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Renal Artery Stenosis in Patients with Resistant Hypertension: Stent It or Not?

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Abstract After three large neutral trials in which renal artery revascularization failed to reduce cardiovascular and renal morbidity and mortality, renal artery stenting became a therapeutic taboo. However, this is probably unjustified as these trials have important limitations and excluded patients most likely to benefit from revascularization. In particular, patients with severe hypertension were often excluded and resistant hypertension was either poorly described or not conform to the current definition. Effective pharmacological combination treatment can control blood pressure in most patients with renovascular hypertension. However, it may also induce further renal hypoperfusion and thus accelerate progressive loss of renal tissue. Furthermore, case reports of patients with resistant hypertension showing substantial blood pressure improvement after successful revascularization are published over again. To identify those patients who would definitely respond to renal artery stenting, properly designed randomized clinical trials are definitely needed.

Keywords Resistant hypertension · Renal artery stenosis · Angioplasty and stenting · Blood pressure

This article is part of the Topical Collection on *Resistant Hypertension*

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Abbreviations

ACEi	ACE inhibitors
AHA	American Heart Association
ARAD	Atherosclerotic renal artery disease
ARAS	Atherosclerotic renal artery stenosis
ARB	Angiotensin II receptor antagonists
BP	Blood pressure
CKD	Chronic kidney disease
CHF	Congestive heart failure
CI	Confidence interval
CV	Cardiovascular
eGFR	Estimated glomerular filtration rate
ESH/ESC	European Society of Hypertension/ European Society of Cardiology
FMD	Fibromuscular dysplasia
GFR	Glomerular filtration rate
HF	Heart failure
HTN	Hypertension
HR	Hazard ratio
MDRD	Modification of Diet in Renal Disease
MRI	Magnetic resonance imaging
NYHA	New York Heart Association
PTRAS	Percutaneous Transluminal Renal Angioplasty and Stenting
RAAS	Renin-angiotensin-aldosterone system

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RAS	Renal artery stenosis
RCT	Randomized controlled trial
RHTN	Resistant hypertension
RVH	Renovascular hypertension
US	Ultrasound

The authors of this review make the case for revascularization in patients with atherosclerotic renal artery stenosis (ARAS) and resistant hypertension (RHTN) and emphasize the need for well-designed randomized trials to test benefits of stenting in this poorly explored indication. Fibromuscular dysplasia (FMD) will not be covered as all major trials refer to atherosclerotic disease. Furthermore, hypertension (HTN) cure after revascularization is much more common in FMD than in ARAS [1, 2•].

Pathophysiology of Renal Artery Stenosis and Rationale for Revascularization

The prevalence of renovascular hypertension (RVH) is estimated at 5% of all hypertensive persons but varies depending on the screened cohort from <1% in mild to >50% in severe HTN [3]. The most common causes of renal artery stenosis (RAS) are atherosclerotic renal artery disease (ARAD) and FMD in a 9/1 ratio [2•, 3]. The prevalence of ARAS is particularly high in patients with documented atherosclerotic disease (up to 18% in coronary artery disease and 25% in peripheral artery disease), end-stage renal failure (up to 41%), and heart failure (up to 54%) [4]. The prevalence of renal FMD varies between <1 to 6% depending on the cohort studied [5], but for aforementioned reasons will not be discussed further.

Progressive atherosclerotic stenosis of the renal artery leads to hypoperfusion of the juxtaglomerular apparatus, which in its turn stimulates the renin-angiotensin-aldosterone system (RAAS) and subsequently increases sympathetic nerve activity, synthesis of intrarenal prostaglandin, aldosterone, and nitric oxide, and decreases renal sodium excretion, resulting in vasoconstriction and secondly in sodium and water retention, causing HTN [6]. On the long run, impaired renal blood flow leads to rarefaction of post-stenotic distal arterioles, renal fibrosis, kidney atrophy, and decreased glomerular filtration rate (GFR) [7]. Furthermore, in unilateral disease, the non-stenotic contralateral kidney may be exposed to higher pressures and blood flows, resulting in hypertensive arteriolosclerosis [8•].

Notably, however, not every RAS is responsible for an elevation in blood pressure (BP). Since renal hypoperfusion is necessary for the chain of events described above, BP elevation depends on the degree of the lumen reduction [9]. Only a critical degree of arterial stenosis produces kidney ischemia sufficient to activate this hormonal system. This implies that the diagnosis of RVH is based a priori on clinical and radiological arguments and can only be confirmed retrospectively when BP is lower than it was before the intervention [10].

Revascularization of Stenotic Renal Arteries Did Not Meet Its Expectations in Randomized Controlled Trials

Until a recent past, the increasing incidence of chronic kidney disease (CKD) due to ARAD, amplified by uncontrolled BP, the associated higher risk of cardiovascular (CV) disease and mortality, and the wide availability of endovascular revascularization techniques have encouraged widespread use of Percutaneous Transluminal Renal Angioplasty and Stenting (PTRAS) in hypertensive patients with ARAS [11]. Renal revascularization for RAS was anticipated to restore blood flow, improve BP and kidney function, according to the pathophysiology of the Goldblatt kidney [12]. Actually, this is the case for RAS due to FMD, with a probability of HTN cure depending on age and duration of HTN [1]. For ARAS lesions, the clinical response to revascularization is much less predictable. Despite decades of expertise in treating RAS, uncertainty still exists whether, besides maximal medical therapy, revascularization is warranted or not [13]. While observational and not randomized controlled studies often showed a significant reduction in BP, and/or in the number of antihypertensive drugs, and/or in serum creatinine after PTRAS, the randomized controlled trials (RCT) were less convincing (Tables 1, 2, and 3) [10, 14–16]. The meta-analysis of Caielli et al. included seven studies comprising a total of 2155 patients (1741 at follow-up). Compared with baseline, diastolic BP fell more at follow-up in patients in the endovascular than in the medical treatment arm (standard difference in means −0.21, 95% confidence interval (CI) −0.342 to −0.078, $p = 0.002$) despite a larger reduction in the mean number of antihypertensive drugs (standard difference in means −0.201, 95% CI −0.302 to −0.1, $p < 0.001$). However, these changes were of little clinical relevance. Follow-up changes of systolic BP, serum creatinine, and incident CV event rates did not differ between treatment arms (Figs. 1 and 2) [14].

These disappointing results may be partly explained by the complexity of interactions between the RAAS, oxidative stress and inflammation, with accumulation of downstream irreversible cortical damage via oxidative stress injury, vascular rarefication, and the recruitment of profibrotic mediators [17•, 18••, 19]. However, at least in some subgroups of patients, the jury is still out. Indeed, all randomized studies of renal artery revascularization have been criticized on grounds of inadequate number of participants, non-standardized inclusion criteria (e.g., in ASTRAL, no clear definition of uncontrolled/refractory HTN was given), inadequate selection of patients (exclusion of "high-risk" patients, wide range of kidney function between 15 and 80 mL/min (see Table 1)), inclusion of patients with mild RAS or poor assessment of stenosis severity (see Table 1), patient

Table 1 Prospective, randomized, clinical trials of balloon angioplasty, with and without stenting, versus medical therapy in atherosclerotic renal artery stenosis

