Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med 2014;370:13-22. DOI: 10.1056/NEJMoa1310753

Supplementary Appendix

Stenting and Medical Therapy for Atherosclerotic Renal Artery Stenosis

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C. Roll-in Approval Process for Clinical Centers

If potential sites met all criteria for study participation, they were required to undergo a roll-in phase before being approved for participation in the randomized trial. Initially, to complete the roll-in phase, the lead interventionalist was required to successfully conduct two consecutive cases using the Angioguard® (Cordis, Inc., Warren, NJ) distal embolic protection device and the Genesis® stent (Cordis, Inc.). After modification of the study protocol in the fourth quarter of 2006 to remove the requirement for use of a distal embolic protection device, only one roll-in subject was required to be submitted.

The roll-in images and case report forms were reviewed by the angiographic core laboratory at the University of Virginia (principal investigator: Alan Matsumoto, M.D.), and evaluated using uniform criteria for the quality of the study and the technical results. Sites that did not submit appropriate images demonstrating all renal arteries in profile, enrolled participants that had lesions inappropriate for enrollment, or that had complications related to the stent procedure such as thromboembolism, dissection, or arterial perforation were required to perform additional roll-in cases. Those who passed the review by the angiographic core laboratory were approved to enter the randomization phase of the study.

Interventional investigators were required to have performed at least 25 renal artery stent procedures, and to have board certification in interventional radiology, interventional cardiology, or vascular surgery. Each site was required to identify a separate hypertension specialist who would be responsible for medical management. Before initiation of the study at each site, the Institutional Review Board approved the protocol and informed consent documents.

There were 12 of 115 (10%) sites that applied but did not qualify for the randomized phase of the study for either performance and/or submission-related issues. Six of these were eventually approved for randomization after submitting additional data and images.

D. Inclusion Criteria, including criteria for enrollment using magnetic resonance (MRA) or computerized tomographic angiography (CTA.)

1. Either:
    a. Documented history of hypertension on 2 or more anti-hypertensive medications OR
    b. Renal dysfunction defined as Stage 3 or greater CKD based on the new National Kidney Foundation classifications (estimated GFR < 60 mL per minute per 1.73 m2 calculated by the modified MDRD formula)
2. One or more severe renal artery stenoses by any of the following pathways:
    a. Angiographic: ≥ 60% and < 100% by renal angiogram OR
    b. Duplex: systolic velocity of >300 cm/sec OR
    c. Core lab approved Magnetic Resonance Angiography (MRA) demonstrating:
        - Stenosis > 80% OR
        - Stenosis > 70% with spin dephasing on 3D phase contrast MRA OR
        - Stenosis > 70% and two of the following:
            i. Ischemic kidney is > 1 cm smaller than contralateral kidney.
            ii. Ischemic kidney enhances less on arterial phase.
            iii. Ischemic kidney has delayed gadolinium excretion.
            iv. Ischemic kidney hyper-concentrates the urine.
            v. 2-D phase contrast flow waveform shows delayed systolic peak
            vi. Post-stenotic dilatation
    d. Core lab approved Computerized Tomographic Angiography (CTA) demonstrating:
        - Stenosis is > 80% on high quality CTA.
        - Stenosis is > 70% on CTA and there are two of the following:
            i. The length of ischemic kidney is > 1 cm smaller than contralateral kidney.
            ii. Reduced cortical thickness of ischemic kidney.
            iii. Less cortical enhancement of ischemic kidney on arterial phase.
            iv. Post-stenotic dilatation

E. Exclusion Criteria CORAL Trial

- Unable to provide informed consent
- Unable or unwilling to comply with study protocol or procedures
- Age <18
- Fibromuscular dysplasia or other non-atherosclerotic renal artery stenosis known to be present prior to randomization
- Pregnancy or unknown pregnancy status in female of childbearing potential
- Participation in any drug or device trial during the study period, unless approved by the Steering Committee
- Prior enrollment in the CORAL Study
- History of stroke within 6 months, if associated with a residual neurologic deficit
- Any major surgery, major trauma, revascularization procedure, unstable angina, or myocardial infarction within 30 days prior to study entry
- Any planned major surgery or revascularization procedure, outside of the randomly allocated renal stenting dictated by this protocol, after randomization
- Hospitalization for heart failure within 30 days
- Comorbid condition causing life expectancy <3 years
- Allergic reaction to intravascular contrast, not amenable to pre-treatment
- Allergy to stainless steel
- Allergy to all of the following: aspirin, clopidogrel, ticlopidine
- Known untreated aneurysm of the abdominal aorta >5.0 cm
- Previous kidney transplant
- Stenosis of >50% of a previously treated revascularized renal artery OR Treatment of any renal artery stenosis within the past 9 months.
- Kidney size <7 cm supplied by target vessel
- Hydronephrosis, nephritis or other known cause of renal insufficiency, not due to large vessel renal artery stenosis
- Visualized stenosis of only an accessory renal artery supplying <1/2 of the ipsilateral renal parenchyma, without stenosis in a dominant renal artery
- Local lab serum Cr >4.0 mg/dl on the day of randomization
- Presence of a renal artery stenosis not amenable for treatment with a stent, known to be present prior to randomization
- The index lesion cannot be treated with a single stent (i.e. >18 mm in length)
- The placement of a stent will necessitate covering a renal artery branch renal artery with the stent
- The stenosis is in an artery <3.5 mm in diameter

