Research Support: Abbott Vascular
Equity Interest (modest): Boston Scientific
Equity Interest (modest): Johnson and Johnson
Equity Interest (modest): Medicines Company
Equity Interest (modest): Medtronic
SCOPE OF PRESENTATION

SUBCLAVIAN ARTERY DISEASE
RENAL ARTERY DISEASE
LOWER EXTREMITY PERIPHERAL ARTERY DISEASE
RENAL SYMPATHETIC DENERVATION

Common non-coronary vascular problems in a primary care setting
Excludes: critical limb ischemia, trauma, stroke and cerebrovascular disease, thoracic aortic aneurysm, abdominal aortic aneurysm
SUBCLAVIAN ARTERY DISEASE

RENAL ARTERY DISEASE

LOWER EXTREMITY PERIPHERAL ARTERY DISEASE

RENAL SYMPATHETIC DENERVATION
Arm or hand angina, especially when using the arm above the head
Left subclavian 3 to 4 times as often as the right subclavian
2% of the general population, 7% in patients with risk factors for atherosclerosis*, most patients are asymptomatic
Tobacco use
Subclavian steal
Thromboembolism and acute limb ischemia
Angina in patients with LIMA CABG
Persistent difference in arm blood pressures more than 10%
Elevated Arm Stress Test (EAST)
Chest X-Ray to look for cervical rib

*JACC 2004;44: 18-23
Figure 1.8 Subclavian “steal.” (a) Drawing of simultaneous radial artery palpation and clinically detectable delay of left radial artery pulsation. (From Spittell J.A. Jr & Spittell P.C. (2000) Peripheral Vascular Disease in ACCSAP. By permission of the American College of Cardiology.) (b) Arch aortogram in a 65-year-old woman, a veteran smoker, demonstrating stenosis of the proximal left subclavian artery (a “smoker’s lesion”). (c) Later phase of arch aortogram showing opacification of the left vertebral artery – the subclavian “steal.” (From Spittell J.A. Jr (1994) Peripheral arterial disease. Disease-A-Month 40(12): 641–704. By permission of Mosby, Inc, St Louis, MA.)
SYMPTOMS!

- Screening with ultrasound
- Rarely CT angiography or MRI
- Catheter angiography for intervention or if diagnosis unclear
- Need for LIMA conduit for CABG
LEFT SUBCLAVIAN STEAL
LEFT SUBCLAVIAN ARTERY ANGIOPLASTY AND STENTING
FOLLOW UP

- Observation for symptoms including arm or hand angina, dizziness, chest pain (in patients with prior LIMA CABG)
- Blood pressure in BOTH ARMS
- Ultrasound, particularly if at high risk (1 month, 6 months, 1 year)
- Rarely CT angiography or catheter angiography
- Dual antiplatelet therapy
SUBCLAVIAN ARTERY DISEASE

RENAL ARTERY DISEASE

LOWER EXTREMITY PERIPHERAL ARTERY DISEASE

RENAL SYMPATHETIC DENERVATION
- Young patients with onset of hypertension before age 30
- Onset of severe hypertension after age 55
- Accelerated hypertension
- Resistant hypertension
- Malignant hypertension
- Worsening renal function after administration of ACE inhibitor or angiotensin receptor blocker
- Unexplained atrophy of a kidney
- Sudden unexplained pulmonary edema

High index of suspicion
DIAGNOSIS

- DUPLEX ULTRASOUND
- CT ANGIOGRAPHY
- MRI
- CATHETER ANGIOGRAPHY IF SUSPICION HIGH AND NON-INVASIVE TESTS INCONCLUSIVE
BILATERAL RENAL ARTERY STENOSIS
LEFT RENAL ARTERY ANGIOPLASTY
UNILATERAL RENAL ARTERY STENOSIS WITH CONTRALATERAL HYDRONEPHROSIS
Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D’Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators

BACKGROUND
Atherosclerotic renal-artery stenosis is a common problem in the elderly. Despite two randomized trials that did not show a benefit of renal-artery stenting with respect to kidney function, the usefulness of stenting for the prevention of major adverse renal and cardiovascular events is uncertain.

METHODS
We randomly assigned 947 participants who had atherosclerotic renal-artery stenosis and either systolic hypertension while taking two or more antihypertensive drugs or chronic kidney disease to medical therapy plus renal-artery stenting or medical therapy alone. Participants were followed for the occurrence of adverse cardiovascular and renal events (a composite end point of death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal-replacement therapy).

