



Review

The “Silent Enemy” Called Renal Artery Stenosis: A Mini-Review

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Abstract: Renal artery stenosis (RAS) is a vascular condition characterized by narrowing of one or both renal arteries, leading to reduced blood flow to the kidneys, activation of the renin–angiotensin–aldosterone system (RAAS), and subsequent renovascular hypertension. Overactivation of the same cascade potentiates the production of angiotensin II, which induces systemic vasoconstriction, increases sodium and water retention via aldosterone, and activates the sympathetic nervous system. Angiotensin II is also implicated in endothelial dysfunction, oxidative stress, and chronic inflammation, thus impairing vascular remodeling and arterial stiffness, all of which serve to accelerate cardiovascular complications, such as left ventricular hypertrophy, heart failure, and myocardial infarction. RAS is usually due in at least 90% of cases to atherosclerosis, which typically affects older people with diabetes and smoking as risk factors. There are two types of RAS: unilateral and bilateral. Bilateral RAS is commonly associated with flash pulmonary edema, a life-threatening emergency condition in which alveolar space flooding can occur within minutes. RAS typically remains asymptomatic until the late stage with complications of hypertension, ischemic nephropathy, or chronic kidney disease. FMD tends to create structural abnormalities of the artery, whereas atherosclerosis causes plaque formation and endothelial dysfunction of the artery. Epidemiological surveys have revealed that the prevalence of RAS ranges from 4% to 53% and is especially high among patients with hypertension, cardiovascular disease, or CKD. Diagnosis is based on clinical suspicion and supported by imaging studies, including Doppler ultrasound, computed tomography angiography, and magnetic resonance angiography. Early detection also relies on certain laboratory biomarkers, especially in identifying high-risk patients. These markers would include increased plasma renin activity, elevated aldosterone-renin ratio, and inflammatory markers, including C-reactive protein and endothelin-1. Treatment would also involve pharmacological approaches, including RAAS inhibitors, beta-blockers, and statins, and interventional treatments, including angioplasty and stenting in patients with severe forms of the disease. However, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) Trial showed that most patients would likely require medical therapy, and that intervention should be reserved for those with uncontrolled hypertension, progressive renal dysfunction, or recurrent episodes of pulmonary edema. Other emerging therapies include drug-eluting balloons, bioresorbable stents, and gene-editing techniques, all of which have shown great promise in the few studies that have been conducted, although further evaluation is needed. Despite these advances, there are still gaps in knowledge regarding patient stratification, biomarker validation, and the development of personalized treatment strategies. This article reviews the complexities of RAAS and its systemic impact on cardiovascular and renal health. Future research can therefore focus on improving early diagnosis, optimizing patient selection for intervention, and developing new therapies to slow disease progression and mitigate complications.



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1. Introduction

Renal artery stenosis (RAS) is a vascular disease described by significant constriction of the arterial lumen of one or both renal arteries, thus reducing blood flow to the renal parenchyma. This process may cause renal ischemia and hyper-compensatory activation of the renin–angiotensin–aldosterone system (RAAS), contributing to the development of renovascular hypertension, a secondary subtype of systemic arterial hypertension (SAH) [1]. Recent studies point out that RAS is not only a solitary problem, but represents a high-risk marker for systemic cardiovascular events, such as acute myocardial infarction and stroke, especially in at-risk populations, which are usually elderly and people with generalized atherosclerotic disease [2,3].

Etiologically, the causes of RAS are predominantly related to atherosclerosis, responsible for approximately 90% of cases, and fibromuscular dysplasia (FMD), comprising around 10% of diagnoses [2–4]. While atherosclerosis tends to affect older individuals, those with hypertension, diabetes, and smokers, FMD strikes young women and is classically described by noninflammatory, nonatherosclerotic changes in arterial walls [2,3]. Renal atherosclerosis is also associated with other arterial disease processes, specifically peripheral arterial disease (PAD) and coronary artery disease (CAD), suggesting extensive involvement of the vascular tree [2,3].

Most cases of RAS are asymptomatic until they reach more advanced degrees of obstruction, at which time even more severe complications, including chronic kidney failure, may appear [5–7]. In turn, FMD is a rare condition, usually diagnosed incidentally on the basis of imaging studies; however, it may also present with significant clinical features, such as intractable hypertension [5–7].

This clinical entity poses concern for its potential, initially silent effects on renal function and blood pressure control, and it is associated with severe cardiovascular complications, among which are heart failure and left ventricular hypertrophy when not diagnosed and treated accordingly [1–3]. Appropriate management is not just limited to control of arterial obstruction but requires a comprehensive approach to mitigate the related risk factors involved [1–3].

2. Epidemiology

The determination of the true prevalence of RAS is challenging in the general population because a large part of the population has not been covered in such studies; most have not been performed since there is no screening test that is both accessible, reliable, and widely applicable. Most of the research conducted so far has been in high-risk individuals with established risk factors, such as hypertension and/or cardiovascular disease, which may create a bias in understanding the actual frequency of the disease. This bias is of concern because there are cases of hemodynamically significant RAS without obvious alterations in blood pressure or accompanied by other cardiovascular disease.

Commonly used alternatives for disease burden estimation are autopsy studies, which have been considered a possible source of unbiased data. Most of these analyses were conducted in patients who died in a hospital setting, where atherosclerosis might have been a major determinant for death, thus influencing these findings. Furthermore, the performance of an autopsy is not standardized across all hospitals, which may limit the representativeness of data obtained through this procedure. Zoccali and coworkers (2002)

pointed out in their work that the exact incidence of RAS is difficult to determine due to the often asymptomatic nature of the condition [8].

Quantification of different populations has enabled estimation of the numbers of persons affected by RAS. The prevalence of RAS in the general population is expected to range between 4% and 53%. Endo et al. (2010), in a series of 410 patients, found that the prevalence of RAS $\geq 50\%$ was 22.9%, and for RAS $\geq 75\%$, it was 11% [9]. In general, it is to be noticed that in larger studies, a smaller prevalence is found [8].

Furthermore, one may notice a large variation in prevalence when the studied group has comorbidities. Among hypertensive patients, prevalence ranges from 1% to 5%, while in patients with coronary artery disease, the numbers vary between 11% and 23%. Among patients with either peripheral or abdominal vascular disease, the prevalence of RAS ranges from 14% to 42%. Among those with congestive heart failure (CHF), the rates are still higher, between 30% and 50% [8].

On the other hand, something more well established in the literature is that the RAS more commonly presents unilaterally. In a cohort based on data from 3,987 patients who had undergone abdominal aortography immediately after coronary angiography, it was observed that 4.8% of patients had severe stenosis ($\geq 75\%$ narrowing), but of these, only 0.8% had bilateral disease (severe stenosis in both renal arteries) [10].

Gender, Age, and Race Influence on RAS Prevalence

The effect of gender on the incidence of RAS has not been very elucidated. Some studies suggested that females might have a higher tendency to RAS than males [11]. The exact mechanism behind this difference has not been fully elucidated but might be related to different hormonal levels, underlying cardiovascular risk factors, and control of blood pressure. In contrast, other studies showed that gender is not a statistically significant variable [11]. Furthermore, some investigators have hypothesized that there may be some bias in those studies in which there was a higher incidence of RAS among women. They suggested that females are more likely to be subjected to catheterization at higher stages of life, which is likely to increase the detectable rate of the pathology [12].

