Renal artery stenosis

Aspects of diagnosis and endovascular treatment

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Cover illustration: *Renal artery stenosis before and after revascularization with stent*

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To my late father Bo F Zachrisson,

a pioneer of renal artery angioplasty.

You would probably have enjoyed reading this.

ABSTRACT

Background: Renal artery stenosis (RAS) becomes haemodynamically significant when it reduces the arterial pressure below the threshold for autoregulation of renal perfusion. Physiological responses to reduced renal perfusion include activation of hormonal cascades, causing hypertension, and reduction of glomerular plasma filtration, causing renal insufficiency. The optimal diagnostic work-up and treatment for symptomatic RAS remains to be determined.

Methods. Patients with hypertension and suspicion of RAS were examined with renal artery duplex ultrasound, using the indirect method of recording flow velocities in the inter-lobar arteries (paper I, n = 169), and the direct method of recording flow velocities in the main renal artery (paper II, n = 58). Duplex ultrasound criteria for haemodynamically significant RAS were analyzed with invasive trans-stenotic pressure gradient measurement as reference. Clinical outcomes after percutaneous transarterial renal angioplasty (PTRA) were retrospectively studied in two populations. The long-term outcome (more than one decade) was evaluated in patients with or without angiographic restenosis at one year (paper III, n = 57), and medium-term outcome (mean 4.3 years) was studied in consecutive patients treated with contemporary indications for endovascular treatment (paper IV, n = 224).

Results. The new index for indirect renal duplex ultrasound, maximal acceleration index (AI_{max}), did not outperform the established early systolic pulse acceleration (ACC_{max}) in detecting haemodynamically significant RAS (paper I). For direct renal duplex ultrasound, a renal-aortic ratio (RAR) of ≥ 2.6 as a sole criterion for significant RAS had advantages compared to the established combined criteria of peak systolic velocity (PSV) ≥ 180 cm/s and RAR ≥ 3.5 (paper II). The long-term prognosis after PTRA was dismal, with high mortality and morbidity and reduced renal function, despite maintained hypertension control. Restenosis did not affect late outcome (paper III). The number of PTRA procedures decreased over time. Patients treated in 2010–

2013 had a significant and persistent reduction in systolic and diastolic blood pressures and in anti-hypertensive medication compared to before the intervention (p-values < 0.01). In contrast, renal function increased only transiently following PTRA, without sustained improvement later during follow-up (paper IV).

Conclusions. Ultrasound duplex criteria for haemodynamically significant RAS affects the diagnostic accuracy. With contemporary indications and techniques, PTRA appears to have a beneficial effect on blood pressure control.

Keywords: hypertension, renal artery stenosis, duplex ultrasound, trans-stenotic pressure measurement, percutaneous transarterial renal angioplasty

LIST OF PAPERS

This thesis is based on the following studies, which are referred to in the text by their Roman numerals.

I. Saeed A, Bergström G, Zachrisson K, Guron G, Nowakowska-Fortuna E, Fredriksen E, Lönn L, Jensen G, Herlitz H
Accuracy of colour duplex sonography in the diagnosis of renal artery stenosis
Journal of Hypertension 2009;27:1690-1696

II. Zachrisson K, Herlitz H, Lönn L, Falkenberg M, Eklöf H
Duplex ultrasound for identifying renal artery stenosis: direct criteria re-evaluated
Acta Radiologica 2017;58:176-182

III. Zachrisson K, Elverfors S, Jensen G, Hellström M, Svensson M, Herlitz H, Falkenberg M
Long-term outcome of stenting for atherosclerotic renal artery stenosis and the effect of angiographic restenosis
Accepted for publication in Acta Radiologica 2018

IV. Zachrisson K, Krupic F, Svensson M, Wigelius A, Jonsson A, Dimopoulou A, Stenborg A, Jensen G, Herlitz H, Gottsäter A, Falkenberg M
Medium-term results of renal artery revascularization in the post-ASTRAL era
Manuscript

CONTENT

ABBREVIATIONS

ACC_{max}	Early systolic pulse acceleration
ACE	Angiotensin-converting enzyme
AI_{max}	Maximal acceleration index
ARB	Angiotensin II receptor blocker
ARVD	Atherosclerotic renovascular disease
AT	Acceleration time
AUC	Area under the curve
BMT	Best medical therapy
BP	Blood pressure
CI	Confidence interval
CKD	Chronic kidney disease
CTA	Computed tomography angiography
DBP	Diastolic blood pressure
DSA	Digital subtraction angiography
EDV	End-diastolic velocity
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
ESV	Early systolic velocity
ESVS	European Society for Vascular Surgery

FMD	Fibromuscular dysplasia
IHD	Ischaemic heart disease
MAPG	Mean arterial pressure gradient
MDRD	Modification of the diet in the renal disease study
MRA	Magnetic resonance angiography
PGM	Pressure gradient measurement
PI	Pulsatility index
PSV	Peak systolic velocity
PTRA	Percutaneous transarterial renal angioplasty
RAAS	Renin-angiotensin-aldosterone system
RAR	Renal-aortic ratio
RAS	Renal artery stenosis
RCT	Randomized controlled trial
RI	Resistive index
RIS	Radiology Information System
ROC	Receiver-operating characteristic
RRT	Renal replacement therapy
SBP	Systolic blood pressure
SD	Standard deviation
SPG	Systolic pressure gradient
TI	Treatment index

INTRODUCTION

Renal artery stenosis (RAS) is associated with hypertension, renal failure, cardiovascular events, and increased mortality. Management of RAS has evolved over the last decades, with less invasive revascularization techniques and improved pharmacological therapy.

For many years, percutaneous transluminal renal angioplasty (PTRA) was the established, first-line treatment for RAS, often on wide indications. However, recent randomized controlled trials (RCTs) have failed to prove the benefits of PTRA compared to best medical treatment (BMT) alone (1, 2). This led to a shift in treatment strategy, and the practice of routinely revascularizing RAS is no longer appropriate. However, the large randomized trials had several flaws, and guidelines still recommend PTRA for certain indications. In addition, a few patients improve remarkably after PTRA, with imminent threat of dialysis transformed into almost normal renal function. But perhaps the most consistent, and durable, effect of RAS revascularization is to ameliorate treatment of severe secondary renovascular hypertension in patients who do not respond sufficiently to pharmacological therapy. The challenge for clinicians and interventionists is to differentiate those patients who will benefit from PTRA from those who will do just as well on medical treatment alone.

The purpose of this thesis has been to evaluate and improve diagnosis of haemodynamically significant RAS with duplex ultrasound, to investigate long-term outcomes after PTRA with and without restenosis, and to determine medium-term outcomes in patients treated with contemporary, more conservative indications.

Hypertension

Hypertension is a condition in which the blood pressure (BP) in the arteries is persistently elevated, defined as a systolic blood pressure (SBP) of 140 mmHg or more, or a diastolic blood pressure (DBP) of 90 mmHg or more (3, 4). It is a common condition with a prevalence of around 30-45% in the general population, and an increase in prevalence with age (5, 6).

Untreated hypertension may lead to serious complications such as stroke, ischaemic heart disease (IHD), heart failure, and kidney damage (5, 7). Stroke-related mortality is strongly associated with hypertension, and death from other cardiovascular causes is moderately associated with it (7). The risk is lowest at a BP of around 115/75, although above this level it is continuously increasing (7). In middle-aged men and women, an increase in SBP of 20 mmHg is associated with a more than twofold increase in the death rate from stroke, and with a twofold increase in death rate from IHD or other vascular causes (7). Lowering of the BP can reduce the risk.

In adults, 90–95% of cases are primary or essential hypertension, meaning that it arises from environmental or genetic causes (8). Secondary hypertension is caused by some other medical condition, and it accounts for 5–10% of cases (9).

With secondary hypertension, when its underlying cause is known, proper treatment can lead to control of the condition, and perhaps even cure. However, as primary hypertension is as common in patients with secondary hypertension as it is in the general population (9), it may also maintain a residual hypertension, after treatment of the underlying cause of the secondary hypertension.

Secondary hypertension

Secondary hypertension is most commonly caused by sleep apnea, renal parenchymal disease, renal artery stenosis, or primary aldosteronism (9-13). Uncommon causes of secondary hypertension are hyperparathyroidism, Cushing's syndrome, pheochromocytoma,

aortic coarctation, and intracranial tumour. Clinical characteristics giving suspicion of secondary hypertension, which should lead to further investigations, are shown below.

- Early onset of hypertension (< 30 years) in patients with no other risk factors, increased blood pressure in prepubertal children
- Therapy resistant hypertension (> 140/90 mmHg despite three anti-hypertensive drugs, including a diuretic)
- Severe hypertension (> 180/110 mmHg) or hypertensive emergencies
- Rapid and lasting worsening of previously controlled hypertension
- Non-dipping or reverse dipping during 24 h of ambulatory blood pressure monitoring
- Presence of target organ damage (e.g. left ventricular hypertrophy or hypertensive retinopathy).

Resistant hypertension

Secondary hypertension is frequently found in patients with resistant hypertension. Resistant hypertension is defined as a BP that remains above 140/90 mmHg despite three anti-hypertensive drugs, including a diuretic, at the optimal dosages. By definition, it thus also includes patients who require four or more medications to control their BP. The prevalence of resistant hypertension in these patients is unknown, as is the prevalence of secondary hypertension (13).

Renal artery stenosis

The prevalence of RAS is 1–8% in patients with known hypertension and 2.5–20% in patients with resistant hypertension (9, 14). In western populations, atherosclerosis is the cause in 90% of patients with RAS and fibromuscular dysplasia (FMD) causes less than 10% of cases. Atherosclerotic renal artery stenosis usually involves the ostium and the proximal third of the main renal artery, and often the perirenal aorta. FMD is most commonly found in girls and women between 15

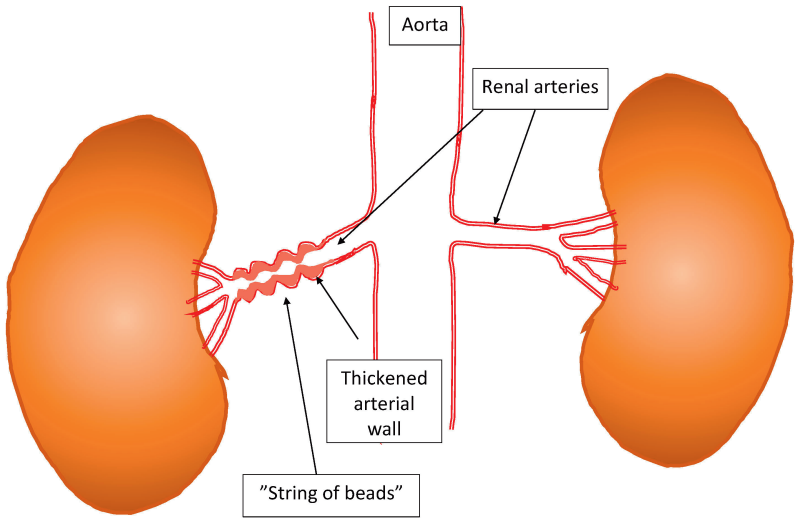
and 50 years of age, and it usually involves the distal two-thirds of the renal artery and its branches. On angiography, it is characterized by a beaded appearance (15) (Figure 1).
Symptoms that should raise suspicion of RAS rather than other causes of secondary hypertension (in addition to the ones previously described) are:

- Age over 55 years and onset of severe hypertension (> 180 mmHg) when associated with chronic kidney disease
- Resistant hypertension (other secondary forms excluded)
- Onset or worsening of hypertension combined with impaired renal function or heart failure
- Renal function impairment during treatment with renin-angiotensin-aldosterone system (RAAS) blockers
- Recurrent episodes of flash pulmonary oedema or heart failure
- Hypertensive crisis such as acute renal failure, acute heart failure, hypertensive encephalopathy, or grade 3–4 retinopathy.

Flash pulmonary oedema is a condition with sudden onset of left ventricular failure in patients with no previous cardiac history and well-preserved cardiac function. It is caused by fluid retention and can sometimes be the first presenting symptom in patients with RAS, and it is more common in patients with bilateral RAS.

Figure 1. ***A.*** *Schematic drawing illustrating vessel wall changes typical of fibromuscular dysplasia (FMD).* ***B.*** *Schematic drawing illustrating vessel wall changes typical of atherosclerotic renal artery stenosis (RAS).* ***C.*** *Digital subtraction angiography (DSA) image of a renal artery with FMD, showing a typical "string of beads".* ***D.*** *DSA image of an atherosclerotic RAS, typically located at the origin of the renal artery.*

A



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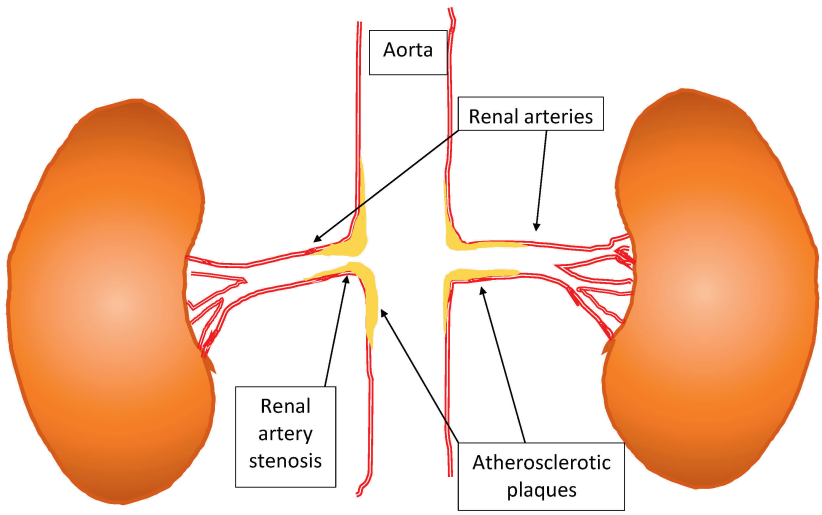

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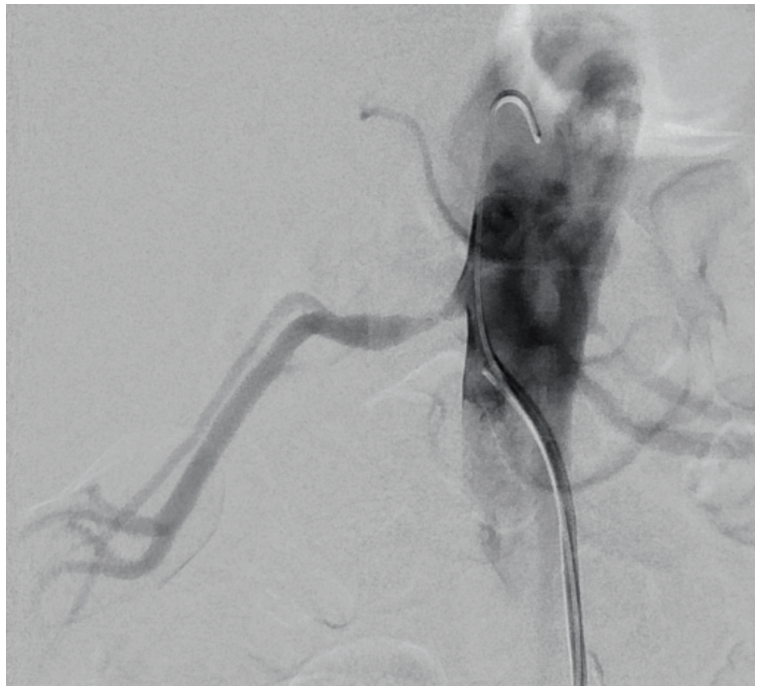


Haemodynamically significant RAS lesion

There is no perfect clinical method to diagnose RAS. Evaluation of magnetic resonance angiography (MRA), computed tomography angiography (CTA), and duplex ultrasound can be difficult depending on, for example, vessel anatomy, the extent of atherosclerotic disease, patient body constitution, and the experience of the investigator. In a clinical setting, it is essential to find out whether or not the stenosis is "functionally significant", i.e. is tight enough to reduce the arterial pressure below the threshold for autoregulation of renal perfusion (16).