RESULTS
Over a median follow-up period of 43 months (interquartile range, 31 to 55), the rate of the primary composite end point did not differ significantly between participants who underwent stenting in addition to receiving medical therapy and those who received medical therapy alone (35.1% and 35.8%, respectively; hazard ratio with stenting, 0.94; 95% confidence interval [CI], 0.76 to 1.17; P=0.58). There were also no significant differences between the treatment groups in the rates of the individual components of the primary end point or in all-cause mortality. During follow-up, there was a consistent modest difference in systolic blood pressure favoring the stent group (−2.3 mm Hg; 95% CI, −4.4 to −0.2; P=0.03).

CONCLUSIONS
Renal-artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease. (Funded by the National Heart, Lung and Blood Institute and others; ClinicalTrials.gov number, NCT00081731.)
CORAL TRIAL PERSPECTIVE

Did not support renal stenting as the initial treatment for renovascular hypertension, but neither do the guidelines

Both groups had similar increase in number of medications and similar decreases in systolic pressure implying that the medical treatment group had not actually failed a three drug regimen

Enrollment impeded because of perceived lack of clinical equipoise for very severe or only mild stenosis. Average stenosis of 67% by the core laboratory.

Angiography poor at determining hemodynamic severity of moderate stenosis

Unanswered questions: 1. Does stenting plus medical therapy benefit patients who are refractory to medical therapy? 2. What is the benefit of stenting for hemodynamically confirmed renovascular ischemia?
# Renal Artery Stenosis: Indications for Revascularization

**Table IV: Clinical Scenarios in Which Treatment of Significant RAS May be Considered**

<table>
<thead>
<tr>
<th>Appropriate Care</th>
<th>May Be Appropriate Care</th>
<th>Rarely Appropriate Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disturbance Syndromes (Flash Pulmonary Edema or acute coronary syndrome (ACS)) with severe hypertension</td>
<td>Unilateral RAS with CKD (eGFR &lt; 45 cc/min)</td>
<td>Unilateral, Solitary, or Bilateral RAS with controlled BP and normal renal function</td>
</tr>
<tr>
<td>Resistant HTN (Uncontrolled hypertension with failure of maximally tolerated doses of at least three antihypertensive agents, one of which is a diuretic, or intolerance to medications)</td>
<td>Unilateral RAS with prior episodes of congestive heart failure (Stage C)</td>
<td>Unilateral, solitary, or bilateral RAS with kidney size &lt;7 cm in pole-to-pole length</td>
</tr>
<tr>
<td>Ischemic nephropathy with chronic kidney disease (CKD) with eGFR &lt; 45 cc/min and global renal ischemia (unilateral significant RAS with a solitary kidney or bilateral significant RAS) without other explanation</td>
<td>Anatomically challenging or high risk lesion (early bifurcation, small vessel, severe concentric calcification, and severe aortic atheroma or mural thrombus)</td>
<td>Unilateral, Solitary, or Bilateral RAS with chronic end stage renal disease on hemodialysis &gt;3 months. Unilateral, Solitary, or Bilateral renal artery chronic total occlusion</td>
</tr>
</tbody>
</table>

*Significant RAS is an angiographically moderate lesion (50-70%) with physiologic confirmation of severity or >70% stenosis (see Table III).*

**CARDIAC DISTURBANCE**
- Hemodynamically Significant RAS with:
  - Recurrent unexplained CHF OR
d  - Sudden, unexplained pulmonary edema
  (Class I, LOE D)
  
**RESISTANT HYPERTENSION**
- RAS with:
  - Accelerated, Resistant or Malignant HTN
  - HTN with unilateral small kidney
  (Class IIa, LOE E)

**ISCHEMIC NEPHROPATHY**
- RAS and CRI with:
  - Bilateral RAS OR
  - RAS to a solitary functioning kidney (Class IIIa, LOE C)

**Fig. 2.** Review of Multi-Societal Guidelines Recommendations Adapted from [10]: Multisocietal Guideline indications for renal artery revascularization. RAS, renal artery stenosis; CRI, chronic renal insufficiency; LOE, level of evidence.

