Renal Artery Stenosis: Current Evidence for Management

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ARAS: What We Believe to be True...

- ARAS occurs frequently in patients with CAD and vascular disease elsewhere
- ARAS predicts CAD-related mortality
- No direct evidence that renal revascularization improves survival
- Progressive renal dysfunction leading to ESRD is undefined though believed to be relatively low
- However, despite TWO large RCTs, renal stenting is STILL a controversial topic...why?

The Complex Clinical Milieu of RAS



Interrelation among Renal Artery Stenosis, Hypertension and Chronic Renal Failure

Safian R, Textor S. Renal-artery stenosis. NEJM 2001; 344

ACC/AHA Recommendations: Indications for Renal Revascularization

- Hypertension:
 Class IIa [LOE: B]
- Preservation of renal function:



- CHF and Unstable Angina:
 - Class I: Unexplained pulmonary edema [LOE: B]
 - Class IIa: RAS and USA [LOE: B]

Rationale for RCTs in ARVD

- Very common condition : annual rate of ARVD diagnosis ³x between 1992-2004
- High level of associated co-morbidity and mortality
- Revascularization procedures frequently performed (e.g., 16% of newly diagnosed Medicare patients) and are NOT without risk
- Four previous RCTs investigating revascularization – all small (largest 106 patients) and inconclusive
- Uncertainty regarding renal functional, CVS events and mortality outcomes

ASTRAL Trial Schema

Diagnosis of significant ARVD (Unilateral or Bilateral) Revascularization not contraindicated

Uncertain whether to revascularize: Randomization

Revascularization

with angioplasty and/or stent (and medical treatment)

No revascularization

Medical Treatment only

Main questions asked within ASTRAL

What is the effect of renal revascularization upon:

Renal functional outcome: (rate of change of renal function over follow-up – reciprocal creatinine plot; 750 patients for 80% power to show 20% difference)

Secondary end-points

- Survival
- Other (CVS) macrovascular events
- Blood pressure control
- Cardiac function and structure (sub-study)

Mean Change in SCr



TIME TO FIRST RENAL EVENT (ARF, Dialysis, Transplant, Nephrectomy, Renal Death)



TIME TO FIRST OF MI, STROKE, VASCULAR DEATH OR HOSPITALISATION FOR ANGINA, FLUID OVERLOAD OR CARDIAC FAILURE



MEAN CHANGE IN SYSTOLIC BP



ASTRAL Summary

- Currently no evidence of a benefit for revascularization on renal function in the ARVD patients entered into ASTRAL – *those in whom clinicians were 'uncertain' of whether to revascularize*
- No evidence of differences between the arms for any of the secondary endpoints (i.e. blood pressure, major events, mortality)
- No evidence of differences in treatment effect across the various subgroups – for renal functional end-point only

Criticisms of ASTRAL...Just a Few of the BIG ones!

- 1. Selection bias and inexperienced operators with a high complication rate
- **2. There was a reduction in the number of antihypertensive drugs in stent treated patients**
- 3. Patients with severe RAS were not enrolled nor confirmed prior to study entry
- 4. Uncertainty as to whether patients were on the right drugs?



Prospective, multi-center, two armed, randomized, unblinded survival (time to event) clinical trial

 To test the hypothesis that optimal medical therapy + stenting reduces the incidence of cardiovascular and renal events compared to optimal medical therapy alone in patients with systolic hypertension

- >100 centers participating
- 1,080 patients

CORAL Primary Endpoints

- **Composite of major CV or renal** events:
 - Cardiovascular or Renal Death
 - Stroke
 - Myocardial Infarction
 - CHF Hospitalization
 - Progressive Renal Insufficiency
 - Permanent Renal Replacement Therapy

CORAL Inclusion Criteria

Clinical Syndrome:

– Hypertension ≥ 2 anti-hypertensive medications

AND/OR

 Renal dysfunction defined as Stage 3 CKD or greater

Atherosclerotic Renal Artery Stenosis:

- Angiographic: ≥ 60% and < 100%, OR</p>
- Duplex: systolic velocity of > 300 cm/sec, OR
- Core lab approved MRA or
- Core lab approved CTA

Screening and Enrollment





CORAL Trial (n = 947)Renal Artery Stenting in Preventing Cardiovascular and Renal Events 160-What does a -11 mmHg SBP drop after 3 months tell us? Mean Systolic Blood Pressure 150-**Medical Therapy** 140 130-**Stent + Medical Therapy** =0.03 120-3 months 6 months 1 year $\mathbf{0}$ 2 years 3 years

NEJM 2014; 370

CORAL CRITIQUE:

- What was the degree of operator selection bias (...shades of ASTRAL)?
- Were the renal artery lesions "critical"?
- Were these patients on MAXIMAL tolerable antihypertensive therapy?
- How do you explain the -11 mmHg decline in the non-sham control arm?



- RAS is a relatively unusual cause of hypertension but a common finding in patients with vascular disease
- RAS identifies patients with very poor prognosis and a high risk for CV events...it is a marker
- Revascularization will benefit selected RAS patients but convincing evidence of improved cardiovascular outcomes in most patients is lacking...RCT design flaws and patient selection bias remain major obstacles to assessing the true clinical value of renal stenting

