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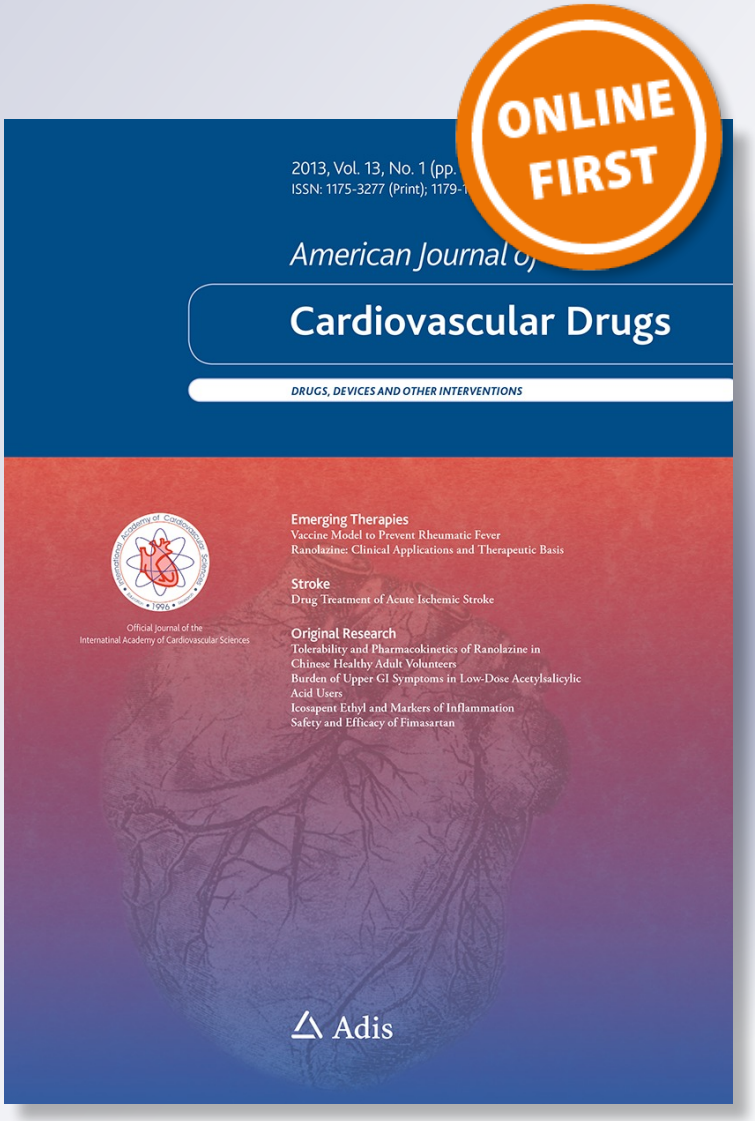

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THERAPY IN PRACTICE

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Abstract Renovascular hypertension refers to the rise of arterial pressure due to reduced perfusion of the kidney caused by the stenotic renal artery/ies. The most common cause of stenotic renal artery is atherosclerosis. Atherosclerotic renal stenosis is usually part of a systemic syndrome that involves hypertension, intrinsic renal damage, and cardiovascular morbidity. So far, large trials have not proven the superiority of interventional therapies to medical management. As a result, renal artery stenosis should be treated mainly as a coronary artery disease equivalent focusing on rigorous management of hypertension, hyperglycemia, and hyperlipidemia. Antihypertensive treatment should include renin-angiotensin system blockade medication in most cases, while HMG-CoA reductase inhibitors (statins) can be used even in chronic kidney disease with safety. Lifestyle modifications, such as cessation of smoking, and antiplatelet therapy have reduced the risk of cardiovascular events in high-risk patients.

1 Introduction

It has been more than 70 years since Henry Goldblatt investigated the pathophysiology of renovascular hypertension in animals, and yet much controversy still exists in this field. Renovascular hypertension refers to the rise of arterial pressure due to reduced perfusion of the kidney caused by the stenosed renal artery/ies. In contrast to renovascular hypertension, renal artery stenosis is an anatomic diagnosis, which is not always the cause of hypertension. The American Heart Association (AHA) in 2008 defined critical renal artery stenosis as a reduction by more than 60 % in renal artery diameter [1]. Critical renal artery stenosis can lead to the clinical syndromes of renovascular hypertension and deterioration in renal function of the affected kidney, commonly referred to as ischemic nephropathy. In renovascular hypertension, renal hypoperfusion causes activation of the renin-angiotensin-aldosterone system (RAAS), which stimulates secretion of angiotensin II.