The autoregulation in the kidney maintains sufficient parenchymal perfusion and normal glomerular filtration rate (GFR) as long as the renal artery pressure is within 180–80 mmHg. A decline in perfusion pressure below 80 mmHg reduces renal function, i.e. the capacity to eliminate waste products and excess fluid from the body.

With this knowledge, trans-stenotic pressure measurement to determine the gradient between the aorta and the distal renal artery has become the most reliable method for evaluation of RAS. However, the optimal cut-off level of the trans-stenotic pressure gradient to predict whether or not a stenosis is clinically significant has not yet been universally agreed upon.

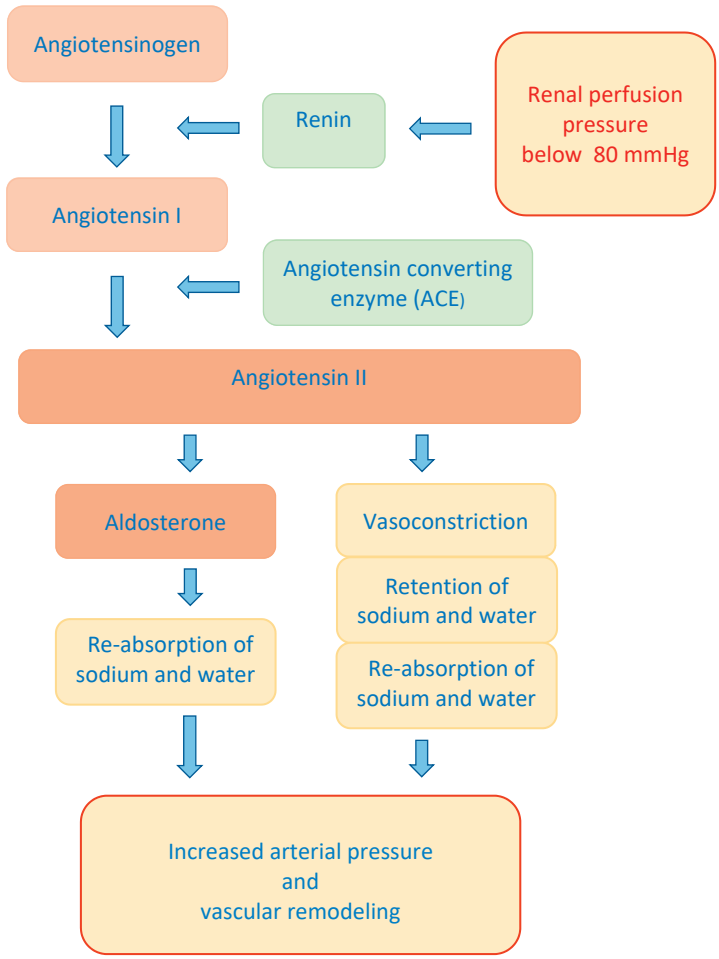
The pressure gradient for defining functionally significant RAS has varied between studies. Some studies have relied on a systolic pressure gradient greater than 15 mmHg, associated with a more than 50% lumen reduction (17), and others have used a systolic pressure gradient (SPG) of 20 mmHg as the cut-off (18). The latter matches a SPG of 10–20% and a mean arterial pressure gradient (MAPG) of at least 10–20 mmHg, which is associated with a reduction in lumen exceeding 60%. Other authors have defined significant RAS as a distal renal to aortic pressure ratio of < 0.9 (19-21), corresponding to a more than 65% reduction in the cross-sectional area of the vessel lumen (20).

The renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) is important in the function of preserving haemodynamic stability in response to loss of

blood, salt, and water. It consists of a renin-triggered cascade of hormones with systemic effects, activated by a decline in kidney perfusion pressure below 80 mmHg (16). This is shown schematically in Figure 2.

Figure 2. The renin-angiotensin-aldosterone system (RAAS).



In the kidneys, triggering of the RAAS leads to changes in systemic blood pressure and in intravascular volume regulation. Angiotensin II raises blood pressure by direct vasoconstrictor effects on systemic vessels, and also—in order to maintain GFR despite renal underperfusion—by its influence on renal haemodynamics, reducing the medullary blood flow and thereby reducing salt and water excretion (22). This in turn contributes to a rise in systemic blood pressure to promote the excretion of sodium and fluid, but it is counteracted by the direct effects of angiotensin II on renal tubules, increasing the re-absorption of the same components (22). In combination, this causes excessive circulating blood volume and hypertension. Aldosterone stimulates the sodium re-absorption and the potassium secretion in the kidneys, leading to volume-induced elevation in BP (23). In pathological situations, it may also injure the kidney by profibrotic effects (24).

The RAAS initially protects renal function. Overactivation of the system is, however, malicious as it may lead to progressive and irreversible injury of the affected kidney—chronic kidney disease (CKD). The parenchymal changes emerge from renal ischaemia, because of low renal blood flow with renal hypoxia, and from the direct renal effects of angiotensin II and aldosterone, causing glomerulosclerosis and tubulo-interstitial fibrosis (25). In the setting of unilateral RAS, the non-stenotic kidney may also suffer long-term damage from severe hypertensive injury and also direct effects of angiotesin II and aldosterone (22, 25, 26).

Excessive activation of the RAAS has a damaging effect also on other cardiovascular end-organs.

Chronic activation of the adrenergic nervous system affects the heart and may lead to myocardial cell dysfunction and cell death, hypertrophy, fibrosis, tachycardia, and arrhythmias. An overactive RAAS also affects the coronary circulation, with extensive effects on the coronary arteries (vasoconstrictive, hypertrophic, atherosclerotic, inflammatory, and pro-thrombotic) (25). The risk of adverse outcomes due to RAS depends on the degree of stenosis, on the rate of progression, and on associated co-morbidities. In patients with cardiovascular disease, the co-existence of atherosclerotic RAS is

associated with a significantly increased risk of cardiovascular mortality: 30% in 4 years (27).

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) inhibit activation of the RAAS system and are clinically important anti-hypertensive medications, often complemented with an aldosterone receptor antagonist for additional cardiorenal protection.

Atherosclerotic renovascular disease

Atherosclerotic renovascular disease (ARVD) includes not only RAS but also renal artery occlusion—as well as more peripheral changes in the renal parenchymal vasculature. This may explain the lack of a relationship between the severity of a RAS and the degree of renal function in some studies (28-30). Theories of increasingly severe RAS being solely responsible for renal dysfunction seen in patients with ARVD are contradicted by the fact that the majority of patients with severe RAS show no improvement in renal function after revascularization. Some patients even show a progressive decline in renal function despite restoration of renal artery patency (31).

The prevalence of ARVD increases with age and is highly associated with other atherosclerotic manifestations such as coronary artery disease, peripheral vascular disease, and stroke. It is also associated with diabetes and hypertension (32-36). There is a high prevalence of ARVD in patients with congestive heart failure (37).

In co-existing hypertension and ARVD, it is tempting to diagnose it as renovascular hypertension, caused by the RAS. However, to know for sure that RAS is the actual cause, and not merely the effect, of increased blood pressure, demonstration of cure or improvement after a revascularization procedure is necessary.

The strategy of diagnostic imaging

When screening for significant RAS, renal artery duplex ultrasound is the first-line imaging modality (38). Magnetic resonance angiography (MRA) and computed tomography angiography (CTA) are commonly used as complementary imaging when examination with duplex ultrasound raises suspicion of haemodynamically significant RAS.

Duplex ultrasound

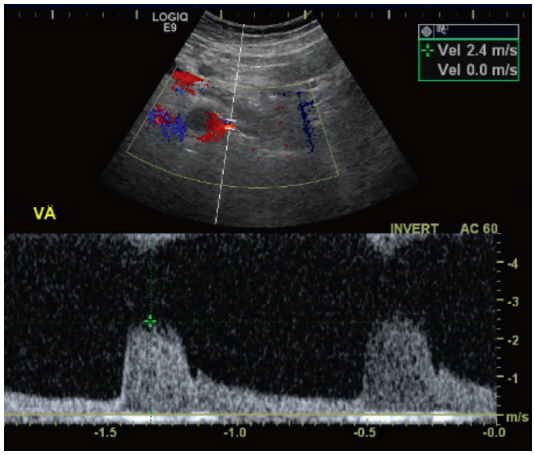
Duplex ultrasound is a cheap and safe method, and is therefore well suited as a screening method—and for following the results of invasive treatments. It is performed either with a trans-abdominal or a trans-lumbar approach, also called the *direct* or the *indirect* method.

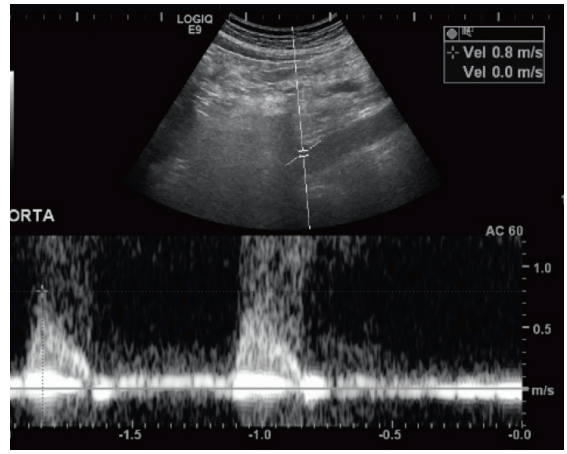
Direct renal artery duplex ultrasound

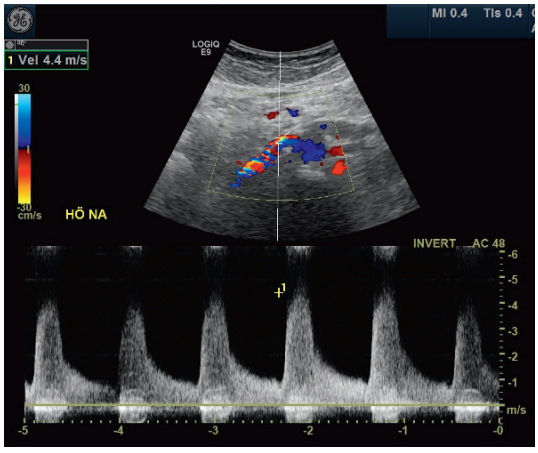
With the direct method, the aorta and renal arteries are visualized. Flow velocities are measured in the aorta at the level of the renal arteries, as well as in the main renal artery close to the ostium and in its middle and distal segment. Established cut-off values for predicting RAS with a greater than 60% lumen reduction on angiography are a peak systolic velocity (PSV) of > 180 cm/sec combined with a renal-aortic ratio (RAR) of > 3.5 (39, 40) (Figure 3). This criterion has been re-evaluated in many studies, reflecting what authors consider to be most important in the balance between sensitivity and specificity (41-44). The direct method can sometimes be difficult to perform, due to the body constitution of the patient, the presence of bowel gas, and the experience of the investigator.

*Figure 3. Direct renal artery duplex with images and velocity pattern of the left renal artery (panel **A**) and the aorta (**B**) from the same patient, with a peak systolic velocity (PSV) of 2.4 m/s in the renal artery and of 0.8 m/s in aorta, with a renal-aortic ratio (RAR) of 3.0. The third image (**C**) shows the colour-Doppler flow spectra and velocity pattern of a more prominent haemodynamically significant stenosis in the right renal artery of another patient with a PSV of 4.4 m/s.*

A ***B***







C

Indirect renal artery duplex ultrasound

With the indirect method, the investigator identifies the arterial blood flow in the arcuate and inter-lobar arteries in the kidneys. The changes in blood flow velocity are registered in the upper pole, the central part, and in the lower pole of each kidney. The evaluation is based on the pattern of the flow velocity cycle, noting the presence or absence of certain elements within the waveform, and on calculated velocimetric indices, as shown in Figure 4.

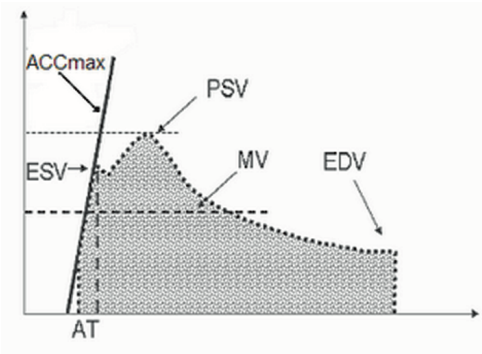


Figure 4. Intrarenal velocimetric measurement and indices. AT, acceleration time; ESV, early systolic velocity; EDV, end-diastolic velocity; MV, mean velocity; PSV, peak systolic velocity; ACC_{max}, early systolic pulse acceleration=$\Delta V_{max}/AT_{max}$.

Not shown: AI_{max}, maximal acceleration index=ACC_{max}/PSV; RI, resistive index=(PSV- EDV)/PSV; PI, pulsatility index=(PSV-EDV)/MV.

