Studies on Diagnosis and Treatment of Renal Artery Stenosis

Pieta Krijnen

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Voor Edo

Voor mijn moeder
Ter nagedachtenis aan mijn vader

Contents

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Introduction

Renal artery stenosis, a narrowing of the luminal diameter of the renal artery, has been a subject of clinical research for several decades. Nevertheless, this condition still poses a challenge to the medical profession because the consequences of the presence of stenosis are not straightforward. Renal artery stenosis can occur alone, or in association with hypertension or renal insufficiency or both.[1] Thus, renal artery stenosis is a potential cause of secondary hypertension, and successful treatment of renovascular hypertension can lead to a substantial reduction of cardiovascular morbidity and mortality.[2] However, the coexistence of renal artery stenosis and hypertension is often accidental, which means that an anatomic stenosis is not always the cause of the hypertension.[3] For this reason, relief of the stenosis will not result in a normalization or even improvement of blood pressure levels in many cases. Renal artery stenosis can also lead to a progressive deterioration of the renal function,[4,5] and has been recognized as an increasingly important cause of end-stage renal disease.[6] Progression of renal dysfunction varies among patients with renal artery stenosis, however, and leads to end-stage renal disease in only a minority of cases.[7,8] Because of the complex associations between renal artery stenosis, hypertension and renal failure, the most effective way to diagnose and treat renal artery stenosis is still unclear. At the start of the studies described in this thesis, the clinical management of patients with renal artery stenosis was focused on the treatment of hypertension. Only recently, the focus has shifted towards the preservation of renal function.

Prevalence, etiology and natural history

The prevalence of renal artery stenosis in the general population is unknown. Most studies involve selected populations with risk factors for renal artery stenosis. An early prospective series of hospital autopsies showed a prevalence of 24%, with a marked increase among older patients.[9] Renal artery stenosis was found to be more prevalent in patients with vascular disease such as cardiovascular disease,[10,11] stroke,[12] and peripheral vascular disease.[13,14] Among patients with hypertension, the prevalence of renal artery stenosis depends on the clinical setting. The prevalence is less than 1% in unselected hypertensive patients, about 5% in hospital-based populations, and up to 40% in patients referred to hypertension clinics.[15] Several clinical findings suggestive of renovascular hypertension have been identified, such as cigarette smoking, sudden or recent onset of hypertension, presence of an abdominal bruit, severe retinopathy, vascular disease outside the kidney, drug-resistant hypertension, and increased serum creatinine levels.[3,16-21]

Many studies have described the progressive nature of renal artery stenosis.[4,5,22,23] Progression of stenosis occurred in approximately half of the patients in a period between 3 to 5 years. The incidence of end-stage renal disease has not been clearly established. It was estimated that renal artery stenosis accounted for 14% to 16% of new patients entering dialysis programmes in the US in the mid 1990s,[24] and this proportion is increasing.[6]

The most common cause of renal artery stenosis is atherosclerosis in 75% to 90% of the cases.[1,17] Atherosclerotic renal artery stenosis is typically found in elderly patients, who often have comorbidity.[25,26] The remainder of the cases of renal artery stenosis are mainly caused by fibromuscular dysplasia, a vascular disease affecting small to medium-sized vessels.[27] Fibromuscular dysplasia is the common cause of renal artery stenosis in young to middle-aged patients, and is found predominantly among women.[28]

Diagnosis

In the early 1990s, at the start of the studies described in this thesis, intra-arterial digital subtraction angiography was considered the reference standard in the diagnosis of renal artery stenosis. The advantages of this procedure are that it generally provides clear images of the renal arteries and that it can be combined with a percutaneous intervention if a treatable stenosis is found. The disadvantages of angiography are that it is invasive, expensive, and is associated with a risk of serious complications such as anaphylactic reactions, contrast-induced nephropathy, renal artery dissection and cholesterol embolization.[2,29,30] Furthermore, there is no consensus what degree of stenosis reflects a clinically significant stenosis: levels from 50% to 75% have been used in various studies.[2,31] More importantly, the use of intra-arterial angiography as the reference standard is questionable, because it provides information only on the presence of an anatomic lesion. Thus, one cannot differentiate an incidental lesion from one producing reversible renovascular hypertension or ischemic nephropathy on the basis of angiography.[2]

Because the prevalence of renal artery stenosis among unselected patients with hypertension is low, and because intra-arterial angiography is an invasive and expensive diagnostic test, only hypertensive patients with an increased risk of renal artery stenosis should be selected for intra-arterial angiography.[32] Selection criteria have been suggested on the basis of clinical characteristics, such as a sudden onset of hypertension or malignant hypertension.[20] and hypertension resistant to two-drug treatment.[33] No studies have been performed, however, to quantify the exact increase in the risk of stenosis for any of these clinical characteristics.

Various tests have been proposed for assessing the presence of a functionally significant stenosis, such as the captopril renin challenge test,[34] captopril stimulated renal vein renin sampling,[35] and captopril renography.[36] Of these 'functional' tests, only captopril renography is used as a screening test for renovascular hypertension on a large scale. The usefulness of captopril renography for this purpose is questionable, however, because the diagnostic accuracy of captopril renography varied widely between studies.[37-39] In part, this may be caused by a lack of interobserver agreement in the evaluation of captopril renography, because the interpretation is a complex task.[40,41] The interobserver agreement of captopril renography, however, has not been studied as yet.

Treatment

Several forms of intervention are available to revascularize the renal artery. Initially, surgical revascularization was the only invasive treatment option. This procedure is associated with significant perioperative morbidity and mortality rates especially in elderly patients with comorbid disease.[42-45] Since the introduction of balloon angioplasty for renal artery stenosis[46], this less invasive procedure became the preferred treatment. Balloon angioplasty was shown to be equally effective compared to surgery with respect to blood pressure control and the preservation of renal function.[47,48]

For patients with fibromuscular dysplasia, it has been established that balloon angioplasty is the treatment of choice. In these patients, angioplasty is successful for the treatment of hypertension.[49-53] For patients with atherosclerotic renal artery stenosis, however, the benefit of balloon angioplasty is disappointing with respect to both the technical success rate and blood pressure outcomes after successful procedures.[54] Moreover, restenosis occurs frequently in this type of patients, especially if the stenosis is located in the ostium of the renal artery.[55] Until the start of the studies described in this thesis, the supremacy of angioplasty over medication in the treatment of hypertension in patients with atherosclerotic renal artery stenosis had not been confirmed in randomized controlled trials. Also, the use of stents in renal arteries was in an experimental stage by that time, and results of randomized comparisons between treatment with angioplasty and treatment with additional stent placement were not available.

Research questions addressed in the thesis

The studies described in this thesis started in the early 1990s and addressed questions on both the diagnosis and the treatment of renal artery stenosis.

Research questions concerning diagnosis:

- What is the interobserver agreement of captopril renography for the detection of renal artery stenosis?
- What is the value of clinical characteristics for predicting the probability of renal artery stenosis in patients suspected of renal artery stenosis?

Research questions concerning treatment:

- Are the clinical outcomes for patients with hypertension and atherosclerotic renal artery stenosis after balloon angioplasty better than those after antihypertensive-drug therapy?
- What is the cost-effectiveness of different treatment strategies for patients with hypertension who are suspected of renal artery stenosis?

The DRASTIC study

The studies described in this thesis were based, entirely or in part, on the data of the Dutch Renal Artery Stenosis Intervention Cooperative ('DRASTIC') study.[56] Between January 1993 and November 1998, this prospective randomized trial was conducted in 26 hospitals in the Netherlands. The study aimed to assess the prevalence of renal artery stenosis in patients with well-defined drug-resistant hypertension, and to determine the predictive value of clinical characteristics and diagnostic tests in these pre-selected patients. With regard to treatment, the study aimed to compare the effects of balloon angioplasty and antihypertensive medication on blood pressure in patients with atherosclerotic renal artery stenosis.

In the diagnostic phase of the study (Figure 1.1), 1205 patients aged between 18 and 75 years were included who were referred for analysis of hypertension to one of the participating centers. Only patients with a normal or mildly impaired renal function were included. Patients without a known diagnosis (N=1133) were randomly allocated to one of two standardized antihypertensive drug regimes, if possible. The blood pressure was monitored at 3 consecutive visits. Drug-resistant hypertension was established if the diastolic blood pressure remained 95 mm Hg or more despite standardized medication. Patients with drug-resistant hypertension (N=455) and patients with a rise in serum creatinine concentration after use of an angiotensin-converting-enzyme (ACE) inhibitor (N=43) underwent diagnostic workup. The diagnostic workup involved various laboratory tests, non-invasive tests for renal artery stenosis (the captopril renin challenge test and captopril renography), and intra-arterial angiography (the reference standard). Renal artery stenosis, defined as a narrowing of lumen diameter of 50% or more on angiography, was found in 107 of the 478 patients

who underwent angiography (22%).[57] Atherosclerosis was the underlying cause of stenosis in 81% of the patients with renal artery stenosis.

