activity; SBP=systolic blood pressure

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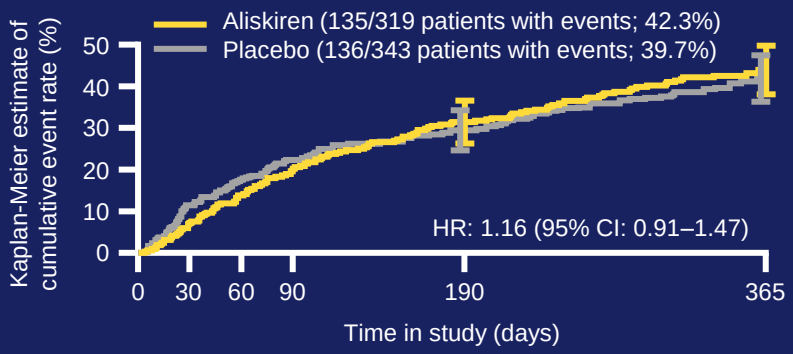
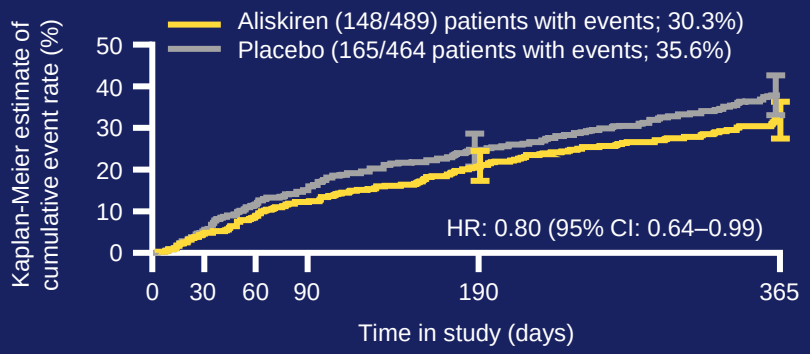
Secondary Endpoints of CV Death or HF Re-hospitalization Within 12 Months or All-cause Death Within 12 Months by Diabetes Status

CV death or HF re-hospitalization within 12 months

Diabetes



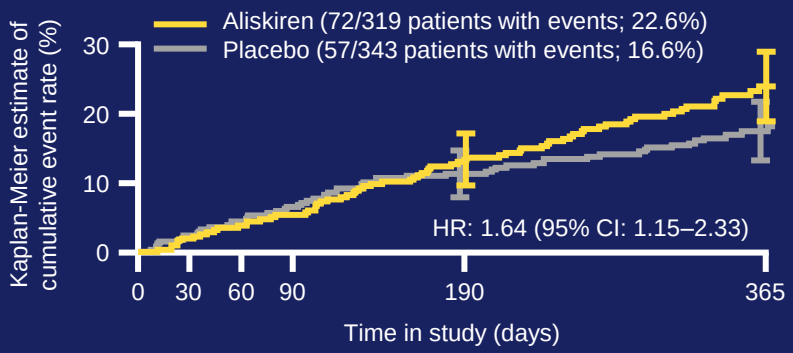
No diabetes



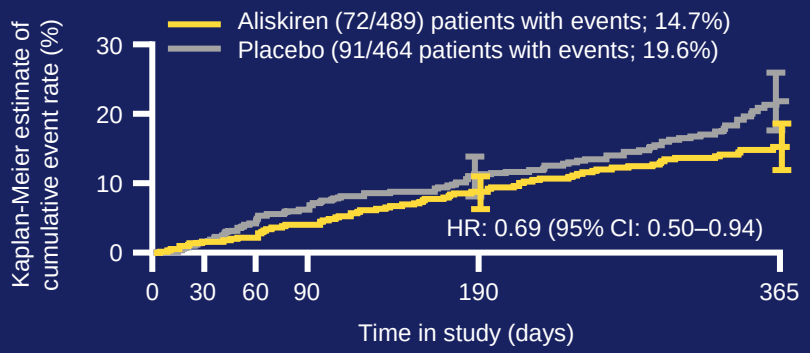
p-value for treatment by diabetes interaction = 0.03

All-cause death within 12 months

Diabetes



No diabetes



p-value for treatment by diabetes interaction <0.01

Overall 41.0% of patients randomized had a history of diabetes mellitus
CI=confidence interval; CV=cardiovascular; HF=heart failure; HR=hazard ratio

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Conclusions

- In patients recently hospitalized with worsening chronic HF and reduced ejection fraction, aliskiren did not improve post-discharge mortality and/or hospitalizations when added to evidence-based therapy for HF
- Aliskiren was associated with a significant and sustained decrease in NT-proBNP through 1 year follow-up
- Hyperkalemia, renal dysfunction and hypotension were reported more frequently in the aliskiren group than the placebo group
- For all pre-specified subgroups there was no difference in treatment effect for the primary endpoint
- Subgroup analysis for secondary endpoints was consistent with previous reports of poor outcomes with the use of aliskiren in patients with diabetes already receiving RAAS inhibitors. Contrasting effects of aliskiren in patients with vs without diabetes warrant further analysis
- ASTRONAUT did not support the routine administration of aliskiren in patients recently hospitalized for worsening chronic HF

CV=cardiovascular; HF=heart failure; NT-proBNP=N-terminal pro-B-type natriuretic peptide

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Directions for Future Research

- ASTRONAUT demonstrated again that post-discharge mortality and re-hospitalization rate is unacceptably high in spite of evidence-based therapies, even in patients who are stabilized at discharge and have a relatively preserved renal function
- Further investigations are needed to evaluate the effects of direct renin inhibition in addition to standard therapy in patients without diabetes who have recently been hospitalized for worsening HF

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