INHibition of the renin angiotensin system in hypertrophic cardiomyopathy and the **E**ffect on hypertrophy – a **R**andomized **I**ntervention **T**rial with losartan

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Anna Axelsson, Kasper Iversen, Niels Vejlstrup, Carolyn Ho, Jakob Norsk, Lasse Langhoff, Kiril Ahtarovski, Pernille Corell, Ole Havndrup, Morten Jensen and Henning Bundgaard
DENMARK

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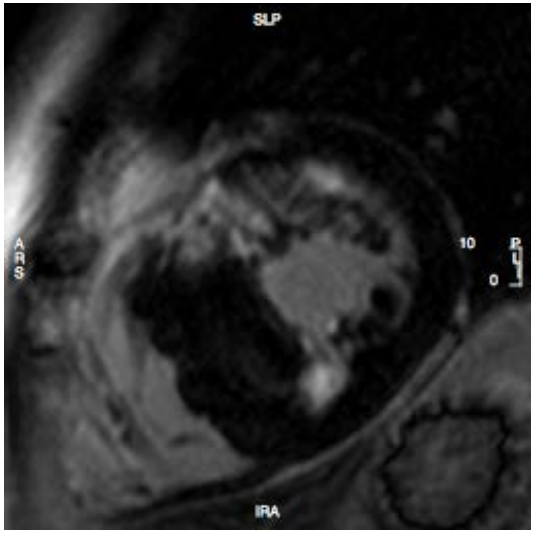
REGION H Rigshospitalet

UNIVERSITY OF COPENHAGEN

Background - hypertrophic cardiomyopathy

- HCM is the most common inherited cardiomyopathy with a prevalence of 1/500
- HCM is characterized by hypertrophy and fibrosis of the left ventricle
- Extent of hypertrophy and late gadolinium enhancement (LGE) on MRI are associated with an adverse outcome



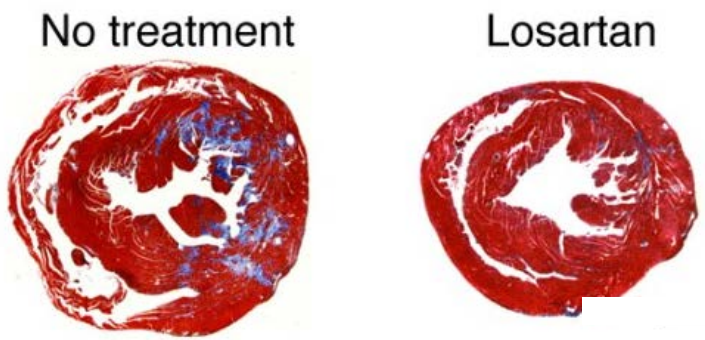
INHERIT Maron Circ 1995, Spirito NEJM 2000, Elliott JACC 2000, Olivotto JACC 2008, Green JACC Cardiovasc Imaging 2012 (review)

Background – pilot studies

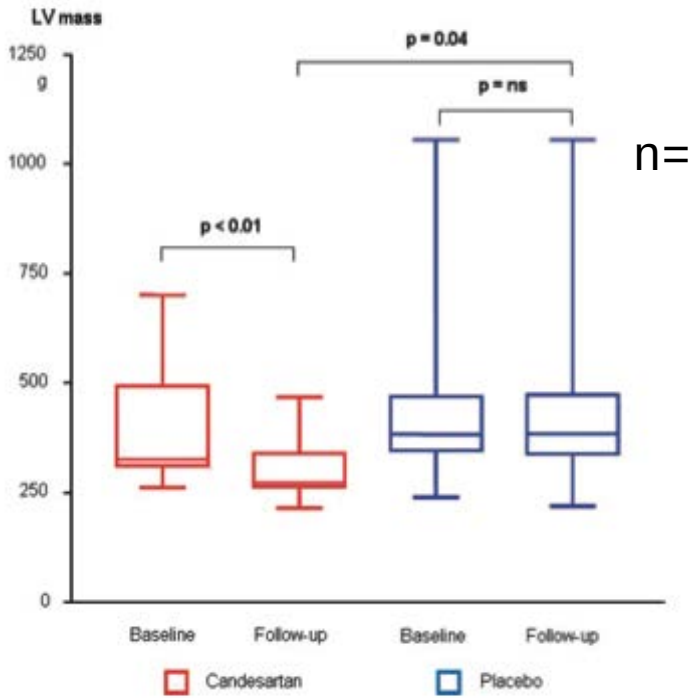
Animal studies and pilot studies in humans have suggested an effect of Angiotensin Receptor Blockers (ARB) on:

