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Full Reviews

Treatment of atherosclerotic renovascular hypertension: review of observational studies and a meta-analysis of randomized clinical trials

Paola Caielli[1], Anna Chiara Frigo[2], Martino F. Pengo[1], Giacomo Rossitto[1], Giuseppe Maiolino[1], Teresa Maria Seccia[1], Lorenzo A. Calò[1], Diego Miotto[1] and Gian Paolo Rossi[1]

[1]Department of Medicine—DIMED, Internal Medicine 4, University of Padua, Padua, Italy and [2]Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Padua, Italy

Correspondence and offprint requests to: Gian Paolo Rossi; E-mail: gianpaolo.rossi@unipd.it

ABSTRACT

Atherosclerotic renal artery stenosis can cause ischaemic nephropathy and arterial hypertension. We herein review the observational and randomized clinical trials (RCTs) comparing medical and endovascular treatment for control of hypertension and renal function preservation. Using the Population Intervention Comparison Outcome (PICO) strategy, we identified the relevant studies and performed a novel meta-analysis of all RCTs to determine the efficacy and safety of endovascular treatment when compared with medical therapy. The following outcomes were examined: baseline follow-up difference in mean systolic and diastolic blood pressure (BP), serum creatinine, number of drugs at follow-up, incident events (heart failure, stroke, and worsening renal function), mortality, cumulative relative risk of heart failure, stroke, and worsening renal function. Seven studies comprising a total of 2155 patients (1741 available at follow-up) were considered, including the recently reported CORAL Study. 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 greater reduction in the mean number of antihypertensive drugs (standard difference in means −0.201, 95% CI: −0.302 to −0.1, P < 0.001). At variance, follow-up changes (from baseline) of systolic BP, serum creatinine, and incident cardiovascular event rates did not differ between treatment arms. Thus, patients with atherosclerotic renal artery stenosis receiving endovascular treatment required less anti-antihypertensive drugs at follow-up than those medically treated. Notwithstanding this, they evidenced a better control of diastolic BP.

Keywords: controlled randomized clinical trials, renal artery stenosis, renovascular hypertension, transluminal angioplasty

INTRODUCTION

Atherosclerotic renal artery stenoses (ARAS) are increasingly found due to ageing of the population and account for ∼90% of all renal artery lesions [1]. They have several nefarious effects, including inflammation, oxidative stress, and endothelial dysfunction, and thus can lead to ischaemic nephropathy and, through the activation of the renin–angiotensin–aldosterone system, to high blood pressure (BP) and to widespread cardiovascular disease [2]. It is generally held that a stenosis attains haemodynamic significance only when the luminal narrowing is at least 70%, when compared with the nearby unaffected vessel or, if between 50 and 70%, when the trans-stenotic peak or mean pressure gradient is >20 or >10 mmHg, respectively [3]. All these threshold values are, however, to be regarded cautiously because of the difficulty of measuring precisely the renal artery narrowing due to marginal blurring and/or selection of a reliable reference point, and also to the fact that an accurate estimation of the degree of narrowing would require a 3D reconstruction of the vessel lumen, which has never been exploited in clinical studies in this field thus far. In most of these studies, estimates were obtained on planar images, which can lead to over- or under-estimation depending on the orthogonal projection chosen [4].

Until 1978, when Grüntzig introduced percutaneous transluminal coronary angioplasty (PTCA) [5], patients with ARAS were treated medically or surgically. A wide array of observational, retrospective, and controlled trials thereafter suggested that PTRA could be beneficial over medical treatment for preserving renal function and improving BP control (Tables 1 and 2) [6–17]. Accumulated experience, however, showed that PTRA was hampered by a high rate of restenosis in ARAS patients [9, 18, 19]. Moreover, randomized clinical trials (RCTs) that compared medical therapy with PTRA could not prove the superiority of the latter for controlling hypertension and preserving renal function [18, 20, 21]. Stenting was introduced as a valuable addition to PTRA [22], but not even PTRA plus stenting (PTRAS) could unequivocally be shown to overcome medical therapy in the very few available RCTs [23–25] (Tables 3–5). These trials, however, had limitations in study design and treatment options, which overall led to challenging their results and conclusions. Accordingly, available guidelines on treatment of ARAS could not be based on class I level of evidence A [26]. Therefore, the optimal treatment of ARAS patients remains a highly controversial issue among physicians, which translates into ample variation in clinical practice.

To the aim of highlighting current evidences on the management of ARAS patients, we will first review the results of observational studies and published meta-analyses of available RCTs that compared PTRAS with medical treatment. We will then report on the results of a novel meta-analysis that was based on criteria that differed from the previous ones and furthermore comprised a yet unpublished RCT [27], alongside the recently reported CORAL study [25].

METHODS

A Medline search of the English-language literature published from January 1995 to November 2013 using the Population Intervention Comparison Outcome (PICO) strategy [28] and the keywords reported in the Supplementary data was performed to identify the cohort studies and the RCT on renal arterial revascularization with PTRA, alone or associated with stenting.

Observational studies

We found three retrospective and nine prospective cohort studies (Tables 1 and 2) that investigated the usefulness of PTRA alone or of PTRAS. Among the retrospective studies, two evaluated the effect of revascularization on renal function in chronic kidney disease (CKD) patients. In one study, 99 patients with an eGFR of <80 mL/min treated with PTRA were divided into two groups: those with poorly controlled BP and those with rapid deteriorating renal function. In the latter group, most ARAS were either bilateral or in a solitary kidney. After 29 ± 10 months of follow-up, the patients with rapid deteriorating renal

Table 1. Clinical retrospective studies on PTRA ± stenting outcome in ARAS patients

Reference	Sample size (*n*)	Population	Intervention	Primary endpoint	Renal function outcomes	Blood pressure outcomes
Cognet *et al.* 2001 [6]	99	• ARAS >70% • GFR <80 mL/min – Group A: stable CKD – Group B: rapid worsening renal function	PTRA ± stent	10% variation versus baseline in GFR	• No differences between baseline and final GFR in overall population • Larger GFR gain in Group B than in Group A	
Alhadad *et al.* 2009 [7]	234	Significant ARAS	PTRA	• BP cure (DBP <90 and SBP <140 mmHg off antihypertensive drugs) • BP 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)		• SBP and DBP decrease • Decrease in antihypertensive drugs
Dichtel *et al.* 2010 [8]	118	• ARAS >75% • Moderate-to-severe CKD (GFR >15 and <60 mL/min/1.73 m^2)	• Medical therapy (n = 71) • PTRA ± stent (n = 47)	Change in GFR over the first year after diagnosis/ treatment	No GFR difference between the two groups	• No difference in SBP and DBP between the two groups • Number of antihypertensive drugs in medical group significantly higher than in PTRA group at 12 months. Difference disappeared at 24 and 36 months

BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; DDD, defined daily dose; PTRA, percutaneous transluminal renal angioplasty; SBP, systolic blood pressure; SCr, serum creatinine.

