

Effect of renal revascularization on the development of renal dysfunction in atherosclerotic ischemic nephropathy

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ABSTRACT

Chronic kidney disease (CKD) is characterized by a progressive loss of renal function and its main causes are hypertension and *diabetes mellitus*. Among the causes of hypertension is atherosclerotic renal disease (ARD). The development of CKD in patients with ARD appears to be due not only to the involvement of the main renal arteries, but also of the renal microcirculation, which may explain the fact that the success of the procedure does not guarantee an improvement in the progression of CKD. To date there is no evidence of benefit of angioplasty compared to medical treatment alone in patients with ARD. The present paper analyzes the most significant studies on renal outcomes in patients with ARD undergoing revascularization or medical treatment alone.

Keywords: angioplasty; renal insufficiency, chronic; renin-angiotensin system; re-vascular, hypertension.

INTRODUCTION

The main causes of chronic kidney disease (CKD) are *diabetes mellitus* and hypertension.¹ Since the experiments carried out by Goldblatt,² renal artery stenosis (RAS) has been known as a possible cause of hypertension. RAS is also a common yet generally underestimated cause of CKD. Forty percent of the patients aged 40 years and over started on dialysis for undefined causes develop atherosclerotic renal artery stenosis (ARAS).³ Surgical revascularization was the first

treatment for RAS.⁴ Angioplasty has subsequently become the treatment of choice for most patients.

More recently, several randomized controlled studies have challenged the routine use of revascularization to treat patients with ARAS. The mechanisms involved in the inflammation and impairment of the microcirculation may explain the discrepancy between angiographic success and failure to preserve renal function or correct hypertension.⁵ Moreover, revascularization has been associated with serious complications, ranging from renal function deterioration to death. This paper presents a review comprising recent studies on renal revascularization of patients with ARAS.

UNCONTROLLED STUDIES

Ramsay & Waller⁶ wrote a systematic review comprising ten series in which the efficacy and safety of angioplasty for patients with RAS was discussed. Anti-hypertensive drug protocols were unclear, and significant differences were seen in the enrollment criteria and definitions used for blood pressure improvement adopted by the authors. These differences complicate the analysis of the combined results. None of the series included in the review described renal function before and after angioplasty for every patient. Complications were reported for 9.1% of the 691 patients, three of whom died.

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Liao *et al.*⁷ selected 125 patients with ARAS (lumen involvement greater than 70%) diagnosed by CT angiography or MRA treated with angioplasty and stenting. The reasons for prescribing the procedure were hypertension in 63.2% of the cases, renal failure in 5.6%, and hypertension combined with renal failure in 31.2%. Two patients died within seven days of the procedure. Nineteen had complications related to the procedure. The rate of restenosis was 20.8%. Systolic and diastolic blood pressure (BP) levels were significantly lowered and patients were since on fewer antihypertensive drugs. Renal function improved only in patients with a glomerular filtration rate under 60 ml/min and in subjects with bilateral stenosis.

Trani *et al.*⁸ found that elevated levels of inflammatory markers predicted the response to angioplasty. Only patients with higher creatinine and lower CRP levels benefited from the procedure.

No agreement was found between blood pressure levels and restenosis in 40 patients with ARAS offered angioplasty and tested routinely with angiography for one year following the procedure.⁹

Harden *et al.*¹⁰ looked into the data of an uncontrolled prospective series to analyze the progression of renal function in a group of patients with ARAS treated with stenting. Thirty-two patients with unexplained renal function deterioration and angiographic evidence of vascular disease were selected. Twenty-three individuals had serum creatinine at a level high enough to model the slope of inverse creatinine before and after stenting. The main complications were three femoral artery pseudoaneurysms and three episodes of bleeding requiring transfusion. Eleven of the 32 patients had decreases in creatinine levels greater than 20%, including two patients who left dialysis. Eleven other patients presented with stable renal function (variation under 20%) and nine had renal function deterioration. The inverse creatinine slope was attenuated in 18 of 23 patients, showing a reduction in the rate of progression of renal disease.