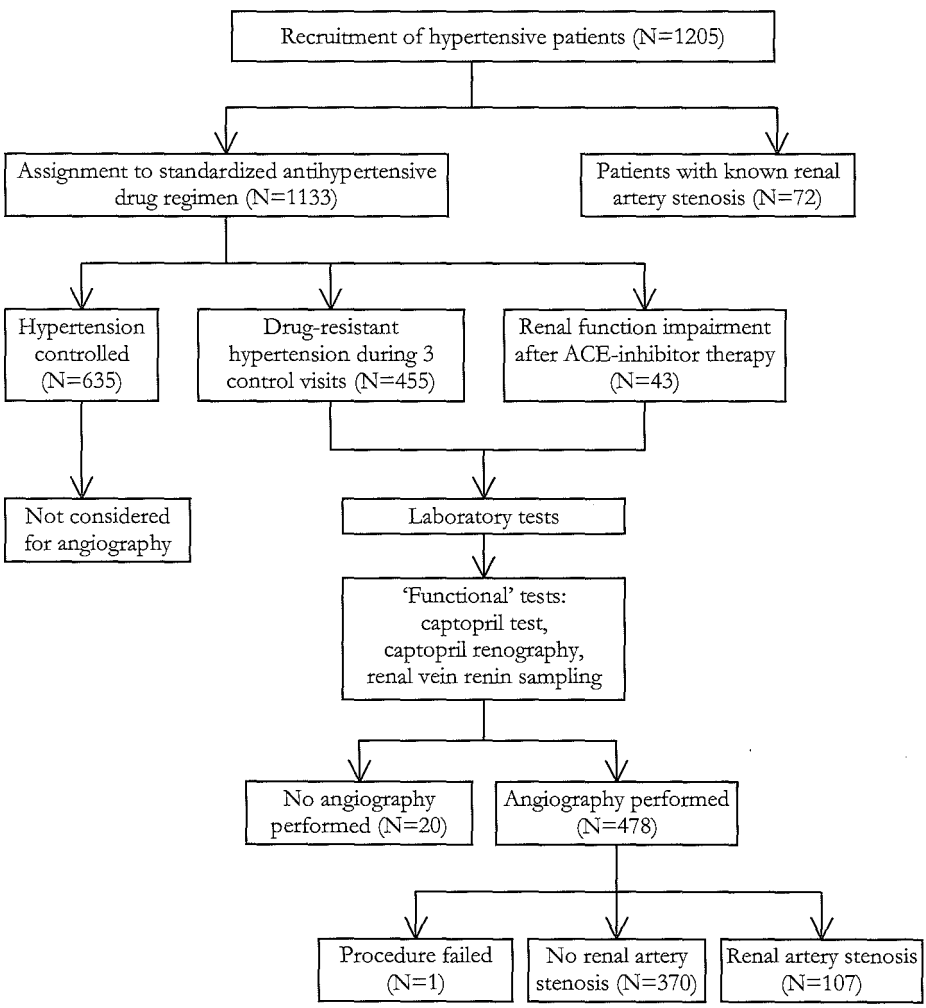

Figure 1.1. Design of the diagnostic phase of the DRASTIC study.

In the therapeutic phase of the study, 106 patients with atherosclerotic renal artery stenosis were randomly allocated to either balloon angioplasty (N=56) or medication (N=50). After 3 months of follow-up, the blood pressure and renal function were evaluated. In accordance with the study protocol, 22 patients randomized to medication (44%) underwent balloon angioplasty after 3 months because of persistent hypertension or deterioration of the renal function. Blood pressure and renal function were evaluated again 12 months after randomization.

Outline of the thesis

The first part of the thesis describes three studies on non-invasive diagnostic tests to select patients suspected of renal artery stenosis for renal intra-arterial angiography. Chapter 2 studies the interobserver agreement of captopril renography as a possible explanation for differences in diagnostic accuracy of this test for finding renal artery stenosis. In Chapter 3, an alternative for the available non-invasive tests is presented. This chapter describes the development of a clinical prediction rule for renal artery stenosis based on readily available clinical characteristics. In Chapter 4, the prediction rule is validated in a sample of new patients in a different setting.

The second part of the thesis describes several studies on the treatment of hypertensive patients diagnosed with atherosclerotic renal artery stenosis. In the Chapters 5 and 6, the clinical outcomes after balloon angioplasty are compared to those after medical treatment followed by angioplasty if needed, for patients with hypertension resistant to a two-drug regimen and atherosclerotic renal artery stenosis. Chapter 5 describes the blood pressure and renal function outcomes of a randomized comparison of the two treatment strategies for the study group as a whole. The purpose of Chapter 6 was to identify subgroups of patients for whom immediate intervention might be indicated. In the Chapters 7 and 8, the quality of life of patients with hypertension is studied. In Chapter 7, a questionnaire for measuring quality of life in patients with hypertension is validated. Chapter 8 studies the effect of treatment on health-related quality of life in patients with hypertension and renal artery stenosis. In Chapter 9, a decision analytical approach is followed to determine the optimal treatment strategy for patients with atherosclerotic renal artery stenosis. In this chapter, the cost-effectiveness of seven treatment strategies for patients with atherosclerotic renal artery stenosis is compared. Data of the DRASTIC study and literature data on long-term consequences renal artery stenosis are combined to estimate the optimal treatment strategy for patients with hypertension who have renal artery stenosis demonstrated on computed tomography angiography or magnetic resonance angiography.

In Chapter 10, the main findings of the preceding chapters are summarized and discussed, and the diagnostic workup and treatment for renal artery stenosis are elaborated on. Finally, conclusions and recommendations are given.

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2

Interobserver agreement on captopril renography for assessing renal vascular disease

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Abstract

Background: Captopril-stimulated renography is widely used to screen selected groups of hypertensive patients for renal vascular disease. Evaluation of the test is a complex task. Lack of interobserver agreement on the assessment and interpretation of renographic parameters may contribute to differences in sensitivity and specificity between studies.

Methods: Three experienced nuclear medicine physicians evaluated 658 renograms of 503 hypertensive patients suspected of having renal vascular disease from a large Dutch multicenter study (the Dutch Renal Artery Stenosis Intervention Cooperative [DRASTIC] study). Interobserver agreement on several renographic parameters was assessed by the κ statistic and the intraclass correlation coefficient (ICC).

Results: The interobserver agreement on the time to excretion was high: The pooled ICC was 0.90. The pooled κ was $\geq$0.65 for the pattern of the time-activity curves, the visual aspect of the renographic images (visible uptake and kidney size), and the judgment on the presence of renal artery stenosis. However, the interobserver agreement on cortical retention and pelvic retention by visual inspection of the images was rather low (pooled κ=0.46 and 0.52, respectively). Pelvic retention was found to complicate the interpretation of renography.

Conclusions: Interobserver agreement on most of the renographic parameters was satisfactory, but the assessment of cortical retention was more difficult, in particular, in the presence of pelvic retention. Captopril renography should be interpreted with caution if pelvic retention is suspected. Interobserver variability offers one of several explanations for the differences in diagnostic test performance that are found between studies.

Introduction

Captopril-stimulated renography is a noninvasive test that is widely used to screen selected groups of hypertensive patients for the presence of renal vascular disease. In patients with renovascular hypertension, captopril induces changes in the renographic images of the kidney distal to the stenosis by revealing decreased uptake or delayed excretion with cortical retention (or both). Accordingly, the time-activity curves may reveal these alterations. Evaluation of renographic images and time-activity curves is encouraged in the investigation of renal vascular disease.[1-3] Patients with such captopril-induced changes on the renogram are generally expected to benefit from intervention with balloon angioplasty or with stent insertion.[4-6]

Interpretation of captopril renography is not a straightforward task. The nuclear medicine physician must assess several renographic parameters and subsequently integrate this information to form a judgment on the presence of renal vascular disease. Efforts have been made to standardize the test.[1,7-9] These guidelines focus mainly on the procedure and not on interpretation of the results. Moreover, diagnostic criteria are not uniform, and different renographic parameters are considered. The diagnostic performance of captopril renography has been variously described with sensitivity ranging between 70% and 100% and specificity ranging between 60% and 100%.[6,10,11] A lack of interobserver agreement on interpretation of the test results may have contributed to these differences. Despite the vast literature on captopril renography for diagnosing renal vascular disease, the interobserver variability has not yet been described.

In this study, 3 experienced nuclear medicine physicians, working in different university hospitals, evaluated 658 renograms of 503 patients suspected of having renal vascular disease. We analyzed the interobserver agreement on the assessment of renographic parameters and the agreement on the judgment on the presence of hemodynamically significant renal artery stenosis.

Patients and methods

Study design

The study was part of the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study. The aim of this multicenter study was to optimize the diagnosis and treatment of renal artery stenosis.[12] The DRASTIC study included 1205 hypertensive patients, 18-75 years old, who had been referred for unsatisfactory control of blood pressure or an adverse drug effect during the course of antihypertensive treatment or for analysis of possible secondary hypertension. Exclusion criteria were suspected secondary hypertension other than renal vascular disease, unstable coronary artery disease, heart failure, renal failure (serum creatinine ≥200 μmol/L [2.26 mg/dL]), and inadequate

contraception. Patients with drug-resistant hypertension (diastolic blood pressure ≥95 mm Hg on 2 drugs during 3 visits) (N=455) or with a rise in serum creatinine concentration after angiotensin-converting enzyme (ACE) inhibitor therapy (N=43) as well as patients in whom renal artery stenosis had been diagnosed before their referral to the participating center (N=72) underwent diagnostic workup for renal artery stenosis. Patients with atherosclerotic renal artery stenosis, defined as ≥50% reduction of lumen diameter according to renal digital subtraction angiography (gold standard test), were randomly assigned to either the balloon angioplasty (N=56) or the medical treatment (N=50) group. Captopril renography was performed and evaluated by the local nuclear medicine physicians in 22 participating hospitals. In the diagnostic workup, the sensitivity and specificity for finding stenosis according to the local nuclear medicine physician were 72% and 90%, respectively.[11] Furthermore, renography was performed to evaluate treatment after 3 and 12 months of follow-up.

