A Randomized Multicenter Clinical Trial of Renal Artery Stenting in Preventing Cardiovascular and Renal Events: Results of the CORAL Study

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on behalf of the CORAL Investigators

NIH National Heart, Lung, and Blood Institute

Disclosures

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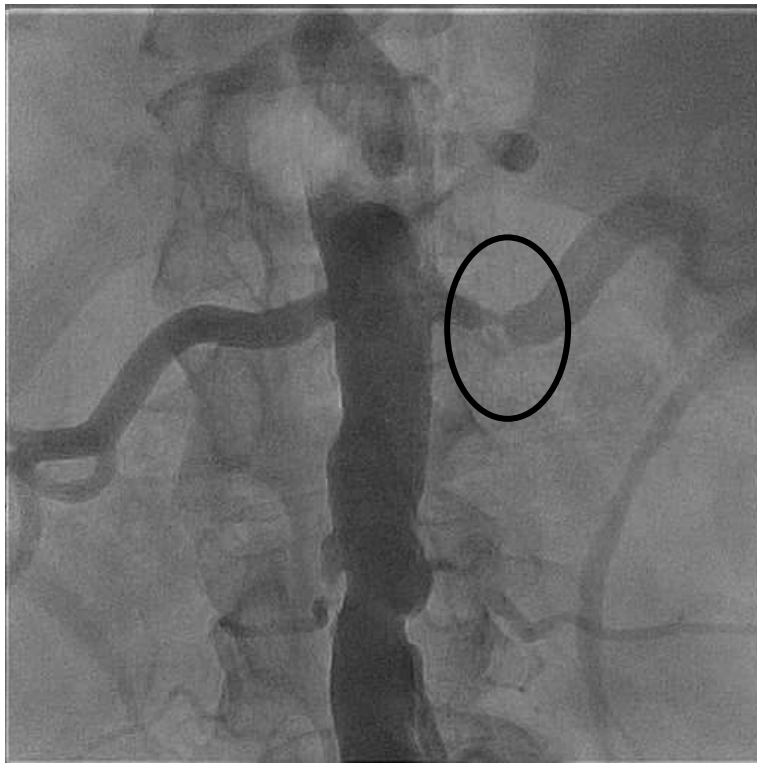
Study drugs provided by:

- Astra Zeneca
- Pfizer

Background

- Atherosclerotic renal artery stenosis is a common problem in the elderly.
- Despite several randomized trials, the utility of revascularization for prevention of major adverse renal and cardiovascular events is controversial



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Methods

- Open label, randomized, international, multicenter controlled clinical trial

- All received Medical Therapy:
  - BP, Diabetes and Lipids to goal, with participants provided free:
    - Candesartan ± hydrochlorothiazide (Atacand ®)
    - Atorvastatin + Amlodipine (Caduet ®)
  - Anti-platelet therapy

Inclusion Criteria

Clinical Syndrome:

- Hypertension ≥2 anti-hypertensive medications, OR
- Renal dysfunction defined as Stage 3 or greater CKD

-AND-

Atherosclerotic Renal Artery Stenosis:

