Endovascular Management of Atherosclerotic Renal Artery Stenosis: Post-Cardiovascular Outcomes in Renal Atherosclerotic Lesions Era Winner or False Alarm?

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Renal artery stenosis (RAS) is frequently associated with severe comorbidities such as reduced renal perfusion, hypertension, and end-stage renal failure. In approximately 90% of patients, renal artery atherosclerosis is the main cause for RAS, and it is associated with an increased risk for fatal and non-fatal cardiovascular and renal complications. Endovascular management of atherosclerotic RAS (ARAS) has been recently evaluated by several randomized controlled trials that failed to demonstrate benefit of stenting. Furthermore, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions study did not demonstrate any benefit over the revascularization approach. In this review, we summarized the available data from retrospective, prospective and randomized trials on ARAS to provide clinicians with sufficient data in order to produce useful conclusions for everyday clinical practice.

Key Words: Renal artery obstruction, Atherosclerosis, Angioplasty, Stents

INTRODUCTION

Renal artery stenosis (RAS) is defined in general as reduction of lumen's diameter in one or both renal arteries, and it is frequently associated with severe comorbidities such as ischemic nephropathy, secondary hypertension, and end-stage renal failure [1]. In the majority of patients (over 90%), renal artery atherosclerosis (RAA) is the main cause for RAS although fibromuscular dysplasia (FMD), dissection, systemic vasculitis, and post-radiation transplant graft scarring have also been associated with RAS [2-6]. According to hemodynamics, a stenosis is significant only when the luminal stenosis is at least 70%, compared to nearby unaffected vessel or, if between 50% and 70%, when the trans-stenotic peak or mean pressure gradient exceeds 20 mmHg or 10 mmHg, respectively [1] The therapeutic strategies for atherosclerotic RAS (ARAS) include medical therapy, angioplasty±stenting, or bypass surgery. In this review, we summarized the available data from retrospective, prospective and randomized trials on ARAS to provide clinicians with an update for everyday clinical practice.

SEARCH CRITERIA

The MEDLINE/PubMed, Embase and Scopus databases

was searched for publications (including articles published from July 1960 to July 2016) referring to the medical subject "Atherosclerotic Renal Artery Stenosis". Keywords included the terms: "renal artery stenosis"; "atherosclerosis/atherosclerotic"; "hypertension"; "renovascular hypertension"; "secondary hypertension"; "medical treatment"; "renal artery angioplasty"; "renal artery stenting" and "renal artery surgery". The search was conducted both on basis of the MeSH tree and as a text search. Only articles written in English were eligible, and the literature search lasted overall two months (July-August 2016). We sought to review all updates on the subject after the introduction of endovascular surgery in the treatment armamentarium.

CAUSE AND PREVALENCE OF RAS

The main causes of RAS are presented in Table 1. RAS is caused by a heterogeneous group of conditions such as atherosclerosis, FMD, neurofibromatosis, systemic vasculitis, renal artery dissection, post radiation transplant graft scarring and rarely extrinsic compression of the renal artery [1-6]. Atherosclerosis remains the primary cause of flow-limiting lesions of the renal arteries [7]. The involved site of atherosclerotic renal artery is mainly the ostium of the artery and the proximal portion of the vessel, frequently in continuity with atherosclerotic disease of the abdominal aorta. Moreover, these patients suffer from atherosclerosis in multiple vascular beds including coronaries, carotids, abdominal aorta, aortoiliac axis and other peripheral vessels. The prevalence of ARAS in these patients is high and could reach 30% in those who undergo screening renal angiography at the same time of coronography [8-10]. In general population, the prevalence of ARAS is not well studied. Screening renal duplex ultrasonography (DUS) has demonstrated over 60% RAS in 6.8% of the "healthy" Medicare population [11]. Men are more frequently affected whereas no racial differences have been reported in the

Table 1. Causes of renal artery stenosis

Atherosclerosis
Fibromuscular dysplasia
Vasculitis (mainly Takayasu's arteritis) or other collagen
 vascular disease
Neurofibromatosis
Dissection of the renal artery/aorta
Thromboembolic disease
Trauma
Post-transplantation graft stenosis
Renal artery aneurysm
Renal artery coarctation
Extrinsic compression (mass, nutcracker syndrome and others)
Radiation injury

literature [11]. Likewise, ARAS is the primary cause of end-stage renal disease (ESRD) in approximately 10% to15% of patients starting dialysis, and 20% to 25% of elderly patients with creatinine values >2.0 mg/dL [7].

