Renal Stent Trials: ASPIRE II, RESIST & CORAL Trials

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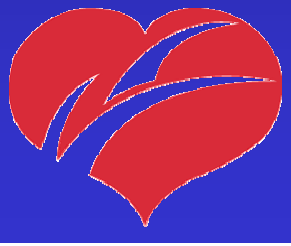
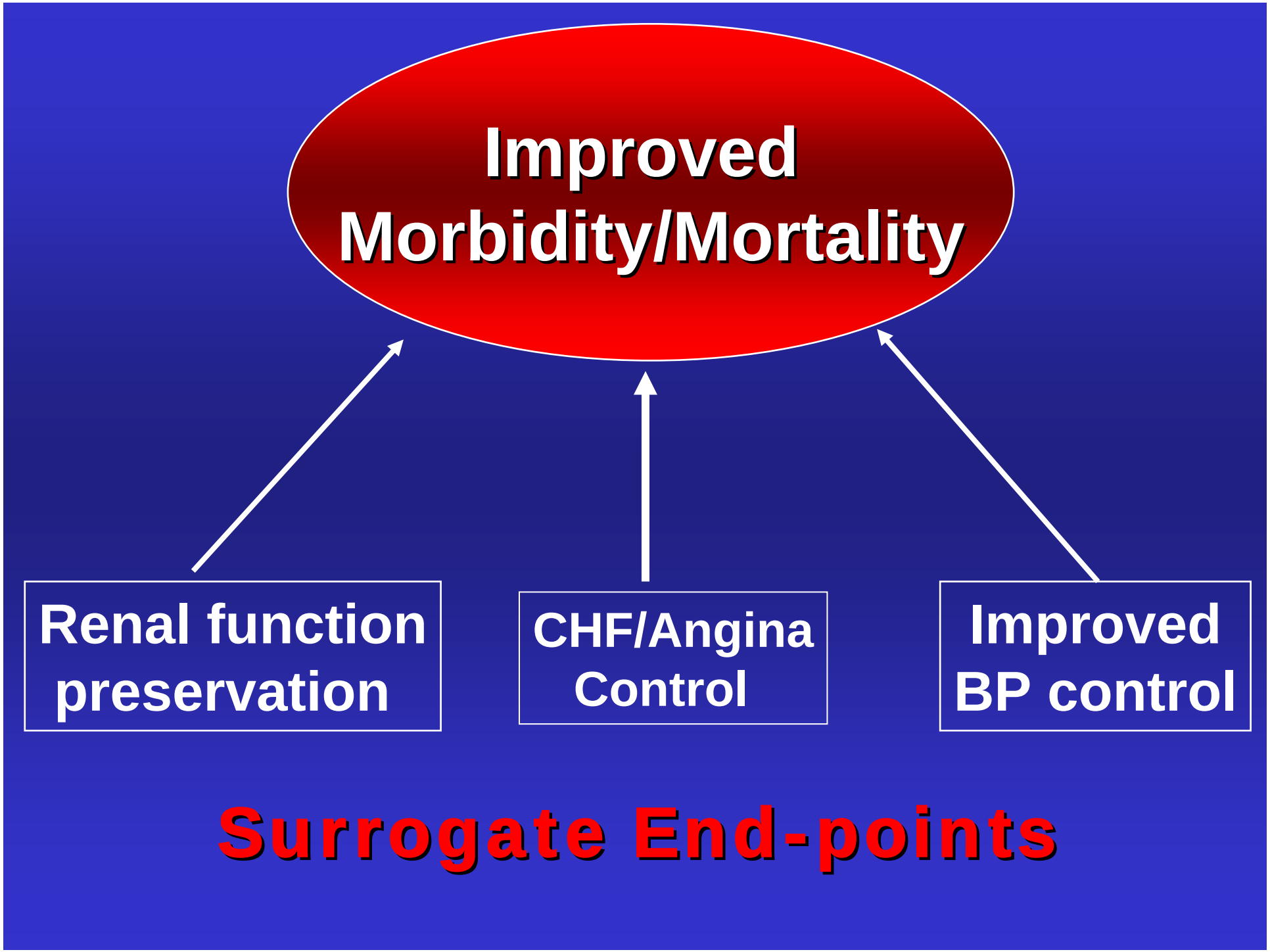


The Challenges of Renal Stenting:

- No U.S. FDA approved ***clinical*** indication
- Angiographic indication only: Failed / suboptimal PTA

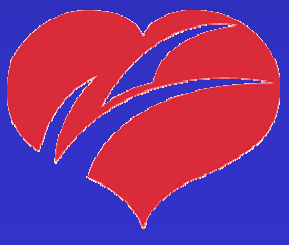
This fact reflects:

- Diverse population w / variety of indications (HTN, renal insufficiency, cardiac disturbances)
- Difficult 'hard' surrogate end-points