By far the most common renovascular lesion (90 % of all cases) causing obstruction is atherosclerotic renal artery stenosis. The remaining 10 % of the lesions include fibromuscular dysplasia, arteritis, and rare syndromes, mostly reported in children [2–4]. In almost one-third of patients with atherosclerotic renal artery stenosis, stenosis is bilateral. Renal artery stenosis is usually part of a systemic syndrome that involves an interaction between intrinsic renal damage, hypertension, and cardiovascular disease (CVD), so that patients are at high risk of further renal decline and cardiovascular events [5]. Percutaneous interventional procedures that correct renal artery stenosis lesions have been widely available for over two decades. Although there seems to be a consensus regarding their benefit in specific clinical cases, there is no unanimous agreement on applying interventional treatment for the vast majority of patients with atherosclerotic renal artery stenosis. Since randomized trials have failed to prove any advantage of interventional procedures over medical treatment, it is crucial to treat patients with atherosclerotic renal artery stenosis applying CVD treatment guidelines

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and recommendations strictly. This review focuses only on the optimal medical treatment of renovascular hypertension.

2 Epidemiology

The true epidemiology of atherosclerotic renovascular disease is probably underestimated, as many cases go clinically unnoticed. Data from the literature present a wide variance in prevalence numbers, as studies are based on populations with different characteristics and various diagnostic tools for defining renal artery stenosis. However, a harmful link between the heart and kidneys in atherosclerotic renovascular disease is well established.

The prevalence of atherosclerotic renal artery stenosis (defined as >60 % stenosis in renal duplex sonography) in a population-based study of people aged 65 years or over was 7 % [6]. Mean systolic/diastolic blood pressure levels were higher in patients with renal artery stenosis than in those without renal artery stenosis (142/73 mmHg vs. 134/72 mmHg). Renal artery stenosis was more frequent in patients with a history of clinical or subclinical CVD than in those without such conditions. Age, low serum high-density lipoprotein (HDL) levels and increasing systolic blood pressure did show a significant association with renal artery stenosis. In this study, African Americans had similar prevalence rates to Caucasian patients (6.7 % vs. 6.9 %), while data on Chinese patients did not differ compared with Caucasian populations [7].

The incidence of atherosclerotic renovascular disease in a large study of Medicare patients aged 65 years or more was 3.7 cases per 1,000 patient-years [8]. Increased prevalence rates for atherosclerotic renal artery stenosis were reported in small studies of patients with an acute decrease of glomerular filtration rate during treatment with an angiotensin-converting enzyme inhibitor (ACEI) [9], end-stage renal failure, or congestive heart failure [10]. Atherosclerotic renovascular disease is commonly associated with atherosclerotic lesions in other arterial beds. It is detected in 38 % of patients with abdominal aortic aneurysm, in 39 % with lower extremity occlusive disease, and in 30 % of those with coronary artery disease [8, 11].

In a systematic review of 40 studies [12] that included in total 15,879 patients, the mean prevalence of renal artery stenosis among patients with hypertension who had undergone any form of angiography (computed tomography [CT]-angiography, magnetic or conventional angiography) was 14 %. Prevalence rates for renal artery stenosis were 18 % in patients with hypertension who underwent coronary angiography, 20 % in patients with diabetes mellitus and hypertension, 25 % in patients with peripheral vascular disease, and 33 % in those with abdominal aortic aneurysm. In incidentally discovered renal artery stenosis, 65.5 % and 27.5 % of the patients had hypertension and renal failure, respectively.

Regardless of an atherosclerotic renal artery stenosis lesion being pathophysiologically important for the development of chronic kidney disease (CKD) and hypertension, poorly controlled blood pressure in atherosclerotic renovascular disease contributes to further renal decline and target organ damage. Atherosclerotic renovascular disease has been listed as the primary cause of end-stage renal disease (ESRD) in older patients (>67 years of age) in 5.2 % of cases in the US Renal Data System database and 38.3 % of these cases had prior atherosclerotic renovascular disease [13]. A small Dutch study reported higher numbers: 27 % started dialysis due to renal artery stenosis, while in elderly patients renal artery stenosis was responsible for at least 15 % of ESRD [14, 15]. In the 2009 ERA-EDTA Registry, renovascular disease as a cause of ESRD-adjusted prevalence ranges from 3.2 per million people (pmp) in Denmark to 107 pmp in Belgium. These variant numbers can reflect coding issues (such as overuse of hypertension as a default category when rating the cause of ESRD), different thresholds for the use of diagnostic tests of the renal arteries, or a true change in the biological causes of ESRD [16].