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

Primary Endpoint

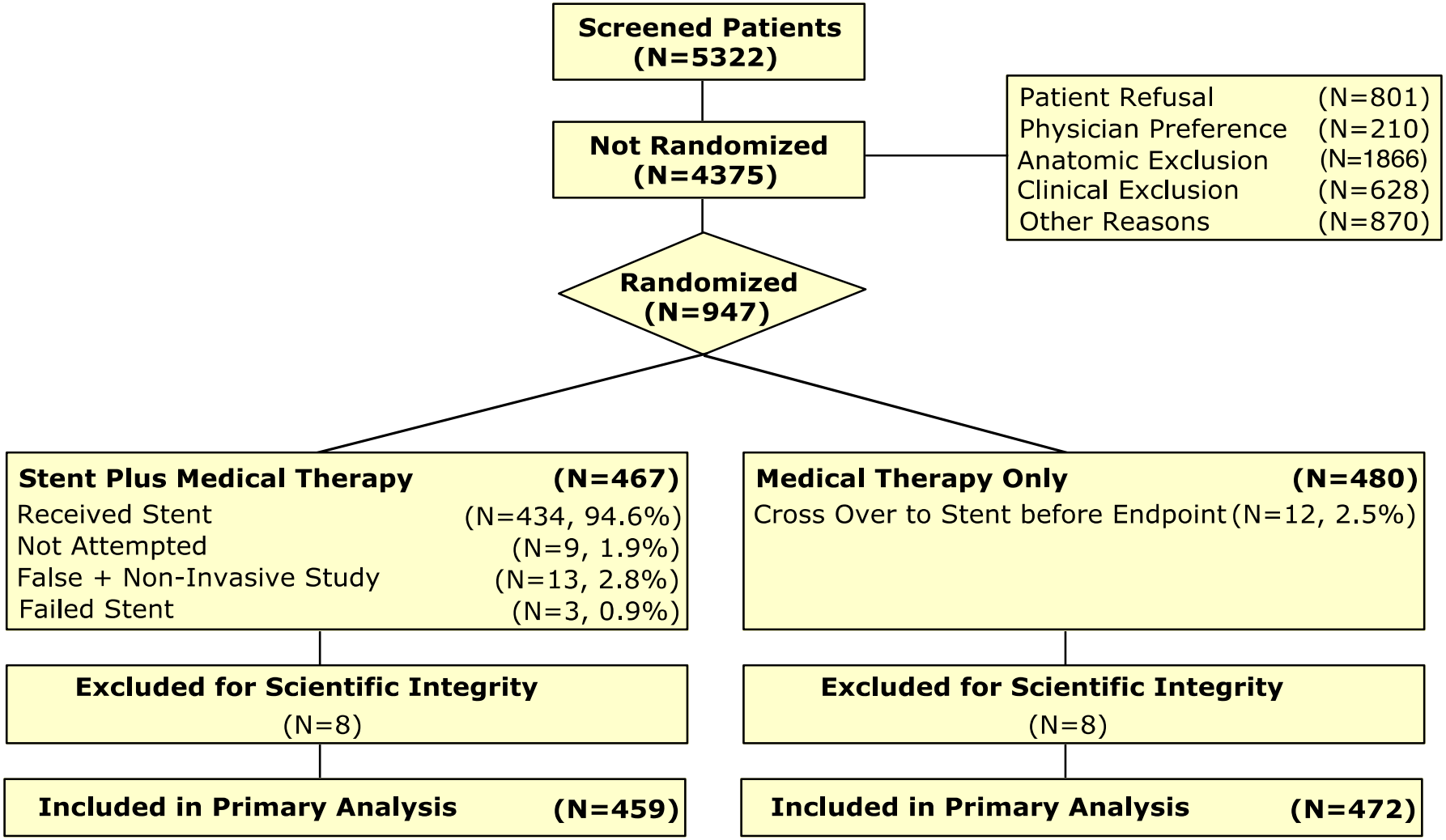
- **Composite of major cardiovascular or renal events:**
  - Cardiovascular or Renal Death
  - Stroke
  - Myocardial Infarction
  - Heart Failure Hospitalization
  - Progressive Renal Insufficiency
  - Permanent Renal Replacement Therapy

Statistical Plan

- Primary endpoint analyzed as time to the first primary endpoint event on an intent-to-treat basis.
  - 16 participants excluded from a single site where scientific integrity issues of consent and eligibility were noted, and the data was administratively withdrawn.

- Sample size selected to provide 90% power to test hypothesis that stenting reduced the incidence of the primary endpoint by 25%.