Renographic protocol

The protocol for conducting the renographic procedures reflected the guidelines of the consensus report on ACE inhibitor renography.[7] In patients who were receiving long-term ACE inhibitor treatment, the ACE inhibitor was withheld for at least 24 hours before renography was performed. According to the protocol, an oral dose of 50 mg captopril was given 1 hour before the examination in 95% of the procedures to induce asymmetry in uptake and intrarenal transit between the kidneys in case of renal vascular disease. In the remaining 5% of the procedures, the physician reduced the dose of captopril to 25 mg to prevent hypotension. To ensure adequate absorption of captopril, patients were required to fast during the 4 hours preceding renography. Sufficient hydration was guaranteed by oral administration of 0.5 L of tap water. Blood pressure was measured with an automatic device before administration of captopril and every 5-10 minutes for 2 hours after administration of captopril. Renography was performed with the patient in supine position, and the detector placed posteriorly. After intravenous administration of 75-100 MBq ^{99m}Tc-mercapto-acetyltriglycine, data were collected in 10-second frames during a 20-minute period, and sequential analog images obtained every minute. The time-activity curves were generated using regions of interest over the whole kidney.[1]

Study

In this study on interobserver agreement, 658 renograms of 503 patients with 2 native kidneys were reevaluated by 3 experienced nuclear medicine physicians (referred to as physicians A, B, and C) who were working in different university

hospitals at the time. Of these renograms, 487 were obtained during the diagnostic workup of patients with and without renal artery stenosis. The remaining renograms were obtained during follow-up of patients with stenosis: 82 renograms after 3 months of follow-up and 89 renograms after 12 months of follow-up.

Renographic evaluation

The renograms were evaluated independently, and the physicians were unaware of patient characteristics and hospital source. The 3 physicians had no additional clinical information, such as the blood pressure response to captopril and the diuresis during the procedure. Before evaluation, the physicians discussed which renographic parameters of the renographic images and time-activity curves would be assessed and how these features would be scored.

The following parameters were scored from the renographic images by each individual observer, separately for the left and right kidneys: visible uptake (scored as present or absent); time to excretion (scored as number of minutes until radioactivity appeared in the renal pelvis, determined by visual evaluation of the 1-minute sequential images, if available; if the excretory phase started only after 20 minutes, no excretory phase was registered); and kidney size (scored as normal or small). Cortical retention and pelvic retention (scored as present or absent) were determined by visual inspection. The presence of pelvic retention was assessed because this was considered to complicate the renographic evaluation of the images and the time-activity curves of the whole kidneys.[1,13] The pattern of the time-activity curves was scored in 6 ordered categories as proposed by Fommei et al.[10] (0=normal, 1=minor abnormalities, 2=marked delayed excretion rate with preserved washout phase, 3=delayed excretion rate without washout phase [accumulation curve], 4=renal failure pattern with measurable kidney uptake, and 5=renal failure pattern without measurable kidney uptake [blood background-type curve]). Interobserver agreement was not applicable for the time to peak activity (T_{max}) and the relative (individual kidney) uptake because these diagnostic criteria were calculated by the computer.

Finally, the judgment on the presence or absence of renal artery stenosis was assessed for each kidney. No specific diagnostic criteria were defined to reflect the clinical practice. The judgment on the presence of stenosis was scored as 1 of 5 ordered categories (1=certainly stenosis, 2=probably stenosis, 3=indeterminate, 4=probably no stenosis, and 5=certainly no stenosis; in the case of a blood background-type curve, the diagnosis was scored as indeterminate).

Interobserver agreement

We used the κ statistic to assess interobserver agreement on the renographic parameters that were measured on a nominal scale. κ reflects the proportion of the maximally achievable agreement that is realized on top of the agreement that is expected by chance.[14-16] κ values usually range from 0 (indicating chance agreement only) to 1 (indicating perfect agreement). The only meaningful interpretation of negative values of κ is that the level of agreement is what would be expected by chance alone.[17] In general, κ values of <0.40 are considered as low and values of >0.80 are considered as high.[15,16,18] Because the value of κ decreases if the number of ordinal categories is increased, we calculated weighted κ values for the pattern of the time-activity curves and the judgment on the presence of stenosis to adjust for the seriousness of different levels of disagreement.[19-21] Linear weights were used: $w(ij) = 1 - |i - j| / (c - 1)$, where i and j are the sequence numbers of the categories, and c is the number of categories. Interpretation of weighted κ is like that of unweighted κ.[15]

The interobserver agreement on the time to excretion, which was measured on an interval scale, was expressed as the intraclass correlation coefficient (ICC). The ICC takes into account systematic differences between observers and ranges from –1 (perfect disagreement) to 1 (perfect agreement), with 0 indicating only random concordance.[22,23] Although there are no universal standards, values of ICC of <0.40 are considered as low and values of >0.75 are considered as high.[24]

Interobserver agreement on renographic parameters was calculated by kidney and on the judgment on the presence of stenosis by kidney as well as by patient. Interobserver agreement was assessed for each pair of observers. A pooled estimate was also calculated on the basis on the mean observed agreement and the mean amount of agreement expected under the null model of independence. A 95% confidence interval (CI) was calculated for each estimate. Estimates of the ICC were calculated with SPSS software (release 9.0.0; SPSS, Chicago, IL) and estimates of κ were calculated with AGREE Statistical Software (version 7.001; ProGAMMA, Groningen, The Netherlands).

Finally, the probability that a physician judged stenosis to be absent given the fact that another did so, corrected for chance agreement, was calculated using the average conditional probability of the absence of stenosis and the average expected probability of stenosis. Similar probabilities were calculated for the judgment on the presence of unilateral stenosis and for the judgment on the presence of bilateral stenosis. These probabilities can be interpreted as a κ-per-outcome category.

Results

Patients

All patients whose renograms were evaluated had drug-resistant hypertension. Their diastolic blood pressure was 105 ± 9 mm Hg (mean ± SD), despite the use of 2 ± 1 antihypertensive drugs. At study entry, the renal function was normal or mildly impaired: The patients had a serum creatinine concentration of 95 ± 27 μmol/L and their creatinine clearance was 85 ± 33 mL/min (Table 2.1). In 5 patients the serum creatinine concentration had increased to >150 μmol/L during follow-up.

Renographic images

The 3 nuclear medicine physicians did not note any uptake on the renographic images of 1%-3% of the kidneys (Table 2.2). Physician C reported the absence of uptake twice as often as physicians A and B. The pooled κ-value for visual uptake was 0.65 (95% CI, 0.51-0.80). A small kidney size was scored more frequently by physician A than by the other physicians (25% vs. 18% and 17%). The pooled κ was 0.70 (95% CI, 0.66-0.74). Because 1-minute images were not obtained routinely in every hospital, the beginning of the excretory phase was assessed for approximately half of the renograms. The beginning of the excretory phase was estimated to start, on average, after 4.29-4.43 minutes. The pooled ICC was 0.90 (95% CI, 0.89-0.91). Cortical retention was reported in 2-3 times as many kidneys by physician A than by the other physicians. The pooled κ was 0.46 (95% CI, 0.42-0.51). Pelvic retention was reported least by physician B (12% vs. 21% and 18%). The pooled κ for pelvic retention was 0.52 (95% CI, 0.47-0.56).

Table 2.1. Characteristics at entry of 503 patients evaluated for renal artery stenosis.

Characteristic	Percentage of patients or mean ± SD
Age, years	52 ± 13
Male	57
Systolic blood pressure, mm Hg	171 ± 23
Diastolic blood pressure, mm Hg	105 ± 9
No. of antihypertensive drugs	2 ± 1
Serum creatinine, μmol/L	95 ± 27
Creatinine clearance, mL/min	85 ± 33
Referred by general practitioner	51
Stenosis ≥50% on angiography	30

Table 2.2. Interobserver agreement on renographic parameters.

Renographic parameter (no. of kidneys studied)	Physician	No. (%) with feature or mean ± SD	Physicians	Agreement *
Renographic images				
No visible uptake	A	14 (1.1)	A and B	0.81 (0.66-0.96)
(N=1306)	B	18 (1.4)	B and C	0.59 (0.43-0.76)
	C	32 (2.5)	A and C	0.60 (0.44-0.77)
			Pooled	**0.65 (0.51-0.80)**
Small kidney	A	323 (25)	A and B	0.69 (0.64-0.74)
(N=1271)	B	229 (18)	B and C	0.79 (0.74-0.83)
	C	210 (17)	A and C	0.64 (0.59-0.69)
			Pooled	**0.70 (0.66-0.74)**
Time to excretion (min)	A	4.29 ± 1.47	A and B	0.88 (0.86-0.90)
(N=708)	B	4.34 ± 1.65	B and C	0.95 (0.94-0.96)
	C	4.43 ± 1.67	A and C	0.88 (0.86-0.89)
			Pooled	**0.90 (0.89-0.91)**
Cortical retention	A	350 (28)	A and B	0.37 (0.31-0.42)
(N=1238)	B	119 (10)	B and C	0.63 (0.56-0.70)
	C	165 (13)	A and C	0.46 (0.41-0.52)
			Pooled	**0.46 (0.42-0.51)**
Pelvic retention	A	257 (21)	A and B	0.48 (0.41-0.54)
(N=1256)	B	147 (12)	B and C	0.46 (0.40-0.53)
	C	231 (18)	A and C	0.59 (0.54-0.65)
			Pooled	**0.52 (0.47-0.56)**
Time-activity curves				
Pattern of the curve	A	*(See Figure 2.1)*	A and B	0.74 (0.70-0.77)
(N=1274)	B		B and C	0.60 (0.57-0.64)
	C		A and C	0.63 (0.60-0.67)
			Pooled	**0.65 (0.62-0.68)**
Conclusion on presence of stenosis				
On the original	A	*(See Figure 2.2)*	A and B	0.05 (0.01-0.09)
5-point scale †	B		B and C	0.14 (0.10-0.17)
(N=1316)	C		A and C	0.32 (0.27-0.37)
			Pooled	**0.16 (0.13-0.18)**
Collapsed into	A	293 (22)	A and B	0.62 (0.57-0.68)
a 2-point scale ‡	B	184 (14)	B and C	0.66 (0.60-0.71)
(N=1316)	C	256 (20)	A and C	0.69 (0.64-0.74)
			Pooled	**0.66 (0.62-0.70)**

* κ with 95% CI, except for time to excretion, where ICC with 95% CI is shown.

