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Percutaneous revascularization for atherosclerotic renal artery stenosis: a meta-analysis

Y. LI[1], W.-H. CUI[1], J. WANG[1], X. CHEN[1], C. ZHANG[1], L.-Z. ZHU[1], S.-J. CUI[2], C.-J. BIAN[1], T. LUO[1]

[1]Department of General Surgery, [2]Department of Vascular Surgery, Xuanwu Hospital, Capital Medical University, Beijing, China

Abstract. – OBJECTIVE: This study investigates whether medication therapy alone is as effective and safe as percutaneous revascularization (PR) in patients with atherosclerotic renal artery stenosis (ARAS).

MATERIALS AND METHODS: The Embase, PubMed, and Cochrane Library databases were searched from their inception to July 31, 2021, for randomized controlled trials (RCTs) reporting PR for ARAS. RevMan 5.3 was employed to analyze the retrieved articles.

RESULTS: Eight studies with a total of 2,225 ARAS patients were included in this analysis, demonstrating that PR and medication therapy alone had a similar effect on both systolic [mean difference (MD)= 0.19, 95% CI: -1.64- 2.02] and diastolic blood pressure (MD= -0.44, 95% CI: -1.68-0.80). Meanwhile, there were no differences in all-cause mortality [Odds ratio (OR) = 0.89, 95% CI: 0.70-1.14], stroke (OR = 0.84, 95% CI: 0.55-1.31), congestive heart failure (OR = 0.89, 95% CI: 0.67-1.19), and perioperative complications (OR = 0.87, 95% CI: 0.68-1.12).

CONCLUSIONS: Medication therapy alone is as effective and safe as PR.

Key Words:
Atherosclerotic renal artery stenosis (ARAS), Meta-analysis, Percutaneous revascularization (PR), Medication therapy alone.

Introduction

Atherosclerotic renal artery stenosis (ARAS) is common in patients with peripheral vascular atherosclerosis[1,2] and is recognized as a cause of secondary hypertension,[3] as well as contributing to cardiovascular disease development[4]. Treatment options for ARAS mainly included percutaneous revascularization (PR) and medication therapy alone[5-8].

PR with or without stenting has gained growing interest for treating ARAS[9,10] as it could lead a better blood pressure control and reduction in the number of antihypertensive agents[11-15]. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines strongly recommend PR for ARAS patients regardless of whether they have resistant hypertension or progressing kidney disease[16]. Additionally, several studies demonstrated that PR is a safe treatment for ARAS[17,18]. However, few investigations compared the efficacy and safety of PR and medication therapy alone. Thus, this meta-analysis was conducted to evaluate the efficacy and safety of PR in ARAS patients.

Materials and Methods

Search Strategy

From inception to July 31, 2021, the Embase, PubMed, and the Cochrane Library were searched using the following terms: ("Atherosclerotic Renal Artery Stenosis" OR "ARAS") AND ("Percutaneous revascularization" OR "PR" OR "Stenting" OR "angioplasty"). The references of other meta-analyses were also manually searched to identify additional trials. Publication language was confined to English.

Inclusion and Exclusion Criteria

The following selection criteria were employed to perform the analysis according to Patient-Intervention-Comparison-Outcome-study (PICOS) principles. Participants (P): patients who were diagnosed as ARAS. Intervention (I): percutaneous revascularization (PR). Comparison (C): medication therapy alone. Outcomes (O): (1) effectiveness: reduction of systolic blood pressure (SBP) and diastolic blood pressure (DBP); (2) safety: all-cause mortality, stroke, congestive heart failure, and perioperative complications. Study de-