Study/author	Methods	Inclusion criteria HTN requirement	Primary and secondary endpoints	Participants	Results
PTA versus medical therapy					
EMMA Plouin et al., 1998 [60]	Multicenter RCT No blinding of intervention Standardized medical treatment FU: 6 months	UL-RAS ≥75% or ≥60% with positive lateralization test[a], **DBP > 95 mmHg or receiving antihypertensive treatment,** eCrCl (C&G) >50 ml/min Exclusion: malignant HTN	Mean 24-h ABP Number and DDD of antihypertensive drugs, creatinine clearance, Rate of occluded arteries Complications	N, 49 Mean age: 59 years (<75 years) 26% women Mean baseline stenosis: NR 0% BL RAS Mean baseline 24-h daytime BP: **150/90 mmHg** Mean baseline n° drugs (DDD): 1.33 Mean baseline eCrCl: 68 mL/min	No significant difference in ambulatory BP. PTA: fewer antihypertensive drugs (1.0 vs 1.78, $p < 0.01$), higher complication rate 27% Crossover 8.7% Stenting Important exclusion criteria: - **Malignant HT** - APE - DBP > 109 mmHg
SNRASCG Webster et al., 1998 [75]	Multicenter RCT No blinding of intervention Standardized medical treatment FU: 6 months	UL or BL-RAS ≥50% stenosis, **DBP ≥ 95 mmHg on ≥ 2 antihypertensive drugs** serum creatinine <5.65 mg/dl	Office BP Serum creatinine Number antihypertensive drugs, Complications	N, 55 Mean age: 61 years (40–75 years) 42% women Mean baseline stenosis: - 50.9% BL RAS Mean baseline BP: **178/94 mmHg** Mean baseline n° drugs: 2.6 Mean baseline eGFR: -	PTA: significant BP reduction only if BL-RAS; no significant difference in CV events or renal function 20% participants assigned to PTA had a surgery.
DRASTIC Van Jaarsveld et al., 2000 [24]	Multicenter RCT No blinding of intervention FU: 12 months	UL or BL-RAS ≥50% stenosis, **DBP ≥ 95 mmHg on ≥ 2 antihypertensive drugs** or >0.2 mg/dl increase in serum creatinine with ACEI, serum creatinine ≤2.3 mg/dl (kidney length ≥ 8 cm)	Mean office BP Number and DDD of antihypertensive drugs Serum creatinine Restenosis Complications	N, 106 Mean age: 60 years (18–75 years) 39% women Mean baseline stenosis: 76% 22.6% BL RAS Mean baseline BP: **179/104 mmHg** Mean baseline n° drugs: 2.0 Mean baseline CrCl: 67 ml/min	No significant difference in systolic and diastolic BP PTA: fewer antihypertensive drugs (1.9 vs 2.4, $p < 0.01$) 44% participants assigned to medical therapy underwent revascularization at 3 months if DBP >95 mmHg despite ≥3 antihypertensive drugs Only 3.6% stenting
PTA with stenting versus medical therapy					
STAR Bax et al., 2009 [61]	Multicenter RCT No blinding of intervention FU: 24 months	Ostial UL or BL AS-RAS ≥50% and C&G eCrCl <80 ml/min/1.7 m^2 but ≥15 ml/min (kidney length ≥ 8 cm) **Stable BP < 140/90 mmHg for 1 month prior to randomization**	Worsening of renal function (>20% decline in eCrCl with C&G formula) Office BP Incidence of refractory or malignant HTN Pulmonary edema CV morbidity, CV mortality, total mortality	N, 140 Mean age: 66.5 years 55% women Mean baseline stenosis: NR 48% BL RAS Mean baseline BP: **162/82 mmHg** Mean baseline n° drugs: 2.9 Mean baseline eCrCl: 45 ml/min/1.73 m^2	No significant difference in renal function, BP, CV mortality and morbidity 28% participants allocated to PTA did not undergo revascularization, mainly due to minimal stenosis 1.3% crossover Important exclusion criteria: - **Malignant HTN**
ASTRAL Wheatley et al., 2009 [62]	Multicenter RCT No blinding of intervention	**Uncontrolled/ refractory hypertension** (no clear		N, 806	

Table 1 (continued)

Study/author	Methods	Inclusion criteria HTN requirement	Primary and secondary endpoints	Participants	Results
	Medical treatment was not standardized Non-standardized imaging - 42% <70% - 58% ≥70% Median FU: 34 months	definition) or unexplained renal dysfunction with UL or BL AS-RAS Physician uncertain of clinical benefit	Renal outcome (reciprocal of serum creatinine) Office BP Time to renal & major CV events & mortality Complications	Mean age: 70.5 years (42–88 years) 37% women Mean baseline stenosis: 76% 53.5% BL RAS Mean baseline BP: **150/76 mmHg** Mean baseline n° drugs: 2.8 Mean baseline eGFR: 40 ml/min	No significant difference in renal function, BP, CV events and mortality 17% participants, allocated to PTA, did not undergo revascularization 6% crossover Important exclusion criteria: - Need of surgery or high **revascularization probability** in 6 months
RASCAD Marcantoni et al., 2012 [76]	Single-center RCT No blinding of intervention Standardized medical treatment FU: 1 years	Ischemic heart disease RAS >50 - ≤80% **No HTN requirement**	Change in LVMi BP control Kidney function CV events	N, 84 Mean age: 69 years Mean baseline stenosis: 59% 7% BL RAS Mean baseline BP: **132/73 mmHg** Mean baseline n° drugs: 2.0 Mean baseline eGFR: 68 ml/min/1.73 m^2	No effect on LVMi Similar significant BP decrease
CORAL Cooper et al., 2014 [63]	Multicenter RCT No blinding of intervention Standardized medical treatment Median FU: 43 months	UL or BL AS-RAS >80% or >60% with >20 mmHg systolic pressure gradient and **SBP > 155 mmHg with ≥ 2 antihypertensive drugs** and/or eGFR <60 ml/min/1.73 m^2 (MDRD) Kidney length > 7 cm, serum creatinine ≤4 mg/dl	Composite of adverse fatal and non-fatal CV & renal events Individual components of PEP All-cause mortality SBP Restenosis Renal resistance index QOL Cost-effectiveness	N, 947 Mean age: 69 years (≥18 years) 50% women Mean baseline stenosis: 67% 20% BL RAS Mean baseline BP: **150/− mmHg** Mean baseline n° drugs: 2.1 Mean baseline eGFR:58 ml/min/1.73 m^2	No significant difference in primary composite endpoint, any of individual components of PEP, or all-cause mortality Almost 17% of participants either withdrew or were lost to FU 5.4% participants, allocated to PTA, did not undergo revascularization 4% participants allocated to medical therapy crossed over Possibly underpowered (1080 participants were required) Important exclusion criteria: - **DBP ≥ 120 mmHg and/or SBP ≥ 200 mmHg** - Heart failure
PTA with stenting versus medical therapy (Not fully published)					
NITER Scarpioni et al., 2009 [77]	RCT FU: 43 months	UL or BL AS-RAS ≥70%; serum creatinine ≤3 mg/dl and/or eGFR ≥30 ml/min/1.73 m^2 (MDRD); kidney length ≥ 8 cm;	Death, Need for RRT, Reduction by 20% in eGFR BP Number antihypertensive drugs Complications	52 patients Mean age: 72 years (45–80 years 40% women Mean baseline stenosis: - 51.5% BL RAS Baseline BP: 149/79 mmHg	Important exclusion criteria: - Heart failure

Table 1 (continued)

Study/author	Methods	Inclusion criteria HTN requirement	Primary and secondary endpoints	Participants	Results
		BP ≤ 150/90 mmHg with < 4 antihypertensive drugs		Baseline n° drugs: 3.3 Mean baseline eGFR: -	
RADAR Zeller et al., 2013 [78, 79]	Multicenter RCT FU 32 months	UL or BL AS-RAS ≥70% eGFR >10 ml/min/1.73 m^2 (MDRD) **Hypertension: BP ≥ 140/90 mmHg** Kidney length ≥ 7 cm	Change in eGFR after 12 months 24-h ABP	N, 67 Mean age: 67 years (≥18 years) 33% women Mean baseline stenosis: NR % BL RAS: NR Mean baseline BP: **150/− mmHg** Mean 24-h BP: **141/− mmHg** Mean baseline n° drugs: 2 Mean baseline eGFR: -	No significant difference in renal outcome. Study was prematurely terminated (reason not mentioned)
Ongoing trials: PTA with stenting and standardized optimized medical treatment versus standardized optimized medical treatment					
RAVE Tobe et al., 2007 [80]	Single-center RCT (pilot) Started 2007	RAS and indication for revascularization*: **BP > 140/90 mmHg despite ≥ 3 antihypertensive drugs**	Composite endpoint, death or dialysis or doubling of serum creatinine CV disease BP Antihypertensive drugs	20 patients Age ≥ 55 years	*Stenting is performed at the discretion of the angiographer
METRAS Rossi et al., 2012 [81]	Multicenter RCT No blinding of intervention FU: 60 months planned Started 2012	AS-RAS >70% and resistance index (RI) <0.55, and **HTN**	Change in eGFR BP Need for RRT CV events Quality of life	Estimated enrolment n°:120 Age > 18 years	
ANDORRA Azzizi et al., 2015 [71]	Multicenter RCT FU: 12 months Started Sept. 2015	**Resistant hypertension (daytime SBP ≥ 135 or DBP ≥ 85 mmHg) on ≥ 3 antihypertensive drugs** and UL or BL-AS-RAS ≥60% Kidney length ≥ 7 cm; eGFR ≥20 ml/min	Mean change in diurnal systolic BP (24-h ABPM)	Estimated enrolment n°: 140 Age: 40–80 years	

