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March 27th, 2007

Steve Phurrough, MD, MPA,
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Centers for Medicare and Medicaid Services,
7500 Security Boulevard,
Baltimore, MD, 21244

Title of NCA: **Percutaneous Transluminal Angioplasty (PTA) and Stenting of the Renal Arteries (CAG-00085R4)**

Dear Dr. Phurrough:

Cordis welcomes the opportunity to comment on this important subject.

We will make specific reference to the conclusions of the AHRQ report based on contemporary, peer reviewed, published data [1-14]. We also seek to provide input on the impact of coverage on both research and utilization of this procedure. However, we are unable to specifically address the recent "increase in concern" cited in the NCA regarding renal artery PTA and stenting as we are not aware of any unusual concerns in this area, and CMS has not provided any insight into what these concerns might be.

Having reviewed both the AHRQ report as well as the available published data, our overall conclusion is that PTA and stenting (PTAS) of ostial lesions (rather than non-ostial lesions) of the renal arteries is a viable and important option for the treatment of patients who have atherosclerotic renal artery stenosis (ARAS) with refractory or uncontrolled hypertension, renal insufficiency, chronic renal disease, unexplained heart failure or sudden pulmonary edema.

It is noted that the body of evidence is fragmented, often with varying definitions, inclusion and exclusion criteria and the type of assessed endpoints. We do acknowledge that this evidence also has limitations because it is primarily from non-randomized, uncontrolled studies. However, this body of evidence continues to grow and is consistent with benefiting patients with RAS.

The AHRQ report seeks to address three main questions:

Key Question 1:
Clinical Outcomes – Angioplasty with Stent versus Aggressive Medical Therapy.

In the case of medical therapy, it is important to note that best medical therapy (BMT), whether it be aggressive or not, for treating atherosclerotic renal artery stenosis (ARAS) has not been consistently defined by AHRQ or, in fairness, within the literature. An additional consideration is patient compliance, something that is always in question with the use of BMT. In a clinical trial setting, it is generally accepted that the rate of patient compliance is relatively high. However in the real world, compliance to medical therapy has been shown to be as low as 33% at 1-year [15]. Such issues are not of relevance when PTAS is the employed modality.

Therefore, it is extremely difficult to draw conclusions on the impact a BMT regimen would have on outcomes in patients who have ARAS with refractory or uncontrolled hypertension, renal insufficiency and / or chronic renal disease. Furthermore, some evidence that does exist for using medical therapy to treat ARAS suggests that there is a significant crossover of patients from medical therapy to endovascular procedures, arguing that medical therapy may fail in a substantial number of patients [16].

We do concur with AHRQ, that there have been no head-to-head investigations comparing PTAS to medical therapy. Therefore, in the absence of such studies, it is challenging to reach a conclusion as to which treatment is *best* for ARAS in patients with refractory or uncontrolled hypertension, renal insufficiency, chronic renal disease, unexplained heart failure or sudden pulmonary edema.

This leads to an important, yet unusual conclusion that the comparator to PTAS used by AHRQ, being BMT, has arguably less consistent and available contemporary supporting data than PTAS, the modality being reviewed in this NCA.

It should be noted that a number of studies referenced in the AHRQ report include medical therapy regimens and revascularization techniques that predate the availability of advanced endovascular techniques (including PTAS) and newer medical therapy. Therefore, any conclusions based on these studies have limited validity within the context of current medical practice.

Another important aspect of the AHRQ report is the apparent inconsistency of the meaning of the term, “revascularization.” Within the report, revascularization is used to reference both PTA and PTAS. Given the notably different outcomes between these two methods of revascularization [17] we feel that it is vital to refer to the specific treatment choice versus the general term.

Specifically, the hypothesis that PTAS is better than PTA for treating atherosclerotic ostial RAS in hypertensive patients was tested in one randomized controlled trial [17]. This prospective study compared the outcomes of angioplasty alone versus angioplasty plus stent placement in 85 hypertensive patients with ostial atherosclerotic renal artery stenosis.

The patients were randomly assigned to one or the other intervention, with stent placement if angioplasty alone failed within the first six months. Angioplasty plus stenting was associated with a significantly higher initial success rate (88% versus 57% for angioplasty alone), a much higher patency rate at six months (75% versus 29%), and a lower restenosis rate (14% versus 48%). The combined procedure lowered the blood pressure (180/105 to 160/90 mmHg) to a similar degree as angioplasty alone over the 6-month follow-up period.

It should be noted that of the 48% of patients with restenosis initially receiving PTA alone, more than half of those patients had a secondary intervention with stent placement. Therefore the similar lowering of BP between groups reflects a large portion of PTA having a stent placed after being assigned to the PTA group.

Blood pressure control

The mounting evidence from PTAS studies suggest that uncontrolled hypertension, renal insufficiency and chronic renal disease can be, at least in part, modified by PTAS. The effect of PTAS on refractory or uncontrolled hypertension has been observed in several studies. Notably, the combined success rate (cure or improvement of hypertension) was 65% to 80%, and the number of medications needed to control hypertension was reduced [6, 16]. Furthermore, restenosis (due to intimal hyperplasia within the stent) occurred in only 11% to 17% of patients receiving a stent [3,4,5,6].

Kidney function

We concur that PTAS has been demonstrated to either stabilize or improve kidney function. Specifically, the plasma creatinine concentration improved in some of the patients with baseline renal insufficiency [1,2] and the deleterious effect of ACE inhibitors on renal function was corrected [2].

Key Question 2:
Baseline Predictors of Outcomes

There are little if any data that are useful in predicting outcomes in patients with ARAS. However, one study suggests that using doppler ultrasound to determine magnitude of flow velocities across the lesion in patients with ARAS with refractory hypertension and renal insufficiency may determine which patients will not respond to treatment. Therefore, this may help predict which patients will respond favorably to PTAS [18]. However, similar studies with best medical therapy have not been undertaken.

Objective assessment of the impact of PTA or PTAS of the renal artery on relevant clinical endpoints such as blood pressure or renal function is fraught with some unique challenges. First, the kidneys are a paired organ system and hence the impact of intervening on the renal artery supplying one kidney may depend substantially on the function of the other kidney, which may be difficult to assess in isolation. Second, renovascular disease and parenchymal disease may coexist and it may be difficult to assess the contribution of each component with accuracy before the intervention. Thus, the outcome in an individual patient may be unpredictable while the outcome in a cohort of patients with RAS is generally salutary.

Key Question 3:
Treatment Variables as Predictors of Outcomes After Angioplasty.

Recent guidelines from The AHA/ACC for treating RAS published in 2006 [19] are consistent with the published evidence. There are nine categories of recommendation regarding treatment of RAS involving PTA and PTAS. AHRQ and CMS should recognize that these guidelines represent a consensus generated across specialties by experts that treat patients with RAS.

Furthermore, the guidelines do not rank order one therapy over another. This is likely due to the lack of randomized controlled trials comparing endovascular procedures with either surgery or medical therapy.

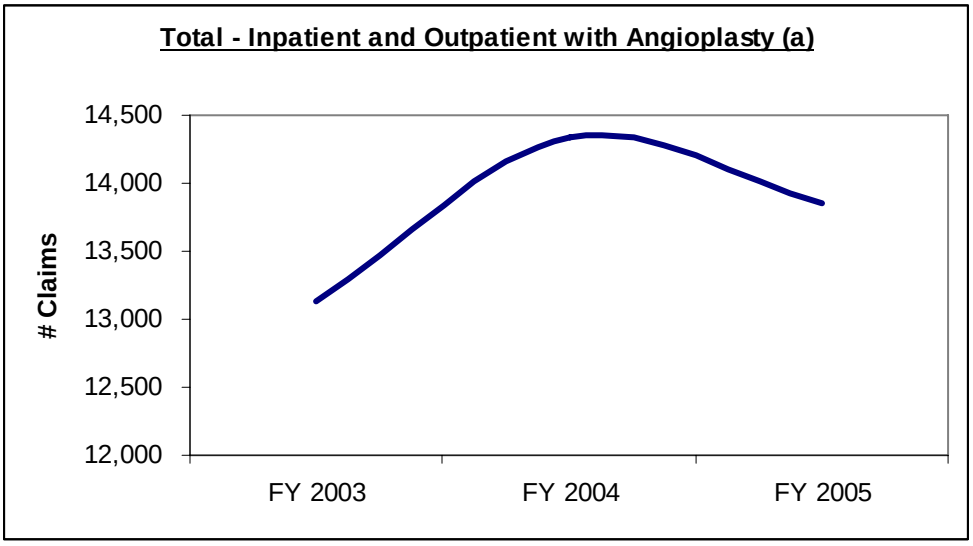
Other Points Raised by CMS and the AHRQ Report

We would also like to comment on the volume of interventions highlighted in the AHRQ report. The report shows an increase from 7,660 interventions in 1996 to 18,520 in 2000. This increase seems to be a strong contributor towards this review of PTAS and therefore it is important to note that the period of time chosen is non-representative of current medical practice and the associated volume of interventions, the nature of which have evolved over time.

The following figures represent up-to-date data on the volume of interventions. One should also view these data against the backdrop of an aging population, increasing rates of obesity (1999 to 2000 alone showed an increase of 3.1% in men and 6.3% in women [20]) and increasing rates of diabetes (23% increase between 2000 and 2004 [21]). With such elements in mind, the following data provide a strong indication of the responsible approach employed by physicians in choosing the optimal mode of treatment for a given patient. These data show a plateau in the utilization of these procedures which might not have been expected given the upward historical trend.