† 1=certainly stenosis, 2=probably stenosis, 3=indeterminate, 4=probably no stenosis, 5=certainly no stenosis.

‡ Indication for stenosis=certainly or probably stenosis or indeterminate, no indication for stenosis=certainly or probably no stenosis.

Physician A

Physician B

Pattern *	0	1	2	3	4	5	Total
0	**735**	141	1		2		879
1	14	**156**	45		4		219
2	4	24	**60**	5	3		96
3			12	**42**			54
4	3	4	3	3	**4**	4	21
5					2	**3**	5
Total	756	325	121	50	15	7	1274

Physician B

Physician C

Pattern *	0	1	2	3	4	5	Total
0	**508**	7					515
1	351	**116**	3		1		471
2	14	91	**69**	3	4		181
3		1	20	**51**	1		73
4	6	4	4		**12**		26
5					3	**5**	8
Total	879	219	96	54	21	5	1274

Physician A

Physician C

Pattern *	0	1	2	3	4	5	Total
0	**496**	19					515
1	250	**205**	16				471
2	8	93	**72**	4	4		181
3			28	**42**	3		73
4	2	8	5	2	**6**	3	26
5				2	2	**4**	8
Total	756	325	121	50	15	7	1274

* 0=normal, 1=minor abnormalities, 2=marked delayed excretion rate with preserved washout phase, 3=delayed excretion rate without washout phase (accumulation curve), 4=renal failure pattern with measurable kidney uptake, 5=renal failure pattern without measurable kidney uptake (blood background-type curve)

Figure 2.1. Interobserver agreement on pattern of time-activity curves for 1274 kidneys according to 3 nuclear medicine physicians.

Time-activity curves

Systematic differences occurred between observers in assigning a pattern to the time-activity curves (Table 2.2; Figure 2.1). Physician C reported more abnormal time-activity curves than physicians A and B. Furthermore, physician A reported more abnormal curves than physician B. The pooled value for the weighted κ was 0.65 (95% CI, 0.62-0.68).

Physician A

Physician B

Conclusion *	1	2	3	4	5	Total
1	**13**	40	5			58
2	2	**22**	14	6	1	45
3	7	31	**30**	11	2	81
4	1	47	47	**264**	1	360
5		5	29	664	**74**	772
Total	23	145	125	945	78	1316

Physician B

Physician C

Conclusion *	1	2	3	4	5	Total
1	**1**		1			2
2	35	**11**	25	16		87
3	21	23	**40**	67	16	167
4	1	10	13	**262**	543	829
5		1	2	15	**213**	231
Total	58	45	81	360	772	1316

Physician A

Physician C

Conclusion *	1	2	3	4	5	Total
1	**2**					2
2	16	**65**	4	2		87
3	4	54	**62**	44	3	167
4	1	24	55	**707**	42	829
5		2	4	192	**33**	231
Total	23	145	125	945	78	1316

* 1=certainly stenosis, 2=probably stenosis, 3=indeterminate, 4=probably no stenosis, 5=certainly no stenosis

Figure 2.2. Interobserver agreement on judgment on presence of renal artery stenosis for 1316 kidneys according to 3 nuclear medicine physicians.

Judgment on presence of stenosis by kidney

The pooled value of the weighted κ for the judgment on the presence of stenosis for separate kidneys, as measured on a 5-point scale, was 0.16 (95% CI, 0.13-0.18) (Table 2.2). Physician B was more outspoken in assigning scores than physicians A and C: Physician B was certain of the presence of stenosis in 4% of the kidneys compared with 2% and <1% (physicians A and C, respectively) and was certain of the absence of stenosis in 59% of the kidneys compared to 6% and 18% (physicians A and C, respectively) (Figure 2.2). When the judgment on the presence of stenosis was dichotomized into certainly or probably stenosis or indeterminate versus certainly or probably no stenosis, an indication for stenosis was found in 14%-22% of the kidneys. The pooled κ for the dichotomized judgment was better than that on the 5-point scale: 0.66 (95% CI, 0.62-0.70) versus 0.16 (95% CI, 0.13-0.18).

κ was calculated separately for those kidneys on which all 3 physicians agreed that pelvic retention had or had not occurred. For kidneys showing pelvic retention (N=90), κ for the dichotomized judgment on the presence of stenosis was significantly lower than that for kidneys without pelvic retention (N=909): κ ranged between –0.07 and 0.12 for kidneys with pelvic retention (pooled estimate, 0.06; 95% CI, -0.04 to 0.15) and between 0.69 and 0.77 for kidneys without pelvic retention (pooled estimate, 0.73; 95% CI, 0.68-0.78).

Judgment on presence of stenosis by patient

The 3 physicians found an indication for stenosis (certainly or probably stenosis or indeterminate) in 20-28% of the renograms. The pooled κ was 0.70 (95% CI, 0.64-0.76). Furthermore, we studied the agreement on whether there was no indication for stenosis or was an indication for unilateral stenosis or an indication for bilateral stenosis (Figure 2.3). An indication for bilateral stenosis was judged variously: Physician B suspected bilateral stenosis in 4% of the patients, whereas physicians A and C suspected bilateral stenosis to be present more frequently (in 12% and 11%, respectively). When 1 of the 3 physicians judged that stenosis was absent, the probability that a second physician concluded the same was, on average, 0.70 (95% CI, 0.61-0.79). When 1 of the 3 physicians judged that unilateral stenosis was present, the probability that a second physician reached the same conclusion was, on average, 0.65 (95% CI, 0.61-0.70). For the presence of bilateral stenosis, this probability was, on average, 0.48 (95% CI, 0.43-0.52).

Physician A

Physician B

Conclusion	No RAS	URAS	BIRAS	Total
No RAS	**387**	26	27	440
URAS	5	**62**	21	88
BIRAS	4	1	**18**	23
Total	396	89	66	551

Physician B

Physician C

Conclusion	No RAS	URAS	BIRAS	Total
No RAS	**401**	13	4	418
URAS	14	**61**		75
BIRAS	25	14	**19**	58
Total	440	88	23	551

Physician A

Physician C

Conclusion	No RAS	URAS	BIRAS	Total
No RAS	**375**	28	15	418
URAS	9	**55**	11	75
BIRAS	12	6	**40**	58
Total	396	89	66	551

Figure 2.3. Interobserver agreement on absence of renal artery stenosis (No RAS) or presence of unilateral (URAS) or bilateral (BIRAS) stenosis according to 3 nuclear medicine physicians on basis of conclusion per kidney.

Discussion

In this study, the interobserver agreement on captopril renography was studied in 658 renograms of patients with drug-resistant hypertension and a normal or mildly impaired renal function. Three experienced nuclear medicine physicians assessed renographic parameters that have been recommended for evaluation[1,2,7] and judged whether hemodynamically significant renal artery stenosis was present or absent. For most of these parameters and for the judgment on presence of stenosis, the interobserver agreement was satisfactory. The agreement on cortical retention was relatively low, however.

Except for the time to excretion, the interobserver agreement was assessed by the κ statistic. Although κ is most commonly used to measure interobserver agreement in categorical data, one has to bear in mind, however, that the interpretation of κ is complicated by some of its properties.[16,17,25] First, the value of κ strongly depends on the underlying prevalence of the parameter under study. For instance, a high value of κ for agreement on the absence of visible uptake is harder to achieve than for agreement on small kidney size because the latter is much more common. Second, although κ does not identify systematic differences between observers (bias), κ will be lower if such bias is present. This is also the case for the ICC, which was used to assess interobserver agreement in continuous data. Therefore, it should be noted that systematic differences between the observers in the assessment of several parameters were found – for instance, for the judgment on the presence of stenosis (Figure 2.2). Third, the way one values discrepancies between categories and consequently chooses the weights for the calculation of weighted κ is arbitrary. For instance, by choosing linear weights in the calculation of κ for the time-activity curves, we assumed that disagreement between normal curves and curves with minor abnormalities (curve types 0 and 1) is as serious as disagreement between renal failure patterns with and without measurable kidney uptake (curve types 4 and 5).

The pattern of the time-activity curves, which is considered to be an important diagnostic parameter,[2,13] was scored in 6 ordered categories.[10] The weighted κ value for the pattern of the time-activity curves was moderately high, especially when one considers that the distinction between some of these types of curves is difficult to make. The interobserver agreement on visible uptake and on kidney size was also satisfactory but could have been affected negatively by the low prevalence of these features.[17,25] The interobserver agreement on time to excretion as assessed from the renographic images was high. Yet, the relative (individual kidney) uptake and the T_{max} are the most reliable parameters in terms of interobserver agreement because the computer calculates them.