ABP ambulatory BP, *ABPM* ABP monitoring, *APE* acute pulmonary edema, *AS-RAS* atherosclerotic renal artery stenosis, *BL* bilateral, *BP* blood pressure, *C&G* Cockroft and Gault, *CrCl* creatinine clearance, *CV* cardiovascular, *DBP* diastolic BP, *DDD* defined daily dose, *eCrCl* estimated CrCl, *eGFR* estimated GFR, *FU* follow-up, *GFR* glomerular filtration rate, *HTN* hypertension, *LVMi* left ventricular mass index, *MDRD* modification of diet in renal disease, *NR* not reported, *N°* number, *PEP* primary endpoint, *PTA* percutaneous transluminal angioplasty, *QOL* quality of life, *RAS* renal artery stenosis, *RCT* randomized controlled trial, *RRT* renal replacement therapy, *SBP* systolic BP, *UL* unilateral

[a] Intravenous pyelography, renal scintigraphy, or renal vein renin concentration performed according to the usual practice of each center

BP criteria are shown in bold

Table 2 Non-randomized, comparative studies of balloon angioplasty with stenting, versus medical therapy in atherosclerotic renal artery stenosis

Study/Author Enrolment dates	Methods	Inclusion criteria HTN requirement	Primary & secondary endpoints	Participants	Results
Arthurs et al, 2007 [83] 2001–2005	Retrospective Mean FU: 2,9 y Decision to stent: multidisciplinary discussion	Patients referred by nephrologist or internist because of **HTN treated with multiple drugs** or worsening kidney function RAS (US) ≥60 %	BP N° of antihypertensive drugs Kidney function (Reciprocal sCr)	N, 40 Mean age: - 72 y (stent; n, 18) - 67 y (medical; n, 22) Mean stenosis: NR BL RAS: 57.5 % Mean BP - **162/75 mmHg** (stent) - 142*/73 mmHg (medical) Mean n° drugs - 3.5 (stent) - 4.0 (medical) Mean serum creatinine: - 1.5 mg/dl (stent) - 1.0 mg/dl* (medical) *p <0.05	No effect on BP The rate of kidney function decline improved from -0.08 mg/dl/ month to 0.00 mg/dl/ month (p <0.05) after intervention. Patients with baseline CKD (sCr ≥1.5 mg/dl) experienced the greatest benefit from RAS.
Cianci et al, 2011 [84] 2004–2009	Prospective FU: 1 y	RAS ≥70 % **Uncontrolled HTN** and CKD	Kidney function	N, 93 Mean age: 64 y Mean % stenosis : NR BL RAS : 28 % Mean BP: - **160/86 mmHg** (stent; n, 53 ; RAS ≥70 %) - 155/83 mmHg (medical; n, 40 ; RAS ≥50 %) Mean n° drugs: NR	No difference in kidney function or BP
Dichtel et al, 2010[85] 1999–2007	Retrospective FU: 34 months Decision to stent: left to individual clinician	RAS >75 % (MRI) + CKD (eGFR 15 – 60 ml/min/m^2) **BP criteria : NR**	Change in eGFR (MDRD) after the first year	N, 118 Mean age: 73 y % Male: - 100 % (stent; n, 47) - 96 % (medical; n, 71) Mean stenosis: NR BL RAS: - 43 % (stent) - 59 % (medical) Mean eGFR: 37 ml/min/m^2 Mean BP - **145/75 mmHg** (stent) - 141/70* mmHg (medical) Mean n° drugs (DDD): - 3.87 (stent) - 4.67 (medical) *p <0.03	No significant differences
Hanzel et al, 2005[86] NR	Prospective, multicentre Mean FU: 21 months Decision to stent: reserved for patients with TOD	ARAS≥70 % (angiography) and serum creatinine ≤2 mg/dl) **BP criteria : NR**	Stenotic kidney GFR BP Kidney function MACE	N, 66 Mean age: - 66 y (stent; n, 26) - 70 y (medical; n, 40) Mean stenosis: NR BL RAS : - 19 % (stent)	No sign. difference in BP NS decrease of n° drugs (2.7) in stent group GFR improved

Table 2 (continued)

Study/Author Enrolment dates	Methods	Inclusion criteria HTN requirement	Primary & secondary endpoints	Participants	Results
				- 18 % (medical) Mean BP - **162/82 mmHg** (stent; n, 26) - 154/77 mmHg (medical; n, 40) Mean n° drugs: - 3.1 (stent) - 2.2 (medical)* *P = 0.002	
Kalra et al, 2010[87] 1995-2007	Retrospective analysis – prospective database of two different centers (UK and Germany) with different policies FU 1 y	UK: RAS ≥60 % or 50–60 % and post stenotic dilatation (MR or CT) Germ: Duplex US criteria UK: revascularization if FPE or **refractory HTN** (not specified); n, 54 or part of ASTRAL trial; n, 35 G: **HTN criteria WHO grade ≥1**	GFR BP (24-h ABPM)	N, 908 % Male:62 % (stent) 72 % (medical) Mean stenosis: NR BL RAS : NR Mean eGFR: 35 ml/min/m^2 Mean BP - **144/78 mmHg** (stent G; n, 472; mean age, 67.4 y) - **157/81 mmHg** (stent UK; n, 89; mean age, 68.9 y) - 156/80 mmHg (medical UK; n, 347; mean age, 71 y) N° drugs: NR	No difference in BP GFR improved in CKD 4 –5
Kane et al, 2010 [33] NR	Retrospective FU 33 months Decision to stent: either **accelerated or medically resistant HTN** or presumed ischaemic nephropathy in the setting of significant bilateral RAS or stenosis to a solitary kidney	Heart failure and RAS >70 % or SPG >10 mmHg CKD 3–5 (non-dialysis dependent)	Renal and CV outcomes	N, 100 54 % Male Mean age: 76 y Mean stenosis: NR BL RAS :53 % (stent) % (medical) Mean serum creatinine: 2.97 mg/dl Mean BP - **154/- mmHg** (stent; n, 50) - **148/- mmHg** (medical; n, 50) N° drugs:3.6 (stent) 3.5 (medical)	Sign. better BP control Sign. fewer antihypertensive drugs No difference in the rate of kidney function decline
Ritchie et al, 2014[37] 1995–2011	Single-centre prospective cohort study; retrospectively analysed. Median FU 3.8 y Different subgroups: low risk patients (n, 237), FPE (n, 37), Rapidly Declining Kidney Function (n, 46), Refractory HTN (ESH definition; n, 116)	RAS ≥50 % **Refractory HTN** according ESH/ESC guidelines, or FPE, or rapidly declining kidney function	Death, CV event, ESKD	N, 467 Mean age: - 67.9 y (stent) - 71.0 y (medical) * Mean RAS: - 60 % (stent) - 51 % (medical)** Mean n° drugs: - 2.8 (stent) - 2.5 (medical) Mean BP - **163/83*** mmHg** (stent; n, 127) - 155**/79 mmHg (medical; n, 340) *p <0.001; **= 0.01; ***= 0.03	In patients with refractory HTN: - Greater reduction in diastolic BP - No differences in risk of death or ESKD Improved clinical outcomes in FPE or in combined rapidly declining kidney function and refractory HTN

Table 2 (continued)

Study/Author Enrolment dates	Methods	Inclusion criteria HTN requirement	Primary & secondary endpoints	Participants	Results
				In refractory HTN: Mean age: - 70.5 y (stent) - 68 y (medical) Mean BP - **175/87** mmHg** (stent; n, 33) - 165/79 mmHg (medical; n, 83) Mean n° drugs: - 3.6 (stent) - 3.5 (medical)	
Sofroniadou et al, 2012 [88] 1997–2003	Prospective Mean FU 88.9 months Indication for screening: - AKI after RASB - Refractory HTN - Asymmetrical kidney size or function	Indication for stenting: - RAS >70 % to unique kidney - AKI - FPE - **RHTN**	Safety of RASB BP Kidney function	N, 36 Mean age:68 y (stent) 72 y (medical) % Male:58 % (stent) 90 % (medical) Mean % stenosis: - 71 % (stent) - 31–53 % (medical) BL RAS :77 % (stent) 0 % (medical) Mean BP - **177/90 mmHg** (stent; n, 26) - 147*/77** mmHg (medical; n, 10) Mean n° drugs: - 1.7 (stent) - 1.8 (medical) *p <0.04 **p = 0.05	No difference in ESKD or death Sign. decrease in BP Sign. higher BP in stent group
Vassallo et al, 2016 [89] 1986–2014	Single-centre prospective cohort study Analysed retrospectively Four groups: - 1: 1986–2000 (n, 265) - 2: 2001–2004 (n, 235) - 3: 2004–2009 (n, 287) - 4: 2009–2014 (n, 85) Median FU: 54.9 months		Death, CV event, ESKD eGFR	N, 872 Mean BP - Group 1: 160/85 mmHg - Group 2: 147/80 mmHg - Group 3: 147/75 mmHg - Group 4: 158/72 mmHg - ≥3 antihypertensive drugs - Group 1: 31.7 % - Group 2: 49.4 % - Group 3: 54.7 % - Group 4: 64.7 % Median eGFR: 33 ml/min/1.73 m^2	

