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CLINICAL RESEARCH
Clinical trials

Fractional flow reserve-guided renal artery stenting in atherosclerotic renovascular hypertension: the FAIR randomized trial

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Abstract

Background and Aims The optimal therapy for patients with atherosclerotic renal artery stenosis (ARAS) remains unresolved. This study compared the efficacy of renal fractional flow reserve (FFR)-guided revascularization and traditional angiography-guided revascularization.

Methods In total, 101 patients with ARAS and hypertension were randomly assigned to either the FFR-guided or angiography-guided group (ClinicalTrials.gov identifier: NCT05732077). Stenting was performed in the angiography-guided group regardless of FFR, whereas stenting was only performed in the FFR-guided group for patients with FFR < 0.80. The primary endpoints were the percentage changes in ambulatory daytime mean systolic blood pressure (DMSBP) and composite index of antihypertensive medicines (CIAHM) after 3 months.

Results The percentage changes in DMSBP (4% [−2%, 11%] vs 4% [−3%, 10%]; $P = .97$) and CIAHM (0% [0%, 3%] vs 1% [0%, 4%]; $P = .33$) did not differ between groups. However, the rate of stenting was significantly lower in the FFR-guided group (46.0% vs 100.0%, $P < .01$). Moreover, compared with the findings in patients with FFR ≥ 0.80 who did not receive stenting, stenting

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was beneficial in patients with FFR < 0.80 (adjusted mean DMSBP reduction, 6.2 [95% confidence interval {CI}, 0.6–11.9] mmHg; mean CIAHM reduction, 3.1 [95% CI, 1.5–4.7]), but not in those with FFR ≥ 0.80 (1.4 [95% CI, −4.5–7.2] mmHg, and 0.7 [95% CI, −1.1–2.5], respectively).

Conclusions FFR-guided revascularization significantly reduced unnecessary stenting compared with angiography-guided revascularization. Both blood pressure and antihypertensive medication usage decreased significantly after stenting in patients with FFR < 0.80.

Structured Graphical Abstract

Key Question

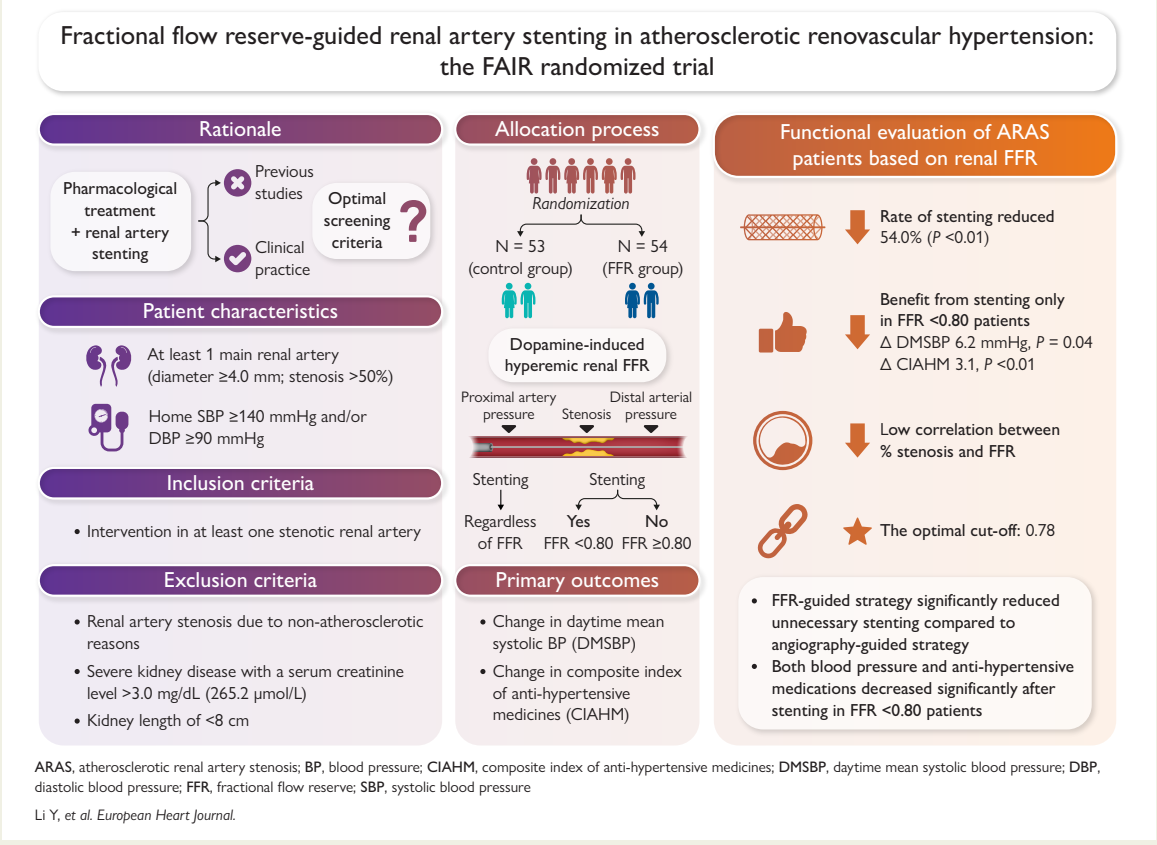
Can fractional flow reserve (FFR)-guided revascularization improve blood pressure control in patients with atherosclerotic renal artery stenosis (ARAS) and hypertension?

Key Finding

In this trial, FFR-guided revascularization significantly reduced the rate of stenting compared with the traditional angiographic-guided strategy, while achieving the same level of blood pressure control.