- The stenosis involves a segmental renal artery branch
- Abrupt vessel closure or dissection after diagnostic angiography [NOTE: Patients with abrupt vessel closure or dissection as a result of diagnostic angiography will not be randomized but will undergo stent revascularization, receive optimal medical therapy and will be followed for the full study period.]

F. End Point Definitions for the CORAL Trial

DEATH CLASSIFICATION

Death was classified in the following categories:

I. CARDIOVASCULAR DEATH

A. Fatal Myocardial Infarction
Death occurring within 14 days after a documented myocardial infarction in which there is no conclusive evidence to another cause of death or autopsy evidence of a recent infarct or abrupt death with either ECG changes indicative of an acute injury, abnormal markers without evolutional changes, or new wall motion abnormality

B. Pump Failure
Death occurring within the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death.

C. Sudden Death
Death that occurred unexpectedly in an otherwise stable patient and last seen up to 24 hours.

D. Presumed Sudden Death
Death that occurred unexpectedly in an otherwise stable patient in which the patient was last seen >24 hours before death and circumstances are suggestive of sudden death.

E. Presumed Cardiovascular Death
Death occurring when the patient was last seen >24 hours before death and presumed cardiovascular death.

F. Stroke
Death occurring after a documented stroke.

G. Pulmonary Embolism
Death occurring after and as a result of a pulmonary embolism.

H. Cardiovascular Procedure-Related
Death occurring during a cardiovascular procedure (CABG, PTCA, other) or as a result of later complications related to the procedure within 15 days.

I. Other Cardiovascular
Death must be due to a fully documented other cardiovascular cause not included above.

II. RENAL

Death due to a renal cause in the setting of:

1. Patient refusal to initiate dialysis (i.e. died of complications of uremia)
2. Treatment of acute renal failure
3. Direct complication of dialysis or other renal procedure (i.e. retransplantation, renal biopsy)
4. Hyperkalemia in association with renal insufficiency
5. Fatal reaction to renally excreted or metabolized medication in association with renal insufficiency
6. Other complications from renal failure

III. NON-CARDIOVASCULAR (Non-Renal)

If an unequivocal and documented non-cardiovascular cause can be established as the primary cause of death, the event will be classified as non-cardiovascular. Non-cardiovascular deaths will be further classified into the following categories:
Infection, Malignancy, Pulmonary, Gastrointestinal, Accidental, Suicide, Diabetes, and other.

IV. UNKNOWN

For cases of death for which there is insufficient data available to determine if the cause was cardiovascular, renal or non-cardiovascular, the event will be classified as unknown.

NON-FATAL ENDPOINT DEFINITIONS

A. Myocardial Infarction
1. Positive cardiac markers (troponin >ULN or CKMB≥ 2xULN AND either ECG changes or clinical presentation,
OR
2. Silent MI: New pathologic Q waves in two or more contiguous leads AND in the absence of corresponding symptoms.

B. Hospitalization for Congestive Heart Failure

Unplanned presentation for new or worsening heart failure that requires a change in a hospitalization calendar day, and requiring IV therapy with either vasodilators, or diuretics, or inotropes and at least one of the following:
a) Increasing dyspnea on exertion
b) Orthopnea
c) Paroxysmal nocturnal dyspnea
d) Increasing peripheral edema
e) Increasing fatigue, decreasing exercise tolerance
f) Renal hypoperfusion (i.e. worsening renal function)
g) Pulmonary edema
h) Elevated jugular venous pressure
i) Radiological sign of CHF

C. Stroke

1. A focal neurological deficit of central origin lasting more than 24 hours, with or without imaging confirmation of cerebral infarction or intracerebral hemorrhage.
OR
2. A focal neurological deficit of central origin lasting less than 24 hours with corresponding imaging evidence of cerebral infarction or intracerebral hemorrhage.
OR
3. A focal neurological deficit of central origin lasting less than 24 hours that was treated with thrombolytic therapy or directed percutaneous intervention.
OR
4. A non-focal encephalopathy lasting more than 24 hours with imaging evidence of cerebral infarction or hemorrhage adequate to account for the clinical state. Strokes were further sub-classified as Ischemic Stroke, Ischemic Stroke with Hemorrhagic Conversion, Primary Intracranial Hemorrhage, or Unknown when imaging is unavailable or inconclusive.