- Left ventricular mass
- Myocardial fibrosis
- Diastolic function
- Exercise capacity

Mouse model treated BEFORE hypertrophy



Teekakirikul P, JCI 2012



n=24

Penicka M, J Mol Diagn 2009

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Araujo, Am J Cardiol 2005, Penicka J Mol Diagn 2009, Teekakirikul JCI 2012, Shimada 2013 JACC Heart Failure

Objective and study design

To investigate the effect of losartan on left ventricular morphology and function in a larger population of patients with HCM

- Single center, double-blind, placebo-controlled, randomized trial
- Randomization 1:1 to losartan 100 mg daily, or placebo for 12 months
- Sample size: 132 patients
  - 90% power,
  - difference in the primary end-point left ventricular mass of 12 g/m^2,
  - two-sided $p<0.05$,
  - drop-out rate of 10%.

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Endpoints

Primary endpoint

- Change in left ventricular mass as assessed by MRI or CT

Secondary endpoints (changes in):

- Left ventricular fibrosis (LGE on MRI)
- Left ventricular maximal wall thickness
- Diastolic function
- Left ventricular outflow tract gradient
- Exercise tolerance
- Symptoms

Eligibility

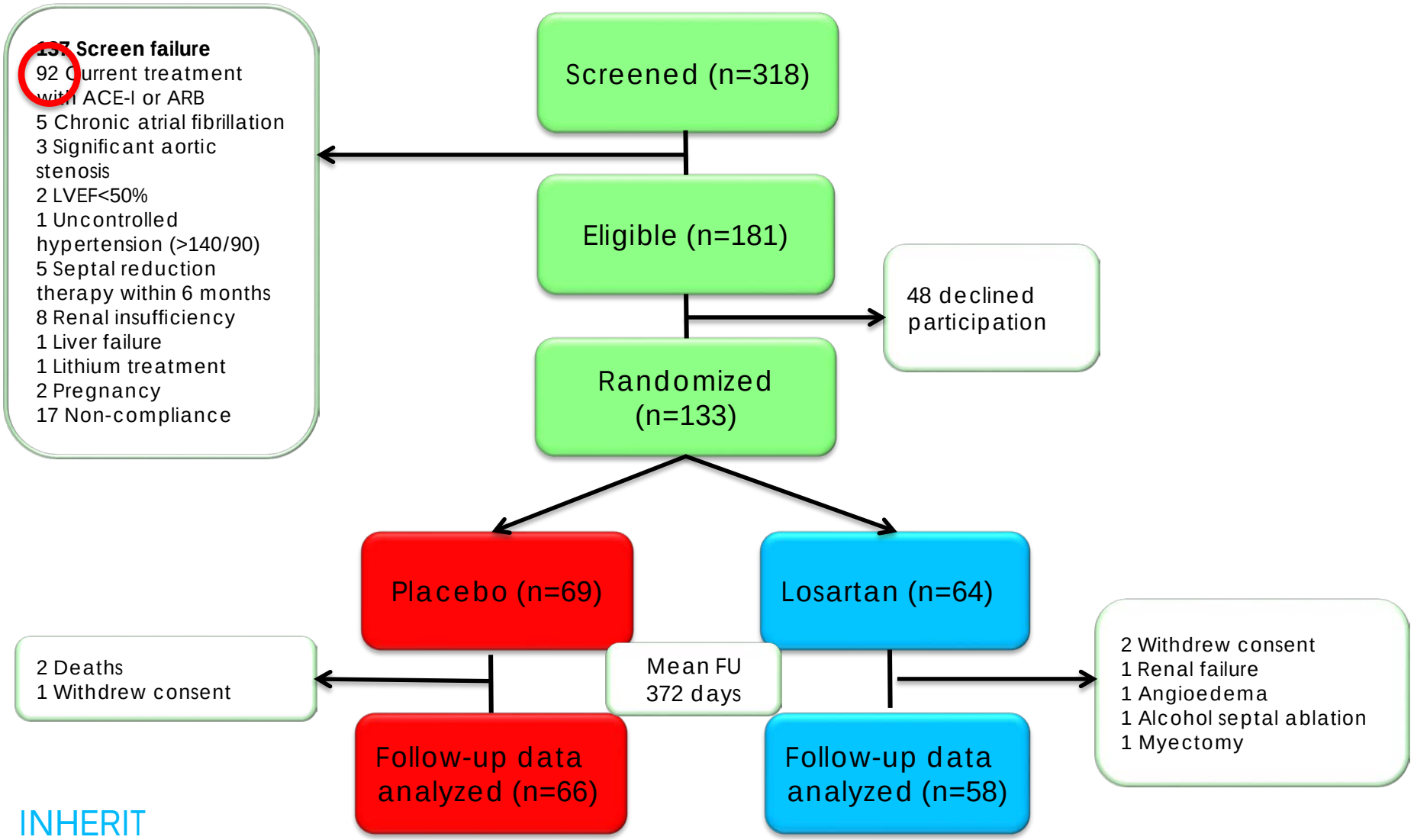
Key inclusion criteria

- Clinical diagnosis of HCM
- ≥18 years
- Sinus rhythm at inclusion

Key exclusion criteria

- Blood pressure > 140/90 mmHg
- ACE-I or ARB
- LVEF < 50%
- Significant valvular disease
- eGFR < 30 ml/min/1.73 m^2
- Recent (≤ 6 months) septal reduction therapy

Study design



