

# Renovascular hypertension 1: Epidemiology and clinical presentation

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**Abstract**

Renovascular disease is present in about 10–40% of patients with end-stage renal disease, and constitutes the fastest-growing group of end-stage renal disease patients. The unselective correction of renal artery stenosis has led to disappointing results. Most studies that have compared conservative treatment with angioplasty have found only modest or no beneficial effects of angioplasty on blood pressure and renal function. It is therefore mandatory to evaluate the functional significance of a stenosis before intervention. Patients most likely to respond favourably to revascularisation should be identified. Factors that affect outcome include the severity of renal artery stenosis and, most importantly, underlying renal disease. This underlying disease can prevent a favourable response despite successful correction of renal artery stenosis. The best methods to classify patients as responders or non-responders to intervention are Doppler ultrasonography – which evaluates the renal resistance index - the percentage reduction of the end-diastolic flow as compared with the systolic flow, calculated as  $[(1 - (\text{end diastolic velocity}/\text{maximum systolic velocity})) \times 100] -$  or captopril scintigraphy. In patients with a renal resistance index  $\geq 80\%$ , improvement of renal function or blood pressure is highly unlikely, despite successful correction of renal artery stenosis. Identifying patients at risk for irreversible loss of renal function, and who may benefit from intervention, is a high research priority.

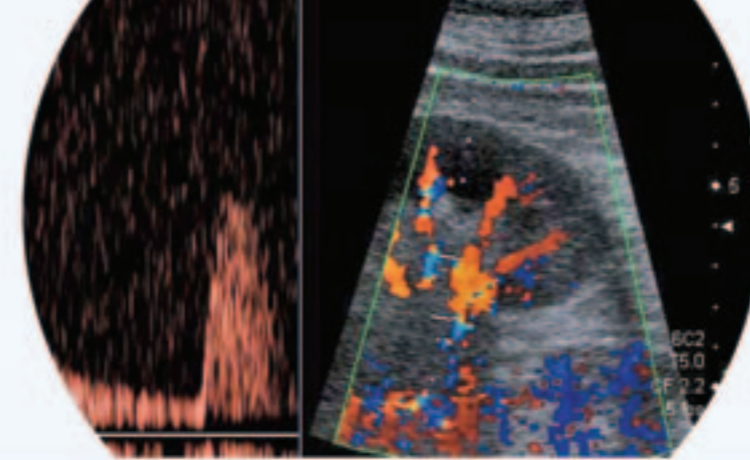
**Introduction**

It is difficult to extract reliable data on the epidemiology and clinical presentation of renovascular hypertension (and renovascular azotaemia). One of the main reasons is the uncritical use of the terms renovascular hypertension and renovascular disease which are frequently considered synonyms. It is important, however, to differentiate between

renovascular disease (i.e. anatomical narrowing or occlusion of one or both renal arteries) and renovascular hypertension or renovascular azotaemia. Not all patients will respond favourably to correction of renal artery stenosis. In unselected populations only 60–80% of patients will show improved blood pressure and only 25–50% will have improved renal function despite successful correction of renal artery stenosis.<sup>1,2</sup> Most studies that have compared conservative treatment with angioplasty in unselected patients have reported only slight or no beneficial effects of angioplasty on renal function and blood pressure.<sup>3,4</sup> It is therefore important to identify those patients who will benefit from revascularisation. Classically, the diagnosis of renovascular hypertension or azotaemia can only be made retrospectively after a successful correction of renal artery stenosis has been performed. The purpose of this review is to identify tools which enable the identification of patients with a higher likelihood of improved blood pressure and/or renal function after angioplasty, or after surgical correction of renal artery stenosis.

**Epidemiology of renovascular hypertension**

End-stage renal disease requiring renal replacement places a major economic burden on the healthcare system. Excluding obesity and alcohol abuse, renovascular disease is the most common correctable cause of secondary hypertension and – next to diabetic nephropathy – the most common cause of renal insufficiency, and can lead to difficult-to-control hypertension.<sup>5</sup> In patients with mild-to-moderate hypertension, the prevalence is less than 1%.<sup>6</sup> In certain patient populations, such as those with acute (even if superimposed on chronic) severe or refractory hypertension, or those undergoing diagnostic coronary arteriography, the prevalence is much higher at 10–40%.<sup>7–9</sup> There are no exact numbers for the prevalence of renovascular hypertension.