Take Home Message

Functional evaluation of ARAS with FFR significantly reduces the number of renal stents without compromising the positive effect of stenting on blood pressure. This might impact on the management of stenting for ARAS.



ARAS, atherosclerotic renal artery stenosis; **BP**, blood pressure; **CIAHM**, composite index of anti-hypertensive medicines; **DMSBP**, daytime mean systolic blood pressure; **DBP**, diastolic blood pressure; **FFR**, fractional flow reserve; **SBP**, systolic blood pressure

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Keywords Atherosclerotic renal artery stenosis • Hypertension • Fractional flow reserve • Stenting • Daytime mean systolic blood pressure • Composite index of antihypertensive medicines

Introduction

Renovascular hypertension is a common form of secondary hypertension, occurring in ~0.1%–5% of all individuals with hypertension and up to 20% of patients with secondary hypertension.[1] Atherosclerotic renal artery stenosis (ARAS) is the predominant form of renovascular hypertension, and it is associated with resistant hypertension, ischaemic nephropathy, cardiac complications, and mortality.[1,2] Since its introduction in 1978,[3] percutaneous renal artery intervention had proven effective in reducing blood pressure (BP) and other clinical outcomes in clinical

practice and observational studies.[4,5] Although percutaneous renal artery intervention had been routinely used in clinical practice,[6,7] three recent randomized controlled trials (RCTs) consistently failed to demonstrate the additional benefit of stenting compared with optimal medical therapy alone.[8–10] Consequently, revascularization in ARAS has been weakly recommended (IIb, level of evidence C) by clinical guidelines,[11] and the use of revascularization in patients with ARAS has significant declined over the last decade,[12,13] suggesting that the procedure might be omitted in some patients who would benefit. Thus, identifying patients most likely to benefit from revascularization is an important clinical issue that needs to be urgently resolved.

A major criticism of the previous RCTs is that they enrolled too many subjects who were unlikely to benefit from stenting. For example, fewer than 50% of all participants had severe stenosis, defined as >80% blockage of an artery. Pathophysiological studies described a compensatory mechanism by which the kidney could withstand substantial reductions (30%–40%) in blood flow without exacerbation of tissue hypoxia.[1,14,15] Meanwhile, experience from percutaneous coronary intervention (PCI) clearly demonstrated the superiority of a fractional flow reserve (FFR)-guided strategy over an angiography-guided strategy.[16,17]

Previous studies demonstrated that the hyperaemic translesional gradient or FFR could predict patients' BP response after stenting,[18–23] indicating functional evaluation might play a role in identifying appropriate patients with who are suitable for revascularization. To the best of our knowledge, functional assessment with renal FFR in ARAS revascularization has not been investigated in an RCT. Thus, this investigator-initiated pilot trial was designed to answer the following questions: (i) is it feasible to measure FFR in patients with ARAS; (ii) do clinical outcomes differ between FFR-guided and conventional angiography-guided stenting decisions; and (iii) what is the optimal FFR cut-off for predicting BP reduction after stenting. The results of this pilot study will guide the design of future RCTs.

Methods

Study design

The Fractional flow reserve to determine the Approprlateness of percutaneous Renal artery intervention in atherosclerotic renovascular hypertension patients (FAIR) pilot study was an investigator-initiated, multicentre, open-label, blinded endpoint RCT conducted in 24 centres in China (ClinicalTrials.gov identifier: NCT05732077). The research protocol of this study was approved by the ethics committee of Peking University First Hospital (Beijing, China, No. 2022-457). All participants provided written informed consents during the screening. Outcomes were reviewed and adjudicated by an independent endpoint adjudication committee whose members did not participate in the study. The trial protocol and statistical analysis plan are presented in *Supplement S1*.

Participants

Adults with ARAS who underwent renal artery angiography for uncontrolled hypertension while taking two or more antihypertensive medicines were screened for 1 week. During this screening period, home BP measurements were performed using a validated automated BP monitor (Omron Healthcare, Kyoto, Japan) with Bluetooth functionality to automatically upload results. In addition, antihypertensive medications were fixed to standardize of BP management. If home systolic BP was ≥140 mmHg and/or diastolic BP was ≥90 mmHg, validated 24 h ambulatory BP monitoring (ABPM, ABP-021, Beneware, Hangzhou, China) was conducted during the baseline visit and in each visit during follow-up. After standardized renal artery angiography, patients with >50% stenosis in at least one main artery and diameter ≥ 4.0 mm were enrolled. If the investigators determined that intervention was needed in at least one stenotic renal artery, then the patient was randomized. The main exclusion criteria were similar to those of the CORAL study,[10] including renal artery stenosis attributable to non-atherosclerotic reasons, severe kidney disease with a serum creatinine level exceeding 3.0 mg/dL (265.2 μmol/L) and kidney length shorter than 8 cm. The complete inclusion and exclusion criteria are presented in *Supplement S1*.

Randomization and interventions

Before renal FFR was measured, all eligible patients were randomly assigned to the FFR-guided strategy (FFR group) or traditional angiography-guided strategy group (control group), ensuring unbiased treatment allocation at a 1:1 ratio. A central randomization mobile app with interactive response technology was used in all centres.

Hyperaemic renal FFR was measured in all eligible lesions in all participants using a 0.014 in pressure guidewire (Abbott, Abbott Park, IL, USA) through a 6 F or 7 F guiding catheter according to a previously reported protocol.[21] A bolus of dopamine (50 μg/kg) was administered intrarenally to induce maximal hyperaemia. To guarantee that dopamine was successfully administrated into the renal artery rather than into the aorta, all investigators (one or two experienced operators in each centre) were trained to properly engage the guiding catheter and gently insert it into the renal artery before dopamine and the following saline bolus were administered through the guiding catheter after which the guiding catheter was then positioned back at the ostium. FFR was calculated as the ratio of mean hyperaemic distal renal artery pressure measured by the pressure wire to mean aortic pressure measured by the guiding catheter. FFR was not recorded until the value stabilized, which required more than 10 min in some patients.