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Baseline characteristics - 1

	Placebo (n=69)	Losartan (n=64)
Demographic characteristics		
Age – yr	52±12	51±14
Female sex – no. (%)	23 (33)	24 (38)
Medical history		
Previous cardiac arrest, sustained VT and/or appr. ICD-shock – no. (%)	7 (10)	6 (9)
ICD – no. (%)	19 (28)	24 (38)
Previous septal reduction therapy – no. (%)	14 (20)	12 (19)
History of atrial fibrillation – no. (%)	9 (13)	7 (11)
Treated hypertension – no. (%)	7 (10)	6 (9)
Cardiac medications – no. (%)		
Beta-blocker	37 (54)	39 (61)
Calcium channel blocker	11 (16)	8 (13)
Symptoms and physical function		
New York Heart Association functional class I/II/III – no. (%)	41(59) / 22(32) / 6(9)	44(69) / 18(28) / 2(3)
Maximal work capacity at exercise testing – Watt	140±61	146±54

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Baseline characteristics - 2

	Placebo (n=69)	Losartan (n=64)
Vital signs		
Systolic blood pressure – mmHg	128±11	128±12
Genetics - no. (%)		
Genetic testing performed	57 (83)	51 (80)
Disease-causing mutation identified	29 (42)	28 (44)
Echocardiographic findings		
Left ventricular ejection fraction – %	68±9	69±7
Peak left ventricular outflow gradient ≥ 30 mmHg at rest – no. (%)	6 (9)	10 (16)
Volumetric and mass parameters by CMR or CT		
Left ventricular mass – g /m^2	108±33	105±42
Maximal wall thickness – mm	23±6	23±6
Left atrial volume – ml/m^2	69±25	63±21
LGE by CMR		
Presence of LGE – no. (%)	29 (85)	31 (82)
LGE – % of left ventricular mass	3 (1-8)	2 (1-5)