Figure 1:

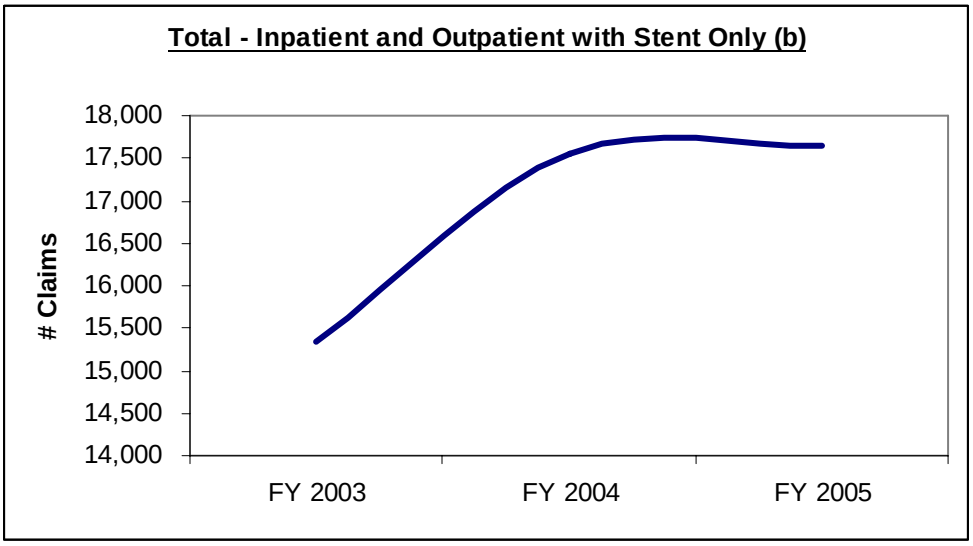
This figure looks at the MedPAR database, combining inpatient and outpatient claims. The inpatient claims were captured under DRG 315 with a principle procedure code of 39.50 (angioplasty) or 39.90 (stent). The outpatient claims were captured using CPT codes 37205 and 37206 (non-coronary stent placement) and codes 35471 and 35490 (percutaneous angioplasty or atherectomy of renal or visceral artery) and a principle diagnosis code of 440.1 (renal artery atherosclerosis). In looking at these data it is apparent that in recent years the volume of interventions actually peaked and has since started to show a decline.



(a) Source: MedPAR Database, Inpatient: DRG 315 - Principal Procedure code = 39.50 (Angioplasty) or 39.90 (Stent), Outpatient: Claims with both non-coronary stent placement (CPT 37205 or 37206) and percutaneous angioplasty or atherectomy of renal or visceral artery (35471, 35490) - Principal Dx 440.1- Renal Artery Atherosclerosis.

Figure 2:

This figure looks at the MedPAR database, combining inpatient and outpatient claims. The inpatient claims were still captured under DRG 315 with a principle procedure code of 39.50 (angioplasty) or 39.90 (stent). However, in this figure the outpatient claims were captured using CPT codes 37205 and 37206 alone(non-coronary stent placement) and a principle diagnosis code of 440.1 (renal artery atherosclerosis). In looking at these data it is apparent that in 2004 the volume of interventions peaked and has since leveled-off.



(b) Source: MedPAR Database, Inpatient: DRG 315 - Principal Procedure code = 39.50 (Angioplasty) or 39.90 (Stent), Outpatient: Claims with only non-coronary stent placement (CPT 37205 or 37206) - Principal Dx 440.1- Renal Artery Atherosclerosis.

Additional Key Points:

Finally we wish to address the "external questions" regarding Medicare's impact on current research referenced in the NCA. While CMS has not shared the specific nature of these external questions, nor their source, we still wish to comment.

We strongly support efforts to further research in patients with renal artery atherosclerotic disease. We agree the preferred form of research is randomization.

Therefore, we fully support the successful completion of the CORAL trial and understand the challenges in enrollment. However, it is inappropriate to restrict patient access to ARAS when this is the best option in the opinion of the treating physician. Not all patients who could benefit from ARAS will be eligible or have access to enable enrollment in CORAL. This is of particular relevance when the treatment option being reviewed by this NCA is acknowledged to be the standard of care, as stated in the AHRQ report. An additional consideration in driving completion of enrollment in randomized studies is the ever-increasing voice of patients, many of whom resist randomization. Changes in coverage would do little to change this driver. Therefore, we hope the enrollment difficulties associated with this trial do not in any way impact the coverage decision.

We believe that physicians' desire to generate further evidence will, in itself, be a strong driver towards completion of CORAL and other important studies. We also encourage CMS to explore options, such as incremental reimbursement for patients enrolled in these studies, as a way of accelerating completion.

Conclusion

PTA and stenting (PTAS) of the renal arteries is a viable and important treatment option for the treatment of patients who have atherosclerotic renal artery stenosis with refractory or uncontrolled hypertension, renal insufficiency, chronic renal disease, unexplained heart failure or sudden pulmonary edema.

While there are a broad range of data, we feel that this is strongly driven by the varied definitions and criteria used in the studies. Although a uniform approach is certainly preferable, this shouldn't overshadow the results of PTAS when used in appropriately indicated patients. In addition, this should be considered in the context of a lack of conclusive, contemporary evidence for the alternative form of treatment, being best medical therapy, a modality that unlike PTAS is not even consistently defined. In light of the lack of randomized data, reference to the AHA / ACC Guidelines, generated by expert physician input, seems most appropriate as guidance for treatment with PTAS.

We are happy to respond to any additional questions you may have concerning this important topic.

If you have any questions about this submission, please contact Dr. Brian Firth (908) 412-3099 or Dr. Liesl Cooper (908) 412-3000.

Sincerely,

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March 28, 2007

Steve Phurrough, MD, MPA
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RE: NCA for Percutaneous Transluminal Angioplasty (PTA) and Stenting of the Renal Arteries (CAG-00085R4)

Dear Dr. Phurrough:

The Society of Interventional Radiology (SIR) appreciates the opportunity to offer our suggestions to help you create a National Coverage Policy for Percutaneous Transluminal Angioplasty (PTA) and Stenting of the Renal Arteries. SIR is the only professional association of Interventional Radiologists in the United States numbering more than 4,300 physician members. Interventional Radiologists perform approximately half of all of the renal artery interventional procedures in the United States.

The first renal artery angioplasty done in the United States was performed in 1976 by Dr. Charles Tegtmeyer, an Interventional Radiologist at the University of Virginia. Renal artery angioplasty was an appealing alternative to renal artery bypass surgery, which was the standard revascularization procedure at that time. Renal PTA has a < 1% 30-day death rate compared to 6% for surgical revascularization. Renal PTA was therefore often used for suitable lesions instead of surgery.

We note that the current policy, NCD for Percutaneous Transluminal Angioplasty (PTA) (20.7), states that the beneficiary category is, “Inpatient hospital services,” “Physician services.” We suspect strongly that most renal artery interventions are performed in outpatients or so-called “short stay” (less than 24 hours) patients. Outpatient renal artery angioplasty and stenting is appropriate care in most cases.

Renal artery stenosis is the most common treatable cause of hypertension, and renal artery stenosis is an important cause of end-stage renal disease and the need for dialysis in the US. Availability of renal artery angioplasty and stenting to Medicare patients is mandatory in our

view. Nevertheless, renal artery angioplasty and stenting are invasive procedures and should be reserved for those in whom medical therapy is clearly not satisfactory.

Eighty-percent of renal artery stenoses involve the origin or ostium of the renal artery[1], and these respond poorly to PTA alone. Since the introduction of vascular stents in 1991, stent placement in the renal arteries has become the standard interventional treatment. Randomized trials have shown renal artery angioplasty to have lower morbidity and mortality than renal artery bypass surgery[2] and renal artery stent placement to have better patient outcomes than balloon angioplasty without stenting[3]. Renal artery bypass surgery has decreased dramatically since stents have become available[4]. Growth in annual procedure volumes among Interventional Radiologists has averaged 13% per year[4], a number consistent with growth in the Medical Price Index and in line with growth and changing demographics in our population.

Some Interventional Physicians have advocated very pro-intervention philosophies, including the theories that all stenoses warrant stenting, and that "renal preservation" is a valid indication for renal artery stent placement[5-7]. However, several randomized clinical trials have shown no difference in patient outcomes comparing medical therapy and renal revascularization[8]. We are aware of the conclusions of the Agency for Healthcare Research and Quality review (http://effectivehealthcare.ahrq.gov/synthesize/reports/execSummary.cfm?Topic=42) that there is no good evidence to support renal artery interventional therapy for any indication. The recommendations for renal revascularization in a recent multispecialty guideline[9] are based heavily on expert consensus rather than trial evidence. Therefore, it is not known if the increased utilization represents an improvement or overuse of medical care. We agree that more scientific evidence is needed to justify the large volume of renal artery interventional work currently being performed in this country. This is the subject of investigation in the on-going CORAL trial.

Traditional indications for renal artery stent placement are hypertension, renal failure, congestive heart failure, and complications of renal transplant. In our view, the way to make certain that renal artery stent placement procedures are performed appropriately is to ensure that appropriate clinical and angiographic indications are present. In funding the CORAL Trial, the NIH has established reasonable criteria and technical protocols for renal artery stent placement. As a minimum, the CORAL eligibility criteria represent a standard for the appropriate performance of renal artery stent procedures. These will be addressed below.

Atherosclerotic Renal Artery Stenosis Indications for Renal Artery Stent Placement

At least one clinical indication AND one angiographic indication should be present to justify a renal artery interventional procedure.

Clinical indications:

1. Hypertension: If hypertension is the indication, patients must have "resistant" hypertension, defined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[10] as

inability to achieve goal blood pressure (< 140/90 mmHg, or < 130/80 mmHg for patients with diabetes or chronic kidney disease) despite an appropriate three-drug regimen that includes a diuretic. CORAL hypertension indications for stenting are documented history of hypertension on 2 or more anti-hypertensive medications. Blood pressure reading should be based on the average of two or more properly measured, seated BP readings on each of two or more office visits. There may be some patients who are intolerant of medications, and in these cases angioplasty or stent treatment of an underlying renal artery stenosis should be reimbursed. It may be helpful to have a nephrologist involved in the care of these patients to ensure that they are truly "resistant" to medical management and require renal revascularization.

2. Renal failure: As recommended in CORAL, the renal failure indication should be Stage 3 or higher chronic kidney disease (CKD) (estimated GFR < 60 mL per minute per 1.73 m2 calculated by the modified MDRD formula); and should only be reimbursed when "global" renal disease is present. This means that an angiographically significant (see below) stenosis is present in all renal arteries (bilaterally severe for people with 2 functional kidneys, and unilaterally severe for people with only one functional kidney, including individuals with unilateral RAS and intrinsic renal disease in the kidney contralateral to the side with RAS). Unilateral renal artery stenosis with a contralateral normally perfused and non-diseased kidney is not consistent with a renovascular cause of CKD and should not be accepted as an indication for revascularization.