Table 2. Clinical prospective studies on PTRA ± stenting outcome in ARAS patients

Reference	Sample size (*n*)	Population	Intervention	Primary endpoints	Renal function outcomes	Blood pressure outcomes
Harden *et al.* [9]	32	• CKD • ARAS >50%	PTRA + stent	• 20% change in SCr from baseline • Renal replacement therapy • Death	• 34% improved, 34% stabilized, 28% worsened • Progression of renal failure slower after PTRA	• DBP decrease after PTRA • No difference in SBP • No difference in antihypertensive drugs
Watson *et al.* [10]	33	• CKD • Bilateral stenosis or unilateral stenosis in SFK	PTRA ± stent	Slopes of 1/SCr before and after PTRA	Mean slope increased after PTRA	• SBP and DBP decrease after PTRA • No difference in antihypertensive drugs
Muray *et al.* [11]	59	• CKD • ARAS >60%	PTRA	Slopes of 1/SCr before and after PTRA	• Renal function improved in 58% and stabilized or worsened in 42% of patients • Slope of 1/SCr before PTRA associated with a favorable change in progression rate after PTRA	
Leertouwer *et al.* [12]	18	ARAS ≥50%	PTRA ± stent	Single-kidney contributions to the total renin secretion, effective plasma flow (131I-hippuran clearance) and (125I-thalamate clearance)	• Vein-to-artery renin ratio at treated side decreased • 131I-hippuran improvement at treated side and contra-laterally • 125I-thalamate improvement at treated side and contra-laterally	
Coen *et al.* [13]	46	• CKD • Unilateral ARAS	PTRA ± stent (*n* = 27) Medical therapy (*n* = 19)	• eGFR • GFR based on NAFS	• No eGFR difference in the two groups • GFR increase in PTRA kidney and decrease in contralateral based on NAFS	• SBP and DBP decrease in PTRA patients • Decrease in antihypertensive drugs at 3 and 6 months after PTRA
Zeller *et al.* [14]	215	ARAS ≥70%	PTRA ± stent	• SCr • Mean BP by 24-h monitoring	SCr decrease at 1 year	Mean arterial BP decrease at 1 year
Zeller *et al.* [15]	340	ARAS ≥70%	PTRA ± stent	• 10% decrease in SCr • eGFR	• SCr decrease • No difference in eGFR	SBP, DBP and mean BP improve after PTRA
Rivolta *et al.* [16]	52	CKD	PTRA ± stent	Slopes of 1/SCr before and after PTRAS	Improvement in renal function in 15.5% patients, stable renal function in 59.5%, reduction in renal function in 25%	
Kalra *et al.* [17]	908	• ARAS >60% • ARAS 50–60% with post-stenotic dilatation	• PTRA ± stent (*n* = 561) • Medical therapy (*n* = 347)	• eGFR • BP	• No eGFR difference in the two groups • eGFR increase in PTRAS compared with the non-PTRAS patients with CKD stage 4 and 5	• No difference in BP control in the two groups • BP decrease in the overall groups and within each CKD category

BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; NAFS, nephroangiophotoscintigraphy; PTRAS, percutaneous transluminal renal angioplasty plus stenting; SBP, systolic blood pressure; SCr, serum creatinine; SFK, single functioning kidney.

Table 3. Randomized clinical trials characteristics: definition of ARAS and inclusion/exclusion criteria

Study name (year)	Definition of 'Substantial' ARAS	Inclusion criteria	Exclusion criteria
EMMA (1998)	Unilateral ≥75% without thrombosis or ≥60% with positive lateralization test[a]	• DBP >95 mmHg • GFR ≥50 mL/min	• Malignant hypertension • Stroke or AMI in previous 6 months • Pulmonary oedema • DBP >109 mmHg at end of run-in
SNRASCG (1998)	Uni- or bilateral ≥50%	DBP >95 mmHg with at least two drugs	• SCr >500 µmol/L • Stroke or AMI in previous 3 months
DRASTIC (2000)	Uni- or bilateral ≥50%	DBP >95 mmHg with at least two drugs	• SCr >200 µmol/L • Cancer • Other forms of secondary hypertension • HF or unstable angina • Single kidney with SCr >150 µmol/L • Stenotic kidney <8 cm • Renal artery occlusion • Aortic aneurism needing surgery
STAR (2009)	Uni- or bilateral ≥50%	GFR (Cockcroft Gault) <80 mL/min	• Stenotic kidney <8 cm • Renal artery <4 mm • GFR <15 mL/min • Diabetes with proteinuria >3 g/die • Malignant hypertension
ASTRAL (2009)	Uni- or bilateral 'substantial anatomical stenosis'	'If the patient's doctor was uncertain that the patient would definitely have a worthwhile clinical benefit from revascularization'	• Need of surgery or high revascularization probability in 6 months • Non-atherosclerotic cardiac disease • Previous renal revascularization
NITER not published	Uni- or bilateral ≥70%	• SCr ≤ 3 mg/dL and/or GFR (MDRD) ≥30 mL/min • Stenotic kidney ≥8 cm • BP ≤ 150/90 mmHg with <4 drugs	• Other cause of CKF • Doppler renal resistance index >0.8 • Renal artery occlusion • Cerebro- or cardiovascular disease in previous 6 months • Cancer with estimated life <1 year • Cholesterol thrombo-embolization episodes • Hepatic failure • HF (NYHA IV) or unstable angina • Intolerance to iodinated contrast, statin or antiplatelets
CORAL (2013)	Uni- or bilateral with: • ≥60% with a ≥20 mmHg systolic pressure gradient, or • if ≥80% (no pressure gradient required)	SBP ≥155 mmHg on ≥2 drugs	• DBP ≥120 mmHg and/or SBP ≥200 mmHg • Stroke or TIA within 3 months or known carotid stenosis ≥70% • Major surgery, trauma, revascularization procedure, unstable angina or AMI in previous 30 days • Hospitalization for HF within 3 months • Ejection fraction <30% • Diabetes with either: a. Proliferative retinopathy and ≥1 + protein on urine dipstick or b. ≥1 + protein on urine dipstick and urine protein/Cr ratio >0.5 • Kidney size <8 cm • SCr >3.0 mg/dL • Aneurysm of the abdominal aorta >4.0 cm • Previous renal artery bypass surgery or angioplasty or stent intervention or kidney transplant • Intolerance to iodinated contrast, statin or antiplatelets

AMI, acute myocardial infarction; BP, blood pressure; CKF, chronic kidney failure; DBP, diastolic BP; GFR, glomerular filtration rate; HF, heart failure; SCr, serum creatinine.

[a]venous pielography, renal scintigraphy and renal venous renin concentration.