**Clinical presentation of renovascular hypertension**

There are no specific clinical signs of renovascular hypertension. Usually, renovascular hypertension is more severe and more difficult to treat than so called 'essential hypertension', although this may have changed with the more widespread use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers. Renovascular hypertension cannot exist without renovascular disease, and the more severe the degree of stenosis the more severe the hypertension (and/or azotaemia) unless there is concomitant heart failure. There are hardly any specific clinical signs for renovascular disease and for renovascular hypertension with the exception of an abdominal bruit which can be heard in about 40% of patients with these diseases.<sup>10</sup> An abdominal bruit which radiates to the flank and is audible in the epigastric area and over the kidney is highly suggestive of renovascular disease. A systolic and diastolic bruit, which may indicate renovascular hypertension, has been associated with a favourable treatment outcome. The other clinical clues for renovascular disease and renovascular hypertension, which are shown in Table 1, are mostly those which decrease the likelihood of essential hypertension or renoparenchymatous hypertension, the two most common forms of hypertension. These clinical clues are by no means specific for renovascular disease or renovascular hypertension, but increase the likelihood of their presence.

Some clinical symptoms occur rarely, but when associated with severe renovascular disease (diameter stenosis >50–60%) should prompt correction of stenosis. These symptoms include flash pulmonary oedema, recent deterioration in renal function or deterioration during treatment with an ACE inhibitor, advanced chronic renal failure, end-stage renal disease, bilateral severe renal artery stenosis or stenosis to a single functioning kidney, and resistant or poorly

controlled hypertension.<sup>1,16</sup> None of the factors mentioned above, however, are specific enough to predict the patients likely to experience a successful interventional outcome, i.e. an improvement in blood pressure or renal function. More reliable predictive tests are needed.

One of the major reasons for treatment failure, despite the successful correction of renal artery stenosis  $\geq 50\%$ , is pre-existent chronic renal failure.<sup>14</sup> The most common diseases responsible for renal failure are hypertensive nephrosclerosis and diabetic nephropathy with glomerulosclerosis. Hypertension and diabetes mellitus are potent inductors of atherosclerosis and can lead to the secondary formation of renal artery stenosis.

**Table 1. Factors associated with an increased likelihood for the presence of renovascular disease and renovascular hypertension**

Renovascular disease	Renovascular hypertension
Age >50 years	Age <65 years
Male sex	Female sex
Diffuse atherosclerosis	No severe atherosclerotic disease
	Proteinuria <1 g/day
Impaired renal function	No severely impaired renal function (no glomerular filtration rate <40 ml/min)
Hypertension despite the use of 3 or more adequate antihypertensive drugs	An unexplained acute elevation in the plasma creatinine concentration or an elevation that occurs shortly after the institution of therapy with an angiotensin converting enzyme (ACE) inhibitor or an angiotensin receptor blocker <sup>11</sup>
Recent onset or worsening of hypertension	Recent onset or worsening of hypertension
Duration of hypertension <10 years	Duration of hypertension <10 years
Diastolic blood pressure >80 mmHg	Diastolic blood pressure >80 mmHg
Systolic blood pressure >160 mmHg	Systolic blood pressure >160 mmHg
Diabetes mellitus	No diabetes mellitus
Smoking	Smoking
	Renal artery stenosis >70%
Systolic abdominal bruit	Systolic and diastolic abdominal bruit
Asymmetric renal size or kidney size <9 cm	Kidney size >9 cm
Caucasians as opposed to black patients	
	Flash pulmonary oedema <sup>12,13</sup>
	Retinal haemorrhages or papilloedema
Negative family history for hypertension (a very weak diagnostic clue)	
No obesity	
Hypercholesteraemia	