THE RAAS

The Renin Angiotensin-Aldosterone System (RAAS) contributes significantly in the development of renovascular hypertension. Based on Dr. Harry Goldblatt's experimental models, it is well established that RAS leads to hypoperfusion of the juxtaglomerular apparatus, causing the release of renin as well as the activation of angiotensin II and aldosterone [12]. As a result of RAAS activation, peripheral vasoconstriction occurs in order to maintain renal perfusion and glomerular filtration. The increased arterial pressure affects renal function differently, depending on whether ARAS is located on one or both sides. In case of unilateral disease, pressure natriuresis via the non-affected kidney leads to normalization of systemic pressure and intravascular volume although the affected kidney re-stimulates the feedback process due to its decreased perfusion [13]. In the setting of bilateral ARAS (defined as global renal ischemia), pressure natriuresis cannot occur, and thus, blood pressure (BP) elevation and volume retention in order to maintain renal perfusion is observed. The result of this stressful reaction reflects to the elevation of preload and afterload, that could cause myocardial ischemia and heart failure [12].

CLINICAL PRESENTATION AND DIAGNOSIS

ARAS may be observed with clinical syndromes such as renovascular hypertension, ischemic nephropathy and cardiac symptoms including "flash" pulmonary edema [1,14]. Renovascular hypertension is the most frequent cause of secondary hypertension, and it is characterized by uncontrolled values of BP (resistant hypertension). Resistant hypertension is defined as failure to reduce BP values <140 mmHg, after an aggressive medical treatment consisting of ≥3 drugs (ideally including a diuretic drug) [15,16]. Recently, a functional classification of RAS in association with hypertension has been proposed [17]:
 • Grade I: asymptomatic renal stenosis,
 • Grade II: RAS with well-controlled hypertension under medication and normal renal function,
 • Grade III: signs of abnormal renal function, undisciplined hypertension despite the medical therapy or volume overload.
In addition, RAS is a potentially reversible form of renal

insufficiency. If it remains unrecognized, it can lead to ESRD. Favorable factors that do not allow the progress to ESRD include rapid recent increase in serum creatinine concentration, glomerular filtration rate (GFR) decrease, and absence of interstitial fibrosis on kidney biopsy [18]. Recent studies suggest that 11% to 14% of ESRD is the result of chronic ischemic nephropathy from RAA, with different risk factors such as diabetes mellitus and hypertension affecting renal outcomes in such patients [19]. Renovascular disease may also be presented with exacerbations of coronary ischemia and chronic heart failure due to increased vasoconstriction and/or volume overload. The most widely recognized clinical situations are the "flash" pulmonary or Pickering syndrome [20,21].

The gold standard for ARAS diagnosis is conventional renal angiography [22]. However, the measurements of the stenosis degree can be performed with less invasive techniques including DUS (sensitivity 84%, specificity 97%) [23], magnetic resonance angiography (MRA, sensitivity 92%-97%, specificity 73%-93%) [24] and/or computed tomographic angiography (sensitivity 59%-96%, specificity 82%-99%) [25]. DUS also allows monitoring of stent patency in cases with stent deployment. The main disadvantage of DUS is dependency from operator's skills [23]. Hemodynamic data such as elevated blood flow turbulence, trans-stenotic velocities and pressure gradients can be evaluated with MRA, DUS and digital angiography, respectively. In patients with suspected ARAS and decreased renal function, a non-contrast method, such as blood oxygen level dependent-magnetic resonance imaging (BOLD-MRI) technique may be appropriate. The BOLD-MRI technique can detect renal hypoxia induced by ARAS although this technique still remains at an early experimental stage [26].

Recently, Captopril Renal Scans (CRS) have been proposed as screening tests but unfortunately the results were disappointing. In the daily clinical practice, their sensitivity and specificity reach 74% and 59%, respectively [27]. Factors that influence CRS include patient's medication use, hydration status and underlying renal function. CRS may have a role in assessing the hemodynamic severity of a known stenosis, thereby providing physiologic information for possible revascularization assessment. However, the American College of Cardiology/American Heart Association guidelines do not recommend the use of CRS for screening of ARAS yet [7].

TREATMENT OPTIONS

Treatment options for the management of ARAS include medical therapy and revascularization (open/endovascular

Table 2. Main studies evaluating medical or endovascular treatment of RAS

Study	Year	Study design	Inclusion criteria	Sample size	Primary outcomes	Secondary outcomes	Follow-up	Limitations	Results
Weibull et al. [28]	1993	PS	Patients without DM; ≤70 years; HTN (BP ≥160/100 mmHg; unilateral RAA; S-Cr levels <300 mmol/L)	PTRA (n=29)/ OR (n=29)	Restenosis rate; death for PTRA group	NR	3, 12, 24 months	Crossover of 4 patients from PTRA to OR group & crossover of 1 patients from OR to PTRA group	Primary patency 75% (PTRA)/96% in OR group at 24 months; secondary patency 90% & 97% respectively
Bonelli et al. [29]	1995	RS	4 groups: RAA, FMD group, previous renal artery bypass or endarterectomy, and RAS in a solitary kidney	PTRA (n=320)	Technical success; BP hypertension treatment; kidney function; 30-day & long term all-cause mortality	NR	33-55 months	Retrospective study; no control group; small sample in surgery & solitary kidney group; follow-up non standardized	Treatment of HTN & long-term mortality: 0% & 33.3% in solitary kidney group; 8.4% & 14.2% in RAA group; 22% & 1.9% in FMD; 23% & 7.7% in prior operation group; reduced BP & no change in kidney function in all groups; 30-day mortality in RAA group 3.7%