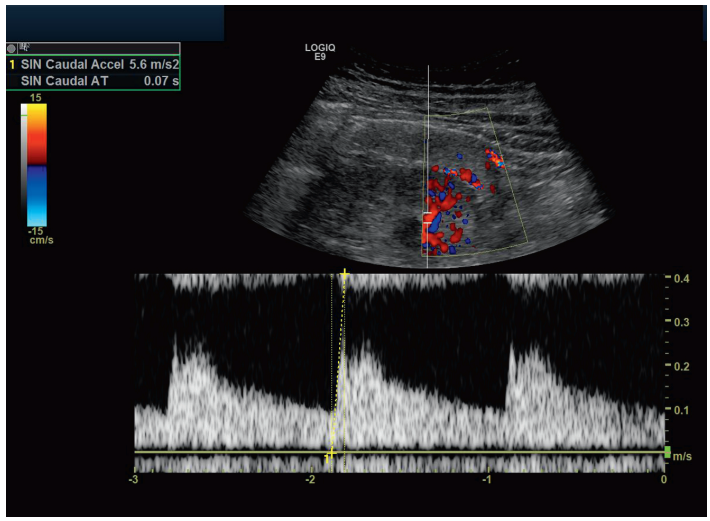
Authors have proposed various quantitative criteria for haemodynamically significant RAS, such as loss of early systolic peak, early systolic pulse acceleration (ACC_{max}) less than 3 m/s^2, acceleration time (AT) > 0.07 s, a difference between the kidneys in resistive index (ΔRI) of > 5%, or a difference in pulsatility index (ΔPI) of > 0.12 (45-48). Flow distal to a haemodynamically significant stenosis becomes damped with a slow rise to the peak systolic flow, a flattened curve with rounded shapes, also called a "tardus-parvus" curve (tardus meaning "late" in Latin and "parvus" meaning "small"): prolonged systolic acceleration; small systolic amplitude and rounding of systolic peak (Figure 5).

In contrast to the direct abdominal approach, the kidneys, if not atrophic or absent, are almost always successfully visualized and the method is less time consuming. Extreme obesity may, however, prevent accessibility with the indirect method also. A limitation is the inability to differentiate between a high-grade stenosis and a total

occlusion of the renal artery. The possibility of performing the investigation with both the direct and the indirect methods, if necessary, would be the optimal approach (48-50).

Figure 5. Indirect duplex ultrasound. ***A.*** *Normal flow velocity.* ***B.*** *Typical flow velocity distal to a haemodynamically significant stenosis: a flattened curve with rounded systolic shapes, also called the "tardus- parvus" curve.*

A



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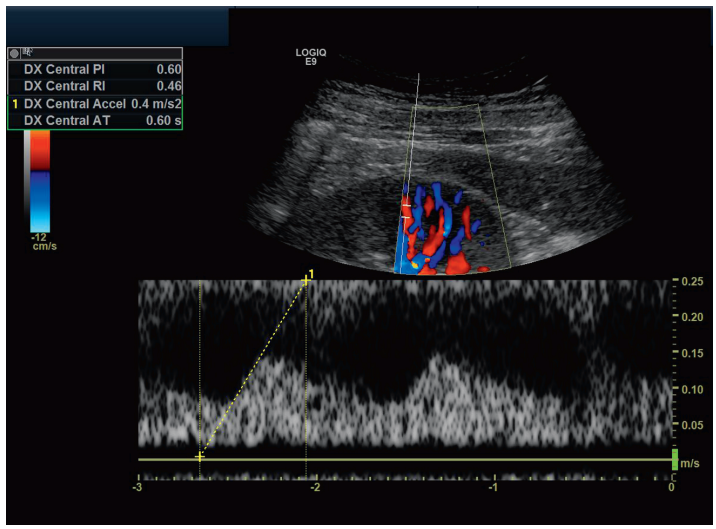


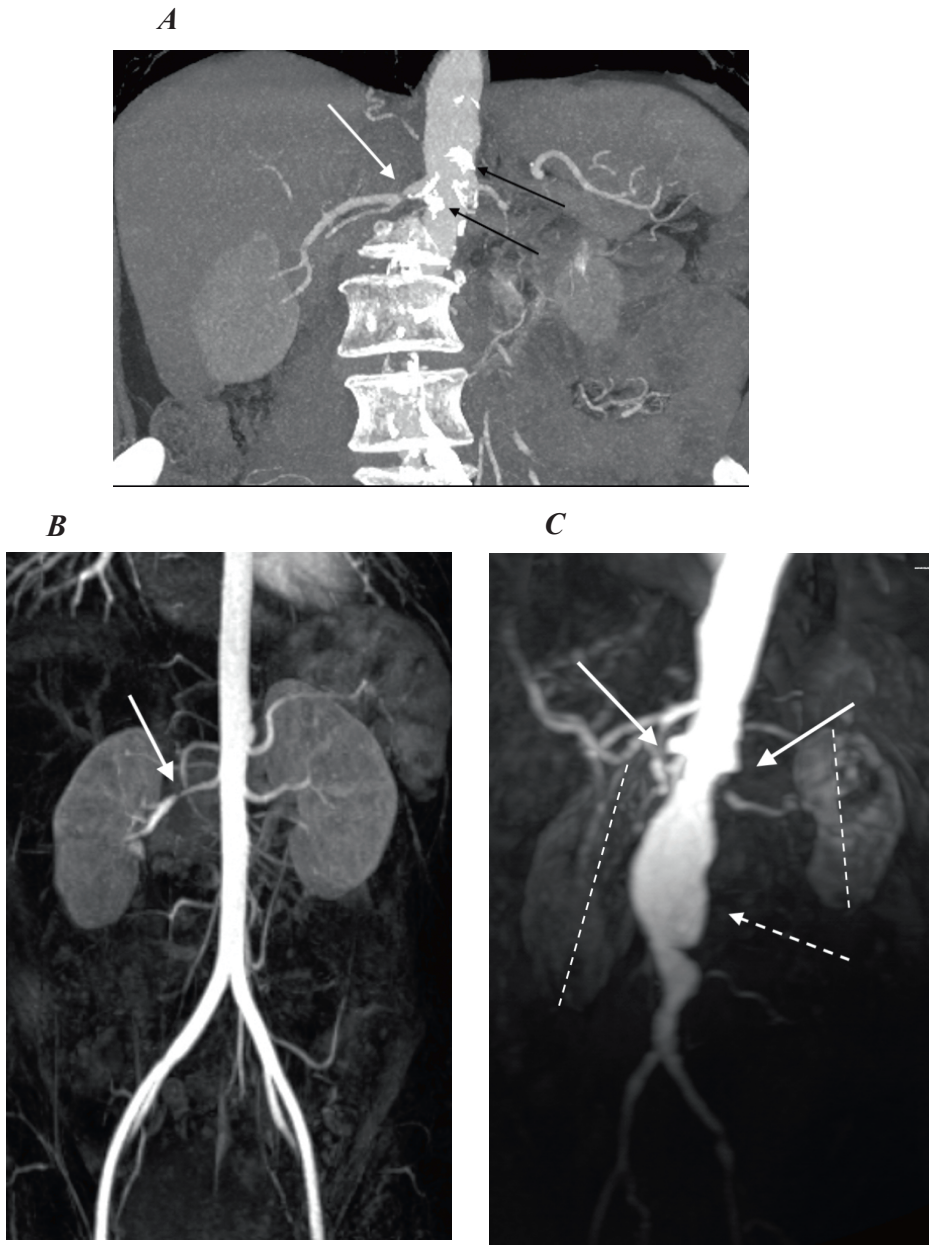
Magnetic resonance angiography and computed tomography angiography

With MRA or CTA, the presence of RAS is confirmed and anatomical information is added. This includes the size and location of RAS, presence of accessory renal arteries, size of the kidneys, and symmetry of the parenchymal contrast medium enhancement. It is of particular importance to also anatomically evaluate the aorta and the iliac arteries if treatment with revascularization is considered. The presence of extensive atherosclerotic disease is a relative contraindication.

The accuracies of MRA and CTA in diagnosing RAS are comparable, with a median sensitivity/specificity of 92–96% (51).

MRA is usually the method of choice, as it, in contrast to CTA, carries no risks of ionizing radiation or nephrotoxicity from iodinated contrast agents. However, one has to bear in mind the risk of nephrogenic systemic fibrosis when gadolinium contrast medium is given to patients with severe renal impairment. Another limitation of MRA is the frequent overestimation of the degree of stenosis. On the other hand, with CTA there can be a problem with severe renal artery calcification, when it obscures the luminal narrowing (Figure 6).

Figure 6. ***A.*** *Computed tomography angiography (CTA) image with a stenosis (white arrow) in the right renal artery; note the vessel wall calcifications (black arrows).* ***B.*** *Magnetic resonance angiography (MRA) of aorta, abdominal arteries, and the iliac arteries. Stenosis and suspected fibromuscular dysplasia (FMD) in the middle of the right renal artery (white arrow) of a young patient (left panel) and bilateral atherosclerotic stenoses in an older patient with a small infrarenal aortic aneurysm(dashed arrow)(right panel). Note the asymmetric kidneys (thin dashed lines) on the right panel, the left kidney being small and atrophic.*



Digital subtraction angiography and trans-stenotic pressure measurements

Finally, to confirm the diagnosis of RAS, often in conjunction with a planned revascularization, the diagnostic evaluation may be completed with digital subtraction angiography (DSA). This is an invasive method where the renal artery becomes visible by injecting contrast through a catheter placed in the aorta at the level of the renal arteries, or in the renal artery. The catheter is inserted percutaneously, usually by puncture of the femoral artery in the groin.

Images acquired with DSA for visualization of the main renal artery and its branches have high spatial and temporal resolution. However, the major advantage of this method is the possibility of directly measuring the pressure gradient caused by the RAS. To obtain the trans-stenotic gradient, the blood pressure is commonly measured simultaneously in the aorta, close to the origin of the renal artery, and in the renal artery, distal to the stenosis. This can be done in different ways. One is by placing a 4F catheter distal to the lesion. But the catheter itself will partially obstruct the flow and may therefore falsely increase the gradient recorded. Smaller catheters, specially made for this purpose, cause less obstruction and can be positioned over a 0.014-inch guide wire without any need for withdrawal of the guidewire, to allow repeated measurements. There are also dedicated 0.014-inch pressure wires available, which most likely give the most accurate pressure measurements (20) (Figure 7).

Cut-off values for determining a haemodynamically significant RAS varies between centres, as described above. A MAPG of > 10 mmHg, or a SPG of > 20 mmHg are commonly used.

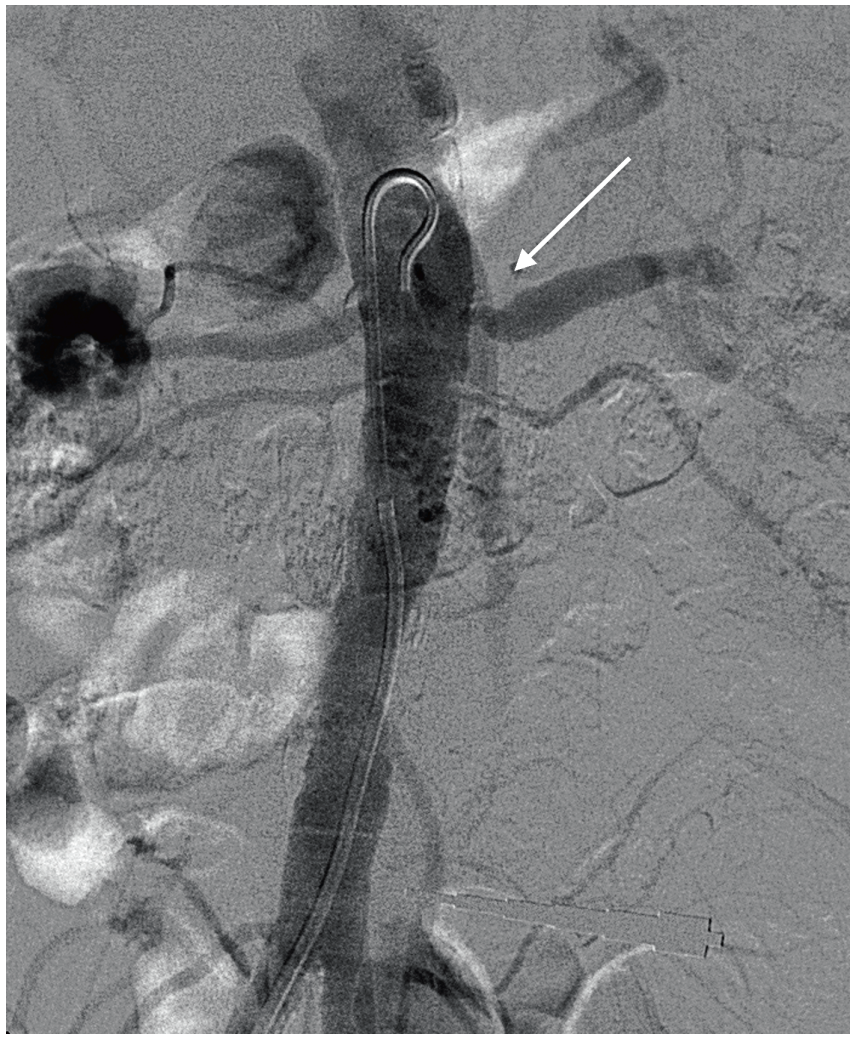
The limitation of DSA is the risk of complications, due to the invasive nature of the procedure—but also due to the ionizing radiation and the iodinated contrast. Though rare, complications such as arterial dissection and perforation, as well as cholesterol embolization and renal artery thrombosis, always have to be considered. Minor complications related to the puncture site such as bleeding and development of a pseudoaneurysm can occur, but are seldom seriously

harmful to the patient. DSA is therefore generally limited to visualization and quantification of the stenosis before an intended vascular intervention. It can also be indicated when the clinical suspicion of RAS is high and the non-invasive examinations are inconclusive (38).

DSA and trans-stenotic pressure measurement is still the scientific reference method of choice for evaluation of other diagnostic modalities.

Figure 7. ***A.*** *Digital subtraction angiography (DSA) of the aorta and the renal arteries. There are two arteries supplying each kidney and a suspected stenosis, with post-stenotic dilatation, in the left cranial renal artery (white arrow).* ***B.*** *A guide catheter is placed, pointing at the left renal artery. A 0.035-inch guidewire is advanced in the suprarenal aorta, to keep the end of the guide catheter from the aortic wall, and a 0.014 guidewire is placed through the stenosis in the left renal artery. A 3F catheter, dedicated to pressure measurements, is pushed over the 0.014-inch guidewire and positioned with the marked end in the renal artery distal to the stenosis (white arrow). Pressure measurements are made simultaneously through the catheters in the renal artery (white arrow) and the aorta (dashed arrow). The measurement revealed a 14-mmHg mean arterial pressure gradient (MAPG).*

A.