Screening and Enrollment



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Baseline Characteristics

- No significant differences in clinical and angiography characteristics
- Approximately 20% global ischemia
- Stenosis severity similar to FDA approval trials [1-3]

1. Rocha-Singh K et. al. ASPIRE-2. JACC 2005;46:776-83
2. Rocha-Singh K et. al. RENAISSANCE. CCI 2008;72:853-62
3. Jaff MR, et. al. HERCULES. CCI 2012;80:343-50

Baseline Characteristics of the Study Population According to Treatment Group

Characteristic	Stent + Medical	Medical
	N = 459	N = 472
Age *(years)*	69.3 ± 9.4	69.0 ± 9.0
Male gender *(%)*	51.0	48.9
White race *(%)*	91.5	90.9
Black race *(%)*	7.0	7.0
Body mass index *(kg/m^2)*	28.2 ± 5.3	28.7 ± 5.7
Systolic blood pressure *(mmHg)*	149 ± 23.2	150.4 ± 23.0
Estimate GFR *(ml/minute)*	58.0 ± 23.4	57.4 ± 21.7
Medical history and risk factors *(%)*		
Diabetes	32.4	34.3
Prior myocardial infarction	26.5	30.2
History of heart failure	12.0	15.1
Smoking in past year	28.0	32.2
Angiography		
% stenosis *(core lab)*	67.3 ± 11.4	66.9 ± 11.9
% stenosis *(investigator)*	72.5 ± 14.6	74.3 ± 13.1
Global ischemia *(%)*	20.0	16.2
Bilateral disease *(%)*	22.0	18.1

Results: Stent Treatment, Angiographic Core Lab Analysis

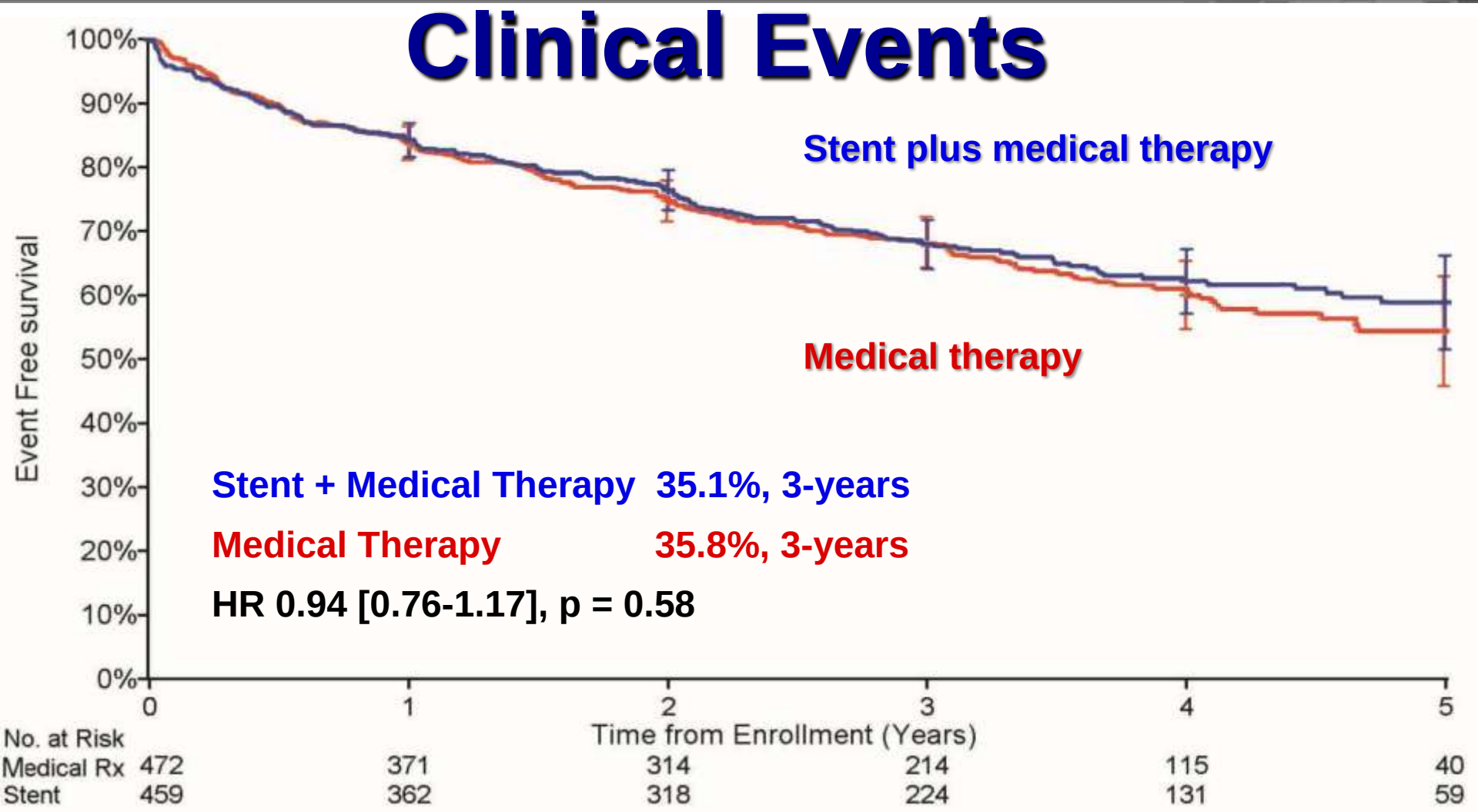
Stenosis reduced to:	**16±8% (p<0.001)**
▪ Stents per vessel	1.04±0.20
▪ Embolic protection device, per vessel	124/543 (22.8%)
Procedural Angiographic complications	
▪ Dissection	11/495 (2.2%)
▪ Branch vessel occlusion	6/495 (1.2%)
▪ Angiographic distal embolization	6/495 (1.2%)
▪ Wire perforation	1/495 (0.2%)
▪ Vessel rupture	1/495 (0.2%)
▪ Pseudoaneurysm	1/495 (0.2%)