Table 2. Continued

Study	Year	Study design	Inclusion criteria	Sample size	Primary outcomes	Secondary outcomes	Follow-up	Limitations	Results
White et al. [30]	1997	PS	Poorly controlled HTN while receiving medical therapy, in the presence of a significant (>50% diameter stenosis on angiography) renal artery aorto-ostial lesion or restenosis lesion or after a suboptimal balloon angioplasty result.	PTRA+stent (n=100)	Technical success; BP; kidney function; complications restenosis	NR	6 months	No control group; in two thirds of patients evaluated the rate of restenosis	99% angiographic success; reduced BP; no difference in kidney function; 19% restenosis and one major complication
Harden et al. [31]	1997	PS	Patients with haemodynamically significant (>50% diametric narrowing) ostial stenoses; restenosis (>50%) after PTRA; flow limiting dissection or occlusion.	PTRA+stent (n=32)	Kidney function; BP; reduced number of anti-HTN drugs	NR	Median 17 months	No randomized trial; short follow-up; biochemical data available in 72% of patients	DBP was significantly lower after PTRA; anti-HTN drugs were unchanged; renal function improved or stabilised in 69% of patients
Webster et al. (SNRASCG study) [32]	1998	RCT	DBP ≥95 mmHg on ≥2 anti-HTN; angiographic stenosis ≥50%	Medical therapy (n=30)/PTRA+ medical therapy (n=25)	BP and S-Cr at 6 months	Adverse events PTRA-related	3-54 months	44% of eligible were randomized, ACE inhibitors were not allowed.	Statistically significant improvement in SBP for bilateral stenosis with PTRA; similar SBP/DBP reduction for unilateral stenosis; no difference in Cr
Plouin et al. (EMMA study) [33]	1998	RCT	DBP >95 mmHg on 3 occasions and/or on anti-HTN medications; renal stenosis ≥75% without thrombosis or ≥60% with lateralization; functional contralateral kidney without significant stenosis	Medical therapy (n=26)/PTRA (2 stents)+ medical therapy (n=23)	24-hour ambulatory BP	Treatment score; PTRA-related events	6 months	30% declined inclusion; no ACE inhibitor or ARB use	Similar SBP and DBP reduction; smaller number of anti-HTN medications in PTRA group

Table 2. Continued

Study	Year	Study design	Inclusion criteria	Sample size	Primary outcomes	Secondary outcomes	Follow-up	Limitations	Results
van Jaarsveld et al. (DRASTIC) [34]	2000	RCT	Resistant HTN with: DBP ≥95 mmHg on 3 occasions on 2 anti-HTN; increase of Cr ≥0.2 mg/dL after administration of ACE inhibitor; normal or mild CKD with S-Cr ≤2.3 mg/dL, angiogram with ostial or non-ostial lesions ≥50% stenosis	Medical therapy (n=50)/PTRA (2 stents)+ medical therapy (n=56)	BP at 3 and 6 months	Number of anti-HTN drugs; kidney function; adverse events	12 months	Crossover of 22 patients medical therapy to PTRA; 10 patients with stenosis <50%	No difference in BP and kidney function; smaller number of anti-HTN medications in PTRA group; GFR improved at 3 months and similar at 12 months; smaller number of abnormal renal scintigrams in PTRA group
Watson et al. [35]	2000	PS	CKD; bilateral stenosis or unilateral stenosis in SFK	PTRA+stent (n=33)	Slope of S-Cr before and after PTRA	NR	20±11 months	No randomization; not all patients completed the follow-up period; underestimation of restenosis	Mean slope increased after PTRA; SBD & DBP decrease after PTRA; no difference in anti-HTN drugs
Cognet et al. [36]	2001	RS	Absence of progressive renal disease (other than RAS); ARAS >70%; kidney's size >7 cm; GFR <80 mL/min	PTRA±stent (n=99)	10% variation versus baseline in GFR	NR	29±10 months	Retrospective study; pre-renal functional renal failure; overestimation of the beneficial effects of PTRA	No differences between baseline and final GFR in overall population; larger GFR improvement in rapid worsening renal function group than in stable CKD group
Muray et al. [37]	2002	PS	Patients with ARAS >60% and CKD	PTRA (n=59)	Slope of S-Cr before and after PTRA	NR	315±191 days	NR	Renal function improved in 58% and stabilized or worsened in 42% of patient; slope of S-Cr before PTRA associated with a favorable change in progression rate after PTRA
Leertouwer et al. [38]	2002	PS	ARAS ≥50%	PTRA±stent (n=18)	Single-kidney contributions to the total renin secretion, effective plasma flow and the concentrations of 131I-hippuran clearence, and GFR (125I-thalamate clearance).	NR	12 months	Study group small in number; young age of patient; single-kidney measurements were available in only 45% of patients; renal blood flow measurements have been influenced by medications	Vein-to-artery renin ration at treated side decreased; 131I-hippuran & 125I thalamate improvement at treated side & contralaterally