A cross-sectional study conducted as part of the Cardiovascular Health Study (CHS) analyzed the prevalence of RAS in 870 elderly persons and its association with various cardiovascular risk factors [13]. No differences were found in the rates of prevalence between white participants, at 6.9%, and African American participants, at 6.7% [13]. However, the prevalence was independently related to aging (every 5 years increase in age increased the risk for RAS by 34%), decreasing levels of HDL cholesterol (low levels of HDL cholesterol raised the risk for RAS 2.63 times), and increasing levels of systolic blood pressure (patients with RAS were having an average 142 ± 20 mmHg systolic blood pressure compared to 134 ± 21 mmHg in those patients without RAS) [13].

Several studies have suggested that the higher prevalence of severe hypertension amongst people of African descent may lead to an increase in the incidence of renal lesions, including RAS [9,14–17]. However, when considering atherosclerotic disease, the risk factor profile (such as for diabetes and dyslipidemia) and access to health care may be more important than ethnicity in determining the severity or onset of RAS [9,14–17].

Svetkey and colleagues (1991) showed that the prevalence of RAS (27% in the white population and 19% in the black population, $p = 0.27$), as well as the rate of renovascular hypertension (18% in the white population and 9% in the black population, $p = 0.25$), was similar between the white and black populations [18]. However, this study acknowledges that severe hypertension is more prevalent among the black population, suggesting that this population may have heightened susceptibility to resistant hypertension and its complications [18]. This finding may be complemented by the study of Novick et al. (1994),

in which the incidence of RAS was similar between the groups, and the black population had a higher prevalence of severe hypertension (37.5% vs. 19.3%; $p = 0.01$) and refractory hypertension (85% vs. 67.9%; $p = 0.05$) [14].

In addition, Deitch et al. (1997) found that African Americans had more severe, earlier-onset hypertension and a higher rate of preoperative severe renal dysfunction (57% of the black population had creatinine > 2.0 mg/dL compared to 40% of the white population, $p = 0.07$) [15]. Despite this, surgical outcomes were similar between the groups, suggesting that early intervention may be effective in mitigating the impacts of renovascular hypertension in this population [15].

Regarding FMD, there is a consensus that most reported cases come from Caucasian patients, mainly women, but the real ethnic distribution remains undefined due to a lack of studies with a population base and samples that properly represent other ethnicities. The available records (mostly from the United States and Europe) end up representing the population that has access to the referral centers in these locations (mostly Caucasian) [19–21]. Therefore, what is today called “higher frequency in whites” may be due to selection bias and to underdiagnosis in other populations. The need for epidemiological studies on different continents and ethnic groups continues to be one of the major points of discussion and gaps in the literature on FMD.

Finally, there is no consensus that ethnicity is a predictive independent factor of worse or better outcomes in post-revascularization procedures for RAS, since comorbidities associated and the control of risk factors (hypertension, diabetes, hypercholesterolemia) generally weigh more heavily in these patients’ prognosis [9,14–17]. Differences in access to the health system, early diagnosis, and adherence to treatment will most likely lead to nonclinical disparities, but this is a matter of social determinants of health that may (or may not) be associated with ethnicity.

3. Physiopathology

The progression of RAS entails a number of structural and functional changes in the arterial walls. In the case of atherosclerosis, apart from the lipid plaque deposition, there is a gain of chronic inflammatory process-induced vascular remodeling [22,23]. This is characterized by smooth muscle cell proliferation, extracellular matrix deposition, and calcification contributing to arterial stiffness and luminal narrowing [22,23]. The development of such unstable, rupture-prone plaques may also lead to episodes of acute ischemia or exacerbations of renal artery occlusion [22,23].

In FMD, the constriction is due to focal anatomic changes in the medium or adventitia layer of the arteries [22–25]. Examples of such irregular patterns include multiple stenoses alternating with focal dilatations to form the classic ‘rosary beads’ appearance on angiographic images [22–25]. Although the exact etiology of FMD remains unknown, genetic and hormonal factors are believed to play a crucial role in the onset of the disease, especially given its high prevalence among young women [22–25].

Besides the decrease in arterial lumen in atherosclerosis and FMD, reduction in blood flow may induce secondary changes in the kidneys that include cortical atrophy and decrease in parenchymal mass [22–24]. These structural changes are further exacerbated by ongoing activation of inflammatory and profibrotic pathways that lead to interstitial fibrosis, hence reducing renal capacity to maintain hydroelectrolytic homeostasis [22–24].

There are two types of RAS: unilateral and bilateral. In patients with unilateral RAS, the renal function has no abnormalities because the healthy kidney compensates. Several studies have demonstrated that many patients with unilateral RAS have subclinical contralateral disease. Messerli and coworkers, summarizing the data from 26 studies including 30,092 patients, quoted that 20.3% of all patients with atherosclerotic RAS had

significant bilateral RAS. Patients with bilateral RAS have a higher risk of fluid retention, loss of kidney function, and congestive heart failure [26].

A recent study by Drieghe et al., using a porcine model of unilateral, graded RAS in the presence of a significant contralateral stenosis, has demonstrated that the rise in renin secretion in the ipsilateral renal vein was more pronounced as compared to graded RAS with a healthy contralateral renal artery. These data suggest that compensatory mechanisms are more addressed in the presence of a contralateral RAS [27].

The bilateral RAS is commonly associated with flash pulmonary edema, also known as Pickering syndrome. The Pickering syndrome presents with sudden respiratory distress with dyspnea, tachypnea, hypoxia, diaphoresis, and altered mentation and may eventually lead to cardiopulmonary arrest and death, being precipitated by anything that leads to increased left ventricular filling pressure [24,28,29]. Coronary artery disease commonly occurs in RAS patients with episodes of pulmonary edema [29].

The pathophysiology of recurrent pulmonary edema is complex, but in bilateral RAS patients it is highly correlated with volume overload [30]. In the bilateral RAS patients, the absence of normal renal function in response to pressure natriuresis leads to volume overload. Patients with a solitary kidney may develop pulmonary edema due to angiotensin-mediated vasoconstriction induced by increased left ventricular afterload [31].

Further progression of stenosis may be accelerated by hemodynamic conditions, such as high levels of systolic pressure that raise the shearing stress at the site of arterial walls, and systemic factors including endothelial dysfunction that in turn may be linked with other precipitating agents, such as hyperglycemia and smoking [22–24]. Endothelial dysfunction impairs the production of nitric oxide, an essential molecule for vasodilation, thus aggravating the narrowing of the lumen [22–24].

Recent studies have also underscored the role of interactions between immune cells and vascular endothelium in the progression of RAS [22–24]. They infiltrate the arterial wall with their monocyte and macrophage derivatives, producing inflammatory cytokines and promoting the oxidation of lipoproteins, thus exacerbating plaque formation and local inflammation [22–24]. Such observations further emphasize the need for therapeutic intervention aimed not only at mechanical debridement of the stenosis but also at modulating the inflammatory process [22–24]. The general aspects of the physiopathology of RAS are shown in Figure 1.

Relationship with the Activation of the Renin–Angiotensin–Aldosterone System (RAAS)

The reduction in renal blood flow due to stenosis causes hypoperfusion of the parenchyma, which is detected by juxtaglomerular cells—a set of modified smooth muscle cells located in the afferent glomerular arterioles. In response, there is a compensatory activation of the RAAS, resulting in the release of renin [32].

Renin converts angiotensinogen, a hepatic-origin plasma protein, into angiotensin I, which is subsequently converted into angiotensin II by the angiotensin-converting enzyme (ACE). Angiotensin II causes systemic vasoconstriction and stimulates the release of aldosterone from the adrenal zona glomerulosa, thus producing sodium and water retention [32]. All these combined effects raise the blood pressure, characterizing renovascular hypertension [22–24,32]. Furthermore, angiotensin II also exerts proinflammatory and profibrotic effects by contributing to an increase in structural alterations of the blood vessels and further progression of the disease [22–24,32].