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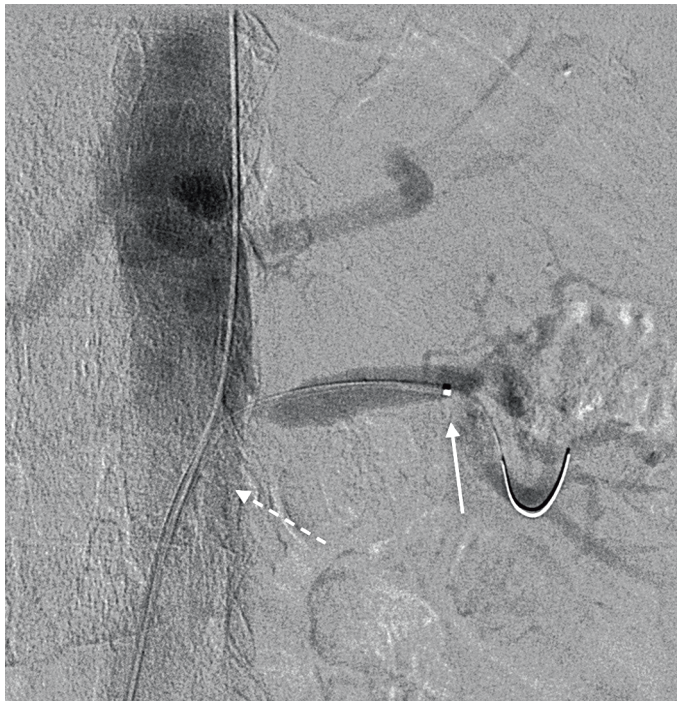


Other diagnostic methods

Technical advancements in radiological imaging products and methodological developments in non-invasive modalities have reduced the need for other methods for the detection of RAS, such as renal scintigraphy, plasma renin measurements before and after ACE-inhibitor provocation, and venous renin measurements. This development is reflected in current European Society of Cardiology (ESC)/European Society for Vascular Surgery (ESVS) guidelines, rejecting these methods when considered for the diagnosis of atherosclerotic RAS (38). Duplex ultrasound, MRA, and CTA provide good diagnostic accuracy and lead to less inconvenience for the patient. Renal scintigraphy is, however, considered a valuable method

for evaluation of renal function, especially to demonstrate the relative function of the right and left kidney in patients with bilateral RAS.

Therapy

Medical treatment

The latest updated ESC/ESVS guidelines (2017) state that medical treatment with anti-hypertensive drugs, statins, and anti-platelet drugs should be the first-line therapy strategy in patients with RAS and hypertension (38).

ACE inhibitors, ARBs, calcium channel blockers, beta-blockers, and diuretics are all effective drugs for treatment of hypertension and may reduce the progression of renal disease. To achieve control of blood pressure, medication should be individualized for each patient, using a combination of different anti-hypertensive drugs when tolerated.

ACE inhibitors or ARBs are recommended as essential medication in patients with atherosclerotic RAS, giving renal and cardiac protection with documented benefits in reducing mortality and morbidity (38). ACE inhibitors or ARBs block the RAAS and are tolerated by most patients with haemodynamically significant RAS. In some patients, however, they reduce the glomerular capillary hydrostatic pressure enough to cause a decrease in GFR and rise in serum creatinine. The patients who are at risk are those with bilateral RAS, patients with RAS in a single functioning kidney, patients with advanced age, patients with exposure to other nephrotoxins, and acutely ill patients (52). If tolerated in these patients, it should be given with caution and with close follow-up.

Some authors have argued that an increase in serum creatinine of > 30% in conjunction with RAAS blockade should evoke discontinuation of this medication (53). Others have proposed this to

be an indication for revascularization when a haemodynamically significant RAS has been identified (19).

The ESC/ESVS guidelines also include HMG-CoA reductase inhibitors, statins, in the recommended pharmacological treatment of symptomatic RAS. Lipid-lowering with statins is associated with improved survival, slower lesion progression, and a reduced restenosis rate after renal stenting (54-56). Anti-platelet therapy should also be part of BMT, as it has been shown that anti-platelet therapy in high-risk patients reduces the combined outcome of non-fatal serious cardiovascular events by about 25% (56, 57).

Renal artery revascularization

PTRA was introduced in 1978 (58). The method has since been refined, with dedicated low-profile devices and reduced complication rates. Open surgical revascularization is seldom relevant in contemporary practice, but it can be indicated in cases with complicated anatomy or complex disease of the renal artery. It may also be indicated in patients requiring simultaneous surgical repair of the abdominal aorta. Surgical revascularization is, however, burdened by relatively high mortality compared to endovascular repair (59).

PTRA is almost always performed in conjunction with a DSA and trans-stenotic pressure measurement that confirms a strong suspicion of haemodynamically significant RAS. A balloon catheter with or without a stent is advanced over a guide wire into the renal artery, positioned over the stenosis, and manually expanded by the interventionist. Atherosclerotic RAS lesions are often located at the ostium of the artery, where stent placement gives best results. RAS lesions in the trunk of the artery can often be satisfactorily dilated with a balloon alone. Balloon dilatation alone is also the preferred treatment for FMD lesions. Post-procedural pressure measurements confirm the treatment effect when the pressure gradient over the lesion has disappeared (Figure 8).

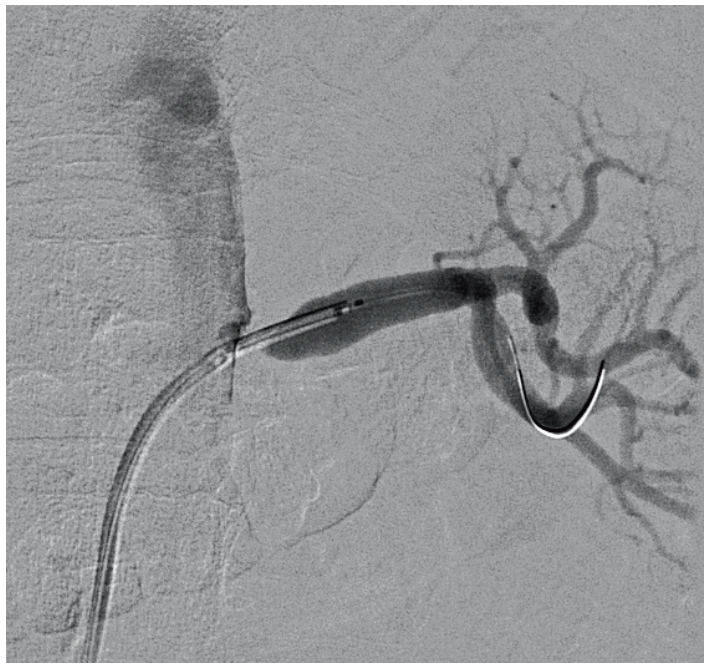
Complications include those mentioned above for DSA, but the active dilatation of the diseased vessel wall further increases the risk of

dissection, perforation, cholesterol embolization, and thrombosis. Cautious instrument manipulation is mandatory, and the procedure should be done by experienced interventionists.

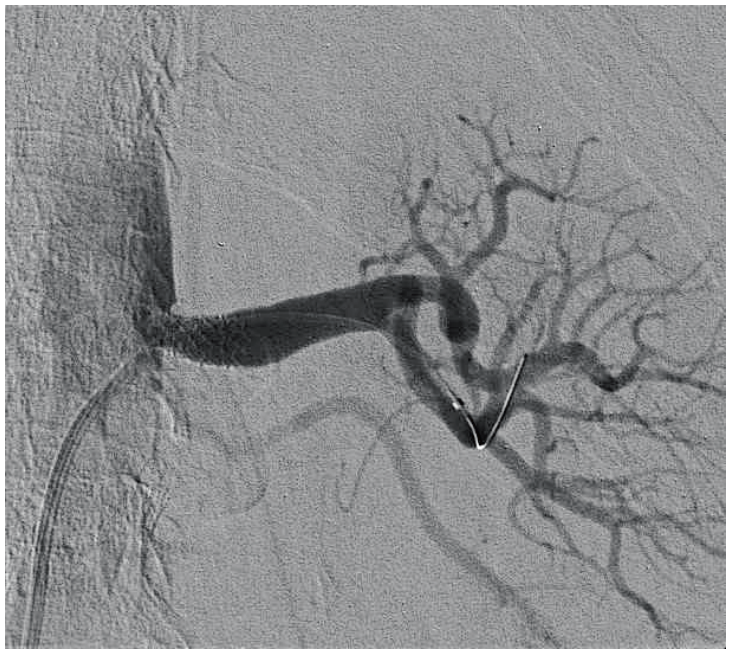
The technical success rate—defined as restoration of the vessel lumen and elimination of the trans-stenotic pressure gradient with PTRA—is high, and the risk of complications is low (60, 61). However, complications do occur and are therefore important to consider when evaluating treatment strategies.

Figure 8. ***A.*** *Renal artery revascularization with a stent pre-mounted on a balloon catheter. Same patient as Figure 7. When the stent is accurately placed in an ostial stenosis, it should protrude a few millimeters into the aorta and its distal end should smoothly merge with healthy renal artery, distal to the stenosis. The balloon is semi-compliant and expanded to its nominal diameter, in this case 7 mm. B. As the balloon empties, the stent stays in place and the stenosis is gone. MAPG 0.*

A.



B.



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For many years in the late 1990s and early 2000s, PTRA was performed on wide indications, including patients with asymptomatic RAS. In parallel, medical treatment was improved, including anti-platelet therapy and lipid lowering. This called for prospective randomized trials to investigate whether PTRA offered additional clinical benefits compared to BMT alone. In November 2009, the ASTRAL trial was published in New England Journal of Medicine and found no additional clinical benefit of PTRA compared to BMT alone.

This led to a shift in treatment strategy for patients with symptomatic RAS (1). The results of the ASTRAL trial were later confirmed by the larger American CORAL trial (2).

Guidelines restrained indications for revascularization to patients with severe clinical consequences, such as sudden onset of "flash" pulmonary oedema unrelated to acute coronary syndrome, congestive heart failure with preserved left ventricular function, and acute oligoanuric renal failure with global kidney ischaemia. Revascularization was also often considered to be indicated in patients with multi-drug-resistant hypertension, advanced CKD, or steadily deteriorating renal function.

Based on the above-mentioned RCTs, the most recently published ESC/ESVS guidelines are even more restrained in terms of invasive treatment, stating—with few exceptions—that BMT should be the cornerstone for the management of patients with atherosclerotic RAS and hypertension (38). Revascularization should only be considered in cases of FMD and hypertension and/or signs of renal impairment, in patients with unexplained recurrent congestive heart failure or sudden pulmonary oedema, and in case of RAS secondary to endovascular or open aortic surgery. Routine revascularization is not recommended for atherosclerotic RAS in patients with drug-resistant hypertension.

Therapeutic considerations

Both the ASTRAL trial and the CORAL trial included only a small proportion of all the patients treated at the participating centres ((62, 63). The question of whether there are patients benefiting from revascularization still remains. This is reflected in a recent review concerning treatment of atherosclerotic RAS over the period 1993–2016, where the authors found low strength of evidence regarding the relative benefits and harms of PTRAs as opposed to medical therapy alone (64).
The trials have shown that asymptomatic patients with RAS should not be treated with PTRA, as the risk from revascularization in these patients clearly exceeds any benefits.

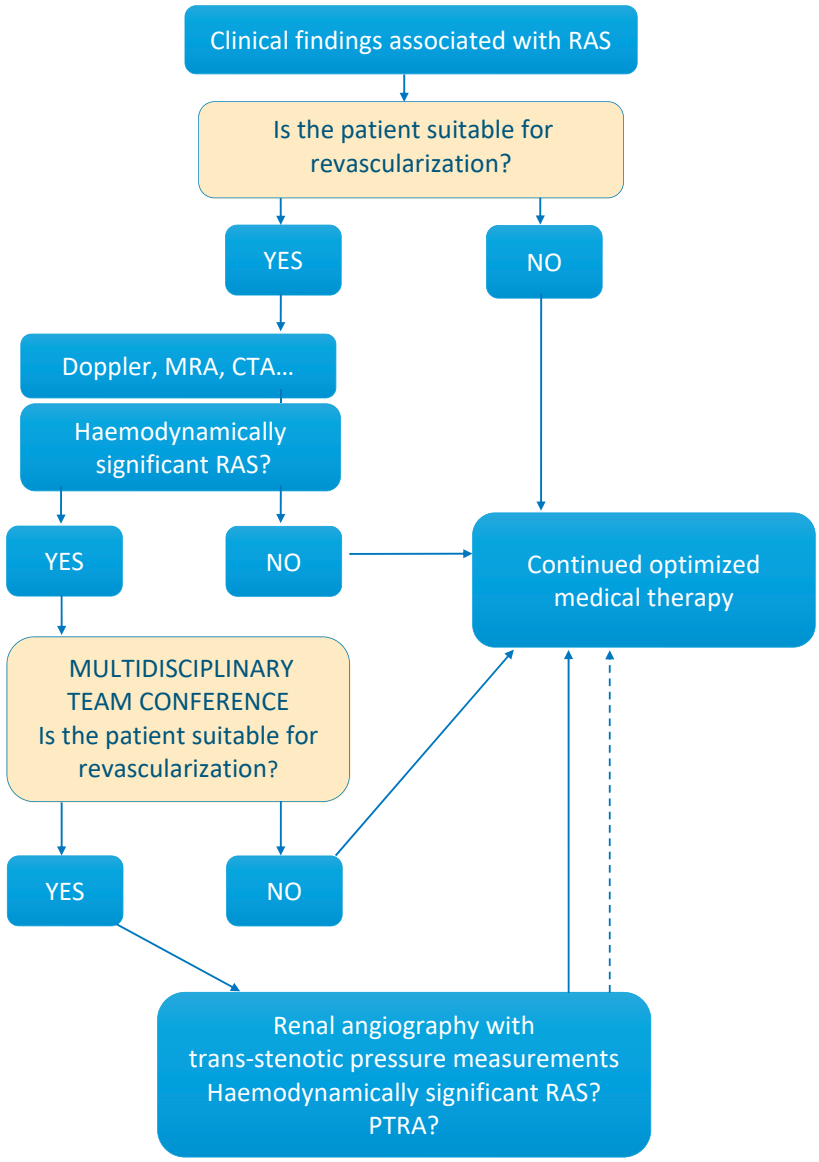
The everyday clinical challenge is still to identify the patients with haemodynamically significant RAS who would respond to PTRA, and to intervene sufficiently early to prevent kidney damage. It is also important to consider the risk of cardiovascular events in patients with resistant hypertension, knowing that a 20-mmHg decrease in SBP reduces the risk of death from stroke and IHD by 50% (7). Even a smaller decline in BP is of value, as the risk reduction is proportional (7). The control of hypertension may be facilitated by revascularization, although cure of hypertension is unusual.

Preservation or improvement of renal function may also be a goal, as in patients with onset of severe, or worsening of, hypertension combined with impaired or chronic renal function. The impact of the identified RAS on the renal dysfunction is, however, not possible to predict, as the severity of the RAS is often unrelated to the severity of the renal function (29, 30). However, kidneys < 7 cm in their longest diameter, with small parenchymal volume and cortical thickness, should not be considered for revascularization, as they are already irreversibly damaged (65).

Revascularization is not recommended if renal function has remained stable over the previous 6–12 months and if hypertension can be controlled with (for the patient) an acceptable medical regimen.