Among patients randomized to the control group, stenting was performed regardless of renal FFR, whereas among those randomized to the FFR group, stenting was only performed in those with FFR < 0.80.

Primary outcome and follow-up

Considering the possible influence of antihypertensive medication changes on BP, the study had two primary endpoints, including the percentage change in daytime mean systolic BP (DMSBP) as measured by ABPM from baseline to 3 months postprocedure and the change in the composite index of antihypertensive medicines (CIAHM), which was calculated as follows:

$$\text{CIAHM} = \text{weight(number of classes of antihypertensive medicines)} \times \text{(sum of doses)}.[24,25]$$

The secondary endpoints included the changes in 24 h and night-time mean systolic and diastolic BP as measured by ABPM, changes in home and office BP during follow-up, cardiovascular and renal outcomes (death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, the need for renal replacement therapy), and all-cause mortality at 1 year.

Participants were scheduled for follow-up visits at 3, 6, and 12 months postprocedure. At each follow-up visit, validated ABPM, vital signs, antihypertensive medication use, concomitant medication use, renal function, and possible adverse cardiovascular and renal events were documented by trained research staff and physicians. The investigators were asked to avoid changing the antihypertensive medications during the 3 months of follow-up in the protocol.

Statistical analysis

All comparisons were made on an intention-to-treat basis, including all participants who were randomized to the study groups. However, participants who were lost to follow-up were excluded from the analysis set for primary endpoints. Sensitivity analyses were conducted to assess the effects of these exclusions. Continuous values were presented as the mean and standard deviation or median (interquartile range [IQR]) as appropriate.

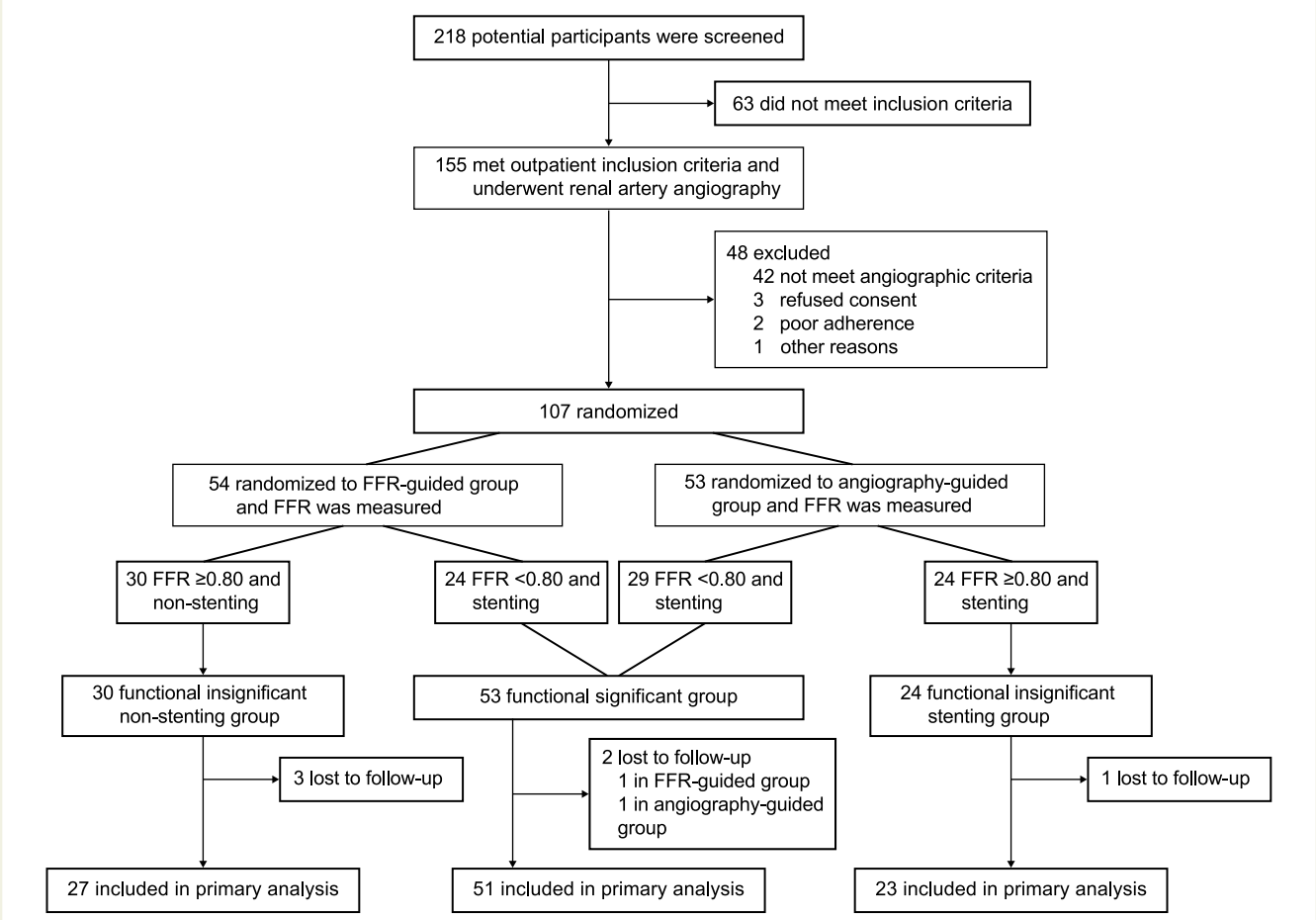

Figure 1 Patient flow diagram. FFR, fractional flow reserve

Categorical variables were reported as frequencies and percentages. Comparisons of continuous data between the two groups were conducted using a *t*-test or Wilcoxon's ranked sum test, whereas analysis of variance and the Kruskal–Wallis test were used for comparisons among three groups. Categorical data were tested using the chi-squared test or Fisher's exact test. A paired *t*-test or McNemar's test was applied for comparisons between before and after treatment.