With ^{99m}Tc-mercaptoacetyltriglycine, which is almost completely cleared by tubular secretion, renovascular hypertension can usually be detected by cortical retention after ACE inhibition.[7] Delayed excretion can also be caused by pelvic stasis, however. In kidneys without a dilated renal pelvis, pelvic retention will be observed because of low diuresis. The patients in this study drank 0.5 L of tap water 30-60 minutes before the renography. Perhaps a more abundant diuresis could be achieved by giving 10 mL/kg of body weight. Another cause of low diuresis is the fact that some of the patients were on diuretics. These patients may produce less urine during the renography.[9] The identification of cortical retention is difficult in the presence of pelvic retention.[1,13] The complicating role of pelvic

retention in the evaluation of captopril renography was evident in our study. For cortical and pelvic retention, the interobserver agreement on the assessment of the presence or absence of these phenomena was not satisfactory. Probably, this can be improved by the assessment of the time-activity curves of the renal cortex.

Which renographic parameters should be used then as diagnostic criteria in the evaluation of renal vascular disease? The diagnostic performance and the interobserver variability should be included in this consideration. When ranked according to the sum of sensitivity and specificity in a by-patient analysis, the order of the renographic parameters was virtually the same for the 3 nuclear medicine physicians (data not shown). However, one must bear in mind that by this way of ranking the sensitivity and the specificity are valued equally. The parameter with the best diagnostic performance was asymmetry in renal uptake. The fact that the individual kidney uptake is measured objectively adds to its usefulness as a diagnostic criterion. Time to excretion as assessed from the renographic images, an abnormal pattern of the time-activity curves, and cortical retention ranked somewhat lower in terms of diagnostic performance. On the basis of the interobserver variability of these parameters, the first 2 are also important diagnostic criteria but the last should be given less weight. The lowest diagnostic performance was found for the visual assessment of the kidneys on the renographic images (i.e., no visible uptake or asymmetry in kidney size) and T_{max}. Diagnostic information is lost if one focuses on just 1 or 2 parameters when evaluating the test results. To maximize the diagnostic value of the test, all parameters might be brought together in multivariate models, one predicting the outcome of angiography and one predicting the response to treatment as primary outcome measures for the value of renography. These models may be used then to support decision-making by nuclear medicine physicians.

The 3 evaluating physicians judged the presence of stenosis on a 5-point scale, which was collapsed into suspect or indeterminate versus not suspect to reflect which patients would normally be referred to further diagnostic workup. The interobserver agreement on the presence of stenosis was moderate. When 1 physician judged stenosis to be absent, the probability that a second physician concluded the opposite was 30%. It would seem that the interobserver agreement found in this study represents the maximum achievable because the evaluating physicians in this study were well trained and experienced and had deliberated their way of scoring beforehand. On the other hand, the renograms were not always obtained according to the protocol (1-minute images were not always acquired) and were not self-managed by the evaluating physicians. Also, to reflect the common clinical practice, diagnostic criteria for identifying stenosis were not specified before evaluation. Thus, the interobserver agreement found in this study

could possibly be improved by performing the procedure and evaluation in a uniform manner.

Conclusion

The interobserver agreement on most renographic parameters was satisfactory. Important parameters for establishing the diagnosis of stenosis with high interobserver agreement were the relative (individual kidney) uptake, the pattern of the time-activity curves, and the time to excretion. The assessment of cortical retention by visual inspection of the images was more difficult – in particular, in the presence of pelvic retention – and should be given less weight in the evaluation. Captopril renography should be interpreted with caution if pelvic retention is present. Besides differences in patient selection, study design, and diagnostic criteria, interobserver variability offers an explanation for differences in diagnostic performance of captopril renography between studies.

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3

A clinical prediction rule for renal artery stenosis

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Abstract

Background: Renal artery stenosis is a rare cause of hypertension. The gold standard for diagnosing renal artery stenosis, renal angiography, is invasive and costly.

Objective: To develop a prediction rule for renal artery stenosis from clinical characteristics that can be used to select patients for renal angiography.

Design: Logistic regression analysis of data from a prospective cohort of patients suspected of having renal artery stenosis. A prediction rule was derived from the regression model for use in clinical practice.

Setting: 26 hypertension clinics in the Netherlands.

Patients: 477 hypertensive patients who underwent renal angiography because they had drug-resistant hypertension or an increase in serum creatinine concentration during therapy with angiotensin-converting enzyme inhibitors.

Results: Age, sex, atherosclerotic vascular disease, recent onset of hypertension, smoking history, body mass index, presence of an abdominal bruit, serum creatinine concentration, and serum cholesterol level were selected as predictors. The regression model was reliable (goodness-of-fit test, P=0.81) and discriminated well between patients with stenosis and those with essential hypertension (area under the receiver-operating characteristic curve, 0.84). The diagnostic accuracy of the regression model was similar to that of captopril renography, which had a sensitivity of 72% and a specificity of 90%.

Conclusions: In the diagnostic workup of patients suspected of having renal artery stenosis, the clinical prediction rule can be considered as an alternative to renography. It can help to select patients for renal angiography in an efficient manner by reducing the number of angiographic procedures without the risk for missing many renal artery stenoses.

Introduction

Renal artery stenosis impairs blood flow to the kidney and can consequently cause renovascular hypertension and renal failure.[1,2] Although the prevalence of this condition among patients with hypertension is low, therapeutic options for relieving renal artery stenosis, such as renal angioplasty and stenting, make the search for renal artery stenosis worthwhile.[2-4] Renal angiography is the gold standard for diagnosing renal artery stenosis, but it is a costly and invasive procedure that can involve serious complications.[5,6]

To diagnose renal artery stenosis efficiently, angiography should be used selectively. Most physicians rely on captopril renography as a selection criterion, but the diagnostic accuracy of this test is low (sensitivity, 65% to 77%; specificity, 90%).[7,8] As an alternative, clinical characteristics can be used to select hypertensive patients for angiography.[9] Patients with normal renal function whose blood pressure can be controlled with one or two drugs can be excluded from angiography.[9,10] In the remaining patients (those with drug-resistant hypertension), such clinical characteristics as atherosclerotic vascular disease, smoking history, and presence of an abdominal bruit can be used to estimate a patient's probability of renal artery stenosis.[11-14] This estimate can then be used in selection for angiography.

We analyzed the clinical characteristics of 477 patients with drug-resistant hypertension or an increase in serum creatinine concentration during therapy with angiotensin-converting enzyme (ACE) inhibitors who participated in the Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) study.[9] We developed a clinical prediction rule for quantifying the probability of renal artery stenosis[15] and demonstrated the potential consequences of this rule for clinical practice by applying it to our patients.

Patients and methods

Patients

The DRASTIC study is a prospective cohort study conducted at 26 departments of internal medicine with an interest in hypertension throughout the Netherlands.[9] The diagnostic phase of the study was designed to find an optimal strategy for diagnosing renal artery stenosis. In the DRASTIC study, 1133 hypertensive patients 18 to 75 years of age with preserved renal function (serum creatinine concentration ≤200 μmol/L [2.26 mg/dL]) were enrolled. These patients were referred for analysis of hypertension by general practitioners (55%) or hospital specialists (45%), in most cases because their hypertension was difficult to treat with antihypertensive drugs. Sixty percent of patients were from four hospitals. After giving written informed consent, patients were randomly

assigned to one of two standard protocols with antihypertensive drugs: amlodipine, 10 mg, plus atenolol, 50 mg, in patients older than 40 years of age or enalapril, 20 mg, plus hydrochlorothiazide, 25 mg, in patients older than 40 years of age. Blood pressure was measured with a standard sphygmomanometer at three consecutive visits at least 1 week apart. Measurements were taken three times per visit after a 5-minute rest with the patient in the sitting position. Patients were selected for diagnostic workup if they had drug-resistant hypertension, defined as a mean diastolic blood pressure per visit of 95 mm Hg or more while receiving the standard drug regimen during all three visits or prescription of an additional drug regardless of blood pressure response. Patients were also selected if the serum creatinine concentration increased 20 μmol/L (0.23 mg/dL) or more during therapy with ACE inhibitors. In these patients, intra-arterial digital subtraction angiography and other, non-invasive tests were performed. In accordance with the study protocol, patients who responded well to standard treatment were not evaluated further. The diagnostic phase of the study was followed by a therapeutic phase in which patients with atherosclerotic stenosis were randomly assigned to receive medication or renal angioplasty.

Definitions

After performing a literature study, we selected 12 clinical characteristics indicative of renovascular disease (predictors)[10,11,16-26]: age, sex, ethnicity (black or other), signs and symptoms of atherosclerotic vascular disease (femoral or carotid bruit, angina pectoris, claudication, myocardial infarction, cerebrovascular accident, or vascular surgery), recent onset of hypertension (within the past 2 years), family history of hypertension (parents, siblings, or children with hypertension), smoking history (ever or never), obesity (body mass index ≥25 kg/m^2), abdominal bruit, advanced hypertensive retinopathy (fundus grade III or IV), serum creatinine concentration, and hypercholesterolemia (serum cholesterol level >6.5 mmol/L [251.35 mg/dL]) or use of cholesterol-lowering agents). These characteristics were used to predict the presence of renal artery stenosis. A patient was considered to have renal artery stenosis when the angiogram showed at least one stenosis of 50% or more in a renal artery according to the local radiologist.

Model development

Data are presented as a proportion or as the mean ± SD. The univariable association between clinical characteristics and presence of renal artery stenosis was studied by computing the value and 95% confidence interval (CI) of the odds ratio. In a multivariable analysis, clinical characteristics were combined as

predictor variables in a logistic regression model predicting the presence of renal artery stenosis (outcome).[27] For each patient in the multivariable analysis, the probability of renal artery stenosis was calculated from the regression model (predicted probability). The reliability, discriminative ability, and validity of the model were assessed. The technical appendix gives details on model development and evaluation.