Table 4. Randomized clinical trials characteristics: endpoints, follow-up timing and types of analysis

Study name	Primary endpoints	Secondary endpoints	Follow-up (months)	Intention-to-treat	Crossing-over No. (%)	Stenting (%)	Bilateral stenosis (%)
EMMA	BP by means of ABPM	• Number of drugs • Complications	6	No	7 (27%)	8.7	0
SNRASCG	• OBP • SCr	• Number of drugs • Events • Complications	12	No	0	0	50.9
DRASTIC	OBP	• Number of drugs • SCr • GFR • Renal scintigraphy • Restenosis • Complications	12	Yes	22 (44%)	3.6	22.6
STAR	GFR increase ≥20%	• OBP • Complication • Malignant hypertension • Pulmonary oedema • Cardiovascular morbility and mortality	24	Yes	1 (1.3%)	71.8	48
ASTRAL	Mean slope of the reciprocal of serum SCr over time	• OBP • Time-to-first renal event • Time to first major cardiovascular event • Mortality	60	Yes	24 (6%)	95	53.5
NITER	• Mortality • Dialysis • SCr increase of >20% or GFR (MDRD) decrease of >20% at 0.5, 1 and 2 years with an extended 2-year follow-up	• SBP and DBP at 0.5, 1 and 2 years with an extended 2-year follow-up • Number of drugs • Renal scintigraphy • Complications due to interventional maneuvers • Incidence of extra-renal vascular complications	42	n.a.	(1.9%)	100	51.5
CORAL	Event-free survival from cardiovascular and renal adverse events (composite of cardiovascular or renal death, stroke, AMI, hospitalization for HF, progressive renal insufficiency or need for permanent renal replacement therapy)	• All-cause mortality • Longitudinal kidney function (1/Cr) • SBP • Durability of renal artery patency • Renal resistive index • Correlation between stenosis severity and kidney function (1/Cr) • Quality of life • Cost-effectiveness	60	Yes	19 (4%)	100	20

ABPM, ambulatory BP monitoring; AMI, acute myocardial infarction; BP, blood pressure; DBP, diastolic BP; GFR, glomerular filtration rate; HF, heart failure; SBP, systolic BP; SCr, serum creatinine; n.a., not available.

function had a greater gain in creatinine clearance than those with poor BP control and stable CKD [6]. In another study of 118 ARAS patients with an average baseline GFR of 37 ± 15 mL/min/1.73 m^2, 71 were treated medically and 47 with PTRAS. They were assigned to either treatment by each patient's clinician at the time of presentation without predetermined criteria. After 34-month follow-up, both groups showed a similar decline in GFR, systolic and diastolic BP values, and a superimposable change in number of drugs prescribed from diagnosis [8].

We could identify nine studies with a prospective design on a total of 1703 patients [9–17] (Table 2). They differed for inclusion criteria, primary endpoints and, moreover, sample size, which ranged from 18 to 908 patients. Only three studies enrolled >100 patients and all of them reported a significantly fall

Table 5. Patients' characteristics at baseline and follow-up

	EMMA	SNRASCG	DRASTIC	STAR	ASTRAL	NITER	CORAL
Total number of PTS	49	55	106	140	806	52	947
Initial number of PTS (medical/endovascular)	26/23	30/25	50/56	76/64	403/403	24/28	480/467
Number of PTS at 1 year (medical/endovascular)	n.a.	21/22	27/53	60/52	348/332	n.a.	371/362
Final number of PTS (medical/endovascular)	18/23	30/24	27/53	53/46	86/77	24/28	40/59
Age (years)	59.4	61	60	66.5	70.5	72	69
Baseline PAS (mmHg) (medical/endovascular)	149/151	175/182	180/179	163/160	152/149	148/149	150/150
Follow-up PAS (mmHg) (medical/endovascular)	141/140	169.5/166	159/160	155/151	148/146	139/146	135/133
Baseline PAD (mmHg) (medical/endovascular)	89/91	91.5/96.5	103/104	82/83	76/76	79/79	n.a.
Follow-up PAD (mmHg) (medical/endovascular)	84/81	91/86.5	91/93	79/77	75/73	74/81	n.a.
Baseline SCr (μmol/L) (medical/endovascular)	105/101	158/160	114/106	145/154	178/179	n.a.	n.a.
Follow-up SCr (μmol/L) (medical/endovascular)	91/88	182/163.5	106/106	168/156	192/196	n.a.	n.a.
Baseline No. drugs (medical/endovascular)	n.a.	2.4/2.8	2/2	2.9/2.8	2.8/2.79	3.3/3.3	2.1/2.1
Follow-up No. drugs (medical/endovascular)	n.a.	2.6/2.3	2.4/1.9	2.9/2.6	2.97/2.77	3.2/2.9	3.5/3.3

PTS, patients; ; SCr, serum creatinine; n.a., not available.

in mean BP of ∼10 mmHg after PTRA ± stenting [14, 15, 17]. However, only one study [17], which enrolled 908 patients, compared two groups of patients according to assignment either to medical treatment or PTRAS. This study reported no differences between treatment arms in BP fall and changes in eGFR. With the exception of patients with CKD stage 4 and 5, eGFR failed to improve significantly in the PTRAS compared with the medical arm [17]. In the other two larger studies, a decrease of sCr was seen [14, 15], but the 1-year decrease was borderline significant in both ($P = 0.047$ and $P = 0.048$); mean BP decreased significantly by ∼10 mmHg in both studies.

Among the smaller studies, the majority showed a decrease of BP and an improvement of renal function with PTRAS. However, only one compared PTRAS and medical treatment in patients with unilateral ARAS and found a significant drop in BP (systolic and diastolic) from baseline after one year, along with a significant fall in number of antihypertensive drugs in the PTRAS patients with no change in the medical treatment arm.

On the whole, these studies showed an improvement of renal function in 58% and a better BP control in 67% of the patients with PTRAS (see Supplementary data), thus supporting the conclusion that PTRA with or without stenting does not preclude achievement of a better control of BP and/or does not harm the kidney, but, rather the opposite. However, by no means does this allow the conclusion that revascularization is better than medical therapy for preservation of renal function and BP control.

Randomized clinical trials

We could identify eight RCTs comparing medical treatment and revascularization in ARAS patients, one of which is yet to be published and one, the METRAS [29], still recruiting. Besides an ample variation in the number of recruited patients, the seven already completed showed heterogeneity of inclusion and exclusion criteria, primary and secondary endpoints, and follow-up time. Nonetheless, they lent themselves to a meta-analysis and some of them were in fact included in four published meta-analyses [30–33].

By meta-analysing the same three trials for changes (from baseline) of BP and sCr at 6 months (on 210 patients in studies published until 2003), two of these four meta-analyses found a greater reduction in systolic and diastolic BP ($P < 0.05$) and a trend ($P = 0.06$) toward a benefit in terms of changes in sCr in the PTRA arm [30, 31]. The other two compared PTRA with/without stenting on top of medical therapy versus medical management alone: Kumbhani *et al.* examined six RCTs (in 1208 patients) and found no between-arm differences in change from baseline of systolic (weighted mean difference = 1.20 mmHg, 95% CI: −1.18 to 3.58 mmHg) or diastolic BP (weighted mean difference = −1.60 mmHg, 95% CI: −4.22 to 1.02 mmHg). However, after 29-month follow-up, there was a reduction in mean number of antihypertensive medications in the PTRAS compared with the medically treated patients (weighted mean difference = −0.26, 95% CI −0.39 to −0.13, $P < 0.001$); sCr did not differ between arms at the end of follow-up [32]. At variance, by meta-analysing five of the same six trials on a total of 1030 patients, Shetty *et al.* found only a trend toward an improvement in systolic, diastolic BP and sCr in the patients assigned to PTRAS [33].

Of note, in all the meta-analysed RCTs, there was a high rate of dropouts, which could have introduced a selection bias, thus conceivably affecting their results. In fact, neither the original studies nor their meta-analyses provided any evidence that the patients available at follow-up were comparable with those originally recruited and that the drop-out rate was comparable between treatment arms. Therefore, to minimize this potential pitfall, unlike previous meta-analyses, we elected to exclude those who dropped-out and to meta-analyse only the patients available at baseline and at 1-year follow-up (Table 5).