3. Congestive heart failure: Congestive heart failure can occur due to diastolic dysfunction in people with renal artery hypertension, especially when compounded by volume overload, and is characterized by good community-based function (New York Heart Association Class 1 Heart Failure) with intermittent bouts of "flash" pulmonary edema requiring hospital admission. As an indication, CHF is supported only when "global" renal ischemia is present as described above[11].

   Renal artery stent placement should NOT be indicated as prophylaxis for renal preservation, to prevent future kidney damage or renal dysfunction, or to prevent loss of renal mass unless the above clinical indications are present.

Angiographic Indications for Renal Artery Stent Placement

At least one angiographic indicator should be present to support reimbursement for renal artery intervention. The angiographic indicators should be:

1. Stenosis $\geq$ 60% by diameter using digital automated or digital manual caliper systems. Renal artery stent placement is indicated only for stenoses that are clinically important. Renal artery stenoses usually do not cause clinical symptoms until they are severe, at least 60% by diameter[13]. To qualify for coverage, renal artery stent placement should be done only in individuals for whom a stenosis is measured to be at least 60% by diameter using electronic, digital caliper measuring

systems by automated or manual measurements. Images with these measurements should be archived in the imaging record. The report should state that digital caliper measurements were done, and the severity of the stenosis according to these measurements should be specifically stated in the report. For patients with duplex or MRA evidence for a hemodynamically significant RAS, coverage for intervention should be extended for angiographic finding of a lesser degree (50-60%) stenosis, recognizing the limitations of angiography in fully defining stenosis severity. CORAL noninvasive duplex and MRA criteria should be used, including an angle adjusted duplex systolic velocity elevation of > 300 cm/sec, or MRA finding of stenosis > 90%, OR stenosis > 75% with spin dephasing on 3D phase contrast MRA OR stenosis > 75% associated with an ischemic kidney which is > 1 cm smaller than contralateral kidney with associated reduced arterial phase enhancement, delayed gadolinium excretion, and/or hyperconcentration of urine.

2. Invasive pressure measurements. As an alternative to digital caliper measurements, a trans-stenotic pressure gradient should be measured and documented with a tracing in the patient record showing a systolic pressure gradient of at least 20 mmHg. If done instead of digital diameter stenosis measurements, the pressure gradient should be specifically stated in the report. Pressures should be measured using the techniques recommended by the American Heart Association[9]. This guideline recommends that pressures should be measured simultaneously between the aorta and renal artery beyond the stenosis using either a 4 French or smaller (such as a 0.014" diameter pressure-sensing guidewire) device within the renal artery and a sheath or guide in the aorta at least 1 French larger than the device in the renal artery.

Technical considerations

Approximately 80% of atherosclerotic stenoses are ostial, and these respond poorly to balloon angioplasty. In this population, "primary" or "direct" renal artery stent placement is the standard technique. Attempts at balloon angioplasty alone with provisional stenting reserved for those with suboptimal results of balloon angioplasty are not the standard of care and not justifiable. One randomized clinical trial showed better patient outcomes with renal artery stent placement compared with balloon angioplasty[3].

For non ostial atherosclerotic renal artery stenosis some Interventional Physicians will attempt balloon angioplasty as a definitive therapy. If successful and a stent is not placed, this should be a reimbursable service.

If bilateral renal artery interventional procedures are required, it is usually in the patient's best interest if they are performed at the same time. If angiographic and clinical indicators are present, we support the use of the bilateral modifier (-50) to allow payment for both sides treated on the same day. However, there may be valid reasons to delay treatment of the second renal artery, such as risk of contrast nephrotoxicity or length of the procedure. In these small number of cases, reimbursement for procedures on separate days is appropriate.

Credentialing and Quality Assurance Considerations

Physicians performing renal artery stenting must meet the training criteria of the AHA for unrestricted competency for peripheral interventions[13] and participate in a facility QA program in which the physician outcomes meet national QA thresholds[14].

Other Considerations

The SIR recognizes the responsibility of all physicians to prove the value of the services that they provide and is an enthusiastic supporter of the NIH-sponsored CORAL Study examining renal artery stenting for atherosclerotic renal artery stenosis. We support reimbursement for renal artery stenting in the context of NIH and/or FDA clinical trials. Furthermore, we support a mechanism where a premium could be paid for enrollment in a clinical trial where patients are randomized to medical vs. interventional therapy, recognizing that interventional physicians who support this important research are likely to experience overall reduced reimbursement due to allocation of half of their patients to the medical treatment group. We believe such economic barriers impede enrollment in these most important clinical trials in the US.

Coverage should not be linked to use of an FDA approved stent device for the renal arteries. There are currently only three devices approved (Genesis and Palmaz stents, Cordis; AVE Bridge stent, Medtronic) but there are many suitable devices in clinical practice, and FDA approval is not feasible for many companies and not a reasonable standard.

Use of distal embolic protection devices should not be required.

An “alternative to surgery” standard for renal artery stent placement is poorly considered and not justifiable. Surgical revascularization of renal artery stenosis is associated with a 10-fold increased risk of 30-day mortality compared with stent placement, and much higher risk of systemic complications such as myocardial infarction, heart failure, respiratory failure, and kidney failure. Medical decisions are based on risk-benefit analyses. There are many, and perhaps most, patients for whom a risk-benefit analysis of stenting would be favorable, given elimination of this amount of risk, who nevertheless would not be suitable for surgical renal artery revascularization.

We thank CMS for the opportunity to comment on the use of percutaneous renal revascularization. We strongly believe that such treatment is beneficial in appropriately selected patients and that reimbursement for these patients is necessary. We understand that definitive proof of benefit over medical treatment is lacking in many patient groups. We have listed those indications that we believe clearly lead to patient benefit. We are hopeful that further research will support further indications.

Thank you again for the opportunity to submit these comments. If we can provide any additional information, or if you have any questions, please do not hesitate to contact me at

(610) 988-8927 or davidsacks@pol.net or Tricia McClenny, SIR's Associate Executive Director, at (703) 691-1805 or tricia@sirweb.org.

Sincerely,

David Sacks, MD
President, SIR

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Timothy Murphy, MD, SIR
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Peter B. Lauer, CAE, SIR
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March 25, 2007

Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
7500 Security Blvd
Baltimore, MD 21244

RE: Proposed Decision for Renal Artery Stenting CAG-00085R4

Dear Dr. Phurrough;

The Society for Vascular Surgery (SVS) represents over 2,300 physicians in the United States. SVS offers the following comments regarding Proposed Decision of the Medicare National Coverage Policy for Tracking Sheet for Percutaneous Transluminal Angioplasty (PTA) and Stenting of the Renal Arteries (CAG-00085R4). SVS appreciates the thorough and ongoing effort expended by the CAG to allow responsible utilization of this technology, established and in place for some twenty years, but still in need of further appraisal.

SVS is in a unique position to comment on renal PTA and stenting, given our community's history of treating this process by open surgical means for the past 40 years and by minimally invasive percutaneous techniques more recently.(1-6) A brief review of these references makes the point in convincing manner that vascular surgeons have set a high standard for treatment of renovascular hypertension and ischemic nephropathy due to atherosclerotic renal artery stenosis (ARAS). Surgical revascularization really has been the standard treatment for this disorder for many years.

Recently, percutaneous renal balloon angioplasty and stenting have gained substantial popularity for treatment of ARAS. As documented in the recent report by the AHRQ EPC, and published by Balk et al, the literature to support percutaneous renal intervention for ARAS has not kept pace with the proliferation of this treatment.(7) Notably, one SVS member (RP Cambria) served as an expert consultant to the EPC. Nevertheless, it is important to point out that lack of Level 1 data does not imply lacks efficacy.

Additionally, SVS finds it paradoxical that CMS would consider rescinding coverage for renal artery stenting based on lack of Level I data at the same time the Agency is expanding coverage for carotid artery stenting in asymptomatic physiologic high risk patients despite the absence of sufficient Level I suppport.

SVS agrees with AHRQ that the question of what constitutes optimal management of renovascular disease remains an open question. The data has been nicely summarized by Hansen.(8) Treatment choices are medical, surgical, and interventional. We can control blood pressure successfully with medical therapy, but the unfortunate endpoint is end-stage renal failure in a substantial portion of patients with ARAS. The K/DOQI guidelines stress the importance of renal preservation; the benefits are clear and numerous.(9) Given that between 8-15% of patients who develop hemodialysis end stage renal disease, (ESRD), have only ARAS as the documented pathology, treatment of this entity is compelling. Natural history studies have shown that ARAS tends to progress over time. Kidneys with stenotic renal arteries are at risk for atrophy and deterioration in renal function.(10, 11) Therefore, adequate control of blood pressure cannot be considered a clinical victory in patients with ARAS.

The excellent durability of surgical revascularization in stabilizing or improving renal function is derived at the cost of some perioperative morbidity and mortality, but hypertension can be cured or improved in 85% of atherosclerotic adults, while renal function among patients with ischemic nephropathy (defined as preoperative serum creatinine $\geq$1.8 mg/dl) demonstrated at least a 20% increase in estimated glomerular filtration rate in 58%, including 28 of 35 patients permanently removed from dialysis-dependence.(3)

Where does percutaneous intervention fit between medical therapy and surgical revascularization? Studies such as CORAL may provide some insight, but recruitment has been slow, and since the study endpoints are general cardiovascular outcomes, prolonged follow-up will be required.

SVS Recommendation #1: Since percutaneous renal angioplasty and stenting is employed extensively by the clinical community for treatment of ARAS, and since the primary problem in this arena appears to be a lack of high-quality research rather than lack of efficacy, SVS recommends that CMS CAG retain its current coverage policy until more data are published.

Clinically Valuable Data are Found Outside the Level 1 Realm

SVS believes that the AHRQ EPC overlooked an important factor during analysis of their Key Question 2, the issue regarding whether there are any baseline predictors of outcomes. The EPC investigators state: "A variety of indicators of the severity of ARAS end of health problems, such as poorer kidney function, worse blood pressure, and coexisting cardiovascular disease, predict poorer outcomes in patients with ARAS. The reviewed studies did not report any indicators that may predict improved outcomes.