Improved Morbidity/Mortality
Renal function preservation
CHF/Angina Control
Improved BP control
Surrogate End-points

U.S. Renal PMA Stent Trials

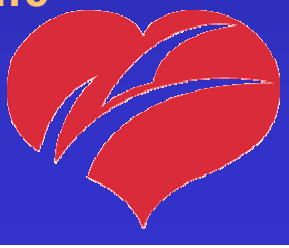
- *Palmaz , (Cordis J&J): ASPIRE I Pilot Trial (Completed)*
- *Palmaz , (Cordis J&J): ASPIRE II (Completed, in press)*
- *Genesis, (Cordis J&J) : GREAT Trial (completed) and RESIST Trial (in progress)*
- *Herculink, (Guidant): HERMES Trial (Completed, not published)*
- *Herculink Plus, (Guidant): ----------*
- *AVE Bridge Stent (Medtronic): SOAR Trial (completed, not published)*
- *IntraStent, (eV3) : ----------*
- *Abbott: ----------*
- *Express stent, (Boston Scientific): Renaissance Trial (Enrollment complete, results pending)*



ASPIRE 2 Study Design

- Design: Prospective, non-randomized study of 208 patients at 23 US sites
- Primary endpoint: 9 mo. restenosis of the PALMAZ stent after failed PTRA
- Secondary endpoints:
  - MACE
    - Device or procedure related death
    - Procedure related Q-wave MI
    - Target lesion revascularization
    - Embolic events (defined as causing end-organ damage or loss of renal function)
  - Effect on control of blood pressure
  - Effect on renal function
    - As defined by a rise in serum creatinine

Rocha-Singh, et al. JACC '05, in press



ASPIRE 2 Results

Lesion Success (% DS < 50%)	99.6% (251/252)
Acute Procedure Success (%DS <30% & gradient <5mmHg)	80.2% (182/227)
Primary Patency (QA/duplex ultrasound @ 9 mo.)	81.0% (149/184)
9-Month Restenosis Rate (by duplex ultrasound & angiography)	17.4% (32/184)
Target Lesion Free at 270 days (K-M Estimate, Lesion Based)	96.7%
Target Lesion Free at 720 days (K-M Estimate, Lesion Based)	85.9%

9 mo.

9 mo.

Rocha-Singh, et al. JACC '05, in press

Effect on Hypertension: Systolic Blood Pressure

Visit	N	Mean ± SD	*P Value*
Baseline	208	167.6 ± 25.2	
Discharge	202	147.6 ± 22.3	< 0.001
1 month	196	151.5 ± 24.4	< 0.001
6 month	182	149.2 ± 22.9	< 0.001
9 month	178	149.5 ± 23.8	< 0.001
24 month	158	149.3 ± 25.3	< 0.001

N.B.

N.B.

Rocha-Singh, et al. JACC '05, in press

Effect on Hypertension: Diastolic Blood Pressure

Visit	N	Mean ± SD	*p*-value
Baseline	208	81.53 ± 13.1	
Discharge	202	70.88 ± 12.1	< 0.001
1 month	196	75.25 ± 11.4	< 0.001
6 month	182	76.85 ± 11.0	< 0.001
9 month	178	77.34 ± 12.1	< 0.001
24 month	158	76.87 ± 11.9	< 0.001

N.B.

N.B.

Rocha-Singh, et al. JACC '05, in press

Effect on Renal Function
Serum Creatinine

Patients with Abnormal Renal Function Only
(Baseline creatinine > 1.5 mg/dl)

Visit	N	Mean±SD	P-value
Baseline	74	1.94±0.39	
1 month	64	1.89±0.72	0.64
6 month	60	1.98±0.66	0.49
9 month	63	1.87±0.58	0.53
24 month	53	1.93±0.71	0.69

Rocha-Singh, et al. JACC '05, in press

ASPIRE II Conclusions

- **17% restenosis rate is comparable to rates in literature**
  - **Extremely favorable compared to PTRA alone**
  - **Comparable to surgical revascularization**
- **Blood Pressure response showed significant reductions in blood pressure at 9 and 24 months**
  - **Systolic:**
    - **18.1 point improvement at 9 mo. (10.8% decrease)**
    - **18.3 point improvement at 24 mo. (10.9% decrease)**
  - **Diastolic:**
    - **4.2 point improvement at 9 mo. (5.1% decrease)**
    - **4.7 point improvement at 24 mo. (5.7% decrease)**