Inclusion and exclusion criteria and data extraction

To be included in the meta-analysis, the RCT had to randomly assign ARAS patients to either medical therapy alone or to PTRA with/without stenting. Studies on ARAS patients allocated to surgical treatment were excluded. Besides the six published RCTs (SNRASCG [20], EMMA [18], DRASTIC [21], STAR [23], ASTRAL [24], CORAL [25]) a yet unpublished study (NITER [27]) could be included, as the relevant data were kindly provided by the corresponding author.

The following features were examined for each eligible study: number of patients, definition of significant ARAS,

percentage of patients with bilateral stenosis, age, comorbidities (hypertension, diabetes mellitus, dyslipidaemia, coronary artery disease, and stroke), risk factors (cigarette smoking), BP, renal function (sCr), number of drugs at baseline, time to follow-up, analysis type (per-protocol and intention-to-treat), drop-out and crossover rate, technique used for BP measurement and for renal function evaluation. The rate of stenting on the total of endovascular procedures was also examined (Tables 3–5).

Endpoints

The outcomes analysed were as follows: between-treatment arm difference in mean systolic and diastolic BP value; sCr; need (number) of antihypertensive drugs at follow-up; incidence of heart failure, stroke, worsening renal function, and death; cumulative relative risk of such events.

Statistical analysis

To preserve the effect of randomization, we used an intention-to-treat analysis like in the previous meta-analyses. However, we excluded dropouts beforehand and considered only patients available at 1-year follow-up. At variance with previous meta-analyses, we elected to use a commercially available software package (Comprehensive Meta-analysis, Statistical Solution, Biostat, Englewood, NJ, USA) to allow for independent replication of results.

For continuous variables, the standard difference in mean (SDM) and corresponding 95% confidence interval were computed using random-effects modelling. The variables for which summary measures of spread (standard deviation or SEM) were not reported in the original publications were excluded from the meta-analysis. Heterogeneity was assessed using inconsistency of treatment effects among trials (I^2). The impact of potential covariates was also examined using meta-regression analysis. The statistical significance (P-value) was set at 0.05.

RESULTS OF RANDOMIZED CLINICAL TRIALS

Six published RCTs (SNRASCG [20], EMMA [18], DRASTIC [21], STAR [23], ASTRAL [24], CORAL [25]) and one unpublished study (NITER [27]) fulfilled the selection criteria and could be included. Overall, a total of 2155 patients were enrolled, but only 81% were available at 1-year follow-up (872 randomized to the endovascular treatment and 869 to the medical therapy arm). As the trials had widely different sizes, which had a marked impact on the outcome analysis, we calculated and reported the relative weight of each trial for each endpoint (Figure 1, Panels A–C). For clarity purposes, results of between-treatment comparison for pre-specified outcomes (Table 6) are herein reported in an itemized way.

Blood pressure, antihypertensive medications, and serum creatinine

There was no evidence of among-study heterogeneity for systolic or diastolic BP ($I^2 = 0$) (Figure 1, Panels A and B). The change of SBP from baseline to follow-up was similar in the endovascular treatment and medical therapy arm (SDM −0.048, 95% CI: −0.145 to 0.050, P = 0.338). At variance, the reduction in diastolic BP was greater in the endovascular treatment than in the medical therapy arm (SDM −0.210, 95% CI: −0.342 and −0.078, P = 0.002).

This larger fall in diastolic BP occurred in spite of a greater reduction in mean number of antihypertensive drugs from baseline to follow-up in the endovascular than in the medical treatment arm (SDM −0.201, 95% CI: −0.302 and −0.100, P < 0.001), with evidence of only mild heterogeneity among studies ($I^2 = 1.214$) (Figure 1, Panel C).

The change of sCr from baseline to follow-up did not differ between treatment arms (SDM −0.099, 95% CI: −0.222 to 0.025, P = 0.119) (Figure 2). There was no evidence of heterogeneity among the studies ($I^2 = 0$).

Worsening renal function, heart failure, stroke and all-cause mortality

The incidence of worsening renal function was high but did not differ between the endovascular treatment and the medical therapy arm (13.7 versus 14.8%, respectively; RR = 0.893, 95% CI: 0.701 to 1.136, P = 0.357).

The incidence of heart failure was lower in the endovascular treatment than in the medical therapy arm (10.8 versus 13.6%, respectively; RR = 0.863, 95% CI: 0.639 to 1.167, P = 0.339), albeit not significantly so. Stroke incidence (5.6 versus 6.1%, respectively; RR = 0.819, 95% CI: 0.542 to 1.237, P = 0.342) and all-cause death rate (21.8 versus 22.4%, RR = 0.894, 95% CI: 0.709 to 1.127, P = 0.342) were similar in the two arms. For none of these endpoints, was there evidence of heterogeneity among the studies ($I^2 = 0$).

The cumulative risk of incident CV and renal events did not differ between the endovascular treatment and the medical therapy arm (40.5 versus 44%, RR = 0.905, 95% CI: 0.751 to 1.090, P = 0.294); was there no evidence of heterogeneity among the studies ($I^2 = 0$).

Meta-regression

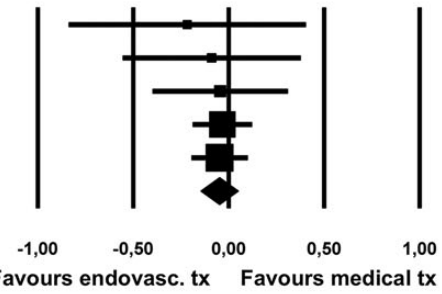
Meta-regression showed that the SDM of number of drugs and percentage of diabetic patients reached statistical significance (Figure 3). This finding indicates that the benefit of endovascular treatment over medical treatment in terms of reduction of number of antihypertensive drugs required to achieve BP control was significantly blunted in the patients with diabetes mellitus. At variance, there were no differences of SDM for systolic and diastolic BP, and sCr, analysed according to the baseline features of the patients (age, percentage of diabetics, smokers, bilateral stenosis among patients, SBP, diastolic BP, mean sCr and mean number of drugs).

DISCUSSION

The results of 12 observational trials herein reviewed support, in our view, the conclusion that PTRA with or without stenting does not harm the kidney and/or preclude achievement of a better control of BP, but rather the opposite. However, unfortunately by no means, did they provide a conclusive answer as to whether PTRA is better than optimal medical therapy,

SYSTOLIC BLOOD PRESSURE

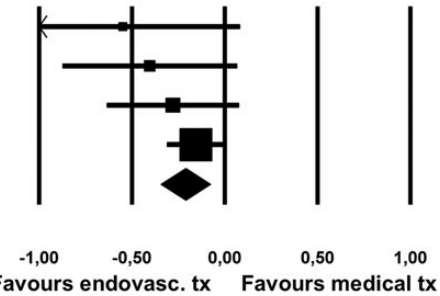
Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
EMMA	-0,217	0,316	0,100	-0,836	0,402	-0,688	0,492	2,47
DRASTIC	-0,089	0,237	0,056	-0,553	0,374	-0,377	0,706	4,40
STAR	-0,044	0,180	0,032	-0,396	0,308	-0,248	0,804	7,63
ASTRAL	-0,033	0,078	0,006	-0,186	0,120	-0,425	0,671	40,41
CORAL	-0,048	0,074	0,005	-0,192	0,097	-0,645	0,519	45,09
	-0,048	0,050	0,002	-0,145	0,050	-0,959	0,338	



