Aortic Disease: What’s in the Medicine Cabinet?

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• No relationships to disclose

• I will discuss the off-label use of ARBs
Thoracic Aortic Aneurysms: Natural History

Asymptomatic TAA → Growth → Rupture, Dissection
Beta Blockers

• Proven benefit in Marfan syndrome
• No trials in TAAs of other etiologies
• Mainstay of therapy.
The Role of Fibrillin-1: Structural

- Fibrillin-1 comprises “connecting filaments” that bind SMCs to elastin laminae in the aortic media.

- Marfan patients have a deficiency of connecting filaments and lose more over time.

The Role of Fibrillin-1: Metabolic

- Hal Dietz, et al
- Fibrillin-1 sequesters TGF-β (transforming growth factor beta) by binding it in an inactive form
- Marfan syndrome = Deficiency of fibrillin-1 in the aortic wall
  - A decrease in TGF-β sequestration
  - An increase in TGF-β signaling
  - Elastolysis
  - Smooth muscle cell apoptosis
Potential Alternative Therapeutic Strategy
For Treating Marfan Syndrome

• Anti-TGF-β antibody blunted aortic growth in mice

• Previous studies had shown that losartan, an angiotensin II type 1 receptor (AT1) blocker, inhibits activity of TGF-β

• So Dietz et al studied the effect of losartan therapy on aortic root growth in a mouse model of MFS.
Efficacy of Losartan in Mouse Model of MFS: Aortic Growth Over 6 Months

Hagashi J, et al. Science 2006;312:117-121
Efficacy of Losartan in Mouse Model of MFS: Aortic Wall Architecture

Hagashi J, et al. Science 2006;312:117-121
COMPARE (COzaar in Marfan PAtients Reduces Aortic Enlargement) Trial

• Multicenter, open-label, randomized, controlled trial with blinded assessments in adults with Marfan syndrome

• 233 subjects (not already on ACEI/ARB) randomized to 50 mg losartan as add on Rx vs. no additional Rx

• Primary endpoint = rate of aortic dilatation by MRI at 3 years

• Aortic root growth sig. slower in losartan group
  – (0.77 vs. 1.35 mm, P < 0.014).

Atenolol vs. losartan for MFS: A randomized blinded placebo-controlled trial

- Pediatric Heart Network, Boston Children’s Hospital
  - 21 Centers

- 608 subjects, ages 6 months to 25 yr (mean 11 yr)

- Randomized to:
  - Atenolol, titrated by heart rate (mean dose ≈150 mg in young adults) or
  - Losartan (mean dose ≈ 85 mg in young adults)

- Followed by echo imaging over 3 years

Atenolol vs. losartan for MFS: A randomized blinded placebo-controlled trial

Freedom from Adverse Clinical Outcomes

This trial differed from the others:

- Losartan vs. atenolol, rather than add-on therapy
- Perhaps combination therapy would be more effective than either agent alone…
Could Losartan Be More Effective as Add-on Therapy?

- **Marfan-Sartan Trial**
  - A randomized, double-blind, placebo-controlled trial comparing add-on losartan vs. placebo in Marfan patients, 86% already on beta-blocker


p=0.37
Bad News!
Pharmacologic Management of Thoracic Aortic Aneurysms in 2019?

• We have yet to define optimal pharmacologic therapy

• For now beta blockers remain the mainstay
  – If intolerant to beta-blockers, consider an ARB
  – If room for two agents, consider beta-blocker plus an ARB
Abdominal Aortic Aneurysm
Pharmacologic Therapy

• Doxycycline
  – Of interest because of its not antibiotic properties
  – Inhibits MMP9 expression and activity
  – Does slow AAA growth in some animal models
  – But has failed to slow growth in randomized placebo-controlled trial in humans
    • Including PHAST (Pharmaceutical Aneurysm Stabilization Trial) trial
    – The multicenter randomized trial N-TA^3CT (Noninvasive Treatment of Abdominal Aortic Aneurysm Clinical Trial) is ongoing.

Pharmacologic Therapy

• Beta-blockers
  – When all beta-blocker trials were combined in a meta-analysis, there was a very small, non-significant protective effect for propranolol on AAA expansion
  – But overall beta-blockers were poorly tolerated
  – 42% dropout rate in treatment arm.

• Statins
  – Meta-analyses have suggested decreased AAA growth rates in patients on statin therapy
  – Older and smaller studies confirmative
  – More recent and larger studies non-confirmative.

Pharmacologic Therapy

• ACE inhibitors
  – Promising results from a population-based case-control study of 15,000 patients
  – Failed in a prospective cohort of 1,700 patients enrolled in the UK Small Aneurysm trial
  – Failed vs. placebo in the randomized AARDVARK trial.

• Angiotensin receptor blockers
  – Telmisartan inhibits AAA growth in animal models
  – ARBs have also been associated with reduced growth in a surveillance study of 1,269 patients with small AAA
  – A randomized placebo-controlled trial of telmisartan (TEDY trial) is ongoing.

Pharmacologic Therapy of AAA

• To date, no medication has been convincingly demonstrated to limit AAA progression

Any Agents of Concern?

• Fluoroquinolone antibiotics are known to be associated with an increased risk of tendinitis and tendon rupture
  – Possibly related to an adverse effect on collagen
  – FDA issued a black box warning regarding this risk

• In 2015 two observational studies raised concern that fluoroquinolone antibiotics increase the risk of aortic aneurysm or dissection
  – Both studies reported more than a twofold increased risk of aortic aneurysm or dissection
  – There was a dose/duration-response to the risk.

Fluoroquinolone use and risk of aortic aneurysm and dissection

- Nationwide historical cohort study in Sweden (2006-2013) using linked registry data on patient characteristics, filled prescriptions, and cases of aortic aneurysm or AoD

- 360,088 treatment episodes of fluoroquinolone use (78% cipro) and propensity score matched comparator episodes of amoxicillin use.

Fluoroquinolone use and risk of aortic aneurysm and dissection

Cumulative incidence of aortic aneurysm or dissection within 60 day risk period from start of study treatment

FDA Issued Warning in 12/2018

Fluoroquinolones should not be used in patients at increased risk unless there are no other treatment options available.
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