ABPM ambulatory BP monitoring, *AKI* Acute kidney injury, *ARAS* atherosclerotic renal artery stenosis, *BL* bilateral, *BP* blood pressure, *CKD* chronic kidney disease, *CrCl* creatinine clearance, *CV* cardiovascular, *CT* computed tomography, *DBP* diastolic BP, *DDD* defined daily dose, *eGFR* estimated glomerular filtration rate, *ESH/ESC* European society hypertension/European society cardiology, *ESKD* end-stage kidney disease, *FPE* Flash Pulmonary Edema, *FU* follow-up, *G* Germany, *HTN* hypertension, *MACE* major adverse clinical events, *MDRD* Modification of diet in renal disease, *MRI* magnetic resonance imaging, *N* number, *NR* not reported, *NS* non-significant, *PEP* primary endpoint, *PTA* percutaneous angioplasty, *QOL* quality of life, *RAS* renal artery stenosis, *RASB* renin angiotensin system blockers, *RCT* randomized controlled trial, *RHTN* resistant HTN, *RRT* renal replacement therapy, *SBP* systolic BP, *sCr* serum creatinine, *SPG* systolic pressure gradient, *TOD* target organ damage, *UK* United Kingdom, *UL* unilateral, *US* ultrasound, *WHO* World Health Organization

Table 3 Uncontrolled non comparative observational prospective or retrospective studies of PTRAS in atherosclerotic renal artery stenosis

Study/author	Methods	Inclusion criteria HTN requirement	Primary and secondary endpoints	Participants	Results
Blum et al., 1997 [89] 1989–1996	Prospective single-center Mean FU: 27 months	ARAS >50% **RHTN**	BP control Kidney function	N, 75 (65% male) Mean age: 60 years Mean % stenosis: NR Mean 24-h daytime BP: 188/105 mmHg Mean n° drugs: 2.9 Mean sCr: 1.23 mg/dl	78% cure or improvement of BP (DBP <90 mmHg) sCr stable
Dorros et al., 1998 [90] 1990–1995	Prospective multicenter FU: 4 years	ARAS ≥50% and HTN and/or chronic renal insufficiency (sCr ≥1.5 mg/dl) and met ≥1 of the following: onset of HTN after 50 years of age; **accelerated, severe, or malignant HTN**; poor response to appropriate antihypertensive therapy; poorly controlled HTN; declining renal function after BP control with pharmacological agents	Restenosis rate BP control Kidney function Survival	N, 163 Mean age: 67 years Mean % stenosis: 81% Mean BP: 166/86 mmHg Mean n° drugs: 2.2 Mean sCr: 2.0 mg/dl	Significant BP decrease to 148/80 mmHg; $p < 0.05$ with no change in n° drugs (mean n° drugs: 2.0)
Dorros et al., 2002 [91]	Multicenter FU:4 years	ARAS **Poorly controlled HTN** or renal failure or congestive heart failure	Kidney function BP control Survival	N, 1058 Mean age: - Mean % stenosis: - Mean BP: 168/84 mmHg Mean n° drugs: 2.4 Mean sCr: 1.7 mg/dl	Significant BP decrease to 147/78 mmHg; $p < 0.05$ with significant change in n° drugs (mean n° drugs: 2.1; $p < 0.05$)
Gray et al., 2002 [32] 1992–1997	Multicenter FU: 21.3 months	(>70%) bilateral RAS or severe RAS to a solitary functioning kidney ($n = 21$) and systolic pressure gradient (>20 mmHg) **Renovascular HTN**, azotemia, or CHF (n, 207) Recurrent HF or FPE (n, 39)	BP Kidney function	N, 39 Mean age: 69.9 years 41% Male Mean % stenosis: NR BL RAS: 46% Mean BP: 174/85 mmHg Mean n° drugs: 3.0 Mean sCr: 3.2 mg/dl	BP improvement (one JNCVI category lower): 72% Mean BP: 148/72 ($p < 0.001$) Mean n° drugs: 2.5 ($p = 0.006$)
Jaff et al., 2012 [92] Chrysant et al., 2014 [59] 2007–2009	Prospective multicenter FU: 9 and 36 months	ARAS ≥60% **Uncontrolled BP ≥ 140 ≥ 90 mmHg despite ≥ 2 antihypertensive drugs**	Restenosis rate BP control CV events	N, 202 Mean age: 72 years Mean % stenosis: 81% Mean BP: 162/78 mmHg N° drugs: - ≥2: 201/202 patients - ≥3: 142/202 patients Mean sCr: 1.2 mg/dL (eGFR: 58 ml/min	Restenosis at 9 months: 10.5% Significant BP decrease at 9 months (145/75 mmHg; $p < 0.0001$) and at 36 months (146/75 mmHg; $p < 0.0001$) with no change in n° drugs
Jokhi et al., 2009 [93] 2000–2007	Prospective single-center 1 month	ARAS ≥70% **Resistant or severe HTN** (n, 73), unexplained renal dysfunction (or	Nature and frequency of complications	N, 106 Mean age: Mean % stenosis: 82%	5.5% decrease in kidney function 20% increase in kidney function BP: NR

Table 3 (continued)

Study/author	Methods	Inclusion criteria HTN requirement	Primary and secondary endpoints	Participants	Results
		induced by ACEi or ARBs) (n, 65), pulmonary edema with preserved systolic function; or the presence of clinically evident atherosclerosis in two vascular territories,		BL RAS: 32% Mean BP:166/74 mmHg Mean n° drugs: Mean sCr:	
Kawarada et al., 2010 [94]	Prospective single-center FU: 2–12	ARAS ≥50% or Systolic pressure gradient ≥20 mmHg **Suboptimal control of HTN by ≥ 2 antihypertensive agents**, or 2) renal impairment, or 3) renal atrophy, or 4) cardiac symptoms including "unstable coronary syndrome" or "CHF"	Cardiac function	N, 61 Mean age: 72 years 59% Male Mean % stenosis: NR BL RAS: 20% Mean BP: 152/81 mmHg 31% RHTN to ≥3 drugs Mean n° drugs: 2.2 Mean sCr: NR	Cardiac function and symptoms significantly improved Mean BP: 139/75 mmHg ($p < 0.001$) Mean n° drugs: 2.1 (NS)
Kobo et al., 2010 [95] 2001–2007	Prospective single-center FU: 1 month – 2 years	ARAS ≥70% Atherosclerotic disease in at least two other beds; or **HTN resistant to medical therapy or controlled by ≥ 3 drugs**; Chronic renal failure (sCr >1.5 mg/dl); or FPE	BP Kidney function	N, 41 Mean age: 70 years 36% Male Mean % stenosis: 88 BL RAS: 20% Mean BP: 164/82 mmHg Mean n° drugs: 3.0 Mean sCr:	HTN cured (<130 mmHg): 21% HTN improved: 64% HTN unchanged: 14% No change in sCr Mean BP: 142*/77 mmHg Mean n° drugs: 2.3** *$p = 0.002$ **$p = 0.001$
Leesar et al., 2009 [28] 2004–2006	Prospective single-center FU: 12 months	RAS ≥50–90% **Accelerated or refractory HTN (≥140/≥90 mmHg) on 2 or 3 antihypertensive drugs**	Accuracy of renal TPG, IVUS, and angiographic parameters in predicting HTN improvement after PTRAS.	N, 62 Mean age: 62 years Mean % stenosis: 61% BL RAS: NR Mean BP: 170/91 mmHg Mean n° drugs: 3.0 Mean sCr: 1.2 mg/dl	HSG ≥21 mmHg (n, 36) - HTN improved: 84% - Mean n° drugs: 2.3 HSG <21 mmHg (n, 26) - HTN improved: 36%* - Mean n° drugs: 3.4* *$p < 0.01$ sCr unchanged
Milewski et al., 2016 [56] 2001–2009	Prospective multicenter Mean FU: 23.8 months	ARAS ≥50% Mean SBP ≥160 mmHg on 3 drugs, or eGFR <60 ml/min, or unexplained HF/FPE	Change in - Kidney function - BP	N, 265 Mean age: 69 years Mean % stenosis: 70% BL RAS: Mean BP: 160/86 mmHg Mean n° drugs: 2.7 Mean sCr:	eGFR improved in 53.3% Mean BP: 135/75 mmHg SBP improved in 77.4% DBP improved in 68.2% Mean n° drugs: 2.5 (NS)
Prajapati et al., 2014 [58] 2010–2012	Prospective Single-center FU: 6 months	ARAS ≥70% and (1) onset of HTN before 30 years and after 55 years; (2) **exacerbation** of previously well controlled HTN; (3) **malignant HTN and**		N, 86 14/86 (16%) patients: malignant HTN 72/86 (84%): stage 2 HTN **RHTN: 71/86 (82.6%)**	BP decreased to 144/88 mmHg ($p < 0.0001$) N° drugs decreased to 2.25 ($p < 0.0001$)

