Renovascular Hypertension

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25.1 Pathophysiology of Renovascular Hypertension

Progressive atherosclerotic stenosis of the renal artery leads to hypoperfusion of the juxtaglomerular apparatus with release of renin and increased production of angiotensin II. The subsequent increases in sympathetic nerve activity and synthesis of intrarenal prostaglandin, aldosterone, and nitric oxide and the decrease in renal sodium excretion result in vasoconstriction and secondly in sodium and water retention, causing hypertension. Moreover, renal perfusion becomes volume and angiotensin II dependent, especially in bilateral RVD [1–3]. In the absence of renin increase or altered renin-angiotensin system modulation in patients with FMD compared to essential hypertensive patients, the applicability of this model to FMD-related renal artery stenosis has been recently questioned [4].

25.2 Atherosclerotic Renovascular Disease

25.2.1 Epidemiology

The prevalence of RVH is estimated at 5% of all hypertensive persons but varies depending on the screened cohort from <1% in mild to >50% in severe hypertension [5, 6]. In patients with extrarenal atherosclerosis, end-stage renal failure, and heart

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A.E. Berbari, G. Mancia (eds.), *Disorders of Blood Pressure Regulation*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-59918-2_25

failure, the prevalence of ARAD is high and varies from 4 to18.4% in patients with proven coronary artery disease and from 12 to 45.5% in patients with peripheral artery disease or aortic disease [7]. The exact prevalence of atherosclerotic (A) RAS is unknown because the disease is often asymptomatic and few patients are screened unless they have symptoms or significant risk factors. Yet, among potential living kidney donors with normal BP and kidney function, renal artery narrowing or atherosclerosis, i.e., "incidental" RAS, can be identified in 5.3% by CT scan [8]. RVD, diagnosed with renal Doppler ultrasound (US) (>60% stenosis suggested by peak systolic velocity (PSV) >1.8 m/s in the main renal artery), was present in 6.8% of free-living, community-dwelling subjects above age 65 [9]. The prevalence of ARAD in autopsy series of patients died in hospital varies between 4.3 and 86% [6].

25.2.2 Clinical Presentation

Patients are often true treatment resistant, can present with recurrent ("flash") pulmonary edema, or suffer acute renal deterioration after BP lowering or administration of renin-angiotensin system blockers [5, 10].

The elevated BP due to RAD is responsible per se for an increased cardiovascular (CV) risk [11]. An increased rate of new CV events, including death, was observed in the 2 years after identification of new ARAS in patients aged >67 years in the United States. CV events were far more frequent than further loss of kidney function [12]. Progressive ARAS can indeed lead to ischemic nephropathy with progressive renal failure and occlusion with renal atrophy. However, it has been shown that renal outcomes in patients with ARAS are influenced by underlying hypertension and diabetes [6, 13]. The underlying mechanisms explaining why ARAD is a strong independent predictor of long-term mortality are not well understood, but excess neurohumoral activation (i.e., increased sympathetic nervous tone and stimulation of the renin-angiotensin-aldosterone axis) may be a major contributor to mortality in ARAD [6].

25.2.3 Diagnostic Evaluation

Not every patient with hypertension should be submitted to an extensive work-up for atherosclerotic RVH. The presence of an abdominal bruit, new onset hypertension or recent loss of BP control, a unilateral small kidney or a difference of at least 1.5 cm, grade 3 or 4 retinopathy, accelerated or malignant hypertension, unprovoked hypokalemia, increased serum creatinine after RAAS blockade or BP decline, absence of family history of hypertension, significant atherosclerotic disease in another vascular bed, elevated plasma renin activity, former or current cigarette smoking, flash pulmonary edema, proteinuria, older age, and true resistant hypertension are all clinical clues to RVH. Krijnen et al. proposed a "clinical prediction rule," derived from three small cohorts of patients with drug-resistant hypertension, based on patient's history (age, gender, presence of atherosclerotic

CV disease, onset of hypertension within 2 years, smoking), physical examination (BMI, abdominal bruit), and some laboratory values (serum creatinine and cholesterol). A nomogram provides the probability of RVH in patients with drug-resistant hypertension [14].

25.2.4 Screening and Diagnostic Tests

Screening for atherosclerotic RVH should be restricted to those patients with at least an intermediate risk for RVH.

Several tests, based on physiologic or anatomic or both parameters, have been evaluated to screen for RVH. Analyzing *plasma renin activity*, unstimulated or after stimulation by a captopril challenge test, is not very sensitive or specific. Determination of renin activity in the blood from renal veins compared to peripheral veins has been abandoned because of the invasive nature of the procedure.

Renal scintigraphy, using ^{99}Tc-DTPA, ^{131}I-hippurate, or ^{99}Tc-MAG3, with and without captopril can be used but is no longer recommended by the American College of Cardiology/American Heart Association as a screening test for RVH. In 2003, the Society of Nuclear Medicine published updated interpretation criteria [15]. The most specific diagnostic criterion for RVH is an ACEI-induced change in the renogram. In patients with normal or minimally reduced renal function (creatinine <1.7 mg/dL) and in azotemic patients, ACEI renography has a sensitivity and specificity of about 90% and 80%, respectively, for diagnosis of RVH. Moreover, ACEI-induced renographic findings of RVH may indicate a high probability of hypertension cure or improvement after revascularization [16]. However, the latter has not been shown in the DRASTIC trial [17]. Furthermore, sensitivity and specificity of ACEI renography are affected by several factors that contribute to confusion in the literature, e.g., use of different isotopes, different clinical characteristics (azotemic and non-azotemic patients), as well as different antihypertensive treatment [16].

