Renal Artery Intervention

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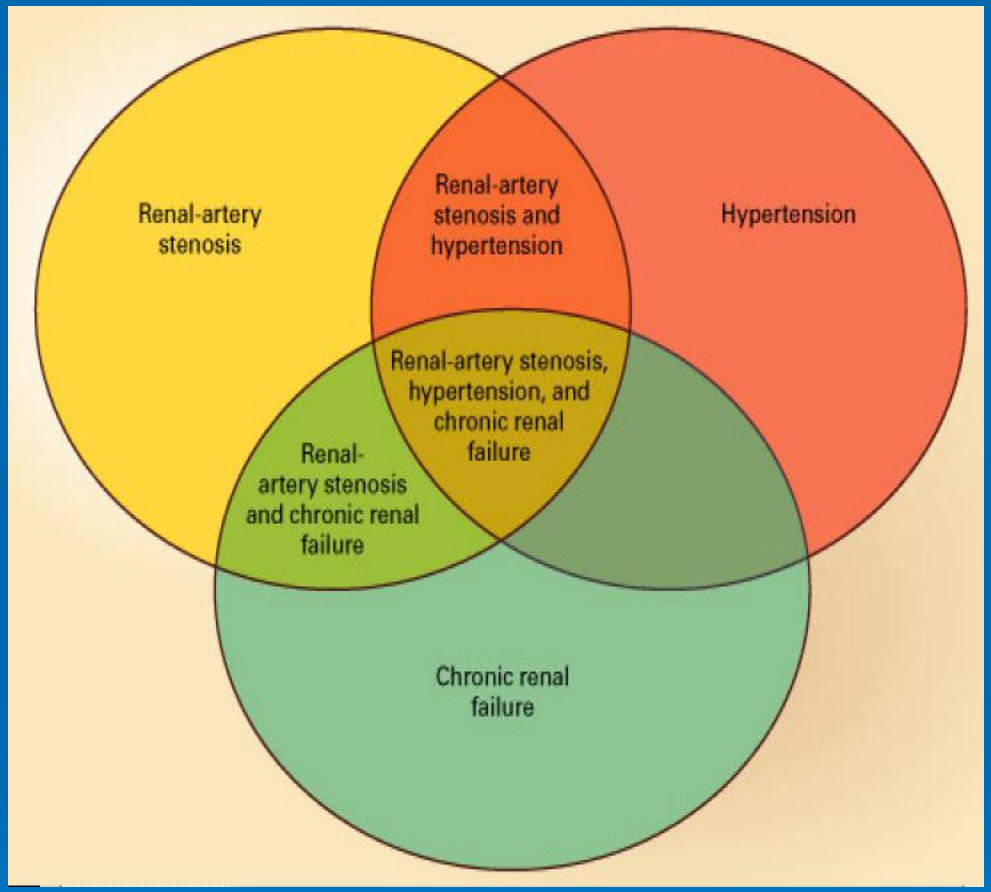
Background



Prevalence:

Asymptomatic, > 65 years: 7%

Coexisting CAD/PAD: 18 – 59%

Safian et al, NEJM. 2001;344:431-42

Current ACC/AHA Guidelines for Revascularization in RAS

Class I

- Recurrent CHF/pulmonary edema (LOE B)

Class IIa

- Unstable angina (LOE B)
- Accelerated, resistant, or malignant hypertension, or due to medication intolerance (LOE B)
- Progressive CRI in b/l RAS or solitary (LOE B)

Hirsch et al, JACC. 2006. Rooke et al, Circulation. 2011.

Current ACC/AHA Guidelines for Revascularization in RAS

Class IIb

- CRI and unilateral RAS (LOE, C)
- Asymptomatic bilateral RAS or unilateral to a solitary kidney (LOE, C)

Hirsch et al, JACC. 2006. Rooke et al, Circulation. 2011.

Meta-analysis by Bhatt et al

Significant renal artery stenosis
AND
Hypertension
AND / OR
Chronic renal insufficiency

Percutaneous revascularization
+
Medical therapy

Medical therapy

SURROGATE OUTCOMES: Changes in blood pressure, creatinine

CLINICAL OUTCOMES: Mortality, CHF, stroke, renal function

Inclusion/ Exclusion Criteria

Inclusion

- Randomized controlled trials in patients with RAS (≥ 50%)
  - Percutaneous revascularization vs. medical management

Exclusion

- Surgical revascularization
- Both arms revascularized

	EMMA	SNRASCG	DRASTIC	ASTRAL	STAR	NITER
	n = 49	n = 55	n = 106	n = 806	n = 138	n = 52
Year	1998	1998	2000	2009	2009	2009
Indication	HTN	Refractory HTN with CRI	Refractory HTN with CRI	Refractory HTN or CRI		Refractory HTN with CRI
% stenosis	75	NA	74	76		NA
Age (years)	59.4	61.1	59.9	70.5		72.0
HTN, %	100	100	82.1	98.0		96.0
HTN medications	NA	NA	2.0	2.8		3.2
Baseline BP (mm Hg)	165/97	178/94	180/104	151/76		149/79
S. creat (mg/dl)	1.2	1.8	1.3	2.0		1.2
Bilat stenosis, %	0	50.9	22.6	53.5	[illegible]	51.5
Cross-over to intervention, %	26.9	6.2	44.0	3.2	1.3	1.9
Balloon angioplasty only, %	91.3	80.0	96.4	7.0	1.6	0

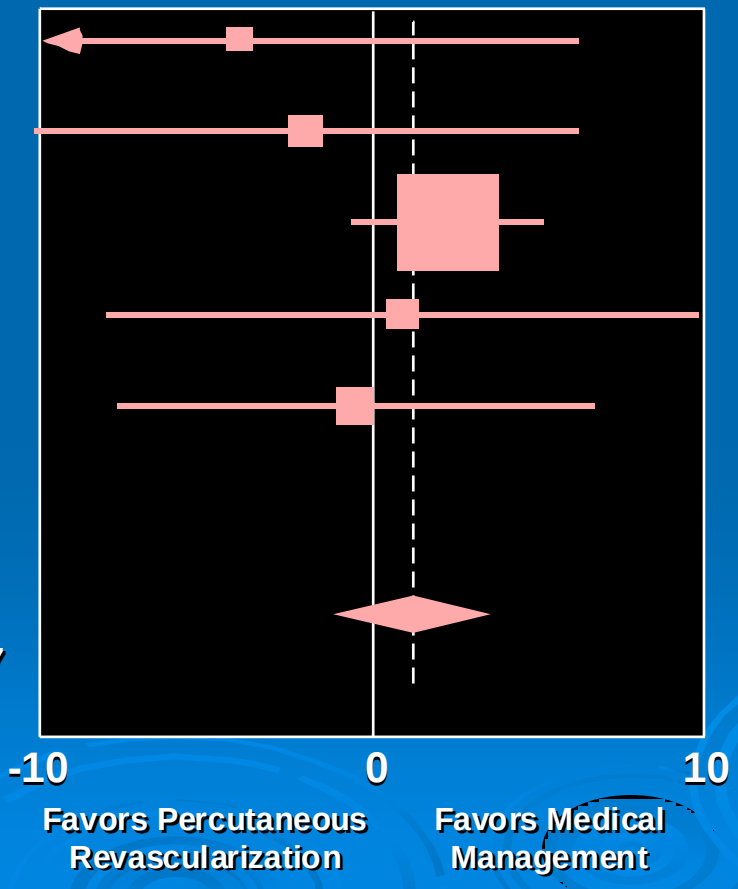
Mean = 2.74 vs. 2.76 (p = 0.76)