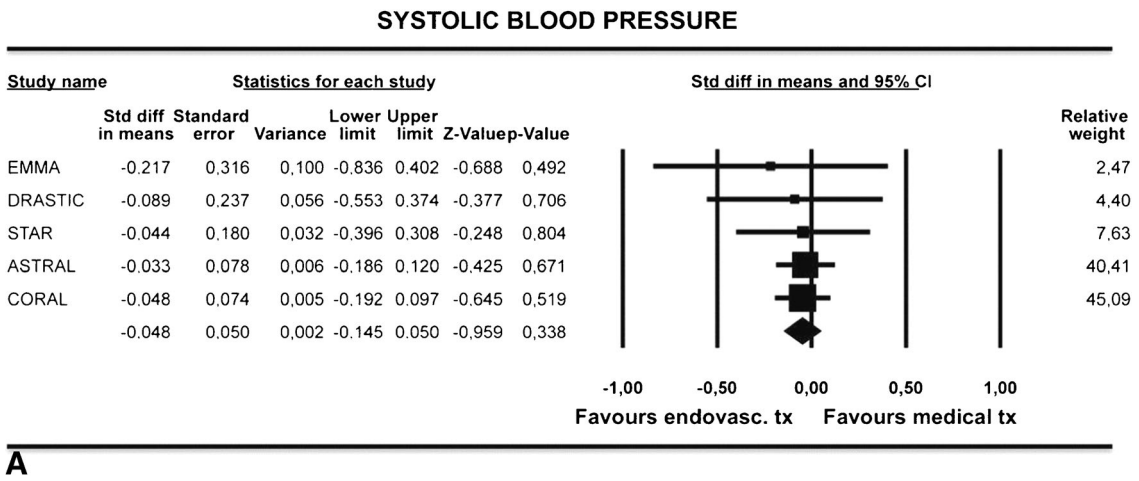
Table 3 (continued)

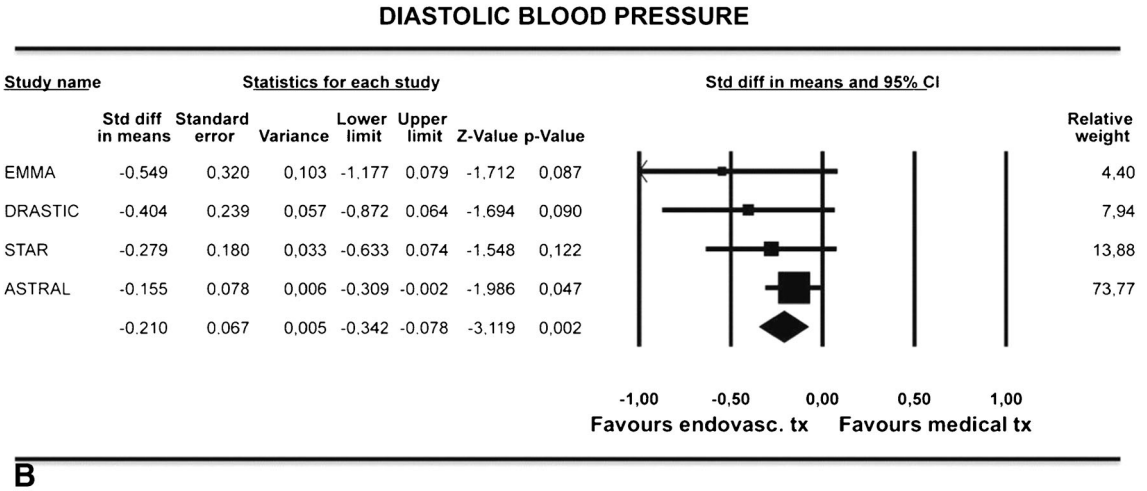
Study/author	Methods	Inclusion criteria HTN requirement	Primary and secondary endpoints	Participants	Results
		Refractory HTN; (4) azotemia shortly after institution of therapy with ACEi or ARB; (5) HTN and atrophic kidney or discrepancy in kidney size (>1.5 cm); (6) HTN and recurrent episodes of FPE or unexplained heart failure; (7) HTN and systolic-diastolic abdominal bruit; and (9) HTN and progressive unexplained azotemia.		Mean BP: 170/93 mmHg Mean n° drugs: 3.07 Mean sCr: 2.0 mg/dl	
Protasiewicz et al., 2013 [96]	Prospective multicenter FU: 3-months	ARAS 50–70% **Resistant HTN according ESH/ESC guidelines**	BP	N, 37 Mean age: 67 years% Male Mean % stenosis: 60% Mean 24-h BP: 141/73 mmHg Mean n° drugs: 4.0 Mean sCr:	Significant decrease in BP without change in n° drugs TPG >22 mmHg is an independent predictor of HTN improvement. BP was sign. Lower in patients with MBG >22 mmHg than in those with MBG <22 mmHg.
Rocha-Singh et al., 2008 [97]	Prospective multicenter FU: 9 months (3 years)	ARAS ≥70% **HTN**, or renal dysfunction, or recurrent FPE or any combination thereof	Restenosis rate BP Kidney function	N, 100 Mean age: 71 years 48% male Mean % stenosis: 68% BL stenosis: 17% Mean BP: 157/75 mmHg Mean n° drugs: NR Mean sCr:	Mean BP - at 9 months: 149*/74 mmHg - at 3 years: 139**/71 mmHg *$p < 0.02$ **$p = 0.0003$
Trani et al., 2013 [98] 2002–2007	Prospective single-center FU:	CKD stage ≥3 or **resistant HTN (not controlled on ≥ 3 antihypertensive drugs)**	Kidney function	N, 62 Mean age: 69 years 56% Male Mean % stenosis: 85% BL RAS: 19% Mean BP: NR Mean n° drugs: NR Mean sCr: 1.4 mg/dL	NS decrease in sCr 1.4 to 1.3 mg/dL

Only studies using "uncontrolled HTN while on ≥2 antihypertensive drugs" as indication for PTRAS

ACEi angiotensin converting enzyme inhibitor, *ARAS* atherosclerotic renal artery stenosis, *ARB* angiotensin receptor blocker, *BL* bilateral, *BP* blood pressure, *CHF* Congestive HF, *CKD* chronic kidney disease, *CrCl* creatinine clearance, *DBP* diastolic BP, *eGFR* estimated glomerular filtration rate, *ESH/ESC* European Society Hypertension/European Society Cardiology, *FPE* Flash Pulmonary Edema, *FU* follow-up, *HF* heart failure, *HSG* hyperemic systolic gradient, *HTN* hypertension, *IVUS* intravascular ultrasound, *JNC VI* Joint National Committee 6, *MBG* mean baseline gradient, *MDRD* Modification of diet in renal disease, *N* number, *NR* not reported, *NS* non-significant, *PTRAS* percutaneous transluminal renal artery stenting, *RAS* renal artery stenosis, *RHTN* Resistant hypertension, *SBP* systolic BP, *sCr* serum creatinine, *TPG* translesional pressure gradients, *UL* unilateral, *US* ultrasound