Duplex ultrasonography not only identifies renal arteries anatomically by using B-mode US but also provides hemodynamic information by using Doppler flow studies. The Doppler US criteria of RAS can be divided into two groups based on direct findings obtained at the level of the stenosis (proximal criteria: peak systolic velocity, PSV, and renal aortic ratio) or on flow changes observed in the renal vasculature distal to the site of stenosis (distal criteria: resistance index, RI, and acceleration time) (Table 25.1). The RI, determined from segmental arterial flow characteristics, reflects the status of the flow in the renal circulation beyond the main renal arteries. An elevated RI may reflect intrinsic parenchymal or small vessel disease. However, reliance upon RI as a predictive parameter for ARAS management remains controversial. Radermacher et al. reported that patients with RI >0.8 before angioplasty had less BP improvement and worse renal outcomes than those with RI <0.8 [19]. In contrast, Zeller et al. reported similar BP and renal outcomes for patients with RI >0.8 and those with RI <0.8 [20]. Finally, Bruno et al. reported that a RI within the contralateral kidney, and using a cut point of

Table 25.1 Doppler ultrasound criteria for the classification of RA stenosis by color Doppler US

Proximal criteria	Peak systolic velocity (cm/s)	Renal aortic ratio (renal PSV/aortic PSV)
Normal RA	<180	<3.5
RA diameter reduction <60%	<180	<3.5
RA diameter reduction ≥60%	>180	≥3.5
Occlusion	No signal	Indeterminable
Distal criteria	Resistance index	Acceleration time (m/s)
RA diameter reduction ≥60%	Side-to-side differences in RI: >0.05	>70

Adapted from Granata et al. [18]
PSV peak systolic velocity, *RA* renal artery, *RI* resistance index

0.73, was the best single predictor of functional outcome (recovery of estimated glomerular filtration rate (eGFR)). No US parameter predicted the response of BP [21]. In a hemodynamically significant stenosis, a "tardus parvus" wave can be observed, as the systolic acceleration of the waveform is slow and the systolic peak is of low height [18, 22].

A meta-analysis showed duplex US had 85% sensitivity and 92% specificity for detection of RAS. PSV had the highest performance characteristics, and additional measurements did not increase accuracy. Operator dependency and sometimes limited quality images because of patient characteristics are responsible for large variations in sensitivity (0–98%) and specificity (73–100%) [23].

Contrast-enhanced *magnetic resonance angiography* (*MRA*) provides good anatomical information with diagnostic sensitivity of 90% and specificity of 94% [24]. Limitations of MRA include a tendency to overestimate moderate stenosis and a reduced accuracy in small and distal arteries. In patients with CKD stage 3b or more, gadolinium has to be avoided because of the risk of nephrogenic fibrosing dermopathy; Dotarem instead can be used. New techniques such as blood-oxygen level-dependent MRI (BOLD-MRI) can identify critically ischemic kidneys and can predict change in renal function post-revascularization [25].

Computed tomographic angiography (*CTA*) has also good sensitivity of 84% and specificity of 91% [24]. A major limitation is the volume of intravenous contrast and the potential nephrotoxic risk. In contrast with MRA, obfuscation of signal by indwelling stents is not a concern. CTA is cost-effective in patients for whom there is low suspicion of RAS [26].

A meta-analysis showed CTA and gadolinium-enhanced MRA gave more accurate diagnosis than US or captopril scintigraphy [27].

The gold standard investigation remains catheter digital subtraction angiography (DSA). It can provide not only accurate anatomical and some functional information but also permits to intervene during the same examination. However, this test is invasive and carries the potential risk of access site complications, embolic events, and contrast-induced nephropathy [28]. Initial diagnostic testing by DSA may nevertheless be considered in those individuals with a high risk for RVH [29].

Figure 25.1 summarizes the diagnostic algorithm for renovascular hypertension.

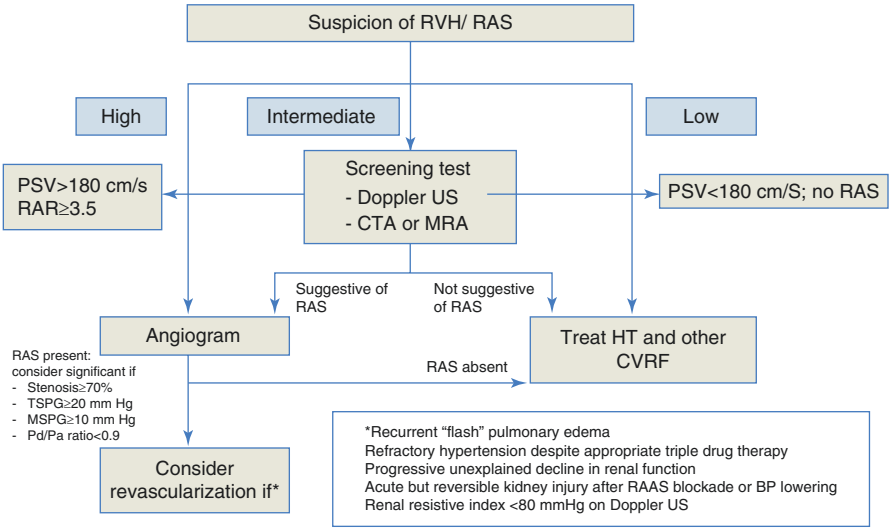

Fig. 25.1 Diagnostic algorithm for renovascular hypertension. *BP* blood pressure, *CTA* computed tomographic angiography, *CVRF* cardiovascular risk factors, *MRA* magnetic resonance angiography, *RAAS* renin-angiotensin aldosterone system, *RAS* renal artery stenosis, *RVH* renovascular hypertension, *US* ultrasound

Table 25.2 Possible indications and contraindications for revascularization

Favorable response after revascularization
Recurrent "flash" pulmonary edema
Refractory hypertension despite appropriate triple drug therapy
Progressive unexplained decline in renal function
Acute but reversible kidney injury after renin-angiotensin system blockade or blood pressure lowering
Renal resistive index <80 mmHg on Doppler ultrasound
Unfavorable response after revascularization
Normalized blood pressure with less than three antihypertensive drugs
Unilateral or bilateral small kidneys (<8 cm length)
Renal resistive index ≥80 mmHg on Doppler ultrasound
Long-standing hypertension (>10 years)
Renal artery stenosis <70%

Adapted from Elliott [5]

25.2.5 Therapy

Despite decades of expertise in treating RAS, uncertainty still exists whether revascularization is warranted. Table 25.2 lists the most widely used potential indications and contraindications that can help in decision-making [30]. See also fig. 25.2 representing a clinical casus of an older patient with acute deterioration of kidney function due to ARAS who benefited from PTAS.

25.2.5.1 Medical Management

Optimal medical therapy is mandatory in these high-risk patients to reduce CV risk. Besides BP lowering, control of other atherosclerotic CV risk factors is required. Maximal medical therapy, including low-dose aspirin, statins, and glycemic control, together with smoking cessation, is recommended [30].