To explore the effect of stenting in populations with different functional significance, we further divided the participants into three groups: FFR ≥ 0.80 and non-stenting (functional insignificant non-stenting group, as the control group), FFR ≥ 0.80 and stenting (functional insignificant stenting group), and FFR < 0.80 and stenting (functional significant stenting group). A linear regression model was used to compare treatment efficacy regarding the primary outcomes defined as the reductions in DMSBP and CIAHM from baseline to 3 months after the procedure among the groups. The covariatees were adjusted for baseline characteristics potentially associated with the treatment groups or efficacy, including age, sex, DMSBP, CIAHM, and estimated glomerular filtration rate (eGFR). We also performed subgroup analyses according to prespecified subgroups including sex (male or female), age (>65 years or ≤65 years), presence or absence of diabetes, eGFR (>45 mL/min/1.73 m^2 or ≤45 mL/min/1.73 m^2) and baseline systolic BP (>150 mmHg or ≤150 mmHg) to identify possible modification effects on treatment efficacy.

Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off of renal FFR in predicting BP improvement (as a dichotomous variable defined as DMSBP reduction > 10 mmHg with no increase in antihypertensive drug use) at 3 months. The cut-offs that yielded the best Youden's index were selected.

All analyses were performed using R software, version 4.3.1 (http://www.R-project.org). $P < .05$ was considered significant, and all tests were two-tailed. Because this was a pilot study, no prior sample size calculation was performed.

Results

Study participants and baseline characteristics

As presented in *Figure 1*, among the 155 candidates screened, 107 patients with a median (IQR) age of 63 years (57, 70) were enrolled from 13 centres throughout China from 6 February 2023 to 21 February 2024. Of these patients, 54 and 53 were randomly assigned to the FFR and control groups, respectively (see Supplementary data online, *Table S1*). The primary endpoints were assessed at the 3-month follow-up in 101 patients, reflecting a 5.6% loss to follow-up. The baseline characteristics of the two groups were similar (*Table 1*). FFR was measured in all stenotic renal arteries, and the mean diameter of stenosis and FFR in all participants were 75.7% ± 14.3% and 0.76 ± 0.17, respectively.

Among all patients, FFR was measured in 147 stenotic renal arteries, and the correlation between FFR and stenosis severity assessed by

Table 1 Baseline characteristics of the study population

Characteristic	Overall *N* = 101	FFR-guided group *N* = 50	Angiography-guided group *N* = 51
Age, median [IQR], years	63 [57, 69]	64 [59, 72]	62 [57, 68]
Male sex, *n* (%)	62 (61.4)	28 (56.0)	34 (66.7)
Baseline 24 h ABPM, median [IQR], mmHg			
Daytime SBP	138 [125, 146]	140 [126, 146]	137 [125, 145]
Daytime DBP	80 [74, 89]	81 [75, 90]	80 [73, 88]
Baseline CIAHM, median [IQR]	4 [3, 9]	4 [4, 10]	6 [3, 9]
Baseline number of medicines, *n* (%)			
2	57 (56.4)	30 (60.0)	27 (52.9)
3	32 (31.7)	12 (24.0)	20 (39.2)
4	9 (8.9)	6 (12.0)	3 (5.9)
≥5	3 (3.0)	2 (4.0)	1 (2.0)
Baseline antihypertensive medication, *n* (%)			
ACEis/ARBs	62 (61.4)	32 (64.0)	30 (58.8)
Diuretics	21 (20.8)	13 (26.0)	8 (15.7)
CCBs	89 (88.1)	44 (88.0)	45 (88.2)
Beta-blockers	62 (61.4)	30 (60.0)	32 (62.7)
Alpha-blockers	9 (8.9)	5 (10.0)	4 (7.8)
Others	15 (14.9)	8 (16.0)	7 (13.7)
Baseline eGFR, median [IQR], mL/min/1.73 m^2	55.8 [39.2, 72.0]	52.0 [33.2, 70.2]	56.0 [42.2, 73.0]
Stage ≥ 3 chronic kidney disease, *n* (%)	63 (62.4)	34 (68.0)	29 (56.9)
Medical history and risk factors, *n* (%)			
Hypertension	95 (94.1)	47 (94.0)	48 (94.1)
Diabetes	49 (48.5)	24 (48.0)	25 (49.0)
Hyperlipidaemia	80 (79.2)	40 (80.0)	40 (78.4)
Prior coronary artery disease	27 (26.7)	13 (26.0)	14 (27.5)
Prior cerebral disease	18 (17.8)	7 (14.0)	11 (21.6)
Peripheral artery disease	13 (12.9)	4 (8.0)	9 (17.6)
Chronic kidney disease	53 (52.5)	28 (56.0)	25 (49.0)
Prior smoking	53 (52.5)	27 (54.0)	26 (51.0)
Prior drinking	22 (21.8)	9 (18.0)	13 (25.5)
Body mass index, median [IQR], kg/m^2	25.7 [23.2, 26.6]	25.6 [22.7, 26.6]	26.0 [23.4, 26.6]
Procedural characteristics			
Renal FFR, mean (SD)	0.76 (0.17)	0.78 (0.19)	0.75 (0.14)
FFR measurement success, *n* (%)	101 (100)	50 (100)	51 (100)
Percent stenosis, mean (SD)	75.7 (14.3)	74.4 (15.1)	76.9 (13.4)
Stenting, *n* (%)	74 (73.3)	23 (46.0)	51 (100.0)
No. of stenotic renal arteries, *n* (%)			
1	68 (67.3)	36 (72.0)	32 (62.7)
2	30 (29.7)	11 (22.0)	19 (37.3)