Results: Peri-Procedural Clinical Complications

- No participant required dialysis within 30-days of randomization.
- 1/459 (0.2%) in Stent + Medical Therapy initiated dialysis between 30 and 90-days after randomization.

- 1 stroke resulting in death, day of randomization, Medical Therapy Only group.

Results: Primary Endpoint



Stent + Medical Therapy **35.1%, 3-years**

Medical Therapy **35.8%, 3-years**

HR 0.94 [0.76-1.17], p = 0.58

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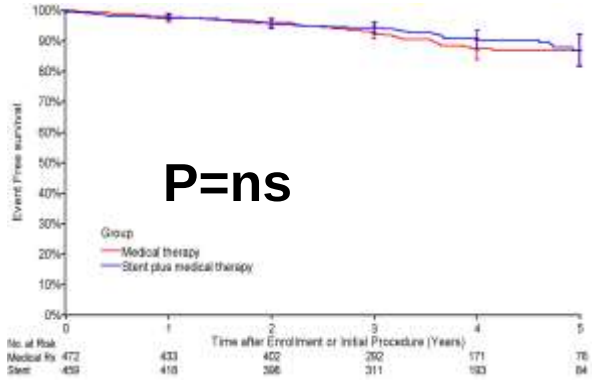
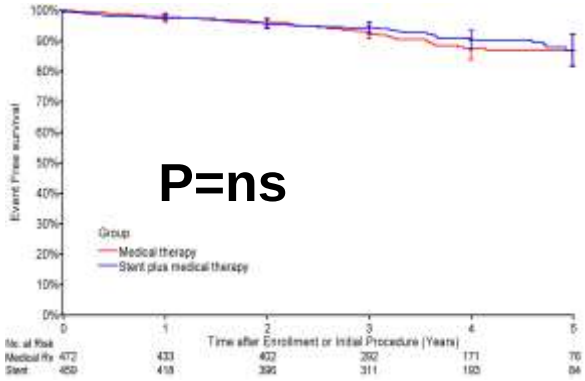
Results: Secondary Endpoints