A major concern about intensive BP lowering with or without RAAS blockers is the risk of acute kidney injury. A maximal increase in serum creatinine of 30% is allowed; discontinuing RAAS blockade or returning to a higher BP will reverse serum creatinine to baseline values [31]. Acute renal function degradation following RAAS blockade can be an indication for revascularization [5].

In an observational study, the use of ACEIs was associated with improved survival and a reduced risk of increasing serum creatinine in both revascularized and medically treated patients [32]. This observation emphasizes the need for RAAS blockers in the treatment of high-risk patients. However, the prevalent use of RAAS blockade prior to randomization in the CORAL trial was only 49% [33].

A population-based cohort study in 4040 patients >65 years with RVD suggests that statins are associated with improved prognosis as well [34].

25.2.5.2 Angioplasty With or Without Stenting

Renal artery angioplasty alone was first performed by Gruntzig in 1978 [35].

Angioplasty without stenting is no longer preferred for atherosclerotic RAS due to high rate of technical failure, restenosis, and failure to lower BP, documented in observational studies and small RCTs. An even poorer outcome is observed in case of ostial stenosis, multiple and branch lesions. There is also little change in renal function after angioplasty [36]. However, large and randomized trials are lacking.

Angioplasty with stenting reduces the risk of restenosis as well as local dissection, prevents elastic recoil eventually responsible for acute restenosis and thrombosis, and can reduce pressure gradients across lesions after angioplasty.

In a multicenter registry including 1058 patients, stent revascularization of RAS, performed for poorly controlled hypertension, preservation of renal function, and/or congestive heart failure, was overall successful. At 4-year follow-up, BP had significantly decreased despite of a decrease in the number of antihypertensive medications, as well as serum creatinine. The cumulative probability of survival was 74% ± 3% at 4 years and was adversely affected by renal dysfunction despite adequate revascularization [37]. Similar results have been obtained in subsequent but smaller studies. In a retrospective analysis of patients treated for RVH, those who had a baseline eGFR of >40 mL/min/1.73 m^2 demonstrated a better response to RA stenting at each follow-up interval, with a significant difference at 2–4 years, compared with patients with a lower eGFR [38]. Another retrospective study in patients with chronic kidney disease (CKD) (creatinine clearance <50 mL/min) and RVD suggested that the rate of renal dysfunction progression before angioplasty with or without stenting is an independent and strong predictor of improvement in renal function after revascularization [39].

Restenosis rates vary between 10 and 50%, depending on location and severity of stenosis and on length of follow-up. Studies have suggested that secondary

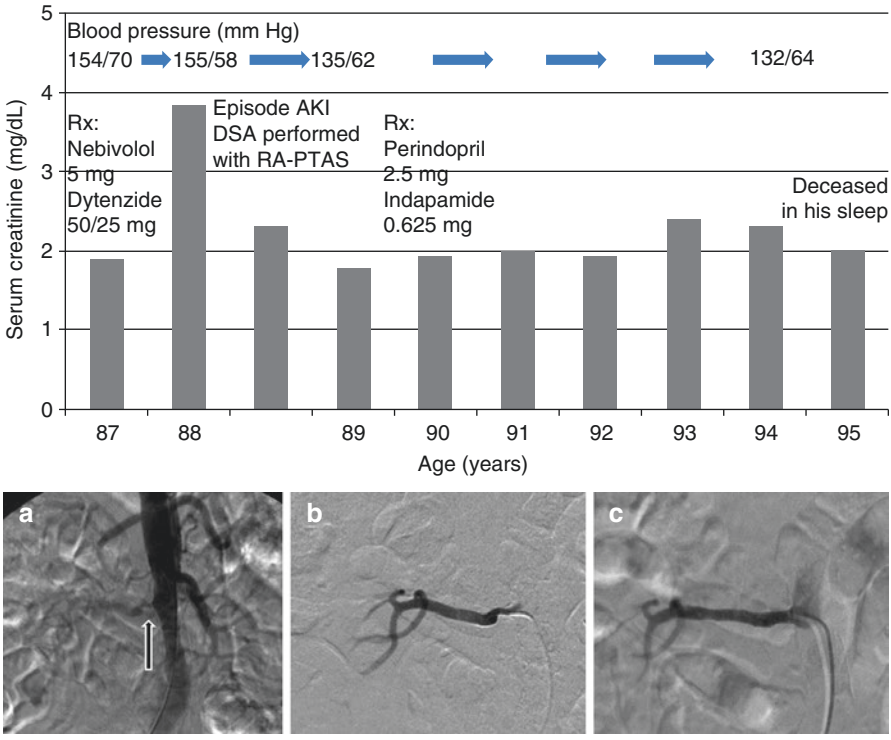

Fig. 25.2 Serum creatinine, blood pressure, and medications over an 8-year period in an elderly patient with unilateral renovascular disease. This elderly atherosclerotic patient developed an acute rise in serum creatinine. Doppler US showed a smaller right kidney (10.1 cm) than the left kidney (11.2 cm) without hydronephrosis. Because of a high suspicion of renal artery stenosis, a DSA was performed, immediately followed by angioplasty and stenting. A marked decrease in serum creatinine was observed and remained stable till his death. An ACEI was started and BP was well controlled. **a** shows the ostial stenosis; **b** and **c** show the renal artery during and after angioplasty with stenting. *ACEI* angiotensin-converting enzyme inhibitor, *AKI* acute kidney injury, *BP* blood pressure, *DSA* digital subtraction angiography, *RA-PTAS* renal artery percutaneous transluminal angioplasty with stenting, *Rx* medical therapy, *US* ultrasound

interventions for recurrent RAS have outcomes that are comparable with those for primary interventions, whereas others have reported worse outcomes. In a retrospective analysis of 57 patients undergoing 65 secondary interventions for recurrent RAS, it was shown that these patients had outcomes (BP and renal function) comparable with 180 patients for 216 primary interventions. These data suggest that repeated endovascular procedures for RAS can be undertaken with similar expectations for clinical improvement [40]. Early renal artery PSV, within 1 week after renal artery percutaneous angioplasty and stenting (RA-PTAS), predicted renal artery restenosis and lower post-procedure renal function [41].

Statin use has been associated with decreased restenosis in 112 patients after primary RA-PTAS, whereby restenosis rates were 65% less likely with

pre-angioplasty statin use, as well as after secondary renal interventions in 51 patients [42, 43]. These findings support the routine use of statins in patients undergoing RA-PTAS.

