Background: Renin inhibition in heart failure with reduced ejection fraction (HF-REF)

- ACE inhibitors reduce mortality and reduce heart failure hospitalization rates in patients with HF-REF, across the spectrum of symptom severity (CONSENSUS, SOLVD).
- ARBs are an *alternative* in patients unable to tolerate an ACE inibitor because of cough (CHARM-Alternative).
- ARBs futher reduce cardiovascular mortality (CHARM-Added) and heart failure hospitalization (CHARM-Added, Val-HeFT) when *added to* an ACE inhibitor.
- Might a direct renin inhibitor (aliskiren) add to the benefit of an ACE inhibitor or be a better alternative to an ACE inhibitor?



<u>Aliskiren Trial to Minimize OutcomeS in Patients</u> with <u>HEart failuRE</u> (ATMOSPHERE)

- Age ≥18 years. NYHA class II-IV. LVEF ≤0.35
- BNP ≥150 pg/ml (NTpro-BNP ≥600 pg/ml) or if HF hosp. within12 mo. BNP ≥100 pg/ml (NTpro-BNP ≥400 pg/ml)
- Background ACEi therapy equivalent to enalapril ≥10 mg/d
- Beta-blocker unless contraindicated/not tolerated
- SBP \geq 95 mmHg run-in/ \geq 90 mmHg at randomization
- eGFR ≥35 ml/min/1.73m² at randomization /no decrease >25% during run in
- Potassium <5.0 mmol/l run-in/ <5.2 mmol/l at randomization

Rando	omization	*89% 10mg bid [†] Target dose (titrated from 150mg qd)				
	Enalapril 5-10mg bid* (n=2336)					
Enalapril Enalapril + 5-10mg bid Aliskiren150mg qd Aliskiren 300mg qd [†] (n=2340)						
	Enalapril 5-10mg bid	+ Aliskiren300mg qd (n=2340)				
• Open-label run-in		ble-blind				
4-12 weeks	Median follow-up = 36.6 months					

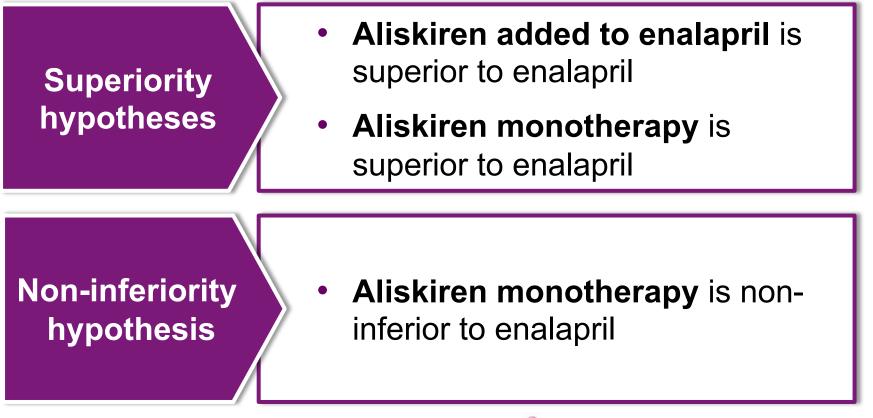
ATMOSPHERE: Baseline characteristics

	Aliskiren+Enalapril (n=2340)	Aliskiren (n=2340)	Enalapril (n=2336)
Age (years)	63.2 ± 11.7	63.3 ± 12.1	63.3 ± 11.7
Women (%)	21.1%	22.7%	21.4%
Ischemic etiology (%)	57.1%	55.3%	55.7%
LVEF (%)	28.5 ± 5.7	28.4 ± 5.7	28.3 ± 5.7
NYHA class II / III (%)	64.0% / 33.7%	64.0% / 34.3%	61.7% / 36.3%
Systolic BP (mm Hg)	124 ± 19	124 ± 18	123 ± 18
Heart rate (beats/min)	72 ± 13	72 ± 12	72 ± 13
NT pro-BNP (pg/ml)	1193 (640-2351)	1167 (627-2173)	1223 (634-2194)
History of diabetes	28.4%	26.8%	27.9%
Digitalis	32.7%	32.0%	31.2%
Beta-blocker	92.0%	91.2%	91.9%
MRA	36.6%	36.9%	37.8%
CRT-P/CRT-D	6.1%	5.1%	5.6%
ICD/CRT-D	15.0%	15.5%	14.4%