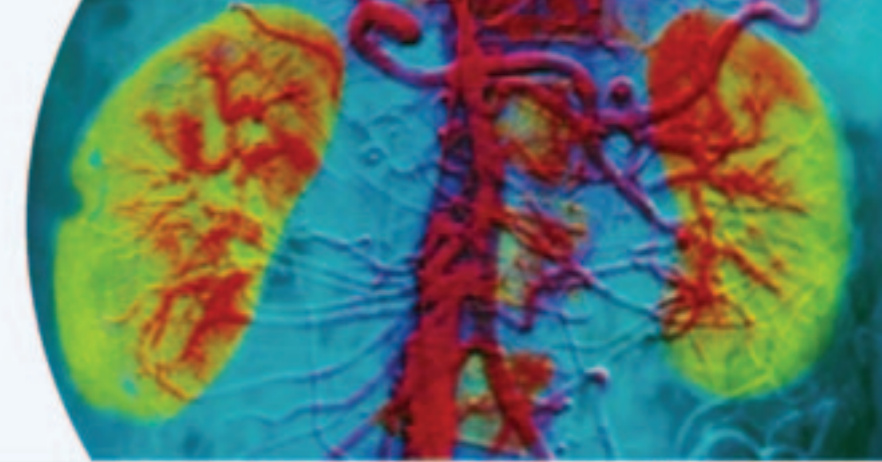
Data from references 4, 14 and 15

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Patients with severe nephrosclerosis or diabetic glomerulosclerosis would therefore be expected to have a more unfavourable outcome after correction of renal artery stenosis. For this reason, the degree of renal artery stenosis cannot be the sole criterion for intervention. Advanced underlying renal disease has to be excluded.<sup>4,14,17</sup>

### Screening tests for renovascular disease

There are numerous screening tests for renovascular disease. Screening tests that have shown acceptable sensitivity and specificity are colour Doppler sonography, captopril scintigraphy, spiral computed tomography (CT) and magnetic resonance angiography (Table 2). A clinical prediction rule for the presence of renal artery stenosis has been established by Krijnen *et al.*<sup>18</sup> and has been independently validated by Marquand *et al.*<sup>19</sup> It showed comparable accuracy to captopril scintigraphy.

However, only a few procedures have been assessed as screening tests for renovascular hypertension or azotaemia. Among these, captopril scintigraphy and Doppler sonography have shown the best results.

### Screening tests for renovascular hypertension

#### Plasma renin activity

Renovascular hypertension is the clinical consequence of activation of the renin-angiotensin-aldosterone system. Renal artery stenosis leads to renal ischaemia, which causes the release of renin from the juxtaglomerular cells of the kidney and a secondary increase in blood pressure. The release of renin activates a cascade system in which renin promotes the conversion of angiotensin I to angiotensin II and increases aldosterone release from the adrenal gland. Increased renin secretion increases angiotensin II and aldosterone release, which causes severe vasoconstriction and sodium and water retention. In unilateral stenosis, the normal contralateral kidney may compensate for the sodium and water retention by increasing filtration, but this compensatory mechanism does not occur in bilateral stenosis.

According to these known pathophysiological causes of renovascular hypertension, measurements of the concentration of renin in the renal vein have been used to predict the potential success of surgical revascularisation. False-negative and false-positive

results are common with this technique, and it is therefore not recommended as a reliable screening test for renal artery stenosis. The accuracy may be enhanced by using an ACE inhibitor (e.g. captopril), which increases renin secretion, blocks the vasoconstrictive effect of angiotensin II on the efferent arteriole of the renal glomerulus, and reduces filtration on the side of the stenosis.<sup>5</sup> The captopril test, which measures plasma renin activity after a dose of 25–50 mg of captopril, is a simple technique but also has low specificity and sensitivity.<sup>20</sup> In addition, antihypertensive drugs that interfere with plasma renin activity limit all tests that rely on the measurement of plasma renin activity.

#### Captopril scintigraphy

Captopril scintigraphy has been shown to be of value in identifying patients whose blood pressure will improve after correcting the stenotic lesion.<sup>14,21</sup> This test, however, has not been shown to predict an improvement in renal function after correction of renal artery stenosis and it cannot locate the site of stenosis or determine its severity.<sup>5</sup> Furthermore, the sensitivity of this test is reduced in patients with renal insufficiency and in patients with bilateral stenoses or a stenosis in a single functioning kidney.<sup>5,22</sup> It is particularly important to identify these patients because the major rationale for performing surgery or angioplasty is to preserve renal function.

#### Duplex Doppler ultrasonography

With duplex Doppler ultrasonography, peak-systolic velocity and renal-aortic or renal-renal-ratio can be measured and used to estimate the severity of a focal arterial stenosis.<sup>23,24</sup> Only stenoses with a >50% diameter reduction are haemodynamically relevant. Additionally, we have shown that Doppler sonography may predict the outcome after successful correction of renal artery stenosis (i.e. predict renovascular hypertension).<sup>14</sup> For this purpose, we determined the renal resistance index in 2–3 segmental arteries of both kidneys.