3 Atherosclerotic Renal Artery Stenosis: A Systemic Syndrome

There is a strong association between atherosclerosis and renal artery stenosis. The epidemiological data reveal that atherosclerotic renal artery stenosis coexists with major cardiovascular risk factors. It is not surprising that in all studies age is the strongest predictor of atherosclerotic renal artery stenosis, as in general age-related intensification of atherosclerosis. In an American study with a population over 67 years of age, Kalra et al. showed that the prevalence of atherosclerotic renal artery stenosis was associated with CKD (adjusted odds ratio [OR] 4.61), hypertension (adjusted OR 4.31), peripheral vascular disease (adjusted OR 3.96), aortic aneurysm (adjusted OR 3.38), and atherosclerotic heart disease (adjusted OR 2.45) compared with patients without atherosclerotic renal artery stenosis [17].

In the Cardiovascular Health Study, a multicenter longitudinal study in adults over 65 years of age, the presence of renal artery stenosis demonstrated a significant univariate association with the occurrence of adverse coronary events (hazard ratio [HR] 2.92; 95 % CI 1.53–5.57) that was largely unchanged by adjustments for age, race, and sex [18]. Furthermore, in patients with coronary disease, atherosclerotic renal artery stenosis independently doubles

the risk of mortality even when coronary revascularization is performed [19]. In turn, the frequent presence of other co-morbid cardiovascular diseases is reflected in the high incidence of premature cardiovascular events and death in patients with atherosclerotic renovascular disease. In a population-based study, the risk of a composite outcome of death, myocardial infarction, stroke, or ESRD was analyzed in almost 3,500 patients with established atherosclerotic renal artery stenosis. In patients who did not receive ACEIs, the incidence of the composite outcome was higher compared with patients who took RAAS blockade medication (13 per 100 patient-years vs. 10 per 100 patient-years) [20]. Furthermore, only 5.1 % of atherosclerotic renovascular disease patients have normal cardiac structure and function [18, 21] and they are almost six times more likely to die than to reach dialysis [20].

Consequently, atherosclerotic renal artery stenosis should be considered as a coronary artery disease equivalent. From that point of view, medical treatment should focus on treating an equal cardiovascular risk factor.

4 Management of Renal Artery Stenosis

The treatment of patients with atherosclerotic renal artery stenosis should aim to reduce cardiovascular mortality, prevent cardiovascular events, stop the decline of renal function, and prevent ESRD. Treatment options include invasive procedures (surgical reconstruction and mainly angioplasty) and medication [22].

The current published randomized controlled trials (RCTs) provide little support for the use of percutaneous revascularization to improve mortality and adverse CVD events or ESRD. Table 1 presents RCTs that compared medical treatment to angioplasty [23–27]. In general, none of these studies proved clear benefit of angioplasty, although medical treatment – especially in older trials – was imprecisely described. Moreover, medical treatment was not a strictly planned arm of the studies and the participating physicians applied medication at their discretion. A meta-analysis of the first three trials indicated that the mean improvement in blood pressure was slightly better in patients undergoing angioplasty [28]. However, the first four trials had small patient numbers and were underpowered to address the main endpoints. To overcome these weaknesses, the ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial was designed and finally published in 2009 [27]. It was a multicenter randomized study that could not prove the superiority of angioplasty over standard medical treatment. On the contrary, a significant number of revascularized patients (6.8 %) experienced serious complications. Nevertheless, the medical treatment is described in detail in the study protocol (antihypertensive, antiplatelet, and cholesterol-lowering medications), although there were no strict guidelines to follow.

Pathophysiological studies in animal models with ischemic kidneys support the theory that inflammatory and fibrogenic factors injure the parenchymal kidney tissue beyond vascular occlusion [29–31]. Therefore exclusive invasive restoration of blood flow to the kidneys – specially for asymptomatic atherosclerotic renal artery stenosis – without intensive medical treatment cannot repair the tissue damage. Medical treatment should focus on intensive and meticulous management of atherosclerosis and modifiable risk factors of CVD, such as lifestyle choices (mainly smoking and obesity), hypertension, hyperlipidemia, and hyperglycemia.