<u>Aliskiren Trial to Minimize OutcomeS in</u> Patients with <u>HEart failuRE</u> (ATMOSPHERE)

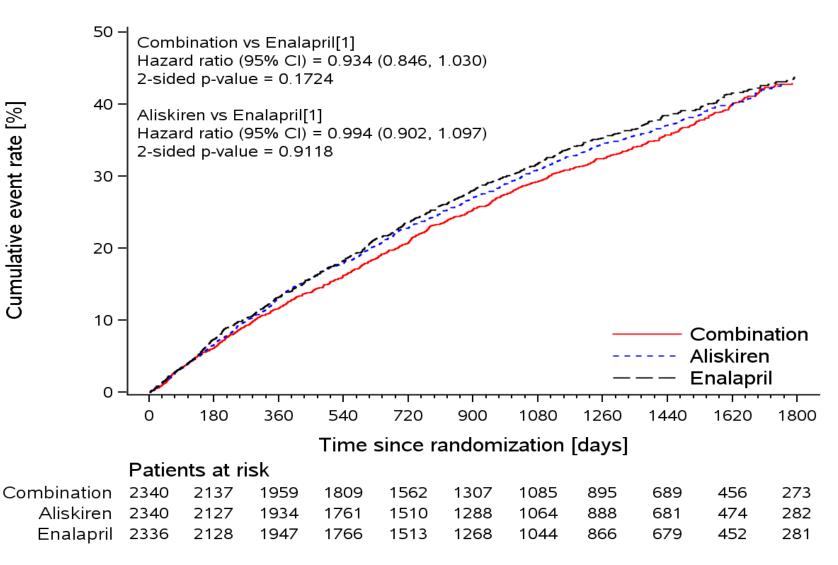
In reducing the risk of the primary composite outcome of cardiovascular death or heart failure hospitalization



https://clinicaltrials.gov NCT00853658



ATMOSPHERE: Primary outcome





ATMOSPHERE: Comparison of enalapril and aliskiren monotherapy (non-inferiority)

Pre-specified criterion for declaring non-inferiority was a P-value ≤0.0123 (one-sided)

	Aliskiren (n=2340)	Enalapril (n=2336)	HR (95% CI)	P value
All patients	791	808	0.99	0.0184*
n (%)	(33.8%)	(34.6%)	(0.90-1.10)	

*Did not meet the pre-specified P-value for significance



ATMOSPHERE: Secondary and exploratory outcomes

Secondary outcome:

 Kansas City Cardiomyopathy Questionnaire (KCCQ) -Change in the clinical summary score (CSS) from baseline to 12 months

Exploratory outcomes (selected):

- Composite CV outcome: CV death, HF hospitalization, MI, stroke or resuscitated cardiac arrest
- Composite renal outcome: renal death, ESRD (initiation of dialysis, renal transplantation, or a serum Cr above 6.0 mg/dl [530 µmol/l]), or doubling of serum Cr from baseline (to >upper limit of normal) sustained for at least 1 month