BP criteria are shown in bold





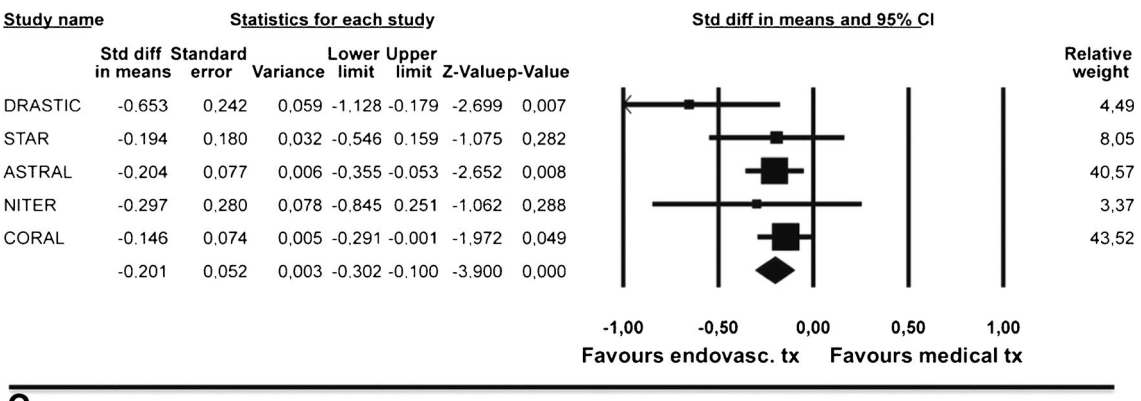


Fig. 1 Forest plot showing the standard differences in means with 95% CI for systolic BP (**a**), diastolic BP (**b**), and drug requirement (**c**) in the endovascular treatment arm versus medical therapy arm in different randomized controlled studies including patients with renal atherosclerotic stenosis [14]. Reproduced with permission from Caielli et al. [14]

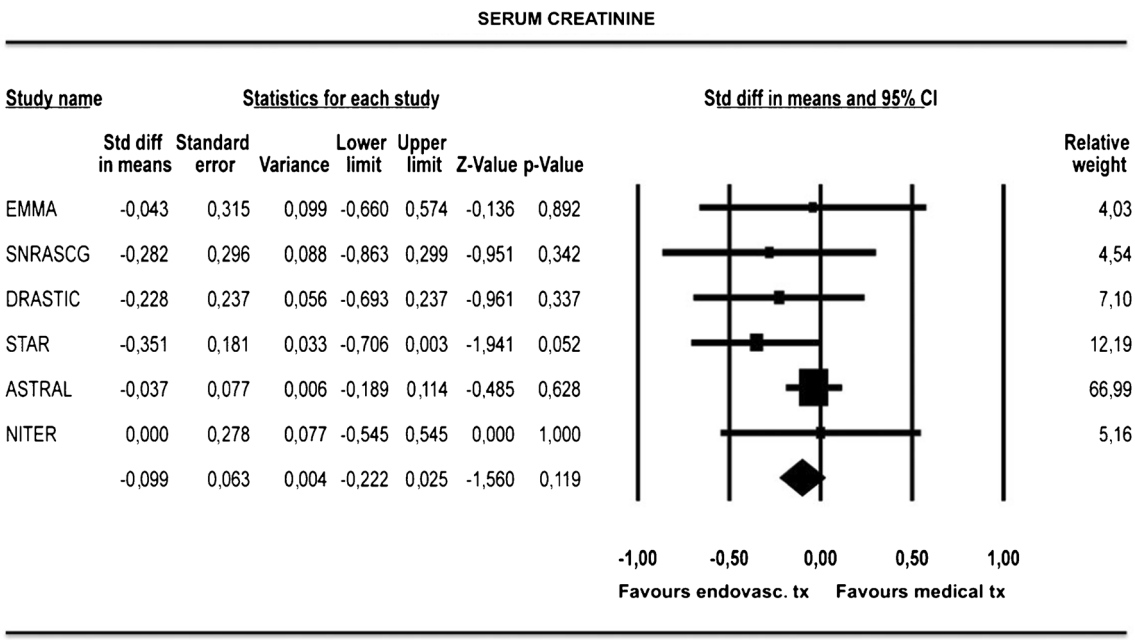


Fig. 2 Forest plot showing the standard differences in means with 95% CI for serum creatinine in endovascular treatment arm versus medical therapy arm in different randomized controlled studies including patients with renal atherosclerotic stenosis [14]. Reproduced with permission from Caielli et al. [14]

enrollment delays, protocol revisions during the trial, and high crossover rates and low event rates [20]. Even worse, several subgroups with clinical presentation highly suggestive of functional RAS (malignant or accelerated HTN, flash pulmonary edema, acutely worsening of kidney function after RAAS blockade) in whom expert would expect a substantial benefit from revascularization have been systematically excluded from RCTs. Therefore, the key point nowadays is to identify proper indications and to select subgroups of patients who would definitely benefit of PTRAS in terms of BP control and CV and renal outcomes, while avoiding unnecessary procedures and complications.

Another problem is that there is no established consensus about the degree of renal arterial narrowing that justifies revascularization. A 50–60% diameter stenosis has been considered significant and used as inclusion criterion in clinical trials [21]. However, due to normal autoregulation, at least 80% lumen stenosis is needed to elicit a >50% reduction in renal perfusion pressure in half of the patients [9]. Moreover, reduction in renal blood flow and activation of the RAAS are only obvious for luminal occlusions of >70–80% [22]. Several other approaches have been proposed to assess the hemodynamic significance of RAS. Peripheral *plasma renin activity*, unstimulated or after stimulation by a *captopril challenge test*, is not very sensitive or specific. Determination of plasma renin activity, in blood from renal veins compared to the contralateral or the peripheral veins, again with and without captopril stimulation, has a better predictive value for BP response after revascularization. However, the procedure is invasive and the measurements are influenced by sodium intake, volume status, and circulating antihypertensive drugs. Accordingly, this procedure has been abandoned. Also *renal scintigraphy*, using ^{99}Tc-DTPA, ^{131}I–hippurate, or ^{99}Tc-MAG$_3$, with and without captopril, is not reliable in patients with bilateral RAS and/or decreased renal function, and as such is no longer recommended by the American College of Cardiology/American Heart Association [10, 23]. The most specific diagnostic criterion for RVH is an ACEI-induced change in the renogram, with a high sensitivity and specificity in patients with normal or minimally reduced renal function (creatinine <1.7 mg/dL). However, the DRASTIC trial failed to show a relationship between the ACEI-induced renographic findings and BP response after revascularization [24]. By contrast, a translesional systolic pressure gradient (i.e., the ratio of distal renal pressure to aortic pressure or Pd/Pa) of <0.9, a resting translesional mean pressure gradient of >10 mmHg, a hyperemic peak systolic pressure gradient of ≥20 mmHg, or a renal fractional flow reserve (Pd/Pa ratio during maximum hyperemia) ≤0.8 are highly predictive of a marked improvement of BP after PTRAS [18••, 22, 25–27••, 28]. Despite their invasive character and the lack of randomized evidence, pressure gradient measurements are thus the most promising approach. Useful information can also be derived from renal Duplex. In particular, a renal resistance-index ([1-(end-diastolic velocity ÷ maximal systolic velocity)] × 100) of at least 80 reliably identifies patients with RAS in whom angioplasty or surgery will not improve BP, kidney function, or survival [29].

The other Duplex ultrasonography parameters have a high sensitivity in detecting RAS, but their specificity for detecting hemodynamically relevant RAS is low [10].

Are There Indications Left for Revascularization of Stenotic Renal Arteries?

According to classical textbook knowledge, patients with resistant or accelerated HTN, flash pulmonary edema, or important decline of kidney function after RAAS blockade or BP lowering are those with the highest possibility of underlying RAS [30]. The Pickering syndrome, a clinical entity consisting of HTN, flash pulmonary edema, and bilateral RAS or unilateral stenosis with a single kidney, is still one of the most widely accepted indications for renal revascularization [31]. Multiple observational studies have documented a substantial improvement of BP and decreased incidence of flash pulmonary edema after PTRAS in patients with this condition [32]. In the single available matched controlled cohort study, PTRAS, compared to medical therapy, improved heart failure (HF) symptoms, reduced HF-related hospitalizations, and increased BP control as well as the ability to use ACE inhibitors (ACEi) or angiotensin II receptor antagonists (ARB) without the risk of causing a decline in kidney function [33]. A systematic review including the aforementioned studies reported that 76% of patients with RAS and flash pulmonary edema did not have any recurrence after angioplasty. Recurrence was associated with either restenosis of the renal artery or cardiac arrhythmias. In patients with congestive heart failure (CHF) and renal insufficiency, the severity of HF symptoms, expressed as New York Heart Association (NYHA) functional class, improved after angioplasty. Evidence derived from this systematic review justifies a weak recommendation in favor of angioplasty in patients with ARAS and either flash pulmonary edema or CHF and renal insufficiency [34].