The EPC appears to have completely overlooked a solid line of evidence indicating the use of Doppler ultrasonography to measure renal arterial resistance as a predictor of outcomes following therapy for renal artery stenosis. This concept was introduced in the U.S. by Cohn et al and in Europe by Radermacher.(12, 13)

In the 2001 study by Radermacher, color Doppler ultrasonography was used to measure the renal resistance index in 138 patients who had unilateral or bilateral renal artery stenosis of more than 50% and who underwent renal angioplasty or surgery. The procedure was technically successful in 95%. Creatinine clearance and 24-hour ambulatory blood pressure were measured before renal artery stenosis was corrected, and at 3, 6, and 12 month intervals and yearly thereafter. Mean follow-up was 32 months. Patients with elevated renal resistance index (27% of the cohort) failed to realize an improvement in blood pressure, while the cohort with normal resistive indices experienced an improvement in mean arterial pressure ($P<0.05$) to three years, with a trend to 5 years. Renal function, as defined by creatinine clearance, declined by more than 10% in 80% of patients with elevated renal resistance indices despite technically successful revascularizations. Forty-six per cent of patients with elevated renal resistance index values became dependent on dialysis during follow-up, while 29% of those with elevated resistance index died during follow up. Patients with normal resistance index experienced a significant increase in creatinine clearance, followed out to 60 months.(13) Radermacher and colleagues have continued to elucidate the value of renal resistive index.(14, 15) We urge CMS CAG to review these manuscripts. The following image is from Radermacher et al, NEJM 2001.

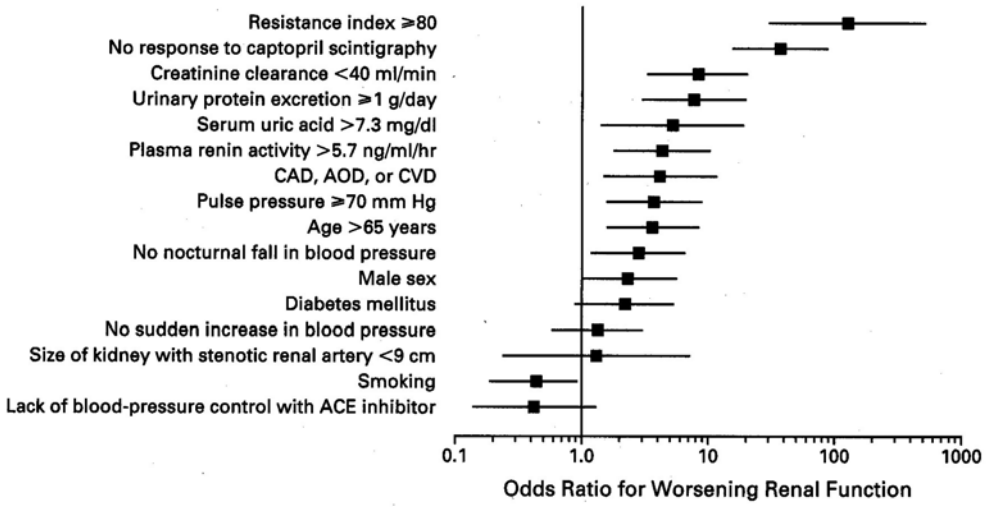

Figure 3. Univariate Odds Ratios for a Worsening of Renal Function after Correction of Renal-Artery Stenosis, with 95 Percent Confidence Intervals, Associated with Various Factors before Revascularization.

The absence of a nocturnal fall in blood pressure was determined from measurements of 24-hour ambulatory blood pressure. The odds ratio for captopril scintigraphy was calculated from published data.[4,18] A "sudden increase in blood pressure" refers to recent worsening of hypertension or recent onset of hypertension. To convert the value for serum uric acid to micromoles per liter, multiply by 59.5. CAD denotes coronary artery disease, AOD arterial occlusive disease of the legs, CVD cerebrovascular disease, and ACE angiotensin-converting enzyme.

SVS Recommendation #2: In view this example, i.e. the literature regarding the predictive value of Doppler ultrasound derived renal resistive index in predicting successful response to treatment of renal artery stenosis, SVS recommends that CMS

CAG consider sources other than the AHRQ EPC analysis of management strategies for renal artery stenosis.

It is recognized that prediction of the functional response to renal revascularization (be it hypertension control and/or renal function preservation) remains an imprecise clinical science. It can be argued that it will always remain such given the multiple clinical variables, especially the variable degree of renal parenchymal damage. Yet, lack of Level 1 data does not mean that therapeutic nihilism is right. This approach will deny many patients genuine benefit, even to the extent of rescue from renal replacement therapy.

Unusual Indications for Renal Revascularization

The two primary traditional indications for percutaneous treatment of ARAS include refractory hypertension on three or more medications and renal insufficiency due to hypoperfusion of the kidney. However, less common indications also exist. These include flash pulmonary edema due to severe renal artery stenosis, renal stent placement for aortic or renal arterial dissection, stent placement when endovascular aortic prostheses impinge upon the renal orifice, and documented renal stenosis in a solitary functioning kidney. SVS realizes that with propensity to examine only level 1 RCTs, the AHRQ is unlikely ever to visit the literature surrounding these less common clinical situations. For the past 40 years, SVS members have contributed to the as yet imprecise science of the worth of renal revascularization including analysis of these unusual situations.

SVS Recommendation #3: In view of the fact that there will never be randomized controlled trials of unusual indications for renal stent placement, and in consideration of any upcoming coverage restrictions for percutaneous renal artery intervention, SVS recommends that CMS CAG offer special consideration and exception to patients with (1) flash pulmonary edema due to RAS, (2) aortic and/or renal artery dissection, (3) impingement on the renal artery by prosthetic devices, (4) prophylactic stenting either prior to or in association with open or endovascular aortic aneurysm repair, and (5) patients with solitary functioning kidneys.

Vascular System FDA Approval of Stents

Recently, the FDA became interested in coaxing the major stent vendors in the United States to obtain vascular system-specific FDA approval for their stent products. Given the idiosyncrasies of the FDA approval process, a large majority of the stents currently used in the renal artery (and in many other vascular beds) are approved by FDA for substantially different indications (e.g. hepatobiliary or tracheobronchial applications).

SVS Recommendation #4: In view of the FDA's interest in obtaining vascular-specific stent approval, and in view of the lack of extant data regarding efficacy of stenting in the renal artery, SVS suggests that the FDA and CMS collaborate in inviting the major stent manufacturers to sponsor clinical trials of renal artery stents using their individual

products. This would provide real world evidence to compliment RCTs such as CORAL.

In conclusion, SVS urges CMS not to rescind coverage for renal artery stent placement in Medicare beneficiaries with ARAS. We understand that more scientific data are needed to determine exactly which patients will benefit the most from renal intervention, but avoidance of ESRD with the need for lifelong hemodialysis is a compelling goal. SVS is committed to the advancement of all forms of renal therapy that will reduce ESRD. We are available at any time for telephone or in-person discussions regarding these comments.

K. Craig Kent, M.D.
President
and the Executive Council of
The Society for Vascular Surgery

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Heart Disease and Stroke. You're the Cure.

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March 28, 2007

Centers for Medicare & Medicaid Services
Department of Health & Human Services
7500 Security Boulevard
Baltimore, MD 21244

Re: CAG-00085R4

Dear Sir/Madam:

On behalf of the American Heart Association (AHA), including the American Stroke Association (ASA) and over 22.5 million AHA and ASA volunteers and supporters, we appreciate the opportunity to submit our comments in response to the Centers for Medicare and Medicaid Services (CMS) national coverage analysis for percutaneous transluminal angioplasty (PTA) and stenting of the renal arteries.

Since 1924, the American Heart Association has dedicated itself to reducing disability and death from cardiovascular disease and stroke – the #1 and #3 leading causes of death in the United States – through research, education, community based programs and advocacy. AHA's efforts include the development of evidence-based clinical practice guidelines and scientific statements designed to raise awareness and advise physicians and other providers on the prevention, treatment, and management of cardiovascular disease and stroke. These are developed jointly with the American College of Cardiology (ACC) using rigorous methodology and an intensive review process. The subject of atherosclerotic renal artery stenosis (ARAS) is covered in the *ACC/AHA 2005 Practice Guidelines for the Management of Patients with Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic).*[1] These guidelines were developed in collaboration with and endorsed by the American Association for Vascular Surgery/Society for Vascular Surgery, the Society for Cardiovascular Angiography and Interventions, the Society for Vascular Medicine and Biology, and the Society of Interventional Radiology. Our comments are based on those guidelines.

[1] See http://circ.ahajournals.org/cgi/reprint/113/11/e463.

American Heart Association . Advocacy Department
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At the end of February, CMS announced its intention to examine the best treatment options for patients with ARAS and develop a national coverage determination for PTA and stenting of the renal arteries. As part of this analysis, CMS will examine what patient population and under what circumstances Medicare coverage of renal artery stenting is reasonable and necessary. AHA supports the Agency's efforts to evaluate this procedure and identify the appropriate patient population. PTA and stenting is an effective treatment option for appropriately selected patients; the procedure has become one of the most frequently used revascularization techniques, despite a limited evidence base.[2] Without additional trials examining PTA and stenting and comparing the procedure to surgical revascularization and medical management, it will be difficult to correctly identify the appropriate patient population for this treatment option.

Current Evidence

Current Medicare policy provides coverage for PTA of the renal arteries for patients in whom there is an inadequate response to a thorough medical management for symptoms and for whom surgery is the likely alternative. AHA agrees that physicians should compare both medical treatment and revascularization techniques for patients with ARAS, and consider revascularization when it has a likely or definite advantage to medical therapy. Medical therapy should follow the recommendations detailed in the ACC/AHA guidelines.

There is some evidence, although limited in nature, that revascularization may benefit selected patients with significant renal artery stenosis (RAS).[3] Based on the evidence currently available, the ACC/AHA guidelines offer the following Class I (there is evidence for and/or general agreement that a given procedure or treatment is beneficial, useful, and effective) or Class IIa (there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment; the weight of evidence/opinion is in favor of usefulness/efficacy) recommendations for revascularization:

<u>Congestive Heart Failure & Unstable Angina</u>

Class I Recommendation

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)*
2. Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and unstable angina *(Level of Evidence: B)*

<u>Hypertension</u>

Class IIa Recommendation

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

[2] See http://circ.ahajournals.org/cgi/reprint/106/12/1572, Pg. 1573.
[3] See http://circ.ahajournals.org/cgi/reprint/106/12/1572, Pgs. 1573-1574.

Preservation of Renal Function
Class IIa Recommendation

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)*

We would suggest that these specific patient groups are currently appropriate for coverage.