5 Medical Treatment of Renal Artery Stenosis

5.1 Control of Hypertension

There is widespread agreement that all patients with atherosclerotic renal artery stenosis require intensive medical treatment and it has unequivocally been shown that these patients require ideal control of hypertension. Most guidelines recommend strict blood pressure goals of less than 130/80 mmHg, as these targets are associated with a lower risk of CVD and progression of renal disease [32]. Use of ACEIs and angiotensin receptor blockers has a central role in medical treatment of atherosclerotic renal artery stenosis, not only by controlling hypertension but also by inhibiting the activation of RAAS. In an earlier mentioned population-based study [20] comprising 3,570 patients with atherosclerotic renal artery stenosis, treatment with ACEIs had a significantly lower risk for the primary outcome during follow-up (10 vs. 13 for CVD events per 100 patient-years at risk, multivariable adjusted hazard ratio [HR] 0.70; 95 % CI 0.59–0.82). In addition, hospitalization for congestive heart failure (HR 0.69; 95 % CI 0.53–0.90), initiation of chronic dialysis (HR 0.62; 95 % CI 0.42–0.92), and mortality (HR 0.56; 95 % CI 0.47–0.68) was lower in treated patients. However, hospitalization for acute renal failure during follow-up was higher (HR 1.87; 95 % CI 1.05–3.33; 1.2 vs. 0.6 events per 100 patient-years at risk) [20]. A more recent study suggests that treatment with RAAS blockade was well tolerated even in patients with severe bilateral atherosclerotic renal artery stenosis and reduced mortality in a large proportion of these patients [33]. The authors recommend that all patients with atherosclerotic renal artery stenosis be considered for RAAS blockade therapy, unless an absolute contraindication exists. In another study with long-term follow-up, a longer survival was associated with the use of ACEIs in both revascularized and medically treated patients [34].

Table 1 Randomized controlled trials comparing medical management to interventional procedures in patients with renovascular hypertension

Trial	Year	Patients (no./mean age [y])	Diabetic (%)	Smokers (%), current and former	Mean creatinine or e-GFR (mg/dL or mL/min)	Medical treatment
Webster et al. [23]	1998	55/61	?	44	1.8	Atenolol, calcium antagonists, diuretics, prazosin, methyldopa, aspirin
Plouin et al. [24]	1998	49/59	20	41	1.17 or 73	Nifedipine, clonidine, prazosin, aspirin 100 mg in angioplasty group
Van Jaarsveld et al. [26]	2000	106/60	5	76	1.2 or 65	Amlodipine, atenolol, ACEIs, diuretics, statin, aspirin 300 mg in angioplasty group
Bax et al. [25]	2009	140/67.5	24	70	1.6 or 45	β-blockers, α-blockers, calcium antagonists, diuretics, aspirin, statins
Wheatley et al. (ASTRAL trial) [27]	2009	806/70	30	74	2.0 or 40	β-blockers, α-blockers, calcium antagonists, ACEIs or ARBs, diuretics, aspirin, statins

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *eGFR* estimated glomerular filtration rate

Proteinuria is not common in atherosclerotic renal artery stenosis (especially when the renal artery stenosis is less than 50 %), but it may be another marker of ischemic damage. Thus nephrotic-range proteinuria has been reported only in ischemic renal artery stenosis when glomerular filtration rate (GFR) is less than 25 % of normal [35]. In CKD patients, aggressive blood pressure targets (<130/80 mmHg) yield benefit in slowing GFR decline only in patients with significant proteinuria, although this is not supported by appropriately powered randomized controlled trials [36].

After initiation of RAAS blockade, a decline in kidney function is often associated with bilateral atherosclerotic renal artery stenosis as well as microvascular renal disease, but this could not be provided as a sensitive or specific finding [37]. It seems to be quite different when there is a reduction of systemic arterial pressure proximal to critical lesions and below the critical perfusion pressures at the levels needed for auto-regulation. This may activate pressor mechanisms to restore perfusion, including activation of the RAAS with sodium retention, adrenergic stimuli, and other mechanisms. Further occlusion triggers a repeating cycle of elevation of systemic blood pressure. This sequence ultimately produces malignant-phase hypertension [38]. Aggressive antihypertensive therapy in these patients may under-perfuse the post-stenotic kidneys and can produce damage and further loss of kidney function [39]. Current recommendations advocate cessation of treatment when serum creatinine rises to 20–30 % above baseline or hyperkalemia develops (serum potassium levels above 5.6 mmol/L), but these data were extrapolated from trials in selected groups and may not apply to the unselected atherosclerotic renal artery stenosis population [40]. It is supported that a serum creatinine increase of more than 30 % should be the cut-off for discontinuation of RAAS blockers [41].