The treatment of patients with suspected RAS should be individualized, including the option of revascularization. This is an opinion shared by many authors (63, 66-68). Diagnostic imaging reveals information that must be considered, such as anatomy of the stenosis, arterial and aortic anatomy, and likelihood of success of the procedure, which in conjunction with the clinical scenario of the patient ends in a therapy decision. Diagnostic images should be demonstrated and discussed in the setting of a specific multidisciplinary team conference involving nephrologists, ultrasound technicians, clinical physiologists, interventional radiologist, and vascular surgeons. An example of such a diagnostic pathway is illustrated in the flow chart in Figure 9.

Figure 9. Flow chart describing the flow of evaluations, diagnostics, and treatment decision in patients with symptomatic suspected renal artery stenosis (RAS).



AIMS

The overall aim of this thesis was to improve duplex ultrasound in the diagnosis of haemodynamically significant RAS and to evaluate outcomes of treatment with PTRA in patients with hypertension and RAS. More specific aims were:

- To compare the accuracy of the novel velocimetric indirect duplex ultrasound index, AI_{max}, in the diagnosis of RAS with that of the established ACC_{max} index (study I)

- To define optimal cut-off values for direct duplex ultrasound parameters when screening for haemodynamically significant RAS, considering a more relevant sensitivity-specificity balance for assessment of patients with hypertension and clinical suspicion of RAS (study II)

- To determine long-term clinical outcomes in patients with symptomatic RAS treated with PTRA and stent, and whether these long-term outcomes are affected by angiographic restenosis after one year (study III)

- To evaluate time trends in PTRA procedures

- To evaluate medium-term clinical outcomes after PTRA in patients with primary RAS treated with contemporary, conservative indications, and to determine whether these outcomes are better or worse for some indications than for others (study IV).

PATIENTS AND METHODS

Study design

The study designs of the four papers are summarized in Table 1. All four studies were retrospective. In studies 1 and 2, diagnostic duplex criteria to detect haemodynamically significant RAS were evaluated. In both studies, duplex ultrasound criteria were related to DSA with trans-stenotic pressure gradient measurement (PGM). Studies 3 and 4 evaluated clinical outcomes in PTRA-treated patients.

Table 1. Design of the four studies in the thesis

	Design	**No. of patients**	**Source**	**Analyses**
Paper I	Retrospective, single-centre cohort study	169	Medical records and duplex data at Sahlgrenska University Hospital	Evaluation of indirect duplex velocity indices for detection of haemodynamically significant RAS
Paper II	Retrospective, single-centre cohort study	58	Images and medical records from Uppsala University Hospital	Re-evaluation of direct duplex criteria for detecting haemodynamically significant RAS
Paper III	Retrospective, single-centre cohort study	57	Medical records of the regional hospitals (Västra Götaland and Halland) and from healthcare registries	Long-term outcome of PTRA with stent, and the impact of angiographic restenosis at one year
Paper IV	Retrospective, multi-centre cohort study	224	Medical records of hospitals, interventional units, and primary care related to the university hospitals in Umeå, Uppsala, Malmö, and Gothenburg	Contemporary medium-term outcome of PTRA

Patients

The inclusion criteria in all four studies included hypertension and clinical suspicion of RAS.

Study I

This was a retrospective analysis of 169 consecutive patients recruited to the prospective Candersartan in Renal Artery Stenosis (CARLAS) study, which was conducted at the Department of Nephrology, Sahlgrenska University Hospital, from 2002 to 2007. All patients were assessed with duplex ultrasound prior to renal artery angiography, both of which had to be done within 4 months.

The study was approved by the Gothenburg Regional Ethical Review Board, and all participating patients had signed an informed consent document.

Study II

In this study, we retrospectively analyzed data from 58 patients who had been consecutively referred to the Department of Radiology, Uppsala University Hospital during the period 2001–2004. The patients were originally recruited to a prospective study comparing diagnostic imaging methods and the ability to detect haemodynamically significant RAS (69). Study II concentrated on duplex ultrasound. Patients were examined with duplex ultrasound prior to renal angiography, and the time interval between the two was kept to within one month.

The local ethics and radiation committees of the Faculty of Medicine in Uppsala approved the study. All the patients gave their informed consent.

Study III

This was a long-term follow-up study involving 57 patients treated with PTRA with stent at Sahlgrenska University Hospital between the years 1995 and 2004, who were investigated for restenosis with angiography after one year. This was a clinical routine during this time period. Patients treated with balloon dilatation only (without stent) were not included. If restenosis was found after one year, the patients were re-treated—mainly with balloon dilatation, and in a five cases with an additional stent. Sixteen patients were alive and sufficiently healthy to undergo a late clinical examination between November 2014 and March 2015.

The study was approved by the Ethical Review Board in Gothenburg. Written informed consent was given by all the patients who underwent the late clinical examination.

Study IV

This study included consecutive patients who were treated with PTRA at four university hospitals in Sweden during the period 2006–2013, and who were identified by using the log book of the interventional radiology departments at each site. The patients were divided according to two equally long time periods, which were separated by the publication of the ASTRAL trial in late 2009 (1). Patients treated during the first period (2006–2009), the pre-ASTRAL group, served as a reference for treatment frequency and only the number of PTRA treatments was recorded. Patients treated during the second period (2010–2013), the post-ASTRAL group, was the study cohort in this study. Detailed pre-, per-, and postoperative information was retrieved from the medical records. Only patients with primary and symptomatic RAS were included. Patients who received re-treatment of recurring primary symptomatic RAS during either time period were included.

The Regional Ethical Review Board in Gothenburg approved the study. Informed consent was obtained from all patients who were alive, before requesting journal extracts from external healthcare units.

Methods

Study I

Duplex ultrasound with the *indirect* technique

Indirect duplex ultrasound was carried out by experienced technicians. Velocity measurements were made in the arcuate and inter-lobar arteries in the kidneys and velocimetric indices were calculated. In patients with two functioning kidneys, the difference in pulsatile index, ΔPI, was calculated and used for analysis. Pulsatility index (PI) and early systolic pulse acceleration (ACC_{max}) were estimated directly at the time of examination, whereas maximal acceleration index (AI_{max}) was calculated retrospectively in stored duplex data.

Blood pressure and laboratory analyses

Blood pressure was measured on the day before renal angiography and blood samples were analyzed for serum potassium, serum cholesterol, and serum creatinine. Estimated glomerular filtration rate (eGFR) was calculated with the 4-variable equation described in the Modification of Diet in Renal Disease study (MDRD)(70).

Digital subtraction angiography and trans-stenotic pressure gradient

DSA was used for evaluation of renal arteries. The trans-stenotic pressure gradient was measured as described earlier, mainly with the 3F-catheter, and it was the reference method of defining haemodynamically significant RAS. The procedures were performed by four interventional radiologists with 3–12 years of experience. Haemodynamically significant RAS was defined as trans-stenotic MAPG of ≥10 mmHg and/or an angiographic reduction in lumen diameter of at least 60%. Missed MAPG measurements were mainly due to technical difficulties with high-grade stenosis and/or luminal occlusion. The morphological degree of stenosis was measured manually. The mean time between the duplex ultrasound and the angiography was 34 days.

Statistical analysis

Statistical analyses were done with unpaired t-test for evaluation of differences between groups and the Pearson correlation coefficient was used to analyze correlations. All tests were two-tailed and p-values less than 0.05 were considered to be significant. The sensitivity and specificity, and also the ideal cut-off limits for duplex ultrasound indices, were determined using receiver-operating characteristic (ROC) analysis.

Study II

Duplex ultrasound with the *direct* technique

Direct duplex ultrasound was performed by four sonographers, with 2–5 years of experience of the investigation technique. Measurements of PSV were done in the aorta at the level of the renal arteries, and in the proximal, middle, and distal parts of the renal arteries.

Digital subtraction angiography and trans-stenotic pressure gradient

The trans-stenotic pressure gradient was measured between an introducer in the aorta, at the level of the renal arteries, and a 4F catheter placed in the distal renal artery. A SPG of ≥ 15 mmHg defined a haemodynamically significant RAS. The median time between the duplex ultrasound and the PGMs was 3 days (range 0–21 days).

Statistical analysis

In order to evaluate the discriminatory power of renal artery PSV and RAR, for the diagnosis of renal artery stenosis, ROC curves were generated. The area under the ROC curve (AUC) was calculated for renal artery PSV and RAR separately and in combination. Optimal cut-off levels were calculated based on Youden's index, which maximizes the sum of sensitivity and specificity. The index is defined for all points of a ROC curve, and the maximum value of the index can be used for selection of the optimum cut-off point. Computation of 95% confidence limits for sensitivity and specificity took account of within-patient clustering by cluster-bootstrap resampling using the percentile method with 1,000 bootstrap samples. Pearson correlation coefficient

was used to assess the strength of the relationship between renal artery PSV, RAR, and SPG.

Study III

Data collection

Information on indication for PTRA, SBP, and DBP measurements, serum creatinine levels, and anti-hypertensive medications pre-PTRA, at the time of the one-year angiography control and from the patient's latest recorded out-patient healthcare visit, was retrieved from the medical records. Dates and causes of death were retrieved from the Swedish cause of death registry. Healthcare utilization (in terms of hospitalizations and diagnoses) was collected from the Swedish national patient register.

Renal function was evaluated using the eGFR calculated according to MDRD. Pharmacological treatment was assessed both by the number of anti-hypertensive drugs prescribed and by a pharmacological treatment index.

Treatment index

To enhance the evaluation of pharmacological hypertension treatment over time, a medication index was calculated for each type of anti-hypertensive drug at each time point according to Delin et al. (71, 72). The score of each type of anti-hypertensive drug ranged from 0 to 10, where 0 indicated no medication and 10 indicated the upper dose level according to recommendations in the Swedish environmental classification of pharmaceuticals (www.fass.se). A treatment index (TI) was calculated by adding the scores of all anti-hypertensive drugs.

Late out-patient control

All patients who were still alive were invited for an out-patient visit in 2015, with a detailed assessment of blood pressure and renal function, including ambulatory 24-hour blood pressure measurements, laboratory tests, duplex ultrasound, Cr-EDTA clearance, and radioisotope renography. For patients who died before 2015, the

medical records from their last out-patient visits were used to obtain late follow-up data.

Statistical analysis

Data are presented as median and range. The Mann-Whitney U-test was used to compare data with skewed distribution. Survival was summarized and illustrated with the help of relative survival curves (73, 74). The relative survival ratio was defined as the observed survival in the patient group divided by the expected survival of the general population with the same gender and year of birth. The population for expected survival was obtained from the Human Life-Table Database (http://www.lifetable.de/).

Study IV

Data collection

Pre-, per-, and postoperative data on patients in the post-ASTRAL group were collected on site at each participating centre. Information on indications for PTRA, preoperative co-morbidities, SBP, DBP, and serum creatinine, postoperative complications, and anti-hypertensive medications were retrieved from the medical records of the hospital and from external healthcare units when required. Specific procedural information including preoperative diagnostic imaging, trans-stenosis PGM, laterality of treated renal artery, size of stent/balloon, and information on peroperative complications was found in the radiology information system (RIS) of each hospital. Clinical outcomes were recorded directly after PTRA (post-PTRA), after one year, and at the latest clinical evaluation. Renal function was evaluated with eGFR, calculated according to MDRD. Pharmacological treatment was evaluated both from the number of anti-hypertensive drugs prescribed and by calculating an anti-hypertensive treatment index (TI; described in Methods of study III). In addition, the use of statins and anti-platelet therapy was recorded.

Statistical analysis

Values are presented as mean and standard deviation (SD) with 95% confidence interval (CI). SBP, DBP, eGFR, TI, and number of drugs at

the follow-up time points (post-PTRA, after one year, and at the last control) were compared with corresponding values before PTRA, using linear regression analysis.

4 RESULTS

Study I

On angiography haemodynamically significant RAS was detected in 99 of the 169 patients. Unilateral RAS was found in 74 patients, 12 patients had bilateral RAS, and 13 patients had stenosis to a solitary kidney. Altogether, 111 stenotic and 206 non-stenotic renal arteries were investigated. Trans-stenotic MAPG was not registered in 21 patients (31 kidneys), which was due to high-grade stenosis and luminal occlusion caused by the low-profile catheter used to cross the stenosis during the procedure (20 kidneys) or miss of registration (11 kidneys). When successfully measured, MAPG was 42.4 ± 26.6 in kidneys with haemodynamically significant RAS (n = 80).

All velocimetric indices were significantly different in stenotic kidneys compared to those without stenosis, as shown in Table 2.

Table 2. Velocimetric indices in kidneys with and without renal artery stenosis

	Without hemodynamically significant RAS (n=206)	With hemodynamically significant RAS (n=111)	p-value
PI	1.37 +/- 0.44	1.10 +/- 0.39	<0.001
ACC_{max} (m/s^{2})	5.39 +/- 2.40	2.37 +/- 1.85	<0.001
AI_{max} (s^{-1})	21.2 +/- 7.4	10.7 +/- 6.1	<0.001

PI, pulsatility index; ACC_{max}, early systolic pulse acceleration; AI_{max}, acceleration index; Data are expressed as mean +/- SD

The ideal cut-off limits of the velocimetric indices detecting haemodynamically significant RAS in the 317 kidneys were defined with ROC curves: $ACC_{max} \leq 3.80$ m/s^2, $AI_{max} \leq 15.0^{-1}$, PI < 1.1, ΔPI > 0.20. There were no statistically significant differences between

different cut-off values of ACC_{max}, AI_{max}, and ΔPI (ROC curves not shown).
The diagnostic accuracies of ACC_{max} and AI_{max} were better than that of PI, especially in patients with eGFR < 30 mL/min per 1.73 m^2 (Table 3).

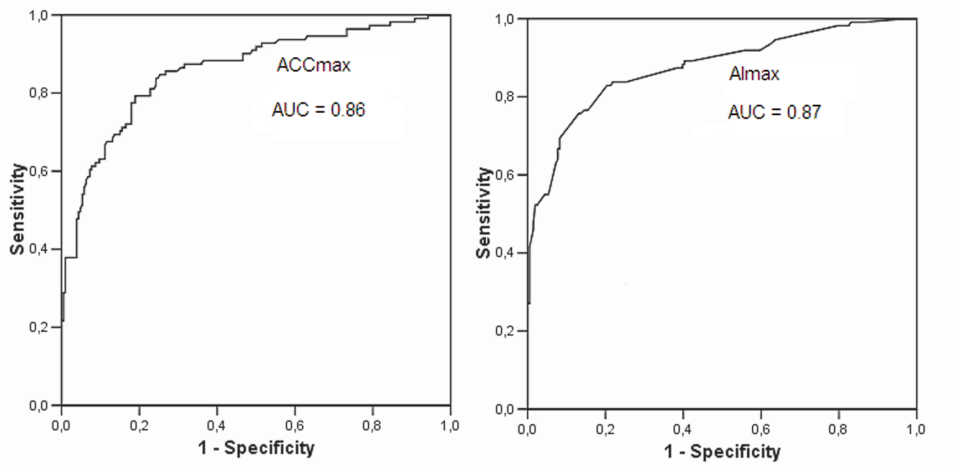
There was no difference between ACC_{max} and AI_{max} for the detection of haemodynamically significant RAS (Figure 10).