D. Progressive Renal Insufficiency
A 30% reduction in estimated glomerular filtration rate using the Modified Diet in Renal Disease formula as determined by the Biochemistry Core lab or local lab creatinine samples on two determinations separated by ≥60 days and in the absence of an explanation for progressive renal failure other than ischemic nephropathy.

E. Renal Replacement Therapy (RRT)

At least one of the following must occur in order to meet the criteria for this event:
a. Renal transplant
OR
b. Hemodialysis or peritoneal dialysis for ≥ 30 days
OR
c. Physician recommended RT and patient refused
OR
d. Patient died within 30 days after the initiation of dialysis for chronic renal failure

G. Kaplan-Meier Curves for components of primary endpoint.

Figure S1. Survival Free from Cardiovascular or Renal death through 5 years of follow-up

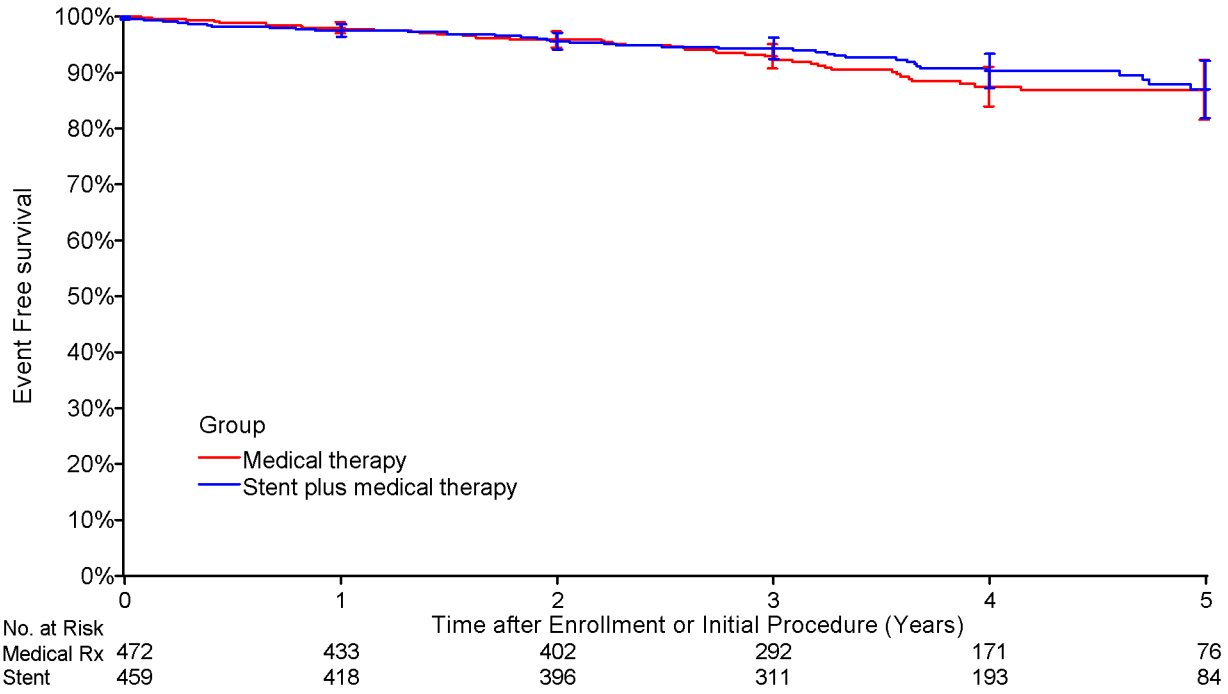


Figure S2. Survival Free from Stroke through 5 years of follow-up

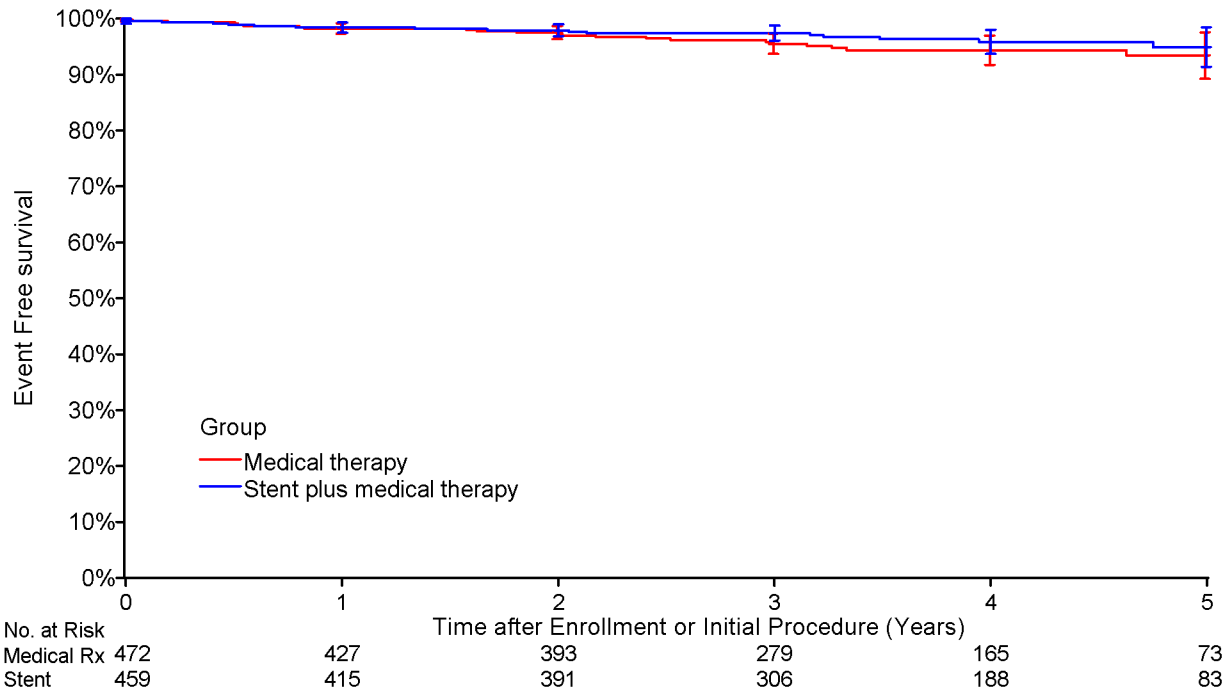


Figure S3. Survival Free from Myocardial Infarction through 5 years of follow-up

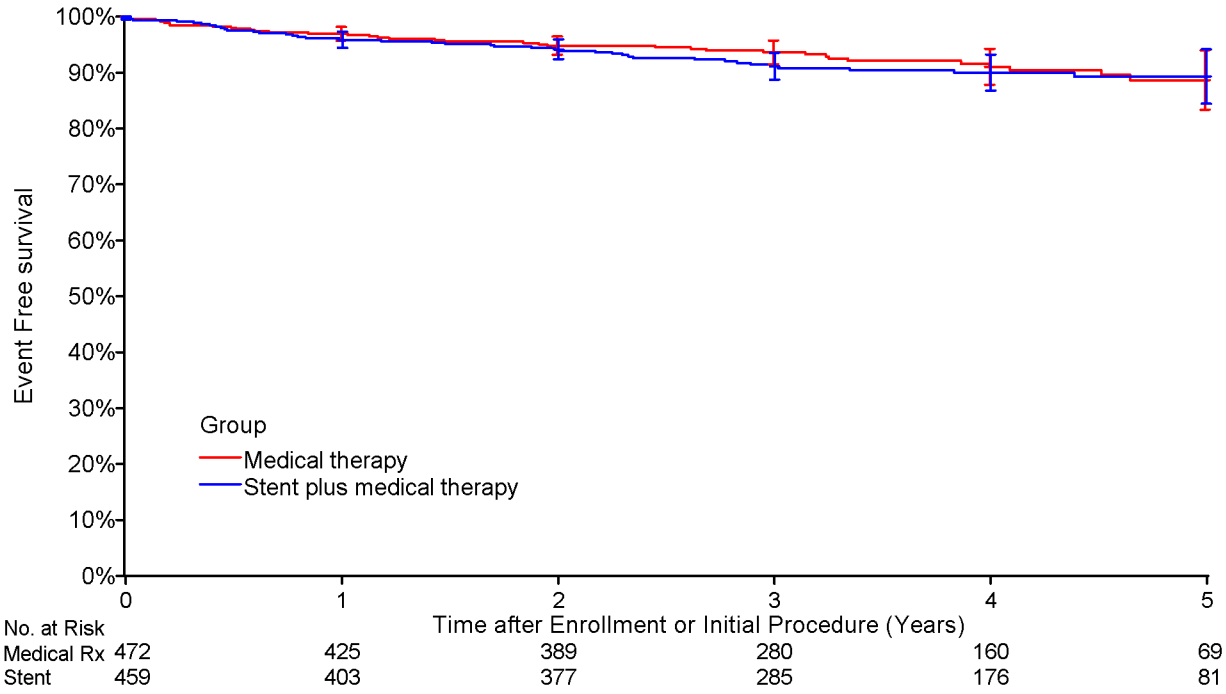


Figure S4. Survival Free from Heart Failure through 5 years of follow-up

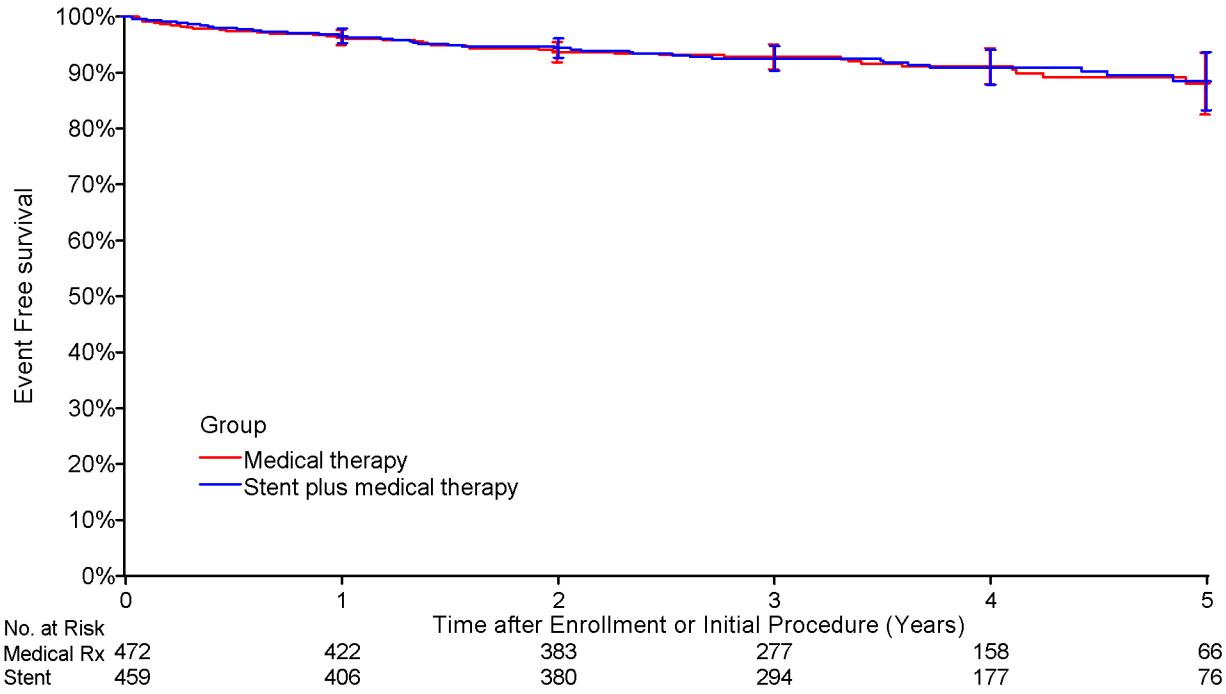


Figure S5. Survival Free from Progressive Renal Insufficiency through 5 years of follow-up