In cases of bilateral stenosis or in patients with a single kidney, a gross reduction in renal perfusion may eventually lead to acute renal failure, especially after the initiation of ACE inhibitors or angiotensin II receptor blockers (ARBs)—drugs frequently prescribed as first-line treatments for hypertension, due to their further lowering effect on the glomerular filtration pressure [22,23].

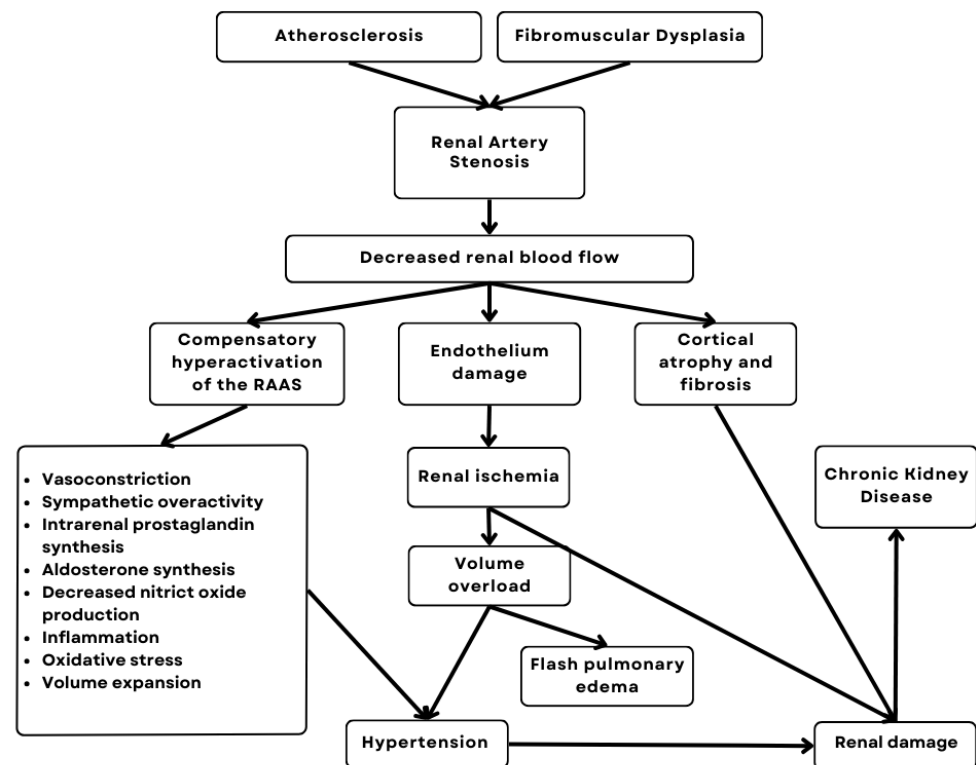


Figure 1. General aspects of RAS's pathophysiology.

4. Diagnosis

The early, accurate diagnosis of RAS is very important in the proper management of the disease, especially when very severe clinical conditions manifest. The diagnostic assessment is based on a combination of clinical data, laboratory, and most of all, diagnostic imaging [2,3,7].

Replicated trials have led to several risk factors that predispose the patients to the development of renal artery stenosis. Atherosclerosis is considered the primary cause of RAS, most especially among the aged population. Other cardiovascular risk factors, such as hypertension, diabetes mellitus, dyslipidemia, smoking, and chronic kidney disease, also predispose to RAS in adults [33]. In addition, PAD and CAD have high relations with RAS. It has been reported from various studies that the incidence of RAS is higher among patients with CAD or three-vessel coronary artery disease [34].

In contrast, FMD is a non-atherosclerotic condition and is a common cause of RAS in young patients, especially females, and is, in fact, unrelated to traditional cardiovascular risk factors. A number of factors have been associated with the development of FMD; its exact etiology, however, is not fully understood. There probably is a genetic predisposition, with a number of studies singling out a few potential genetic markers, including variants in the PHACTR1 gene associated with coronary artery disease and migraine [35].

Additionally, various environmental factors, including but not limited to smoking, have been implicated in the development and progression of FMD. Smokers appear to show earlier onset in this group of patients and even have a more frequent vascular intervention rate [36]. The hormonal influences may also contribute to the higher prevalence of FMD in women, suggesting a potential role for estrogen and other sex hormones in vascular remodeling [37]. Also, connective tissue abnormalities have been noted in some patients with FMD, including increased incidence of myopia and high palate, as well as early-onset osteoarthritis, thus suggesting an overlap with systemic connective tissue disorders [38].

Clinically, patients with RAS may present with resistant hypertension, defined as the failure to control blood pressure despite at least three antihypertensive medications, one of which should be a thiazide diuretic, or present with abrupt worsening of previously controlled hypertension [39]. Other important clinical clues include an unexplained worsening in renal function, particularly after the initiation of inhibitors of the renin–angiotensin system, or the presence of flash pulmonary edema. Physical examination findings suggestive of RAS include the presence of an abdominal bruit, although it is not specific.

An initial noninvasive screening test that is often used is renal ultrasonography with Doppler studies that shows either an asymmetry in kidney size or altered renal blood flow patterns. More definitive imaging techniques, including computed tomography angiography (CTA) and magnetic resonance angiography (MRA), provide high sensitivity and specificity for the detection of significant stenosis [40]. Renal angiography remains the gold standard for diagnosis, particularly when intervention is being considered.

These insights underscore the importance of early detection and risk assessment with a view to preventing progression of disease and guiding appropriate therapeutic interventions in patients diagnosed with RAS.

4.1. Diagnostic Approach Using Imaging Modalities

Doppler ultrasound is a common initial noninvasive test employed in the assessment of RAS. It allows for visualization of the renal arteries and measurement of blood flow velocities [41,42]. Parameters such as high-velocity systolic flow (greater than 200 cm/s) and a renal-aorta ratio > 3.5 have been shown to be highly accurate in identifying hemodynamically significant stenosis [43,44].

Alternatively, a CTA would provide detailed images of the renal arteries and allow assessment of the degree of stenosis. However, it requires the use of iodinated contrast, which may be a limitation in patients with renal dysfunction [3,25,45].

Advancing to methods of imaging, MRA is a noninvasive, contrast-enhanced alternative for evaluating the renal arteries. Its increased risk of nephrotoxicity through exposure to gadolinium contrasts its appropriate use among patients with borderline kidney function [3,46].

Lastly, arteriography—considered the gold standard in RAS diagnosis—provides precise anatomical details and allows simultaneous therapeutic interventions. Nonetheless, it remains an invasive procedure with its own share of associated risks, including atheroembolism and contrast-induced nephropathy [3].

4.2. Change in Laboratory Tests

Although imaging studies are invaluable in the diagnosis of RAS, laboratory investigations also play a big role in detecting associated metabolic and functional derangements.

Electrolyte imbalances are frequently observed in patients diagnosed with RAS. In this respect, hypokalemia is the most common manifestation resulting from the hyperactivation of the RAAS and may be considered even as a sign of secondary hyperaldosteronism in these patients [47,48].

Plasma renin activity (PRA) and even aldosterone levels may be further informative, particularly in cases of treatment of resistant hypertension. A high aldosterone-to-renin ratio increases the suspicion for secondary hyperaldosteronism. In addition, the presence of proteinuria, albeit nonspecific, may suggest renal injury from chronic ischemia at the functional level of compromised parenchyma [23,48].

4.3. The Role of Biomarkers in Early Diagnosis

Early diagnosis of RAS presents a clinical challenge in view of no distinct symptom presentation in its initial stage. Biomarkers have therefore been introduced into the

realm of promising tools for early diagnosis, complementing other traditional imaging methods [49,50].