Table 3. Sensitivity, specificity, and predictive values of velocimetric indices for the diagnosis of haemodynamically significant renal artery stenosis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPP (%)
In 136 patients (excluding patients with bilateral RAS and those with single kidneys)				
ACC_{max}	84	76	55	93
AI_{max}	80	79	59	92
PI	69	71	46	88
ΔPI	78	85	86	76
In all kidneys (n = 317)				
ACC_{max}	85	75	65	90
AI_{max} AI_{max}	83	59	67	90
PI	60	72	54	77
In kidneys of patients with eGFR > 30 mL/min per 1.73 m^2 (n = 265)				
ACC_{max}	84	75	64	90
AI_{max}	85	77	66	91
PI	64	69	52	78
In kidneys of patients with eGFR ≤ 30 mL/min per 1.73 m^2 (n = 52)				
ACC_{max}	90	73	65	92
AI_{max}	74	88	78	86
PI	37	88	64	71

PPV, positive predictive value; NPP, negative predictive value; ACC_{max}, early systolic pulse acceleration; AI_{max}, acceleration index; PI, pulsatility index; ΔPI, difference in PI between the two kidneys; eGFE, estimated glomerular filtration rate.

Figure 10. Receiver-operating characteristic (ROC) curves for ACCmax and AImax. The curves show sensitivity for detection of a haemodynamically significant RAS plotted against 1 − specificity for different cut-off values for early systolic pulse acceleration (ACCmax, left panel) and the maximal acceleration index (AImax, right panel). A haemodynamically significant RAS was defined as a lesion with a trans-stenotic MAPG of at least 10 mmHg or an at least 60%-diameter stenosis on angiography (in cases where the MAPG was not measured). All examined kidneys (n = 317) were included. AUC, area under the curve; MAPG, mean arterial pressure measurement; RAS, renal artery stenosis.



In kidneys with haemodynamically significant RAS, the trans-stenotic MAPG showed a negative correlation to ACC_{max} ($r = -0.26$, $P = 0.02$) and AI_{max} ($r = -0.29$, $P = 0.01$). There was also a negative, though not significant, correlation to PI ($r = -0.22$, $P = 0.054$).
In contrast to ACC_{max} and AI_{max}, PI showed a significant correlation to patient age, serum creatinine levels, eGFR, and pulse pressure in both stenotic and non-stenotic kidneys (Table 4).

Table 4. Analysis of correlations

	ACC_{max}	AI_{max}	PI
In kidneys with hemodynamically significant RAS (n = 111)			
Age, years	r = −0.05 (p = 0.58)	r = 0.20 (p = 0.04)	r = 0.54 (p < 0.001)
S-creatinine, µmol/L	r = −0.10 (p = 0.29)	r = −0.11 (p = 0.23)	r = 0.28 (p < 0.01)
eGFR, mL/min per 1.73 m^2	r = 0.06 (p = 0.56)	r = −0.15 (p = 0.12)	r = −0.40 (p < 0.001)
Pulse pressure, mmHg	r = 0.10 (p = 0.28)	r = −0.10 (p = 0.32)	r = 0.52 (p < 0.001)
Trans-stenotic MAPG, mmHg	r = −0.26 (p = 0.02)	r = −0.29 (p = 0.01)	r = −0.22 (p = 0.054)
In kidneys without significant RAS (n = 206)			
Age, years	r = −0.004 (p = 0.95)	r = −0.02 (p = 0.82)	r = 0.54 (p < 0.001)
S-creatinine, µmol/L	r = −0.09 (p = 0.19)	r = 0.17 (p = 0.01)	r = 0.21 (p < 0.01)
eGFR, mL/min per 1.73 m^2	r = 0.08 (p = 0.15)	r = −0.12 (p = 0.10)	r = −0.33 (p < 0.001)
Pulse pressure, mmHg	r = 0.26 (p < 0.001)	r = 0.21 (p = 0.003)	r = 0.57 (p < 0.001)

ACC_{max}, early systolic pulse acceleration; AI_{max}, acceleration index; PI, pulsatility index; ΔPI, difference in PI between the two kidneys; MAPG, mean arterial pressure gradient; eGFE, estimated glomerular filtration rate; RAS, renal artery stenosis.
Pearsson correlation coefficients between velocimetric duplex indices and clinical variables.

Study II

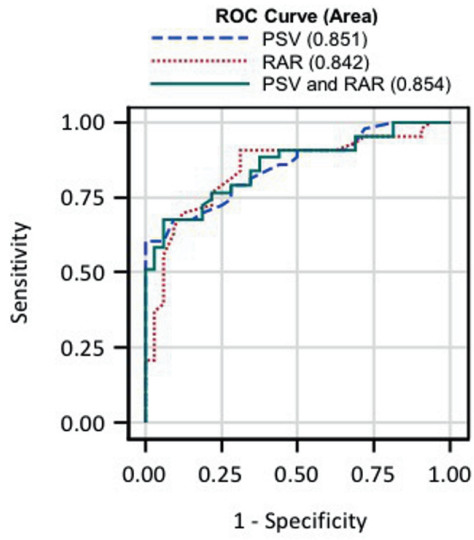
The renal arteries of 58 individuals were examined, and conclusive results of both duplex ultrasound and PGM were obtained for 76 renal arteries. In the remaining arteries, the results from either duplex ultrasound or PGM were missing. Missing results from duplex ultrasound were mainly due to insufficient visualization of the entire renal artery, which was the case bilaterally in five patients, and unilaterally in 15 patients. One kidney was excluded because of an accessory artery and discrepancy between duplex ultrasound and PGM findings. Missing PGM results were due to missed catheterization of both renal arteries in a few patients. Two patients were not examined

with angiography and PGM and two patients only had one kidney after earlier nephrectomy.

Trans-stenotic PGM identified haemodynamically significant RAS in 43 of the 76 renal arteries. To analyze the distribution of PSV, RAR, and PGM in patients with and without significant RAS, Pearson correlation coefficient was used, showing PSV and RAR symmetrically distributed with a high correlation to each other (r = 0.83), while correlations between PGM and either RAR or PSV were modest (r = 0.55 and r = 0.66, respectively).

ROC curves for PSV and RAR were very similar, and we could not detect any consistent difference between them in predicting haemodynamically significant RAS, defined as SPG ≥ 15 mmHg. The same pattern was observed when RAR and PSV were analyzed in combination.

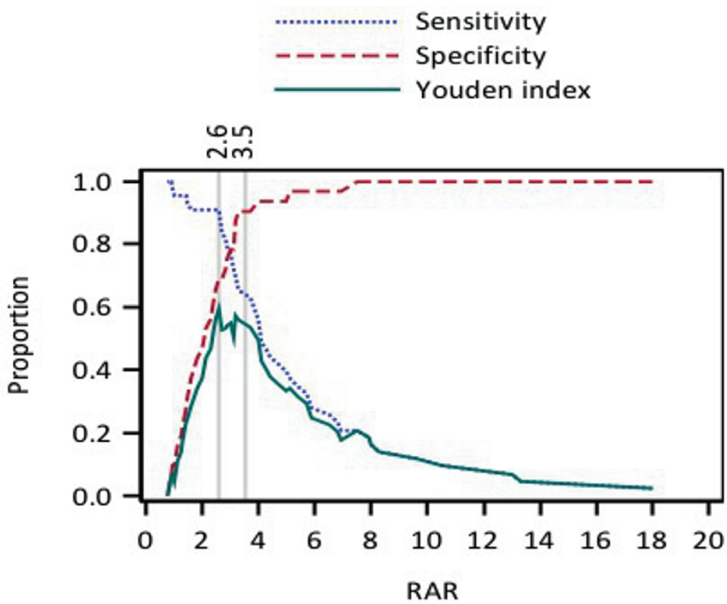
Figure 11. Plots of sensitivity against 1 − specificity for haemodynamically significant renal artery stenosis, systolic pressure gradient (SPG) ≥ 15 mmHg, expressed in receiver-operating characteristic (ROC) curves for PSV, peak systolic velocity (blue), RAR, renal-aortic ratio (red), and PSV and RAR in combination (green).



Optimal cut-off levels were calculated based on Youden's index (Figure 12).

Figure 12. Youden's index was plotted (sensitivity + (specificity − 1)) to find values where the sum of sensitivity and specificity was maximized, indicating the optimum cut-off points. ***A.*** *Proportion of sensitivity and specificity at different renal-aortic-ratios (RARs), with two different cut-off values (2.6 and 3.5).* ***B.*** *Proportion of sensitivity and specificity at different renal artery peak systolic velocities (PSVs), with three different cut-off values (180, 300, and 320 cm/s).*

A.



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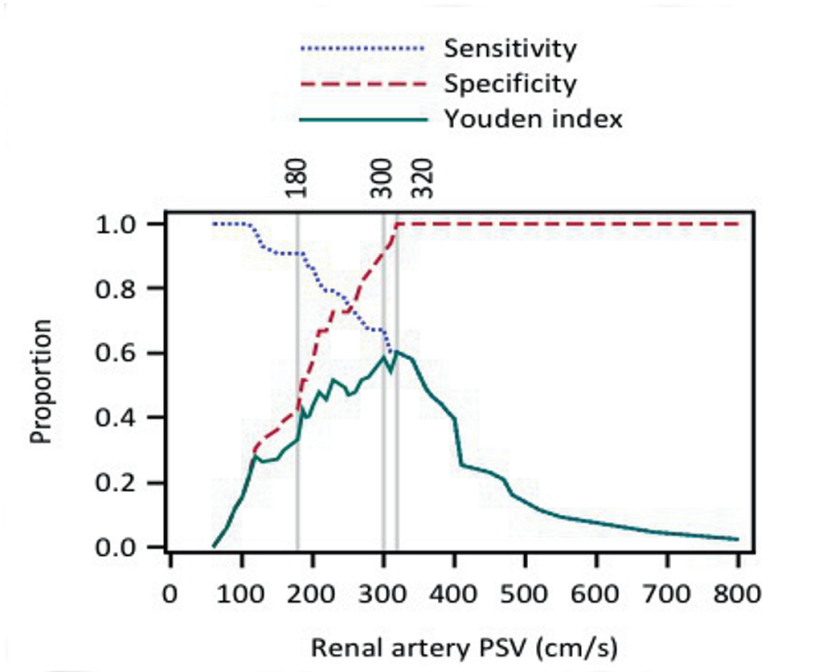


Traditional duplex ultrasound cut-off values, PSV ≥ 180 cm/s and RAR ≥ 3.5, had a sensitivity and specificity of 62% and 91%, respectively.

Calculations to maximize the sum of sensitivity and specificity for the combination of PSV and RAR parameters, using Youden's index, resulted in new cut-off values of PSV ≥ 300 cm/s and RAR ≥ 2.6 (Figure 12). These new cut-off values had a sensitivity of 67% and a specificity of 94% to predict RAS. RAR and PSV measurements are dependent on each other, and supplementing one parameter with the other did not improve the reliability of the test.

When the traditional and the new cut-off values of PSV and RAR were evaluated—both on their own and in combination—it was found that RAR ≥ 2.6 alone had a sensitivity of 89% and a specificity of 69% while other cut-off values of the parameters, or combinations thereof, had either a much lower specificity (PSV ≥ 180) or a clearly lower sensitivity (Table 5).

Table 5. Sensitivity and specificity with different criteria for PSV and RAR in patients with RAS

	Sensitivity, % (range)	Specificity, % (range)
Renal artery PSV ≥ 180 and RAR ≥ 3.5	62 (46–76)	91 (79–100)
Renal artery PSV ≥ 300 and RAR ≥ 2.6	67 (52–80)	94 (83–100)
Renal artery PSV ≥ 180	91 (81–98)	42 (23–62)
Renal artery PSV ≥ 200	86 (74–96)	58 (41–74)
Renal artery PSV ≥ 220	79 (66–91)	67 (48–82)
Renal artery PSV ≥ 250	74 (60–87)	73 (56–87)
Renal artery PSV ≥ 300	67 (52–80)	91 (79–100)
RAR ≥ 3.5	62 (46–76)	91 (79–100)
RAR ≥ 2.6	89 (79–97)	69 (52–85)

PSV, peak systolic velocity; RAR, renal-aortic ratio.

Study III

The most common indications for PTRA were therapy-resistant hypertension and declining renal function, often in combination. Systolic and diastolic blood pressures decreased after the index procedure: median 180 mmHg to 160 mmHg ($p = 0.0011$) and 90 mmHg to 80 mmHg ($p = 0.0037$), respectively.

At the one-year control, angiographic restenosis was found in 21 of the 57 patients (37%). Re-treatment with balloon dilatation was done in 17 of the 21 patients, in five also with an additional stent. Compared to

patients without restenosis, there were no significant differences in systolic or diastolic blood pressure or in TI.

Table 6. Patient data at 1-year follow-up with angiography. Measurements were obtained before any re-intervention took place

	Restenosis	No restenosis	p-value
No. of patients	21	36	
Gender, male/female	8/13 (38%/62%)	17/19 (47%/53%)	
Age at index PTRA, years	63 (40–76)*	65 (46–80)*	0.5
SBP, mmHg	150 (120–220)*	160 (120–220)*	0.34
DBP, mmHg	85 (65–110)*	85 (60–120)*	0.61
eGFR, mL/min per 1.73m^2	61 (34–107)*	53 (16–89)*	0.052
Anti-hypertensive drugs	2 (0–4)*	2 (0–5)*	0.066
Treatment index (TI)	7.5 (0–18.3)*	8.52(0–27.5)*	0.23
MAPG, mmHg	17 (7–140) (n = 16)	2 (0–6) (n = 17)	< 0.01

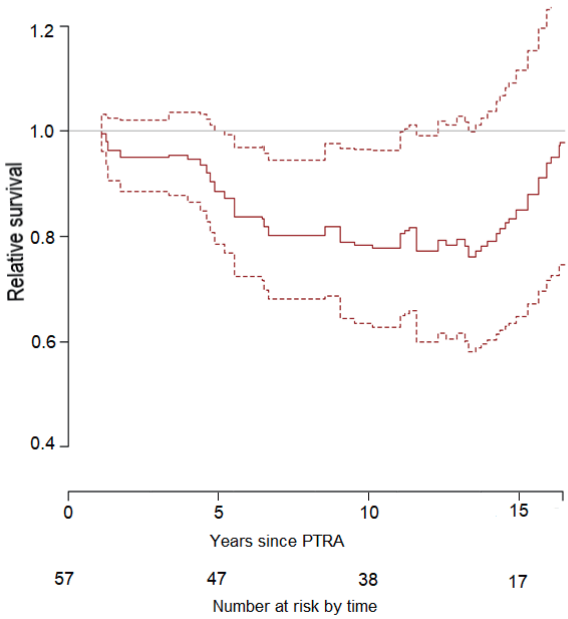
*Median (range).
SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, glomerular filtration rate; MAPG, mean arterial pressure measurement.