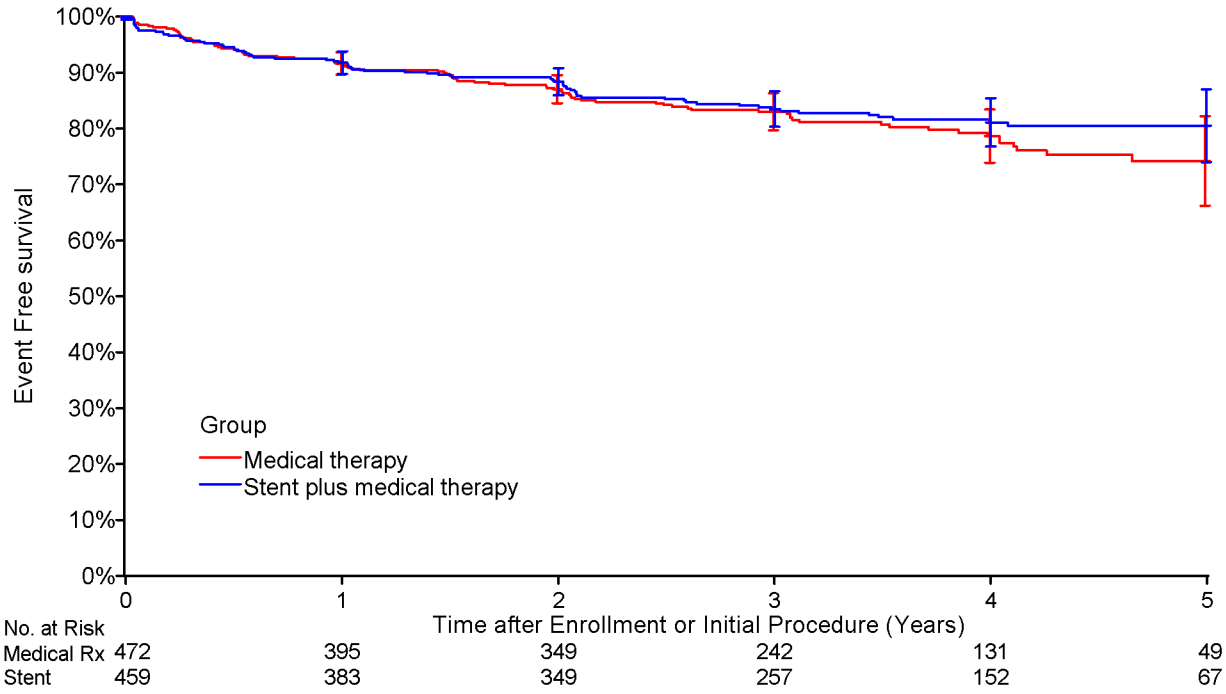
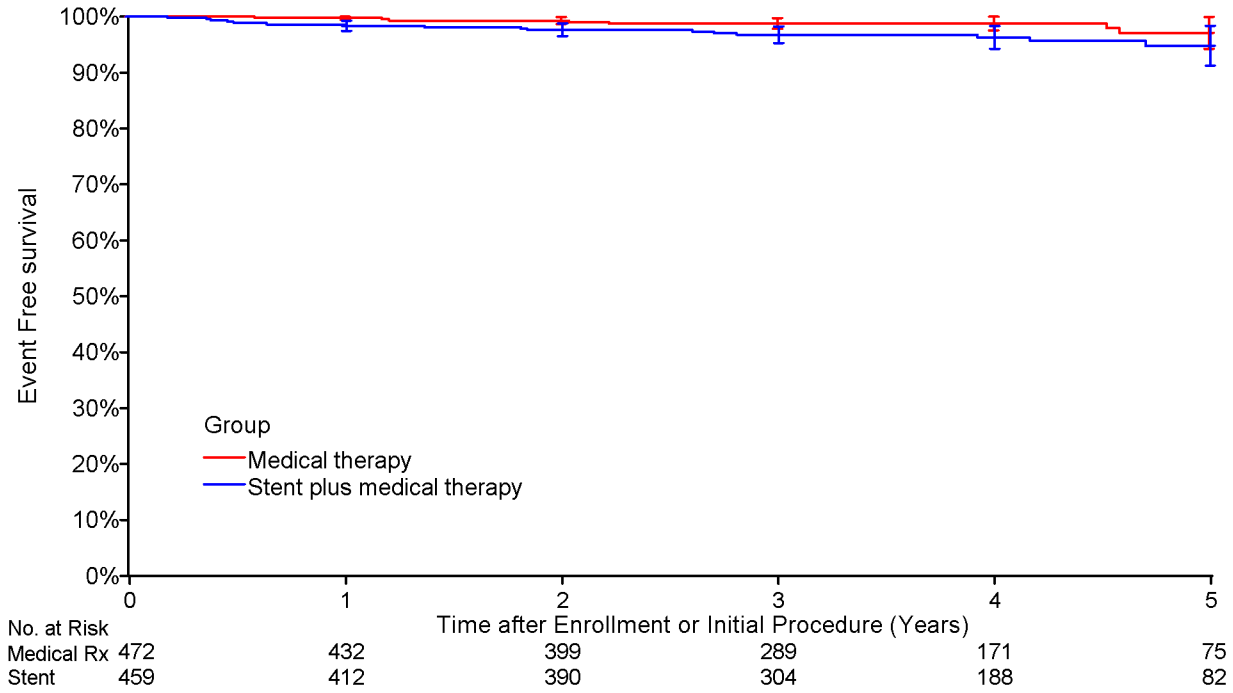