Continued

Table 1 *Continued*

Characteristic	Overall N = 101	FFR-guided group N = 50	Angiography-guided group N = 51
≥3	3 (3.0)	3 (6.0)	0 (0.0)
Procedural success, *n* (%)	101 (100)	50 (100)	51 (100)

IQR, interquartile range; ABPM, ambulatory blood pressure monitoring; ACEis, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers; FFR, fractional flow reserve; SBP, systolic blood pressure; DBP, diastolic blood pressure; CIAHM, composite index of antihypertensive medicines; eGFR, estimated glomerular filtration rate; SD, standard deviation.

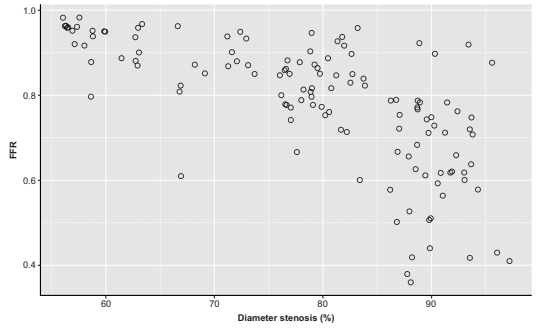

Figure 2 Correlation between renal artery stenosis and renal fractional flow reserve (FFR)

angiography at baseline is presented in *Figure 2*. Even in arteries with severe stenosis, FFR varied over a wide range (correlation coefficient = −0.21, $P = .17$).

Primary endpoints

As presented in *Table 2*, there were no significant differences between the two groups regarding the percentage change in DMSBP reduction (4% [−2, 11] vs 4% [−3, 10]; $P = .97$), absolute change in DMSBP (6 mmHg [−3, 17] vs 5 mmHg [−3, 15]; $P = .99$) or change of CIAHM (0 [0, 3] vs 1 [0, 4]; $P = .33$) at the end of 3 months (*Table 2*). However, the rate of stenting was significantly lower in the FFR group (46.0% vs 100.0%, $P < .01$).

As presented in *Table 3*, subjects with baseline FFR < 0.8 who underwent stenting experienced a significant DMSBP reduction from 140 (128, 154) mmHg to 126 (122, 135) mmHg ($P < .01$), concomitant with a significant reduction in CIAHM from 6 (3, 9) to 2 (1, 5) ($P < .01$). The changes in DMSBP and CIAHM from baseline to 3 months were not statistically significant for the two groups with FFR ≥ 0.80. However, in comparison to the findings in the functional insignificant non-stenting group, stenting was beneficial in the functional significant stenting group (median DMSBP reduction after adjustment, 6.2 mmHg [95% CI, 0.6–11.9], $P = .04$; median CIAHM reduction, 3.1 [95% CI, 1.5–4.7], $P < .01$) but not in the functional insignificant stenting group (median DMSBP reduction after adjustment, 1.4 mmHg [95% CI, −4.5–7.2] mmHg, $P = .65$; median CIAHM reduction, 0.7 [95% CI, −1.1–2.5], $P = .44$) after adjusting for baseline characteristics (*Tables 3* and *4*).

No interaction effect was observed between different prespecified subgroups, including sex, age (>65 years vs ≤65 years), presence or absence of diabetes, eGFR (>45 mL/min/1.73 m^2 vs ≤45 mL/min/1.73 m^2), baseline systolic BP (>150 mmHg vs ≤150 mmHg), with respect to the primary endpoints (see Supplementary data online, *Figures S1–S4*).

Optimal renal fractional flow reserve cut-off for predict BP improvement

All 74 patients who underwent stenting were analysed for improvement in BP, defined as a >10 mmHg improvement in DMSBP with no increase in antihypertensive drug use for 3 months. The ROC curve illustrated that the optimal cut-off of renal FFR for predicting BP improvement was 0.78, with an area under the curve (AUC), sensitivity, and specificity of 0.78, 0.694, and 0.677, respectively (*Figure 3*).

Safety and periprocedural events

Renal FFR measurement, angiography, and stenting were successfully completed in all subjects. The median (IQR) duration to induce hyperaemic FFR for each renal artery lesion during the procedure was 288 s (231, 358). Three (0.28%) periprocedural events were recorded, including haematoma at the puncture site of the femoral artery in one patient in each group. In addition, one person in the control group experienced acute coronary syndrome on the second day after renal artery angiography and FFR measurement, and acute kidney injury occurred after PCI, necessitating dialysis.

Discussion

To the best of our knowledge, this is the first RCT to evaluate the appropriateness of renal FFR in guiding revascularization in patients with ARAS. The main findings of this trial were that renal FFR measurement is feasible and safe in patients with ARAS, the FFR-guided strategy significantly reduced unnecessary stenting and patients with ARAS and hypertension with FFR < 0.8 are most likely to benefit from stenting (see *Structured Graphical Abstract*).