One important concern of RA-PTAS is the risk of cholesterol embolization. According to the results of recent RCTs, acute atheroembolic renal disease, associated with clinical evident bad prognosis, is present in 0–2.2% of cases [44]. The majority of atheroembolic disease is subclinical and perhaps responsible for the frequently observed decline in kidney function, despite successful revascularization. Therefore, embolic devices have been developed. The frequency of atherosclerotic debris recovered in protection devices is >50% [45]. However, in a RCT of 100 patients undergoing RA-PTAS, renal artery stenting alone; stenting with Angioguard, an embolic protection device; and stenting with abciximab, a glycoprotein IIb/IIIa inhibitor, were associated with similar declines in GFR at a 1-month follow-up, whereas combination therapy with embolic protection and abciximab was better than no treatment or either treatment alone [46].

Several *randomized clinical trials comparing angioplasty with and/or without stenting* versus *medical treatment* have been performed. However, their interpretation is often complicated by various confounders, i.e., crossovers from medical to interventional arms, role of comorbid disease, hypertension vintage, proportion of patients with renal insufficiency or bilateral RAS, and different definitions of drug-resistant hypertension. Other limitations of these studies are related to patient selection (exclusion of patients with severe hypertension and progressive renal function decline, nonstandardized therapy for hypertension and dyslipidemia, nonstandardized BP measurement) or outcome (variable definitions of BP goals, variable measurements of kidney function, short duration of follow-up) [47]. The main results from these trials are summarized in Table 25.3.

The EMMA (Essai Multicentrique Medicaments vs. Angioplastie) study, the SNRASCG (Scottish and Newcastle Renal Artery Stenosis Collaborative Group) trial, and the DRASTIC (Dutch Renal Artery Stenosis Intervention Cooperative) study have compared angioplasty without stenting with medical therapy [17, 51, 52].

In the EMMA study, 49 of 76 eligible hypertensive patients with unilateral ARAS of ≥75% (or ≥60% with positive screening test) were randomized (26 patients were medically treated; 23 patients had angioplasty, of whom two had stents). The primary endpoint was ambulatory BP at 6 months or at study termination. Angioplasty reduced the number of antihypertensive drugs but was associated with more complications (one patient had renal artery dissection with segmental renal infarction, five had hematomas, and three developed restenosis, requiring re-intervention) than previously reported [51].

In the SNRASCG study, 55 of 135 eligible hypertensive patients treated with at least two antihypertensive drugs and with ≥50% RAS were randomized and stratified by unilateral (n, 27) or bilateral disease. The primary endpoints were the changes in BP and serum creatinine at baseline and at 6 months. A modest improvement in BP was seen with angioplasty in those with bilateral disease, again at the expense of a higher complication rate. No significant differences in serum creatinine were observed [52].

Table 25.3 Prospective, randomized, clinical trials of balloon angioplasty, with and without stenting, versus medical therapy in atherosclerotic renal artery stenosis

Study/author	Methods	Inclusion criteria	Primary and secondary endpoints	Participants	Results
Surgery versus medical therapy					
Uzzo et al. [48]	Single-center RCT No blinding of intervention No standardized medical treatment FU: 74 months	BL RAS >75% or UL RAS >75% with azotemia (serum creatinine >1.5 and ≤4 mg/dL)	Poorly controlled hypertension, renal events, CV events, mortality	52 patients	No significant difference in mortality or incidence of renal and CV events
Surgery versus PTA					
Weibull et al. [49]	Single-center RCT No blinding of intervention No standardized medical treatment FU: 2 years	UL RAS (diameter stenosis ≤2 mm and renal vein ratio ≥1.5), untreated BP ≥160/100 mmHg, serum creatinine <3.39 mg/dL	Technical success, primary and secondary patency, effect on BP and renal function	58 patients ≤70 years (mean age 57 years) 41% women 0% BL RAS Baseline BP: 195/110 mmHg >3 drugs: 81%	No significant difference in restenosis rate, BP, or renal function Significant decrease in SBP and DBP in both groups Stabilization of renal function
Surgery versus PTA + stenting					
RAOOD Balzer et al. [50]	Single-center RCT* No blinding of intervention No standardized medical treatment FU: 4 years	UL or BL ostial AS-RAS >70%	Technical success, primary and secondary patency, effect on BP and renal function	50 patients Mean age, 64 years (range 44–84 years) 37% women 57% BL RAS Baseline BP: 170/88 mmHg Baseline N° drugs: 3.1	No significant difference in mortality, restenosis rate, BP, or renal function Significant decrease in SBP and DBP in both groups Stabilization of renal function *Final decision to perform revascularization was left to the radiologist or vascular surgeon Six renal arteries were treated by PTRA only

(continued)

Table 25.3 (continued)

Study/author	Methods	Inclusion criteria	Primary and secondary endpoints	Participants	Results
PTA versus medical therapy					
EMMA Plouin et al. [51]	Multicenter RCT No blinding of intervention FU: 6 months Standardized medical treatment	UL RAS ≥75% or ≥60% with positive lateralization test[a], DBP >95 mmHg or receiving antihypertensive treatment CrCl >50 mL/min Exclusion: malignant HTN	Mean 24 h ABP Number and DDD of antihypertensive drugs, creatinine clearance Rate of occluded arteries Complications	49 patients <75 years (mean age 59 years) 26% women 0% BL RAS Baseline BP: 150/90 mmHg Baseline N° drugs: ?	No significant difference in ambulatory BP PTA: fewer antihypertensive drugs (1.0 vs. 1.78, p <0.01), higher complication rate 27% crossover 8.7% stenting Important exclusion criteria: Malignant HT Acute pulmonary edema DBP >109 mmHg
SNRASCG Webster et al. [52]	Multicenter RCT No blinding of intervention Standardized medical treatment FU: 6 months	UL or BL RAS ≥50% stenosis, DBP ≥95 mmHg on ≥2 antihypertensive drugs Serum creatinine <5.65 mg/dL	Office BP Serum creatinine Number antihypertensive drugs Complications	55 patients 40–75 years (mean age 61 years) 42% women 50.9% BL RAS Baseline BP: 178/94 mmHg Baseline N° drugs: 2.6	PTA: significant BP reduction only if BL RAS; no significant difference in CV events or renal function 20% participants assigned to PTA had a surgery
DRASTIC Van Jaarsveld et al. [17]	Multicenter RCT No blinding of intervention FU: 12 months	UL or BL RAS ≥50% stenosis, DBP ≥95 mmHg on ≥2 antihypertensive drugs or >0.2 mg/dL increase in serum creatinine with ACEI, serum creatinine ≤2.3 mg/dL (kidney length ≥8 cm)	Mean office BP Number and DDD of antihypertensive drugs Serum creatinine Restenosis complications	106 patients 18–75 years (mean age 60 years) 39% women 22.6% BL RAS Baseline BP: 179/104 mmHg Baseline N° drugs: 2.0	No significant difference in systolic and diastolic BP PTA: fewer antihypertensive drugs (1.9 vs. 2.4, p <0.01) 44% participants assigned to medical therapy underwent revascularization at 3 months if DBP >95 mmHg despite ≥3 antihypertensive drugs Only 3.6% stenting