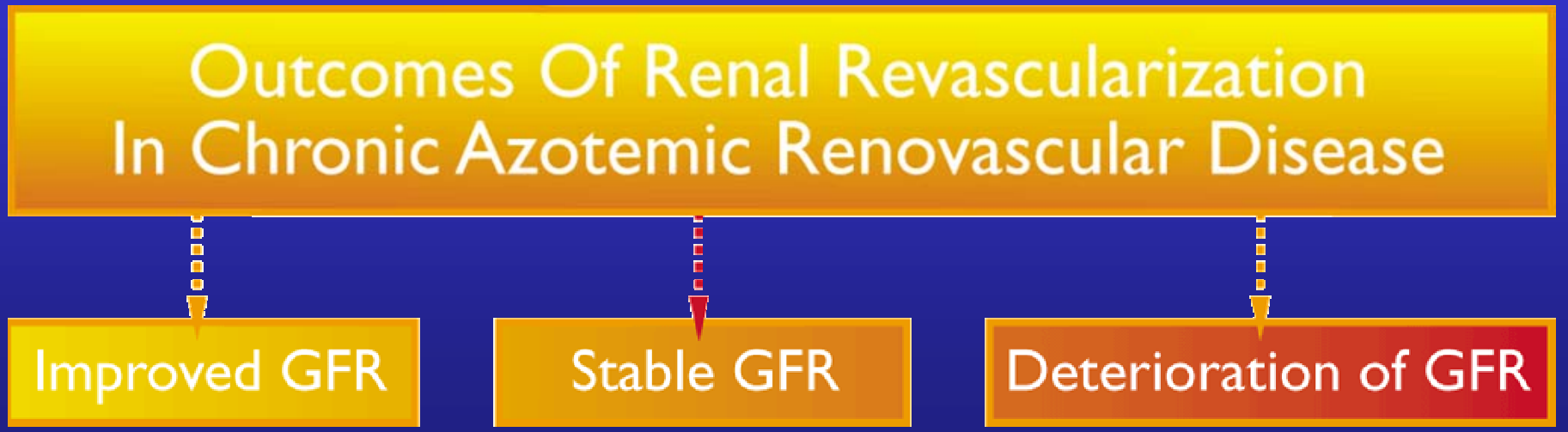
Rocha-Singh, et al. JACC '05, in press

ASPIRE II Conclusions (cont'd)

- No significant changes in serum creatinine levels at 9-month follow-up
  - No change in subset who were abnormal at baseline
  - No significant change when all patients are considered
- BP/Antihypertensive medication response showed 45% of patients were *cured* or *improved* at both 9- and 24-month marks

55% of patients experienced no BP improvement

Outcomes Of Renal Revascularization In Chronic Azotemic Renovascular Disease



25 - 30%

- **Restoration of Blood Flow**
- **Reversible Parenchymal Injury**

45 - 50%

- **No Further Loss of Blood Flow**
- **Stable Tissue Fibrosis**

20 - 25%

- **Progressive Parenchymal Injury**
- **Concurrent Diseases**
- **Atheroemboli**
- **Reperfusion Injury**

Renal Stent Related Complications: ASPIRE II

Major Adverse Events – 9 mos.	10.6%
Stent Thrombosis	1.8%
Significant Embolic Event	5.3%
Target Lesion Revascularization	4.8%
Access Site Complication	4.8%
Worsening Renal Function	3.8%
Complication Requiring Surgery	2.1%
Complication Requiring Nephrectomy	0.0%
30-day Mortality	0.5%

Rosenfield '00

Atheroembolization

- Material impacts in small arteries, arterioles and glomeruli
- Intimal thickening and formation of giant cells
- Distal micro-infarcts and ischemic atrophy