The optimal therapy for ARAS has been intensively debated since the publication of three RCTs reporting no additional benefits of stenting compared with optimal medical therapy alone.[8–10] Previous studies attempted to use functional evaluation to predict BP response after stenting. The rationale of functional evaluation of ARAS was based on the understanding of the pathophysiology of the kidneys after significant stenosis occurs in a renal artery. When blood flow and perfusion pressure decrease to a degree that exceeds the compensatory limit, the pressor system is activated, leading to renin–angiotensin–aldosterone system and sympathetic system activation, vasoconstriction, and sodium retention. The increase in BP is closely related to these changes, and it could be reversed by restoring blood flow. However, if ischaemia persists, then microvessel rarefication and mitochondrial dysfunction

Table 2 Primary outcome assessment

Characteristic	Overall N = 101	FFR-guided group N = 50	Angiography-guided group N = 51	P
Twenty-four–hour ABPM-measured DMSBP, median [IQR], mmHg				
Baseline	138 [125, 146]	140 [126, 146]	137 [125, 145]	.65
Three months of follow-up	129 [123, 140]	132 [123, 142]	129 [123, 137]	.48
Percentage DMSBP reduction, median [IQR], %	4 [−2, 11]	4 [−2, 11]	4 [−3, 10]	.97
Absolute DMSBP reduction, median [IQR], mmHg	5 [−3, 16]	6 [−3, 17]	5 [−3, 15]	.99
CIAHM, median [IQR]				
Baseline	4 [3, 9]	4 [4, 10]	6 [3, 9]	.61
Three months of follow-up	4 [1, 8]	4 [3, 10]	3 [1, 6]	.07
CIAHM reduction, median [IQR]	1 [0, 4]	0 [0, 3]	1 [0, 4]	.33
Renal artery stenting, *n* (%)	74 (73.3)	23 (46.0)	51 (100.0)	<.01

ABPM, ambulatory blood pressure monitoring; IQR, interquartile range; DMSBP, daytime mean systolic blood pressure; CIAHM, composite index of antihypertensive medicines.

Table 3 Primary outcomes in the different treatment groups

Characteristic	FFR < 0.80	FFR ≥ 0.80		P
	Functional significant stenting group N = 51	Functional insignificant non-stenting group N = 27	Functional insignificant stenting group N = 23	
Twenty-four–hour ABPM-measured DMSBP, median [IQR], mmHg				
Baseline	140 [128, 154]	139 [129, 145]	132 [123, 139]	.28
Three months of follow-up	126 [122, 135]	136 [127, 143]	133 [126, 146]	.07
Percentage DMSBP reduction, median [IQR], %	9 [3, 14]	3 [−5, 10]	0 [−4, 4]	<.01
Absolute DMSBP reduction, median [IQR], mmHg	13 [4, 21][a]	4 [−8, 13][b]	0 [−6, 5][c]	<.01
CIAHM, median [IQR]				
Baseline	6 [3, 9]	4 [4, 11]	4 [3, 7]	.21
Three months of follow-up	2 [1, 5]	4 [4, 12]	4 [1, 6]	<.01
CIAHM reduction, median [IQR]	2 [0, 5][d]	0 [0, 2][e]	0 [0, 1][f]	<.01
Renal artery stenting, *n* (%)	51 (100.0)	0 (0.0)	23 (100.0)	<.01

ABPM, ambulatory blood pressure monitoring; DMSBP, daytime mean systolic blood pressure; IQR, interquartile range; CIAHM, composite index of antihypertensive medicines; FFR, fractional flow reserve.
[a]A paired *t*-test was used for comparisons between before and after treatment ($P < .01$).
[b]A paired *t*-test was used for comparisons between before and after treatment ($P = .52$).
[c]A paired *t*-test was used for comparisons between before and after treatment ($P = .39$).
[d]A paired *t*-test was used for comparisons between before and after treatment ($P < .01$).
[e]A paired *t*-test was used for comparisons between before and after treatment ($P = .10$).
[f]A paired *t*-test was used for comparisons between before and after treatment ($P = .34$).

could occur,[26] preventing the recovery of deteriorating kidney function despite the restoration of renal blood flow.[15] Therefore, it is believed that a time window exists in which revascularization could take effect.[1]

Efforts had been made to identify a technique that could capture this time window. Leesar *et al.*[22] identified hyperaemic systolic gradient ≥ 21 mmHg as an independent predictor of BP improvement among 62 patients. Mangiacapra *et al.*[23] conducted a similar study of 53 patients and found that both papaverine- and dopamine-induced renal FFR were predictive of BP response. Because of the limitations of these studies, namely the small sample size and lack of randomization, functional evaluation is not clearly recommended by the current guidelines. Our study is the first to evaluate the advantage of a renal FFR-guided strategy over the traditional angiography-guided strategy in ARAS revascularization. The present

Table 4 Regression analyses of the primary outcomes

Primary outcomes	N	Value Median (IQR)	Unadjusted treatment group effect		Adjusted treatment group effect	
Group			β (95%CI)	P	β (95% CI)	P
Three-month DMSBP reduction						
Functional insignificant non-stenting group	27	4 [−8, 13]				
Functional insignificant stenting group	23	0 [−6, 5]	−3.3 (−9.8, 3.2)	.32	1.4 (−4.5, 7.2)	.65
Functional significant stenting group	51	13 [4, 21]	9.8 (2.9, 16.7)	<.01	6.2 (0.6, 11.9)	.04
Three-month CIAHM reduction						
Functional insignificant non-stenting group	27	0 [0, 2]				
Functional insignificant stenting group	23	0 [0, 1]	−0.5 (−2.6, 1.7)	.66	0.7 (−1.1, 2.5)	.44
Functional significant stenting group	51	2 [0, 5]	2.2 (0.3, 4.2)	.03	3.1 (1.5, 4.7)	<.01

The following variables were adjusted: age, sex, baseline daytime systolic blood pressure, baseline CIAHM, and baseline estimated glomerular filtration rate.
DMSBP, daytime mean systolic blood pressure; CIAHM, composite index of antihypertensive medicines; IQR, interquartile range; CI, confidence interval.