Corresponding Author: Tao Luo, MD; e-mail: TaoLuo35@126.com

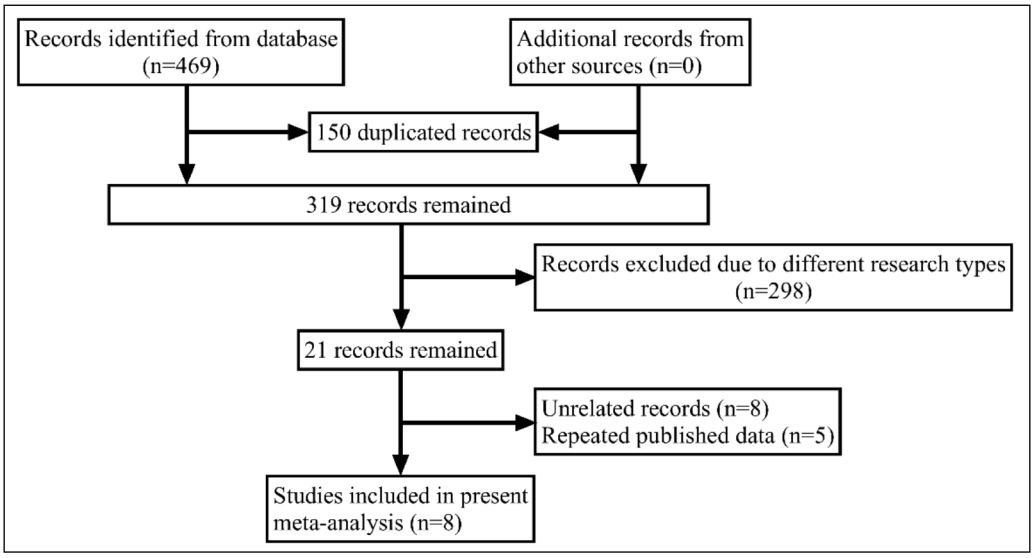

Figure 1. Flow chart of literature screening and selection process.

sign (S): randomized controlled trials (RCTs). Reviews, editorials, letters, case reports, cell and animal studies, or expert opinions were excluded.

Data Extraction and Synthesis

The study characteristics (study title and publication year, design, sample size, gender, mean age, history of diabetes mellitus, and smoking) are summarized in Table I. Reduction of SBP and DBP by the end of the follow-up period were calculated to determine the efficacy of PR compared to medication therapy alone according to the following formula:

$$AVE_{\Delta BP} = \overline{BP}_2 - \overline{BP}_1,\ S_{\Delta BP} = \sqrt{S_2^2 + S_1^2}.$$

Data regarding all-cause mortality, stroke, congestive heart failure, and perioperative complications were recorded to determine whether PR was as safe as medication therapy alone (Table II).

Statistical Analysis

Two reviewers independently screened and evaluated the quality of the included studies. Any discrepancies were resolved through discussion and consultation with a third researcher if necessary. The Cochrane tool was utilized to evaluate the quality of included studies (Table III). For pooled study results, Cochran's Q test and the degree of inconsistency (I^2) were employed to assess heterogeneity. I^2 values of <25%, 25-50%, and >50% were considered low, moderate, and high heterogeneity, respectively. A fixed-effects model was utilized if I^2 was less than 50%; otherwise, a random-effects model was applied. Publication bias was estimated from a funnel plot (**Supplementary Figure 1**), with a symmetrical funnel plot indicating an insignificant publication bias. The odds ratio (OR) and mean difference (MD) were calculated to combine categorical and continuous variables, respectively[19-21]. *p*-values less than 0.05 were considered statistically significant. Review Manager 5.3 software (Cochrane Collaboration, London, United Kingdom) was used for the present analysis.

Ethical approval was not required for this study, and the article has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist[22]. The present meta-analysis was conducted following an established protocol (INPLASY202270052).

Results

Search Results

A total of 469 articles were identified, of which 150 duplicated articles were removed. After reading the titles and abstracts, 298 articles were excluded due to their different research types, and the full texts of the remaining 21 were evaluated. Eight and five studies were excluded because of an unrelated topic and repeated published data, respectively. Ultimately, eight articles[17,18,23-28] comprising 2,225 patients were included in the meta-analysis. Of the eight included studies, seven were RCTs, and the other study was noted in a meeting abstract and not published elsewhere. A flow diagram of selection process is shown in Figure 1.

Table I. Characteristics of included studies.