Table 2. Continued

Study	Year	Study design	Inclusion criteria	Sample size	Primary outcomes	Secondary outcomes	Follow-up	Limitations	Results
Coen et al. [39]	2004	PS	CKD; unilateral ARAS	PTRA±stent (n=27)/medical therapy (n=19)	GFR	NR	12 months	Study group small in number; unilateral RAS	Drop in SBP & DBP in stenting group; no GFR differences in the two groups; a significant fall in number of ant-HTN in stenting group; increase in proteinuria in stenting group (P=0.05)
Zeller et al. [40]	2004	PS	ARAS ≥70%	PTRA±stent (n=340)	10% decrease in S-Cr	GFR	60 months	Lack of control group	S-Cr decrease; no difference in GFR; SBP/DBP and mean BP improve after PTRA
Rivolta et al. [41]	2005	PS	CKD	PTRA±stent (n=52)	Slopes of S-Cr before and after stenting	NR	Median 24 months	lack of control group	Improvement in renal function in 15% patients; stable renal function in 59.5% reduction in renal function in 25%
Alhadad et al. [42]	2009	RS	Significant ARAS	PTRA (n=234)	Cure: (DBP <90 & SBP <140 mmHg); improvement: (DBP <90 mmHg and/or SBP <140 mmHg on the same or reduced number of drugs, or reduction in DBP of ≥15 mmHg with the same or reduced number of drugs)	Benefit: cure or improvement	4.1±3.3 years	Retrospective study; no control group	SBP & DBP decrease; decrease in anti-HTN drugs
ASTRAL trial [43]	2009	RCT	Substantial stenosis in ≥1 renal artery; physician uncertain if patient would have definiteclinical benefit	Medical therapy (n=403); PTRA (95% with stent)+ medical therapy (n=403)	Renal function (measured by the reciprocal of the S-Cr level)	BP; time to CV & renal events; mortality	Median 34 months	Only patient whose doctor was uncertain about PTRA; ACE inhibitors or ARB: PTRA 50% vs. medical therapy 43%	No difference in main outcome; DBP worse in PTRA; no difference in othersecondary outcomes

Table 2. Continued

Study	Year	Study design	Inclusion criteria	Sample size	Primary outcomes	Secondary outcomes	Follow-up	Limitations	Results
STAR trial [44]	2009	RCT	≥50% ostial stenosis; GFR <80 mL/min/1.73 m^2; stable BP 1 month prior, <140/90 mmHg	Medical therapy (n=76); PTRA with stent+medical therapy (n=64)	≥20% decrease in clearance Cr	Safety; CV morbidity and mortality	24 months	50% used ACE inhibitors or ARB; only 46 patients assigned to stent had the procedure	Similar progression of renal dysfunction; no difference in therapy-refractory HTN; malignant HTN; or pulmonary edema
Dichtel et al. [45]	2010	RS	ARAS >75%; Moderate to severe CKD (GFR >15 and <60 mL/min/1.73 m^2)	PTRA±stent (n=47)/ medical therapy (n=71)	Change in GFR over the first year after diagnosis/ treatment	ESRD or death	36 months	RS, small number of patients in each arm	No GFR difference between the two groups; no difference in SBP/DBP between the two groups; higher number of anti-HTN drugs in medical arm than in PTRA arm at 1 year
Karla et al. [46]	2010	PS	ARAS >60%; ARAS 50%-60% with post-stenotic dilatation	PTRA±stent (n=561)/ medical therapy (n=347)	Renal improvement (GFR)	BP improvement, death risk	One year	Heterogeneity among groups	No GFR/BP difference in the two groups; GFR increase in stenting group than those without stenting with CKD stage 4 & 5
CORAL trial (2014) [47]	2014	RCT	Severe stenosis evaluated by angiography >80% or 60%-80% with peak systolic gradient ≥20 mmHg; Evaluation by Duplex, MRA or CTA; SBP ≥155 mmHg on ≥2 anti-HTN; CKD with GFR 60 mL/min/1.73 m^2	Medical therapy (n=480); PTRA with stent+medical therapy (n=467)	The occurrence of a major CV or renal event	Death from CV causes & death from renal causes (as separate end points); all cause mortality	Median 43 months	Difficulties in recruitment lead to changes in enrollement criteria during the course of the trial	Simiral renal and CV events; slightly lower SBP in revascularization group