PTA versus PTA with stenting					
Van de Ven et al. (1999) [53]	Single-center RCT FU: 6 months	UL or BL ostial RAS >50% stenosis + positive scintigraphy or increase in serum creatinine ≥20% on ACEI	Restenosis	84 patients	PTA with stenting: higher success and lower restenosis rates. No difference in systolic and diastolic BP or renal function
PTA with stenting versus medical therapy					
STAR Bax et al. [54]	Multicenter RCT No blinding of intervention FU: 24 months	Ostial UL or BL AS-RAS ≥50% and C and G eCrCl <80 mL/min/1.7m^2 but ≥15 mL/min (kidney length ≥8 cm)	Worsening of renal function (>20% decline in eCrCl with C and G formula) Office BP Incidence of refractory or malignant HT Pulmonary oedema CV morbidity, CV mortality, total mortality	140 patients Mean age 66.5 years 55% women 48% BL RAS Baseline BP: 162/82 mmHg Baseline N° drugs: 2.9	No significant difference in renal function, BP, CV mortality and morbidity 28% participants allocated to PTA did not undergo revascularization, mainly due to minimal stenosis 1.3% crossover Important exclusion criteria: Malignant HT
ASTRAL Wheatley et al. [55]	Multicenter RCT No blinding of intervention Median FU: 34 months Medical treatment was not standardized Nonstandard imaging 42% <70% 58% ≥70%	Uncontrolled/refractory hypertension or unexplained renal dysfunction with UL or BL AS-RAS Physician uncertain of clinical benefit	Renal outcome (reciprocal of serum creatinine) Office BP Time to renal and major CV events and mortality Complications	806 patients 42–88 years (mean age 70.5 years) 37% women 53.5% BL RAS Baseline BP: 150/76 mmHg Baseline N° drugs: 2.8	No significant difference in renal function, BP, CV events and mortality 17% participants, allocated to PTA, did not undergo revascularization 6% crossover Important exclusion criteria: Need of surgery or high revascularization probability in 6 months

(continued)

Table 25.3 (continued)

Study/author	Methods	Inclusion criteria	Primary and secondary endpoints	Participants	Results
CORAL Cooper et al. [56]	Multicenter RCT No blinding of intervention Median FU: 43 months Standardized medical treatment	UL or BL AS-RAS >80% or >60% with >2 mmHg systolic pressure gradient and SBP >155 mmHg with ≥2 antihypertensive drugs and/or eGFR <60 mL/min/1.73 m^2 (MDRD) Kidney length >7 cm, serum creatinine ≤4 mg/dL	Composite of adverse fatal and nonfatal CV and renal events Individual components of PEP All-cause mortality SBP Restenosis Renal resistance index QOL Cost-effectiveness	947 patients ≥18 years (mean age 69 years) 50% women 20% BL RAS Baseline BP: 150/− mmHg Baseline N° drugs: 2.1	No significant difference in primary composite endpoint, any of individual components of PEP, or all-cause mortality Almost 17% of participants either withdrew or were lost to FU 5.4% participants, allocated to PTA, did not undergo revascularization 4% participants allocated to medical therapy crossed over Possibly underpowered (1080 participants were required) Important exclusion criteria: DBP ≥120 mmHg and/or SBP ≥200 mmHg Heart failure
PTA with stenting versus medical therapy (not fully published)					
NITER Scarpioni et al. (2009) [57]	RCT FU: 43 months	UL or BL AS-RAS ≥70%; serum creatinine ≤3 mg/dL and/or eGFR ≥30 mL/min/1.73 m^2 (MDRD); kidney length ≥8 cm; BP ≤ 150/90 mmHg with <4 antihypertensive drugs	Death Need for RRT Reduction by 20% in eGFR BP Number antihypertensive drugs Complications	52 patients 45–80 years Mean age 72 years 40% women 51.5% BL RAS Baseline BP: 149/79 mmHg Baseline N° drugs: 3.3	Important exclusion criteria: Heart failure

RADAR Zeller et al. (2013) [58]	Multicenter RCT FU 32 months	UL or BL AS-RAS eGFR >10 mL/min/1.73 m^2 (MDRD) Hypertension Kidney length ≥7 cm	Change in eGFR after 12 months	67 patients ≥18 years (mean age 67 years) 33% women	No significant difference in renal outcome Study was prematurely terminated (reason not mentioned)
Ongoing trials: PTA with stenting and standardized optimized medical treatment versus standardized optimized medical treatment					
RAVE Tobe et al. [59]	Single-center RCT (pilot) Started 2007	RAS and indication for revascularization*	Composite endpoint Death or dialysis or doubling of serum creatinine CV disease BP Antihypertensive drugs	20 patients Age ≥55 years	*Stenting is performed At the discretion of the angiographer
METRAS Rossi et al. [60]	Multicenter RCT No blinding of intervention FU: 60 months planned Started 2012	AS-RAS >70% and resistance index (RI) <0.55, and HTN	Change in eGFR BP Need for RRT CV events Quality of life	Estimated enrollment N°: 120 Age: >18 years	
ANDORRA Azizi et al. (2015) [61]	Multicenter RCT FU: 12 months Started Sept. 2015	Resistant hypertension (daytime SBP ≥135 or DBP ≥85 mmHg) on ≥3 antihypertensive drugs and UL or BL AS-RAS ≥60%; kidney length ≥7 cm; eGFR ≥20 mL/min	Mean change in diurnal systolic BP (24 h ABPM)	Estimated enrollment N°: 140 Age: 40–80 years	