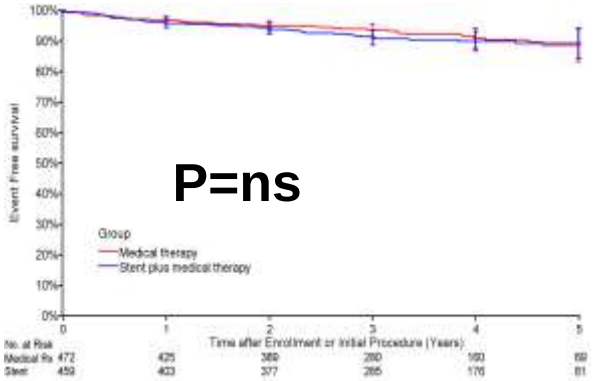
CV + Renal Death



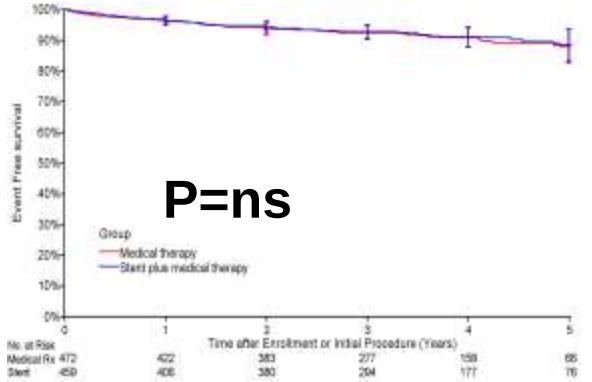
Stroke



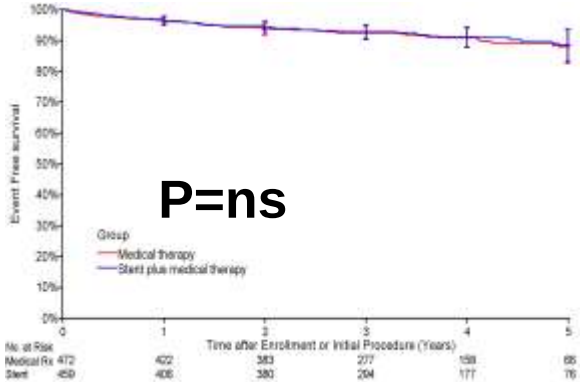
Myocardial Infarction



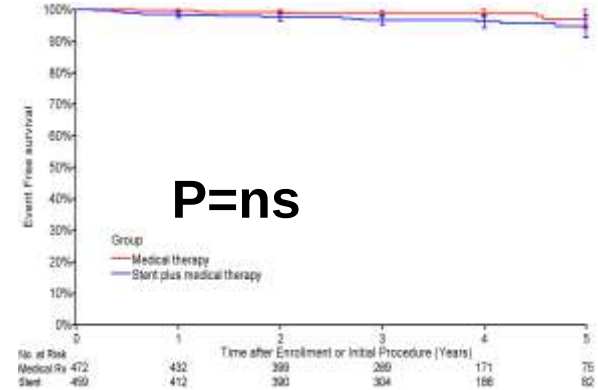