Results

Change in Systolic Blood Pressure from Baseline

Source	Weighted Mean Difference (95% CI)
EMMA	-4.00 (-14.23, 6.23)
DRASTIC	-2.00 (-10.22, 6.22)
ASTRAL	2.30 (-0.58, 5.18)
NITER	1.00 (-7.97, 9.97)
STAR	-0.50 (-7.73, 6.73)
SNRASCG (excluded)	
Overall (95% CI)	1.20 (-1.18, 3.58)

Test for heterogeneity: $I^2 = 0\%$, P = .67
Test for overall effect: P = .32



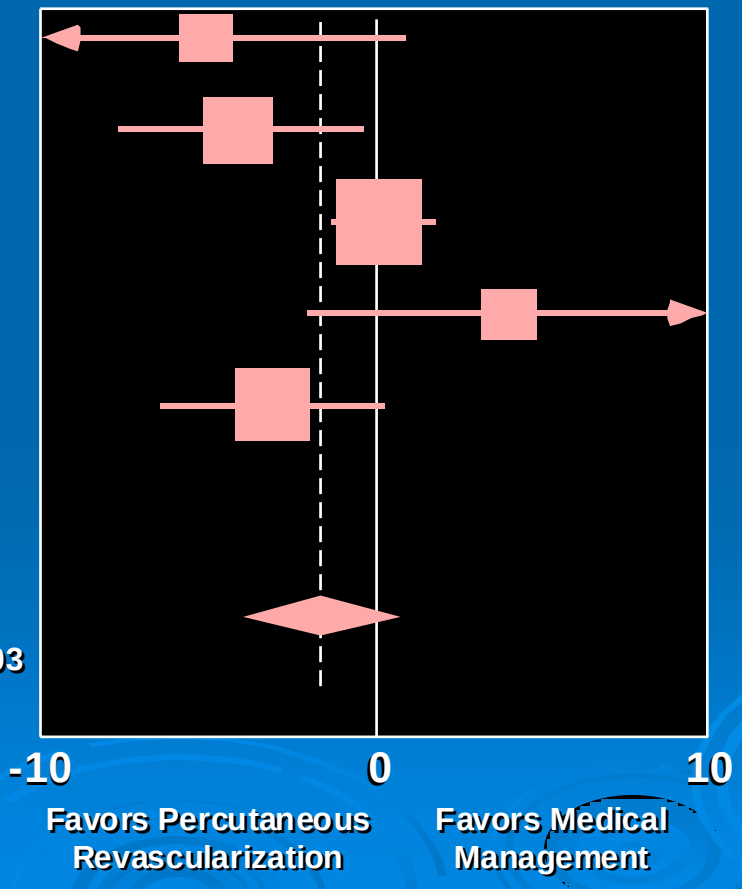
Kumbhani, Bavry, Harvey, de Souza, Scarpioni, Bhatt, Kapadia. AHJ 2011

Results

Change in Diastolic Blood Pressure from Baseline

Source	Weighted Mean Difference (95% CI)
EMMA	-5.00 (-10.91, 0.91)
DRASTIC	-4.00 (-7.62, -0.38)
ASTRAL	0.20 (-1.39, 1.79)
NITER	4.00 (-2.09, 10.09)
STAR	-3.00 (-6.40, 0.40)
SNRASCG (excluded)	
Overall (95% CI)	-1.60 (-4.22, 1.02)

Test for heterogeneity: I^2 = 62%, P = .03
Test for overall effect: P = .23



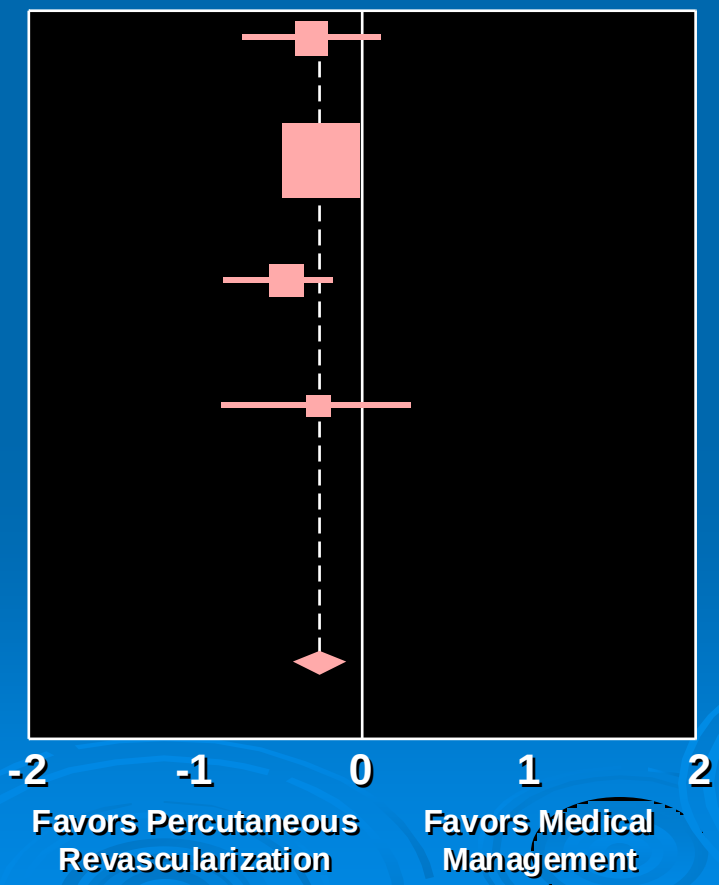
Kumbhani, Bavry, Harvey, de Souza, Scarpioni, Bhatt, Kapadia. AHJ 2011

Results

Number of Anti-hypertensive medications at end of follow-up

Source	Weighted Mean Difference (95% CI)
STAR	-0.30 (-0.72, 0.12)
ASTRAL	-0.20 (-0.36, -0.04)
DRASTIC	-0.50 (-0.84, -0.16)
NITER	-0.28 (-0.87, 0.31)
Overall (95% CI)	**-0.26 (-0.39, -0.13)**