PROSPECTIVE AND RANDOMIZED TRIALS

The main characteristics of six prospective and randomized trials are shown in Table 1.

EMMA (ESSAI MULTICENTRIQUE MEDICAMENTS VS. ANGIOPLASTIE)

Plouin *et al.*¹¹ carried out a prospective randomized multicenter trial in France to compare between changes in BP levels of groups of individuals undergoing drug therapy (control group) and angioplasty plus drug therapy (angioplasty group) within a period of six months. Patients with unilateral atherosclerotic renal artery stenosis and lumen obstruction greater than 75% were selected. The 26 patients in the control group had their treatment adjusted according to the BP follow-up protocol, while the 23 enrolled in the case group underwent angioplasty, two of whom with stent implantation. Renal function was assessed based on creatinine clearance at baseline and at the end of follow-up. No statistically significant differences were seen between groups. The study did not look into renal outcome or the occurrence of cardiovascular events.

In the angioplasty group, three patients had restenosis and one had renal artery dissection with segmental infarction. BP levels verified in ambulatory blood pressure measurements (ABPM) between randomization and the end of follow-up did not differ between groups. However, BP measurements in the office revealed greater BP reductions in the angioplasty group. Six patients in the angioplasty group and none in the control group were off antihypertensive medications at the end of follow up. The number of doses of antihypertensive drugs in the angioplasty group was also lower than in the control group.

The study, however, did not assess the effectiveness of angioplasty in stabilizing renal function, did not enroll patients with creatinine clearance under 50 ml/min, and included only patients with unilateral ARAS.

SNRASC (SCOTTISH AND NEWCASTLE RENAL ARTERY STENOSIS COLLABORATIVE GROUP)

Webster *et al.*¹² performed a prospective randomized multicenter study in the UK to evaluate the effects of renal artery angioplasty *versus* drug therapy on blood pressure control and progression of CKD in patients with unilateral and bilateral ARAS. One hundred and thirty-five patients with hypertension and ARAS were selected, and 55 were randomized.

TABLE 1 PROSPECTIVE RANDOMIZED TRIALS

	Number of cases	% stenosis	Renal function assessment	Angioplasty with or without stenting	ACEi and statins
EMMA	26 controls 23 cases	> 75% unilateral	SCr CrCl CrCl \geq 50	Angioplasty, two patients stented	ACEi
SNRASCG	30 controls 25 cases	> 50% unilateral or bilateral	SCr Cr < 5.6	Angioplasty	ACEi
DRASTIC	50 controls 56 cases	> 50% unilateral or bilateral	SCr CrCl Cr < 2.3	Angioplasty, two patients stented	ACEi Statins
STAR	76 controls 64 cases	> 50% unilateral or bilateral	SCr CrCl CrCl < 80	Angioplasty, 46 patients stented	ACEi Statins
ASTRAL	403 controls 403 cases	> 50% unilateral or bilateral	Inverse creatinine slope 22% with CrCl < 25	Angioplasty with stenting in 95% of the patients	ACEi (more in the case group) Statins
CORAL	472 controls 459 cases	> 80% unilateral or bilateral Between 60-80% with at least 20 mm Hg systolic pressure gradient	CrCl.	Angioplasty with stenting in 95% of the patients	ARBs Statins

	Exclusion criteria	Primary endpoint	Complications	Conclusion
EMMA	Malignant hypertension stroke, APE, MI within the last six months, DBP > 109 despite treatment	BP at the end of follow-up	Three cases of restenosis, one dissection with segmental infarction	Angioplasty allowed better short-term BP management, but was associated with more complications in patients with unilateral ARAS
SNRASCG	Patients under 40 years; stroke or MI within the last three months	Differences in BP and serum Cr between baseline and six months into follow-up	Eight patients with puncture site bleeding; two referred to RRT	BP was not statistically different after six months. No differences seen in serum creatinine levels
DRASTIC	Cancer, hypertension secondary to other diseases, unstable coronary disease, CHF, pregnancy	SBP and DBP three and 12 months after randomization	Two cases of cholesterol embolism; six cases of hematoma requiring blood transfusion	BP levels in the third and tenth months were not significantly different. In the third month, CrCl was higher in the angioplasty group, but on twelfth month the difference disappeared
STAR	Kidney < 8 cm Renal artery diameter < 4 mm. CrCl < 15 DM with proteinuria > 3 g/24h malignant hypertension	Decrease greater than 20% on CrCl	Two procedure-related deaths; 17% had puncture site hematomas; one patient referred to RRT	No differences on primary endpoint. Groups had similar survival

CONTINUED TABLE 1.