Table 2. Continued

Study	Year	Study design	Inclusion criteria	Sample size	Primary outcomes	Secondary outcomes	Follow-up	Limitations	Results
Ritchie et al. [48]	2014	PS	Unilateral ARAS >50%	PTRA+stent: 32% of patient with flush pulmonary edema (n=37); 28% of patient with declining kidney fuction (n=46); 28% of patient with HTN (n=116); 30% of low-risk patient (n=230) vs. medical therapy	CV events, ESRD, death	NR	3.8 years	Retrospective analysis; non randomized; patient treated with PTRA were younger; small sample in each group	PTRA associated with reduced risk for death only in patient with flash pulmonary edema or declining kidney function & refractory HTN in combination

RAS, renal artery stenosis; PS, prospective study; DM, diabetes mellitus; HTN, hypertension; BP, blood pressure; RAA, renal artery atherosclerosis; S-Cr, serum creatinine; PTRA, percutaneous transluminal renal angioplasty; OR, open repair; NR, not reported; RS, retrospective study; FMD, fibromuscular dysplasia; RCT, randomized controlled trial; DBP, diastolic blood pressure; ACE, angiotensin-converting enzyme; SBP, systolic blood pressure; ARB, angiotensin receptor blocker; DRASTIC, Dutch Renal Artery Stenosis Intervention Cooperative; CKD, chronic kidney disease; GFR, glomerular filtration rate; ARAS, atherosclerotic renal artery stenosis; CV, cardiovascular; ESRD, end-stage renal disease; MRA, magnetic resonance angiography; CTA, computed tomography angiography.

approach) of the renal artery. Table 2 summarizes the main studies referring to medical and endovascular treatment of ARAS [28-48]. Surgical renal artery reconstruction has almost entirely been substituted by endovascular repair due to decreased procedure-related morbidity and improved patient satisfaction [49]. Depending on RAS etiology, the management differs, with various levels of evidence supporting each treatment strategy. For less common causes of RAS such as vasculitis and FMD, immunomodulation and angioplasty has been reported, respectively [50].

1) Medical therapy

Medical therapy has been the cornerstone of management in patients with ARAS and all associated clinical manifestations. Unfortunately, limited comparative data are available between different medical regimens in the literature. Preventive measures including BP control, optimal glucose control, lipid lowering therapy, antiplatelet coverage and life-style modifications (smoking cessation, dietary counseling and physical activity) have been proposed. In the early 1980s, the beneficial effects of angiotensin-converting enzyme (ACE) and the angiotensin receptor blockers (ARBs) were noted. Schwietzer and Oelkers [51] studied the effects of captopril treatment in a small number of patients with uncontrollable severe renovascular hypertension. The authors concluded that combination of captopril and diuretics shows a significantly larger benefit in patients with renovascular disease than in those who suffered from essential hypertension. Subsequently, the role of ARBs was further evaluated in a large population (n=3,750) with renovascular disease where it was found that 53% of patients were receiving ARBs [52]. The results were promising concerning the adverse events (death, myocardial infraction, or stroke) observed in these patients (hazard ratio, 0.7; 95% confidence interval [CI], 0.53-0.9). In addition, ARBs were administered prospectively in 92% of a study population with bilateral stenosis (>60%) or occlusion, and they were well tolerated [53]. Although ACE inhibitors and ARBs have been extensively evaluated for the treatment of patients with renovascular hypertension, no randomized trial comparing these agents to other antihypertensives has been performed to date. ARBs in some patients with bilateral severe ARAS, high-grade ARAS in a solitary kidney, or RAS associated with advanced chronic kidney disease (CKD) can cause acute renal failure; however, they should be carefully monitored and introduced slowly [54-60]. Furthermore, recent studies have verified that long-term use of ARBs is safe and efficient, independently of other parameters [61]. A multicenter, prospective study by Evans

et al. [62] showed that this group of agents maintains BP at low levels and keeps patients with ARAS at treatment goal. As an adjunct or alternative to these drugs, b-blockers and calcium channel blockers (second-line treatment) have been recently proposed for the treatment of renovascular disease as well [7].

Lipid lowering therapy is widely accepted as one of the main treatments for atherosclerotic vascular disease [63]. Recently, a retrospective study has shown that statins were associated with lower progression rate of renal insufficiency and lower overall mortality in a mean follow-up period of 11 years [64]. Few research data on the role of single or dual antiplatelet therapy exist also. In patients of high risk with coronary arftery disease equivalent, the benefit of aspirin in reducing risk of myocardial infraction (MI) is believed to outweigh uncommon bleeding complications. RAA is associated with generalized atherosclerosis in other vascular beds (coronary, carotid artery, and others) and antiplatelet therapy is essential for managing RAA [65,66].