Test for heterogeneity: $I^2 = 0\%$
Test for overall effect: $P < 0.001$



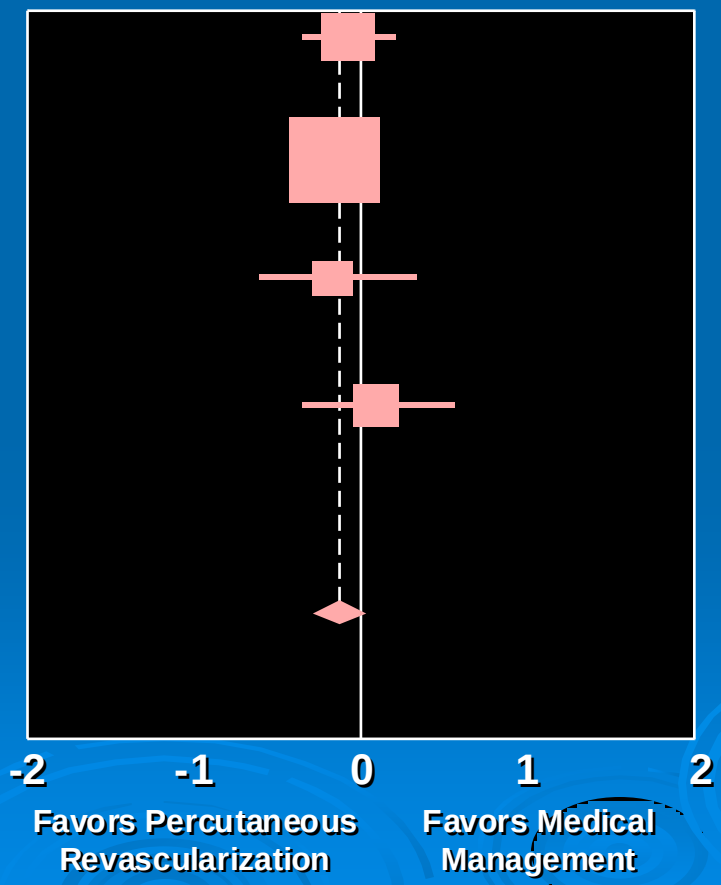
Kumbhani, Bavry, Harvey, de Souza, Scarpioni, Bhatt, Kapadia. AHJ 2011

Results

Serum creatinine at end of follow-up

Source	Weighted Mean Difference (95% CI)
STAR	-0.10 (-0.37, 0.17)
ASTRAL	-0.21 (-0.42, 0.00)
SNARSCG	-0.16 (-0.63, -0.31)
NITER	-0.08 (-0.37, 0.53)
Overall (95% CI)	-0.14 (-0.29, 0.01)

Test for heterogeneity: $I^2 = 0\%$
Test for overall effect: P = 0.06



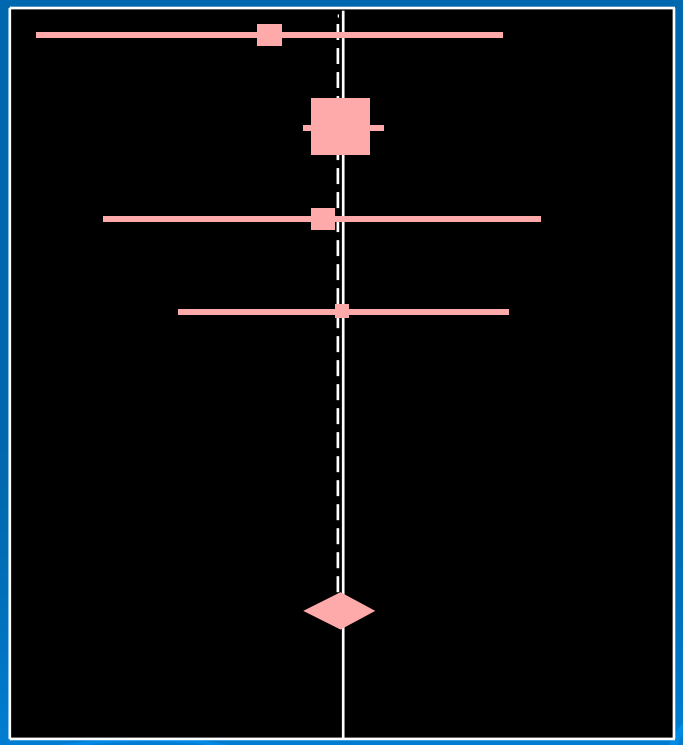
Kumbhani, Bavry, Harvey, de Souza, Scarpioni, Bhatt, Kapadia. AHJ 2011

Results

Mortality

Source	Relative Risk (95% CI)
SNRASCG	0.60 (0.12, 3.01)
ASTRAL	0.98 (0.74, 1.29)
NITER	0.86 (0.19, 3.86)
STAR	0.99 (0.32, 3.09)
EMMA (excluded)	
Overall (95% CI)	0.96 (0.74, 1.25)

Test for heterogeneity: $I^2 = 0\%$, P = .95
Test for overall effect: P = .76



14.9% vs. 15.4%

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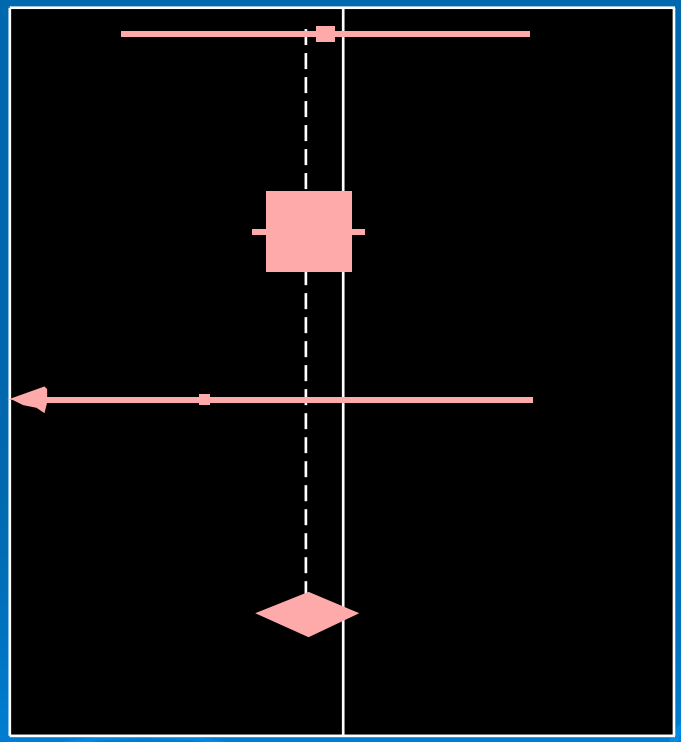
Results