To enable the use of the regression model in clinical practice, a prediction rule was constructed for predicting renal artery stenosis in future patients with drug-resistant hypertension or an increase in serum creatinine concentration during therapy with ACE inhibitors. For the presence or level of each clinical characteristic in the regression model, a score was calculated on the basis of the regression coefficients (see technical appendix). These scores were added into a sum score. All possible sum scores and their corresponding predicted probabilities of renal artery stenosis were combined in a graph with 95% CIs of the predicted probabilities.

Results

Statistical analyses

Angiography was performed in 439 patients with drug-resistant hypertension and 39 patients with an increase in serum creatinine concentration during therapy with ACE inhibitors. The procedure failed in 1 patient. For the remaining 477 patients, angiography showed renal artery stenosis in 107 patients (22%), of whom 90 (84%) had atherosclerotic stenosis and 17 (16%) had fibromuscular dysplasia. Bilateral stenoses were found in 27 of 107 affected patients (25%). Captopril renography was performed in 458 patients; it had a sensitivity of 72% and a specificity of 90% for the diagnosis of renal artery stenosis.

Table 3.1 shows the univariable distribution of the clinical characteristics for patients with renal artery stenosis and those with essential hypertension. Most clinical characteristics were indicative of renal artery stenosis ($P<0.05$ or borderline significant) except sex, recent onset of hypertension, and presence of advanced hypertensive retinopathy. More young women without signs of atherosclerotic disease were found among patients with fibromuscular dysplasia than among those with atherosclerotic stenosis, but abdominal bruits occurred with the same frequency in both groups (29% and 27%, respectively).

The results of multivariable analysis are also shown in Table 3.1. Advanced hypertensive retinopathy was not studied any further because this clinical characteristic was missing for 43% of the patients. Data on 11 clinical characteristics of 460 patients were considered predictive of renal artery stenosis. Ethnicity and family history of hypertension were removed from the regression

Table 3.1. Associations of clinical characteristics with renal artery stenosis.

Clinical characteristic	Patients with renal artery stenosis (N=107)	Patients with essential hypertension (N=370)	Univariable odds ratio (95% CI) *	Multivariable odds ratio (95% CI) †
	Proportion or mean ± SD			
Age, years	57 ± 12	50 ± 12	1.6 ‡ (1.3 – 2.0)	1.8 ‡§ (1.3 – 2.6)
Men	51	58	0.8 (0.5 – 1.2)	0.4 (0.2 – 0.7)
Black ethnicity	1	7	0.1 (0.0 – 0.9)	– ‖
Atherosclerotic vascular disease	63	28	4.5 (2.9 – 7.2)	1.8 (1.0 – 3.3)
Recent onset of hypertension	39	34	1.2 (0.8 – 1.9)	1.9 (1.1 – 3.4)
Family history of hypertension	57	67	0.7 (0.4 – 1.0)	– ‖
Ever smoked	79	65	2.1 (1.2 – 3.4)	1.6 ¶ (1.1 – 2.6)
Obesity	40	70	0.3 (0.2 – 0.4)	0.4 (0.2 – 0.6)
Abdominal bruit	27	4	9.2 (4.6 –18.3)	5.4 (2.4 – 12.2)
Hypertensive retinopathy	22	21	1.1 (0.6 – 2.1)	– ‖
Serum creatinine, µmol/L	112 ± 35	89 ± 22	1.4 ** (1.2 – 1.5)	1.4 ** (1.2 – 1.6)
Hypercholesterolemia	40	30	1.6 (1.0 – 2.5)	1.7 (0.9 – 3.0)

* Performed in 477 patients.
† Performed in 460 patients.
‡ Per 10-year increase.
§ Value for a patient who never smoked (value depends on smoking history).
‖ Not in the multivariable model.
¶ Value for a 60-year-old patient (value depends on age).
** Per 10 µmol/L increase.

model because their contribution to predicting renal artery stenosis was small. Because renal artery stenosis is believed to be more prevalent in young women and old men, interaction between age and sex was tested; this interaction was not statistically significant (P=0.09). We included an interaction term between age and smoking because this was the only biologically plausible interaction term that was

statistically significant (P=0.01). This interaction term accounts for the fact that the predictive value of increasing age was stronger for patients who never smoked than for current and former smokers. Finally, the type of standard treatment did not provide additional diagnostic information when it was included in the regression model (P=0.60). The multivariable odds ratios in Table 3.1 reflect the predictive effect of the individual clinical characteristics while correcting for the other predictors in the multivariable model. For example, the multivariable odds ratio for atherosclerotic vascular disease was lower than the univariable odds ratio because the model also accounted for the effects of age and smoking history.

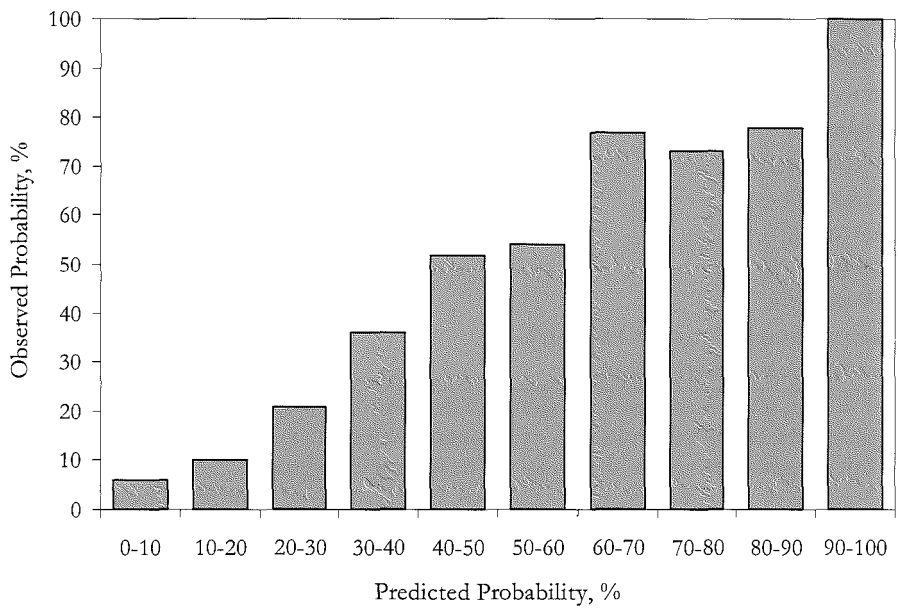

Figure 3.1. Agreement between the observed probability of stenosis and the probability of stenosis as predicted by the regression model in 460 patients with drug-resistant hypertension or an increase in serum creatinine concentration during therapy with angiotensin-converting enzyme inhibitors.

Table 3.2. Prediction rule for quantifying the probability of renal artery stenosis.

Predictor	Score *	
	Persons who never smoked	Former or current smoker
Age †		
20 years	0	3
30 years	1	4
40 years	2	4
50 years	3	5
60 years	4	5
70 years	5	6
Female sex	2	2
Signs and symptoms of atherosclerotic vascular disease ‡	1	1
Onset of hypertension within 2 years	1	1
Body mass index <25 kg/m^2	2	2
Presence of abdominal bruit	3	3
Serum creatinine concentration †		
40 μmol/L	0	0
60 μmol/L	1	1
80 μmol/L	2	2
100 μmol/L	3	3
150 μmol/L	6	6
200 μmol/L	9	9
Serum cholesterol level >6.5 mmol/L or cholesterol-lowering therapy	1	1

* The sum score is obtained by adding all relevant scores. The sum score can be used to obtain the predicted probability of renal artery stenosis from Figure 3.2.

† For intermediate values, the score can be linearly interpolated.

‡ Femoral or carotid bruit, angina pectoris, claudication, myocardial infarction, cerebrovascular accident, or vascular surgery.

Model performance

Figure 3.1 shows the agreement between the predicted and the observed probabilities. For 204 patients (44%), the predicted probability of stenosis was 0% to 10%. The predicted probilities of stenosis obtained from the model agreed well with the observed frequency of stenosis (goodness-of-fit test, P=0.81). The model discriminated well between patients with renal artery stenosis (predicted probability, 49% ± 29%) and patients with essential hypertension (predicted probability, 15% ± 16%); the area under the receiver-operating characteristic

(ROC) curve was 0.84 (95% CI, 0.79 to 0.89). Among patients with stenosis, the discriminative ability of the regression model was better for those with atherosclerotic stenosis (predicted probability, 52% ± 29%) than for those with fibromuscular dysplasia (predicted probability, 34% ± 26%).

The discriminative ability of the prediction rule differed among the four hospitals that included most of the patients. For these hospitals, the area under the ROC curve varied from 0.68 to 0.92. This corresponds with the finding that the associations between stenosis and clinical characteristics of patients from these hospitals were not equally strong or were contradictory. For example, atherosclerotic vascular disease was not predictive of stenosis in one hospital and was even more prevalent in patients with essential hypertension in another hospital. This inconsistency may be explained in part by small sample sizes: The numbers of patients included by these four hospitals were 44, 56, 77 and 151.