On the other hand, it is fairly well established that revascularization should be considered in some patients, especially in those with unstable angina, unexplained pulmonary edema, and hemodynamically significant renal artery stenosis either with worsening kidney function or with difficulty in controlling hypertension. Patients with atherosclerotic renal artery stenosis often have refractory hypertension and require multiple antihypertensive medications. There is now general agreement that curing hypertension with revascularization is uncommon in patients with atherosclerotic renal artery stenosis, but may result in a lower requirement for antihypertensive medications [42].

5.2 Hyperlipidemia and Statin Use

All patients with CVD or CVD risk equivalents are high-risk patients. CVD risk equivalents include non-coronary forms of clinical atherosclerotic disease (atherosclerotic renal artery stenosis can be included here), metabolic syndrome, diabetes, CKD, and more than two CVD risk factors (cigarette smoking, hypertension, low HDL cholesterol (HDL-C) [<40 mg/dL], family history of premature CVD and age [men >45 years; women >55 years]). A high-risk person has a 10-year risk of CVD of more than 20 %. Trials confirm the benefit of cholesterol-lowering therapy in high-risk patients and support the treatment goal of low-density lipoprotein cholesterol (LDL-C) <100 mg/dL [43]. Moreover, when the risk is very high, an LDL-C goal of <70 mg/dL is suggested as the most favorable therapeutic option [44]. In case a high-risk patient has high triglycerides (TGs) or low HDL-C, consideration can be given to combining a fibric acid derivative (e.g., fenofibrate) or nicotinic acid (niacin) with an LDL-lowering drug. In addition, physicians should rule out medication

that may elevate LDL levels (diuretics, ciclosporin, amiodarone, ω-3 fatty acids, and glitazones) or TG levels (β-blockers, diuretics, interferon, retinoic acid drugs, estrogens, and tamoxifen).

In a meta-analysis regarding the use of HMG-CoA reductase inhibitors (statins) in CKD populations not receiving dialysis (almost 25,000 patients included), statins decreased serum levels of total and LDL-C and all-cause and CVD mortality [45]. Interestingly, the rate of adverse events was similar in patients receiving statins and placebo. These results suggest that the use of statins for the prevention of ischemic events in dyslipidemic individuals with early CKD seems to be a safe, reasonable, and evidence-based approach [46, 47].

Especially for patients with atherosclerotic renal artery stenosis, statins with their pleiotropic effects can remodel pathways responsible for decreased blood flow and histologic damage. Clinical observations suggest that statins ameliorate the tissue injury and substantially reduce the interstitial fibrosis in kidneys removed due to total occlusion [48–50].

5.3 Hyperglycemia

In ADVANCE (Action in diabetes and Vascular disease: Preterax and Diamicron MR) – a randomized trial of blood-pressure lowering and intensive glucose control in 11,140 patients with type 2 diabetes – intensive glucose control (hemoglobin A_{1C} of ≤6.5 %) resulted in 14 % reduction in microvascular events and 21 % reduction in nephropathy. No effects were shown on macrovascular events and all-cause or cardiovascular mortality. Similarly, the ACCORD (Action To Control Cardiovascular Risk In Diabetes) trial demonstrated more or less the same results (a therapeutic strategy that targets an A_{1C} <6 % vs. 7.0–7.9 % increased mortality over 3.5 years) [51]. As a result, the American Diabetes Association (ADA) guidelines [52] suggest that pre-prandial capillary plasma glucose levels should be 70–130 mg/dL. Furthermore, ADA guidelines suggest that a reasonable A_{1C} goal for many non-pregnant adults is <7 %, as lowering A_{1C} to below or around 7 % has been shown to reduce microvascular complications of diabetes. Strict A_{1C} goals (such as <6.5 %) could be achieved for selected individual patients (e.g., those with a short duration of diabetes, long life expectancy, and no significant CVD) if this can be achieved without significant hypoglycemia or other adverse effects of treatment.