ATMOSPHERE: Pre-specified subgroups

		on Ena		Interaction		liskiren			Interaction
n	/N (%)	n/N	(%)	P-value	r	n/N (%)	n/N	(%)	P-value
Overall Folerating high dose (10 mg bid) enalapril	770/2340 (32.9)	808/2336 (34.6)	Hell	p=0.1545	Overall Tolerating high dose (10 mg bid) enalapril	791/2340 (33.8)	808/2336 (34.6)	iei iei	p=0.3219
luring the run-in phase No	96/261/36.8)	109/264 (41.3)			during the run-in phase No	95/262 (36.3)	109/264 (41.3)	H	
Yes	674/2079 (32.4)	699/2072 (33.7)			Yes		699/2072 (33.7)	Heri	
Age group: < 65, >= 65				p=0.5570	Age group: < 65, >= 65				p=0.8263
<65		375/1194 (31.4)	Hel		<65	367/1180 (31.1)		Het	
>=65 Age group: < 75, >= 75	393/1126 (34.9)	433/1142 (37.9)	Hei	p=0.5370	>=65	424/1160 (36.6)	433/1142 (37.9)	H	p=0.8906
sge group: < /5, >= /5	617/1943 (31.8)	641/1939 (33.1)	-	p=0.5570	Age group: < 75, >= 75 <75	624/1925 (32.4)	641/1939 (33.1)	Int	p=0.8906
>=75	153/ 397 (38.5)	167/ 397 (42.1)	Heli		>=75	167/415 (40.2)	167/ 397 (42.1)	H	
Gender				p=0.5166	Gender				p=0.0618
Male		668/1837 (36.4)	•		Male		668/1837 (36.4)	H	
Female	137/494 (27.7)	140/499 (28.1)	He-1	p=0.1406	Female	158/ 532 (29.7)	140/499 (28.1)		p=0.3393
Race group Caucasian	518/1547 (33.5)	522/1526 (34.2)	Hel	p=0.1400	Race group Caucasian	510/1519 (33.6)	522/1526 (34.2)	Her	p=0.5595
Black	14/ 32 (43.8)	21/ 40 (52.5)			Black	19/ 37 (51.4)	21/ 40 (52.5)	⊢	+
Asian	197/ 587 (33.6)	204/ 586 (34.8)	H		Asian	190/ 591 (32.1)	204/586 (34.8)	Hei	
Other	34/156 (21.8)	55/166 (33.1)	H		Other Region	64/175 (36.6)	55/166 (33.1)	+	p=0.5188
Region North America	25/ 60 (41.7)	17/ 59 (28.8)		p=0.1641	North America	23/ 58 (39.7)	17/ 59 (28.8)		p=0.5188
Latin America (including Central America)	110/ 371 (29.6)	132/ 371 (35.6)	H+		Latin America (including Central America)	139/ 377 (36.9)	132/ 371 (35.6)	'H+H	
Western Europe	201/616 (32.6)	213/615 (34.6)	HH		Western Europe	195/ 620 (31.5)	213/615 (34.6)	HH	
Eastern Europe	212/649 (32.7)	220/ 649 (33.9)	Hei		Eastern Europe	226/646 (35.0)	220/ 649 (33.9)	Heri	
Asia/Pacific and other	222/ 644 (34.5)	226/642 (35.2)	Hell	0.5007	Asia/Pacific and other NYHA class group at baseline	208/ 639 (32.6)	226/ 642 (35.2)	Het	
NYHA class group at baseline	520/1674 (31.1)	525/1656 (31.7)	Hel	p=0.5927	NYHA class group at baseline I/II	546/1683 (32.4)	525/1656 (31.7)	-	p=0.1224
III/IV	250/ 666 (37.5)	283/ 680 (41.6)			III/IV		283/ 680 (41.6)	H	
GFR group 1 at BL (mL/min/1.73m^2)				p=0.3724	eGFR group 1 at BL (mL/min/1.73m^2)				p=0.4143
< 60 mL/min/1 73 m2		246/621 (39.6)	H		< 60 mL/min/1 73 m2		246/621 (39.6)	Heri	
>= 60 mL/min/1 73 m2	545/1747 (31.2)	562/1715 (32.8)	Hel		>= 60 mL/min/1 73 m2	545/1703 (32.0)	562/1715 (32.8)	H	0.0010
Diabetes mellitus at baseline No	574/1675 (34.3)	592/1684 (35.2)		p=0.3529	Diabetes mellitus at baseline No	619/1713 (36.1)	592/1684 (35.2)		p=0.0358
Yes	196/ 665 (29.5)	216/652 (33.1)	H+++		Yes	172/627 (27.4)	216/ 652 (33.1)	H++	
.VEF group at screening (%)				p=0.3396	LVEF group at screening (%)				p=0.5302
<= 30%		552/1462 (37.8)	Het .		<= 30%		552/1462 (37.8)	H+I .	
> 30% F at baseline based on history	281/940 (29.9)	256/874 (29.3)	H	p=0.8378	> 30% AF at baseline based on history	266/912 (29.2)	256/874 (29.3)	Heri	p=0.9082
No	503/1539 (32.7)	520/1535 (33.9)	Hei	p=0.8578	No No	503/1552 (32.4)	520/1535 (33.9)	Hel	p=0.9082
Yes	267/801 (33.3)	288/801 (36.0)	H		Yes	288/788 (36.5)	288/801 (36.0)	H	
T-proBNP group at baseline				p=0.8745	NT-proBNP group at baseline	373/1320 (28.3)	332/1275 (26.0)		p=0.0972
<= Median	320/1299 (24.6) 450/1041 (43.2)	332/1275 (26.0) 476/1061 (44.9)			<= Median > Median	418/1020 (41.0)	476/1061 (44.9)	Hell	
lypertension at baseline			17	p=0.9415	Hypertension at baseline				p=0.2961
