Topcat: Background and Design

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Consultant: Pfizer, Novartis, Merck, Takeda, Bayer, Relypsa* *Stock options
HF-PEF

- Prevalence: 30-60% of patients with HF have a LVEF ≥ 50%. In patients > 75 years of age >60% of patients with HF have LVEF ≥ 50%
- Prognosis: The mortality rate is similar to that in patients with HF-REF

### Hypertension is the most frequent comorbid condition

Effect of Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction

TOPCAT

• HF with a LVEF > 45%
• Age ≥ 50 years
• At least 1 hospitalization for HF within 12 months or a BNP > 100 pg/ml within 30 days
• Serum K < 5.0 meq/L
• Systolic BP < 140 mmHg

Placebo (n=1750) 4.5 years Spironolactone 15-30-45 mg/day (n=1750)

CV death/Hospitalization for HF
Resistant Hypertension

- Plasma Aldo levels were increased in patients with resistant hypertension vs controls (normotension and controlled hypertension). The significant correlation between 24 hr urinary aldosterone and cortisol suggests corticotropin may underlie the aldosterone excess in resistant hypertension.

Aldosterone

Effect of plasma aldosterone levels (PAC) and “Aldosterone Escape” in patients with hypertension randomized to Losartan or amlodipine

- There was a greater decrease in SBP with amlodipine than with Losartan but PAC decreased more with Losartan.
- Multiple step-wise regression analysis showed that the % reduction in LV mass is related to the % change in PAC + SBP ($r=0.46$, $p<0.01$)

• The effect of eplerenone on mortality, mainly SCD was seen in those with a history of hypertension

Pitt, B. et al Hyp. 2008; 52:271
Relaton of changes in urinary aldosterone concentration after salt intake to LV mass in mildly hypertensive subjects.

- The Baseline Aldosterone Level was not different between the normotensive and mildly hypertensive subjects.
- In patients with mild hypertension the aldosterone concentration after high salt intake correlated with LV mass independent of blood pressure.
Aldosterone increases arterial stiffness associated with an increase in Fibrinonectin which can be prevented by Eplerenone.

Lacolley, p et al. Circ 2003; 106:2848
Large Artery Compliance Correlates Inversely with Plasma Aldosterone

r = -0.795
P < 0.002

4E — LVH Study: Mean Change from Baseline LVM

Final Visit

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Participants</th>
<th>LVM (g)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eplerenone (N = 50)</td>
<td></td>
<td>-15.4</td>
<td>0.258</td>
</tr>
<tr>
<td>Enalapril (N = 54)</td>
<td></td>
<td>-19.9</td>
<td>0.107</td>
</tr>
<tr>
<td>Eplerenone + Enalapril</td>
<td>(N = 49)</td>
<td>-28.8</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Adjusted to treatment, center, and baseline value. All reductions statistically significant vs baseline.

4E-LVH Study:
Mean Aldosterone Levels at Baseline

![Graph showing mean aldosterone levels in different treatment groups.](image-url)

- **Eplerenone (N = 53)**: 10.2 ng/dL
- **Enalapril (N = 57)**: 8.9 ng/dL
- **Eplerenone + Enalapril (N = 58)**: 9.7 ng/dL

11-Beta Hydroxysteroid Dehydrogenase-Type 2

Measurement in aldosterone sensitive sweat gland ducts in patients with essential hypertension and control normotensive subjects

Partial 11-BHSD2 deficiency is present in patients with essential Hypertension.
Mineralocorticoid Receptor

Variants of the 11βHSD2 gene have been found to contribute to the enhanced blood pressure response to salt in humans.

Aldosterone Blockade

Effect of eplerenone in a pressure overload model of aortic banding (4 weeks) with a regular and high salt diet

- Pressure overload resulted in activation of brain epithelial Na channels and AT₁ R through the MR with induction of salt sensitivity and sympathetic activation resulting in LV dysfunction

Aldosterone Blockade

Effect of Spironolactone after 4.5 months of isoproterenol in SHR

• Aldosterone blockade may be sufficient to prevent the adverse effects of Beta adrenoreceptor activation responsible for the transition from LVH to HF

Veliotes, D. G. et al. JCVP 2010;56:203
Age Dependent Decrease in 11 Beta-HSD$_2$ Activity in Hypertensive Patients