AS-RAS atherosclerotic renal artery stenosis, *BL* bilateral, *BP* blood pressure, *CrCl* creatinine clearance, *C and G*, Cockroft and Gault, *CV* cardiovascular, *DBP* diastolic BP, *DDD* defined daily doses, *eGFR* estimated glomerular filtration rate, *FU* follow-up, *MDRD* modification of diet in renal disease, *PEP* primary endpoint, *PTA* percutaneous angioplasty, *QOL* quality of life, *RAS* renal artery stenosis, *RCT* randomized controlled trial, *RRT* renal replacement therapy, *SBP* systolic BP, *UL* unilateral

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

In the DRASTIC study, 106 of 169 eligible patients were randomized (50 patients were medically treated, 56 patients had angioplasty, of whom two with stent). All patients were either taking at least two antihypertensive drugs, or had previous deterioration of renal function with an ACEI, and had ≥50% RAS and serum creatinine <2.3 mg/dL at baseline. The primary endpoint, mean office BP at 3 and at 12 months, was not different between groups, although the number of antihypertensive drugs was lower in the angioplasty group. However, 20 of 50 patients initially assigned to the medical treatment group underwent angioplasty at 3 months, as diastolic BP was >95 mmHg despite ≥3 antihypertensive drugs. At 3 months, estimated creatinine clearance (Cockroft and Gault formula) was slightly but not significantly higher in the angioplasty group. Restenosis rate was high (52%) in the angioplasty group [17].

Several meta-analyses of these RCTs concluded that balloon angioplasty has a modest but significant effect on BP. However, no evidence of improving or preserving renal function was found, although none of the trials were designed to address this issue [36, 62, 63].

The ASTRAL (angioplasty and stenting for renal artery lesions), CORAL (cardiovascular outcomes in renal atherosclerotic lesions), RADAR, NITER (nephropathy ischemic therapy), and STAR (stent placement and blood pressure and lipid lowering for the prevention of progression of renal dysfunction caused by atherosclerotic ostial stenosis of the renal artery) randomized trials have compared initial angioplasty with stenting with medical therapy [54–56, 64, 65].

The STAR trial randomized 140 patients with ostial ARAS of >50% and estimated (Cockroft and Gault) creatinine clearance <80 mL/min/1.73m^2 (74 were assigned to medical therapy, 46 patients of the 64 assigned to balloon angioplasty with stent insertion underwent the allocated treatment). The primary endpoint was a 20% decline in estimated creatinine clearance. The intention-to-treat and the per protocol analysis revealed similar results in both arms after 2 years of follow-up [54].

The ASTRAL trial randomized 806 patients with uncontrolled or refractory hypertension or unexplained renal dysfunction with angiographically proven ARAS. Of the 403 patients assigned to RA-PTAS, only 301 were actually revascularized with stent placement. Of the 403 patients assigned to medical therapy, 24 (6%) crossed over to revascularization. The primary outcome was renal function, measured by the reciprocal of serum creatinine. No significant difference in the primary endpoint was observed. An important bias in this large study was the opinion of the physician: patients were only enrolled if their physician was uncertain as to whether revascularization would be of clinical benefits, which may have led to exclusion of patients most likely to benefit from revascularization [55].

The CORAL trial included 947 patients with ARAS of >80% or 60–79% with a systolic pressure gradient of >20 mmHg across the stenotic lesion on angiography and a systolic BP >155 mmHg on at least two antihypertensive drugs and/or eGFR (MDRD) <60 mL/min/1.73 m^2. The CORAL investigators factually selected patients with less severe RA stenosis but only with evidence of a significant translesional SP gradient. The latter is suggestive for a stenosis responsible

for an upregulation of renin production and, thus, for RVH and consequently may predict hypertension improvement after stenting of RAS [66]. Patients with renal FMD, nonischemic nephropathy, or a kidney length of <7 cm were excluded in the CORAL trial. 467 patients were assigned to RA-PTAS (embolic protection devices were used) and medical therapy (442 actually underwent revascularization) and 480 to medical therapy alone (4% crossover). Medical treatment was standardized. The primary endpoint was a composite of death from CV or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal failure, or the need for renal replacement therapy. The authors concluded that renal artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in patients with ARAS and hypertension or CKD [56].

The RADAR trial was designed to compare the best medical treatment versus the best medical treatment plus RA-PTAS in patients with hemodynamically significant ARAS (>70%). The primary endpoint is the change of eGFR over 12 months. The study was prematurely terminated, and the results of the trial, including 89 patients, have not been fully published [44, 47]. Also the results of the NITER trial have not been fully published [44, 53].

The Cochrane collaboration meta-analysis of Jenks et al. and other reviews all concluded that revascularization using balloon angioplasty, with or without stenting, is not superior to medical therapy for the treatment of ARAS in patients with hypertension. However, balloon angioplasty results in a small improvement in diastolic BP and a small reduction in antihypertensive drug requirements. Balloon angioplasty also appears to be safe and results in similar numbers of CV and renal adverse events as compared to medical therapy [44].

The primary objective of the ongoing METRAS trial is to determine whether RA-PTAS is superior or equivalent to optimal medical treatment for preserving GFR in the ischemic kidney as assessed by 99mTc-DTPA sequential renal scintigraphy [60].

The primary objective of the RAVE study is to determine the frequency of progression to the composite endpoint (death, dialysis, and doubling of serum creatinine) in patients with ARAD and indication for revascularization, randomized to medical therapy or renal revascularization over a minimum of 6 months. The study has been completed, but no results till now were published. [59].

The primary endpoint of the recently started ANDORRA study in resistant hypertension (daytime SBP ≥135 or DBP ≥85 mmHg on ≥3 antihypertensive drugs) and UL or BL ARAS ≥60%; kidney length ≥7 cm; eGFR ≥20 mL/min is the mean change in diurnal systolic BP on 24 h ABPM after 12 months [61].

25.2.5.3 Surgical Revascularization

Surgical revascularization is no longer the first-choice treatment since angioplasty became widely available. Surgery is reserved for difficult and complex lesions or in case of a complication during angiography. To minimize atheroembolism, aortorenal bypass and renal endarterectomies have nowadays been superseded by nonaortic site bypasses (splenic, celiac, mesenteric, hepatic, or ileac arterial).

Few RCTs evaluated surgery versus medical therapy or angioplasty. A small randomized study including 52 patients with ARAS at risk for ischemic nephropathy, comparing surgery with medical therapy, did not show any difference in mortality at 5 years. No data on BP control or kidney function were published [48].