Recent studies explored plasma and urine biomarkers associated with endothelial function, hypertension, and oxidative stress. These included but were not limited to endothelin-1, vascular endothelial growth factor (VEGF), and C-reactive protein (CRP) [49,50]. While nonspecific, these biomarkers are usually elevated in patients with RAS due to endothelial dysfunction and the inflammatory process required for its development [49,50].

Furthermore, identification of specific microRNAs, such as miR-126 and miR-210, may hold diagnostic potential for this condition at an early stage [51]. These small non-coding RNAs regulate critical pathways in angiogenesis and tissue repair and are already detected at altered levels with or without the presence of stenosis [51].

On the other hand, the standardization of the miR-126 and miR-210 biomarkers for diagnosing RAS is still far from being feasible. Among the main ones is the fact that several measurement methods have high variability since the quantification of these microRNAs can be quite influenced by different laboratory techniques. In the study by Park et al. (2015), they used real-time quantitative PCR (qPCR); however, the lack of a satisfactory endogenous control for plasma samples may undermine the reproducibility of their results [51]. In addition, the microRNA levels are directly related to the glomerular filtration rate (GFR), suggesting that their expression may be influenced by renal insufficiency, which further complicates data interpretation. Furthermore, laboratory costs in procedures like qPCR and gene sequencing are also high, hampering their adoption into clinical practice [51].

However, the miR-126 and miR-210 biomarkers differ significantly from conventional diagnostic tools in their characteristics. Methods, such as Doppler ultrasound, are available and noninvasive, but sensitivity may be reduced in obese patients or when performed by inexperienced operators. CTA provides high accuracy in anatomical assessment but is associated with radiation and iodinated contrast. MRA provides good vascular visualization without ionizing radiation but is expensive and is restricted to patients with metal implants [51].

The context makes microRNAs a unique opportunity for early detection of pathophysiological changes associated with stenosis of the renal arteries long before their anatomical exposure on the imaging. In addition, their presence in the plasma allows continuous monitoring of the progress of the disease, which will enable further clarification of the monitoring of the therapeutic response. Relevant differences also relate to possible associations with pathophysiological mechanisms because reductions in levels of miR-126 and miR-210 in patients with stenosis might point to a protective role against progressive renal damage [51].

Consequently, progress in this area might not only further early diagnosis of RAS but also allow more targeted and effective interventions to reduce morbidity and mortality from this condition [49–51].

5. Clinical Impacts

5.1. Renovascular Hypertension

One of the main consequences of RAS is renovascular hypertension: a secondary form of hypertension that results from persistent activation of the RAAS [1]. The process begins with a reduction in renal perfusion, identified by juxtaglomerular cells that respond with an increase in renin release. This increase promotes the conversion of angiotensinogen into angiotensin I, which is subsequently converted into angiotensin II by ACE [23,52].

Classically, the hyperactivation of the RAAS leads to sympathetic overactivity, intrarenal prostaglandin synthesis, aldosterone synthesis, and decreased nitric oxide production, resulting in a direct decrease in renal sodium excretion. This sequence of events

was originally described by Goldblatt et al. [53], but chronically, especially in the presence of chronic kidney disease, the increased plasma renin activity decreases as plasma volume expands.

The reduction in the kidney blood flow due to stenosis causes damage to the endothelium, and small arterioles vasoconstrict in response to the release of other vasoconstrictors, such as endothelin-1, thromboxane A2, prostaglandin H2, and adenosine [54–56]. Excessive vasoconstriction, associated with reduced vasodilation, compromises microcirculation, leading to ischemia. The decline in renal function reduces the excretion of sodium and water, leading to hypervolemia and, consequently, an increase in blood pressure.

Excessive angiotensin II has several roles in the progression of hypertension. During the chronic phase of renovascular hypertension, angiotensin II antagonists and/or arterial stenosis removal can reduce blood pressure and intravascular volume [57]. In addition to inducing systemic vasoconstriction, it stimulates the secretion of aldosterone by the adrenal glands, thus allowing water and sodium retention. This is made possible by a mechanism of expansion of intravascular volume and an increase in peripheral vascular resistance [22].

Additionally, angiotensin II increases the renal sympathetic activation by acting in glial cells and regions of the brain responsible for blood pressure regulation and induces the release of vasopressin from the pituitary, which in addition to causing vasoconstriction, stimulates thirst and water reabsorption from the kidney to expand the intravascular volume [58]. Furthermore, angiotensin II is, in fact, an important pro-inflammatory and pro-fibrotic mediator, stimulating vascular remodeling and worsening long-term damage [8].

Beyond its classical role in the regulation of circulatory homeostasis, angiotensin II is known to act as a powerful proinflammatory mediator through stimulation of the angiotensin II type 1 receptor (AT1R) [59]. Angiotensin II stimulates the production of prostaglandins and VEGF, leading to increased vascular permeability, which initiates the inflammatory responses [60]. Angiotensin II also up-regulates adhesion molecules [61] and the expression of potent chemoattractants and activators of neutrophils [62]. In addition, angiotensin II increases CRP [63], which up-regulates AT1R mRNA and increases AT1R numbers expressed on vascular smooth muscle cells [64].

There is increasing evidence that angiotensin II may activate innate and adaptive immunity, being a potent modulator in the immune system. Monocytes express AT1R and angiotensin II type 2 receptors (AT2R), which have substantial roles in promoting vascular inflammation and metalloproteinase production [65]. The most proinflammatory actions of angiotensin II are mediated by binding to AT1R, which is widely present in many tissues and organs, including kidneys and the heart. Thus, angiotensin II, in addition to causing vascular inflammation, can lead to renal and cardiac inflammation, contributing to increased blood pressure.

Fibrosis is the result of chronic inflammatory reactions induced by a variety of stimuli, including increased levels of angiotensin II. The AT1R stimulation by angiotensin II directly causes cellular changes and cell growth and activates multiple intracellular signaling cascades in cardiac myocytes, fibroblasts, vascular smooth muscle cells, and renal mesangial cells [66]. Ultimately, the deposition of fibrotic tissue in the kidneys, heart, and blood vessels can contribute to cardiovascular dysfunction and increased blood pressure.

Oxidative stress plays a crucial role in the development of hypertension. Angiotensin II binding to AT1R activates redox-dependent pathways, stimulating NADPH oxidases, which produce reactive oxygen species (ROSs). Since AT1R expression is redox-dependent, overproduction of ROSs may result in overstimulation of AT1R-mediated pathways and result in oxidative stress, perpetuating the progression of ischemic nephropathy and, consequently, culminating in irreversible loss of renal function [67]. These effects of angiotensin

II result in proinflammatory, mitogenic, and profibrotic actions, causing cardiovascular and renal remodeling, which, in turn, lead to organ damage and hypertension [67,68].

Some studies suggest the role of endothelin-1 (ET-1) in the physiopathology of renovascular hypertension, since the infusion of angiotensin II can induce the release of ET-1 from endothelial and vascular smooth muscle cells [68]. Furthermore, endothelial cell damage also may cause an increase in plasma ET-1. Despite ET-1 mRNA in the blood vessel wall being slightly elevated [69], the ET-1 antagonism does not consistently decrease blood pressure and expression of the ET system [70]. In patients with renovascular hypertension, urinary ET-1 excretion is increased, whereas plasma ET-1 concentration remains normal [71]. Thus, further studies are needed to elucidate the role of the ET-1 in renovascular hypertension.

It is important to emphasize that hypertension produced by occlusion of a renal artery, with the contralateral kidney intact (Goldblatt hypertension type 2 kidney, 1 clip: 2K1C), appears to have a different pathogenesis than hypertension produced by constriction of a renal artery associated with removal of the contralateral kidney (Goldblatt hypertension type 1 kidney, 1 clip: 1K1C).