2) Revascularization and endovascular therapy

① Open surgery

Surgical repair of ARAS was the only available revascularization approach before the endovascular era. In an observational series of 500 patients who suffered from ARAS and hypertension [67], 12% of them were cured of their hypertension and 73% were improved. The 30-mortality day in this study reached 7.3% whereas the follow-up was up to 10 years [67]. Novick et al. [68] reported their experience on a modest number of patients, and they demonstrated an improvement in two thirds of them during the follow-up period. Additionally, Dean et al. [69] reported the same results in patients with bilateral occlusive disease and serum creatinine values above 3.0 mg/dL. It was clear that this subgroup of patients had the highest apparent benefit from surgical treatment. Finally, in a recent series presented by Marone et al. [70], 94 patients were treated with aortorenal bypass, extra-anatomic bypass or endarterectomy with satisfying results. Almost one third of these cases had bilateral ARAS, and the mean follow-up was almost 40 months. Almost 72% of patients improved or preserved renal function at the same level, with 17% of them progressing to dialysis postoperatively.

One of the first comparisons of surgical approach and medical therapy came from Hunt et al. [71]. In this study, 214 patients with renovascular hypertension were evaluated, and the results were in favor of the surgical revascularization group (BP control/lower mortality). However, complications (infections, surgery-related bleeding, urinary tract infection and others) of surgery have

been reported as well [46]. Even after failed endovascular approach, open revascularization is safe and feasible for ARAS, with restenosis rates reaching up to 18% [72]. Overall, a significant association between the degree of stenosis and the benefit of revascularization has yet to be determined.

② PTRA

Percutaneous transluminal renal angioplasty (PTRA) is a less invasive approach compared to surgical repair. This technique has gained field in the treatment of RAS due to FMD and it has been combined with stenting in case of ARAS. The only randomized study between PTRA and surgical revascularization has been reported by Weibull et al. [28]. The authors studied the impact of revascularization on primary and secondary patency, improvements in BP and renal failure, and they came to the conclusion that PTRA had similar outcomes compared to surgical revascularization. One of the largest non-controlled studies evaluating the results of renal artery revascularization with PTRA has been published in 1995 [29]. In this retrospective study, 320 patients were divided into 4 groups: RAA (70%), FMD, previous renal artery bypass or endarterectomy and RAS in solitary kidney. All the groups experienced a statistically significant reduction in mean BP and the number of medications used. It is noteworthy that in the group of RAA, 8.4% experienced resolution of hypertension after revascularization with PTRA. However, no significant improvement in serum creatinine level was noted in any group of the procedure. In 1998, a Scottish collaborative performed a randomized comparison of PTRA versus medical treatment for patients with hypertension and RAA (unilateral n=27, bilateral n=28) [32]. The patient's serum creatinine levels were <5.6 mg/dL. The primary and secondary endpoints were the improvement of BP and renal preservation respectively. After intervention and a follow-up of 6 months, the difference between the 2 groups was not statistically significant, but after 54 months follow-up, systolic BP (SBP) was lower in the revascularization group. Moreover, no difference in serum creatinine value was observed between groups at any time of the follow-up. In this trial, the authors concluded that the use of PTRA is useful in hypertensive atherosclerotic RAS only for patients for whom BP could not be managed by medical therapy or for patients whose kidney function was decreased even with medical therapy.

In another randomized controlled trial published in the same year [33], patients were randomized at the time of renal angiography, with the effect on 24-hour ambulatory BP as a primary endpoint, whereas patients with GFR <50 mL/min/1.73 m^2 were excluded. No difference was reported

in the primary endpoint although there a decreased need for antihypertensives was observed in the PTRA group.

In the Dutch Renal Artery Stenosis Intervention Co-operative (DRASTIC) study [34], patients with ARAS (>50% stenosis) and resistant hypertension (diastolic BP [DBP] >95 mmHg despite therapy under 2 antihypertensive medications) were randomly assigned to either angioplasty (n=56) or medical treatment (n=50). Creatinine clearance was higher in PTRA group at 3 months although the same at 12 months, whereas no difference in BP improvement has been noted between the two groups.

In 2002, Muray et al. [37] published their experience on the treatment of ARAS. Fifty nine patients were eligible in the study with CKD (creatinine clearance <50 mL/min). Angiography study was performed in all patients, with 42.5% of them showing bilateral disease. Primary end point was the slope of serum creatinine before and after PTRA. This study revealed renal function improvement in 58% of the patients, and stabilization or worsening of the renal function in 42%. In a similar study by Alhadad et al. [42], 234 patients underwent PTRA for RAA, and primary end point was the slope of DBP (<90 mmHg) or SBP (<140 mmHg). After PTRA, SBP and DBP decreased (P<0.001) and remained lower (P<0.001) despite the reduction of the anti-hypertensive (anti-HTN) drugs.