PANEL A

DIASTOLIC BLOOD PRESSURE

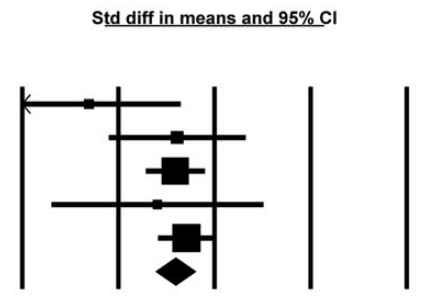
Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
EMMA	-0,549	0,320	0,103	-1,177	0,079	-1,712	0,087	4,40
DRASTIC	-0,404	0,239	0,057	-0,872	0,064	-1,694	0,090	7,94
STAR	-0,279	0,180	0,033	-0,633	0,074	-1,548	0,122	13,88
ASTRAL	-0,155	0,078	0,006	-0,309	-0,002	-1,986	0,047	73,77
	-0,210	0,067	0,005	-0,342	-0,078	-3,119	0,002	



PANEL B

NUMBER OF ANTIHYPERTENSIVE DRUGS

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
DRASTIC	-0,653	0,242	0,059	-1,128	-0,179	-2,699	0,007	4,49
STAR	-0,194	0,180	0,032	-0,546	0,159	-1,075	0,282	8,05
ASTRAL	-0,204	0,077	0,006	-0,355	-0,053	-2,652	0,008	40,57
NITER	-0,297	0,280	0,078	-0,845	0,251	-1,062	0,288	3,37
CORAL	-0,146	0,074	0,005	-0,291	-0,001	-1,972	0,049	43,52
	-0,201	0,052	0,003	-0,302	-0,100	-3,900	0,000	



PANEL C

FIGURE 1: Forest plot showing the SDMs with 95% CI for systolic BP (**Panel A**), diastolic BP (**Panel B**) and drug requirement (**Panel C**) in the endovascular treatment arm versus medical therapy arm in different studies. Relative weight shows the impact of every single trial, proportional to number of patients enrolled.

either in the entire population of ARAS patients or in the high-risk subgroups as the diabetics.

Some responses, however, came from the meta-analysis including a novel one that included all available RCTs and also the most recently published [25].

Effect of treatment on BP

Two smaller meta-analyses [30, 31] of three older trials (EMMA, SNRASCG and DRASTIC) demonstrated a mild benefit on BP control, but these results were not confirmed by the two larger meta-analyses [32, 33] that included STAR and ASTRAL. In the latter study, the number of patients was 403 in each arm, but because of dropouts only 82% in the medical arm and 86% in the PTRAS arm were available at 1-year follow-up [24]. The high dropout rate, ranging from 1 to 10%, seen also in the other trials, suggests that a selection bias affected their results. This is why to avoid an untoward effect of the high dropout rate and to obtain a more realistic weight of the impact of each trial, only the patients available at follow-up were considered in our meta-analysis.

Table 6. Meta-analysis outcomes

Systolic and diastolic BP
Renal function
Number of antihypertensive drugs
Incidence of heart failure
Incidence of worsening in renal function[a]
Incidence of stroke
Mortality
Cumulative incidence of events

[a]An eGFR decrease of ≥20% from basal value, and/or an SCr increase of ≥50%, and/or need for dialysis.

This meta-analysis differs from previous meta-analyses [30–33] not only for including more RCTs, but also excluding the selection bias due to dropouts. Of note, our enlarged meta-analysis showed that diastolic BP was significantly better controlled in patients treated with revascularization than in those assigned to medical treatment only (Figure 1, Panel B). This important finding was altogether evident notwithstanding the major impact, due to a much higher sample size than of all other five RCTs, of the widely criticized ASTRAL study [24, 34–36] and the just published CORAL study [25]. It is worth noting that both of these studies enrolled patients who were not necessarily hypertensive, which could explain their negative results as revascularization of normotensive patients has little chances to lower an already normal BP.

In keeping with the previously published meta-analyses, our meta-analysis could not show a significantly greater fall in SBP in the PTRAS arm (Figure 1, Panel A). This negative finding could be explained on multiple grounds: revascularization would lower BP if hypertension was caused by the ARAS alone, which most likely is the pressor mechanism only early in the course of ARAS. Moreover, SBP is a composite phenotype that derives from several other factors, including the highly prevalent isolated systolic hypertension due to large artery stiffening [37]. In the CORAL trial [25], which had the largest relative weight on the meta-analysis, the patients were recruited based only on SBP, which led to including many patients with isolated systolic hypertension, in whom the lowering of BP could be negligible, particularly, if they were old and/or had a long-standing history of high BP.

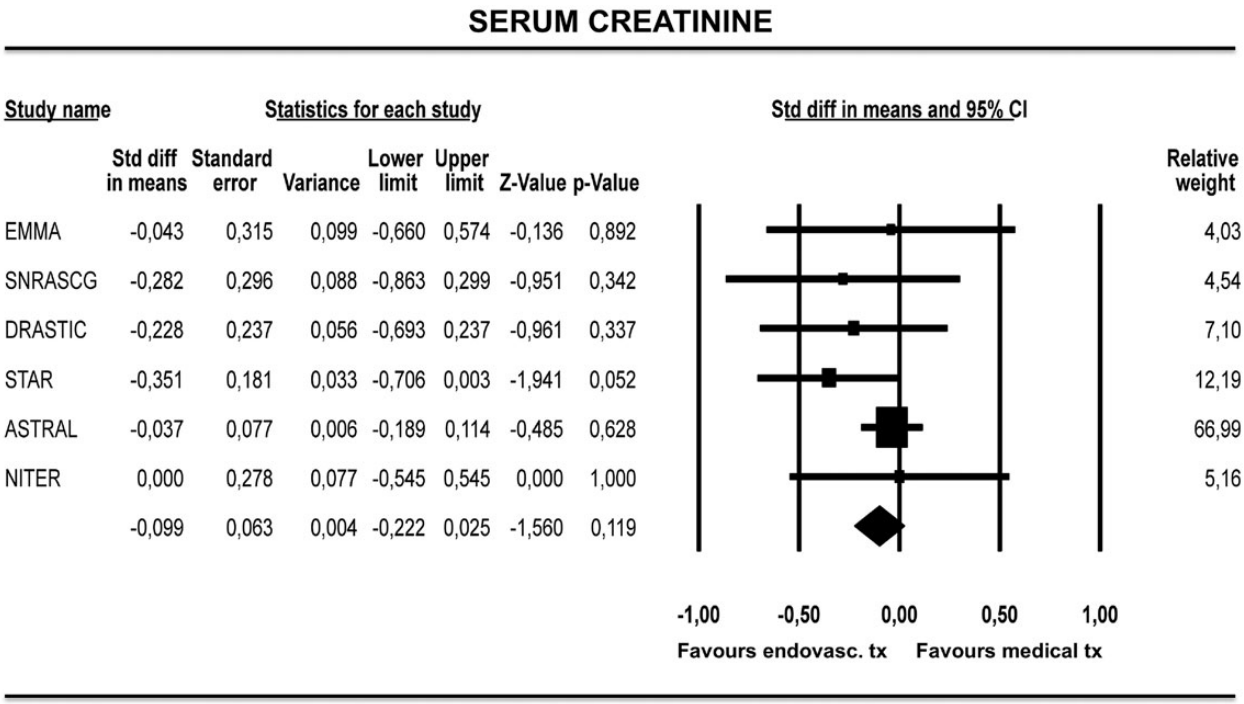


FIGURE 2: Forest plot showing the SDMs with 95% CI for serum creatinine in endovascular treatment arm versus medical therapy arm in different studies. Relative weight shows the impact of every single trial, proportional to number of patients enrolled.