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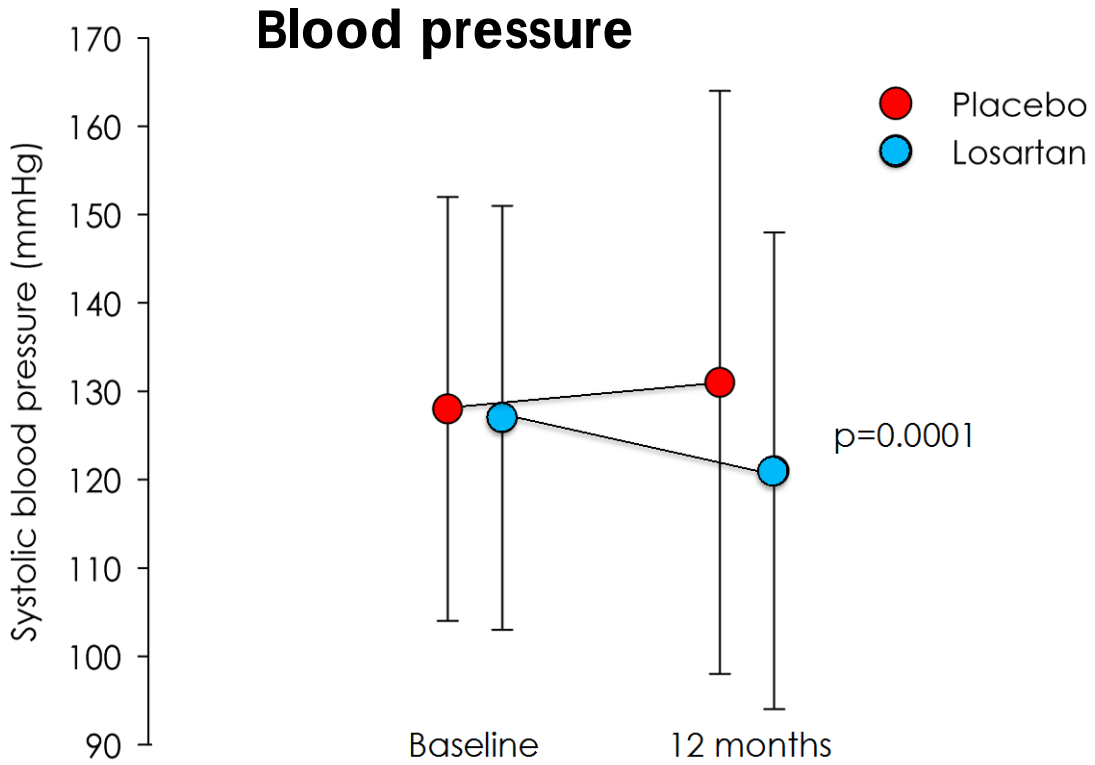
Compliance

Of the 124 patients completing the study, 115 (93 %) were compliant (>80 %) as assessed by pill count