Patients with a rapid deterioration of renal function, defined as a >30% decrease in eGFR over ≤3 months and ARAS may also benefit from revascularization, as has been shown by several small trials, case series, and case reports [35]. Even in dialysis-dependent patients, PTRAS may potentially improve renal function [36]. Moreover, in a single-center prospective cohort study, patients presenting with a combination of rapidly declining kidney function and refractory HTN, revascularization was associated with reduced risk of death (HR 0.15; 95% CI 0.02–0.9; $p = 0.04$) and CV events (HR 0.23; 95% CI 0.1–0.6; $p = 0.02$) [37•]. Finally, in accelerated or malignant HTN, with or without acute kidney injury, and caused by ARAD, surgical revascularization improved BP control and improved or stabilized renal function in most patients [38]. However, no clinical trial has evaluated the efficacy of PTRAS compared to medical therapy alone in this indication. Only a few case reports are available [39].

Rationale of Renal Revascularization in Patients with Drug-Resistant Hypertension

Treatment RHTN is defined as a BP above goal (≥140/90 mmHg) despite appropriate lifestyle measures and optimal treatment with adequate doses of ≥3 antihypertensive drugs of different classes, including a diuretic [40, 41], or controlled BP in the presence of adequate doses of ≥4 antihypertensive drugs [42, 43•]. Resistant HTN is associated with an increased incidence of target organ damage and CV risk as well as end-stage kidney disease [44]. Depending on cohorts and definition used, the prevalence of RHTN in the general hypertensive population varies between 10 and 20%, but may prove much lower (<5%) after ruling out pseudo-resistance (poor BP measurement technique, non-adherence to medications, white-coat hypertension, lifestyle) and secondary causes of HTN [41–43•, 45•]. It is two to three times more frequent in patients with CKD than in patients without CKD [46, 47]. Notably, ARAS is present in 5.5% of patients with CKD of the US Medicare population [48], and the prevalence of RAS in RHTN is between 5 and 25% [41, 49]. Not only the prevalence of RAS is higher in RHTN but also the stenosis per se is more likely to be functional in RHTN. Besides increased sympathetic tone, the mechanisms underlying RHTN include excessive salt and fluid retention [50]. Accordingly, the combination of ARAS, the associated higher risk of CV morbidity and mortality, and RHTN represents a deadly cocktail [11]. More effective and appropriate drug treatment in the recent era has made possible BP control in most initially resistant hypertensive patients [51]. However, complex drug treatments are not always well tolerated in the long run, can negatively influence drug adherence, and impose additional costs. Furthermore, in the presence of functional unilateral and bilateral RAS, BP control with a proper combination of drugs may aggravate hypoperfusion of the post-stenotic kidney(s) and thus lead to progressive loss of viable renal tissue. Therefore, neutral RCTs performed outside the specific setting of RHTN or functional RAS cases should not lead to the end of proper diagnostic evaluation of RAS and revascularization in appropriate patients [52].

Case Reports

Despite the fact that all published RCTs to date excluded patients who are more likely to benefit from revascularization, case reports of typical patients continue to be published and many clinicians have witnessed reversal of RHTN after successful PTRAS [39, 53–55]. An example of such a patient is illustrated below. A 72-year-old man, known with a well-controlled HTN and treated with a beta-blocker (metoprolol 190 mg OD), was referred for recent deterioration of BP. He was a former smoker, and had untreated dyslipidemia and hyperuricemia. He consulted his general practitioner for severe headache. His BP was as high

as 216/150 mmHg. Blood tests showed an elevated serum creatinine of 2.13 mg/dL (MDRD-eGFR of 31 mL/min/1.73 m^2). Urinalysis did not show proteinuria or hematuria. His general practitioner increased antihypertensive medication to a combination of a beta-blocker (metoprolol 190 mg OD), a calcium channel blocker (amlodipine 10 mg OD) and a diuretic (chlorthalidone, 25 mg OD), and referred him for further investigation. Physical examination was unremarkable, no abdominal bruit was heard. A renal ultrasound revealed only a slightly smaller left kidney (9 vs 10 cm), but on duplex, a specific tardus parvus wave was found. The angiography showed a bilateral RAS of 35% on the right side and of >85% with a poststenotic dilatation at the left side. A PTRAS was performed on the left side, and the patient received clopidogrel as well as a statin. Following PTRAS, BP immediately dropped to 107/66 mmHg; 24 h later, the patient was discharged with a BP of 132/78 mmHg, and antihypertensive treatment was reduced to amlodipine 5 mg in combination with metoprolol 95 mg, both OD. Six months later, BP was still at goal (124/80 mmHg) with the same bitherapy, and kidney function had recovered (creatinine, 1.16 mg/dL, eGFR–MDRD, >60 mL/min/1.73 m^2). Six years later, the patient has still a well-controlled BP and a stable kidney function.

Observational Studies

Multiple, relatively small, prospective, and retrospective series have shown benefit of PTRAS in terms of BP decrease and prevention of end-organ damage in patients with RHTN [37•, 56–59]. A recent international registry (2001–2009) included 265 consecutive patients with ARAS (≥50% de novo stenosis) treated by renal artery stenting and at least one of the following: (1) poorly controlled HTN (mean SBP ≥ 160 mmHg on at least three antihypertensive medications including diuretic), (2) impairment of renal function (MDRD-eGFR <60 mL/min/1.73 m^2), and (3) unexplained CHF or recurrent acute pulmonary edema. Median follow-up was 23.8 months (interquartile range 3–90). Mean percent diameter stenosis was 70% (range 59–80%) at baseline. Following PTRAS, systolic BP was reduced from 160 (145–171) to 135 mmHg (125–146) and DBP from 86 (80–95) to 75 mmHg (70–80); $p < 0.01$. Systolic and diastolic BP improvement was observed in 77.4 and 68.2% of patients, respectively, while the average number of antihypertensive medications before and after revascularization did not change significantly (2.70 ± 1.0 vs 2.49 ± 0.9, $p = 0.1$). MDRD-eGFR improved in 53.9% of patients and did not change in 15.5%, while in 30.6% patients, kidney function continued to deteriorate. Patients in whom eGFR or BP improved or stabilized had lower preprocedural SBP, more severe lesion type at baseline (longer lesion with higher diameter stenosis), and lower diameter of the stenosis at control angiography as compared to patients in whom renal function deteriorated. The results of the study suggest that interventional treatment of ARAS may preserve renal function and improve BP control at relative long-term follow-up. Moreover, the authors suggest that in patients with moderate ARAS and decreased renal function in whom compensatory mechanisms are able to maintain a lower BP, interventional procedures may still be valuable [56]. These results are partially in contrast with previous reports showing the highest decrease in SBP in patients with the highest initial SBP [57, 59].

The prospective single-center study of 467 patients with underlying ARAD and a high-risk clinical phenotype (i.e., presenting with flash pulmonary edema, refractory HTN defined according the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines, or rapidly declining kidney function) mentioned higher, documented a dramatic survival improvement after PTRAS in patients with flash pulmonary edema (HR for death 0.4 [95% CI 0.2–0.9], $p = 0.01$) and in those with the combination of rapidly declining renal function and refractory HTN (HR for death 0.15 [95% CI 0.02–0.9], $p = 0.04$), but not when the latter conditions presented alone [37•, 40].

Non-randomized Comparative Studies

In the HERCULES trial, 99.5 and 70% of patients respectively had a BP ≥ 140/≥90 mmHg despite being on ≥2 and ≥3 antihypertensive drugs. PTRAS resulted in a significant BP decrease at 36 months (from 162/78 to 146/75 mmHg) in the absence of change in the number of antihypertensive drugs. The magnitude of absolute reduction in SBP was related to the severity of baseline systolic HTN prior to intervention. Notably, for patients with a preprocedural SBP ≥180 mmHg, a reduction of 46 mmHg in SBP at 36 months was observed [59].

Randomized Clinical Trials

Clinical evidence to support intervention in ARAS and RHTN is controversial, as the RCTs did not focus on patients with RHTN (Table 1). The inclusion criteria for BP in the different RCTs did not meet the definition of RHTN. The BP inclusion criterion in the EMMA trial was a diastolic BP > 95 mmHg on three occasions and/or on antihypertensive medications; patients with malignant HTN were excluded [60]. Also, both the SNRASCG and the DRASTIC trials used diastolic BP as an inclusion criterion, i.e., a diastolic BP ≥ 95 mmHg on three occasions despite being on two antihypertensive medications [24]. The BP inclusion criterion in STAR was a stable BP control with BP < 140/90 mmHg for 1 month prior to randomization [61], and in the ASTRAL trial, no clear definition was given. Moreover, an important bias in this large study was the opinion of the physician, as patients were only enrolled if their physician was uncertain as to whether revascularization would be of clinical benefit, which may have led to exclusion of patients most likely to benefit from revascularization [62].

