July 2007 MedCAC Questions

Background

Patients with generalized atherosclerosis and renal artery stenosis (RAS) more often die from cardiovascular causes than renal failure. While physicians speak to patients about expanding narrowed renal arteries and controlling blood pressure (BP), patients desire to live longer, have fewer heart attacks and fewer strokes. In October 2006, the Agency for Healthcare Research and Quality (AHRQ) issued a Comparative Effectiveness Review summarizing the evidence evaluating the management of patients with atherosclerotic RAS. This review found no adequately powered clinical trials exist demonstrating any difference in mortality, cardiovascular event rates or kidney function after re-establishment of renal blood flow. They also found no published studies directly comparing percutaneous transluminal renal angioplasty with stenting (PTRAS) to aggressive medical treatment with currently available drugs, and there was no prospective randomized controlled trial (RCT) directly comparing state-of-the-art percutaneous endovascular therapy, best medical therapy and open surgical renal artery reconstruction (RAR).

However, several ongoing international RCTs are investigating the relative risks and benefits of endovascular and medical treatments for patients with atherosclerotic RAS. They include:

- STAR: "STent placement and blood pressure and lipid-lowering for the prevention of progression of renal dysfunction caused by Atherosclerotic ostial stenosis of the Renal artery" (Netherlands)
    - Primary endpoint: Progressive renal function loss, defined as reduction in estimated creatinine clearance by >20% after 2 years follow-up, with an extended follow-up of 5 years
    - ClinicalTrials.gov Identifier: NCT00150943
    - "Study start: June 2000"; "This study has been completed"
    - Anticipated publication date not known

- RAVE: "Renal Athersosclerotic reVascularization Evaluation" (Canada)
    - Primary endpoint: "Frequency of progression to the composite endpoint, death or dialysis or doubling of creatinine, in patients with ARVD stratified by the renal resistance index"
    - ClinicalTrials.gov Identifier: NCT00127738
    - "Study start: January 2005; Study completion: December 2006"
    - Anticipated publication date not known

- ASTRAL "Angioplasty and STent for Renal Artery Lesions" (U.K.)
    - Primary endpoint: Decline in renal function assessed by slope of the reciprocal creatinine plot against time
    - International Standard RCT Number: ISRCTN59586944
    - Recruitment due to close April 2007
    - Preliminary results not anticipated until mid-2008

- NITER: "Nephropathy Ischemic ThERapy" (Italy)
  - Primary endpoint: Consists of reaching one of the following: death, initiation of dialysis therapy, or either serum creatinine increased >20% or reduction by >20% in estimated creatinine clearance
  - Randomization started January 2003, with "completion expected by January 2007" and "2 years of follow-up with an extended 2 year follow-up"

- CORAL: "Cardiovascular Outcomes in Renal Atherosclerotic Lesions" (U.S., Canada, Australia and New Zealand)
  - Primary endpoint: Event-free survival from CV and renal adverse events, defined as composite of CV or renal death, stroke, MI, hospitalization for CHF, progressive renal insufficiency, or need for permanent renal replacement therapy
  - ClinicalTrials.gov Identifier: NCT00081731
  - "Study start: April 2004; Expected completion: March 2010"; recently expanded to Australia and New Zealand

In view of the uncertainty regarding optimal strategies for the evaluation and management of patients with atherosclerotic RAS, as well as controversy about the risks and benefits of treatment, the Centers for Medicare and Medicaid Services (CMS) internally generated in February 2007 a national coverage analysis to examine the best treatment for patients with atherosclerotic RAS and to develop a national coverage determination for the treatment of RAS. The treatments under consideration include surgery, medical therapy, and percutaneous transluminal renal angioplasty and stenting (PTRA and PTRAS). These interventions have procedural risks with potential for considerable morbidity and mortality in some patients. The most common major complication of percutaneous procedures is acute renal failure, and in addition to contrast-induced nephropathy, dissection, thrombosis, segmental infarction, perforation or bleeding, there are serious safety concerns regarding renal and systemic atheroembolization, especially in patients with concomitant advanced aortoiliac disease. Surgery additionally adds all the risks of a major abdominal procedure.

Two existing FDA approvals for renal stents (P890017/S010 and P020007), indicated for use only after suboptimal or failed PTRA, were based on non-randomized studies with large amounts of missing and/or unpublished post-approval data. The device labeling warnings section for transhepatic biliary stents (K033394), commonly used for renal stenting procedures, includes the limitation that safety and effectiveness have not been established in the vascular system. There are no FDA approved devices for primary stenting of the renal arteries, drug-eluting stenting of the renal arteries, or distal embolic protection in the renal arteries. The focus of this discussion is on currently available devices, drugs and surgical treatments.