In patients with type 2 diabetes and persistent microalbuminuria (Steno-2 trial), intensive intervention with multiple drug combinations and behavioral modification had sustained beneficial effects with respect to death from any cause and from cardiovascular causes [53].

5.4 Lifestyle Changes

Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g, obesity, physical inactivity, elevated TGs, low HDL-C, or metabolic syndrome) is a candidate for modifying these risk factors regardless of LDL-C level [54].

Smoking is not only a well established cardiovascular risk factor, it is also associated with CKD (estimated GFR <45 mL/min). In a large cross-sectional study from Norway the relative risk for CKD was 1.52 for those who had smoked >25 packet-years [55]. Smoking also increases the risk of progression in various nephropathies [56].

5.5 Antiplatelet Therapy

Clinical trials demonstrate that antiplatelet therapy in high-risk patients reduces the combined outcome of non-fatal myocardial infarction, non-fatal stroke, or vascular death ('serious vascular events') by about 25 %. Reduction in the risk of having a serious vascular event was 22 per 1,000 treated for 2 years among high-risk patients, including those with stable angina, peripheral arterial disease, and atrial fibrillation [57]. In each of these high-risk categories, the absolute benefits substantially outweighed the absolute risks of major bleeding complications. The available evidence supports daily doses of aspirin (acetylsalicylic acid) in the range of 75–100 mg for the long-term prevention of serious vascular events in high-risk patients. This favorable effect is more prominent in secondary prevention.

Clopidogrel (75 mg/day) or ticlopidine (250 mg twice daily) is an effective alternative in the approximately 5 % of patients who cannot tolerate aspirin [58]. In the CHARISMA (Clopidogrel For High Atherothrombotic Risk, Ischemic Stabilization, Management, And Avoidance) trial, addition of clopidogrel to standard low-dose aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes in patients with stable cardiovascular disease or multiple cardiovascular risk factors [59]. Warfarin either without (international normalized ratio [INR] 2.5–3.5) or with low-dose aspirin (75–81 mg/day; INR 2.0–2.5) may be reasonable for patients at high CHD risk and low bleeding risk who do not require or are intolerant to clopidogrel [60].

6 Future Directions and Treatments

6.1 Antifibrotic Treatments

Recent experimental evidence suggests that atherosclerotic renal artery stenosis is associated with the activation of

intra-renal fibrogenic and inflammatory pathways, oxidative stress, and microvascular remodelling. Experimental data suggest that blockade of these mechanisms can improve renal hemodynamics and function.

In an experimental chronic renal artery stenosis model in pigs [61], intra-renal infusion of autologous endothelial progenitor cells (EPC) preserved microvascular architecture and function and decreased vascular remodelling, restoring the hemodynamics and function of the ischemic kidney. The capability of EPC to preserve the stenotic kidney may therefore enable development of novel therapeutic reno-protective strategies in chronic renovascular disease.

In the clipped kidney of a two-kidney, one-clip (2K1C) hypertension rat model [62], direct angiotensin II type 2 receptor stimulation reduced early renal inflammatory responses and improved production of nitric oxide and cGMP in renovascular hypertension independent of blood pressure reduction.

6.2 The CORAL Study

The CORAL (Cardiovascular Outcome in Renal Atherosclerotic Lesions) study (NCT00081731) is a prospective, multicenter, randomized trial designed to test the hypothesis that medical therapy with stenting of significant renal artery stenosis ($\geq$60 % and $<$100 %) in patients with resistant systolic hypertension reduces the incidence of adverse cardiovascular and renal events compared with medical therapy alone. In this study, 1,080 patients are randomized to the two arms of the trial and followed for $\leq$5 years. Medical treatment includes optimal treatment of all risk factors according to guidelines. The study has been completed and will soon provide definite answers for our dilemmas about indications for endovascular intervention in patients with renal artery stenosis [63].

7 Conclusion

Renal artery stenosis is an expression of systemic atherosclerosis that involves intrinsic renal damage, concomitant cardiovascular disease, and hypertension, and leads to further renal decline and cardiovascular morbidity. As randomized controlled trials have not proven the superiority of angioplasty, treatment should focus on modification of the concomitant CVD risk factors. Meticulous control of hypertension, dyslipidemia, and hyperglycemia, and cessation of smoking should be the cornerstone of treating patients with renal artery stenosis.

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