– *Becomes clinically evident 1 day to 2 months after the procedure*

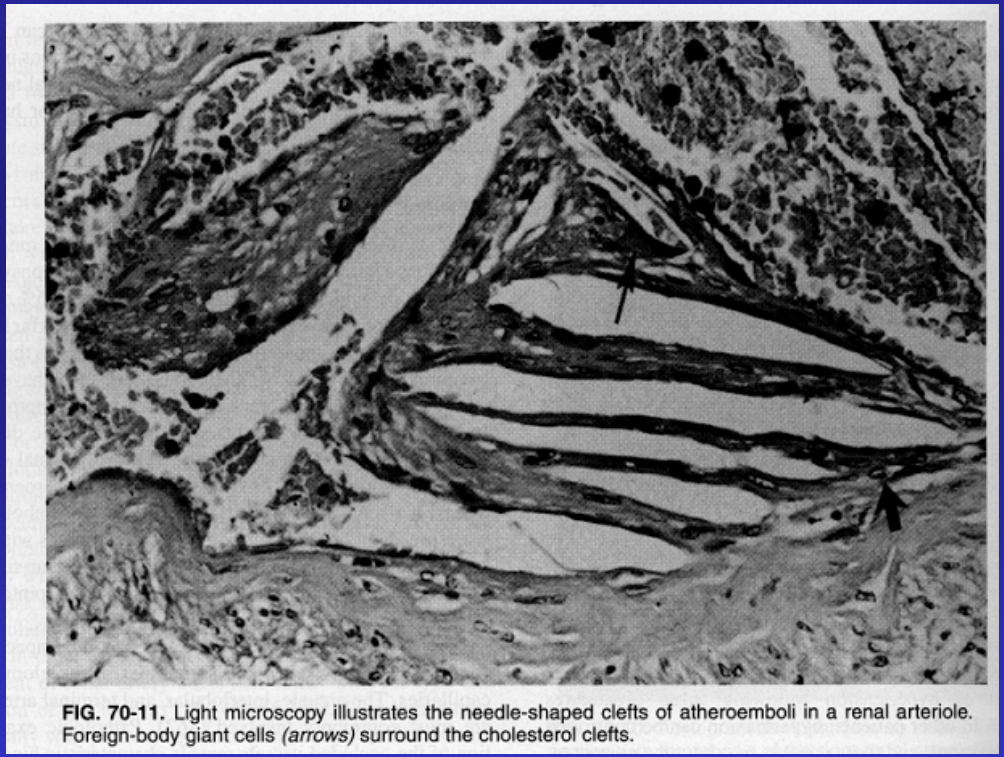
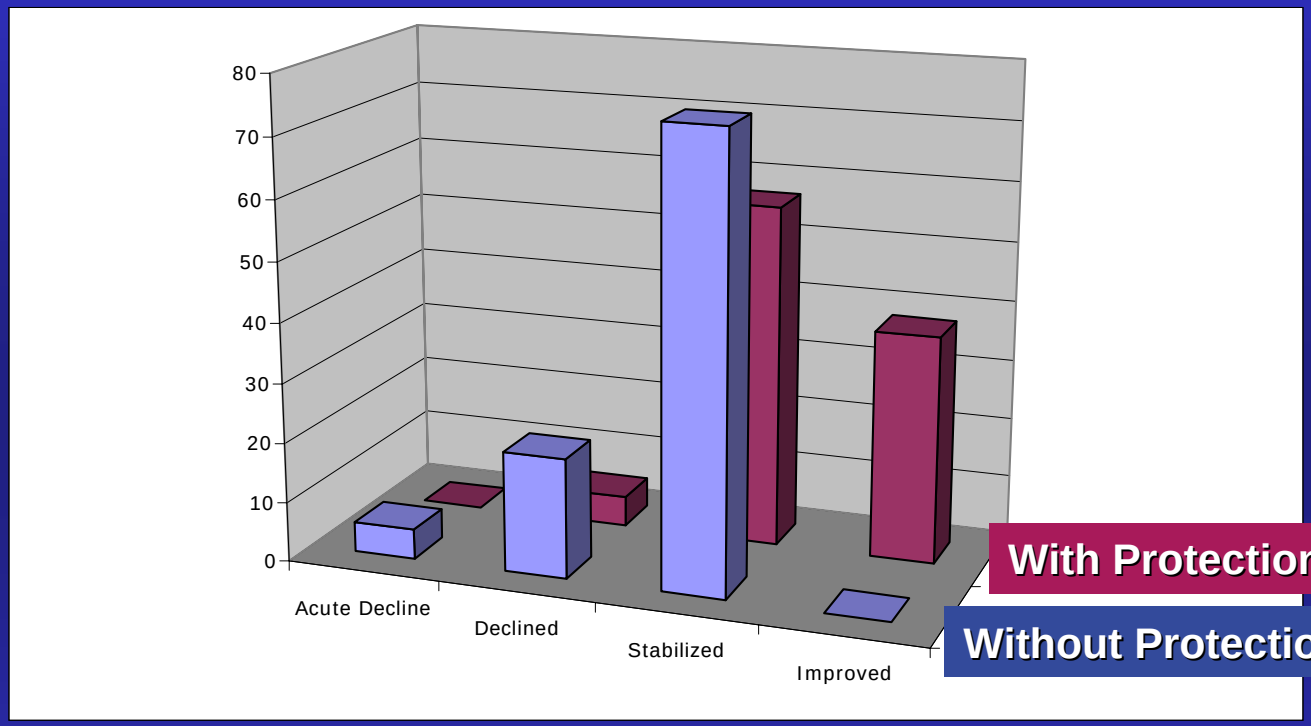


FIG. 70-11. Light microscopy illustrates the needle-shaped clefts of atheroemboli in a renal arteriole. Foreign-body giant cells *(arrows)* surround the cholesterol clefts.

From Schrier, 7th ed.