ASTRAL	Need for surgical revascularization; non-atheromatous disease; previous revascularization for renal artery stenosis	Renal function alteration by inverse creatinine slope	38 complications in 31 of the 359 patients offer angioplasty (9%); 19 severe events	No differences seen in renal function progression
CORAL	Need for surgical revascularization; fibromuscular dysplasia; Cr > 4.0; Kidney < 7 cm; stenosis not treatable with one stent	Major cardiovascular or renal event; death for cardiovascular or renal causes; stroke; MI; hospitalization for CHF; deteriorating renal disease; need for permanent RRT	Arterial dissection in 11 patients	Angioplasty with stenting did not offer additional benefits <i>versus</i> optimized drug therapy for patients with ARAS, SH, or CKD

ACEI: Angiotensin-converting enzyme inhibitors; EMMA: Essai Multicentrique Medicaments vs. Angioplasties; Cr: Creatinine; CrCl: Estimated creatinine clearance; Stroke: Cerebrovascular accident; APE: Acute pulmonary edema; MI: Myocardial infarction; DBP: Diastolic blood pressure; BP: Blood pressure; ARAS: Atherosclerotic renal artery stenosis; SNRASC: Scottish and Newcastle Renal Artery Stenosis Collaborative Group; RRT: Renal replacement therapy; DRASTIC: Dutch Renal Artery Stenosis Intervention Cooperative Study Group; SH: Systemic hypertension; CHF: Congestive heart failure; SBP: Systolic blood pressure; STAR: Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and Impaired Renal Function; DM: *Diabetes mellitus*; ASTRAL: Angioplasty and Stenting for Renal Artery Lesions; CORAL: Cardiovascular Outcomes in Renal Atherosclerotic Lesions; ARBs: Angiotensin-receptor blockers.

Participants had diastolic BP persistently greater than 95 mmHg and had been treated with at least two drugs. All patients had their antihypertensive medications adjusted and were not allowed to take angiotensin-converting enzyme (ACE) inhibitors in this stage of the study. Twenty-five patients had angioplasties without stenting and 30 were offered drug therapy alone. Forty angioplasties were carried out. Eight patients had bleeding in the puncture site and two progressed to CKD and required renal replacement therapy (RRT). BP values dropped consistently in all groups. Patients with bilateral ARAS did not have statistically different BP levels *versus* patients on drug therapy six months into follow-up. However, the last set of tests revealed that patients with bilateral stenosis submitted to angioplasty had statistically lower systolic BP levels. Survival was similar in both groups. The combined analysis of the 135 patients showed that systolic and diastolic BP, number of antihypertensive drugs and serum creatinine levels at the end of follow-up were directly influenced by their values after initial adjustment, illustrating the importance of drug therapy.

This study enrolled patients with bilateral ARAS. However, their mean creatinine levels ranged between 1.5 to 2 mg/dL and progression of renal function was not assessed. The individuals in the procedure group were not offered stenting.

DRASTIC (DUTCH RENAL ARTERY STENOSIS INTERVENTION COOPERATIVE STUDY GROUP)

The prospective randomized trial by van Jaarsveld *et al.*¹³ was carried in 26 centers in the Netherlands. One hundred and six patients with RAS were selected (unilateral or bilateral stenosis greater than 50%) to undergo balloon angioplasty without stenting (56 patients) or receive drug therapy alone (50 patients). Arteriography was performed prior to treatment initiation and twelve months into follow-up.