There are additional patient groups that have Class IIb (there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment; the usefulness/efficacy is less well established by evidence/opinion) recommendations:

Preservation of Renal Function
Class IIb Recommendation

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

Asymptomatic Stenosis
Class IIb Recommendation

1. Percutaneous revascularization may be considered for the 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)*

The current justification for coverage in these patients is weaker.

It is important to emphasize that the recommendations are based on the current evidence base. The Class I and IIa recommendations are Level of Evidence B, i.e., data derived from a single randomized trial or nonrandomized studies. The prospective clinical trials that have been published generally have significant methodological problems. While revascularization with stent-assisted angioplasty has gained increasing acceptance and has undergone tremendous procedural growth,[4] replacing much of what had been done with traditional surgery, "many questions remain, partly because of the continuing evolution of tools and techniques and partly because of the paucity of large prospective randomized trials."[5] For example, the Class IIb recommendations for patients with asymptomatic stenosis are largely based on expert opinion (Level of Evidence C) instead of evidence that this treatment improves any renal or systemic outcome. (See Attachment A for additional information on the classification of recommendations and levels of evidence).

The relative paucity of clinical trial evidence has created controversy around the role of revascularization in patients with ARAS. Questions remain over the clinical clues that should be

[4] See http://circ.ahajournals.org/cgi/reprint/106/12/1572, Pg. 1572.
[5] See http://circ.ahajournals.org/cgi/reprint/109/21/2643, Pg. 2463.

considered when selecting medical versus revascularization therapy, the degree of renal arterial narrowing that justifies an attempt at revascularization,[6] and the relative effect of the different treatment options on patient outcomes. As acknowledged in AHRQ's report on renal artery stenosis, "there remains considerable uncertainty on which intervention provides the best clinical outcome… Overall, the evidence does not currently support one treatment approach over the other for the general population of people with ARAS."[7] Simply put, "It is still unknown if percutaneous renal artery angioplasty or stent placement is superior to medical therapy or surgical revascularization in reducing cardiovascular mortality, providing prolonged improvements in blood pressure control, or preserving renal size and function."[8]

The need to resolve this controversy and identify the appropriate patient population for PTA and stenting of the renal arteries appears to be at least partially responsible for the Agency's decision to develop a national coverage determination for this procedure under Medicare. According to the CMS tracking sheet, the Agency initiated this coverage analysis because of a "recent increase in concern regarding renal artery PTA and stenting and external questions regarding Medicare's impact on current research and utilization of these procedures."[9] We support CMS' efforts to examine this revascularization technique and attempt to identify the patients who are likely to benefit from it.

Additional Evidence is Needed

PTA with stent placement across the stenosis may ultimately prove to be the treatment standard for patients with ARAS; however, we do not yet have enough clinical evidence to adequately compare the treatment options and accurately identify the appropriate patient population. "Despite extensive clinical experience over the past 10 years and the publication of multiple articles describing renal revascularization with renal artery stents, renal angioplasty, and surgical renal revascularization, few prospective randomized controlled trials have been reported."[10]

The need for additional studies is supported by AHRQ's review of the existing scientific evidence related to revascularization. As AHRQ found, there is no published evidence comparing aggressive medical therapy with PTA and stenting; and of the limited studies that have been completed to date, almost two-thirds were of poor methodological quality and more than half were of limited applicability to the population of interest.[11]

Data from research studies currently in-progress such as the National Institutes of Health-sponsored Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial and other broad-based studies will play a significant role in helping the medical community determine the appropriate role for stent-assisted angioplasty in patients with ARAS. Without this additional evidence from well-designed, controlled randomized trials, it will be difficult to identify the patient population and circumstances under which Medicare coverage of PTA and stenting of renal arteries is reasonable and necessary.

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[6] See http://circ.ahajournals.org/cgi/reprint/106/12/1572, Pg. 1573.
[7] See http://effectivehealthcare.ahrq.gov/repFiles/RAS_Executive_Summary.pdf, Pgs. 2-3.
[8] See http://circ.ahajournals.org/cgi/reprint/106/12/1572, Pg. 1573.
[9] See CMS National Coverage Analysis (http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=202).
[10] See http://circ.ahajournals.org/cgi/reprint/106/12/1572, Pg. 1572.
[11] See http://effectivehealthcare.ahrq.gov/repFiles/RAS_Executive_Summary.pdf, Pg. 3.

Conclusion

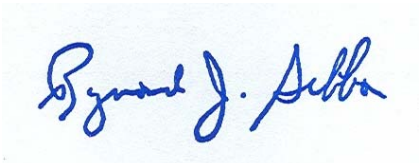
In closing, we reiterate our support for CMS' decision to examine the best treatment for patients with ARAS. The patient population that could potentially benefit from some form of revascularization therapy is substantial; approximately 30% of patients with coronary artery disease and approximately 50% of the elderly and those with diffuse atherosclerotic vascular diseases are afflicted with ARAS.[12] A growing number of these patients are being treated with PTA and stenting, and the procedure has become the standard for revascularization in many patients with ARAS.

The number of PTA and stenting procedures has grown rapidly despite a lack of strong supporting clinical evidence. While there is some evidence that revascularization will benefit the specific patient groups described above, the overall evidence base is generally far less than desirable. This reinforces the need for additional data from well conducted clinical trials (such as CORAL) to strengthen the evidence in support of this procedure. Data from such clinical trials is crucial to the advancement of this treatment option for patients with ARAS. Without these data, physicians will be forced to continue to make treatment decisions, and CMS will be forced to make coverage decisions, based on a limited and incomplete database of evidence. Given the magnitude of the patient population that could benefit from selection of the *appropriate* treatment, this is not an acceptable option.

We strongly support efforts by CMS to encourage enrollment in the ongoing CORAL trial and other studies of treatment options for ARAS. To encourage enrollment, we suggest that the Agency consider aligning reimbursement for this procedure with participation in clinical trials. If providers continue to offer PTA and stenting outside of a clinical trial, patients have little incentive to enroll in a clinical trial and it will be difficult, if not impossible, to obtain strong, scientific data that compares the benefits and risks of this procedure.

If you have any questions or need any additional information, please do not hesitate to contact Susan Bishop, MA, Regulatory Relations Manager, at 202-785-7908 or via email at susan.k.bishop@heart.org.

Sincerely,



Raymond Gibbons, MD, FAHA
President, AHA

[12] See http://effectivehealthcare.ahrq.gov/repFiles/RAS_Executive_Summary.pdf, Pg. 1.

Attachment A

ACC/AHA 2005 Practice Guidelines for the Management of Patients with Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic)

Classification of Recommendations

Class I: Conditions for which there is evidence for and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence

Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analysis.

Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies.

Level of Evidence C: Only consensus opinion of experts, case studies, or standard of care.

VIA ELECTRONIC SUBMISSION

March 28, 2007

Steve Phurrough, M.D., M.P.A.
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services

RE: Percutaneous Transluminal Angioplasty (PTA) and Stenting of the Renal Arteries (CAG-00085R4)

Dear Dr. Phurrough:

The Society for Cardiovascular Angiography and Interventions (SCAI) is a professional association representing over 3,700 invasive and interventional cardiologists. SCAI promotes excellence in cardiac catheterization, angiography, and interventional cardiology through physician education and representation, and quality initiatives to enhance patient care.

The Society for Vascular Medicine and Biology (SVMB) is a professional organization that was founded in 1989 to foster a broad mission. The goals of the Society are to improve the integration of vascular biological advances into medical practice, and to maintain high standards of clinical vascular medicine.

We are responding to the Centers for Medicare and Medicaid Services' request for public comments on percutaneous angioplasty and stenting of the renal arteries (CAG-00085R4).

The recently published multidisciplinary ACC/AHA practice guidelines clearly state that renal artery stent placement is a Class I (conditions for which there is evidence for, or general agreement that a given procedure or treatment is beneficial, useful, and effective) indication for ostial atherosclerotic renal artery stenosis (RAS) lesions that meet the clinical criteria for intervention.[1] We note that this guideline was endorsed by the NIH's National Heart Lung and Blood Institute.

Unique to this discussion, is that surgical treatment is not a common or preferred option for RAS. Surgery has been relegated to patients already undergoing major abdominal surgery, such as abdominal aortic aneurysm repair. Despite this, in many centers, renal stent placement is still preferred to surgery in AAA repair patients to reduce the excess morbidity and mortality that renal surgery adds to these procedures.

It is important to clarify the relatively unique environment that percutaneous renal artery revascularization holds with regard to peripheral arterial disease. As for many well-accepted treatments in medicine, there is honest debate and discussion regarding the most appropriate methods for patient selection for renal artery stent placement. There is uncertainty regarding the overall cardiovascular morbidity and mortality effect of renal revascularization compared to medical therapy being investigated in the CORAL trial. It

should be clear, however, that there is no debate that the current clinical *standard of practice* for renal artery revascularization, in anatomically suitable candidates, is percutaneous stent placement.

INTRODUCTION

Renal artery bypass surgery is a therapy of historic significance only. In 1974, Hunt described lower rates of mortality, stroke, myocardial infarction, and azotemia, and better blood pressure control in surgically revascularized patients than a comparison medical group[2]. Surgery, however, has been associated with significant and unacceptably high peri-operative complications and mortality[3]. Most patients with RAS have lesions in other vascular beds making them higher surgical risk candidates. Thus, percutaneous transluminal renal angioplasty (PTRA) was and is an attractive alternative. Notably, the results of PTRA and surgery are equivalent when compared directly[4]. Thus, renal bypass surgery is only appropriate as an adjunct for patients undergoing open abdominal aortic procedures or for patients who are not suitable anatomical candidates for angioplasty or stenting.

The clinical acceptance of renal stent placement as the standard-of-care for patients with clinical indications for renal artery revascularization has become a major factor retarding enrollment in randomized clinical trials. The NIH funded CORAL trial is an ongoing comparative study that will evaluate the effectiveness of stent revascularization with optimal medical therapy compared to optimal medical therapy alone. We accept that there is ongoing debate about the role for revascularization in many patients with RAS and is supportive of efforts to resolve these issues through research. The evidence supporting our position regarding renal stent revascularization is provided below.