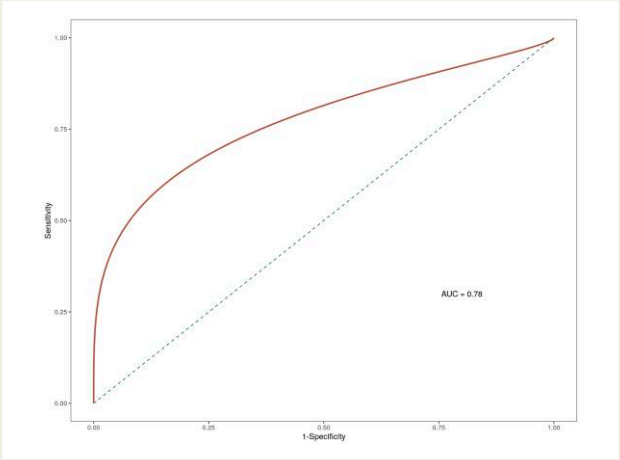

Figure 3 ROC curves of renal fractional flow reserve for hypertension improvement. ROC, receiver operating characteristic; AUC, area under the curve

results confirmed the feasibility and safety of dopamine-induced renal FFR measurement in a renal artery. The procedure was successful in all 147 lesions in 107 patients without side effects. Consistent with the findings of Subramanian *et al*,[20] the correlation between angiographic stenosis severity and FFR was poor, even in the range of 70%–90% stenosis. Employing the BP change at the end of 3 months of follow-up as the primary endpoint of the current study, instead of renal function or major adverse cardiovascular events (MACE), was based on the consideration that BP is the most sensitive and specific indicator of haemodynamic change after restoring blood perfusion, whereas renal function or MACE is easily influenced by co-existing disease and other risk factors, such as diabetes, dyslipidaemia and smoking. Moreover, we used dual primary endpoints including the percentage changes in DMSBP measured by ABPM and CIAHM to incorporate the influence of drug adjustment on BP. Our study demonstrated for the first time that the FFR-guided strategy reduced revascularization by 54%. This aligns with the results of the FAME study in which an FFR-guided strategy in coronary intervention resulted in a 37% reduction in unnecessary PCI.[16] We did not find a significant difference in the primary endpoints between the two randomized groups. However, our results revealed that subjects with baseline FFR < 0.8 who underwent stenting experienced a significant DMSBP reduction from 140 (128, 154) mmHg to 126 (122, 135) mmHg ($P < .01$), concomitant with a significant reduction of CIAHM from 6 (3, 9) to 2 (1, 5) ($P < .01$), whereas this effect was not observed in subjects with baseline FFR ≥ 0.8 who underwent stenting, strongly indicating that only subjects with functional significant lesions recognized by renal FFR would benefit from stenting. This result aligns with Mitchell's finding that BP improved in 86% of participants with FFR < 0.8, vs only 30% of subjects with normal FFR.[19] Our results also identified an FFR cut-off of 0.78 for predicting BP improvement. These data are critical for the design of future major studies. Combining our results with previous findings, we believe that functional evaluation using FFR could guide revascularization interventions in patients with ARAS, but additional randomized studies are warranted to confirm our discovery.

This study had multiple limitations. First, this was an underpowered pilot study, and its results were indicative rather than conclusive, the subgroup analysis showing no interaction effect also met the same problem. Second, the primary endpoints were based on BP rather than clinical outcomes. Although we believe that BP is the most sensitive and specific indicator of haemodynamic changes in the kidneys, whether such effect would translate into a clinical benefit must be verified in future large-scale studies. Third, we only assessed 3-month outcomes in this study, and further follow-up data, especially the 1-year outcomes, could provide more information on the predictive utility of renal FFR. Finally, stenting was beneficial in patients with FFR < 0.80, as indicated by greater reductions in BP and CIAHM compared with that observed in the other two groups in multivariate regression analysis. However, a formal RCT should be conducted in the future to investigate whether revascularization provides better outcomes than medication.

In conclusion, among patients with ARAS and hypertension, renal FFR-guided revascularization significantly reduced unnecessary stent usage and potentially identified patients most likely to benefit from

stenting. Functional evaluation of renal FFR is practical and safe based on this pilot trial, which provided critical data supporting the design of future randomized trials.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Ethical Approval

The research protocol of this study was approved by the ethics committee of Peking University First Hospital, Beijing, China (No. 2022-457). All participants gave written informed consent.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is Clinicaltrials.gov Identifier: NCT05732077.