Another small study randomized 58 hypertensive patients with ARAS to surgery versus balloon angioplasty without stenting. The technical success rate was 83% in the RA-PTAS and 97% in the surgical group and not significantly different. The primary patency rate at 2 years was significantly higher for surgical than for angioplasty-treated patients (96% vs. 75%, $p < 0.05$). A significant decrease in BP in both groups was observed, but without intergroup differences. The number of patients receiving more than three antihypertensive drugs was reduced to a similar extent in both groups. There was also no difference between the two methods with regard to influence on renal function [49].

Balzer et al. randomized 50 patients with hypertension and renal artery ostial occlusive disease (RAOOD) to surgical revascularization or RA-PTAS. Four-year follow-up mortality was 18% in the stent group and 25% in the surgical group (NS). Both groups showed significant ($p < 0.01$) improvement of hypertension and nonsignificant improvement (surgery) or stabilization of renal function. Freedom from recurrent RAOOD (>70%) was achieved in 90.1% of the surgical group and 79.9% of the stent group (NS). Despite the nonsignificant differences in outcome, the authors concluded that surgical reconstruction remains the gold standard for patients with RAOOD [50]. Other advocates of surgery also question the predominance of endovascular intervention in ARAS and advance the need for more RCTs [67].

25.2.6 Future Perspectives

Despite the neutral results of the RCTs, it is obvious that patients with ARAD constitute a heterogeneous group. To date, the available RCTs have been subject to selection bias, excluding high-risk patients. Therefore, their data may not apply for all patients. Revascularization should still be considered in patients with true resistant hypertension, recurrent flash pulmonary edema, or rapid decline in kidney function [10, 68–70]. However, no hard evidence is available.

Which technique (US or DSA) or which parameter (i.e., RI, PSV, translesional pressure gradient) can reliably identify patients likely to benefit from revascularization remains controversial. Perhaps BOLD-MRI could help to resolve this problem [25].

Technical improvement of endovascular revascularization is continuing, with the use of drug-eluting stents, resulting in less complications [23, 28, 56, 68, 71].

It is increasingly recognized that atherosclerosis is a systemic disorder, characterized by inflammation. Poststenotic porcine and human kidneys release—even despite successful revascularization—several inflammatory cytokines and oxidative stress markers that may accelerate target organ injury. Recent research strategies try to ameliorate inflammation and oxidative stress by a single intrarenal infusion

of allogeneic adipose tissue-derived mesenchymal stem cells during PTRA. These experiments preserved stenotic kidney function, reduced systemic oxidative stress and inflammation, and thereby improved cardiac function, oxygenation, and myocardial injury 4 weeks after revascularization [72]. Endothelin-1 receptor blockers, angiogenic factors like vascular endothelial growth factor or hepatocyte growth factor, and mitochondria-targeted peptides also confer renoprotective effects in the stenotic kidney [73–76]. Whether these interventions might improve clinical outcome awaits further research.

25.3 Renal Artery Stenosis Due to Fibromuscular Dysplasia

25.3.1 Definition, Prevalence, and Classification

FMD-related renal artery stenosis has been for long considered a rare entity, with an estimated prevalence of <1% in the general population [77]. However, recent data suggest that FMD is much more common. A meta-analysis based on kidney donor data indeed found silent renal FMD lesions in 4% of the potential kidney donor population [78]. Furthermore, in the CORAL trial, where FMD was an exclusion criterion, the prevalence of FMD was 5.8% [78].

Three main histopathological types of renal FMD have been described according to the arterial wall involved, i.e., intimal FMD (5%), medial FMD (>85%), and perimedial FMD (10%) [79]. However, nowadays, as few cases of FMD require surgery and pathological documentation is lacking, this classification has become largely obsolete. Based on pathological-angiographic correlations, Kincaid proposed three types of renal artery FMD: multifocal ("string-of-beads" appearance), unifocal (solitary stenosis <1 cm in length), and tubular (stenosis at least 1 cm in length) FMD [80]. As the two last categories differ only by the length of the diseased segment, Savard et al. have proposed to group them under the generic term "unifocal" [81]. This pragmatic classification has been endorsed by the authors of the European consensus on FMD [82] and the American Heart Association [83].

Multifocal FMD accounts for over 80% of cases of renovascular FMD, and its histological substrate is medial FMD. It affects mainly women between 30 and 50 years old. The lesions commonly involve the middle or distal thirds of the main renal artery, and there is often extension into the proximal portion of the first-level branches. Lesions are bilateral in 60% of cases. Although the "string-of-beads" appearance is almost pathognomonic of multifocal (medial) FMD, the diagnosis requires exclusion of intoxication by sympathomimetic agents and ergotamine derivatives [77, 82].

Unifocal FMD can be found at the ostium, the trunk, or the bifurcation of the renal arteries. The diagnosis is suspected in young (usually <40 years old) patients with no atherosclerosis, after exclusion of other less frequent diseases. The differential diagnosis of unifocal FMD includes compression of the proximal renal artery by the median arcuate ligament; Takayasu or giant cell arteritis, usually associated with biological inflammation and vascular thickening; and rare monogenic or congenital

diseases (type 1 neurofibromatosis, tuberous sclerosis, pseudoxanthoma elasticum, vascular Ehlers-Danlos syndrome, Alagille syndrome, Williams syndrome, and Turner syndrome) [73, 78].

25.3.2 Clinical Presentation

Hypertension of variable severity is the most common clinical presentation of FMD. Occasionally, an epigastric or flank bruit at physical examination can also lead to the diagnosis. Flank pain may be a manifestation of renal artery dissection or aneurysm. FMD-associated arterial aneurysms at any location have been reported in 17% (33% in renal artery) and dissections in 20% (22% in renal artery) of patients in the US registry [84]. Renal insufficiency is uncommon and often due to renal artery dissection and renal infarction. Progression to end-stage renal disease is very rare. Finally, occurrence of FMD in at least another relative has been reported in 7–11% of cases [84, 85].

25.3.3 Diagnosis

The European consensus on fibromuscular dysplasia has recommended screening in patients <30 years old, especially in women and/or patients with severe, resistant, or malignant hypertension [82]. However, as the mean age at diagnosis of FMD in the US registry [84] and other recent cohorts is ~50 years, it appears reasonable to consider screening up to the fifth decade of life, especially in hypertensive women. Additional indications for screening include patients with small kidney in the absence of history of uropathy and abdominal bruit without apparent atherosclerosis and patients with demonstrated FMD in at least another vascular territory [82]. However, the true prevalence of FMD in these different subgroups has not been documented.