NATURAL HISTORY AND PREVALENCE

While there are excellent prevalence data in specific patient populations (i.e., those with coronary artery disease, aortic aneurysm, peripheral arterial disease), the prevalence of RAS in the general population is not known. In a recent population based study, the prevalence of renovascular disease in a cohort of 834 elderly participants of the Cardiovascular Health Study underwent renal duplex ultrasound [5]. Fifty-seven individuals (6.8%) had anatomic RAS. There was no difference in the prevalence of RAS in whites (6.9%) compared to African Americans (6.7%).

Several series have looked at the prevalence of renovascular disease in patients who have atherosclerotic disease elsewhere. To determine the prevalence of atherosclerotic RAS, Olin et al studied 395 consecutive patients who had undergone arteriography as part of an evaluation for an abdominal aortic aneurysm, aortoiliac occlusive disease, and peripheral arterial disease[6]. In addition, 78 patients had an aortogram performed for suspected RAS. These patients did not have the usual clinical clues to suggest RAS. The prevalence of RAS was approximately 40% in these patients with atherosclerotic disease of other vascular beds. In the 319 patients reported in six different studies 44% of patients had bilateral RAS [7]. Other studies have shown that 22-59% of patients with peripheral arterial disease have significant RAS [8].

In the largest series of screening renal arteriography, 1,235 unselected consecutive patients had both coronary arteriography and abdominal aortography. Thirty percent of patients were found to have some

evidence of RAS and 15% had lesions ≥ 50% diameter stenosis [9]. In a selected population of 297 hypertensive patients referred for coronary arteriography who also had concurrent abdominal aortography during the same procedure, 34% of patients had evidence of RAS, and 19% had atherosclerotic RAS lesions ≥ 50% diameter stenosis [10]. Bilateral atherosclerotic RAS was noted in 19% to 29% of patients with ≥ 50% atherosclerotic RAS.

Natural History of Renal Artery Stenosis: Most natural history studies reported in the literature are retrospective studies. The rates of RAS progression ranged from 36% to 71% [11]. Serial ultrasound studies in patients with RAS confirmed that lesion progression to occlusion only occurred if baseline atherosclerotic RAS was > 60% [12]. A recent randomized trial of hypertensive patients, with lesions ≥ 50%, demonstrated that 16% of the medical treatment group progressed to occlusion at one-year [13].

Scoble et al [14] found that atherosclerotic renovascular disease was the cause of end stage renal disease (ESRD) in 14% of patients starting dialysis therapy. Mailloux and colleagues[15] reviewed the causes of ESRD in 683 patients over a 20-year period of time. Eighty-three patients (12%) had documented RAS as a cause of ESRD. Since these investigators only performed arteriography in patients in whom they highly suspected RAS, it is entirely possible that the true incidence of RAS as a cause of ESRD was seriously underestimated. A recent study reported that 16% of 49 patients starting renal replacement therapy had > 50% bilateral RAS or RAS to a single functioning kidney[16]. RAS should be searched for in every patient starting dialysis if a clear-cut etiology for the ESRD is not known[17-19].

Survival in Renal Artery Disease: In patients with RAS, the risk of cardiovascular morbidity and mortality is substantial. A 6-year cardiovascular-event-free survival of only 53% is associated with the severity of the renal stenosis[20]. Others have suggested that the risk of adverse cardiovascular events is high and occurs in excess of the hypertension severity[21-23]. More recently a significant decrease in 4-year survival was seen in patients with incidental RAS undergoing coronary angiography [24]. Thus, the risk of cardiovascular events appears to be high in RAS and blood pressure control alone may be a poor surrogate for clinical outcomes.

It is not known whether the high cardiovascular event rate in patients with atherosclerotic RAS is attributable to the effects of renal ischemia and subsequent neuroendocrine activation, or is simply a marker for advanced atherosclerosis and cardiovascular risk. However, a biologically plausible link is present between renal ischemia and subsequent events that may be independent of blood pressure. Angiotensin II is implicated in smooth muscle proliferation, plaque rupture, endothelial dysfunction, and inhibiting fibrinolysis[22]. Angiotensin II also promotes medial and cardiac myocyte hypertrophy[25-33]. Importantly, myocardial hypertrophy occurs when Angiotensin II is present even when blood pressure is controlled[34]. Angiotensin II interacts with other peptides like endothelin, TGF-β, and PDGF-β, each of which is implicated in end-organ damage, ventricular hypertrophy, and vascular hypertrophy[23, 33-35]. Excess aldosterone has been related to extracellular matrix and collagen deposition and therefore to myocardial fibrosis[36].

While the mechanism(s) responsible for the relationship between RAS and heart failure is not well characterized, there is little doubt that ventricular hypertrophy, sustained hypertension, activation of the renin-angiotensin and sympathetic nervous systems, and volume retention associated with renal ischemia are likely important contributors. Recent work suggests a relationship between brain natriuretic peptide (BNP) and RAS, with high BNP levels (>80 pg/ml) associated with better outcomes after renal artery intervention[37]. Angiotensin II, endothelin or an insulin-like growth factor, sympathetic activation all may

be involved in the process of ventricular thickening and stiffening[28-31, 35]. Angiotensin has been implicated in the mechanism of cardiac hypertrophy and is known to induce protein synthesis in myocardial cells [32], even when the mean arterial pressure is lowered [34]. Endothelin has also been implicated in cardiac hypertrophy in RAS[33]. Interestingly, the use of endothelin receptor blockers reverses left ventricular hypertrophy in rats with RAS[30, 33].

Remodeling of the wall of the left ventricle and peripheral arteries in response to renovascular hypertension has been noted. In patients with RAS with hypertension, cardiac remodeling permits maintenance of normal cardiac function despite increased left ventricular wall stress resulting from systemic hypertension [38]. Ventricular performance, determined by afterload, chamber size, mass index, and functional shortening or contractility, is often abnormal in people with renovascular hypertension [39, 40].

Congestive heart failure (CHF) is common in patients undergoing renal artery revascularization [41-43] just as RAS is common in patients presenting with CHF [44]. Left ventricular hypertrophy and decreased contractility, risk factors for development of overt heart failure[45], are significantly more common in those with renovascular hypertension than essential hypertension [26, 46] even when matched for age and gender[39] RAS is prevalent in those with CHF, and may be implicated in its cause or severity in a large proportion of patients. In one series of patients over the age of 70 presenting with New York Heart Association Class II-IV heart failure, 34% were found to have stenosis of at least 50% involving at least one renal artery [44].

As discussed above, left ventricular hypertrophy (LVH) is an important risk factor for cardiovascular events and cardiovascular death [47-54]. Regression of LVH is favorable prognostically [52], and left ventricular mass index, a measure of ventricular hypertrophy, has been shown in one study to decrease after renal artery revascularization[55]. When CHF accompanies RAS, renal artery revascularization is often associated with symptomatic improvement[43, 56]. Currently though this may be under-recognized in clinical practice.

The two-year renal survival (percent of patients remaining off dialysis) was 97.3% for patients with unilateral RAS, 82.4% in patients with bilateral RAS and 44.7% in patients with stenosis or occlusion to a solitary functioning kidney[57]. Patients on dialysis have a shortened life expectancy. The average life expectancy in a patient with end-stage renal disease (ESRD) greater than age 65 is only 2.7 years[58]. The survival estimates are even worse if the patient has atherosclerotic renovascular disease as the cause of ESRD. The median survival for patients with renovascular disease was 25 months compared to 55 months with malignant hypertension and 133 months for patients with polycystic kidney disease[15]. For patients on dialysis, the two-year survival with renovascular disease was 56%, five-year survival 18% and ten-year survival only 5%. These data underscores the fact that patients with atherosclerotic RAS who progress to ESRD and require dialysis have extremely high mortality rates.

In addition, the mere presence of RAS, even prior to developing ESRD, portends a poor prognosis. Patient survival decreases as the severity of RAS increases[24] with two-year survival rates of 96% in patients with unilateral RAS, 74% in patients with bilateral RAS and 47% in patients with stenosis or occlusion to a solitary functioning kidney[57]. Dorros and associates[59] demonstrated that as the serum creatinine increases, the survival decreases in patients with atherosclerotic RAS. The three year probability of survival was 92 ± 4% for patients with a serum creatinine <1.4 mg/dL, 74 ± 8% for patients with a serum creatinine of 1.5-1.9 mg/dL and 51 ± 8% for patients with a serum creatinine >2.0 mg/dL.

Long-term survival in 3,987 patients with showed the four year survival was 57% with severe stenosis (≥ 75%) compared to 89% in those subjects with <7 5% stenosis. The negative impact of RAS on survival was not affected by coronary artery revascularization [24]. ???? IS THIS CORRECT? IT DOESN"T SEEM TO SUPPORT COVERAGE.

NON-INVASIVE TESTING

Despite the rapid advances in technology in recent years, the most important component in the diagnosis of RAS (RAS) is a high clinical suspicion. This results in improved accuracy of diagnostic tests, and provides guidance on treatment strategies. The clinical clues suggestive of RAS include: (1) Onset of hypertension <30 years or >55 years of age; (2) Accelerated, resistant, or malignant hypertension; (3) Sudden, unexplained pulmonary edema; (4) Unexplained renal dysfunction, including those patient recently starting dialysis; (5) New or worsening azotemia after administration of an angiotensin converting enzyme inhibitor or angiotensin receptor antagonist; (6) Multivessel coronary artery or peripheral arterial disease; and (7) Unexplained CHF or refractory angina[1].

Nuclear scintigraphy with captopril has also been used as a screening test for RAS. However, the accuracy of this test is suboptimal when there is bilateral RAS or azotemia. When captopril renography was compared to catheter angiography in a clinical practice setting, the sensitivity was only 74% and the specificity was only 59%[60].

Several investigators have demonstrated the validity of renal artery duplex ultrasonography to diagnose RAS. In one prospective series, 29 patients (58 renal arteries) underwent duplex ultrasonography and contrast arteriography. The sensitivity of renal artery duplex ultrasonography was 84%, specificity of 97%, and positive predictive value of 94% for a detection of > 60% stenosis [61]. Utilizing criteria of peak systolic velocity within the renal artery >180 cm/sec, duplex ultrasonography was able to discern between normal and diseased renal arteries with sensitivity of 95% and specificity of 90% [62]. The ratio of peak systolic velocity (PSV) in the area of RAS compared to the PSV within the aorta (Renal to Aortic Ratio (RAR)) of >3.5 predicts the presence of >60% RAS. Using this criterion, renal artery duplex demonstrated a sensitivity of 92%.