- Analysis of the metabolites of cortisone in 165 consecutive patients with Hypertension (THS=tetrahydro metabolite of cortisone)

- Reduced 11 Beta-HSD$_2$ is a risk factor contributing to the rising prevalence of arterial hypertension in the elderly

Results from Ephesus

Death from any cause

Age
<65 yr
≥65 yr

Eplerenone Better  Placebo Better

P = 0.23

HFPEF

Determinants of the progression from the asymptomatic to the symptomatic stage of HFPEF in patients with DM

- The progression from the asymptomatic to the symptomatic stage of HFPEF is due to worsening compliance rather than LV relaxation. Impaired compliance is associated with an increase in collagen formation.

Takeda, Y. et al. EHJ 2011;13:664
Hypertensive Heart Disease/HF Normal EF

Incidence of myocardial fibrosis and diastolic dysfunction in patients with hypertension (115 with LVD, 38 without LVH, and 38 control normotensive subjects)

- Myocardial fibrosis and diastolic dysfunction are present in patients with hypertension before LVH develops

Hypertensive Heart Disease/HF Normal EF

Myocardial collagen Turnover in patients with hypertensive heart disease without diastolic HF compared to those with diastolic HF

- Myocardial collagen formation is increased in patients with Diastolic HF

Change in Serum PIIINP (Marker of ECM Turnover) in EPHESUS and RALES

[NOTE: Dissimilar Units]

* $P=0.002$

EPHESUS 0–9 Months

RALES 0–6 Months

* $P=0.004$
Aldosterone Blockade

- Effect in hypertensive patients with diastolic HF


- Aldosterone blockade improves diastolic function independent of changes in blood pressure
Aldosterone

- Effect of Aldosterone Blockade and an ACE-I on endothelial function

- Combined treatment with an aldosterone antagonist and an ACE-I has additive protective effects on endothelial function and atherosclerosis

Imanishi, T et al. Hyp 2008;51:734
Aldosterone Blockade

Effect of spironolactone in patients with early CKD

•Spironolactone reduces LV mass and arterial stiffness in early stage CKD without a significant increase in hyperkalemia or renal dysfunction

Edwards, N.C. et al JACC 2009. 54:505
Diabetes Mellitus/Aldosterone

- In 45 patients with Type 2 DM and early nepropathy treated with an ACE-I for 40 weeks 18 patients were found to have aldosterone “escape” and higher urinary albumin secretion than those without escape.

- In 13 of the 18 patients with aldosterone escape spironolactone 25 mg/day was added to ACE-I therapy and urinary albuminum excretion determined after 24 weeks.

- Aldosterone Blockade may be of value in preventing progressive CKD in patients with DM and escape of Aldosterone

Sato, A. et al Hyp. 2003;41:64
Hypertensive Heart Disease/HF Normal EF

Aldosterone

\[ \text{NA}^+ \rightarrow \text{ROS} \]

MR

\[ \uparrow \text{ACE}, \uparrow \text{AT}^1 \text{R}, \downarrow \text{AT}^2 \text{R}, \downarrow \text{ACE}_2, \uparrow \text{LOX-1 R}, \uparrow \text{Endothelin} \]

Cortisol

\[ \text{Aldosterone Blockers} \]

\[ \text{ROS, NO, NFKappa-B, AP-1} \]

Cytokine Activation, endothelial dysfunction, perivascular fibrosis, sympathetic activation

Renal Dysfunction, Albuminuria

Sodium Retention, potassium loss

Heart Failure Normal EF

Diastolic Dysfunction, LVH

Atrial Fibrillation

Comorbid Triggers

Anemia, Diabetes, Ischemia

Pitt, B. 2008
TOPCAT

- Current Status:
  - >3000 patients randomized
  - Recruitment ends January 31\textsuperscript{st} 2012
  - Last patient visit January 31\textsuperscript{st} 2013
  - Results expected late 2013
Conclusions

• Aldosterone Blockade is effective in treating resistant hypertension and in reducing target organ damage in patients with hypertensive heart disease

• Although ARBs have not been successful in treating HFNEF it can be postulated that an aldosterone blocker + an ACE-I or ARB will be effective in reducing mortality and morbidity