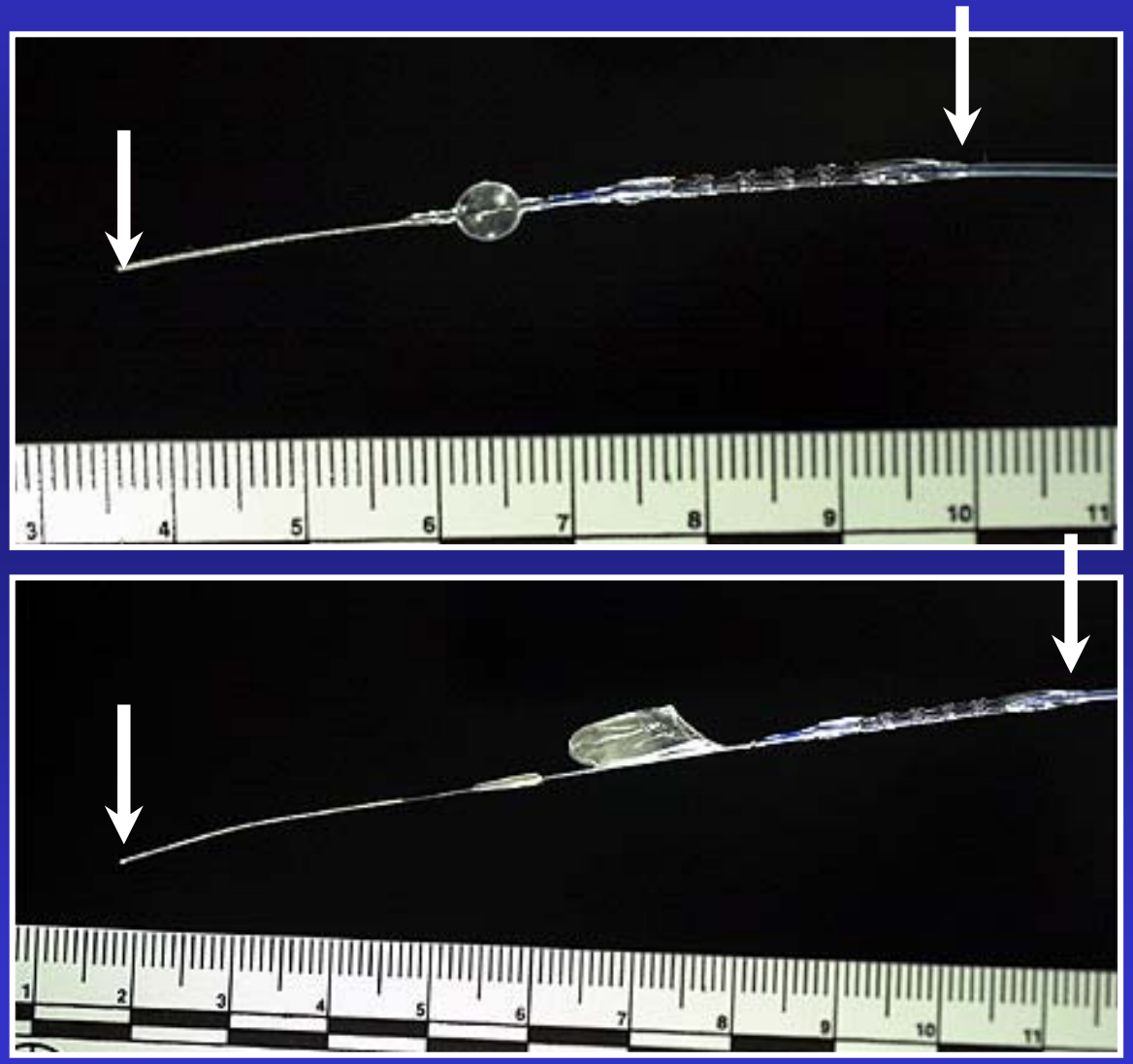
Atheroembolic Protection: Holden et. al.



- Retrospective review of patients prior to and with embolic protection
  - 20 before, and 37 after
- Mean follow up 1 year

JVS 2003; 38:962-968.