The resistance index is calculated as the percentage reduction of the end-diastolic flow as compared with the systolic flow  $[(1 - (\text{Minimum diastolic velocity} / \text{Maximum systolic velocity})) \times 100]$ . Figure 1 shows two typical examples for a normal and high renal resistance index.

We have shown that, in patients with renal artery stenosis, an increase in renal resistance index to  $\geq 80\%$  in either kidney was associated with poor outcome after revascularisation and identified patients at risk of progressive renal disease.<sup>4</sup> After intervention, mean arterial blood pressure was not reduced by at least 10% in 97% of patients whose renal resistance index was  $\geq 80\%$  (Figure 2).

**Table 2. Sensitivity and specificity of screening methods for renal artery stenosis**

Screening method	Sensitivity/ Specificity (%)	Disadvantage
Duplex ultrasonography	92/95	Investigator dependent Technical failure due to - Obesity - Excessive bowel gas - Poor blood flow in main renal artery
Captopril scintigraphy	86/93	Less accurate in patients with - Renal impairment - Unilateral or bilateral renal artery stenosis
MR-angiography	96/74	High cost Claustrophobia in 10% of patients
Spiral computed tomography	98/94	High cost Radiocontrast toxicity

MR: magnetic resonance

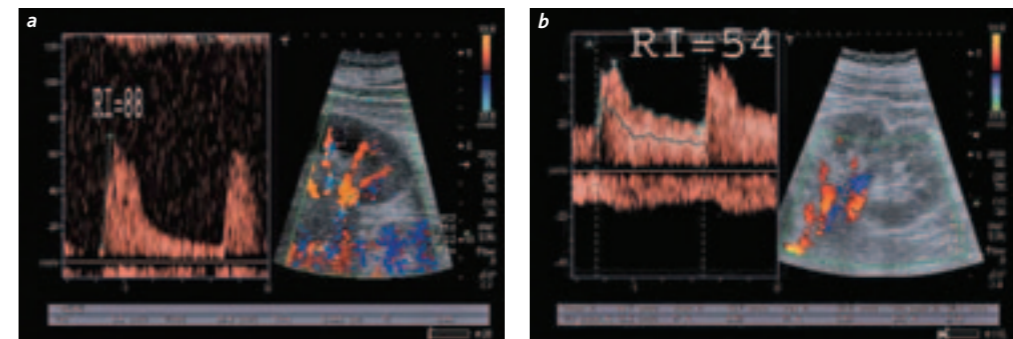


Figure 1. Resistance index values derived from renal segmental arteries. (a) High resistance index, (b) normal resistance index.

# Renovascular hypertension: Epidemiology and clinical presentation *continued*

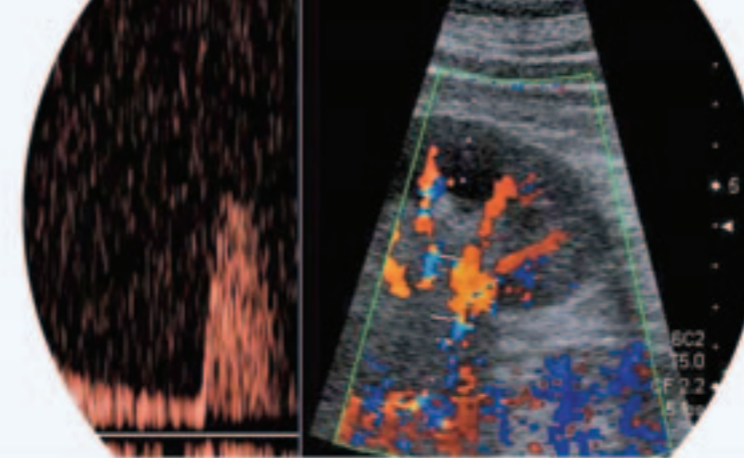
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Renal function deteriorated in 80% of these patients, of which 46% required dialysis and 29% died during follow-up. In contrast, in patients with a low renal resistance index (<80%), correction of renal artery stenosis with revascularisation reduced the mean arterial blood pressure by at least 10% in 94% of patients, of which 3% required dialysis and 3% died. After both uni- and multivariate analysis, only a renal resistance index  $\geq 80\%$ , proteinuria >1 g/day and a creatinine clearance value below 40 ml/min reliably predicted progression of renal disease in patients with renal artery stenosis, and identified those whose blood

pressure or renal function was unlikely to improve with intervention (Table 3).<sup>4,25,26</sup> This study has at present, however, not been validated by other groups.