In a large prospective series of 102 consecutive patients who underwent both duplex ultrasonography and contrast arteriography within one month of each other, 62 of 63 arteries with < 60% stenosis, 31 of 32 arteries with 60-79% stenosis, and 67 of 69 arteries with 80-99% stenosis were correctly identified by duplex ultrasonography. Occluded renal arteries were correctly identified by ultrasonography in 22 of 23 cases. The overall sensitivity of duplex ultrasonography was 98%; specificity 99%; positive predictive value 99%; and negative predictive value 97%[63]. Limitations of ultrasound imaging of the renal arteries include large body habitus and overlying bowel gas obscuring identification of the renal arteries. Magnetic resonance arteriography (MRA) is a non-invasive diagnostic test to identify RAS. Minimally invasive, requiring only a peripheral intravenous cannula, the results of renal MRA have been very impressive[64]. Correlation with arteriography has varied based on equipment, technique, and the skill of the interpreter[65]. However, approximately 10% of patients cannot undergo MRA due to implanted metal (i.e. permanent pacemakers) or claustrophobia. In patients who have undergone renal revascularization with metallic stents, MRA cannot be used to determine patency of the stent due to signal dropout from the

metal. Finally, recent reports suggest a potentially fatal complication of gadodiamide, in patients with compromised renal function resulting in nephrogenic systemic fibrosis[66].

RENOVASCULAR HYPERTENSION

Blood pressure control is largely mediated through the renin-angiotensin-aldosterone system. Hypoperfusion or hyponatremia within the juxtaglomerular apparatus with the kidney stimulates renin release, which converts angiotensinogen into angiotensin I. Angiotensin I is in turn cleaved by angiotensin converting enzyme (ACE) into angiotensin II. Angiotensin II acts as a potent vasoconstrictor to restore blood pressure, while also stimulating the adrenal gland to release aldosterone. Aldosterone independently acts to increase Na^+ reabsorption within the distal segment of the nephron. This increases plasma sodium concentration resulting in volume expansion, which raises blood pressure. The effects of RAS can be considered both in terms of the direct ischemia on the affected kidney and on the systemic hemodynamic responses that ensue.

One of the major confounders in determining benefit derived from revascularization is a persistent misunderstanding regarding of the role of balloon angioplasty, which is a relatively ineffective tool for treating atherosclerotic aorto-ostial atherosclerosis of the renal artery, the most common etiology of RAS. It has been demonstrated that renal stents yield superior hemodynamic results compared to balloon angioplasty alone[67]. Balloon angioplasty alone yields a suboptimal result in approximately 50% of the atherosclerotic renal artery lesions attempted[68, 69].

Balloon angioplasty was compared to medical therapy in a randomized trial in 49 patients with uncontrolled hypertension and severe RAS[70]. One patient in the medical arm suffered a major event and no patients in the balloon angioplasty suffered a major complication. Treatment failure occurred in seven (27%) of the medical therapy group and in none (0%) of the angioplasty group. At follow-up, diastolic blood pressure was significantly lower in the balloon angioplasty group compared to medical therapy ($P < 0.05$). A British trial randomized 55 patients to renal balloon angioplasty compared to medical therapy. [71] The group with bilateral RAS had better blood pressure improvement after balloon angioplasty compared to medical therapy ($P < 0.05$).

The Dutch DRASTIC trial randomized 106 patients with ≥ 50% RAS artery stenosis by visual estimation, diastolic blood pressure ≥ 95 mmHg, and/or an increase in serum creatinine with an angiotensin converting enzyme (ACE) inhibitor to medical therapy or balloon angioplasty[13]. After three months the balloon angioplasty group's blood pressure was significantly better than baseline ($p < 0.01$), while the medical treatment group was not different from baseline. Twenty-two (44%) medical treatment failures were identified at three months and permitted to crossover to balloon angioplasty. By intention to treat analysis, these crossover patients continued to be counted in the "medical" treatment group, which diluted differences between the groups. At one year, renal artery occlusion was seen in 16% of the medical group and in none (0%) of the balloon angioplasty group. There was a 3-fold greater incidence of worsening renal function in the medical group compared to balloon angioplasty. This trial demonstrated a dramatic benefit for PTA compared to medical therapy for control of blood pressure, number of hypertensive medications required, patency of renal arteries, and preservation of renal function, if crossover patients are counted, as they should have been, as treatment failures. Further, a meta-analysis comparing balloon

angioplasty to medical therapy for blood pressure control also demonstrated superiority for balloon angioplasty[72].

To assess the effects of percutaneous renal artery revascularization, one must separate balloon angioplasty, an inferior technique for treating atherosclerotic RAS, from renal stent placement, a much more reliable method for percutaneous revascularization. There was a dramatic advantage for stents compared to balloon angioplasty with regards to procedural success rate and late restenosis[73]. Unfortunately in this trial, almost one-third of the balloon angioplasty patients received stent therapy, which blurred any differential beneficial effect on hypertension or renal failure in this small series. Two published meta-analyses have also confirmed the technical superiority of renal stent placement compared to balloon angioplasty[74, 75]. The larger meta-analysis demonstrated superior technical results, lower restenosis rates, and greater improvement in hypertension for stent placement than for balloon angioplasty. These results are a major reason that clinicians do not believe that there is clinical "equipoise" for medial treatment.

According to the most recently published ACC/AHA guidelines, percutaneous treatment is reasonable (Class IIa indication) for patients with hemodynamically significant stenosis associated with malignant hypertension, resistant hypertension (three medications one of which is a diuretic), accelerated hypertension, hypertension with an atrophic kidney (≤ 1 cm smaller than the contralateral kidney), and hypertension in a patient intolerant of medications[1].

ISCHEMIC NEPHROPATHY

A common dilemma is the approach to the patient with atherosclerotic RAS and ischemic nephropathy. Factors that seem to identify irreversible dysfunction include severe diffuse intrarenal atherosclerosis, proteinuria > 1 gram / 24 hours (especially in a diabetic patient), unilateral ARAS with serum creatinine > 2.5 mg/dL, renal resistive index > 80, and marked atrophy of the renal cortex, although none of these factors is individually highly predictive of irreversible dysfunction.

In considering the results of percutaneous and surgical revascularization, most studies have classified serum creatinine as improved in 55%, unchanged in 25%, and worse in 20%[73, 76-80]. Some clinicians assess serial changes in reciprocal serum creatinine or calculated creatinine clearance using the Cockroft-Gault formula, which suggest the beneficial effect of renal revascularization on ischemic nephropathy[79-81]. Analysis of the slope of reciprocal creatinine relationship suggests that most patients have stabilization or slower progression of renal dysfunction, and a minority have long-term improvement. Potential explanations for failure of renal revascularization to improve renal function include underlying renal parenchymal disease that persists despite revascularization, revascularization-induced renal atheroembolization, radiocontrast nephropathy, or acute tubular necrosis. Late decline in renal function most often is due to progressive glomerular slerosis and less commonly in- stent restenosis, or bypass graft failure.

In properly selected patients, renal artery revascularization can stabilize or improve renal function. In one study, surgical revascularization resulted in significant improvement in postoperative total- and single-kidney nuclear ??? SPELL OUT spell outGFR[82] . Linear regression models suggested arrest of renal dysfunction manifested by a slower decline in GFR from 3.25% per week before surgery to 0.94% per

week after surgery[83]. In other studies, stenting was associated with preservation of renal size after two years[81]. In a prospective observational study, medical therapy was associated with a decline in single kidney-GFR and total GFR, whereas stenting resulted in significant improvement in single kidney-GFR and total GFR[84]. The most consistent predictor of improvement in renal function is the absence of parenchymal disease prior to intervention[80, 85]. Patients with ischemic nephropathy should be treated before the development of advanced renal failure. The best candidates for revascularization are those with baseline serum creatinine < 2.0 mg/dL, bilateral atherosclerotic RAS, normal renal resistive indices, and no proteinuria. In these patients, renal revascularization is best accomplished by stenting, although surgical revascularization may be considered in patients with concomitant severe aortic aneurysmal or occlusive disease.

According the most recently published ACC/AHA practice guidelines, percutaneous treatment is reasonable (Class IIa) for patients with hemodynamically significant bilateral RAS or RAS and a solitary functioning kidney with progressive chronic kidney disease. Percutaneous treatment may be considered (Class IIb) for patients with RAS and chronic renal insufficiency with unilateral RAS[1].

CARDIAC DESTABILIZATION

The pathogenesis of flash pulmonary edema associated with hypertension was studied in 38 patients with acute and follow-up echocardiography. Left ventricular function was well preserved with normal systolic wall motion in these subjects without evidence of severe mitral regurgitation during any acute episode. It was concluded that acute pulmonary edema was most likely the result of diastolic dysfunction in this group of patients[86]. In patients with renovascular hypertension and renal failure, bilateral RAS and the presence of coronary disease were associated with pulmonary edema [87].

In a series of 48 patients with RAS (> 70% diameter stenosis) and medically refractory hypertension, the chief complaint in 40% (n = 20) was unstable angina pectoris (UAP), and in 60% (n = 28) decompensated CHF (pulmonary edema) [43]. Two-thirds of all patients had bilateral RAS (UAP = 60%, CHF = 72%). All of the UAP patients and 86% of the CHF patients had significant (> 70% diameter stenosis) coronary artery disease.

After renal stent placement there was improvement of at least one angina class in 90% of the unstable angina patients treated. There was also significant improvement in both the systolic and diastolic blood pressure compared to baseline. There was no change in renal function. At six-month follow-up 72% maintained the clinical benefit with a persistent benefit in their angina symptoms. There continued to be a significant improvement in blood pressure control and no significant change in renal function.

The patients (n = 28) with CHF and pulmonary edema had bilateral RAS in 72%. After renal stent placement there was improvement of at least one heart failure class in 86% of the patients treated. There was a significant improvement in both the systolic and diastolic blood pressure compared to baseline. There was no change in renal function. At six month follow-up, 73% maintained the clinical benefit with a persistent improvement in heart failure. There continued to be a significant improvement in blood pressure control and no change in renal function.