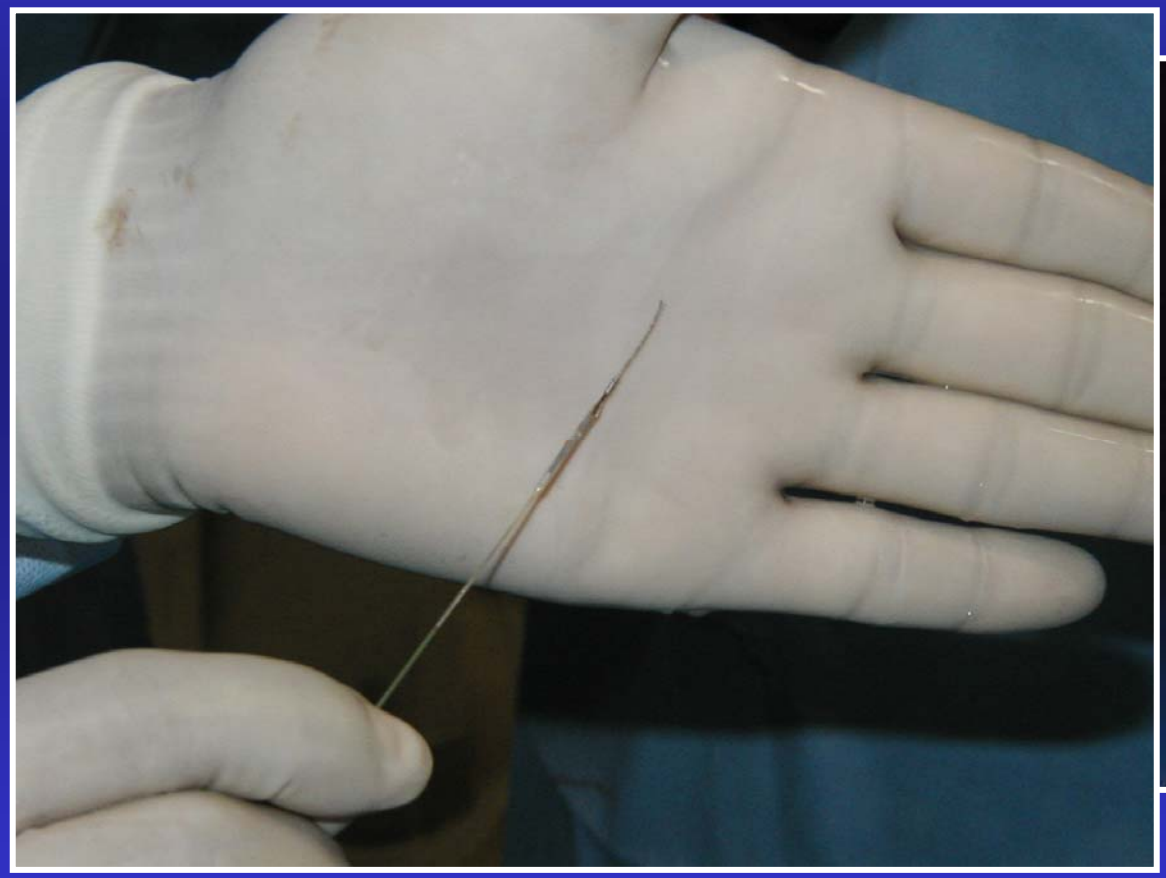
Commercially Available DP Technology



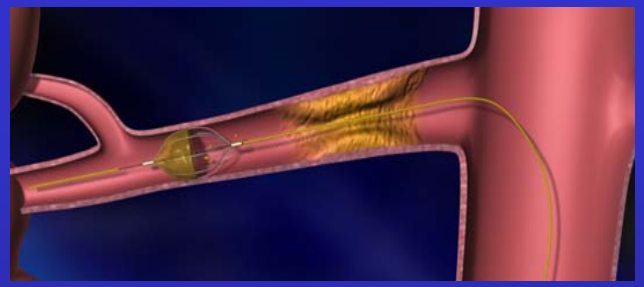
PercuSurge™

FilterWire EX™

AngioGuard™ Short-tip



RESIST Trial



A Prospective Randomized Multicenter Study Comparing the Safety & Efficacy of Renal Artery Stenting with & without the use of a Distal Protection Device (Angioguard) and with & without the use of Reopro.

- Multi-center, prospective, randomized, feasibility Trial
- 100 patients stented with PALMAZ® GENESIS® Stent
- 50 patients randomized to stent + ANGIOGUARD™ and 50 patients to stent alone
- 50 patients randomized to receive Reopro
- Patient follow-up at 1 and 6 months
- Enrollment at 66 patients to date

Primary Aims of the RESIST Study:

1. Determine whether embolic protection with the **Angioguard XP Short Tip** device during stent implant results in:

    a. Retrieval of atheroembolic material...amount
    b. Improved renal function at 1 month post-procedure
    c. Evidence of decreased injury in the kidney(s)
    d. Is it safe?

Primary Aims of RESIST Study

2. Determine whether the inhibition with ReoPro results in:

    a. Improved renal function 1 month post-procedure.
    b. Decreases evidence of injury in the kidney(s)
    c. Is it safe?

RESIST Follow-up:

1 month visit:

a. Blood pressure assessment
b. Creatinine assessment with BMP
c. Renal function assessment with DTPA scan to assess GFR and Iohexal clearance
d. Hypertensive medication assessment

6 month visit:

a. Blood pressure assessment
b. Creatinine assessment with BMP
c. Hypertensive medication assessment