The median follow-up time to the late clinical evaluation in 2015, or death, was 139 months (11 years and 7 months) (range 15–232 months). Thirty-six patients (60%) died during follow-up. The main cause of death was cardiovascular events (54%) including myocardial infarction (23%), heart failure (7.7%), and stroke (7.7%). Malignant disease was the second most common cause of death (27%). There was no difference in mortality between patients with restenosis and those without (p = 0.9). Compared to expected survival in the background population, PTRA-treated patients had shorter survival and the difference reached statistical significance 5 years after the index procedure (Figure 13).

The patients used a considerable amount of healthcare resources after treatment for RAS, with a median number of ten in-hospital care episodes (range 2–32). Most hospitalizations were caused by cardiovascular diseases (58%), followed by urogenital diseases including renal failure (9%) and malignant diseases (4.1%). There was

no significant difference in hospitalizations during follow-up between patients with restenosis and those without.

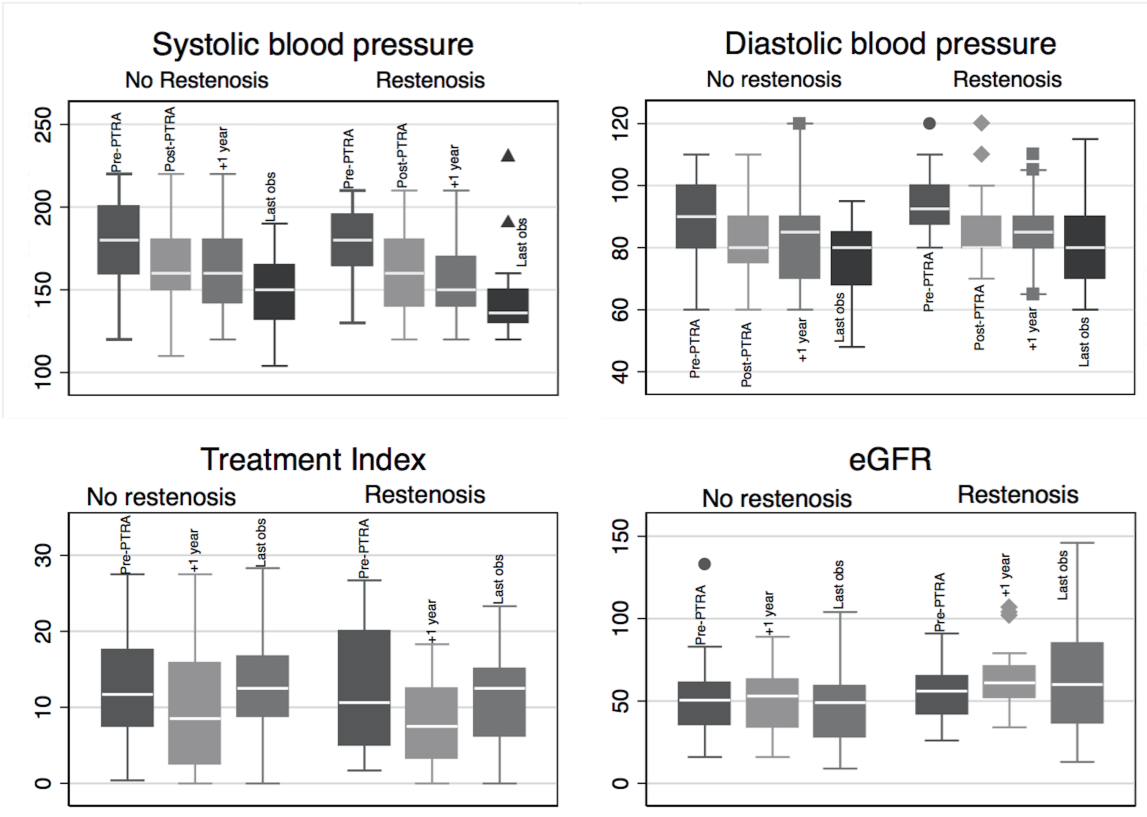
Figure 13. Relative survival. The relative survival (y-axis) for the PTRA-treated patients plotted as the observed survival in the study group divided by the expected survival of an age- and gender-matched population (1.0 on the y-axis). The solid line indicates the relative survival and the dashed lines indicate the associated pointwise 95% CI. Note that the number of patients with a follow-up period of > 13 years was only 17.



There were no differences in renal function or pharmacological treatment index over time between patients with restenosis and those without. Systolic and diastolic blood pressures, eGFR, and TI over time are shown in Figure 14.

Six patients eventually needed dialysis, and one of them subsequently had kidney transplantation. Two of these six patients had had a restenosis at the one-year follow-up angiography.

Figure 14. Outcome in the 57 PTRA-treated patients. Data from the time of index treatment (Pre- and Post-PTRA), at the one-year angiography control (+1 year), and at the last clinical control (Last obs), shown separately for patients with and without restenosis after one year. Median and interquartile range are shown. Symbols outside the interquartile range mark outliers.
The median follow-up time (from index treatment to Last obs) was 139 months (11 years and 7 months; range 15–232 months). Units on y-axis: systolic and diastolic blood pressure, mmHg. Therapy index, pharmacological anti-hypertensive treatment index; eGFR, estimated glomerular filtration rate, mL/min per 1.73m^2.



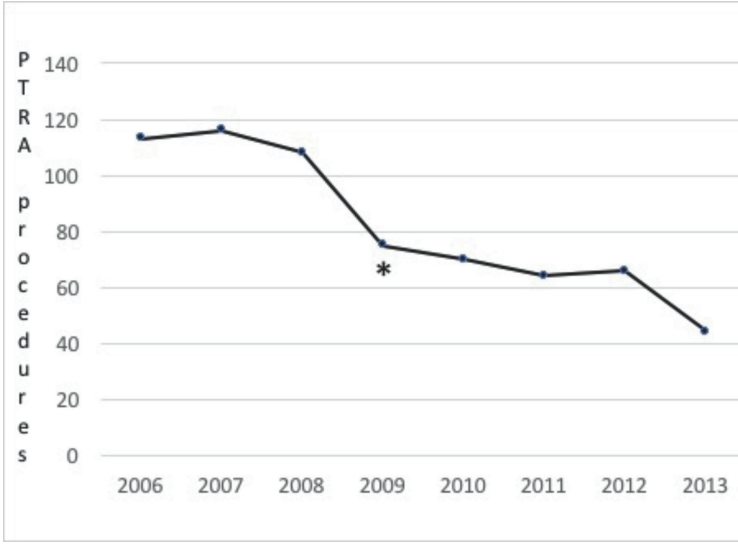
Sixteen of the 21 surviving patients underwent a detailed late out-patient assessment of hypertension, pharmacological treatment, and renal function, while the remaining five were too frail to participate in such assessments due to old age and co-morbidity. Two of these five had dialysis treatment. None of the 16 patients assessed needed dialysis. Seven of the 16 had had a restenosis after one year. Overall, after a median follow-up period of 12 years from the index procedure, hypertension control in the group was stable, although renal function was impaired, with Cr-EDTA clearance reduced by 40% compared to an age-adjusted reference (75).

Study IV

The number of PTRA procedures per year decreased between 2006 and 2013 (Figure 15). During the period 2006–2009, 412 PTRA procedures were done at the participating centres, whereas between 2010 and 2013, the post-ASTRAL study period, 244 procedures were done. Between the first three years of the study period (2006–2008) and the last three years (2011–2013), the number of PTRA procedures was reduced by approximately 50%.

The 244 procedures were done in 224 patients. Twenty patients with two separate interventions were either re-treated due to a restenosis in the same renal artery or they underwent new treatment of symptomatic RAS in the contralateral kidney.

Figure 15. Diagram showing numbers of PTRA procedures performed in the period 2006–2013. The asterisk denotes the time of publication of the ASTRAL trial.



All patients were on anti-hypertensive medication. The most common indication for PTRA was therapy-resistant hypertension, requiring three or more anti-hypertensive drugs (177 patients, 79%), often in combination with declining renal function (103 patients, 46%) or impaired renal function associated with prescription of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) (23 patients, 10.2%). In 26 patients (11%), only one kidney was functioning.

Cardiovascular co-morbidities were common. Two patients (0.9%) had temporary renal replacement therapy at the time of the PTRA. Baseline demographics of the study cohort (2010–2013) are shown in Table 7.

Table 7. Baseline demographics of study cohort (2010–2013)

No. of patients	**224**
Gender, male/female	117/107 (52%/48%)
Age, years	66.6 (41.9–81.4)*
SBP, mmHg	168 (165–172)*
DBP, mmHg	85 (83–86)*
eGFR, mL/min per 1.73m^2	52.5 (49.0–56.0)*
No. of anti-hypertensive drugs	3.5 (3.4–3.7)*
Treatment index	21.8 (20.1–23.4)*
Anti-platelet drug	
- any	119 (53%)
- double	19 (9%)
Lipid-lowering drug	132 (59%)
Smoking habits:	
Current smoker	61 (27%)
Former smoker	73 (33%)
Never smoked	67 (30%)
Missing data	23 (10%)
Type of renal artery stenosis:	
Atherosclerotic lesion	195 (87%)
Fibromuscular dysplasia	21 (9%)
Other stenosis	8 (4%)
Re-intervention**	18 (8%)
Indications (combinations of indications in some patients):	
Hypertension, $\leq$ 2 drugs	48 (21%)
. Hypertension, $\geq$ 3 drugs	177 (79%)
Declining renal function	103 (46%)
Declining renal function related to ACE and ARB***	23 (10%)
Acute renal impairment	11 (5%)
Pulmonary oedema and heart failure	11 (5%)
Single kidney	26 (12%)
Preoperative co-morbidities:	
Essential hypertension	159 (71%)
Ischaemic heart disease	44 (20%)
Endocarditis	3 (1%)
Atrioventricular conduction disorders	20 (9%)
Heart failure	48 (21%)
Cerebrovascular disease	11 (5%)
Peripheral arterial disease	194 (87%)
Renal impairment, acute and chronic	70 (31%)
Diabetes	43 (19%)
Cerebrovascular disease	11 (5%)

SBP, systolic blood pressure; DBP diastolic blood pressure; *Mean (95% CI),
**Patients with restenosis in previously treated artery (before 2010);
***Renal failure correlated to anti-hypertensive therapy with antio-tensin-converting-enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB).

Table 8. Procedure-related data in the 224 patients who were subjected to PTRA

No. of patients	**224**
Preoperative diagnostic imaging	
n = 220	
CTA	46 (21%)
MRA	74 (34%)
duplex ultrasound	39 (18%)
duplex ultrasound + CTA	15 (7%)
duplex ultrasound + MRA	24 (11%)
Angiography	18 (8%)
Other combinations of methods	4 (2%)
Trans-stenotic pressure measurements	
Pre- and post-PTRA	84 (37%)
Only pre-PTRA	56 (25%)
Only post-PTRA	29 (13%)
Not done	55 (25%)
No. of arteries treated	**260**
Bilateral treatment	34
2 arteries treated on one side	2
PTRA with stent	228
PTRA without stent	32
Stent/balloon diameter	
3–3.5 mm	6 (2%)
4 mm	12 (5%)
5 mm	57 (22%)
6 mm	132 (51%)
7 mm	50 (19%)
8 mm	2 (1%)
Technical success	256 (98%)
Complications	
Major	4 (2%)
Minor	24 (11%)

CTA, computed tomography angiography; MRA, magnetic resonance angiography; PTRA, percutaneous transluminal renal angioplasty.

Table 8 shows peri-procedural data. CTA and MRA were the most common preoperative diagnostic modalities. Intravascular pressure measurements were done in 169 of 224 patients (75%), but only in 84 (37%) were the measurements done both before and after dilatation.

In four patients with bilateral RAS, revascularization was possible in only one renal artery. All other revascularizations (256 of 260, 98%) were successful. There were four major complications (1.8%). Cholesterol embolism was suspected in two patients, with rapid renal impairment after the procedure. One patient suffered from thromboembolism to the lower extremities and to a kidney. Puncture site occlusion of an atherosclerotic common femoral artery in one patient was treated with thrombendarterectomy. Minor complications occurred in 24 patients (10.71%). They were mainly small puncture-site haematomas in the groin.

The mean follow-up time was 4.31 years (95% CI 1.43–6.95). Clinical outcome of PTRA is shown in Table 9.

Table 9. Changes in blood pressure, renal function, and anti-hypertensive treatment over time in the 224 patients who were subjected to PTRA

	Systolic blood pressure	Diastolic blood pressure	eGFR	Treatment index	No. of drugs
Pre-PTRA	168 (165–172)	85 (83–86)	52.5 (49.0–56.0)	21.75 (20.13–23.37)	3.54 (3.38–3.70)
Post-PTRA	146** (144–149)	76** (75–78)	54.9** (51.3–58.5)	16.92** (15.59–18.25)	3.05** (2.86–3.24)
1-year follow-up	144** (141–147)	76** (74–77)	54.0 (50.2–57.9)	18.01** (16.51–19.52)	3.32* (3.12–3.53)
Last follow-up	144** (141–147)	76** (75–78)	51.9 (47.6–56.2)	17.83** (16.28–19.39)	3.28* (3.07–3.49)

Numbers are mean (95% CI).
* p-value < 0.05, ** p-value < 0.01 compared to the mean value at the index operation based on linear regression analysis.
Blood pressure is shown in mmHg. eGFR, estimated glomerular filtration rate in mL/min per 1.73m^2.

In summary, both systolic and diastolic blood pressures were significantly reduced compared to pre-PTRA levels, and this reduction was sustained at one year and at the last follow-up. Both the number of anti-hypertensive drugs and the TI were reduced after PTRA, and this reduction was sustained at one year and at the last follow-up. There was a transient increase in eGFR directly after PTRA, but after one

year and at the last follow-up there was no significant difference in eGFR compared to before PTRA.

The two patients with renal replacement therapy at the time of the recanalization could permanently stop dialysis treatment after PTRA.

Thirteen patients (5.8%) reached end-stage kidney disease with the need for dialysis during follow-up.

In subgroup analyses based on indication for the PTRA treatment, there were no significant differences in clinical outcomes between different indications (data not shown).

DISCUSSION

Duplex ultrasound

Duplex ultrasound is a cheap, accessible, and safe method that can be used on most patients with clinical suspicion of RAS. There are two different approaches available: the direct, trans-abdominal method, where flow velocities are measured in the main renal artery and the aorta, and the indirect, trans-lumbar method, where flow velocities are measured in the inter-lobar and arcuate arteries in the kidney. With duplex ultrasound, it is possible to evaluate flow-velocities and the haemodynamic impact of a RAS on the kidney perfusion. Relevant criteria are crucial.