### Conclusions

There is at present no sufficiently tested, accurate, non-invasive screening test that absolutely proves the presence of renovascular hypertension (i.e. correctable hypertension). Until such tests – if ever – exist, Doppler sonography, using the renal resistance index, and captopril scintigraphy are the most suitable screening tests for renovascular hypertension and azotaemia.



### Key Learning

- Renovascular disease is a common, correctable cause of secondary hypertension, and constitutes the fastest-growing group of end-stage renal disease patients
- Not all patients respond favourably to correction of renal artery stenosis; severity of stenosis and underlying renal disease influence outcome
- Patients most likely to respond to intervention must be identified
- Clinical signs (e.g. abdominal bruit) suggestive of renovascular disease or renovascular hypertension lack sensitivity and specificity in predicting response to intervention
- Doppler ultrasonography (evaluating renal resistance index) or captopril scintigraphy are currently the best methods to screen for renovascular hypertension and predict response to intervention; high renal resistance index ( $\geq 80\%$ ) is associated with a poor outcome despite successful correction of stenosis
- The development of accurate non-invasive tests to identify at-risk patients likely to benefit from intervention is a research priority

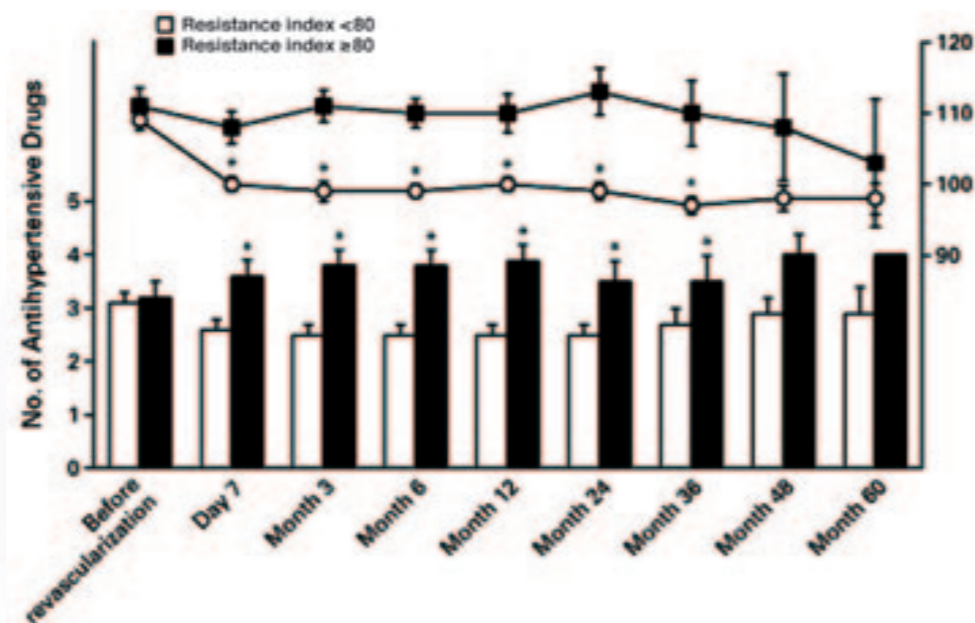


Figure 2. Mean ( $\pm$ SE) change in mean arterial pressure and the number of antihypertensive drugs taken after the correction of renal-artery stenosis, according to the resistance-index values before revascularisation. \* =  $p < 0.05$  for comparison between resistance index <80 and  $\geq 80$ .

Table 3. Risk factors and odds ratios for worsening renal function or death

	Odds ratio for worsening renal failure or death*	
	Univariate	Multivariate**
Resistance index $\geq 80$	110 (23–519)	211 (10–4269)
Proteinuria >1 g/day	77 (23–259)	46 (4–481)
Creatinine clearance <40 ml/min	121 (35–423)	4.3 (0.7–24)

Decreasing renal function means decrease in creatinine clearance of at least 50% or dependence on dialysis. \*Odds ratio (with 95% confidence intervals in parenthesis). \*\*Stepwise logistic regression analysis was used. Only findings that remained independent predictors after stepwise forward logistic regression analysis are listed. Data from Radermacher et al.<sup>17</sup>

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