The primary endpoint was systolic and diastolic BP in the third and twelfth months after randomization. Cardiovascular events and mortality were not assessed. As far as complications were concerned, two patients in the angioplasty group and six in the control group had increases greater than 50% in their serum creatinine levels; two in the control group progressed to cholesterol embolism; two in the procedure group and four in the control group required blood transfusions due to bleeding at the puncture site.

In the group offered drug therapy alone, angioplasties were carried out in 14 patients with uncontrolled BP levels after three months of treatment and in eight with progressing ARAS. Systolic and diastolic BP levels in the third and twelfth months were not significantly different between groups. The dose of antihypertensive drugs

prescribed to the patients in the angioplasty group was lower than that of the drug therapy group in the third month, but this difference was not maintained in the twelfth month. Three months into the study, lower levels of serum creatinine were observed in the patients submitted to angioplasty, but in the twelfth month values were similar for both groups.

As 44% of the patients in the control group were allowed to cross over into the angioplasty group in the third month of follow-up, the purpose of the study was changed from a comparison between angioplasty and drug therapy into a comparison between performing angioplasty without a specific indication *versus* angioplasty indicated due to unfavorable clinical response. Re-analysis of the study revealed early intervention was beneficial for patients with bilateral ARAS.¹⁴

STAR (STENT PLACEMENT IN PATIENTS WITH ATHEROSCLEROTIC RENAL ARTERY STENOSIS AND IMPAIRED RENAL FUNCTION)

This study involved ten centers (nine in the Netherlands and one in France).¹⁵ Patients were randomized to undergo renal angioplasty and drug therapy or drug therapy alone. They were followed for two years. Subjects with impaired renal function, renal artery stenosis greater than 50%, aortic atherosclerosis, and stable blood pressure were included.

Seventy-six patients were included in the drug therapy group and were given diuretics, calcium channel blockers, beta-blockers and alpha-blockers, followed by ACE inhibitors, angiotensin receptor blockers (ARBs) and increasing doses of diuretics. Angiography and stenting could be offered as salvage procedures to individuals in the control group with resistant hypertension, malignant hypertension and in cases of pulmonary edema. The same medications were prescribed to the 64 patients submitted to angioplasty. Stents were implanted in the site of ostial stenosis in 46 of them. Seventeen percent of the patients treated with angioplasty had hematomas at the puncture site. Two patients in the angioplasty group died of procedure-related causes and one required renal replacement therapy after repeating an arteriogram.

The primary endpoint was renal function deterioration, defined as a decrease of 20% or more in the estimated glomerular filtration rate. In the procedure group, patients achieving this outcome

underwent imaging tests to rule out restenosis. The groups were not different in terms of renal function, severity and type of stenosis, and imaging test used. Sixteen patients (22%) in the drug therapy group and 10 (16%) in the angioplasty group reached the primary endpoint. Median time to primary endpoint was 10 months in both groups. Event-free survival was not statistically different between groups.

This was the first study in which stents were implanted in most patients undergoing angioplasty. It failed to show the benefits of the procedure over drug therapy. One possible explanation is the prescription of ACEIs/ARBs and statins to patients.

ASTRAL (ANGIOPLASTY AND STENTING FOR RENAL ARTERY LESIONS)

Between 2000 and 2007, 806 patients from 57 hospitals (53 in the UK, three in Australia, and one in New Zealand) were randomized and assessed prospectively.¹⁶ Patients with vascular lumen stenosis greater than 50% in at least one artery were randomized to drug therapy or drug therapy plus angioplasty (95% treated with stenting). The patients were followed for five years. Use of ACE inhibitors was greater at baseline and one year into follow-up among angioplasty patients, but no differences were seen between groups on the mean number of prescribed antihypertensive drugs.

Thirty-eight complications were reported in 31 of the 359 patients (9%) submitted to angioplasty, nineteen of which severe.

The primary endpoint was renal function alteration measured by the slope of the inverse creatinine plot. Secondary endpoints were BP control, time to first renal event, time to major cardiovascular event, and death. Renal events were defined as acute kidney injury, start of dialysis, renal transplantation, nephrectomy, or death from kidney failure.