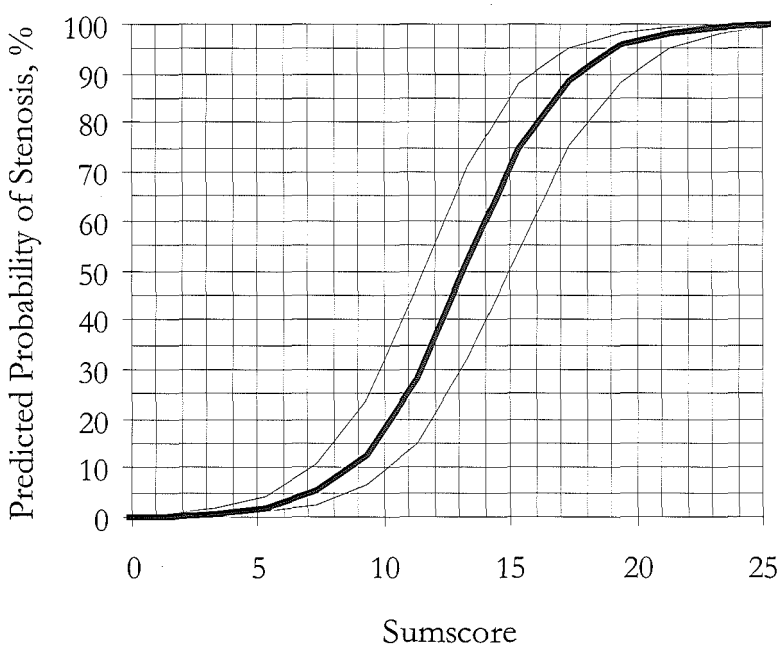

Figure 3.2. Predicted probability of renal artery stenosis in patients with drug-resistant hypertension as a function of the sum score. The sum score was derived from the prediction rule (Table 3.2). Thin lines represent 95% CIs.

Table 3.3. Implications of using the prediction rule in clinical practice.

Predicted probability at which angiography is performed	Sensitivity *	Specificity †	Patients undergoing angiography
	%		
≥ 0	100	0	100
≥ 10	90	47	61
≥ 20	81	73	40
≥ 30	68	87	25
≥ 40	59	92	20
≥ 50	44	96	14
≥ 60	33	98	9
≥ 70	24	99	6
≥ 80	17	99	4
≥ 90	7	100	2

* Patients with stenosis identified by angiography.
† Patients with essential hypertension who did not undergo angiography.

Using the model in clinical practice

In the prediction rule for renal artery stenosis, a score was assigned to the level or presence of each clinical characteristic in the regression model (Table 3.2). The scores were added into a sum score that, through the logistic formula, corresponded with a predicted probability of renal artery stenosis. In Figure 3.2, the predicted probabilities and their 95% CIs can be derived from the sum scores in a graphical manner. For instance, the sum score for a 46-year-old male patient who smoked in the past; has no signs or symptoms of atherosclerotic vascular disease; received a diagnosis of hypertension 1 year ago; has a body mass index of 23 kg/m^2, no abdominal bruit, a serum creatinine concentration of 112 μmol/L (91.27 mg/dL), and a serum cholesterol level of 5.4 mmol/L (208.82 mg/dL); and does not take cholesterol lowering drugs is 11 (4.5 + 0 + 0 + 1 + 2 + 0 + 3.5 + 0). The scores for age and creatinine concentration were obtained by linear interpolation. Figure 3.2 shows that the predicted probability of renal artery stenosis for this patient is 25% (CI, 13% to 43%). The probability can also be calculated by using the formula given in the technical appendix.

The probability of stenosis according to the prediction rule can be used to select patients for renal angiography. If angiography is performed only in patients with a probability of stenosis above a certain cut-off level, the number of angiograms performed in the total group of patients will be reduced. Table 3.3 shows the results of using different cut-off levels for the predicted probability of

stenosis. The first row in Table 3.3 gives the scenario of performing angiography in every patient and therefore identifying all patients with stenosis (sensitivity, 100%). If angiography is performed only in patients whose predicted probability of stenosis is, for example, 10% or more, the number of patients undergoing angiography will be reduced to 61%. However, 1 of every 10 stenoses will be missed (sensitivity, 90%). With increasing cut-off levels, the number of patients undergoing angiography is reduced more and more; as a consequence, however, the number of missed stenoses increases. When a probability of 30% was chosen as the cut-off level, the diagnostic accuracy of the prediction rule (sensitivity, 68%; specificity, 87%) approximated that of captopril renography (sensitivity, 72%; specificity, 90%) in our patient population.

Discussion

We developed a clinical prediction rule to predict the presence of renal artery stenosis from the clinical characteristics of 477 patients with drug-resistant hypertension or an increase in serum creatinine concentration during therapy with ACE inhibitors who participated in a prospective study on diagnosis and treatment of renal artery stenosis (the DRASTIC study).[9] By attributing a score to the presence or absence of nine clinical characteristics, a sum score was obtained that corresponded to a probability of renal artery stenosis. The prediction rule proved to be reliable and discriminated well between patients with renal artery stenosis and those with essential hypertension. By applying the prediction rule in clinical practice to select patients for renal angiography, the number of angiograms obtained may have been reduced considerably in a cost-effective manner.

Clinical characteristics have been mentioned before as a means of identifying patients with renal artery stenosis.[16,20-23] Several studies have described the relative frequency of characteristics in patients with renal artery stenosis and those with essential hypertension, such as age, duration of hypertension, atherosclerosis, cigarette smoking, and presence of an abdominal bruit. Some of these clinical characteristics are interrelated, such as those suggestive of atherosclerotic vascular disease. In our multivariable model, we assessed the independent associations between clinical characteristics and the presence of renal artery stenosis. Moreover, our simple prediction rule enables the clinician to quantify the probability of stenosis for any specific patient. Unlike other studies describing schemes for selecting patients suspected of having renal artery stenosis on the basis of their clinical characteristics,[10,11] our study provides quantitative insight into the potential consequences of applying our selection criteria.

The prediction rule predicts the presence of anatomic renal artery stenosis in patients with preserved renal function (serum creatinine concentration ≤200 μmol/L [2.26 mg/dL]) who have drug-resistant hypertension or an increase in serum creatinine concentration during therapy with ACE inhibitors. The prediction rule should not be applied if other secondary causes of hypertension are not adequately ruled out (such as parenchymal renal disease) and should not be applied to patients with impaired renal function in general. Our study group included some patients who received more medication than the standardized schemes allowed because their blood pressure was very high. Regardless of their blood pressure response to the additional drugs, these patients were considered to be resistant to the standardized regimen and underwent angiography. The prediction rule can therefore be used for patients in whom blood pressure control was achieved with more than two drugs, provided that control could not be achieved on a two-drug regimen. Before introduction on a wide scale, the model must be tested further to establish whether its predictions are valid in other settings.

Although the clinical characteristics of patients with atherosclerotic stenosis and those with fibromuscular dysplasia clearly differ somewhat, the prediction rule can be used to predict the presence of either type of renal artery stenosis. Some clinical characteristics (such as the presence of an abdominal bruit) were found to be relevant for both patients groups, but in other respects (such as signs of atherosclerotic vascular disease), patients with fibromuscular dysplasia resembled those with essential hypertension more closely than they resembled those with atherosclerotic stenosis. Thus, patients with fibromuscular dysplasia are not a distinct group of patients that can be excluded before the prediction rule is applied in clinical practice. For example, only 4 of the 17 patients with fibromuscular dysplasia in our study group were women younger than 40 years of age. We decided not to exclude patients with fibromuscular dysplasia from the analysis because the prediction rule should be applicable to all future patients who present themselves in our clinics. Although the prediction rule performed somewhat better for patients with atherosclerotic stenosis than for patients with fibromuscular dysplasia, the predicted probability in the latter group was significantly higher than that of patients with essential hypertension. Thus, the prediction rule distinguished well between both groups of patients with stenosis and patients with essential hypertension.

In this analysis, anatomic renal artery stenosis was predicted from clinical characteristics. We acknowledge that prediction of functional stenosis (that is, renovascular hypertension) would have been preferable. Unfortunately, no good definition of renovascular hypertension exists. This condition is often defined as

being characterized not only by the presence of renal artery stenosis but also by the cure of the hypertension after repair of the stenosis. However, several factors may explain why relief of renal artery stenosis that has caused hypertension does not always result in cure of hypertension, such as advanced-stage hypertension (third phase of two-kidney, one-clip Goldblatt hypertension), technical failure of the intervention, or restenosis. The most important objection to the use of blood pressure response to intervention is that it is a diagnosis made a posteriori. Therefore, the most practical approach is to search for renal artery stenosis instead of renovascular hypertension.

This prediction rule is a practical and simple tool for selecting patients with drug-resistant hypertension or an increase in serum creatinine concentration during therapy with ACE inhibitors. To obtain the probability of stenosis for a specific patient, information is needed on nine clinical characteristics; this information is generally readily available in clinical practice. After prespecified scores are added to form a sum score, the corresponding probability of stenosis can be read from a graph. The usefulness of the prediction rule was shown in our data set. The prediction rule was almost as accurate as captopril renography (sensitivity, 72%; specificity, 90%) in predicting renal artery stenosis if angiography was performed in patients for whom the rule predicted a probability of stenosis greater than 30%. In contrast to renography, however, the results of the prediction rule are immediately available and free. We therefore conclude that the prediction rule can be used as an alternative to renography in the selection of hypertensive patients for renal angiography, provided that the predictions prove to be valid in other settings. Embedded in the diagnostic workup of hypertensive patients who do not respond well to antihypertensive drugs, the prediction rule can help to reduce the number of negative angiograms without missing many patients with renal artery stenosis.

Technical appendix

Model development

Deletion of cases with missing data may cause a bias and increases variance.[28] For 40 patients for whom one clinical characteristic was missing, the value was therefore predicted from the other clinical characteristics by multiple regression on values of the other predictors and was subsequently imputed.[28,29] Values for 17 patients for whom more than one value was missing were not imputed because the predicted values for these predictors would have been less reliable. These 17 patients were excluded from the multivariable analysis.