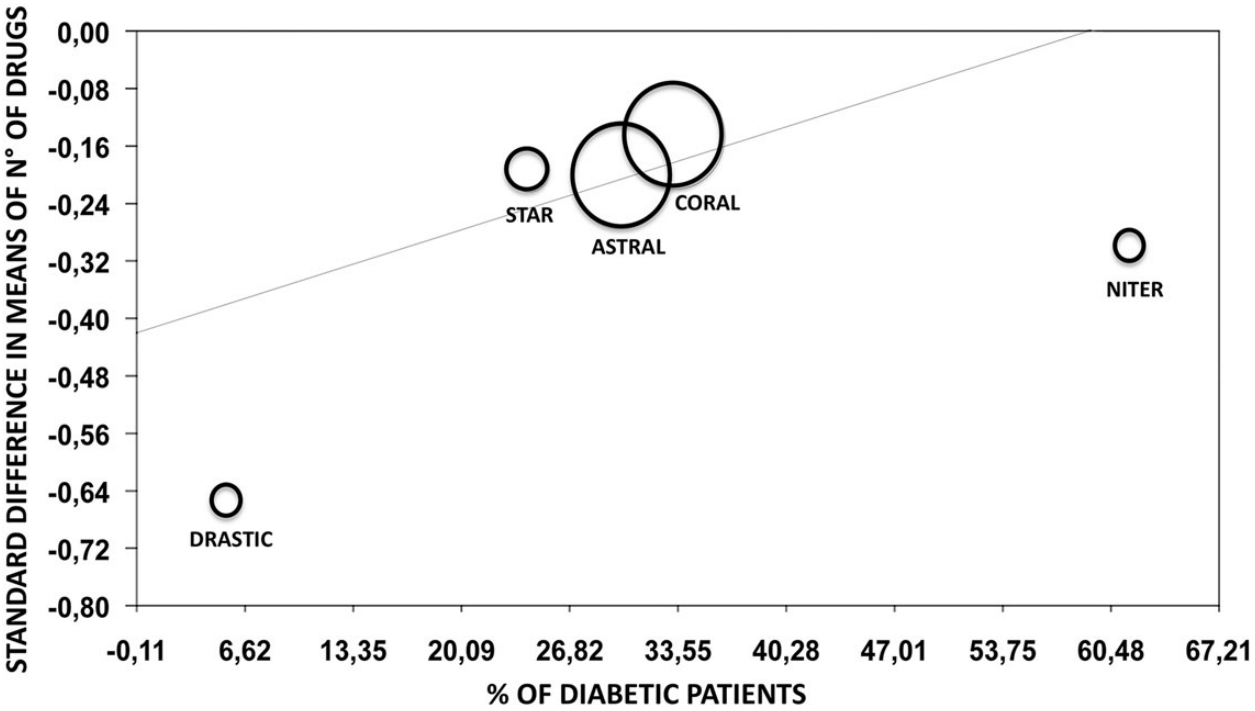


FIGURE 3: Meta-regression of percentage of diabetic patients on SDMs of number of drugs in different studies.

The beneficial effects of endovascular treatment on BP could be prominent in bilateral stenosis, as found in SNRASCG study, the only RCT that analysed separately patients with unilateral and bilateral stenosis.

Effect of treatments on need of antihypertensive drugs and renal function

The lower diastolic BP in the revascularization group evidenced by our meta-analysis is an important result that has to be further emphasized, because it occurred in spite of a greater reduction of the number of antihypertensive agents at follow-up in the endovascular treatment than in medical treated arm (Figure 1, Panel C). This finding agrees with the conclusions of all previous meta-analyses [32, 33] of the four studies (DRASTIC, STAR, ASTRAL, and NITER) for which suitable information on drug treatment regimen was available.

Assessing the change of antihypertensive drugs needed at follow-up is a key piece of information for judging the effect of each treatment not only on BP, but also on renal function, because a successful revascularization can allow use of drugs, such as ACE inhibitors, angiotensin receptors blockers or renin inhibitors, which are often avoided in patients with bilateral ARAS, or with ARAS in a solitary kidney, given the inherent risk of inducing acute renal failure. Moreover, after a successful PTRAS, the reduction in number and/or doses of antihypertensive drugs that raise the GFR could bias the assessment of the effect of endovascular treatment on renal function. These considerations might explain why we could evidence only a favourable trend in preserving or improving renal function with endovascular treatment, a finding that differs from the improvement seen in the observational studies [9, 10, 12–14]. The different selection criteria used might also explain these divergent results: in two studies [9, 10], 89% of the 65 patients had bilateral stenosis, whereas in most meta-analysed RCTs, the majority of the patients had unilateral stenosis. Moreover, many of them did not have even mild CKD and some (ranging from 5% to 60%) had diabetes mellitus. Exclusion of CKD patients, who have a higher likelihood of improving after PTRAS, minimized the chances of finding advantages on renal function with revascularization [38]. Inclusion of diabetics, whose renal function can deteriorate regardless of the ARAS, could have diminished differences between treatment arms, particularly in the RCTs where the allocation of diabetics to either treatment was unbalanced. Consistently with this contention by reviewing retrospectively the effects of surgical revascularization in diabetic and non-diabetic patients, Hansen *et al.* found that diabetics had a significantly lower rate of beneficial BP response, alongside an increased risk of dialysis or death during follow-up [39].

Our finding of a decreased need for antihypertensive drugs with endovascular treatment has profound implications from the pharmaco-economic standpoint because of the costs of a long-standing polytherapy and also for clinical practice given that there is an inverse relationship between number of antihypertensive drugs needed to control BP and patients' adherence to treatment [40].

Besides these considerations, some even more important concerns exist: it is well known that sCr-based eGFR is inaccurate for estimating early renal dysfunction. This is even more so in the baseline evaluation of renovascular disease with/without treatment in that the stenotic kidney has a reduced GFR, whereas the contralateral likely undergoes high BP-induced hyperfiltration. After PTRAS, the GFR increases in the treated kidney and decreases in the contralateral kidney, because of the fall in BP [13]. Due to these divergent effects on the two kidneys, it is altogether unlikely that overall estimates

of GFR can show any differences between PTRAS and medical treatment. Accordingly, it comes as no surprise that eGFR did not show any improvement after PTRAS [6, 8, 13, 15, 17, 18, 21]. The benefit of stenting could instead be detected by estimating GFR separately in the two kidneys as planned in the Medical and Endovascular Treatment of Atherosclerotic Renal Artery Stenosis (METRAS study, http: //clinicaltrials.gov/ct2/show/NCT01208714) [29]. This now-recruiting RCT is aimed at comparing PTRAS on top of an optimized medical therapy targeted to most cardiovascular risk factors with such optimized medical therapy alone.