In the 2K1C model, the renin secretion is increased in the kidney supplied by the clipped stenotic artery, while the renin content of the contralateral kidney is diminished [72]. Plasma renin activity in Goldblatt 1K1C hypertension is completely normal, probably because removal of the normal kidney reduces sodium excretion and water elimination in the urine, leading to an increase in extracellular fluid volume, which could influence renin levels. During the chronic phase of this model, sympathetic overactivity is the major factor driving hypertension [73].

The RAS can be unilateral or bilateral, and studies have shown that many patients with unilateral stenosis have subclinical contralateral disease. However, a recent study suggests that in bilateral RAS, the same cut-off values to define the hemodynamic significance of RAS can be applied as in unilateral RAS, which is important in the clinical work-up of bilateral RAS, which is frequently encountered in clinical practice [27].

Therefore, renovascular hypertension has some other clinical findings that help to support its diagnosis: age at onset of symptoms, with young patients (under 30 years) generally associated with FMD and patients over 50–60 years, in whom the predominant cause is atherosclerosis; semiological signs suggestive of turbulent flow in the stenosed renal artery, such as audible murmurs in the periumbilical region or in the flanks; resistant hypertension, defined as difficulty in controlling blood pressure, even with the combined use of at least three classes of antihypertensives, including a diuretic; hypokalemia, resulting from persistent activation of the RAAS, especially in patients who do not use potassium-sparing diuretics; rapid progression of renal function impairment or worsening of blood pressure, often accompanied by unexplained weight loss, fatigue and other systemic symptoms; and discrepancies in renal size identified in imaging tests, attributed to chronic hypoperfusion [22,41,74].

Thus, the treatment of renovascular hypertension is multidisciplinary. Some pharmacological approaches include the use of ACE inhibitors and ARBs. However, due to the risk of acute kidney injury, their use should be monitored, especially in cases of bilateral RAS or a single functional kidney. Interventional procedures, such as renal angioplasty with or without stent placement, may be indicated in specific cases [3,6,7].

Early Diagnosis of Renovascular Hypertension: The Role of Laboratory Biomarkers

Laboratory biomarkers are important tools in the differentiation between renovascular hypertension and other forms of secondary hypertension. Some of the most selective biomarkers include increased levels of plasma renin and PRA. For cases of hypoperfusion, they rise in response to renal artery stenosis [29]. In these cases, plasma aldosterone is high

as well, aiding in the differential diagnostic process from other causes of hypertension [29]. Another relevant biomarker is angiotensin-II, which tends to be increased due to higher conversion of angiotensin-I by the ACE [17]. Erythropoietin also may be increased due to renal hypoxia resulting from stenosis [75]. Natriuretic peptides, including brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), are frequently elevated in advanced cases, reflecting cardiac overload [76]. Cystatin C and creatinine are used in the assessment of renal function and may show further progression of renal dysfunction in chronic renovascular hypertension [77].

These biomarkers not only assist in the diagnosis of renovascular hypertension but are also used in the identification of acute kidney injury (AKI) and CKD. Cystatin C and creatinine enjoy wide applications in the assessment of renal function. Renin and aldosterone may be altered in patients with CKD, especially in hypertensive nephropathy [75]. However, the difference in the pattern of change in biomarkers allows the conditions to be differentiated: in renovascular hypertension, renin and aldosterone tend to be proportionally higher than in AKI or CKD, where factors such as inflammation and tubular damage are more prevalent [77].

5.2. Ischemic Nephropathy

A relatively common consequence of RAS is large vessel atherosclerotic renovascular disease (ARVD). This process develops gradually over years, and when it reaches a “critical threshold” of around 70–80% vascular occlusion, distal perfusion pressures and blood flows begin to fall measurably [78]. The ARVD leads to distal microvascular disturbances with loss of medium and small diameter vessels and ultimately with parenchymal fibrosis [77,79].

Although the hemodynamic changes caused by ARVD can be reversed with the restoration of blood flow, subsequent microvascular remodeling and rarefaction eventually fail to be reversible. Some authors often refer to the loss of renal function as a result of a stenotic lesion as ischemic nephropathy [80], assuming that loss of blood flow must induce tissue hypoxic injury [81].

Ischemic nephropathy is defined by the gradual reduction in the GFR or a loss of renal parenchyma caused by vascular occlusion, not attributable to the other causes [82]. The main macroscopic feature of ischemic nephropathy is the reduction of kidney size. In the histology of ischemic nephropathy, both reversible tubular atrophy and glomerular collapse and irreversible glomerulosclerosis and interstitial fibrosis are present [82]. Tubulointerstitial lesions are the most pronounced histopathologic feature of ischemic nephropathy [83].

The relationship between RAS intensity and the presence of ischemic nephropathy or the severity of renal dysfunction is not completely understood. Some studies have demonstrated that a decrease in GFR in patients with RAS is not determined by the severity of RAS but rather by the extended kidney lesions downstream of the RAS [84].

In ischemic injury, the reduced blood flow causes damage to the endothelium, and small arterioles in postischemic kidneys vasoconstrict in response to increased tissue levels of endothelin-1, angiotensin II, thromboxane A₂, prostaglandin H₂, leukotrienes C₄ and D₄, and adenosine, as well as sympathetic nerve stimulation [54–56].

Vasodilatation in response to acetylcholine, bradykinin, and nitric oxide is also reduced [85]. These effects on the arterioles are augmented by vasoactive cytokines [86]. Increased vasoconstriction, together with activation of the coagulation system, compromises microcirculation, leading to ischemia.

Vascular remodeling in atherosclerosis is caused by a variety of mechanisms. Dynamic changes in the endothelium, fibroblasts, smooth muscle cells, pericytes, or other vascular

wall cells underlie remodeling. Furthermore, immune cells, such as macrophages and lymphocytes, also infiltrate vessels and initiate inflammatory signaling. All these factors contribute to a dynamic interplay between cell proliferation, apoptosis, migration, inflammation, and extracellular matrix reorganization [87]. All these processes involve molecular pathways that include growth factors, inflammatory cytokines, reactive oxygen species, and signaling pathways, such as Rho/ROCK, MAPK, and TGF- β /Smad [87].

Atherosclerosis is a disease characterized by low-grade, chronic inflammation of the arterial wall and is triggered by the subendothelial retention of plasma-derived, apolipoprotein B (apoB)-containing lipoproteins [88]. Infiltrated plasma lipoproteins initiate the local innate and adaptive immune responses in the intima [89]. Then, the inflammatory cells present in the intima respond by secreting pro-inflammatory chemokines and cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- α), that in turn activate circulating leukocytes and the local endothelial cells [90].

Several pieces of evidence indicate that inflammatory factors play an important role in renal injury in ARVD. Stenotic swine kidneys in ARVD have increased tissue levels of monocyte chemoattractant protein (MCP-1), which is associated with endothelial dysfunction and microvascular loss [91]. Patients with atherosclerotic RAS have elevated levels of MCP-1 and TNF- α that persist after revascularization [75]. Increased renal tissue inflammation may directly cause microvascular injury and endothelial dysfunction [92].

Studies have shown that atherosclerotic RAS is associated with disturbed local and cellular immunity even before it affects renal blood flow [93]. After acute injury, some degree of macrophage infiltration can be observed within the kidney parenchyma. Infiltrating macrophages change their cellular function from phagocytic to reparative structural actions, promoting angiogenesis and tubular regeneration [94,95].