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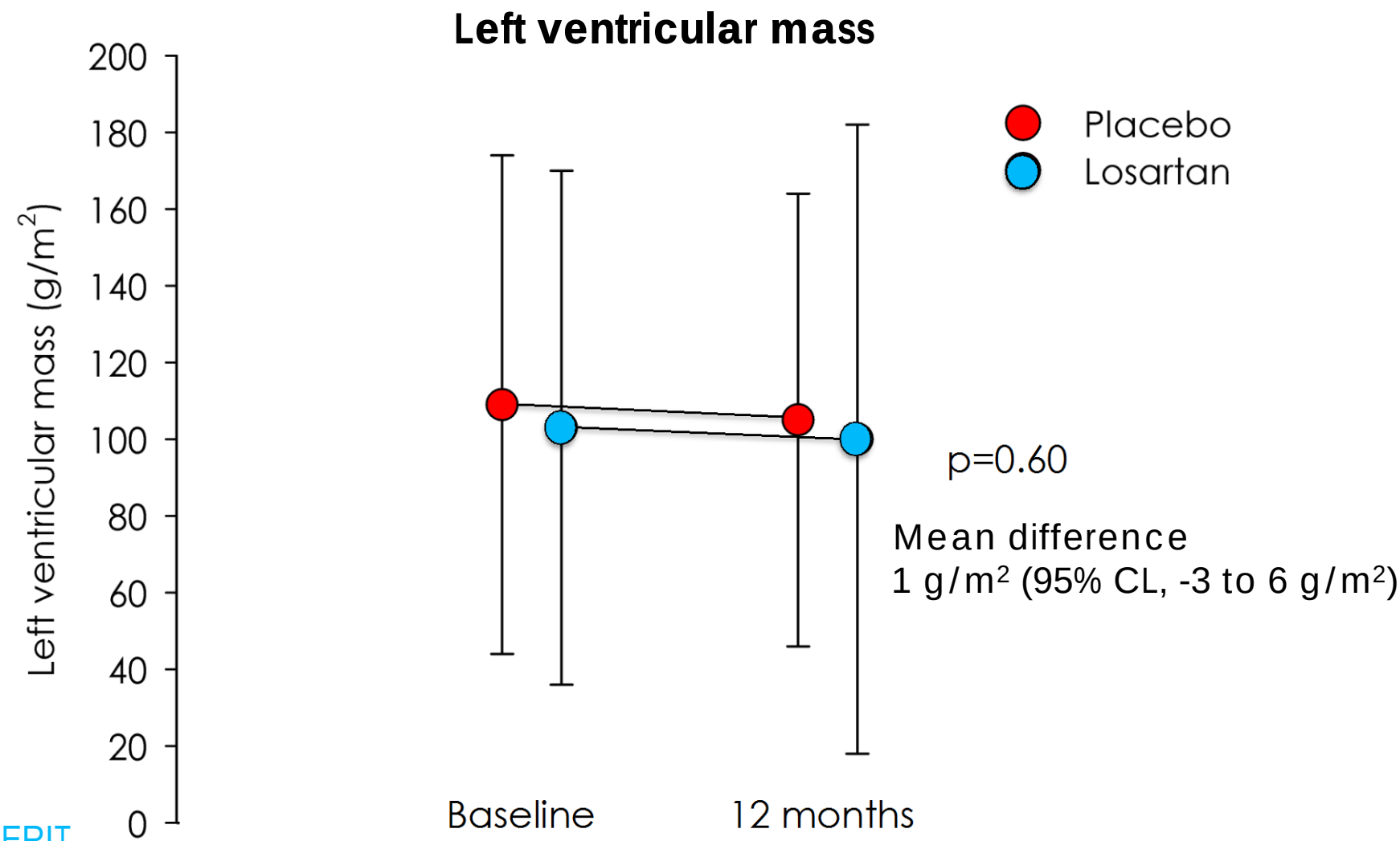
Primary endpoint



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Secondary endpoints

	Placebo (n=66)			Losartan (n=58)			
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	p
Volumetric parameters by CMR							
Maximal wall thickness - mm	24±6	24±6	1±3	23±6	24±6	1±4	0.26
Left atrial volume - ml/m^2	69±25	77±28	7±14	63±21	69±26	6±14	0.69
LGE by CMR - %	3 (1 -9)	7 (2-18)	2 (0-6)	2 (1-5)	6 (2-20)	3 (0-10)	0.62
Echocardiographic findings							
e' (septal) - cm/sec	5.1±1.8	5.0±2.0	-0.1±1.3	5.4±2.1	5.6±2.1	0.1±1.8	0.50
E/e' (septal)	15.3±6.9	15.8±8.2	0.6±6.7	15.1±7.7	14.3±6.7	-0.9±7.9	0.30
Peak LV outflow gradient at rest - mmHg	9 (5-14)	9 (6-18)	0 (-1-3)	7 (5-12)	7 (5-13)	1 (-1-2)	0.88
Peak LV outflow gradient during Valsalva - mmHg	21 (10-37)	16 (9-59)	7 (-2-25)	12 (7-29)	11 (7-67)	2 (-5-21)	0.47
Laboratory measurements							
NT-pro-BNP - pmol/l	22 (9-47)	24 (14-53)	3 (-6-18)	17 (10-48)	26 (15-59)	4 (-1-15)	0.67
Exercise test							
METS	7.3±3.0	7.7±2.9	0.2±1.7	7.6±2.5	7.5±2.5	-0.2±1.6	0.21