No significant differences were seen in the renal function of the 317 patients submitted to renal angioplasty *versus* the 379 offered drug therapy alone. No differences were observed in subgroup primary endpoints. Systolic BP levels dropped in both groups, with no statistical differences between them. Survival was not different between groups.

The study confirmed that revascularization by angioplasty offered indiscriminately to patients with ARAS is not beneficial. Nonetheless, it had its limitations: the drug therapy group progressed

quite well when compared to other studies (and that may have impacted the absence of visible benefits from angioplasty) and patients more likely to have benefitted from the procedure were excluded. Thus, more clarity is required on the selection of subgroups that could benefit from revascularization treatments.

CORAL (CARDIOVASCULAR OUTCOMES IN RENAL ATHEROSCLEROTIC LESIONS)

This randomized multicenter trial sponsored by the National Heart, Lung and Blood Institute (NHBL)¹⁷ enrolled 947 patients with ARAS (80% unilateral or bilateral obstruction or 60-80% obstruction and 20 mm Hg of systolic pressure gradient). Renal function assessment was based on the estimated glomerular filtration rate. Ninety-five percent of the 459 patients offered angioplasty were stented. Both groups were prescribed ARBs and statins. Patients with fibromuscular dysplasia, creatinine levels above 4 mg/dL, kidneys measuring less than seven centimeters, or stenosis not treatable with a single stent were excluded.

The primary endpoint was major cardiovascular or renal event, and the main complication was arterial dissection, seen in 11 patients. Patients were followed up for a mean of 43 months. The primary endpoint occurred in 35% of the subjects. A modest but consistent difference between groups was observed in systolic BP ($p = 0.03$) in favor of the procedure group, although without clinical benefit.

SYSTEMATIC REVIEW WITH META-ANALYSIS

In 2009, Nordmann and Logan¹⁸ published a meta-analysis comprising three trials: DRASTIC,¹³ EMMA,¹¹ and SNRASCG.¹² According to these trials, angioplasty had no effect on blood pressure or renal function preservation. The assessment of cardiovascular endpoints also failed to produce satisfactory results.¹⁹

STUDIES IN PROGRESS

The RADAR trial (A randomized, multi-center, prospective study comparing best medical treatment *versus* best medical treatment plus renal artery stenting in patients with hemodynamically relevant atherosclerotic renal artery stenosis)²⁰ will compare renal function progression of patients

offered angioplasty with stenting plus drug therapy *versus* individuals on drug therapy alone. Patients will be followed up for 36 months. The primary endpoint is change in the glomerular filtration rate after 12 months.

LITERATURE ANALYSIS

When Harden *et al.*¹⁰ published their paper, no controlled randomized trials on drug therapy *vs.* angioplasty in patients with CKD secondary to ARAS had been published. Thus, their series became the first evidence of the possible benefits of angioplasty in ARAS patients with deteriorating renal function.

In prospective randomized trials,^{11-13,15-17} the criteria used to define hemodynamically significant stenosis was obstruction greater than 50% of the vascular lumen, except for the EMMA¹¹ (75%) and CORAL trials.¹⁷ The interventions offered were not the same; in the EMMA,¹¹ SNRASCG¹², and DRASTIC¹³ trials, angioplasty was not followed by stenting.

Renal function assessment also varied. Serum creatinine levels were used in the SNRASCG¹² trial, whereas the ASTRAL¹⁶ trial looked at the inverse creatinine slope. Serum creatinine and estimated glomerular filtration rate were used in other trials^{11,13,15,17}. Only two trials^{15,16} enrolled patients with severe CKD.

The lack of evidence to support the benefits of renal revascularization over drug therapy, coupled with the risk of possibly fatal complications,¹⁶ reinforces the need to identify a subgroup of patients who may benefit from angioplasty, despite the risks inherent to the procedure. A series of controlled yet not randomized cases published by Hagemann²¹ revealed that angioplasty should be indicated only for patients with CKD and progressing renal function deterioration. A recent review of the ASTRAL trial supports this idea.²² However, further controlled randomized studies are needed to confirm this hypothesis.

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