Congestive Heart Failure

Source	Relative Risk (95% CI)
SNRASCG	0.90 (0.22, 3.65)
ASTRAL	0.80 (0.55, 1.16)
STAR	0.40 (0.04, 3.71)
Overall (95% CI)	0.79 (0.56, 1.13)

Test for heterogeneity: $I^2 = 0\%$, P = .82
Test for overall effect: P = .20



9.8% vs. 12.2%

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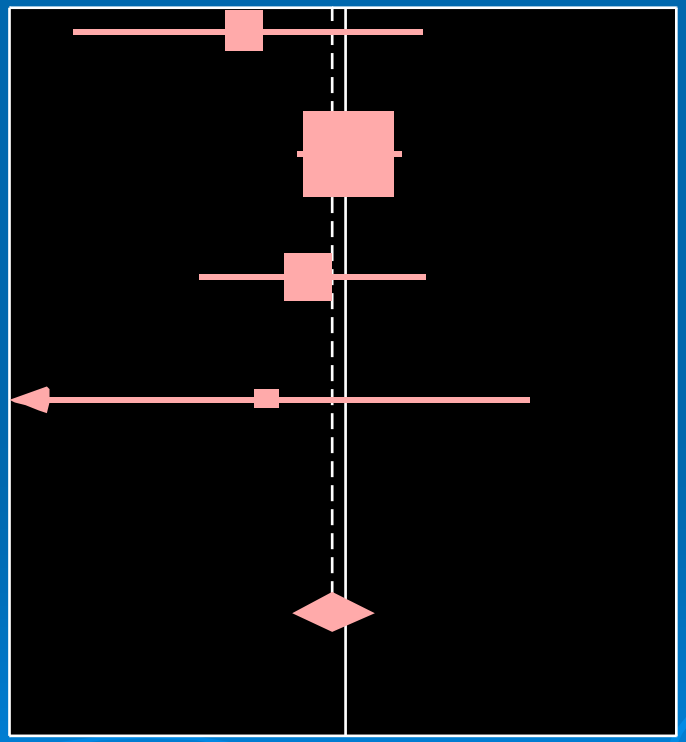
Results

Stroke

Source	Relative Risk (95% CI)
SNRASCG	0.30 (0.04, 2.51)
ASTRAL	1.06 (0.56, 1.98)
NITER	0.64 (0.16, 2.59)
STAR	0.39 (0.02, 9.53)
Overall (95% CI)	0.86 (0.50, 1.47)

Test for heterogeneity: $I^2 = 0\%$, P = .63
Test for overall effect: P = .57



4.4% vs. 5.1%

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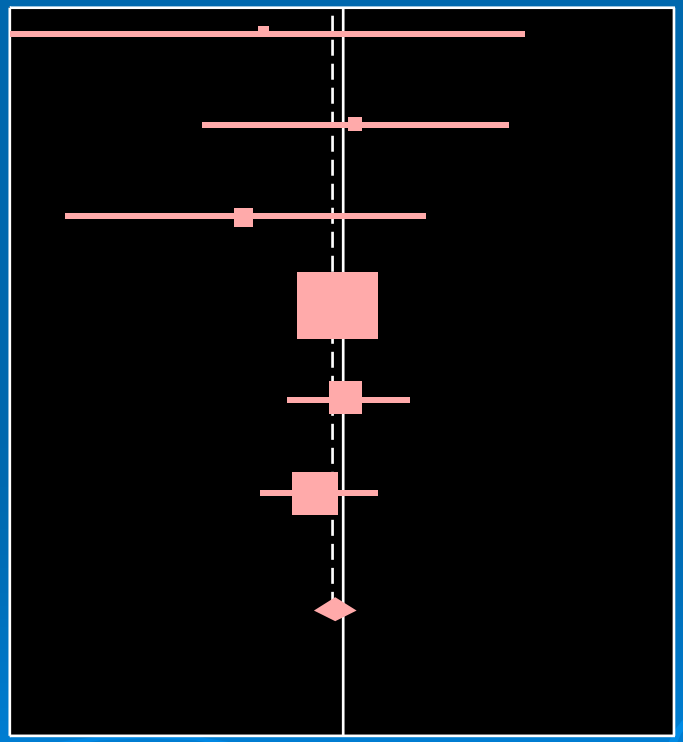
Results

Worsening renal failure

Source	Relative Risk (95% CI)
EMMA	0.38 (0.02, 8.78)
SNRASCG	1.20 (0.18, 7.92)
DRASTIC	0.30 (0.03, 2.77)
ASTRAL	0.98 (0.67, 1.43)
NITER	1.07 (0.50, 2.28)
STAR	0.74 (0.36, 1.52)
Overall (95% CI)	0.91 (0.67, 1.23)

Test for heterogeneity: $I^2 = 0\%$, P = .91
Test for overall effect: P = .54



11.5% vs. 12.6%

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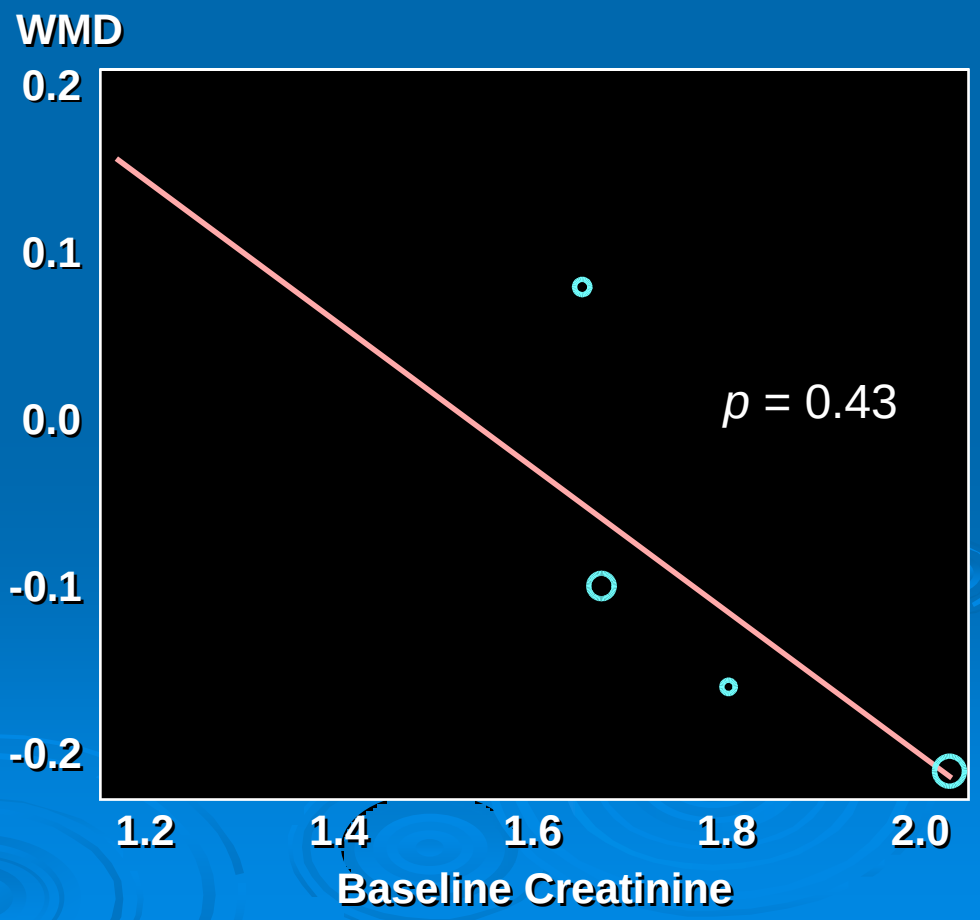
Meta-regression