Regarding pooled data, a limited number of meta-analyses have been published comparing medical therapy and PTRA only. Nordmann et al. [73] included only three trials consisting of 210 patients in their study, and they concluded that a significant although modest incremental improvement in BP rate was observed in the PTRA arm.

③ Stenting
(1) Clinical prospective/retrospective studies: Stent deployment appears to provide a better restenosis-free long-term patency than angioplasty only, while remaining to be less invasive and more appealing than surgery [74]. Since 1990, where stenting appeared as a bailout procedure, it remains until today a first-line revascularization technique for ARAS treatment.

A prospective study evaluating the safety and efficacy of stenting in patients with poorly controlled hypertension and RAS, has been published by White et al. [30]. One hundred patients (67 unilateral RAS/37 bilateral RAS) had undergone stenting due to hypertension and ARAS. The published results from this study included 99% angiographic success, reduced BP, whereas no difference in kidney function has been observed. Likewise, a 19% restenosis rate and one major complication were noted.

Furthermore, Harden et al. [31] assessed 32 patients with unexplained renal deficiency and clinical signs of vascular disease for underlying renovascular disease. All patients had undergone digital angiography whereas renal stent placement was considered in patients with haemodynamically significant (>50% reduction of diameter) ostial stenoses, restenosis (>50%) after PTRA or flow-limiting dissection/occlusion. The study revealed decrease in DBP and renal function improvement or stabilization in 69% of patients after PTRA. Watson et al. [35] studied patients with CKD and bilateral or unilateral stenosis in single functional kidney. Mean slope increased in serum creatinine after PTRA, and reduction in the BP were noted.

In another study by Cognet et al. [36], 99 patients with GFR <80 mL/min who were treated with PTRA, were divided into two arms: those with poorly controlled BP and those with rapidly deteriorating renal function. In the latter group, most patients had either bilateral lesions or located in a solitary kidney. The renal function in this group showed a greater benefit concerning creatinine clearance compared to those with poor BP control and stable CKD [64]. However, in another study of 118 patients with an average baseline GFR of 37 ± 15 mL/min/1.73 m^2, patients treated both with stenting or medical regimens showed a similar decline in GFR, SBP, and DBP values and a significant change in number of drugs prescribed from diagnosis, after 34-months follow-up [45].

Moreover, five other studies with a prospective design were identified in the literature [38-41,46], although only two studies out of them enrolled >100 patients [40,46]. All of these studies reported a significantly fall in serum creatinine values or improvement in GFR levels, and SBP or DBP improvement in stenting group. Finally, the latter study [46] that was the largest in size (n=908), showed that revascularization improved renal function in twice as many patients compared to medical treatment, and it reduced the death risk by 45% in all patients.

(2) Randomized clinical trials (RCTs): Despite the development of stenting technology, no RCT was available in the literature until 2009. In that year, two clinical trials were published, the ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) [43] and the STAR (Stent Placement and Blood Pressure and Lipid-Lowering or the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery) trial [44]. They both were designed to compare kidney endpoints as well as cardiovascular events, BP control, and mortality rates in patients with ARAS treated with either medications or PTRA±stenting.

The ASTRAL trial [43] published in 2009, was the first randomized trial where 806 patients were randomly assigned to PTRA±stent placement plus medical treatment or to medical treatment alone (403 patients in each arm).

The included population was explicitly deemed by the referring physician to have an uncertain benefit from revascularization. Therefore, after a mean follow-up of 34 months, the study did not find any significant difference in any of the endpoints (P=0.06).

The STAR trial [44], also published in 2009, was a randomized multicenter trial (10 European Medical Centers) including a total of 140 participants. Patients were randomly assigned to stent placement and medical treatment (n=64) or to medical therapy only (n=76). Medical treatment included anti-HTN drugs, a statin, and aspirin. Inclusion criteria were GFR <80 mL/min/1.73 m^2 and ARAS ≥50% of the lumen. No difference in primary/secondary endpoint was observed, although the investigators reported a small number of procedure-related complications (3%).

In addition, RADAR trial [75] (a randomized, multicenter, prospective study) was designed in the same year, comparing best medical treatment versus best medical treatment plus renal artery stenting. Two hundred fifty patients were eligible and they were collected from 30 centers in Europe and South America. Primary endpoint was change of GFR over 12 months. Secondary endpoints included technical success, change of renal function, clinical events overall such as renal or cardiac death, stroke, MI, hospitalization or target lesion revascularization, change in average SBP, DBP, change of left ventricular mass index, difference in kidney size, total number, drug name/class, daily dose and change in New York Heart Association (NYHA) classification. Unfortunately, the trial was terminated prematurely.

The largest trial to date to compare survival free of cardiovascular and kidney events in patients with ARAS treated with stenting or medical therapy, CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions), was recently published [47]. In the CORAL trial, 947 patients with ARAS and either systolic hypertension or CKD were randomized into two arms: optimal medical treatment only (ARB, atorvastatin, and antiplatelet, with or without thiazide/amlodipine) or medical treatment plus stent placement. The primary endpoint of the trial was a composite of death from cardiovascular or renal causes, stroke, MI, hospitalization for congestive heart failure, progressive loss of renal function, or need for permanent Renal replacement therapy. There was no difference in the occurrence of primary composite endpoint or any of its individual components between the stent group and medical treatment only group, and no difference in all cause mortality. The only difference was noted in SBP that was modestly lower in the stenting arm compared to the medical treatment only group (95% CI; P=0.03). This difference persisted during the entire follow-up period (31-55 months).

Finally, two other randomized trials have been designed recently although no results have been reported yet. The first study is the Nephropathy Ischemic Therapy (NITER) trial [76], designed to compare patients under medical treatment and patients undergoing PTRAS for ARAS. It includes patients with stable renal failure (GFR ≥30 mL/min) and hypertension, and hemodynamically significant atherosclerotic ostial RAS (≥70%) diagnosed by DUS and confirmed by MRA. The combined primary endpoint includes death or dialysis initiation or reduction by >20% in estimated GFR after 0.5, 1, and 2 years of follow-up, and an extended follow-up until the 4th year. Medical treatment includes antihypertensive, antilipidemic and optimal antiplatelet drugs. The second study is the Medical and Endovascular Treatment of Atherosclerotic Renal Artery Stenosis (METRAS) study [77] that has been designed to compare whether PTRA with stenting is superior or equivalent to optimal medical therapy for preserving GFR in the ischemic kidney as evaluated by 99mTc DTPA (diethylene-triamine-pentaacetate) sequential renal scinti-scan. Secondary objectives of this study include BP reduction, preservation of overall renal function and reduction of target organ damage, prevention of cardiovascular events and quality of life improvement. Inclusion criteria include ARAS affecting the main renal artery or its major branches, either >70% or, if <70, with post-stenotic dilatation.

POST-CORAL ERA

In post-CORAl era, queries of whether the revascularization is beneficial in high-risk patients such as those with rapidly decreasing kidney function and flash pulmonary edema remain still unresolved. A new prospective study [48] tried to give a clear message in this group of patients through its results. A cohort of 467 patients with ARAS ≥50%, were managed by PTRA plus stenting versus medical therapy alone. They were divided in 4 groups according to their presentation symptoms (flash pulmonary edema 7.8%, refractory hypertension 24.3%, rapidly declining kidney function 9.7% and none of these phenotypes 49%). During a mean follow-up of 3.8 years in the medically treated arm, flash pulmonary edema was correlated with increased risk of death (P<0.001), and cardiovascular complications (P<0.001). On the other hand, stenting group was associated with reduced death risk only in flush pulmonary edema subgroup or declining kidney function and refractory HTN in combination.

Several meta-analyses have been published to date in order to shed light to proper ARAS treatment, yielding

similar results. Caielli et al. [78] found that the reduction in DBP was higher at follow-up in patients in the endovascular compared to the medical therapy arm (CI, −0.342 to −0.078; P=0.002), despite a greater reduction in the mean number on anti-HTN drugs (CI, −0.302 to −0.1; P<0.001). Thus, patients with RAA receiving endovascular treatment required a smaller number of anti-HTN drugs at follow-up compared to those medically treated. However, SBP, serum creatinine and cardiovascular events rate did not differ between treatment arms. Kumbhani et al. [79] seem to concur with the aforementioned results in their systematic review as well. Zhu et al. [80] evaluated seven randomized trials, including overall 1,916 patients. The authors found that revascularization treatment led to a significant reduction in the number of anti-HTN drugs although deteriorating renal function, congestive heart failure, or stroke rates showed no significant difference between the two groups. Finally, Riaz et al. [81] (n=2,139) underline in their study that angioplasty with or without stent placement was not superior to medical treatment with respect to any outcome.

CONCLUSION

In general, patients with ARAS will be referred for refractory hypertension, deteriorating renal function, abrupt congestive heart failure, or a combination of these symptoms. Revascularization shows no additional benefit, at least in low-risk and stable ARAS, where optimal medical treatment seems to be the 'golden standard'. However, patients of higher risk, especially those with recurrent flash pulmonary edema or truly resistant hypertension, could benefit from angioplasty or stenting, although there is no definitive evidence and the selection of treatment should take into consideration the potential risks and benefits of the procedure. Finally, evidence suggests that stenting is not detrimental to renal function, through stabiliziation of renal function or delay of renal deterioration.

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