Study, year		STAR, 2009[23]	DRASTIC, 2000[24]	ARSTRAL, 2009[17]	Webster, 1998[18]	EMMA, 1998[25]	CORAL, 2014[26]	RADAR, 2017[27]	NITER, 2009[28]
Study design		RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Country		Netherland	Netherland	UK	Scotland	France	USA	Germany	Italy
Sample size	PR	64	56	403	25	23	459	45	28
	MED	76	50	403	30	26	472	41	24
Mean age (year)	PR	66±8	59±10	70 (42-86)	61.1	59.2±8.4	69.3±9.4	67.2±8.4	72
	MED	67±9	61±10	71 (43-88)		59.5±10.8	69.0±9.0	64.8±12.1	
Gender (M/F)	PR	43/21	37/19	254/149	44,879	44,699	234/225	32/13	31/21
	MED	45/31	28/22	253/150	44,913	44,791	230/242	28/13	
Diabetes mellitus-no. (%)	PR	16 (30)	3(5)	121 (30)	N-R	6 (26)	149 (32.4)	14 (31.1)	32 (61.6)
	MED	18 (31)	3(6)	115 (28.5)		4 (15)	162 (34.3)	16 (39.0)	
Smoking-no. (%)	PR	46 (72)	46 (82)	276 (68.5)	9 (36)	15 (65)	128 (28)	25 (55.6)	25 (48.2)
	MED	52 (68)	35 (70)	301 (74.7)	15 (50)	16 (62)	152 (32.2)	20 (48.8)	

RCT: randomized controlled trial; PR: percutaneous revascularization; MED: medication therapy; N-R: Not report.

Table II. Outcomes of included studies.

Study, year		STAR, 2009[23]	DRASTIC, 2000[24]	ARSTRAL, 2009[17]	Webster, 1998[18]	EMMA, 1998[25]	CORAL, 2014[26]	RADAR, 2017[27]	NITER, 2009[28]
Reduction of SBP (mmHg)	PR	-9±33.97	-19±36.07	-5.8±21	N-R	-12±20	-16.6±21.2	-7±11.5	-5±18
	MED	-8±36.77	-17±33.97	-8.1±20.7		-8±16	-15.6±25.8	-5±14	-6±15
Reduction of DBP (mmHg)	PR	-6±14.59	-11±16.4	-3.4±11.3	N-R	-10±11	N-R	-4±8	-3±14
	MED	-3±16.28	-7±12.81	-3.6±11.8		-5±10		-4±6.5	90-7±8
All-cause mortality	PR	5	N-R	79	2	N-R	63	1	N-R
	MED	6		81	4		76	1	
Stroke	PR	0	N-R	19	1	N-R	18	N-R	N-R
	MED	1		18	4		23		
Congestive heart failure	PR	1	N-R	44	3	N-R	39	N-R	18
	MED	3		55	4		39		14
Perioperative complications	PR	10	1	46	2	0	77	N-R	N-R

PR: percutaneous revascularization; MED: medication therapy; SBP: systolic blood pressure; DBP: diastolic blood pressure; N-R: Not report.

Table III. The Cochrane risk of bias tool for assessing the quality of randomized controlled trials included in meta-analysis.

RCTs	Random sequence generation	Allocation concealment	Blinding of participants and Personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other biases
STAR, 2009[23]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
DRASTIC, 2000[24]	Un-report	Un-report	High risk	Un-report	Low risk	Low risk	Low risk
ARSTRAL, 2009[17]	Low risk	Low risk	High risk	Un-report	Low risk	Low risk	Low risk
Webster, 1998[18]	Low risk	Low risk	High risk	Un-report	Low risk	Low risk	Low risk
EMMA, 1998[25]	Low risk	Low risk	High risk	Un-report	Low risk	Low risk	Low risk
CORAL, 2014[26]	Low risk	Low risk	High risk	Un-report	Low risk	Low risk	Low risk
RADAR, 2017[27]	Low risk	Un-report	High risk	Un-report	Low risk	Low risk	Low risk
NITER, 2009[28]	Low risk	Low risk	High risk	Un-report	Low risk	Low risk	Low risk

RCT: randomized controlled trial.

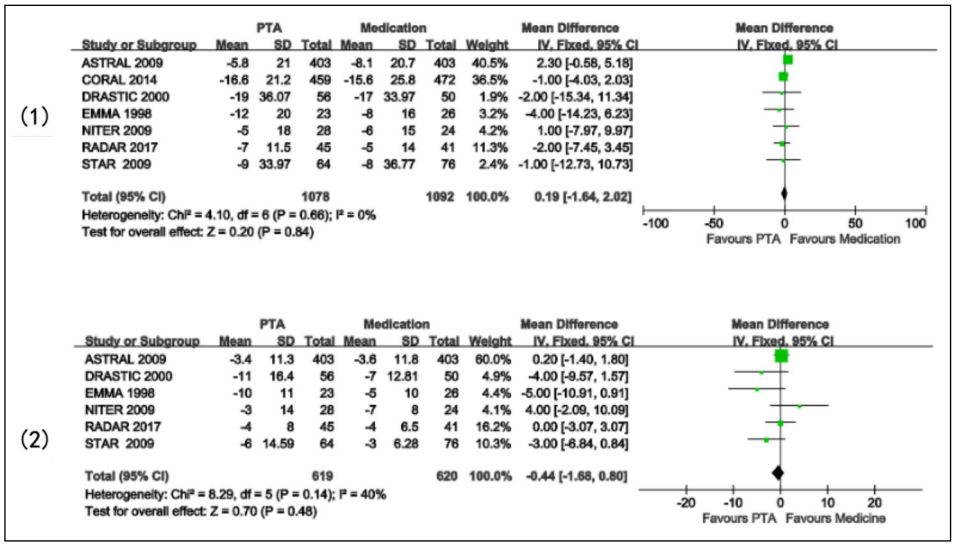

Figure 2. Meta-analysis of reduction of systolic blood pressure (1) and diastolic blood pressure (2)

Characteristics of Included Studies

Characteristics of all included studies published between 1998 and 2017 are summarized in Table I. Most studies were conducted in Europe, while one was performed in the USA. The study sample size ranged from 49 to 931, and the meta-analysis comprised 2,225 patients, including 1,103 with a stenotic renal artery undergoing PR and 1,122 treated with medication therapy alone.

Efficacy and Safety of PR for ARAS

Seven studies reported the data about SBP reduction[17,23-28], and six reported DBP reduction[17,23-25,27,28]. Detailed data about efficacy and safety is provided in Table II. The pooled results revealed no significant differences between PR and medication therapy alone regarding SBP reduction (MD = 0.19, 95% CI: -1.64-2.02) and DBP reduction (MD =-0.44, 95% CI: -1.68-0.80) (Figure 2). Five[17,18,23,26,27], four[17,18,23,26], five[17,18,23,26,28] and six[17,18,23-26] studies reported data about all-cause mortality, stroke, congestive heart failure, and perioperative complications, respectively. There were no significant differences between PR and medication therapy alone in all-cause mortality (OR = 0.89, 95% CI: 0.70-1.14), stroke (OR = 0.84, 95% CI: 0.55-1.31), congestive heart failure (OR = 0.89, 95% CI: 0.67-1.19), and perioperative complications (OR = 0.87, 95% CI: 0.68-1.12, Figure 3).

The methodological quality assessment of included studies is shown in Table III. Due to the limitation of study characteristics, all scores of "Blinding of Participants and Personnel" were "high risk". The symmetrical funnel plots indicate a slight publication bias (**Supplementary Figure 1**).

Discussion

This meta-analysis of eight RCTs investigating the efficacy and safety of PR and medical therapy for ARAS indicated that PR had a similar impact on efficacy (reduction of SBP and DBP) and safety (mortality, stroke, congestive heart failure, and perioperative complications) compared with medication therapy alone in ARAS patients, consistent with the results from several published studies[29-31]. PR is a common treatment for ARAS. However, it seems counterintuitive that PR was not associated with reduced blood pressure and complications.

ARAS could result in ischemic nephropathy, which is defined as a reduction in glomerular filtration rate (GFR) and ultimately, could result in resistant secondary hypertension[32]. However, secondary hypertension caused by ischemic nephropathy is not only caused by renal artery stenosis. Since the kidney needs only 10% blood flow to maintain normal metabolism, a decrease in blood flow alone cannot account for secondary hypertension and a decline in kidney function[33]. Numerous studies have demonstrated that a kidney with insufficient blood supply could activate the renin-angiotensin-aldosterone (RAS) path-

way,[34,35] which may be the major cause of secondary hypertension in ARAS patients. In addition, the RAS pathway could activate inflammatory and profibrogenic pathways and produce reactive oxygen species, resulting in irreversible glomerular damage[36-38]. Therefore, PR of renal artery may not be able to reverse the pathological change. Several investigations have attempted to elucidate the mechanism and pathways of irreversible kidney injury[39].Therefore, future studies should focus on elucidating the pathways of irreversible kidney injury from ARAS.