Endovascular and medical treatment effect on incidence of events

According to the AHA guidelines, PTRAS should be performed in patients with unexplained heart failure, flash pulmonary oedema, and refractory or unstable angina [26], thus implying that revascularization is superior to medical treatment for preventing/regressing these complications. In fact, an improvement of symptoms was reported after PTRAS in patients with angina and with heart failure [41]. However, our meta-analysis showed a trend toward a lower rate in the PTRAS arm of major events, including acute decompensated heart failure, worsening renal function, stroke, mortality and their composite in keeping with previous results [32]. It is, nonetheless, important to underline that most of meta-analysed RCTs excluded the sickest patients beforehand (for example those with heart failure, pulmonary oedema, and refractory angina), because they had compelling indications to revascularization according to the guidelines [26]. This strategy obviously minimized the chances of showing any benefit with either treatment. Furthermore, the length of follow-up in all the meta-analysed RCTs was probably too short to provide enough statistical power for a proper assessment of the effect of each treatment on renal and cardiovascular events and mortality. Our meta-analysis did not obviate to this problem as we could analyse only changes at 1-year follow-up.

Effects of confounders on endpoints

We used meta-regression to adjust for the effect of potential confounders. This analysis showed a significant inverse relationship between the change of number of drugs from baseline and percentage of diabetics in the study populations (Figure 3). This result indicates that the higher the rate of diabetics in the population the lower the reduction (of SDM) of the number of necessary antihypertensive drugs, and thereby the difference between endovascular and medical treatment arm during follow-up. It suggests that also in the renovascular microcirculation, like in the coronary vasculature [42–44], the diabetic microangiopathy can hamper the outcome of successful revascularization on BP control [45].

Limitations

To preserve the balanced distribution of known and unknown potential confounders between treatment arms provided by the randomization, all RCTs (except EMMA and SNRASCG trials [18, 20]) and meta-analyses, including ours, used an intention-to-treat approach. However, a substantial percentage of patients assigned to the medical treatment arm were revascularized, leading to a high crossover rate (Table 4), and thus biasing the interpretation of results. For example, in the DRASTIC trial, 44% of the patients in the medical therapy arm underwent PTRA. This is a further issue that suggests caution before drawing conclusions concerning equivalence or superiority of either treatment, as it minimized the chances of detecting any advantages of revascularization over medical therapy. It is also probable that the tight inclusion criteria and the short follow-up did not provide enough power to demonstrate significant differences of SBP, sCr and incidence of adverse cardiovascular events between endovascular and medical arms.

CONCLUSIONS

The results of observational studies overall indicate that PTRA with or without stenting neither precludes achievement of an improved BP control nor harms the kidney but, if any, the opposite.

A meta-analysis of all available RCTs comparing endovascular treatment with medical therapy showed that the former allows a lowering of the antihypertensive treatment and, notwithstanding this, is associated with a better control of diastolic BP at follow-up. Whether patients with diabetes mellitus represent a cohort at higher risk that mandates a more aggressive revascularization strategy needs to be addressed in specific RCTs as available literature does not provide any conclusive evidence.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Krijnen P, van Jaarsveld BC, Steyerberg EW *et al.* A clinical prediction rule for renal artery stenosis. Ann Intern Med 1998; 129: 705–711
2. Montecucco F, Pende A, Mach F. The renin-angiotensin system modulates inflammatory processes in atherosclerosis: evidence from basic research and clinical studies. Mediat Inflamm 2009; 2009: 752406
3. Olin JW. Role of duplex ultrasonography in screening for significant renal artery disease. Urol Clin North Am 1994; 21: 215–226
4. Paul JF, Cherrak I, Jaulent MC *et al.* Interobserver variability in the interpretation of renal digital subtraction angiography. AJR Am J Roentgenol 1999; 173: 1285–1288
5. Grüntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet 1978; 1: 263
6. Cognet F, Garcier JM, Dranssart M *et al.* Percutaneous transluminal renal angioplasty in atheroma with renal failure: long-term outcomes in 99 patients. Eur Radiol 2001; 11: 2524–2530
7. Alhadad A, Mattiasson I, Ivancev K *et al.* Predictors of long-term beneficial effects on blood pressure after percutaneous transluminal renal angioplasty in atherosclerotic renal artery stenosis. Int Angiol 2009; 28: 106–112
8. Dichtel LE, Gurevich D, Rifkin B *et al.* Renal artery revascularization in patients with atherosclerotic renal artery stenosis and impaired renal function: conservative management versus renal artery stenting. Clin Nephrol 2010; 74: 113–122
9. Harden PN, MacLeod MJ, Rodger RS *et al.* Effect of renal-artery stenting on progression of renovascular renal failure. Lancet 1997; 349: 1133–1136
10. Watson PS, Hadjipetrou P, Cox SV *et al.* Effect of renal artery stenting on renal function and size in patients with atherosclerotic renovascular disease. Circulation 2000; 102: 1671–1677
11. Muray S, Martín M, Amoedo ML *et al.* Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. Am J Kidney Dis 2002; 39: 60–66
12. Leertouwer TC, Derkx FH, Pattynama PM *et al.* Functional effects of renal artery stent placement on treated and contralateral kidneys. Kidney Int 2002; 62: 574–579
13. Coen G, Moscaritolo E, Catalano C *et al.* Atherosclerotic renal artery stenosis: one year outcome of total and separate kidney function following stenting. BMC Nephrol 2004; 5: 15
14. Zeller T, Frank U, Müller C *et al.* Predictors of improved renal function after percutaneous stent-supported angioplasty of severe atherosclerotic ostial renal artery stenosis. Circulation 2003; 108: 2244–2249
15. Zeller T, Frank U, Müller C *et al.* Stent-supported angioplasty of severe atherosclerotic renal artery stenosis preserves renal function and improves blood pressure control: long-term results from a prospective registry of 456 lesions. J Endovasc Ther 2004; 11: 95–106
16. Rivolta R, Bazzi C, Stradiotti P *et al.* Stenting of renal artery stenosis: is it beneficial in chronic renal failure? J Nephrol 2005; 18: 749–754
17. Kalra PA, Chrysochou C, Green D *et al.* The benefit of renal artery stenting in patients with atheromatous renovascular disease and advanced chronic kidney disease. Catheter Cardiovasc Interv 2010; 75: 1–10
18. Plouin PF, Chatellier G, Darne B *et al.* BP outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. Essai Multicentrique Medicaments vs Angioplastie (EMMA) Study Group. Hypertension 1998; 31: 823–829
19. Zeller T, Müller C, Frank U *et al.* Gold coating and restenosis after primary stenting of ostial renal artery stenosis. Catheter Cardiovasc Interv 2003; 60: 1–6
20. Webster J, Marshall F, Abdalla M *et al.* Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. Scottish and Newcastle Renal Artery Stenosis Collaborative Group. J Hum Hypertens 1998; 12: 329–335
21. Van Jaarsveld BC, Krijnen P, Pieterman H *et al.* The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. Dutch Renal Artery Stenosis Intervention Cooperative Study Group. N Engl J Med 2000; 342: 1007–1014
22. Katzen BT, Chang J, Lukowsky GH *et al.* Percutaneous transluminal angioplasty for treatment of renovascular hypertension. Radiology 1979; 131: 53–58
23. Bax L, Woittiez AJ, Kouwenberg HJ *et al.* Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. Ann Intern Med 2009; 150: 840–848
24. Wheatley K, Ives N, Gray R *et al.* Revascularization versus medical therapy for renal-artery stenosis. N Engl J Med. 2009; 361: 1953–1962
25. Cooper CJ, Murphy TP, Cutlip DE *et al.* Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med 2014; 370: 13–22
26. Hirsch AT, Haskal ZJ, Hertzer NR *et al.* ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006; 113: e463–752654
27. Scarpioni R, Michieletti E, Cristinelli L *et al.* Atherosclerotic renovascular disease: medical therapy versus medical therapy plus renal artery stenting in preventing renal failure progression: the rationale and study design of a prospective, multicenter and randomized trial (NITER). J Nephrol 2005; 18: 423–428
28. da Costa Santos CM, de Mattos Pimenta CA, Nobre MR. The PICO strategy for the research question construction and evidence search. Rev Lat Am Enfermagem 2007; 15: 508–511
29. Rossi GP, Seccia TM, Miotto D *et al.* The medical and endovascular treatment of atherosclerotic renal artery stenosis (METRAS) study: rationale and study design. J Hum Hypertens 2012; 26: 507–516
30. Ives NJ, Wheatley K, Stowe RL *et al.* Continuing uncertainty about the value of percutaneous revascularization in atherosclerotic renovascular disease: a meta-analysis of randomized trials. Nephrol Dial Transpl 2003; 18: 298–304
31. Nordmann AJ, Woo K, Parkes R *et al.* Balloon angioplasty or medical therapy for hypertensive patients with atherosclerotic renal artery stenosis? A meta-analysis of randomized controlled trials. Am J Med 2003; 114: 44–50
32. Kumbhani DJ, Bavry AA, Harvey JE *et al.* Clinical outcomes after percutaneous revascularization versus medical management in patients with significant renal artery stenosis; a meta-analysis of randomized controlled trials. Am Heart J 2011; 161: 622–630
33. Shetty R, Biondi-Zoccai GG, Abbate A *et al.* Percutaneous renal artery intervention versus medical therapy in patients with renal artery stenosis: a meta-analysis. EuroIntervention 2011; 7: 844–851
34. White CJ. Kiss my Astral: one seriously flawed study of renal stenting after another. Catheter Cardiovasc Interv 2010; 75: 305–307
35. Henry M, Benjelloun A, Henry I *et al.* Renal angioplasty and stenting: is it still indicated after ASTRAL and STAR studies? J Cardiovasc Surg 2010; 51: 701–720
36. Sarac TP. Influence and critique of the ASTRAL and CORAL Trials. Semin Vasc Surg 2011; 24: 162–166
37. Giannattasio C, Failla M, Hennig M *et al.* Different relation between 24-h blood pressure and distensibility at different peripheral arteries. Data from the European Lacidipine Study on Atherosclerosis (ELSA). J Hypertens 2005; 23: 557–562
38. Safian RD, Madder RD. Refining the approach to renale artery revascularization. J Am Coll Cardiol Cardiovasc Interv 2009; 2: 161–174
39. Hansen KJ, Lundberg AH, Benjamin ME *et al.* Is renal revascularization in diabetic patients worthwhile? J Vasc Surg 1996; 24: 383–393
40. Burnier M, Brown RE, Ong SH *et al.* Issues in blood pressure control and the potential role of single-pill combination therapies. Int J Clin Pract 2009; 63: 790–798