References

1. Bhalla V, Textor SC, Beckman JA, Casanegra AI, Cooper CJ, Kim ES, *et al.* Revascularization for renovascular disease: a scientific statement from the American Heart Association. *Hypertension* 2022;**79**:e128–43. https://doi.org/10.1161/HYP.0000000000000217
2. Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. *Kidney Int* 2001;**60**:1490–7. https://doi.org/10.1046/j.1523-1755.2001.00953.x
3. Grüntzig A, Kuhlmann U, Vetter W, Lütolf U, Meier B, Siegenthaler W. Treatment of renovascular hypertension with percutaneous transluminal dilatation of a renal-artery stenosis. *Lancet* 1978;**1**:801–2. https://doi.org/10.1016/s0140-6736(78)93000-3
4. Plouin PF, Chatellier G, Darné B, Raynaud A. Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. *Hypertension* 1998;**31**:823–9. https://doi.org/10.1161/01.HYP.31.3.823
5. Webster J, Marshall F, Abdalla M, Dominiczak A, Edwards R, Isles CG, *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**:329–35. https://doi.org/10.1038/sj.jhh.1000599
6. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, *et al.* 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J* 2024;**45**:3912–4018. https://doi.org/10.1093/eurheartj/ehae178
7. Mazzolai L, Teixido-Tura G, Lanzi S, Boc V, Bossone E, Brodmann M, *et al.* 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases. *Eur Heart J* 2024;**45**:3538–700. https://doi.org/10.1093/eurheartj/ehae179
8. Bax L, Woittiez AJ, Kouwenberg HJ, Mali WP, Buskens E, Beek FJ, *et al.* Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med* 2009;**150**:840–8, W150–151. https://doi.org/10.7326/0003-4819-150-12-200906160-00119
9. ASTRAL Investigators; Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, *et al.* Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009;**361**:1953–62. https://doi.org/10.1056/nejmoa0905368
10. Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, *et al.* Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014;**370**:13–22. https://doi.org/10.1056/nejmoa1310753
11. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;**71**:1269–324. https://doi.org/10.1161/HYP.0000000000000066
12. Sag AA, Inal I, Okcuoglu J, Rossignol P, Ortiz A, Afsar B, *et al.* Atherosclerotic renal artery stenosis in the post-CORAL era part 1: the renal penumbra concept and next-generation functional diagnostic imaging. *J Am Soc Hypertens* 2016;**10**:360–7. https://doi.org/10.1016/j.jash.2016.02.009
13. Lee P, Reeves RA, Lee P, Leung SS, Rao V, Ford RW. Updated trends in percutaneous renal arteriography among radiologists and other specialties. *Clin Imaging* 2023;**102**:14–8. https://doi.org/10.1016/j.clinimag.2023.06.020
14. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, *et al.* 2023 ESH guidelines for the management of arterial hypertension the task force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and The European Renal Association (ERA). *J Hypertens* 2023;**41**:1874–2071. https://doi.org/10.1097/hjh.0000000000003621
15. Hicks CW, Clark TWI, Cooper CJ, de Bhailís ÁM, De Carlo M, Green D, *et al.* Atherosclerotic renovascular disease: a KDIGO (Kidney Disease: Improving Global Outcomes) controversies conference. *Am J Kidney Dis* 2022;**79**:289–301. https://doi.org/10.1053/j.ajkd.2021.06.025
16. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, van' t Veer M, *et al.* Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;**360**:213–24. https://doi.org/10.1056/nejmoa0807611
17. De Bruyne B, Pijls NHJ, Kalesan B, Barbato E, Tonino PAL, Piroth Z, *et al.* Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;**367**:991–1001. https://doi.org/10.1056/nejmoa1205361
18. Colyer WR, Cooper CJ, Burket MW, Thomas WJ. Utility of a 0.014″ pressure-sensing guidewire to assess renal artery translesional systolic pressure gradients. *Catheter Cardiovasc Interv* 2003;**59**:372–7. https://doi.org/10.1002/ccd.10508
19. Mitchell JA, Subramanian R, White CJ, Soukas PA, Almagor Y, Stewart RE, *et al.* Predicting blood pressure improvement in hypertensive patients after renal artery stent placement: renal fractional flow reserve. *Catheter Cardiovasc Interv* 2007;**69**:685–9. https://doi.org/10.1002/ccd.21095
20. Subramanian R, White CJ, Rosenfield K, Bashir R, Almagor Y, Meerkin D, *et al.* Renal fractional flow reserve: a hemodynamic evaluation of moderate renal artery stenoses. *Catheter Cardiovasc Interv* 2005;**64**:480–6. https://doi.org/10.1002/ccd.20318
21. Manoharan G, Pijls NHJ, Lameire N, Verhamme K, Heyndrickx GR, Barbato E, *et al.* Assessment of renal flow and flow reserve in humans. *J Am Coll Cardiol* 2006;**47**:620–5. https://doi.org/10.1016/j.jacc.2005.08.071
22. Leesar MA, Varma J, Shapira A, Fahsah I, Raza ST, Elghoul Z, *et al.* Prediction of hypertension improvement after stenting of renal artery stenosis. *J Am Coll Cardiol* 2009;**53**:2363–71. https://doi.org/10.1016/j.jacc.2009.03.031
23. Mangiacapra F, Trana C, Sarno G, Davidavicius G, Protasiewicz M, Muller O, *et al.* Translesional pressure gradients to predict blood pressure response after renal artery stenting in patients with renovascular hypertension. *Circ Cardiovasc Interv* 2010;**3**:537–42. https://doi.org/10.1161/circinterventions.110.957704
24. Wang J, Sun N, Ge J, Jiang H, Yin Y, Chen M, *et al.* Rationale and design of sympathetic mapping/ablation of renal nerves trial (SMART) for the treatment of hypertension: a prospective, multicenter, single-blind, randomized and sham procedure-controlled study. *J Cardiovasc Transl Res* 2022;**16**:358–70. https://doi.org/10.1007/s12265-022-10307-z
25. Wang J, Yin Y, Lu C, Lu Z, Hu J, Wang Y, *et al.* Efficacy and safety of sympathetic mapping and ablation of renal nerves for the treatment of hypertension (SMART): 6-month follow-up of a randomised, controlled trial. *EClinicalMedicine* 2024;**72**:102626. https://doi.org/10.1016/j.eclinm.2024.102626
26. Reckelhoff JF, Romero JC. Role of oxidative stress in angiotensin-induced hypertension. *Am J Physiol Regul Integr Comp Physiol* 2003;**284**:R893–912. https://doi.org/10.1152/ajpregu.00491.2002