In paper I, we evaluated and compared the velocimetric indices that are used in the indirect method. We could confirm that the early acceleration indices, ACC_{max} and AI_{max}, are reliable for diagnosis of haemodynamically significant RAS, with similar diagnostic accuracy. Both ACC_{max} and AI_{max} were significantly correlated to the degree of stenosis, as measured by the trans-stenotic MAPG. This contrasted with the often-used pulsatility index PI (76), which had no significant correlation to the trans-stenotic MAPG. However, by adding ΔPI, the difference in PI between the two kidneys, to the early acceleration indices ACC_{max} and AI_{max}, the diagnostic accuracy was even higher, but only in patients with unilateral RAS and two functioning kidneys. This has also been reported by other groups (45). We could not confirm previously published studies claiming that the AI_{max} (i.e. ACC_{max} /PSV) is a more reliable index than the ACC_{max} (47), but we shared the findings of the same authors that PI is not useful as a screening test.

In paper II, we re-evaluated direct duplex ultrasound criteria for haemodynamicaly significant RAS and found that RAR $\geq$ 2.6 as a sole criterion is sufficient for detection of significant RAS with an acceptable balance of sensitivity and specificity (sensitivity 89% and specificity 69%). Analysis of the same cohort with the older, established combined criterion of PSV > 180 cm/s and RAR > 3.5 resulted in an overall sensitivity of only 62% and a specificity of 95%. This means a poorer ability to detect patients with

haemodynamically significant RAS. However, optimal criteria for detection of haemodynamically significant RAS, with an effect on the balance between sensitivity and specificity, are debated and they vary between centres. We favour catching more true-positive patients in the ultrasound assessment rather than catching more true-negative patients, since positive ultrasound findings of significant RAS in modern clinical practice are routinely confirmed by either MRA or CTA in patients who are candidates for PTRA. We argue that the inconvenience of a few false-positive patients having unnecessary complementary investigations is justified by the gain in sensitivity. This opinion is shared by other authors (77, 78).

In the literature, various combinations of duplex ultrasound parameters and cut-off values have been reported using either angiographic appearance or intra-arterial PGM as reference. Intra-arterial PGM is the preferred reference method, however, since pressure measurements are more specific in defining a haemodynamically significant RAS than angiographic appearance alone (20, 21).

Tradition and experience of the investigators often dictate the choice of duplex ultrasound method. Success rate varies with experience, which is also demonstrated in studies, where some authors claim the direct method to be superior to the indirect method, and vice versa. Lee et al achieved a 75–80% success rate with the direct method on 1500 patients with hypertension (79), and found more problems with the indirect method. Others had a success rate of 95% with the direct method, however, in a smaller study group including only healthy individuals (80). On the other hand, Johansson et al described 100% success rate with the indirect method (45). Bardelli et al considered the indirect method to be superior and evaluated new velocity indices to improve the reliability with this approach. Some authors claim that visualization of the renal artery is the main problem while others find it difficult to obtain sufficient flow-signals in the inter-lobar arteries of the kidneys.

To summarize, there are technical difficulties and inter-observer variations with both methods (81, 82). Both require a learning curve. There is no evidence in literature proving that one method is easier to perform or learn than the other, and there are no direct comparisons

between them in terms of accuracy or prognostic value. Many authors consider a combination to be optimal, with less inconclusive examinations and possibly improved diagnostic accuracy (50, 79). Utilizing standardized scanning protocols in and between sites within vascular networks would probably minimize inter-observer and inter-site differences and improve reproducibility (81), as well as training. When duplex ultrasound is optimized, regardless of method used, in experienced hands it is a reliable method for detection of haemodynamically significant RAS. We believe it is well motivated to identify patients for further diagnostic work-up including MRA, CTA and possible DSA with confirmatory pressure measurements in patients with proper clinical indications, please see below.

Limitations of papers I and II are their retrospective designs. In paper I this was balanced by the relatively large number of patients. A limitation of paper II is the fact that not all renal arteries could be analyzed by both ultrasound and PGM.

Endovascular treatment

The clinical effects of endovascular treatment of RAS is challenged by the recent large RCTs: first, the ASTRAL trial published in 2009 and later the CORAL trial from 2014 (1, 2). Neither study showed any benefits of PTRA over BMT. However, both trials included only a small proportion of patients treated at the participating centres, most likely those with milder symptoms. During 7 years of recruitment to the ASTRAL trial 65% of centres randomized less than 10 patients, and 42% randomized only between 1 and five patients (62, 63).

The Astral trial enrolled patients with ”uncertain” indications for revascularization (1). The hypertensive patients enrolled were taking an average of 2.8 antihypertensive medications, with blood pressures averaging 150/75 mmHg. The guidelines at the time did not, however, recommend intervention for blood pressure control unless the patient had uncontrolled pressures despite at least three different medications (83, 84). Furthermore, 41% of enrolled patients had a stenosis of <

70%, hence *not* hemodynamically significant according to definition (1).

The CORAL trail primarily included patients with RAS > 60% on angiography, again with a low SBP threshold of > 155 mmHg, and it accepted patients with as little as two anti-hypertensive medications. Despite these liberal inclusion criteria, recruitment was slow and during ongoing trial it was decided that a SBP > 155 mmHg was no longer required. Patients could be enrolled even in the absence of hypertension if they had an eGFR below 60 mL/min (2).

PTRA is still recommended in guidelines (38), for certain patients, and PTRA is an alternative treatment in many centres, though on more restrained indications than earlier. The question remains: do some patients benefit from PTRA, and if so, for what indications?

In paper III, we investigated the long-term outcomes after PTRA in a cohort of 57 patients treated with stent between 1995 and 2003, and controlled with angiography after one year. In paper IV, we investigated the medium-term outcomes in 224 patients treated with contemporary, more conservative indications between 2010 and 2013—the "post-ASTRAL era".

Similar treatment effects were seen in paper III and paper IV, with a decline in blood pressure and medications, and a stabilization of renal function—although the changes were more prominent and statistically significant in the "post-ASTRAL" study, paper IV. This may be due to the stricter indications to treat that followed in the "post-ASTRAL era", possibly leading to a higher likelihood of improvement in treated patients, and to the larger number of patients in this study. As this was a retrospective analysis, there are however limitations that have to be considered. Measurements of blood pressures and collection of blood samples for serum creatinine were not done in a standardized way. But the significant improvement in blood pressure after PTRA, with a mean reduction of SBP of > 20 mmHg ($p < 0.01$), and of DBP of 8 mmHg ($p < 0,01$), persisted over time and suggests a real clinical benefit of PTRA in these patients.

In both studies, cardiovascular co-morbidities were frequent and many of the patients in the long-term follow-up died earlier than expected, mainly from other cardiovascular causes. These patients also required multiple hospital admissions, again mainly due to cardiovascular events. These findings support those of Johansson et al. who reported that mortality in patients with renovascular disease equalled the mortality in patients diagnosed with colon malignancy (85).

There was no difference in short- and long-term outcome between patients with angiographic findings of restenosis after one year and those without. However, it should be noted that any restenosis that occurred after one year was re-treated and that our results thus do not necessarily apply to untreated restenosis.

The restricted indications for PTRA are reflected in the declining numbers of PTRA procedures between 2006 and 2013, a reduction of approximately 50%. In the "post-ASTRAL" evaluation at four university hospitals, we found that endovascular treatment was safe, with a complication rate of only 1.8%. This is similar to some other studies (60) but lower than in the ASTRAL trial, with a complication rate of 4.7%. We believe that this reflects the fact that patient selection and revascularizations were done by highly trained nephrologists and operators, with long experience in treating this group of patients.

Limitations of paper III and IV include the limited numbers of patients, the retrospective designs, and the absence of defined control groups.

In summary, our results indicate that PTRA is a safe treatment in experienced hands and should be considered in patients with therapy resistant hypertension with inadequate blood pressure control, despite optimal pharmacological treatment with three or more anti-hypertensive drugs, and with a haemodynamically significant renal artery stenosis. Normalization of blood pressure in this high-risk population is likely to reduce future cardiovascular complications. In addition, current guidelines recommend PTRA in patients with FMD and hypertension and/or signs of renal impairment, unexplained recurrent congestive heart failure or sudden pulmonary oedema, and RAS secondary to endovascular or open aortic surgery. Whether

PTRA should also be recommended for other patients with declining renal function and RAS remains uncertain. We found no persistent improvement in renal function after PTRA, but there was no significant deterioration either, which is similar to other trials (66). To achieve stabilization of renal function, should also be considered worthwhile.

CONCLUSIONS

The indirect duplex ultrasound indices ACC_{max} and AI_{max} provide equal diagnostic accuracy for detection of haemodynamically significant RAS.

Traditional criteria for haemodynamically significant renal artery stenosis, when assessed with direct duplex ultrasound, can be replaced by the criterion of RAR > 2.6 alone in patients with hypertension and clinical suspicion of RAS.

The long-term prognosis in patients treated with PTRA for atherosclerotic RAS is dismal, with high mortality and morbidity and reduced renal function—despite maintained control of hypertension. Restenosis at one year after PTRA does not appear to affect late outcome.

The frequency of PTRA procedures has decreased.

PTRA with contemporary indications reduces systolic and diastolic blood pressures and the need for anti-hypertensive medications, compared to before the treatment.

FUTURE PERSPECTIVES

The previously published large randomized trials comparing PTRA + BMT with BMT alone, have, despite their limitations, had a substantial impact on the care of patients with hypertension and RAS. Many nephrologists, and other physicians with responsibility for these patients, are unwilling to consider treatment with invasive re-vascularization. Indeed, many now even hesitate to search for RAS in patients with severe hypertension, given the apparent lack of any specific remedy.

In contrast, our results suggest that PTRA may in fact be beneficial in patients with drug therapy-resistant hypertension and haemodynamically significant RAS; the reduction in blood pressure observed is likely to reduce the future risk of cardiovascular complications.

The absence of improvement in renal function after successful PTRA, even in patients in whom reduced renal function has no other obvious cause, is interesting and this is an important target for future research.

For Swedish research in the field of renovascular interventions, creation of a national registry including this patient cohort would be valuable. Such a registry would enhance opportunities for future observational and interventional trials.

Finally, to test whether PTRA has substantial and lasting value for patients with *severe* secondary hypertension and renal impairment due to RAS (patients who were not included in the ASTRAL or CORAL trials), additional prospective RCTs should be conducted.

SAMMANFATTNING PÅ SVENSKA

Förträngning av njurartären (njurartärstenos, renal artery stenosis, RAS) kan orsaka högt blodtryck (hypertoni), njurfunktionsnedsättning och hjärt-kärlsjukdom. Ungefär var femte patient med svårbehandlat högt blodtryck har RAS. Den vanligaste orsaken till uppkomst av RAS är åderförkalkningssjukdom (atheroskleros). Patienter med RAS har en högre sjuklighet och dödlighet än normalt, oftast beroende på hjärt-kärlsjukdom. Behandling av RAS har under de senaste årtiondena utvecklats med förfinade mindre påfrestande operativa ingrepp och bättre medicinsk behandling.
Kateterledd ballongvidgning (perkutan transluminell renal angioplastik, PTRA) var länge förstahandsalternativet vid behandling av RAS, och utfördes ofta på vida indikationer, även på patienter utan kliniska symtom av RAS. Två stora randomiserade studier som utförts på senare tid har inte kunnat påvisa fördelar med PTRA jämfört med läkemedelsbehandling enbart. Studierna har dock en del brister, framför allt avseende patienturvalet. Trots den kraftiga förändring i behandlingsstrategi som dessa studier medförde, så behandlas fortfarande patienter med PTRA, i vissa fall med en tydlig förbättring av njurfunktionen men framför allt med en sänkning av blodtrycket. Utmaningen ligger i att identifiera och utskilja de patienter som kan förbättras av PTRA från dem som klarar sig lika bra med enbart läkemedelsbehandling.

Målet med detta arbete var att värdera och förbättra ultraljudsdiagnostiken av RAS med så höggradig förträngning av njurartären att blodflödet till och i njuren minskar (hemodynamiskt signifikant RAS), att undersöka långtidseffekten efter PTRA för patienter med och utan återförträngning efter ett år, samt att följa effekten av PTRA för patienter som behandlats på senare tid med striktare indikationer.

I arbete I jämförde vi det diagnostiska värdet av att mäta blodflödeshastigheten tidigt i en pulskurva med två olika metoder, maximal systoliskt acceleration (ACC_{max}) och maximalt accelerations index (AI_{max}), för påvisande av hemodynamiskt signifikant RAS vid indirekt dopplerultraljud, d v s vid bedömning av artärflödet inne i njuren. 169 patienter undersöktes. Intra-arteriellt uppmätt

transstenotisk tryckgradient (pressure gradient measurement, PGM) var referensmetod. Vi fann att båda dessa metoder har hög och likvärdig diagnostisk säkerhet.
I arbete II sökte vi i ett material med 58 patienter bästa gränsvärde, kriterium, för att påvisa hemodynamiskt signifikant RAS genom att med direkt dopplerultraljud mäta flödeshastighet i njurartären och i aorta. Med PGM som referensmetod framkom att renal-aortic-ratio (RAR) ≥ 2,6 räckte för detektion av hemodynamiskt signifikant RAS, och var mer fördelaktigt än det etablerade kriteriet med en kombination av peak systolic velocity (PSV) ≥ 180 cm/s och RAR ≥ 3,5.
Arbete III och IV är retrospektiva studier av två kohorter behandlade med PTRA. En långtidsuppföljning av 57 patienter som också undersöktes med angiografi avseende eventuell återförträngning efter ett år. Med en uppföljning på över 10 år framkom att dessa patienter, trots att blodtrycket hålls kontrollerat, har en ökad sjuklighet och dödlighet jämfört med normalbefolkningen, men att diagnostiserad återförträngning efter 1 år inte påverkar långtidsprognosen. Antalet behandlingar med PTRA har minskat tydligt över tid och de 224 patienterna i delarbete IV, som behandlades under åren 2010-2013, var behandlade med mer stringenta behandlingsindikationer. Under uppföljningen på median 4,3 år framkom att dessa patienter hade en omedelbar behandlingsrelaterad sänkning av såväl systoliskt som diastoliskt blodtryck, och en minskning av blodtrycksmedicinering, som var statistiskt signifikant och som bibehölls över tid ($p < 0,01$). Njurfunktionen förbättrades tillfälligt direkt efter PTRA, men återgick snart till samma nivåer som före behandling, men utan försämring under observationstiden

Sammanfattningsvis visar vi att de kriterier som används vid njurartärdiagnostik med Dopplerultraljud har betydelse för påvisande av hemodynamiskt signifikant RAS. Våra fynd antyder också att PTRA har en positiv effekt på blodtryckskontrollen när metoden används med stringenta behandlingsindikationer.

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