Post-stenotic kidneys evaluated by tissue biopsies presented infiltration of CD68+ cells in peri-glomerular and tubular structures, which are not present in normal kidneys [96]. Levels of inflammatory markers in affected kidneys are quantitatively related to the severity of measured tissue hypoxia and GFR loss [97].

The mechanisms underlying T cell and macrophage functions are complex, but evidence indicates that inflammatory pathways with phenotypic direction to fibrosis and loss of tubuloglomerular structure are involved in the transition from AKI to CKD [94,98].

Taken together, these studies indicate that atherosclerosis activates mechanisms that can aggravate loss of stenotic kidney micro-vessels beyond the effects of the vascular occlusive lesion alone. Intensified inflammatory activation may lead to local proteolysis, plaque rupture, and thrombus formation, which causes ischemia and infarction.

5.3. Chronic Kidney Disease (CKD)

In the advanced stages of early-onset renal artery stenosis, prolonged ischemia can lead to renal cortical atrophy and interstitial fibrosis with a progressively reduced renal function [23]. When GFR persists at <60 mL/min/1.73 m² for more than 3 months, a diagnosis of chronic kidney disease (CKD) is established [99].

CKD resulting from RAS is commonly associated with a series of metabolic and systemic complications. The main complications are as follows: anemia, metabolic bone disease, and metabolic acidosis. Reduced production of erythropoietin by the kidneys leads to normocytic and normochromic anemia, contributing to fatigue, decreased functional capacity, and increased cardiovascular risk. At the same time, the imbalance in the metabolism of calcium, phosphorus, and vitamin D, associated with reduced renal function, can result in secondary hyperparathyroidism and renal bone disease, increasing the risk of fractures and impacting quality of life levels. Finally, the reduction in the tubular capacity

to excrete acids can lead to metabolic acidosis, which favors the loss of muscle mass and the exacerbation of bone complications [100].

The prognosis for CKD secondary to early-onset renovascular disease largely depends on the stage of the disease at which the patient presents for treatment and therapeutic intervention. Progression to end-stage renal disease occurs in advanced cases, particularly among those patients with suboptimal blood pressure control and with related comorbid conditions, such as diabetes and dyslipidemia. When GFR falls to below 15 mL/min/1.73 m², renal replacement therapy is indicated [101].

Early Detection of CKD: Role of Biomarkers and Advanced Imaging Techniques

Recognition of CKD due to RAS is a clinical dilemma but quite important in the attempts to retard further progression of renal impairment and reduce associated morbidities. Various measures that attempt to improve the early recognition of such changes have been investigated, including inflammatory biomarkers and new imaging techniques.

The use of serum and urine biomarkers has evolved as a new promising approach for the early diagnosis of renal injury in patients with RAS. Recent studies have shown that oxidative stress and inflammation are activated and linked to the development of renal dysfunction in association with RAS, thereby making new potential biomarkers even more important for their follow-up. Among these are neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitors of metalloproteinases-2 (TIMP-2), and insulin-like growth factor binding protein-7 (IGFBP7). These are biomarkers that show elevations well before the onset of a significant decline in GFR and therefore hold promise for their early identification of renal injury [50].

Other than biomarkers, developments in imaging techniques enable a more detailed evaluation of renal function and structure, furthering early diagnosis of CKD related to RAS. These include innovative methods, such as functional magnetic resonance imaging (MRI) and magnetization transfer-magnetic resonance imaging (MT-MRI), that allow quantification of perfusion and the presence of fibrosis in the kidneys without the need for an invasive biopsy. A study by Ebrahimi et al. (2013) found that MT-MRI could differentiate fibrotic renal tissue from normal tissue, aiding in early detection of structural changes even before significant functional loss [102].

Another emerging technique is non-contrast magnetic resonance angiography, which has been demonstrated to be a useful tool for assessing the severity of arterial stenosis in patients with CKD. This approach does not require iodinated or gadolinium-based contrast agents, which may be specific for patients with advanced renal failure. The study by Parienty et al. (2011) demonstrated that this technique had high sensitivity and specificity in the detection of RAS and thus represented a potential alternative to conventional catheter angiography [103]. Other investigations focus on further potential in developing blood oxygen level-dependent magnetic resonance imaging (BOLD-MRI) as a non-invasive tool to assess renal tissue hypoxia—a very important marker of disease progression. This would then enable the measurement of the concentration of deoxyhemoglobin in the urine specimens, providing a non-invasive evaluation of the level of ischemia and renal dysfunction, which may be critical for the selection of patients that would benefit from early interventions [104].

This would allow for the early identification of patients at risk of developing CKD secondary to RAS and the institution of preventive measures before there is severe renal impairment. The use of early biomarkers with advanced imaging may further improve clinical management to decrease progression to end-stage disease and replacement therapies.

5.4. Other Cardiovascular Events

RAS is not just a local condition but is also a systemic risk marker for major cardiovascular events, such as myocardial infarction, stroke, and heart failure [105]. This link occurs due to the overlap in risk factors for severe arterial hypertension, systemic atherosclerosis, and endothelial dysfunction—each of them also encompassed within the RAS. Sustained renovascular hypertension promotes increased afterload and results in left ventricular hypertrophy. This type of cardiac structural alteration is associated with a greater risk of arrhythmias, valvular inadequacy, and sudden cardiac death [105–107].

Concomitant with the volume overload caused by sodium and water retention, it may precipitate worsening of pre-existing heart failure or provoke new episodes of decompensation [107]. Accordingly, patients with RAS present a significantly higher cardiovascular risk when compared to the general population, due to the interrelationship between renal and cardiac dysfunction, widely known as cardiorenal syndrome [107]. This condition reflects the bidirectional interaction between the heart and kidneys, where dysfunction in one organ worsens that of the other [108].

6. Management

The medical management of RAS involves both medical and interventional approaches, the choice of which depends on the severity of stenosis and the presence of symptoms and/or comorbidities.

6.1. Distinguishing Between Approaches for Unilateral and Bilateral Stenosis

Treatments for renal artery stenosis, depending on whether the condition is unilateral or bilateral, are quite different. As recommended in the European Society of Cardiology (ESC) Guidelines for the year 2024, for patients diagnosed with unilateral atherosclerotic RAS, optimal medical management forms the general approach, including angiotensin-converting enzyme inhibitors (ACEIs), ARBs, and calcium channel blockers [109]. Nevertheless, care should be taken to monitor renal function, since during the use of these medications, there might be a reduction in renal function in such patients [109]. Percutaneous revascularization can be considered in selective cases, particularly in patients with refractory hypertension or worsening of renal function despite good medical management [109].

For patients with bilateral RAS or those with a solitary functioning kidney, the administration of ACEIs and ARBs should be undertaken with great caution, as it significantly increases the risk of developing acute renal failure [109]. This would invariably lead to the increased consideration of revascularization in the attempts to preserve renal function and control hypertension [109]. It is widely acknowledged in the scientific literature that revascularization improves blood pressure control and slows the progression of renal failure in such patients [109]. The decision between the best medical therapy and intervention will be individualized to the severity of stenosis, presence or absence of symptoms, presence of comorbid conditions, and effectiveness of drug therapy [109]. This decision requires meticulous assessment of renal viability and continuous monitoring of renal function to guide towards the most appropriate therapeutic strategy for each patient.

6.2. Drug Treatment

Recent updates in the medical management of RAS advocate for an individualized approach with an emphasis on tight blood pressure control and amelioration of cardiovascular risk factors, including diabetes, dyslipidemia, and smoking [110–112]. Furthermore, it is worth highlighting that the patients who benefit most from exclusive pharmacological

treatment are those who have the following characteristics: controllable hypertension, stable renal function, and absence of serious clinical complications [113,114].