- No difference in any of above outcomes noted
  - Baseline creatinine
  - Diabetes status
  - % bilateral stenosis
  - % cross-over
  - % angioplasty only

Sensitivity analyses showed similar results



Conclusions

Surrogate outcomes:

- Change in SBP
- Change in DBP
- Antihypertensive medications
- Serum creatinine

Clinical outcomes:

- Mortality
- CHF
- Stroke
- Change in renal function

Flaws of recent trials

- Most of the trials including Star and Astral had only requirement of 50% renal artery stenosis for enrollment.
- Complication rate procedural arm in Star trial – 3% mortality and 17% major hematomas – was much higher than contempory practice.
- Only 72% of the patients in Star trial and 83% in Astral trial, who were assigned to stenting actually got the stent. 6% of the patients in Astral trial designated for medical Rx actually ended up having a stent.
- In Astral trial, the patients which physicians thought might benefit from renal artery stenting were excluded – many of them got revascularized outside the study (the very patients in whom this procedure might have been beneficial)

Future Considerations

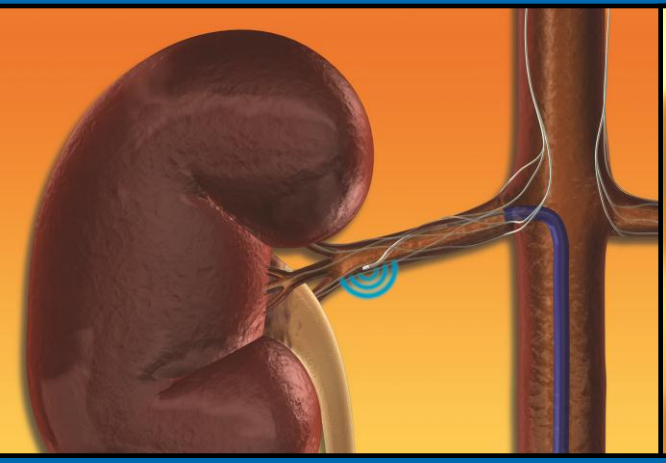
- Other clinical trials in RAS ongoing CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions), STRETCH (in heart failure patients), RADAR
- Benefit in select populations
  - Critical (> 90%)
  - Bilateral stenosis
  - Lower renal resistance index (<80)
- Benefits of innovations in interventions

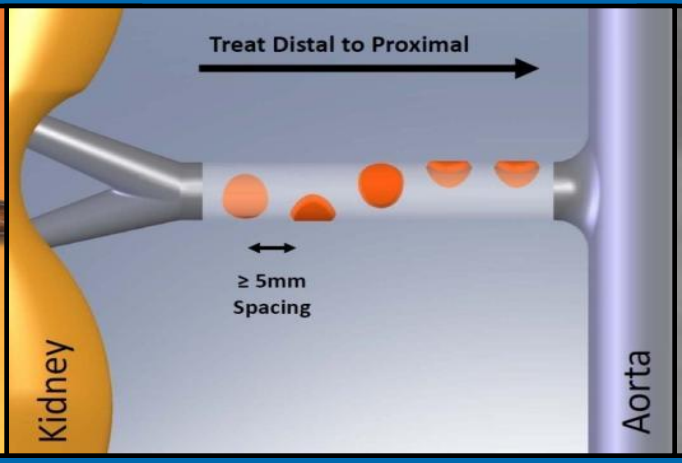
Resistant Hypertension - DEFINITION

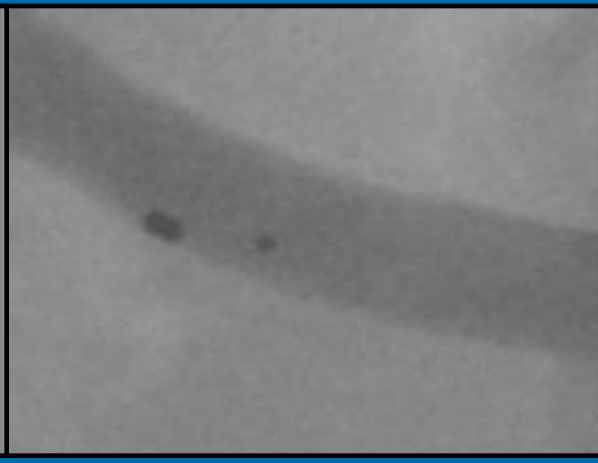
- Failure to achieve goal BP (<140/90 mmHg) using 3 different drugs with pharmacologically complementary mechanisms, one of which is an appropriately dosed diuretic
- All three drugs given in maximally tolerated doses
- Patients adhering to an adequate and appropriate drug regimen

Chobanian A et.al. Hypertension 2003

Renal Nerve Anatomy Allows a Catheter-Based Approach







- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF generator
  - Automated
  - Low power
  - Built-in safety algorithms