**Peripheral Vascular Disease**

**Core Curriculum**

SCAI Expert Consensus Statement for Renal Artery Stenting Appropriate Use

Sahil A. Parikh, MD, FACC, FSCAI, Mohdi H. Shishehbord, MD, MM, FACC, FSIR, Bruce H. Gray, MD, FACC, Christopher J. White, MD, FACC, and Michael R. Jaff, MD, FACC, FSCAI
Asymptomatic Stenosis
Class IIb
1. Percutaneous revascularization may be considered for treatment of an asymptomatic bilateral or solitary viable kidney with a hemodynamically significant RAS. (Level of Evidence: C)
2. The usefulness of percutaneous revascularization of an asymptomatic unilateral hemodynamically significant RAS in a viable kidney is not well established and is presently clinically unproven. (Level of Evidence: C)

Hypertension
Class IIa
1. Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, and hypertension with intolerance to medication. (Level of Evidence: B)

Preservation of Renal Function
Class IIa
1. Percutaneous revascularization is reasonable for patients with RAS and progressive chronic kidney disease with bilateral RAS or a RAS to a solitary functioning kidney. (Level of Evidence: B)

Class IIb
1. Percutaneous revascularization may be considered for patients with RAS and chronic renal insufficiency with unilateral RAS. (Level of Evidence: C)

Impact of RAS on Congestive Heart Failure and Unstable Angina
Class I
1. Percutaneous revascularization is indicated for patients with hemodynamically significant RAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema. (Level of Evidence: B)

Class IIa
1. Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and unstable angina. (Level of Evidence: B)
SUBCLAVIAN ARTERY DISEASE

RENAL ARTERY DISEASE

LOWER EXTREMITY PERIPHERAL ARTERY DISEASE

RENAL SYMPATHETIC DENERVATION
PERIPHERAL ARTERY DISEASE STATISTICS

- 8 MILLION PEOPLE IN THE UNITED STATES
- GENERAL POPULATION AWARENESS ONLY 25%

Source: Centers for Disease Control and Prevention Website
- Claudication, literally lameness
- Pain, discomfort, cramping or tiredness that occurs during walking and is relieved with rest
- Most common in the calves, but can occur in the buttocks, hips, thighs, feet, and arms
- Careful physical exam, have patients take off their shoes and socks!
- Pulses
- Bruits
- 60 degree leg raise for pallor
## TRUE VERSUS PSEUDOCLaUDICATION

<table>
<thead>
<tr>
<th></th>
<th>CLAUDICATION</th>
<th>PSEUDOClaUDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ONSET</strong></td>
<td>WALKING</td>
<td>ERECT POSTURE, i.e. WALKING OR STANDING</td>
</tr>
<tr>
<td><strong>DISCOMFORT</strong></td>
<td>CRAMP, ACHE, FATIGUE</td>
<td>PARESTHESIA, PAIN, WEAKNESS</td>
</tr>
<tr>
<td><strong>BILATERAL?</strong></td>
<td>+/-</td>
<td>GENERALLY BILATERAL</td>
</tr>
<tr>
<td><strong>RELIEF</strong></td>
<td>STAND STILL</td>
<td>SIT DOWN, LEAN ON SOMETHING, FLEX SPINE</td>
</tr>
<tr>
<td><strong>CAUSE</strong></td>
<td>OCCLUSIVE PERIPHERAL ARTERY DISEASE</td>
<td>SPINAL STENOSIS</td>
</tr>
</tbody>
</table>

FROM: Peripheral Vascular Disease for Cardiologists A Clinical Approach. John A. Spittell, Jr. 2004 Futura, page 3, Table 1.1
ANKLE BRACHIAL INDEX
EXERCISE ANKLE-BRACHIAL INDEX
ANGIOGRAM
ABNORMAL ANKLE-BRACHIAL INDEX
- Ankle-brachial index
- Toe-brachial index (non-compressible vessels)
- Segmental pressures
- Exercise ankle-brachial index
- Duplex ultrasound
- CT angiography
- MR angiography
- Catheter angiography
  - When diagnosis unclear despite non-invasive imaging
  - Revascularization planned
DUPLEX ULTRASOUND
- Smoking cessation
- Lipid lowering
- Diabetes treatment
- Hypertension treatment
- Antiplatelet therapy (aspirin 81 mg po daily or clopidogrel)
- Supervised exercise training
- Cilostazol 100 mg po BID (in the absence of heart failure)
- Pentoxiphylline 400 mg po TID (second line therapy - Class IIB)
- Ramipril 2013 article retracted from JAMA, 1 December 2015 following admission of data fabrication by the first author)
DRUG ELUTING BALLOON
DRUG ELUTING STENT
NEW DEVICES

Covidien HawkOne

Spectranetics laser

cSi Diamondback
Zilver® PTX®
DRUG-ELUTING PERIPHERAL STENT

NOW FDA APPROVED

2 Year Drug Effect - Patency (PSVR < 2.0)
(Provisional Zilver PTX vs. Bare-Metal Stents)
Randomized study

Primary Patency

83.4%
(Zilver PTX)

90.2%

72.9%

P < .01

64.1%
(Bare-metal stent)

Year

0 1 2

Provisional Zilver PTX
Provisional bare-metal stent
Primary Patency Results through 2 Years

Log-rank $P < 0.001$

78.9%

50.1%

DCB

PTA

Number at risk

DCB 220

PTA 111

Time after Index Procedure (Months)

0 6 12 18 24

Primary Patency

1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSV < 2.4) or clinically-driven target lesion revascularization through 24 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment).

2. Number at risk represents the number of evaluable subjects at the beginning of the 30-day window prior to each follow-up interval.
DRUG ELUTING BALLOON FOR ILIAC IN-STENT RESTENOSIS
SUBCLAVIAN ARTERY DISEASE

RENAL ARTERY DISEASE

LOWER EXTREMITY PERIPHERAL ARTERY DISEASE

RENAL SYMPATHETIC DENERVATION
- Sympathetic nervous system and hypertension
- Ardian Symplicity I (n=153) pilot studies
- Symplicity II (n=106) randomized controlled study
- Medtronic acquired Ardian for $800 million in 2010
- Not just hypertension!

INITIAL ENTHUSIASM

Data from Medtronic Symplicity website
A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O’Neill, M.D., Ralph D’Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Mingjie Liu, Ph.D., Laura Mauri, M.D., Manuel Negro, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Opari, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPPLICITY HTN-3 Investigators

ABSTRACT

BACKGROUND

Prior unblinded studies have suggested that catheter-based renal-artery denervation reduces blood pressure in patients with resistant hypertension.

METHODS

We designed a prospective, single-blind, randomized, sham-controlled trial. Patients with severe resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure. Before randomization, patients were receiving a stable antihypertensive regimen involving maximally tolerated doses of at least three drugs, including a diuretic. The primary efficacy end point was the change in office systolic blood pressure at 6 months; a secondary efficacy end point was the change in mean 24-hour ambulatory systolic blood pressure. The primary safety end point was the composite of death, end-stage renal disease, embolic events resulting in end-organ damage, revascularization complications, or hypertensive crisis at 1 month or new renal-artery stenosis of more than 70% at 6 months.

RESULTS

A total of 515 patients underwent randomization. The mean (±SD) change in systolic blood pressure at 6 months was −143±23.3 mm Hg in the denervation group compared with −117±25.0 mm Hg in the sham-procedure group (P=0.001 for both comparisons of the change from baseline, for a difference of −2.39 mm Hg (95% confidence interval (CI), −4.89 to 1.25). P=0.26 for superiority with a margin of 5 mm Hg). The change in 24-hour ambulatory systolic blood pressure was −45±15.1 mm Hg in the denervation group and −4.7±12.6 mm Hg in the sham-procedure group, for a difference of −1.06 mm Hg (95% CI, −1.87 to 0.55), P=0.80 for superiority with a margin of 2 mm Hg). There were no significant differences in safety between the two groups.

CONCLUSIONS

This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPPLICITY HTN-3 ClinicalTrials.gov number, NCT01418261)
Possible reasons for failure
- Placebo effect: blinded, sham procedure made all the difference!
- Possibly incomplete or ineffective denervation, no markers
- Inclusion criteria required a certain blood pressure level
- Rigorous medical therapy
- Cancelled, redesigned, or delayed trials

What is going on now?
- New trial with redesigned catheter

DAMPENED ENTHUSIASM
THANK YOU!
<table>
<thead>
<tr>
<th></th>
<th>Claudication</th>
<th>Pseudoclaudication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Walking</td>
<td>Erect posture, i.e. walking or standing</td>
</tr>
<tr>
<td>Discomfort</td>
<td>Cramp, ache, fatigue</td>
<td>Paresthesia, pain, weakness</td>
</tr>
<tr>
<td>Bilateral?</td>
<td>±</td>
<td>Generally bilateral</td>
</tr>
<tr>
<td>Relief</td>
<td>Stand still</td>
<td>Sit down, lean on something, flex spine</td>
</tr>
<tr>
<td>Cause</td>
<td>Occlusive peripheral arterial disease</td>
<td>Spinal stenosis</td>
</tr>
</tbody>
</table>
EXERCISE ANKLE-BRACHIAL INDEX

PT WALKED FOR 5 MINUTES AT 2 MPH AND 12% INCLINE
AT 1:30 PT STATED HE HAD BILAT LEG PAIN
AT 3:00 PT STATED HE HAD WORSENIG PAIN RT CALF
PT EXPERIENCED SHORTNESS OF BREATH, BUT NO OTHER CARDIAC SYMPTOMS