No Yes	299/ 893 (33.5) 471/1447 (32.6)	317/911 (34.8) 491/1425 (34.5)	Het I		No Yes	286/ 880 (32.5) 505/1460 (34.6)	317/911 (34.8) 491/1425 (34.5)	H	
Patients with baseline hypertension by age	4/1/144/ (32.0)	491/1425 (54.5)		p=0.7383	Patients with baseline hypertension by age	303/1400 (34:0)	450.1465 (54.5)		p=0.3376
group (<65 years, >=65 years)					group (<65 years, >=65 years)	1001/000 000			
< 65 years >= 65 years	207/667 (31.0) 264/780 (33.8)	208/ 630 (33.0) 283/ 795 (35.6)	H H		< 65 years >= 65 years	195/ 613 (31.8) 310/ 847 (36.6)	208/ 630 (33.0) 283/ 795 (35.6)	1	
Patients with baseline hypertension by age	2010 100 (00.0)	203 133 (33.0)		p=0.2158	Patients with baseline hypertension by age				p=0.6714
roup (<75 years, >=75 years)	270/3177 (22.0)	100/11/12 (22.25			group (<75 years, >=75 years)	377/1148 (32.8)	380/1143 (33.2)		
< 75 years >= 75 years	370/1155 (32.0) 101/ 292 (34.6)	380/1143 (33.2) 111/ 282 (39.4)	Her I		< 75 years >= 75 years	128/ 312 (41.0)	111/282 (39.4)	H-H	
Primary HF etiology at screening				p=0.6177	Primary HF etiology at screening				p=0.0611
Ischemic Non-ischemic	456/1335 (34.2) 314/1005 (31.2)	467/1300 (35.9) 341/1036 (32.9)	H∎H H⊕H		Ischemic Non-ischemic	426/1295 (32.9) 365/1045 (34.9)	467/1300 (35.9) 341/1036 (32.9)	Hel	
rior HHF within 6 months of screening				p=0.5631	Prior HHF within 6 months of screening			1-1	p=0.6904
No Yes	542/1642 (33.0) 228/ 698 (32.7)	562/1653 (34.0) 246/ 683 (36.0)			No Yes	538/1646 (32.7) 253/ 694 (36.5)	562/1653 (34.0) 246/ 683 (36.0)	HH H	
Yes odium group at baseline				p=0.8758	Sodium group at baseline				p=0.3055
<= Median	453/1413 (32.1)	479/1434 (33.4)	Het.		<= Median	471/1349 (34.9)	479/1434 (33.4)	, HH	P
> Median Seta-blocker use at baseline	317/ 927 (34.2)	329/ 902 (36.5)	н	==0.6169	> Median Beta-blocker use at baseline	319/ 989 (32.3)	329/ 902 (36.5)	HeH	p=0.3192
No	70/188 (37.2)	85/189 (45.0)		p=0.6168	No	78/207 (37.7)	85/189 (45.0)		p=0.5192
Yes	700/2152 (32.5)	723/2147 (33.7)	101		Yes	713/2133 (33.4)	723/2147 (33.7)	. IH	
t least 50% of target BB at baseline				p=0.2321	At least 50% of target BB at baseline				p=0.8980
No Yes	628/1866 (33.7) 142/ 474 (30.0)	637/1840 (34.6) 171/ 496 (34.5)			No Yes	631/1844 (34.2) 160/ 496 (32.3)	637/1840 (34.6) 171/ 496 (34.5)	H	
Idosterone antagonist use at baseline	142 4/4 (30.0)			p=0.8316	Aldosterone antagonist use at baseline	100 490 (34.3)	110 450 (54.5)		p=0.1600
No	471/1484 (31.7)		H	F	No	466/1476 (31.6)	495/1454 (34.0)	I	P
Yes	299/ 856 (34.9)	313/882 (35.5)	Hei		Yes	325/ 864 (37.6)	313/ 882 (35.5)	Hert	
Cardioverter-defibrillator implanted (ICD) or CRT (CRT-P or CRT-D)				p=0.6864	Cardioverter-defibrillator implanted (ICD) or CRT (CRT-P or CRT-D)				p=0.1708
No	618/1948 (31.7)	669/1967 (34.0)	101		No No	660/1946 (33.9)	669/1967 (34.0)	Iel	
Yes	152/ 392 (38.8)	139/ 369 (37.7)	H+H		Yes		139/ 369 (37.7)	H++	
systolic BP group at baseline (mmHg)		359/042/29/0		p=0.9681	Systolic BP group at baseline (mmHg)				p=0.1068
< 120 mmHg >= 120 mmHg	342/951 (36.0) 427/1388 (30.8)	358/942 (38.0) 450/1394 (32.3)	Het Het		< 120 mmHg		358/942 (38.0)	He-I He-I	
>= 120 mmHg Heart rate group at baseline	427/1388 (30.8)	450/1594 (52.5)		p=0.2173	>= 120 mmHg Heart rate group at baseline	425/1428 (29.8)	450/1394 (32.3)	1-1	p=0.4808
<= Median	392/1223 (32.1)	371/1158 (32.0)	Hei	F	<= Median	400/1223 (32.7)		HH	p 0.4000
> Median	377/1116 (33.8)	437/1178 (37.1)	H	- 0.1070	> Median	391/1116 (35.0)		H.	
Baseline QRS =<130 , > 130 msec and/or LBBB <= 130 msec	363/1311 (27.7)	391/1295 (30.2)		p=0.1872	Baseline QRS =<130 ,> 130 msec and/or LBB <= 130 msec	B 391/1316 (29.7)	301/1205 (30.2)		p=0.3685
> 130 msec and/or LBBB		240/ 581 (41.3)	HH		<= 130 msec > 130 msec and/or LBBB	230/ 543 (42.4)	240/ 581 (41.3)	T.	
					A D C MARKED CARGO OF AND A AD				