Renal Denervation - Staged Clinical Evaluation

Symplicity HTN-1
- First-in-Man ✓

↓

Series of Pilot studies ✓

↓

Symplicity HTN-2 ✓
EU/AU Randomized Clinical Trial

↓

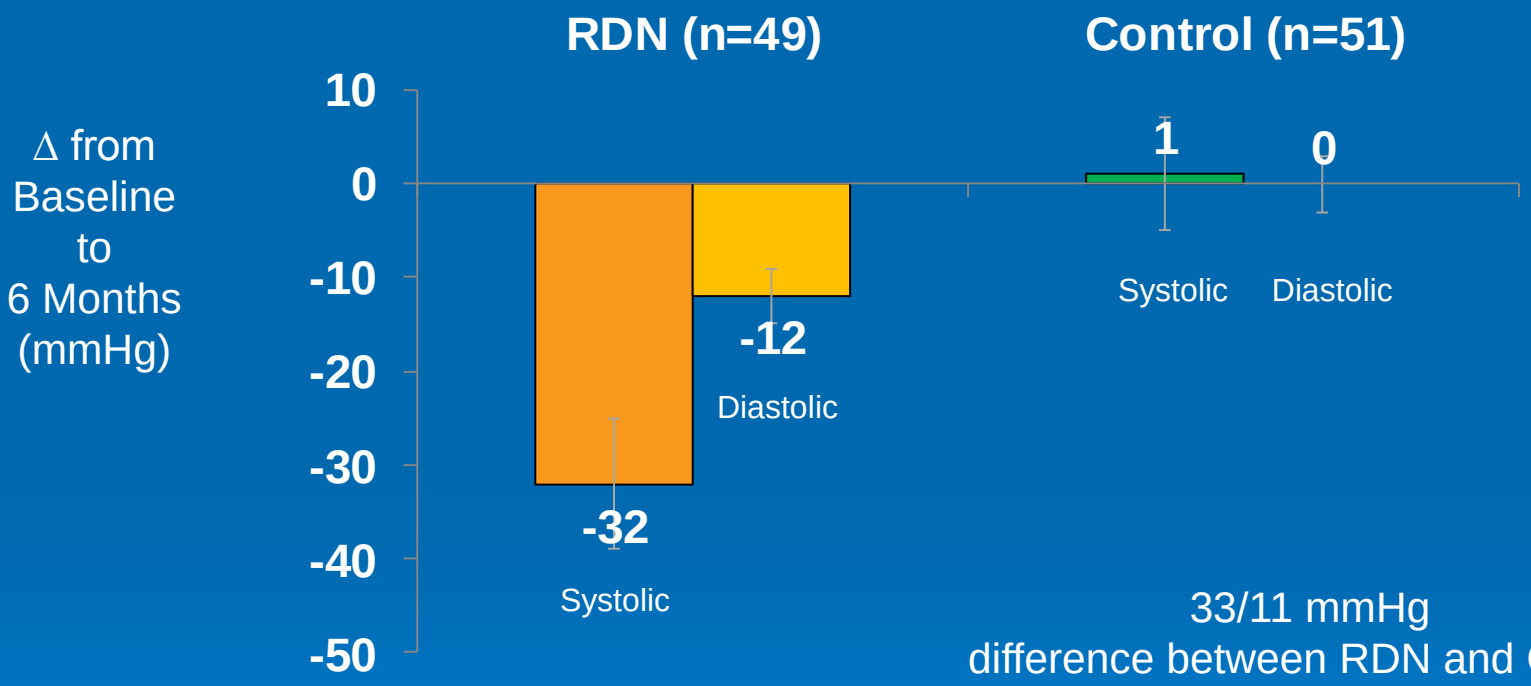
USA

Symplicity HTN-3
US Randomized Clinical Trial
(ongoing)

EU/AU

Other Areas of Research:
Insulin Resistance, HF/Cardiorenal, Sleep Apnea, More

Primary Endpoint: 6-Month Office BP

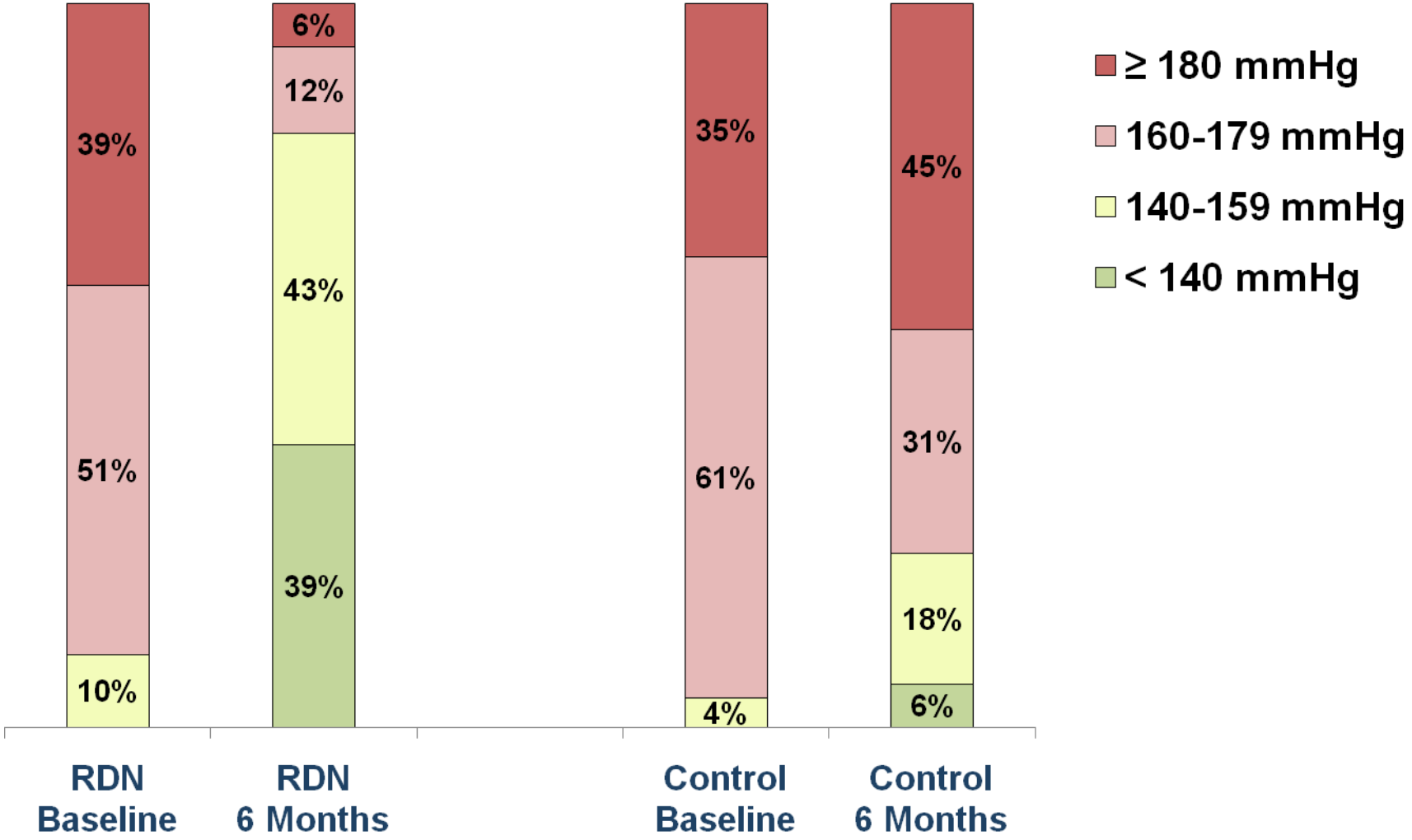


33/11 mmHg
difference between RDN and Control
(p<0.0001)