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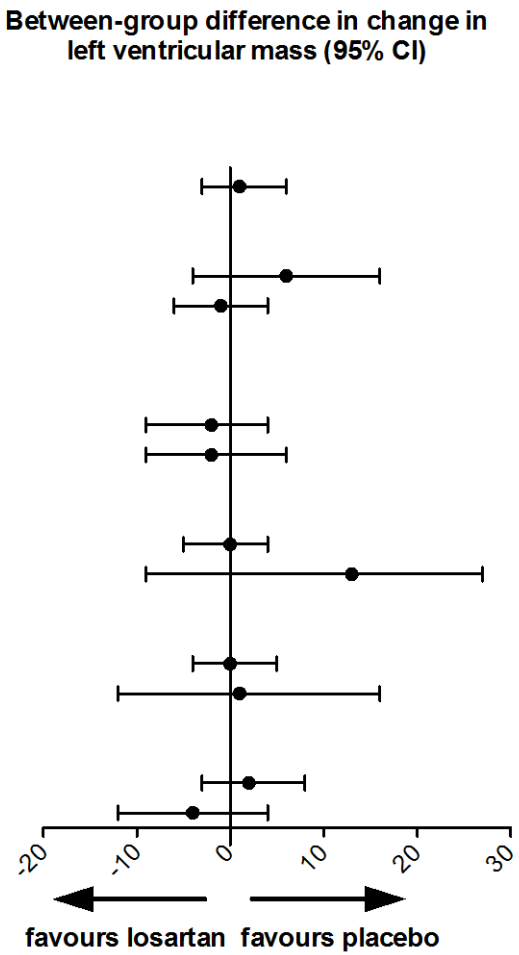
Data are presented as mean±SD or median (IQR)

Losartan vs placebo on primary endpoint, by prespecified subgroups

Subgroup	n	Placebo Change in LV mass - g/m^2	Losartan Change in LV mass - g/m^2	Mean diff (95% CI)	Test of interaction
Overall	124	-4	-3	1 (-3-6)	p=0.60
Age					
< 40 years	25	-12	-5	6 (-4-16)	p=0.23
≥ 40 years	99	-2	-2	-1 (-6-4)	
Genetics					
Mutation identified	53	-5	-7	-2 (-9-4)	p=0.86
No mutation identified	46	0	-2	-2 (-9-6)	
LVOT obstruction					
< 30 mmHg	112	-4	-4	0 (-5-4)	p=0.08
≥ 30 mmHg	12	-9	4	13 (-9-27)	
Maximal wall thickness					
< 30 mm	104	-3	-3	0 (-4-5)	p=0.65
≥ 30 mm	20	-9	-7	1 (-12-16)	
Previous myectomy or ASA					
No	100	-5	-3	2 (-3-8)	p=0.28
Yes	24	-2	-7	-4 (-12-4)	



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Adverse events

	Placebo (n=69)	Losartan (n=64)	p
Identified adverse events			
Sudden cardiac death	2	0	NS
Angioedema	0	1	NS
Hyperkalemia (>4.8 mmol/l)	0	1	NS
Renal impairment	1	0	NS
Adverse events related to LVOT gradient ≥ 30 mmHg			
Worsening of NYHA class	1	1	NS
Increase in LVOT gradient ≥10 mmHg	2	1	NS
Discontinuation for adverse events			
Angioedema	0	1	NS
Unspecific symptoms leading to withdrawal of consent	1	2	NS

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Conclusions and future perspectives

- The INHERIT trial did not demonstrate an effect of losartan on left ventricular mass compared to placebo in patients with overt HCM
- There was no effect on the secondary endpoints including maximal wall thickness, left ventricular fibrosis, diastolic parameters or exercise capacity
- The observed safety suggests that losartan may be used for other indications in patients with obstructive physiology
- Future studies may determine if treatment with ARB can prevent development of disease in pre-clinical or earlier stages of HCM

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