The diagnosis of renal FMD can be made by using noninvasive imaging studies including duplex ultrasonography and angiography by computed tomography or magnetic resonance. While, in the European consensus on FMD, renal duplex was still recommended as the first-line screening test [82], CT angiography—or, if contraindicated, MR angiography—is increasingly considered as a reasonable first-line imaging modality, in view of its higher resolution, especially for distal lesions, ability to detect FMD lesions without hemodynamic consequences, and decreasing costs and radiation exposure. This is especially true in case of high diagnostic probability or expected low performance of renal duplex (obese or hypo-echogenic patients, lack of local expertise, etc.).

Digital subtraction angiography remains the gold standard, but, in view of its invasiveness, it is usually reserved for patients in whom performing a simultaneous percutaneous angioplasty (PTA) is justified. DSA is also advised in the case of a high clinical suspicion of FMD-related stenosis, when the diagnosis remains uncertain after performing noninvasive tests [82]. In equivocal cases, intravascular

ultrasound (IVUS) and pressure measurements can help to assess the hemodynamic significance of a stenosis and the anatomical success after percutaneous intervention [86, 87].

25.3.4 Screening for FMD Lesions of Other Vascular Beds

Analysis of various cohorts of FMD patients from Europe and the United States suggests that up to one third of patients with FMD may harbor lesions of two or more vascular beds [82]. As vascular investigations were neither systematic nor standardized, these figures are likely underestimated. Notably, in the US registry, 65% of patients with renal FMD also have carotid FMD lesions [84]. Therefore, screening for cervico-cephalic FMD lesions in patients with renal FMD is recommended, provided there are arguments that identification of lesions in the second vascular bed could modify management [82]. CT- or, if contraindicated, MR angiography should be preferred to carotid duplex, first because cervical FMD lesions are often distal and thus may escape carotid duplex and secondly because CT angiography also allows detecting associated cerebral aneurysms [82, 88]. Screening of other, less often involved vascular beds (mesenteric, lower, or upper limb arteries) should also be considered in the presence of suggestive symptoms (claudication, abdominal angina, etc.) or medical history.

25.3.5 Therapy

The treatment of patients with renal FMD may include medical therapy with surveillance, endovascular therapy (angioplasty without stenting), or surgery. The decision depends on the nature and location of vascular lesions (stenosis/dissection/aneurysm), the presence and severity of symptoms, prior vascular events related to FMD, and comorbid conditions.

25.3.5.1 Medical Management

Medical therapy includes antihypertensive drugs, preferably blockers of the renin-angiotensin system, treatment of other cardiovascular risk factors, and antiplatelet or antithrombotic drugs after angioplasty or in case of renal artery dissection or thrombosis. Furthermore, it has been suggested that smoking is associated with a more aggressive course of the disease [89, 90]. Accordingly, smoking cessation is strongly encouraged in patients with FMD.

25.3.5.2 Angioplasty With or Without Stenting

There are no randomized controlled studies comparing revascularization to medical treatment only or revascularization by percutaneous angioplasty (PTA) to surgical revascularization in patients with FMD. In contrast with atherosclerotic RAS, hypertension cure is fairly common following revascularization of FMD-related RAS (30–50% according to the definition of normotension) [91]. As shown in a

meta-analysis, cure rates are higher in younger patients, those with more recent onset of hypertension, and in unifocal FMD compared with multifocal FMD [91]. It appears appropriate to propose revascularization in hypertensive patients with FMD-related RAS, especially if hypertension is of recent onset or in case of drug-resistant hypertension [82].

The two options available for renal artery revascularization are PTA and renal artery surgery. In view of its less invasive character and of the large experience acquired, PTA is currently the first-line revascularization technique. There is no evidence of superiority of renal artery PTA followed by stenting vs. PTA alone in FMD patients. Furthermore, cases of stent kinking of fracture have been reported in patients with renal FMD [92]. Therefore, stenting is not indicated after primary PTA unless needed due to a significant per-procedural dissection [82]. Surgery remains the primary approach for patients with complex lesions of arterial bifurcation or branches, stenoses associated with complex aneurysms, or following PTA failure. A second PTA may be attempted following PTA failure, but a third PTA is not recommended so as to prevent arterial trauma, which could jeopardize surgical results [82].

25.3.6 Future Perspectives

One of the major aims of current research is to identify the genetic and environmental factors involved in the pathogenesis of FMD. Besides candidate gene studies, which have proven disappointing so far [77], non-hypothesis-driven strategies such as genome-wide association studies performed in large discovery and replication cohorts and whole exome sequencing in selected familial, severe, early-onset cases [93] may contribute to unravel the genetic determinants of the disease. Environmental factors, including tobacco and hormones, and possible gene-environment interactions also need further evaluation. Additional research efforts should be devoted to identification of the disease subtypes more likely to progress, definition of an evidence-based screening and follow-up algorithm, and improvement in quantification of FMD-related renal artery stenosis. A common prerequisite of most of these investigations is to collect systematically and prospectively in a standardized way all FMD cases into national and international registries such as US [84], French [94], and European registries.

Conclusions

The prevalence of renovascular hypertension is highly variable according to the studied cohorts. Renal angiography remains the gold standard for the diagnosis of renal artery stenosis.

In atherosclerotic renal artery disease, medical therapy remains the cornerstone of treatment, and cardiovascular risk factors should be aggressively targeted. Revascularization with balloon angioplasty and stent placement should be considered for selected patients with atherosclerotic renal artery stenosis and poorly controlled hypertension and/or rapidly declining kidney function and/or

flash pulmonary edema. Recent research highlights the transition from a pure hemodynamic condition to a complex inflammatory process in the ischemic kidney, creating new opportunities for innovative therapies [95].

For FMD-related renal artery stenosis, angioplasty without stenting should be considered in most cases, especially in young patients with recent onset of hypertension and/or patients with resistant hypertension. FMD appears more and more as a systemic disease with a heritable component. Therefore, management should also include screening for lesions of other vascular beds, particularly cervicocephalic FMD, and careful family history taking [82].

Acknowledgments The authors are indebted to Dr. Elena Berra for her assistance in preparing and checking the references and to Mrs. Nadia Fenners for editing the tables.

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