- **84% of RDN patients had ≥ 10 mmHg reduction in SBP**
- **10% of RDN patients had no reduction in SBP**

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Office Systolic BP Distribution-Symplicity-2



Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Procedural Safety Symplicity-2

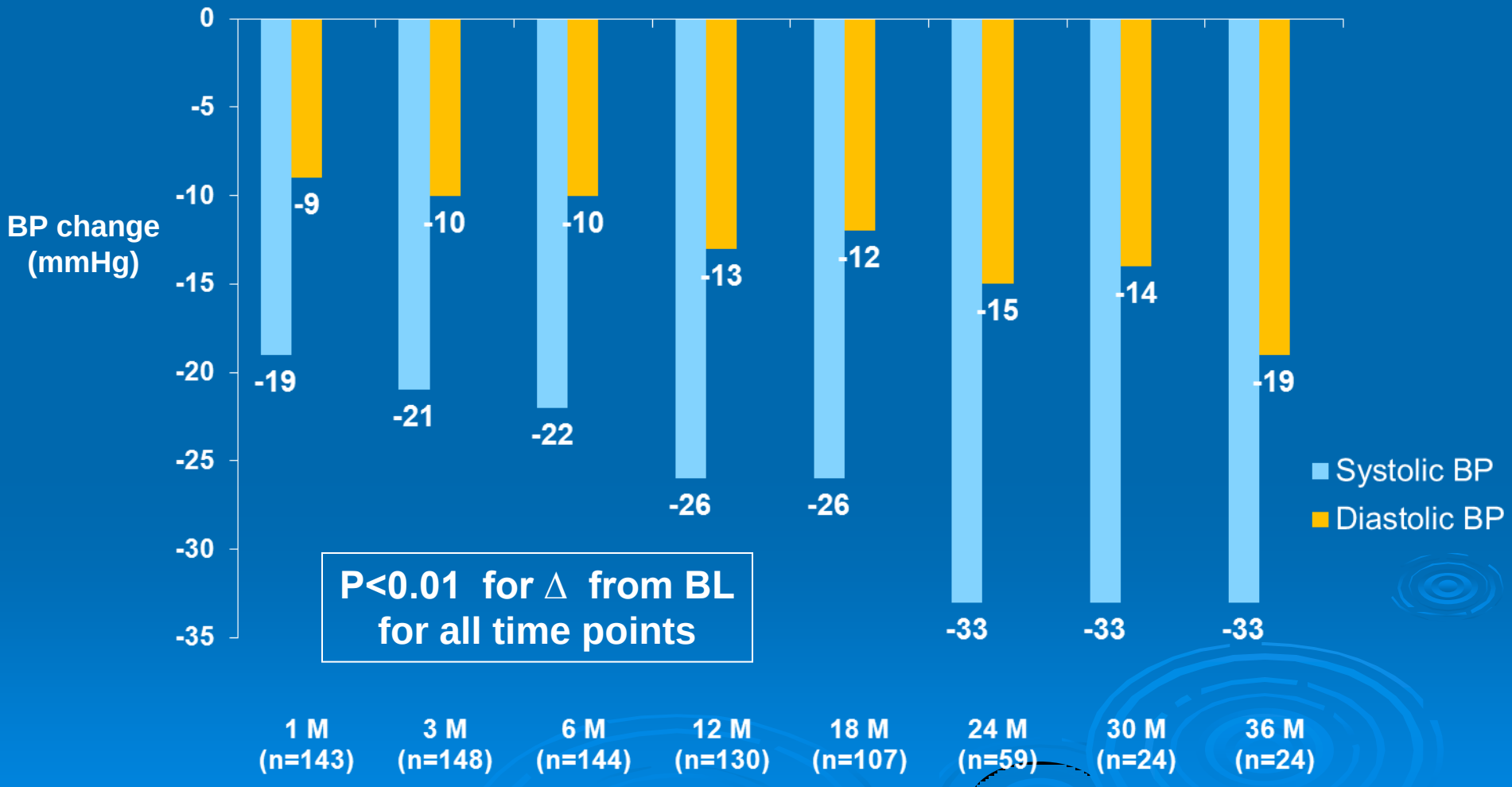
- No serious device or procedure related adverse events (n=52)
- Minor adverse events
- 1 femoral artery pseudoaneurysm treated with manual compression
- 1 post-procedural drop in BP resulting in a reduction in medication
- 1 urinary tract infection
- 1 prolonged hospitalization for evaluation of paresthesias
- 1 back pain treated with pain medications & resolved after one month

➢ 6-month renal imaging (n=43)

- No vascular abnormality at any RF treatment site
- 1 MRA indicates possible progression of a pre-existing stenosis unrelated to RF treatment (no further therapy warranted)
- Renal function remained stable in up to 2 years of follow-up

Symplicity HTN-2 Investigators. Lancet. 2010;376:1903-1909.

Change in Office Blood Pressure Through 36 Months



Sobotka P et al. Symplicity HTN-1. Long term follow up. ACC 2012.

Symplicity HTN-3 Trial: Inclusion Criteria

- Average SBP ≥160mmHg (measured per guidelines)
- On stable medication regimen of full tolerated doses of 3 or more antihypertensive meds, with one being a diuretic
  - No changes for a minimum of 2 weeks prior to screening
  - No planned medication changes for 6 months
- Age 18-80
- eGFR ≥45mL/min