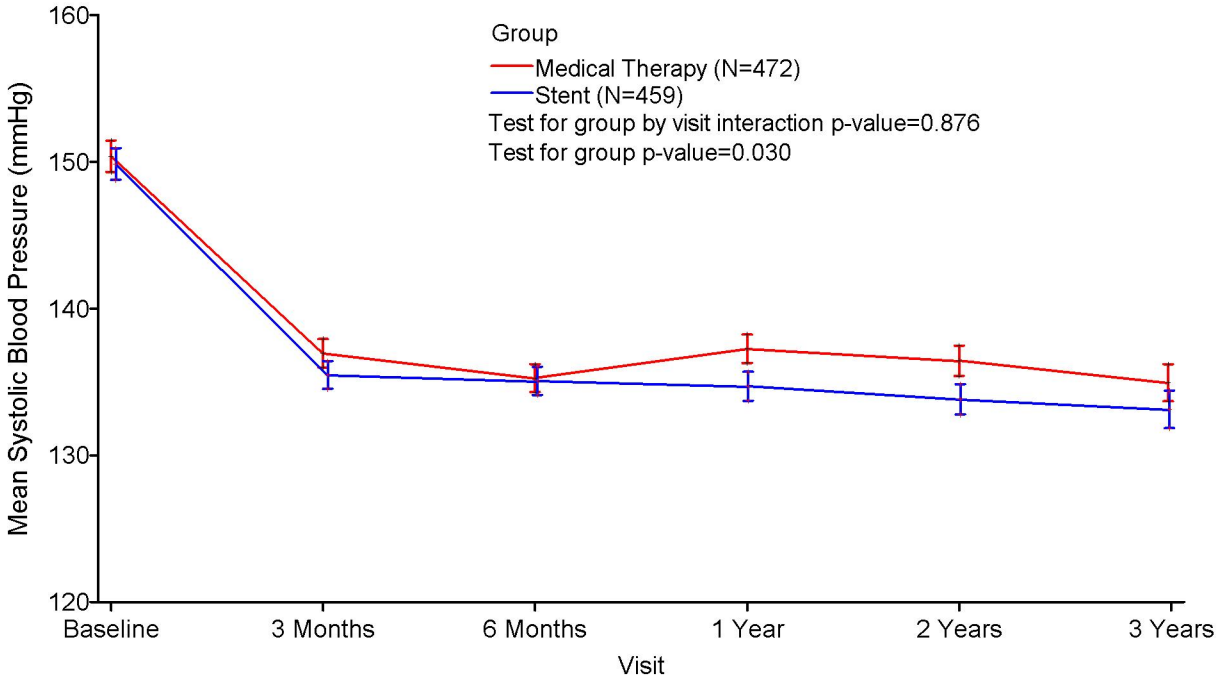


Figure S6. Survival Free from Permanent renal replacement therapy through 5 years of follow-up



H. Systolic blood pressure over time

Figure S7. CORAL study systolic blood pressure in mmHg.



I. Table S1. Changes in Clinical End Point Definitions

Non-Fatal Event	Old CORAL Definitions	New CORAL Definitions
Stroke	A focal neurological deficit (resulting from a vascular cause involving the central nervous system) of sudden onset that is not reversible within 24 hours (including death) and which is not due to a readily identifiable cause (ie brain tumor, trauma). In addition, a brain imaging study showing infarction or hemorrhage is also required to meet criteria for this event. Transient ischemia attacks (TIAs) are defined as a focal neurological deficit lasting < 24 hours. If a brain imaging study was performed, there should be no evidence of new infarction or new hemorrhage. Strokes will be further classified in one of the following categories: *Hemorrhagic*: when there is documentation of a hemorrhage. *Non-hemorrhagic:* when there is documentation a stroke occurred but a hemorrhage was not documented or seen on exam. *Unknown:* when there is no clinical, radiological, or other substantial evidence to document either a hemorrhagic or non-hemorrhagic stroke but a stroke is believed to have occurred.	1. A focal neurological deficit of central origin lasting **more than** 24 hours, with or without imaging confirmation of cerebral infarction or intracerebral hemorrhage. **OR** 2. A focal neurological deficit of central origin lasting **less than** 24 hours with corresponding imaging evidence of cerebral infarction or intracerebral hemorrhage. **OR** 3. A focal neurological deficit of central origin lasting **less than** 24 hours that was treated with thrombolytic therapy or directed percutaneous intervention. **OR** 4. A non-focal encephalopathy lasting **more than** 24 hours with imaging evidence of cerebral infarction or hemorrhage adequate to account for the clinical state. Patients with non-focal global encephalopathy will not be considered to have stroke without support from neurological imaging. Stroke will be further classified as on of the following: *a.Ischemic Stroke* – stroke with imaging suggesting ischemic changes *b.Ischemic Stroke with Hemorrhagic Conversion* - stroke with evidence of hemorrhage on imaging, judged to be hemorrhagic transformation of a primary ischemic stroke *c.Primary Intracranial Hemorrhage* – stroke with evidence on imaging of intracerebral hemorrhage not due to transformation of an ischemic stroke *d. Unknown:* when imaging is unavailable or inconclusive
MI	Patient must have a) positive cardiac markers (see below) ***AND either*** b) ECG	Patient must have a) positive cardiac markers (see below) ***AND either*** b) ECG