Heart Failure



Progressive Renal Insufficiency



Renal Replacement



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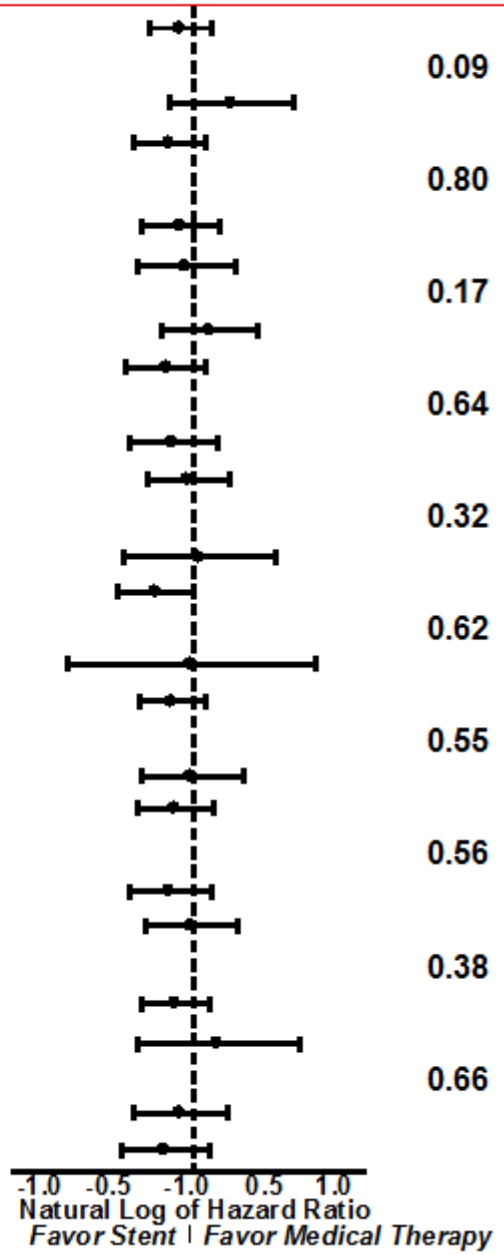
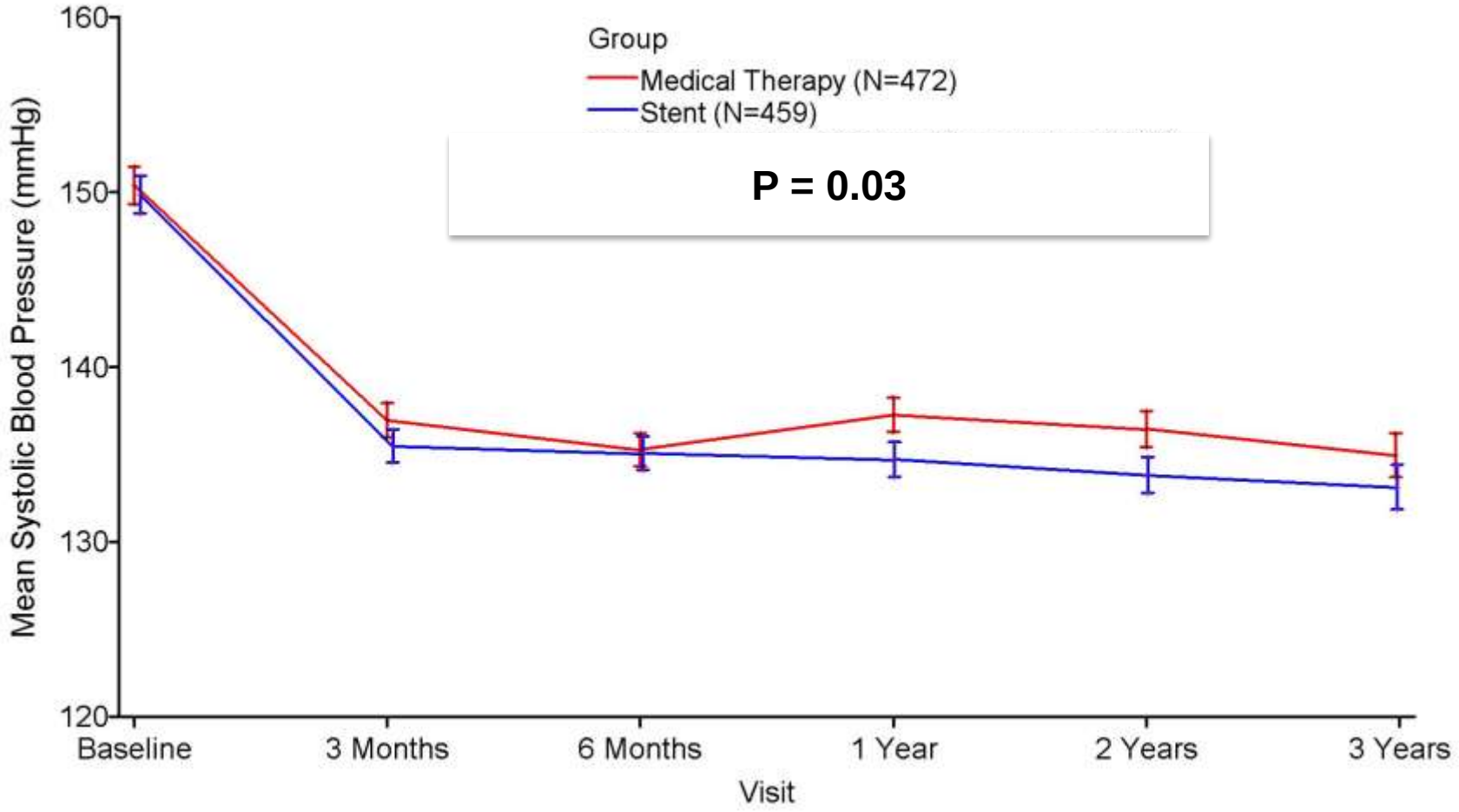
Results: Subgroups