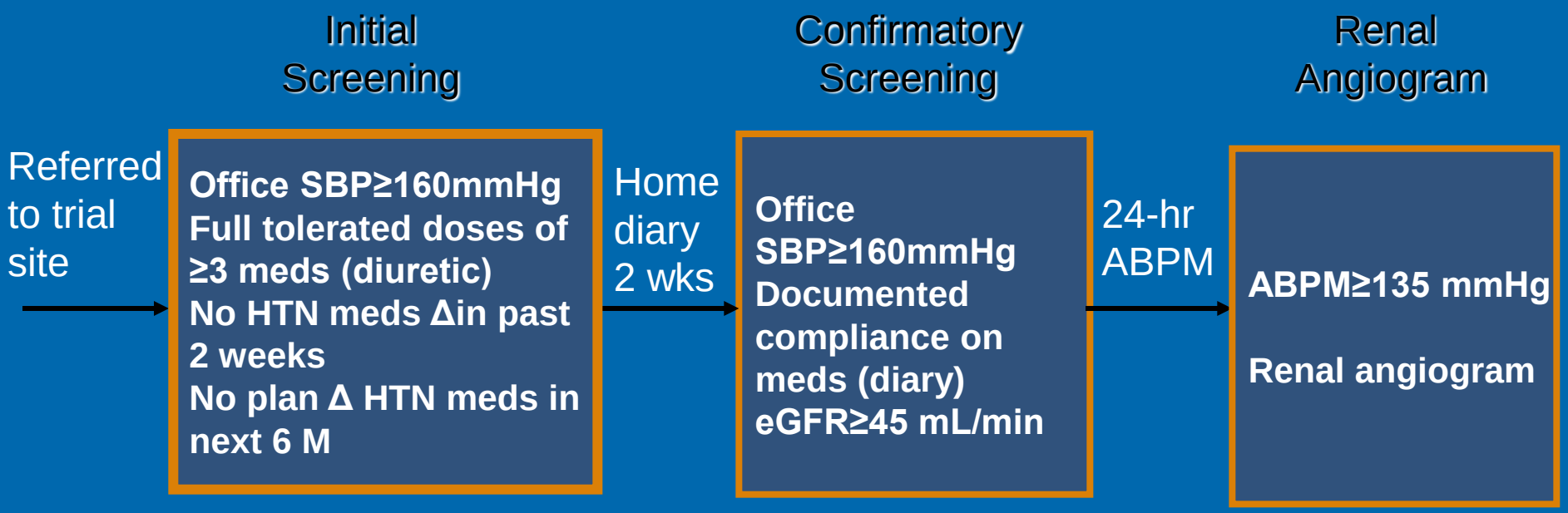
Randomization

- N = 530 randomized (enrolled at 90 US sites)
- Randomization
  - 2:1 ratio – Treatment or Control
  - Stratified by study center and by race (African American vs. non-African American)
- Single Blind
  - Specific staff & subject until 6 months post randomization

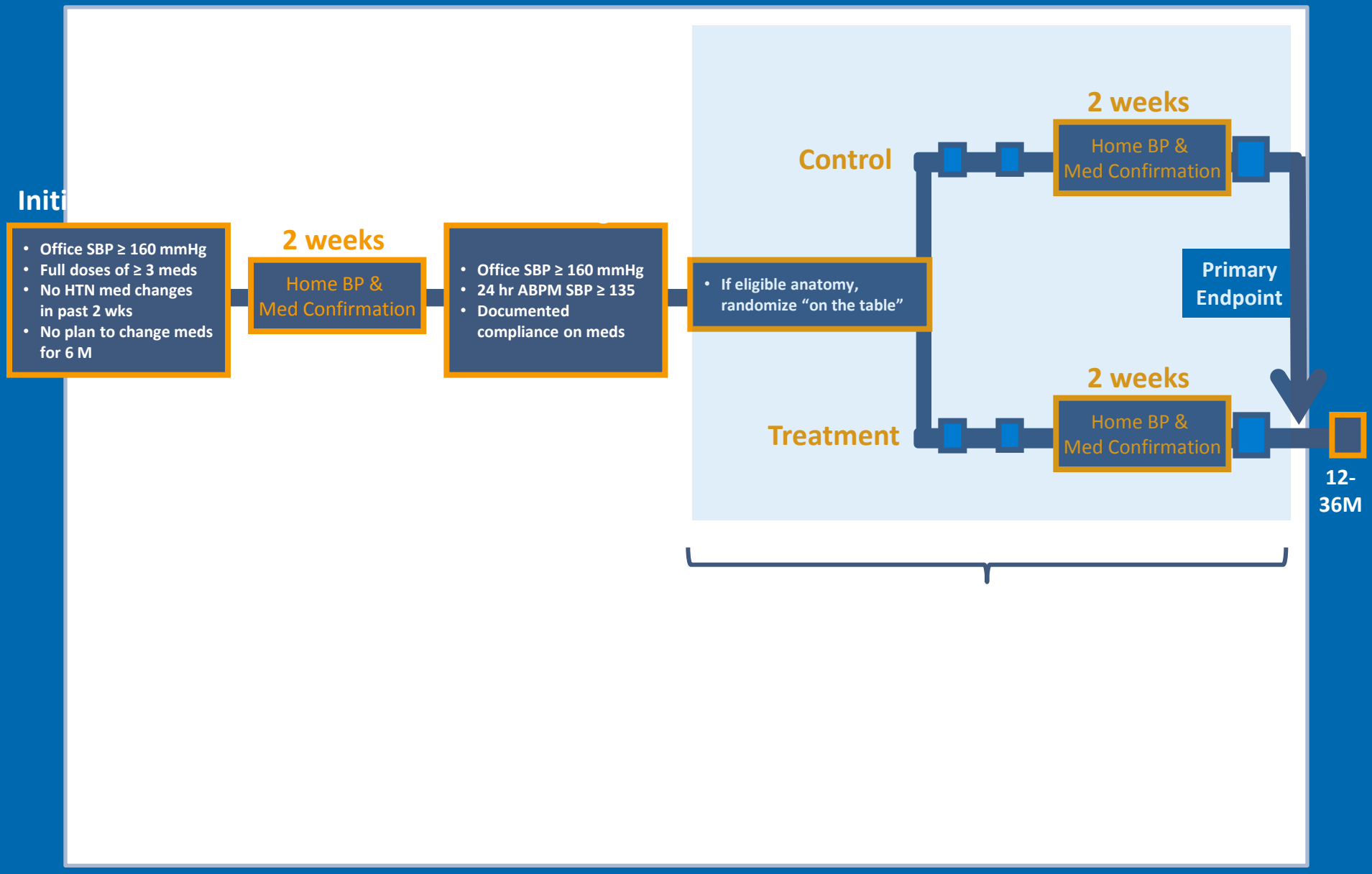
Endpoints

- Primary efficacy endpoint: Change in office SBP from baseline to 6 months post randomization
- Secondary efficacy endpoint: Change in 24hr ABPM SBP average from baseline to 6 months
- Primary safety endpoint: Mortality, ESRD, or procedural complications w/in 1 month or new RAS w/in 6 months post randomization

Symplicity HTN-3 Trial: Referral to Randomization Steps



Study Design Flow Chart

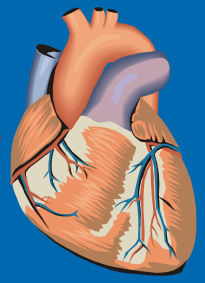


Summary

- Resistant hypertension is becoming more prevalent and is a challenge for clinicians
- Renal denervation data to date seem promising
- Symplicity-3 will be the pivotal US study for FDA approval
- Trial underway, with a design developed by the co-PIs, Medtronic/Ardian, and the FDA

Renal Afferent Nerves:
Kidney as Origin of Central Sympathetic Drive

Vasoconstriction
Atherosclerosis

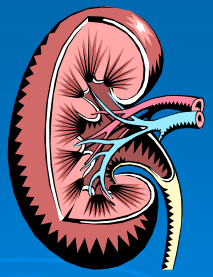


Hypertrophy
Arrhythmia
Oxygen Consumption

Sleep
Disturbances

Insulin
Resistance

Renal Afferent
Nerves



↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow