Aliskiren, a direct renin inhibitor, suppresses the atrial structural remodeling and fibrotic gene expressions in the canine atrial fibrillation model.

Kitasato University, School of Medicine, Department of Cardio-Angiology, Sagamihara, Japan.

A. Satoh
Disclosure

✓ There was no financial support for this study or any conflicts of interest, and no specific unapproved usage of any compound or product occurred.
We have previously reported the suppressive effect of aliskiren, a direct renin inhibitor, on electrophysiological changes in the canine AF model.

In the same model, Aliskiren has also exhibited a suppressive effect on the atrial structural remodeling.
Electrophysiological data

AERP

Conduction Velocity

Inducibility of AF

*: p<0.05 vs. control group
+: p<0.05 vs. day 0

control n=12  aliskiren=12
UCG parameters

**LAV**

- **3W**: Control: 16, Aliskiren: 8 (p=0.03)
- **6W**: Control: 16, Aliskiren: 8 (p=0.03)

**LAD**

- **3W**: Control: 30, Aliskiren: NS
- **6W**: Control: 32, Aliskiren: NS

**LVDd**

- **3W**: Control: 30, Aliskiren: NS
- **6W**: Control: 30, Aliskiren: NS

**LVEF**

- **3W**: Control: 60, Aliskiren: NS
- **6W**: Control: 60, Aliskiren: NS
Purpose

✓ In the present study, we evaluated the effect of aliskiren on the structural and histological changes of atrial tissue and expressions of fibrotic and inflammatory related genes.
Canine atrial rapid stimulation model

All dogs underwent the following surgical procedure:

I. 2 pairs of electrodes were sutured at the left atrial appendage (LAA) and right atrial free wall for the electrophysiological studies.

II. The endocardial lead for rapid stimulation was positioned at the right atrial appendage (RAA) through the jugular vein.

III. The rapid stimulation device was connected to the RAA lead, and was implanted at the neck.

IV. The epicardial electrodes were sutured at 3 epicardial sites and used for electrophysiological evaluation. (Not shown in this presentation).
Study protocol

(initial surgery)

day -14

day 0
day 14
day 28
day 42

Non-pacing
(n=4)

Pacing control
(n=12)

Pacing + Aliskiren
(n=12)

Tissue Sampling
n=4

Tissue Sampling
n=8

Tissue Sampling
n=4

Tissue Sampling
n=8

Aliskiren 30mg/kg/day

1 wk recovery

Pacing 400bpm

3W

6W
Atrial tissue evaluation

**Histology**

① H.E. staining  
② Azan staining

**mRNA expressions** (real time RT-PCR)

① Monocyte chemotactaictic protein-1 (MCP-1)  
② Fibronectin 1 (FN1)  
③ Transforming growth factor-β (TGF-β)  
④ Collagen type 3 (COL3)

**Immuno-fluorescent staining**

① Fibronectin 1 (FN1)  
② Collagen type 3 (COL3)
Histological findings in HE staining

Non-pacing group

Pacing control group

Pacing + Aliskiren group

3W

6W
Histological findings in Azan staining

Non-pacing group

Pacing control group

Pacing + Aliskiren group

3W

6W
Tissue fibrosis

% area of fibrotic tissue

- **3W**
  - Non-pacing (6W)
  - Pacing control
  - Pacing + aliskiren

- **6W**
  - Non-pacing
  - Pacing control
  - Pacing + aliskiren

* \( p < 0.05 \) vs. non-pacing group

† \( p < 0.05 \) vs. Control group
mRNA expressions of fibrotic and inflammation related genes

**TGF-β**

- **3W**
  - Non-pacing (6W)
  - Pacing control
  - Pacing + aliskiren

- **6W**
  - Non-pacing
  - Pacing control
  - Pacing + aliskiren

**FN1**

- **3W**
  - Non-pacing (6W)
  - Pacing control
  - Pacing + aliskiren

- **6W**
  - Non-pacing
  - Pacing control
  - Pacing + aliskiren

**MCP-1**

- **3W**
  - Non-pacing (6W)
  - Pacing control
  - Pacing + aliskiren

- **6W**
  - Non-pacing
  - Pacing control
  - Pacing + aliskiren

**COL 3**

- **3W**
  - Non-pacing (6W)
  - Pacing control
  - Pacing + aliskiren

- **6W**
  - Non-pacing
  - Pacing control
  - Pacing + aliskiren

* : p<0.05 vs. non-pacing group  † : p<0.05 vs. Control group
Immuno–fluorescent staining of FN1

Non-pacing group

Pacing control group

Pacing + Aliskiren group

3W

6W
Immuno-fluorescent staining of COL3

Non-pacing group

Pacing control group

Pacing + Aliskiren group

3W

6W
Discussion

Mechanical stress → Angiotensin II → Matricellular proteins (CTGF, Periostin, Osteopontin, TSP-2 etc.) → Monocyte → MCP-1

Migration

Monocyte → Atrial fibrillation (Rapid atrial firing)

Structural remodeling
- Atrial fibrosis

Endothelial → myofibroblast → COL3 → differentiation

FN1
Conclusions

- In the canine AF model, Aliskiren suppressed AF inducibility and a decrease in CV. (Previous report).
- Tissue fibrosis was also suppressed by Aliskiren at both relatively earlier and later phases of rapid pacing.
- Aliskiren was considered to suppress the excess of MCP1 and FN1 in the relatively earlier phase of the atrial remodeling and it resulted in the later suppression of COL3 up-regulation.