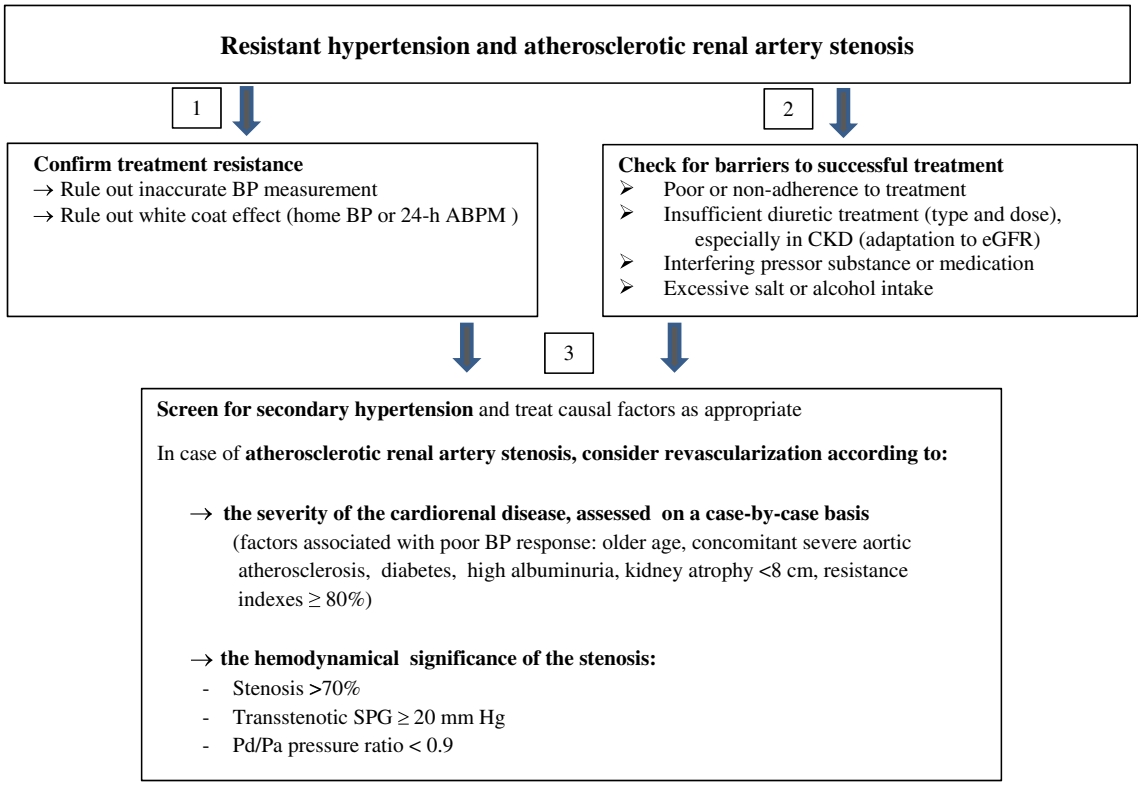


Fig. 3 Algorithm for the management of resistant hypertension and renal artery stenosis. General work-up for resistant hypertension and renal artery stenosis. *ABPM* ambulatory blood pressure measurement, *BP* blood pressure, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *Pd/Pa ratio* ratio of distal renal artery pressure to aortic pressure, *SPG* systolic pressure gradient. Data adapted from Sarafidis et al. [50] and Rossignol et al. [45•]

The most recent RCT, the CORAL study, required a systolic BP ≥ 155 mmHg on ≥2 antihypertensive medications. However, as the trial had problems recruiting the prespecified amount of patients, the inclusion criteria changed: The threshold of 155 mmHg for defining systolic HTN was abandoned, and patients with RAS and controlled BP could be enrolled provided that eGFR was less than 60 ml/min/1.73 m^2. Notably, in an analysis of different patient subgroups, treatment effect did not differ in patients with baseline systolic BP below or above 160 mmHg [63]. The inclusion of different grades of renal function is another important issue of the RCTs, as kidneys in severe CKD are already severely and often irreversibly damaged.

Guidelines

Several guidelines, supported by level 2 evidence cohort studies which consistently found benefit of revascularization in groups with the highest likelihood of clinically significant RAS, propose PTRAS in patients with RHTN, progressive and/or acute decline of renal function, and flash pulmonary edema [23, 64]. The American Heart Association (ACC/AHA) and the ESH/ESC guidelines provide a Class 2a (Loeb) recommendation in this subset of patients [40, 41].

However, despite anecdotic evidence and data from some observational studies, it still remains unknown whether these "high risk" patients have benefits in survival and in avoiding CV events and renal replacement therapy, compared to medical therapy alone. Therefore, this recommendation needs to be tested in properly designed RCTs.

Ideal Randomized Controlled Trial Testing Revascularization in Patients with RHTN

The "ideal" trial to test the benefits of revascularization in RHTN should include only patients with true RHTN (excluding apparent RHTN due to poor drug adherence, white coat HTN, secondary causes of HTN, use of substances that may increase BP, inappropriately high dietary sodium intake, etc.) and hemodynamically significant RAS (i.e., stenosis >70%, verified by functional measurements such as transstenotic systolic pressure gradient ≥20 mmHg or Pd/Pa pressure ratio < 0.9, and perhaps in the future more sophisticated magnetic resonance imaging (MRI) diagnosing kidney tissue at risk and/or reversible tissue damage) [18••, 27••, 65]. Eligible patients should be treated following a strict, rigorous protocol with standardized antihypertensive medications, statins, and antiplatelets. Drug adherence should be assessed throughout

the trial, preferably by drug dosages in plasma or urine [66, 67•]. The primary efficacy endpoint should be based on 24-h ambulatory BP, and not solely on office BP, as ambulatory BP is per se blinded, minimizes white coat and placebo effects and physician-related biases, and is an independent predictor of CV events. [44, 68, 69•]. Follow-up should be extended to several years, and the primary endpoint for safety should be based on eGFR. In anatomical successful PTRAS, the incidence of renal artery restenosis, in-stent stenosis, or stenosis progression on the long run should be evaluated by CT scan, which is the gold standard or, if contra-indicated, by MRI [70]. The ANDORRA trial may meet most of these requirements [71].

Conclusions

The indications of revascularization of the renal arteries remain a matter of controversy. Based on the results of the large RCTs, indiscriminately revascularizing ARAS is no longer tenable. The challenge is to identify those patients who are most likely respond and to prevent kidney damage. patient selection implies diagnosis of true RHTN in combination with demonstration of anatomically and hemodynamically significant RAS, as discussed above and summarized in Fig. 3.

Take-Home Messages for Future Research

While the application of PTRAS expanded rapidly at the turn of the latest century, the "neutral" results of the large RCT's tempered this enthusiasm and many physicians subsequently abandoned this invasive treatment [72]. However, outcome data from RCT's apply only to the populations enrolled, which in the majority of cases did not include patients at high risk of RVH. Antihypertensive drug therapy (i.e., RAAS blockers) combined with lipid and glucose control and antiplatelet therapy can achieve BP control and improve clinical outcome in patients with moderate atherosclerotic renal disease, even in the absence of PTRAS [73]. In more severe cases, renal revascularization to restore blood flow to the stenotic kidney appears logical in view of the pathophysiologic mechanisms that are initiated by RAS [12]. Identification of biomarkers of response to PTRAS should be done within the context of properly designed randomized controlled trials. However, certain patient populations who probably benefit from renal revascularization will never be studied because they cannot be ethically withheld from a potentially life-saving treatment; in this setting, registries may provide relevant information. On the other hand, we should not forget that patients with ARAS-related HTN often have coexisting essential HTN that will not be cured by intervention. Still, revascularization may lead to switch from RHTN to a more controllable HTN.

Awaiting the results of future trials, such as the ANDORRA study [71], clinicians should try to distinguish between HTN associated with ARAS and true RVH, and to identify those patients at risk of resistant/refractory/accelerated/malignant HTN and end-organ damage (ischemic nephropathy, heart failure) who would definitely benefit from revascularization [20, 52]. Preliminary biomarker studies within registries may help identifying patients who may potentially benefit from revascularization, biomarker-guided strategies being subsequently tested in properly designed double-blind randomized trials [74].

Compliance with Ethical Standard

Conflict of Interest Patricia Van der Niepen, Patrick Rossignol, Jean-Philippe Lengelé, Elena Berra, Pantelis Sarafidis, and Alexandre Persu declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Recently Published Papers of Particular Interest Have Been Highlighted:
- • of Importance
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