ATMOSPHERE: Safety outcomes

	Aliskiren+ Enalapril (n=2340)	Aliskiren (n=2340)	Enalapril (n=2336)	P value (1)	P value (2)
Hypotension n (%) Symptoms Symptoms and SBP <90mmHg	322 (13.8%) 87 (3.7%)	249 (10.6%) 31 (1.3%)	258 (11.0%) 55 (2.4%)	0.005 0.008	0.67 0.009
Renal impairment n (%) Cr ≥2.5mg/dl Cr ≥3.0mg/dl	95 (4.1%) 46 (2.0%)	63 (2.7%) 35 (1.5%)	62 (2.7%) 29 (1.2%)	0.009 0.06	1.00 0.53
Hyperkalemia n (%) K ⁺ >5.5mmol/l K ⁺ >6.0mmol/l	401 (17.1%) 116 (5.0%)	255 (10.9%) 70 (3.0%)	291 (12.5%) 83 (3.6%)	<0.0001 0.02	0.10 0.29
Cough n (%)	290 (12.4%)	241 (10.3%)	284 (12.2%)	0.83	<0.05

(1) = Comparison of enalapril plus aliskiren versus enalapril; (2)= Comparison of aliskiren versus enalapril



Summary and conclusions

Combination therapy

- The addition of aliskiren to an evidence-based dose of enalapril led to more adverse events without an increase in benefit.
- This finding differs from the prior ARB "add-on" trials and may reflect a difference in study design (the previous trials did not require an evidence-based dose of background ACE inhibitor).
- There is probably a ceiling to RAS blockade in heart failure, above which there is no further benefit

Aliskiren monotherapy

• Non-inferiority was not demonstrated for aliskiren compared with enalapril.