Renal artery revascularization removes the stimulus for renin production with normalization of renal perfusion. The withdrawal of renin stimulation reduces angiotensin secretion and aldosterone secretion. The absence of the vasconstrictor effects of angiotensin and the salt and water retaining effects of aldosterone result in clinical benefit. Both afterload (blood pressure) and plasma volume decrease, helping to stabilize the heart failure patient. The reduction in blood pressure (afterload) and preload act to decrease myocardial oxygen consumption which benefits patients with severe coronary artery disease. Renal stent placement also helps these patients by restoring normal blood flow to the kidney resulting in natiuresis (in addition to lowering aldosterone levels) which prevents volume overload. Additionally, once the renal stenosis has been treated, these patients can then receive life-saving angiotensin converting enzyme inhibitor medications without precipitating renal failure.

According the most recently published ACC/AHA guidelines, percutaneous treatment is indicated (Class I) for patients with hemodynamically significant RAS and recurrent, unexplained CHF or sudden, unexplained pulmonary edema. Percutaneous treatment is reasonable (Class IIa) for patients with hemodynamically significant RAS and unstable angina[1].

EMBOLI PROTECTION

Several mechanisms are implicated in post-procedural declines in renal function that occur after renal artery stenting including contrast nephrotoxicity and atheroembolization. This has led to interest in embolic protection devices to capture emboli that might be liberated during stenting. Recent studies suggest that embolic protection was associated with better directional changes in renal function when contrasted against historical controls[88-90]. However, these devices increase procedural complexity and their effectiveness is not established.

In the largest published single center prospective series, 63 patients (83) renal arteries underwent renal artery stenting with embolic protection[91]. All patients had baseline renal dysfunction with an eGFR <60 cc/min (24% had an eGRF <30 cc/min) and evidence of deterioration in renal function for six months prior to intervention. Sixty percent of the filter baskets had gross evidence of macroscopic debris. Six months after intervention, 97% of patients had stabilization or improvement in renal function.

The first multicenter randomized trial of renal artery atheroembolic protection for preservation of renal function during renal artery stenting was very recently presented at the American College of Cardiology 2007 meeting in New Orleans. This study, which evaluated changes in renal function, is the first to suggest that emboli protection devices with antiplatelet therapy improves renal function outcomes in patients undergoing stent revascularization.

COST EFFECTIVENESS

There have been detailed cost-effectiveness analyses of percutaneous renal artery revascularization for renovascular disease in a broad range of patients. In an effort to determine the incremental cost-effectiveness of percutaneous renal artery revascularization with renal artery stent placement, various analyses have compared stenting to medical therapy, intensified medical management with deferred

intervention for unilateral RAS once refractory hypertension or renal insufficiency develops, renal artery balloon angioplasty without stenting, and renal artery bypass surgery. Some analyses have focused on the incremental cost-effectiveness of both diagnosis and treatment of renovascular disease in patients with medication-resistant hypertension comparing CT angiography, MR angiography, radionuclide methods, and conventional angiography.

These cost-effectiveness analyses have been based on best available pooled event rates and meta-analyses from the literature, direct costs derived from Medicare reimbursements and the literature, foreign health ministries, and validated utilities using standard decision-analytic and Markov models by highly reputable health economic and outcomes researchers and centers. Detailed sensitivity analyses have been performed to assess the robustness of the estimated cost-effectiveness ratios reported from the base-case best-estimate analyses.

In the highest quality published US analysis, Axelrod et al. estimated the incremental cost-effectiveness of prophylactic percutaneous stent placement in asymptomatic patients with incidentally discovered significant unilateral renal artery disease at $12,466 (US1999) per quality-adjusted life-year (QALY) saved compared to a strategy of deferred intervention with stent placement only when refractory hypertension or renal insufficiency supervened[92]. The estimated cost-effectiveness only crossed above the $50,000 per QALY threshold in two-way sensitivity analysis at the more extreme range of estimated probabilities. All base case probability ranges were derived from exhaustive literature review and confirmed by an expert consensus panel. Output of the Markov model as patients 'click through the health states' using a lifetime time horizon accurately simulated natural history data. The base case assumed the extreme value for procedural mortality with renal artery stenting at 1%, which is conservative, compared to several modern series and multi-center registries.

In the Netherlands, Nelemans et al. compared eight strategies to diagnose renovascular hypertension followed by treatment with percutaneous angioplasty with stenting for ostial/proximal lesions compared to treatment with medical therapy alone[93]. Cost-effectiveness analysis was performed using a Markov model with a ten year time horizon from the perspective of the health care system including direct medical costs related to diagnostic modalities, renal intervention, complications, follow-up office visits, anti-hypertensive medications, and follow-up events including MI, stroke, and chronic renal failure. The diagnosis with CTA and treatment of renovascular hypertension with stenting had an incremental cost-effectiveness of Dfl 64,700 in 1996 (approximately $37,000 US1996), assuming a pre-test probability of renovascular hypertension of $\geq$ 20%. This prior probability can be estimated clinically based on validated prediction rules/algorithims [94].

Duda et al. compared medical therapy, balloon angioplasty, stenting, and renal bypass surgery in hypertensive patients with RAS based on economic input data and the cost of medical care in Germany [95]. They concluded that stenting was the most cost-effective treatment over a three-year time horizon with cost per event-free (stroke, dialysis, major vascular bleeding, and /or repeat arterial revascularization) patient of 11,663 Euros (approximately $8,745 US2000) per event-free stent patient, 51,752 Euros per event-free medically treated patient, 78,766 per event-free balloon angioplasty patient, and 36,454 Euros per event-free surgical patient. "The accelerated cost-development after balloon dilatation was caused by higher rates of restenosis compared with primary stent implantation" as described above in this letter for the relatively low efficacy of PTA alone for ostial/proximal atherosclerotic disease.

In a more detailed and updated best-estimate probabilities of events employing meta-analysis and meta-regression methods, Hillegass et al. have estimated an incremental cost-effectiveness of $14,117 (US2005) per QALY for routine stenting of ≥ 75% unilateral RAS in hypertensive patients with uncontrolled blood pressure control on three or more medications. The base analysis probability is a 3% absolute decrease in total patient-years of dialysis over the lifetime of the patients in the stent with medical therapy versus medical therapy only cohorts. The result is highly sensitive to reduction in the need for dialysis. For example, at a 4% absolute reduction in total patient-years of dialysis, stenting becomes the dominant strategy with improved cost, survival, and quality-of-life adjusted survival.

Overall, several high quality analyses using best available data and methods from several US and international investigators/centers have concluded that renal artery stenting appears highly cost-effective compared to medical therapy alone in several subsets of patients including hypertensive patients with significant angiographic RAS compared to traditional cost-effectiveness thresholds. The ongoing CORAL trial is collecting additional data to further prospectively address the quality-of-life and cost-effectiveness of renal artery intervention with stenting [96].

INTERVENTIONAL ENVIRONMENT

Renal intervention should be performed by competent and appropriately trained physicians [97], and in facilities that have the necessary imaging equipment, hemodynamic monitoring capabilities, and device inventory to achieve optimal outcomes. Specific minimum facilities requirements include the following:

- High-resolution, digital x-ray imaging systems with the capability of subtraction, magnification, road mapping and orthogonal angulation are necessary. Image storage, retrieval, and archiving capability are necessary. Renal intervention has been performed effectively with image intensifiers of a variety of field sizes, ranging from 9” to 16”, and with both fixed and advanced mobile units. The quality of the image is more important than size of the image intensifier.

- Advanced physiologic monitoring must be available in the interventional suite. This includes real-time physiologic, hemodynamic, and cardiac rhythm monitoring equipment, and support staff who are capable of interpreting the findings and responding appropriately. The ability to measure the activated clotting time (ACT) at the point of care is desirable. If conscious sedation is employed, the ability to measure transcutaneous oxygen saturation is necessary.

- A large and diverse inventory of disposable supplies is critical to a successful renal intervention program. This includes, but is not limited to, an array of guidewires, balloons, stents, and shaped sheaths and/or guide catheters, suited to accommodate most anatomical variations that one might encounter during renal revascularization. Covered stents, coils, snares, and vascular access closure devices should also be available.

- Emergency management equipment and systems must be readily available in the interventional suite, including resuscitation equipment, a defibrillator, vasoactive and antiarrhythmic drugs, and endotracheal intubation capability with anesthesia support is necessary.

- Each institution should have clearly delineated requirements and qualifications for granting privileges in renal intervention. Criteria for credentialing should be consistent with nationally accepted standards [97]. Facilities must also conduct quality reviews and monitor outcomes including assessments of the quality of individual interventionalists, and the safety/quality of the program as a whole. Quality assurance requires ongoing oversight and review of case selection, as well as procedural complications.

CONCLUSION

We recommend that CMS withdraw its plans to develop a new national coverage decision. Renal stenting is a Class 1 indication in the PAD guidelines from the ACC/AHA. Those guidelines were endorsed by the National Institutes of Health's National Heart Lung and Blood Institute. There is no evidence supporting surgical options except in patients undergoing open procedures for other reasons. The available data supports the cost-effectiveness of renal stent placement. Many Medicare Carriers have developed local coverage policies for renal angiography and interventions that seem to be working well. Additionally, we note that after the initial peak increase in renal angiography and stenting that was a response to a national educational awareness initiative, they do not appear to be rapidly growing in volume.

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Sincerely,

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/s/

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March 28, 2007
Electronic Submission
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Re: NCA Tracking Sheet for Percutaneous Transluminal Angioplasty (PTA) and Stenting of the Renal Arteries (CAG-00085R4)

The American College of Radiology (ACR), representing over 32,000 diagnostic radiologists, interventional radiologists, radiation oncologists, nuclear medicine physicians and medical physicists is pleased to submit comments on the NCA Tracking sheet for Percutaneous Transluminal Angioplasty (PTA) and Stenting of the Renal Arteries (CAG-00085R4). The ACR understands and fully endorses the Society of Interventional Radiology's (SIR's) comment letter (see enclosure) with respect to this Tracking sheet.

The ACR feels that percutaneous renal revascularization is beneficial for select patient groups and, therefore, this procedure should be appropriately reimbursed. As listed in the SIR recommendations, the ACR supports the respective indications that benefit the patient health outcome.

Thank you for your thoughtful consideration and opportunity to comment. If you have any questions or would like to further explore the recommendations given, please contact Anita K. Pennington at (800) 227-5463, ext. 4923 or email apennington@acr.org.

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