Limitations

We acknowledged the limitations of our study. First, the data remained limited with small sample size, although all included studies were RCTs. Second, some subgroups may be excluded due to their limited number of studies. Finally, most studies were performed at a single center; therefore, multicenter studies with a larger sample size should be conducted to validate the findings. Accordingly, the conclusions must be interpreted in the context of individual studies.

Conclusions

This meta-analysis demonstrated that medication therapy alone had a similar impact on efficacy (reduction of SBP and DBP) and safety (mortality, stroke, congestive heart failure, and perioperative complications) compared with PR in ARAS patients.

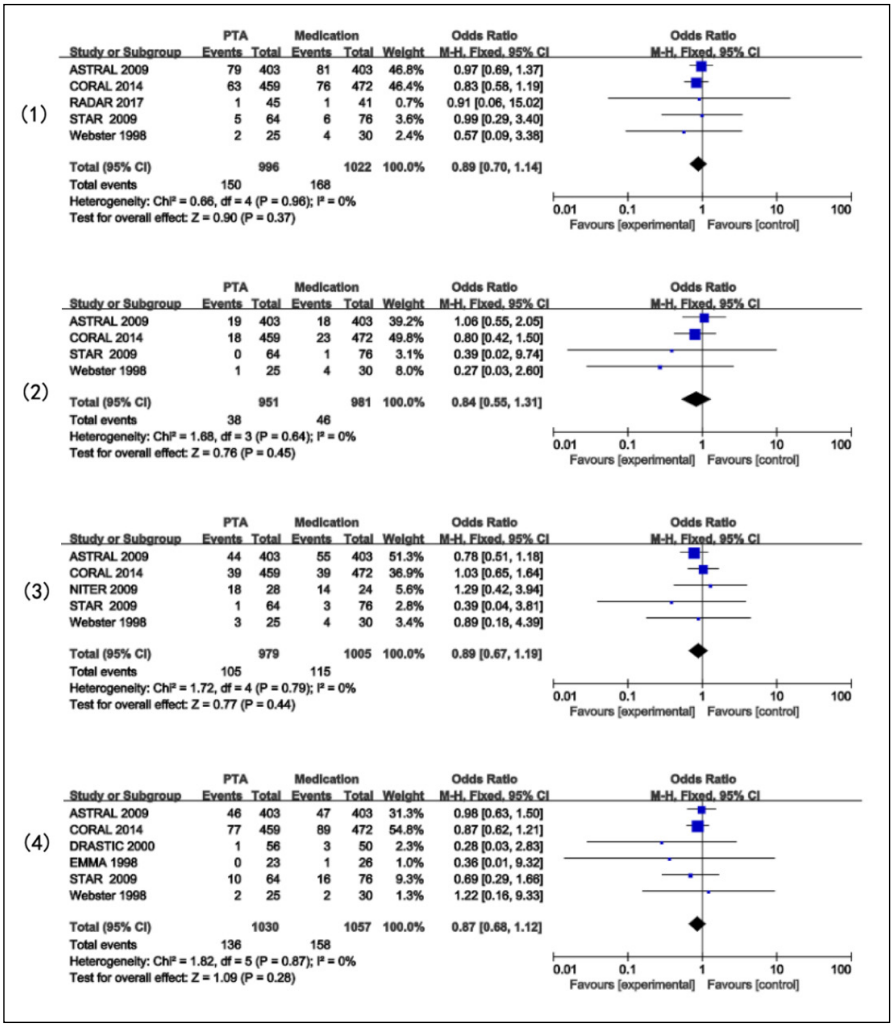

Figure 3. Meta-analysis of PTA for all-cause mortality (1), stroke (2), congestive heart failure (3), and periprocedural complications (4).

Conflict of Interest

The authors have declared that no conflict of interest exists.

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None.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Authors' Contributions

(I) Conception and design: Shijun Cui, Tao Luo; (II) Administrative support: Linzhong Zhu, Chunjing Bian, Tao Luo; (III) Provision of study materials or patients: Yu Li, Wenhao Cui, Jukun Wang; (IV) Collection and assembly of data: Yu Li, Wenhao Cui, Jukun Wang; (V) Data analysis and interpretation: Yu Li. Xin Chen, Chao Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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