Strategies to Avoid Distal Embolization

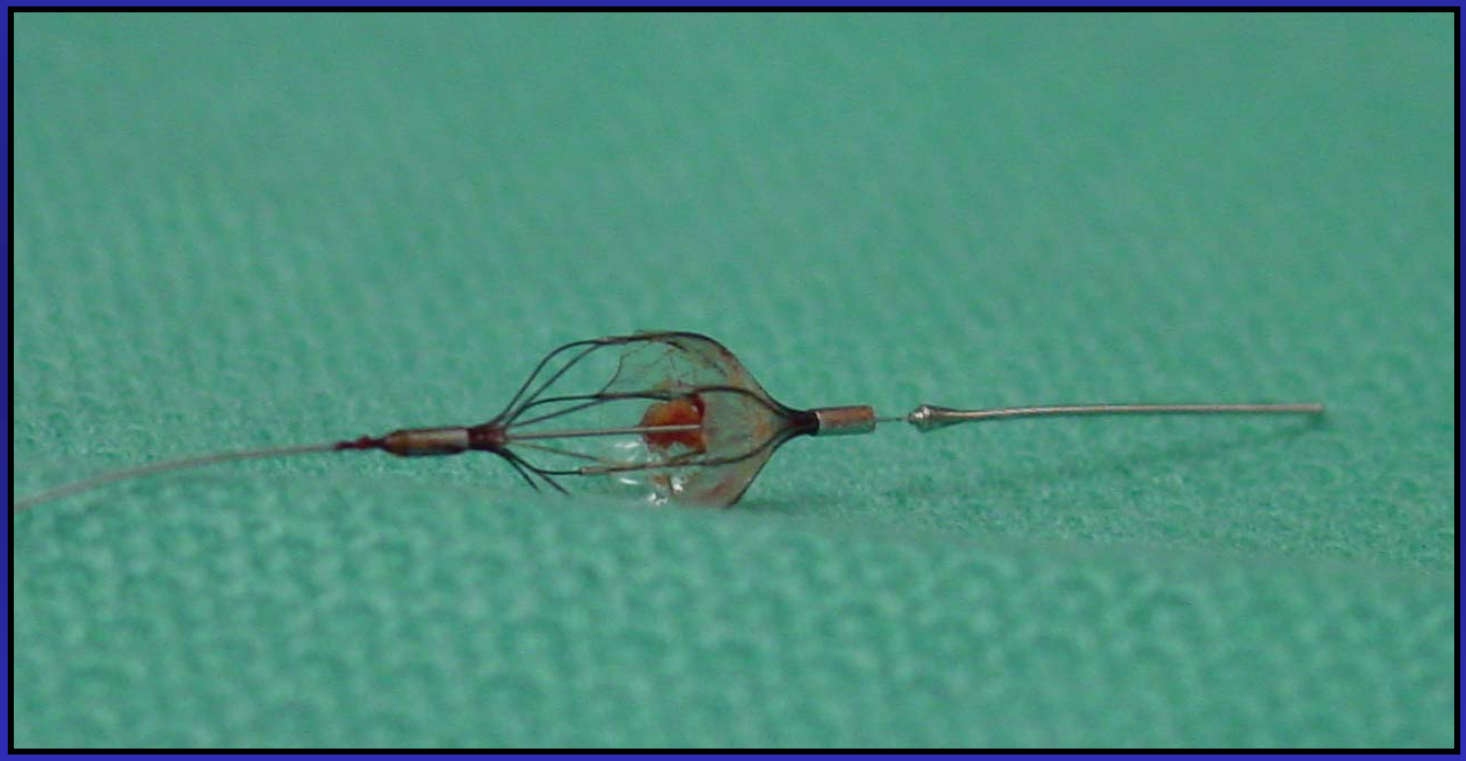
- **Patient selection: 'High risk' cohort**
  - Elderly
  - Renal dysfunction, bilateral disease
  - Diseased aorta

  } **Appropriate Anatomy**

- **Active Protection: Technical Points**
  - Atraumatic catheter intubation: Use 'No touch'
  - Choice of the device:
    - Small french diagnostic and guiding catheters
    - 0.014" guide wires, balloons, short stents…
    - Coronary devices & techniques

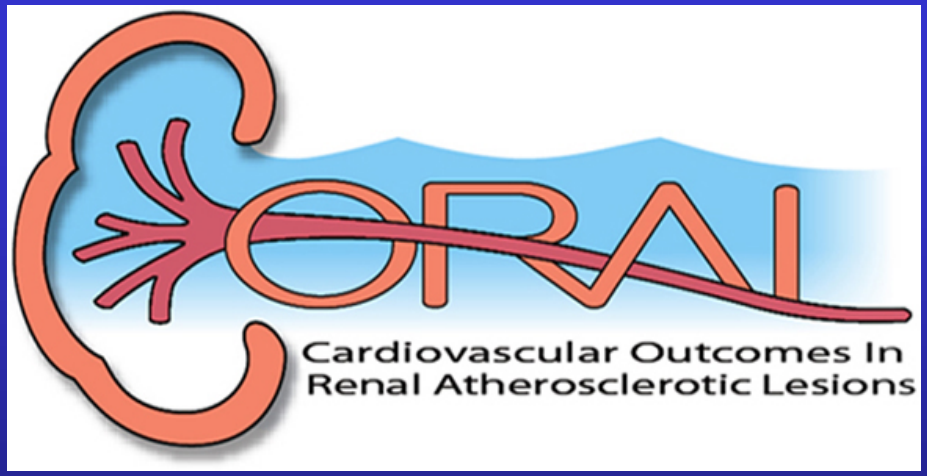
➡ **Passive Protection: DP Devices**

AngioGuard-XP Wire



CORAL is designed to test a singular hypothesis:

Does 'best medical therapy' combined with stenting of hemodynamically-significant renal artery stenoses in patients with systolic hypertension reduce the incidence of adverse cardiovascular and renal events compared with 'best medical therapy' alone.