6.2.1. Renin–Angiotensin–Aldosterone System Inhibitors

These include ACE inhibitors and ARBs, which remain front and center in the treatment of hypertension associated with RAS [110–112]. Recent guidelines have further underscored their effectiveness in pressure control and renoprotective effects due to their dual ability to inhibit the RAAS while reducing intraglomerular pressure with it, thus attenuating renal injury [110–112]. Nevertheless, monitoring renal function and potassium levels remains mandatory upon initiation and, above all, in those with bilateral, high-grade renal artery stenosis or a single functional kidney due to the potential risk of induced hyperkalemia and renal insufficiency [110–112].

6.2.2. Beta-Blockers and Combination Therapy

Beta-blockers remain a viable therapeutic option, especially in the presence of cardiovascular comorbidities, such as coronary artery disease [110–112]. They help control heart rate and blood pressure, acting as a complement to RAAS inhibitors [110–112]. A combination of different classes of antihypertensives is often necessary to achieve the goal of blood pressure control in patients with RAS [110–112]. In addition to ACE inhibitors, ARBs, and beta-blockers, diuretics and calcium channel blockers can be incorporated into the therapeutic regimen according to the individual needs of the patient [110–112].

6.2.3. Recent Issues

Currently, although there are no new drugs specific for RAS, guidelines emphasize the importance of individualized treatment, considering the clinical characteristics of each patient [3,41,45]. Monitoring renal function and K^+ at regular intervals plays a crucial role in the ability to adjust therapy safely and effectively [3,41,45].

In addition to antihypertensives, these guidelines recommend the prescription of statins and antiplatelets, particularly in cases of RAS of atherosclerotic origin [110–112].

6.3. Interventionist Treatment

The interventional treatment of RAS consists of the revascularization of the affected arteries and is indicated in particular cases in which the medical therapy alone is not sufficient to control the symptoms or to avoid complications. The major approaches include balloon angioplasty and bypass grafting [52,112,115,116]. The eligibility criteria for choosing this form of treatment are: Refractory hypertension—patients with uncontrolled hypertension, even with the use of at least five antihypertensive agents, including a long-acting thiazide diuretic and a mineralocorticoid antagonist; rapid decline in renal function—patients with a significant reduction in GFR (greater than 20% in weeks to months) or progressive increase in serum creatinine (greater than 30% in relation to the baseline value); recurrent pulmonary edema (more than one episode in 6 months to 1 year or more than one episode associated with hemodynamic instability); favorable arterial anatomy—lesions treatable with angioplasty confirmed by hemodynamic tests or imaging studies, such as CTA [111].

6.3.1. Percutaneous Transluminal Angioplasty (PTA)

Percutaneous Transluminal Angioplasty (PTA) is a minimally invasive procedure that involves introducing a balloon catheter through the femoral artery to the affected renal artery. The balloon is inflated in the narrowed region to dilate the vessel and restore adequate blood flow. In FMD, PTA without stent placement is usually the first choice of

treatment, as it has high success rates in improving arterial flow and blood pressure control, in addition to a relatively low risk of complications [117].

6.3.2. Stent Angioplasty

The most common approach is percutaneous transluminal angioplasty with stent placement, a procedure whereby a balloon catheter is introduced into the narrowed region of the artery, similar to PTA [52,112,115,116]. However, unlike the first approach, after the balloon is inflated to widen the arterial lumen, a stent is implanted to keep the vessel open [52,112,115,116]. This procedure is frequently used in cases of atherosclerotic RAS, especially when the lesion is ostial (close to the origin of the renal artery) or there is a high risk of restenosis [118]. As already mentioned, this method is generally indicated for those patients with renovascular hypertension that is difficult to control, unstable angina, pulmonary edema, abrupt congestive heart failure, deteriorating renal function, and hemodynamically significant RAS [52,112,115,116]. A retrospective analysis of all patients who had undergone renal artery stenting in a defined geographical area in the west of Scotland across three centers between 2008 and 2021 showed that intervention for hypertension achieved significant reduction in systolic blood pressure and antihypertensive agents at 1 year without detrimental impact on renal function. The intervention for renal dysfunction reduced serum creatinine, and for pulmonary edema was universally successful with a significant reduction in systolic blood pressure and serum creatinine sustained at 1 year [119].

On the other hand, several studies, such as Tuttle et al. (2016), which evaluated the effects of stenting for atherosclerotic RAS on eGFR and predictors of clinical events in the CORAL Trial, have concluded that stenting did not influence eGFR in participants with atherosclerotic RAS [120]. Kądziela et al. (2024), analyzing 343 patients in the ARCADIA-POL registry concluded that renal stenting in FMD-RAS may carry a high risk of late complications, including stent occlusion [121].

While some benefit specific patients, such an approach is not without potential dangers, most commonly including hematomas at the catheter site, arterial dissection, and stent thrombosis [52,112,115,116]. The stent restenosis (ISR) is a serious potential setback with renal artery stent placement in patients with atherosclerotic RAS. The stent insertion ruptures the internal elastic lamina of the artery, resulting in smooth muscle cell migration and intimal hyperplasia. These intimal lesions incorporate atherosclerotic elements leading to ISR [122–124]. Secondary to ISR, an intractable hypertension and renal insufficiency may arise [125].

6.3.3. Renal Revascularization Surgery

Surgical revascularization, including aortorenal bypass or endarterectomy, is a far less common approach generally reserved for more complex cases not amenable to stenting angioplasty [52,112,115,116]. This modality is favored in patients with inadequate arterial anatomy for angioplasty due to severe tortuosity or extensive calcification, or in situations where another abdominal operation is being planned [52,112,115,116]. While providing a definitive solution in select cases, such as patients who are not candidates for percutaneous interventions or who have failed angioplasty, surgery is an invasive procedure with higher morbidity and recovery time and risks including infections, bleeding, and acute kidney injury [52,112,115,116].

6.4. Comparison of Efficacy Between Drug and Interventional Therapies

This comparison between the efficacy of drug and interventional therapies for RAS is among the most discussed topics in the medical literature. Several studies to test the

efficacy of angioplasty against medical therapy were performed after renal angioplasty and stents became available in the 1980s.

Three prospective, randomized clinical trials were carried out in Europe: the Dutch Renal Artery Stenosis Intervention Cooperative Study Group (DRASTIC) in the Netherlands [126], the Essai Multicentrique Medicaments vs. Angioplastie (EMMA) in France [127], and the Scottish and Newcastle Renal Artery Stenosis Collaborative Group (SNRASCG) in Scotland [128]. Regarding hypertension control or slowing renal disease progression, none of these studies showed angioplasty to be superior to medical treatment.

The stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function (STAR), a randomized clinical trial involving 140 patients with RAS of 50% or greater, showed that stent placement with medical treatment had no clear effect on the progression of impaired renal function but led to a small number of significant procedure-related complications [129].

A large-scale randomized controlled trial, the ASTRAL (Angioplasty and Stent for Renal Artery Lesions) trial, showed that the combination of percutaneous transluminal renal angioplasty with medical therapy for RAS had no significant therapeutic effect on antihypertensive effect, renal prognosis, development of cardiovascular disease, or recurrence of heart failure, as compared to medical therapy alone [130].

One of the most relevant milestones is the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) study from 2014 [52,131]. This large, multicenter, randomized clinical trial compared optimized medical treatment alone with the combination of medical treatment and stent revascularization in 947 patients with significant RAS (obstruction greater than or equal to 70% of the renal artery lumen, or obstruction of at least 50% when accompanied by signs of functional impairment) [52,131].