41. Khosla S, White CJ, Collins TJ *et al.* Effects of renal artery stent implantation in patients with renovascular hypertension presenting with unstable angina or congestive heart failure. Am J Cardiol 1997; 80: 363–366
42. Vis MM, Sjauw KD, van der Schaaf RJ *et al.* In patients with ST-segment elevation myocardial infarction with cardiogenic shock treated with percutaneous coronary intervention, admission glucose level is a strong independent predictor for 1-year mortality in patients without a prior diagnosis of diabetes. Am Heart J 2007; 154: 1184–1190
43. Ergelen M, Uyarel H, Cicek G *et al.* Which is worst in patients undergoing primary angioplasty for acute myocardial infarction? Hyperglycaemia? Diabetes mellitus? Or both? Acta Cardiol 2010; 65: 415–423
44. Cicek G, Uyarel H, Ergelen M *et al.* Hemoglobin A1c as a prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. Coron Artery Dis 2011; 22: 131–137
45. Garovic VD, Textor SC. Renovascular hypertension and ischemic nephropathy. Circulation 2005; 112: 1362–1374

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The ESA scenario gets complex: from biosimilar epoetins to activin traps

Wolfgang Jelkmann

Institute of Physiology, University of Luebeck, Luebeck, Germany

Correspondence and offprint request to: Wolfgang Jelkmann; E-mail: Jelkmann@physio.uni-luebeck.de

ABSTRACT

Recombinant human erythropoietin (rhEpo, epoetin) has proved beneficial in preventing transfusion-dependent anaemia in patients with chronic kidney disease. Apart from copied epoetins distributed in less regulated markets, 'biosimilar' epoetins have gained currency in many regions, where they compete with the originals and with rhEpo analogues with prolonged survival in circulation ('biobetter'). Recombinant erythropoiesis stimulating agents are potent and well tolerated. However, their production is costly, and they must be administered by the parenteral route. Hence, other anti-anaemia treatments are being evaluated. Clinical trials are being performed with stabilizers of the hypoxia-inducible transcription factors (HIFs), which increase endogenous Epo production. HIF stabilizers are chemical drugs and they are active on oral administration. However, there is fear that they may promote tumour growth. Epo mimetic peptides have also raised expectations. Yet the prototype peginesatide was recalled after just 1 year of its widespread use in the USA because of serious side-effects including cases of death. Most recently, clinical trials have been initiated with sotatercept, a recombinant soluble activin receptor type 2A IgG-Fc fusion protein. Sotatercept binds distinct members of the transforming growth factor-β family, thereby preventing the inhibitory action of these factors in erythropoiesis. Taken together, rhEpo and its long-acting recombinant analogues will likely remain mainstay of anti-anaemia therapies in the near future.

Keywords: activin, anaemia, biosimilars, chronic kidney disease, erythropoiesis-stimulating agents

INTRODUCTION

Erythropoietin (Epo) is essential for the growth of colony-forming units-erythroid (CFU-Es) and other erythrocytic progenitors. Insufficient Epo production contributes to the anaemia associated with chronic kidney disease (CKD). Treatment with erythropoiesis-stimulating agents (ESAs) can reduce the requirements for red blood cell (RBC) transfusion. Recombinant human Epo (rhEpo, epoetin) has been applied in the renal setting for over 25 years. Recently, copy versions of epoetins have received marketing authorization in many regions, including the European Union (EU). In addition, second-generation rhEpos with improved pharmacokinetic properties have become therapeutic options.

The administration of rhEpo and its analogues is effective and rarely associated with serious adverse events (SAEs). However, recombinant ESAs are expensive and they require a parenteral route of administration. Hence, alternative