Subgroup	Stent N (%)	Medical Therapy N (%)	Hazard Ratio (95% CI)	P-Value for Interaction Stent vs. Medical Therapy
Overall	161/459 (35)	169/472 (36)	0.94 (0.76,1.17)	
Creatinine				0.09
> 1.6 *(mg/dl)*	43/84 (51)	34/87 (39)	1.35 (0.86,2.11)	
≤ 1.6 *(mg/dl)*	112/352 (32)	128/367 (35)	0.87 (0.67,1.12)	
MDRD eGFR				0.80
≥ 45 *(ml/min/1.73 m^2)*	91/288 (32)	105/311 (34)	0.93 (0.70,1.23)	
< 45 *(ml/min/1.73 m^2)*	64/148 (43)	57/143 (40)	0.98 (0.68,1.40)	
Diabetes				0.17
Yes	69/148 (47)	66/162 (41)	1.15 (0.82,1.61)	
No	92/309 (30)	103/310 (33)	0.84 (0.64,1.12)	
Gender				0.64
Male	75/234 (32)	78/231 (34)	0.89 (0.65,1.22)	
Female	86/225 (38)	91/241 (38)	0.99 (0.74,1.33)	
Global Ischemia				0.32
Yes	39/89 (44)	20/51 (39)	1.07 (0.62,1.83)	
No	119/356 (33)	106/264 (40)	0.78 (0.60,1.01)	
Race				0.62
African American	11/29 (38)	10/30 (33)	1.01 (0.42,2.43)	
Other	126/356 (35)	136/357 (38)	0.88 (0.69,1.13)	
Baseline SBP				0.55
> 160 *(mmHg)*	66/148 (45)	58/139 (42)	1.02 (0.71,1.45)	
≤ 160 *(mmHg)*	95/309 (31)	108/328 (33)	0.90 (0.68,1.18)	
Age				0.56
> 70 *(years)*	91/226 (40)	94/220 (43)	0.87 (0.65,1.16)	
≤ 70 *(years)*	70/233 (30)	75/252 (30)	1.00 (0.72,1.39)	
US Sites				0.38
Yes	137/385 (36)	146/387 (38)	0.90 (0.71,1.14)	
No	27/74(32)	23/85(27)	1.22 (0.69,2.16)	
Site Reported Max Stenosis				0.66
> 80%	77/198 (39)	64/166 (39)	0.93 (0.67,1.30)	
≤ 80%	77/231 (33)	79/208 (38)	0.84 (0.61,1.14)	



Results: Systolic Blood Pressure



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Conclusion

- Renal artery stenting did not confer a benefit to the prevention of clinical events when added to comprehensive, multi-factorial medical therapy in people with atherosclerotic renal artery stenosis and hypertension or chronic kidney disease.

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Acknowledgements