Prospective, multicenter, two armed, randomized, un-blinded trial

Interventions:

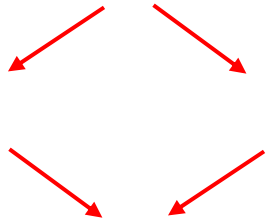
1. ***Optimal Medical Therapy***
   - All receive Candesartan, Angiotensin Receptor Blocker
   - LDL, BP and HbA1c to guideline
2. ***OMT plus Stent Revascularization***
   - AngioGuard embolic protection
   - Genesis balloon expandable stent

Randomization and Follow-up

RANDOMIZATION OF ALL ANGIOGRAPHICALLY ELIGIBLE PATIENTS

- Performed in angiography lab immediately after diagnostic angiogram confirms eligibility

1080 Patients



Medical Therapy
540 Patients

Stent + Medical Therapy
540 Patients

Follow-up

1st Year of Follow-up

- q 2 Weeks up to 2 Months for BP Control
- q 3 Months Physician Office Visits
- Monthly Coordinator Phone Contact

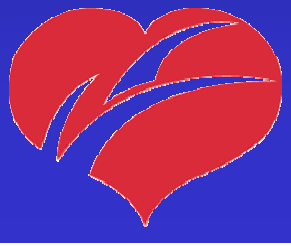
2nd Year through End of Study Follow-up

- Semi-annual + Annual Physician Office Visits
- Quarterly Research Coordinator Visits
- Monthly Coordinator Phone Contacts

Primary Outcome:

- **Survival free from a composite of clinically important Cardiovascular and Renal Adverse Events: Hard End-points**
  - **Cardiovascular or Renal Death**
  - **Stroke**
  - **Myocardial Infarction**
  - **Hospitalization from CHF**
  - **Progressive Renal Insufficiency**
    - ***Doubling of Cr from baseline, persisting on 2 core lab draws separated by 60 days***
  - **Renal Replacement Therapy (HD)**

Adjudicated by an independent CEC



OMT vs OMT plus Protected Stenting

Why is Optimal Medical Therapy critical?

- If stenting wins, it wins against the best.
- If blood pressure or renal function benefits emerge, it isn't because of poor medical therapy!
  - OMT needs to be balanced for effect of stenting to be evaluable.
- ***Every*** patient in this trial will be treated well.

Why is "State-of the-art" intervention critical?

- Comparison should be best vs best
- Interventional committee will continue to review "best" interventional care
- Results should be relevant in 2010 and beyond

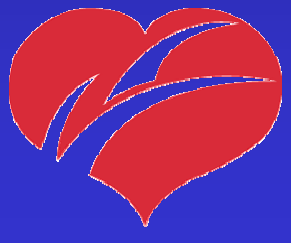
Optimal Medical Therapy

Required Therapies

- BP to target
  - ARB (Candesartan) based
  - <140/90
  - <130/80 with DM
- LDL to goal
  - Currently <100 mg/dl
- Diabetes Management
  - HbA1c to target, <7
- Smoking Cessation

Monitoring

- Compliance
  - Candesartan
- BP Quarterly
- LDL annually
- HbA1c annually
- Document smoking status and education



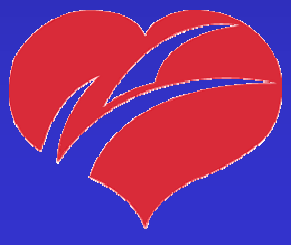
Secondary Endpoints

- All Cause Mortality
- Subgroup Interactions:
  - Men vs Women
  - African American vs non-African American
  - Diabetes vs non-Diabetes Mellitus
  - Global vs Partial Renal Ischemia
- Longitudinal Kidney Function (1/Cr)
- Systolic Blood Pressure
- Durability of Renal Artery Patency
- Renal Resistive Index: Preservation of Microvascular Renal Function
- Correlation between Stenosis Severity and Kidney Function (1/Cr)
- Quality of Life
- Cost Effectiveness

CORAL Population

Points of Emphasis:

1. Enrollment decision based on ***clinical***, not anatomic criteria.
2. If patients with severe stenoses or global ischemia are excluded, no inference can be made.
3. As a federally funded project, inclusion of women and minorities is critical for generalizability



So, in the next 5 years:

- Clinical indications for medical v. percutaneous intervention will be better defined
- Angiographic v. Duplex doppler restenosis rates will be known
- Impact of medical therapy v. renal intervention on ‘hard end-points’ (death, MI/CVA, BP control & ESRD) will be determined