Initial Discussion Questions

1. Considering the common incidental nature of atherosclerotic RAS, discuss the:

- Degree of correlation between %RAS and kidney function

- Role of treatment choice based upon the patient's existing medical condition and comorbidities, i.e., renovascular hypertension with or without diabetes, chronic kidney disease, hyperlipidemia, peripheral vascular disease, coronary artery disease or left ventricular abnormalities

2. Discuss the ability to compare studies, perform meta-analyses and draw valid evidence-based conclusions based upon existing published definitions, measurement techniques, and criteria for reporting patient selection, methods and outcomes. Please specifically discuss:

- Definition of "ischemic nephropathy" and measurements of renal function by glomerular filtration rate, serum creatinine concentration and cystatin C

- Definitions for "uncontrolled", "resistant" and "severe" hypertension

- Measurements and uniform thresholds for BP - systolic, diastolic, mean, ambulatory and office BP in elderly Medicare patients

- Imaging methods, uniform thresholds and translesional gradients for "critical", "severe" and "hemodynamically significant" RAS

- Impact of heterogeneous patient presentation, disease progression and limited understanding about the current natural history of atherosclerotic RAS upon appropriate inclusion and exclusion criteria for clinical trials

- Use of intermediate/surrogate outcomes (BP improvement or number of medications) versus hard health outcomes (mortality, decreased MI, stroke or CHF)

- Causal attribution of treatment outcomes to renal artery interventions, in view of variable pre- and post-procedure medications and changing best medical treatment since the introduction of ACEIs, ARBs, statins and new direct renin inhibitor (aliskiren)

- Current state of primary surgical correction and surgical renal artery reconstruction following stenting

- Variable experience of interventionalists plus evolution of stents and embolic protection devices

- Role of an adequately powered RCT evidence-based process versus general agreement or consensus processes

3. For both state-of-the-art PTRA with stenting (PTRAS) utilizing embolic protection and surgical renal artery reconstruction (RAR), please specifically discuss:

- Diagnostic tests or baseline patient characteristics that accurately predict post-treatment renal function outcomes

- Subgroups of Medicare patients with atherosclerotic RAS who clearly and consistently benefit from either PTRAS with embolic protection or surgical RAR

- Risks of complications for patients (particularly the older Medicare population) with progressive renal dysfunction and multiple comorbidities, especially the risk of post-treatment worsening renal function and hastening of dialysis

Voting Questions

For the first three questions, vote not confident (1) to highly confident (5).

In explaining your votes, be specific regarding devices/treatments utilized, patient subgroups, relevant key health outcomes (mortality, cardiovascular event rates and kidney function) and supporting clinical trial(s). Discuss design limitations of studies referenced, and use numbers rather than adjectives such as "uncontrolled", "severe" or "hemodynamically significant".

1. For the treatment of patients with atherosclerotic RAS, how confident are you that the evidence is adequate to draw conclusions about safety and clinical effectiveness of the following renal artery interventions:

a) Surgical renal artery reconstruction (RAR)?
b) PTRA without stent placement?
c) PTRAS with bare metal stents?
d) PTRAS with drug-eluting stents?

2. Based on the evidence presented, how confident are you that the published results apply to:

a) Medicare patients with typical comorbidities?
b) Providers (facilities/physicians) in community practice?

3. Based on the evidence presented for patients with atherosclerotic RAS, how confident are you that compared to aggressive medical treatment alone there are improved key health outcomes attributable to the following co-interventions:

a) Surgical renal artery reconstruction (RAR)?
b) PTRA without stent placement?
c) PTRAS with bare metal stents?
d) PTRAS with drug-eluting stents?

For the following fourth question, vote strongly agree (1) to strongly disagree (5).

4. Based on the evidence presented, should Medicare national coverage of any non-medical treatments for atherosclerotic RAS be limited only to patients enrolled in qualified clinical research studies?

Final Discussion Questions

1. Discuss strengths and weaknesses of the following ongoing international trials, any protocol changes, and in your opinion the anticipated validity of the data and applicability of key health outcomes to Medicare patients with typical comorbidities in community settings for:

- STAR: "STent placement and blood pressure and lipid-lowering for the prevention of progression of renal dysfunction caused by Atherosclerotic ostial stenosis of the Renal artery" (Netherlands)
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2. Discuss practical issues and medical/interventional advances for future RCTs that may be planned or nearly ready to begin, including:

- Role of pre-procedural interspecialty consultations, i.e., between nephrologists, cardiologists, radiologists and surgeons, to optimally inform risk/benefit assessment

- What is known regarding the comparative safety and clinical effectiveness of:

    - Different antihypertensive, lipid-lowering and antiplatelet combinations

    - Different embolic protection devices: proximal occlusive, distal occlusive, filters

    - Post-procedure dual antiplatelet therapy

- Nephroprotective agents, plus prevention strategies for iodinated as well as gadolinium contrast-induced nephropathy

- Long term durability considerations for stents versus surgical renal artery reconstruction

- What is known regarding safety and clinical effectiveness of drug-eluting stents and cutting balloon angioplasty for restenosis

- Disincentives and barriers limiting recruitment and randomization in clinical trials

- Role of potential mandatory registration and publication of trials

- Incentives to promote effective health outcomes research and participation in RCTs