The results of the CORAL study indicated that the addition of stent revascularization to optimized medical treatment did not translate into a significant reduction in the primary outcomes, which included major cardiovascular events, such as acute myocardial infarction and stroke [52,131]. Furthermore, there was no clinically significant improvement in renal function progression compared with drug therapy alone [52,131]. These findings further weaken the efficacy of a routine interventional approach for most patients with RAS, reinforcing the central role of drug therapy [52,131].

The study also highlighted that optimized medical treatment, based on the use of RAAS inhibitors, strict blood pressure control, statins, and antiplatelet agents, was effective in reducing adverse events and stabilizing the clinical condition of most patients [52,131]. These results suggest that, in the absence of specific complications, conservative management should be the initial approach for RAS [52,131]. However, CORAL identified subgroups in which revascularization may be beneficial, namely patients with severe clinical features, such as uncontrollable hypertension, recurrent pulmonary edema, or progressive decline in renal function [52,131].

The Agency for Healthcare Research and Quality commissioned a review asking key questions related to the effectiveness of aggressive medical therapy compared with renal artery angioplasty with stent placement. In this review, 78 studies and 20 case reports were included, and the authors concluded that there is a low strength of evidence of not statistically significant or minimal clinically important differences in important clinical outcomes (death, cardiovascular events) or blood pressure control between percutaneous transluminal renal angioplasty with stent placement (PTRAS) and medical therapy alone [132].

Guidelines suggest that stenting for RAS is beneficial in patients with hemodynamically significant stenosis and accelerated, resistant hypertension in either unilateral or bilateral atherosclerotic RAS, and progressive chronic kidney disease with bilateral atherosclerotic RAS or atherosclerotic RAS in a solitary functioning kidney (class IIa: American

College of Cardiology/American Heart Association 2005 Practice Guidelines for the Management of Patients with Peripheral Arterial Disease) [133,134].

Retrospective studies suggest that an RRI < 0.80 Doppler measurement on renal ultrasonography might be predictive of the success of revascularization in patients with RAS [135,136]. A study involving more than 230 patients with RAS showed that renal artery stent implantation controls blood pressure and reduces the number of antihypertensive drugs needed for blood pressure control, but it has no protective effect on renal function [137].

7. Emerging Therapies

Emerging therapies for the management of early allograft rejection explore new technologies and biological approaches aimed at achieving improved clinical outcomes beyond current treatment limitations.

Experimental technologies associated with angioplasty involve the furtherance of highly advanced devices, including drug-eluting balloons and bioabsorbable stents [138]. Drug-eluting balloons hold promise in decreasing restenosis, a common problem following angioplasty, by acting to release drugs at the site of the lesion [138]. Bioabsorbable stents, while offering these advantages of giving initial support to the vessel and then being reabsorbed, will reduce long-term complications, such as stent thrombosis [138].

Studying the area of genetic and biological therapies, several studies have focused on the use of mesenchymal stem cells for renal tissue regeneration and reduction of interstitial fibrosis [102]. Those cells possess immunomodulatory and anti-inflammatory properties and could, therefore, assist in the preservation of renal function in cases of chronic ischemia [102]. In addition, gene editing approaches, including CRISPR-Cas9, are being explored for the correction of genetic mutations contributing to FMD, which is a less common cause of RAS [139].

Although promising, these therapies remain at early stages of development and require robust clinical evaluation for both safety and efficacy.

8. Review and Knowledge Gaps

There have been significant gains in the management of RAS, but several areas still point to clinically important knowledge gaps. Among the major issues in the field, highly heterogeneous clinical trial results are observed.

Trials such as CORAL brought out that while revascularization has limited effectiveness in broad general populations, certain selected subgroups could benefit rather dramatically from these interventions [130]. This heterogeneity makes uniform guideline development difficult and underscores the need for further patient stratified studies according to clinical, anatomical, and functional characteristics [111]. Another area that requires further investigation is the role of new biomarkers and advanced imaging techniques in the diagnosis and patient selection for revascularization [42].

Methods to more accurately identify hemodynamically significant lesions or predict the response to therapy remain lacking in clinical practice [42]. Further, larger, and more diversified studies are needed, including under-represented populations, such as women and different ethnic backgrounds in patients, to ensure general applicability of findings [42].

Finally, emerging therapies, including biological and genetic interventions, require further investigation for their feasibility and clinical impact. The incorporation of such novel approaches into the management of RAS could potentially alter clinical practice; again, this remains dependent upon high-quality research to prove these new approaches safe, effective, and cost-effective [42]. This, therefore, provides a good opportunity to fill this gap and move forward in the treatment of RAS.

9. Conclusions

Renal artery stenosis is a complex condition that goes beyond the concept of arterial narrowing and includes a spectrum of systemic and renal alterations with significant clinical implications.

Although often asymptomatic in its early stages, RAS can progress to renovascular hypertension, chronic renal failure, and serious cardiovascular events, which confirm the importance of early diagnosis and effective management.

The development of more targeted therapeutic strategies, as a result of advances in the understanding of the pathophysiology of the disease, includes optimized drug treatment and, in specific cases, interventions such as stent angioplasty. These and other previous studies, such as CORAL, have redefined the role of invasive interventions, highlighting how effective clinical management is for the majority of patients, while new technologies and biological therapies emerge as promising for specific subgroups. Although there are important gaps in knowledge, the focus is mainly on patient selection for interventions and validation of biomarkers for diagnosis and monitoring. The future of RAS is closely linked to personalized treatment, with integrated approaches that combine therapeutic advances with better-developed diagnostic tools.

Consequently, optimal treatment of RAS will involve not only controlling the disease itself but also mitigating systemic risk factors and providing ongoing monitoring to avoid long-term complications. As research and innovation advance, the clinical impact of RAS should be progressively reduced, benefiting patients and optimizing healthcare.

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Abbreviations

The following abbreviations are used in this manuscript:

RAS	Renal artery stenosis
RAAS	Renin–angiotensin–aldosterone system
SAH	Systemic arterial hypertension
FMD	Fibromuscular dysplasia
PAD	Peripheral arterial disease
CAD	Coronary arterial disease
CKD	Chronic kidney disease
CHF	Congestive heart failure
CHS	Cardiovascular Health Study
ACE	Angiotensin-converting enzyme
ARBs	Angiotensin II receptor blockers
CTA	Computed tomography angiography
MRA	Magnetic resonance angiography
PRA	Plasma renin activity
VEGF	Vascular endothelial growth factor
CRPqPCR	C-reactive proteinReal-time quantitative PCR
GFR	Glomerular filtration rate
AT1R	Angiotensin II type 1 receptor
AT2R	Angiotensin II type 2 receptors

ROS	Reactive oxygen species
ET-1	Endothelin-1
BNP	Brain natriuretic peptide
NT-proBNP	N-terminal pro-B-type natriuretic peptide
AKI	Acute kidney injury
ARVD	Atherosclerotic renovascular disease
Apo B	Apolipoprotein B
IL-1	Interleukin-1
IL-6	Interleukin-6
TNF- α	Tumor necrosis factor alpha
MCP-1	Monocyte chemoattractant protein
NGAL	Neutrophil gelatinase-associated lipocalin
TIMP-2	Tissue inhibitors of metalloproteinases-2
IGFBP7	Insulin-like growth factor binding protein-7
MRI	Magnetic resonance imaging
MT-MRI	Magnetization transfer-magnetic resonance imaging
BOLD-MRI	Blood oxygen level-dependent magnetic resonance imaging
ESC	European Society of Cardiology
ACEIs	Angiotensin-converting enzyme inhibitors
PTA	Percutaneous transluminal angioplasty
ISR	In-stent restenosis
CORAL	Cardiovascular outcomes in renal atherosclerotic lesions
PTRAS	Percutaneous transluminal renal angioplasty with stent

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