	changes consistent with infarction or ischemic symptoms. **Non-Procedural:** troponin or CKMB≥2xULN **PCI-MI:** troponin or CKMB≥3xULN* **CABG-MI:** CKMB≥5xULN* *within 24 hours CK can only be used in absence of CKMB and troponin data for Non-procedural and PCI-MI	changes consistent with infarction or ischemic symptoms. **Non-Procedural:** troponin or CKMB>1xULN **PCI-MI:** troponin or CKMB≥3xULN* **CABG-MI:** CKMB≥5xULN** and new Q waves or new wall motion abnormalities *within 48 hours **within 72 hours CK can only be used in absence of CKMB and troponin data for Non-procedural and PCI-MI
Progressive Renal Insufficiency	A doubling of serum Cr as determined by the Core Lab, on two determinations separated by ≥ 60 days. When such increases are observed, causes other than progression of chronic renal disease will be excluded on clinical grounds.	A 30% reduction in eGFR (from baseline or earliest available value) using MDRD formula as determined by Core lab or local labs on two determinations separated by ≥ 60 days. When such reductions are observed, causes other than progression of chronic renal disease will be excluded on clinical grounds.

J. Table S2. Reasons for non-enrollment of screened patients as reported by investigators.

4375 Patients screened but not enrolled. The reasons for not enrolling are listed below:

Number of Patients	Reason
801	Patient refused
210	Physician preference
1512	Renal artery stenosis <60%
203	Failed blood pressure or chronic kidney disease criteria
146	Prior renal artery stent or bypass
78	Restenosis >50% of prior renal artery stent or bypass OR renal stent in past 9-months
87	Fibromuscular dysplasia
18	Translesional pressure gradient <20 mmHg systolic
17	Blood Pressure >200 mmHg systolic or >120 mmHg systolic
12	Reference Vessel Diameter <3.5 mm or >8.0 mm
10	Previous kidney transplant
94	Creatinine >3.0 mg/dl
22	Diabetic (retinopathy/proteinuria)
47	Kidney <7 cm
17	Accessory renal artery supplying <½ of the ipsilateral renal parenchyma
107	Major surgery or endpoint event within 30 days
166	Comorbid condition
9	Aneurysm of the abdominal aorta >5.0 cm
1116	Other (reason for exclusion not specified)

K. Table S3. Stent treatment in the stent plus medical therapy group

	Number (%)
• Patients assigned to stent plus medical therapy	467
• Administratively withdrawn due to scientific misconduct	8
• Number in intention to treat analysis	459
o Stent successfully placed	434 (94.6)
o No attempt to place stent	9 (1.9)
▪ Refused stent	1 (0.2)
▪ Too ill to undergo procedure	1 (0.2)
▪ Lost insurance	1 (0.2)
▪ Withdrew prior to procedure	6 (1.3)
o Unable to implant stent	3 (0.9)
o Non-invasive pathway enrollment, stenosis did not qualify	13 (2.8)
▪ Stenosis <60%	12 (2.6)
▪ Stenosis 100% occluded	1 (0.2)
• Angiographic complications noted by Angiographic Core Lab, per vessel treated	
o Dissections	11/495 (2.2)
o Branch vessel occlusion	6/495 (1.2)
o Angiographically evident distal embolization	6/495 (1.2)
o Wire perforation	1/495 (0.2)
o Vessel rupture	1/495 (0.2)
o Pseudoaneurysm formation	1/495 (0.2)