Age and serum creatinine concentration were entered into the logistic regression model as continuous variables. We studied whether transformations of

these variables offered a better fit. Smoking was dichotomized as ever or never smoked; the fit of more complex classifications, such as never, past or present smoker or number of pack-years was also studied. Advanced hypertensive retinopathy was not included in the multivariable analysis because this characteristic was missing in a substantial number of the patients (43%). Nine clinical characteristics were selected for the regression model by backward deletion of the least significant characteristics, done by using the Akaike Information Criterion.[30] As a result, ethnicity and family history of hypertension were dropped from the model ($P>0.20$). Interaction between clinical characteristics in predicting renal artery stenosis was studied in two ways to control for deviation from the additivity assumption.[28] First, a likelihood ratio test on all first-order interaction terms was performed ($P=0.63$). Second, biologically plausible interaction terms were tested, which led to the inclusion of age × smoking in the model ($P=0.01$).

Model evaluation

The reliability of the regression model was evaluated by using the Hosmer-Lemeshow goodness-of-fit test.[27] The discriminative ability of the regression model was evaluated by the area under the ROC curve and its 95% CI.[31,32] The ROC curve is a plot of the false-positive rate (1 minus the specificity) against the true-positive rate (sensitivity), evaluated for consecutive cut-off points of the predicted probability. The area under the ROC curve can be interpreted as the probability that the regression model will assign a higher probability of stenosis to a randomly chosen patient with renal artery stenosis than to a randomly chosen patient with essential hypertension. The area can range from 0.5 to 1 (no to optimal discriminative ability) for sensible models.

The internal validity of the regression model[28,33] was assessed by using bootstrapping techniques, including variable selection.[34] Random bootstrap samples were drawn with replacement from the full sample (200 replications). The discriminative ability of the regression models was determined on the bootstrap samples and on the full sample, in which predictions were based on the regression models fitted on the bootstrap samples. This validation replicates the situation in which the prediction model based on our patients is applied to a group of similar patients. The area under the ROC curve was 0.84 on the full data set and 0.82 after this procedure. Next, four hospitals that included most of the patients were left out of the sample one by one, and regression models were fitted on the remaining data. The discriminative ability of these models was externally assessed on the hospital not included in the fitting procedure. This procedure

replicates the situation in which the prediction model is applied in another hospital with a patient population that may be somewhat different.

Derivation of scores in the prediction rule

The multivariable logistic regression model can be written as:

predicted probability of stenosis = $1/1 + e^{-(LP)}$,

where linear predictor $LP = -7.859 + 0.059 \times \text{age} + 0.033 \times (75 - \text{age}) \times \text{ever smoked} - 0.996 \times \text{sex} + 0.585 \times \text{atherosclerotic vascular disease} + 0.642 \times \text{recent onset} - 1.027 \times \text{obesity} + 1.693 \times \text{abdominal bruit} + 0.502 \times \text{hypercholesterolemia} + 0.032 \times \text{serum creatinine concentration}$.

(In this formula, sex is coded as 1 for male, and as 0 for female; all other dichotomous predictors are coded as 1 when present, and as 0 when absent).

The regression coefficients were multiplied by a shrinkage factor of 0.88, which was derived from bootstrapping procedures. Shrinkage of the regression coefficients aims to improve calibration of predictions in future patients: that is, to prevent low predictions that are too low and high predictions that are too high.[28,35] The intercept was adjusted so that the sum of predicted probabilities equalled the number of events (106 patients with stenosis in a total of 460 patients). The shrunk formula was:

P(stenosis) = $1/1 + e^{-(LP_S)}$,

where $LP_S = -7.033 + 0.052 \times \text{age} + 0.029 \times (75 - \text{age}) \times \text{ever smoked} - 0.877 \times \text{sex} + 0.515 \times \text{atherosclerotic vascular disease} + 0.565 \times \text{recent onset} - 0.904 \times \text{obesity} + 1.490 \times \text{abdominal bruit} + 0.441 \times \text{hypercholesterolemia} + 0.028 \times \text{serum creatinine concentration}$.

This formula can be used to calculate the exact probability of stenosis. The average standard error (SE) of the rounded linear predictor values was used to calculate the 95% CIs of the predicted probabilities ($1/1 + e^{-(LP_S \pm 1.96 \times SE)}$).

For presentation as a prediction rule, the rescaled regression coefficients were multiplied by 2 and were rounded to simplify the computation for clinical practice.

Software

Descriptive analyses were performed by SPSS statistical software (SPSS, Inc., Chicago, Illinois). Imputation of missing values, logistic regression, and validation were carried out in the Design Library for S-plus by using the transcan, impute, lrm, and validate functions.[36]

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4

Validation of a prediction rule for renal artery stenosis

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Submitted for publication

Abstract

Background: We previously developed a prediction rule to estimate the probability of renal artery stenosis. This rule should be validated before it can be used reliably to select patients with hypertension for renal angiography. We determined the validity of the prediction rule in recently treated patients in other settings.

Methods: We studied three aspects of validity (agreement between predicted and observed probability of stenosis, discriminative ability, and clinical usefulness) in 180 consecutive patients with drug-resistant hypertension without severe renal failure, who visited 6 hypertension clinics in the Netherlands. Thirty-five patients (19%) had a stenosis of 50% or more on intra-arterial angiography.

Results: The clinical characteristics in the rule (age, sex, vascular disease, recent onset of hypertension, smoking, body mass index, abdominal bruit, serum creatinine concentration, and hypercholesterolemia) had similar predictive value in the validation sample and development sample. The predicted probabilities of stenosis agreed well with the observed probabilities (Hosmer-Lemeshow goodness-of-fit test, P=0.87). The prediction rule discriminated reasonably between patients with and without stenosis in the validation sample with an area under the receiver operating characteristic curve of 0.71. If only patients with predicted probabilities of stenosis of 5% or higher were referred for renal angiography, the number of referrals was reduced by 20%, while 9% of patients with a stenosis were missed.

Conclusions: The prediction rule was valid in more recently treated patients in other settings. If used conservatively, the rule can reliably exclude a small proportion of patients from angiography.

Introduction

Renal artery stenosis may cause hypertension and renal failure. Many of the patients with renal artery stenosis who have hypertension or renal insufficiency can be treated successfully with balloon angioplasty, with or without stenting.[1] For this reason, the presence of renal artery stenosis should be evaluated in patients with renal failure and in patients whose hypertension cannot be controlled adequately by aggressive medical therapy. The reference test for finding renal artery stenosis, intra-arterial subtraction angiography, is, however, an invasive and costly procedure.

Clinical characteristics are useful to select patients with hypertension for renal angiography.[2-4] We previously developed a clinical prediction rule to identify patients with a high risk of renal artery stenosis on the basis of their clinical characteristics (Chapter 3). The rule was developed in a sample of 460 patients with drug-resistant hypertension and normal or mildly impaired renal function. The predictions of the rule were internally validated for this patient group. The prediction rule seems to be accepted on a wide scale.[5-16]

Before the rule can be applied reliably in clinical practice, the validity of its predictions should be tested in other groups of similar patients and in other settings.[17,18] The purpose of this study was to determine the validity of the prediction rule in patients who were more recently treated in other hospitals than the patients in the development sample.

Patients and methods

Development of the prediction rule

The prediction rule was developed in a sample of 460 patients (Chapter 3), who participated in a large multicenter study in the Netherlands designed to evaluate the diagnostic workup and treatment of patients suspected of having renal artery stenosis (the 'DRASTIC' study).[19] Patients were included if they had persistent hypertension (defined as a diastolic blood pressure of 95 mm Hg or higher) despite a standardized two-drug regime and a normal or mildly impaired renal function (defined as a serum creatinine concentration of 200 μmol/L or less). The rule predicted the presence of angiographically proven renal artery stenosis of at least 50% in lumen diameter (outcome) according to the local radiologist. It included the following risk factors for renal artery stenosis (predictors): age, sex, signs and symptoms of vascular disease, recent hypertension, smoking history, obesity, abdominal bruit, serum creatinine concentration and hypercholesterolemia. Logistic regression coefficients for the clinical predictors were estimated. To facilitate practical use, a simple score chart was constructed on the basis of the regression coefficients. The risk score for an individual patient

(see Table 3.2, Chapter 3) can be used to read the patient's probability of stenosis from a graph (see Figure 3.2, Chapter 3).

Validation of the prediction rule

The validation sample consisted of 180 patients who participated in a prospective multicenter cohort study in the Netherlands designed to compare the value of computed tomography angiography (CTA) and magnetic resonance angiography (MRA) to that of conventional intra-arterial subtraction angiography for the diagnosis of renal artery stenosis (the 'RADISH' study; paper submitted for publication). The study was approved by the Medical Ethics Committee at each of 6 participating centers. Written informed consent was obtained from all patients. In the study, 402 consecutive patients were referred for evaluation of hypertension between November 1998 and November 2001. These clinics had previously contributed 12% of the patients in the development sample. Of the 402 patients, 213 met the inclusion criterion of drug-resistant hypertension (defined as a diastolic blood pressure of 95 mm Hg or higher, despite the use of two or more antihypertensive drugs) and a normal or mildly impaired renal function (defined as a serum creatinine concentration lower than 200 μmol/L). Eleven patients were excluded from the validation sample because conventional angiography (the reference test) was not performed and 16 patients were excluded because of missing data on one or more of the clinical predictors. Six patients with an increase in the serum creatinine concentration after use of an angiotensin-converting-enzyme inhibitor were also excluded from the validation sample, because this is considered an indication for angiography given the high risk of renal artery stenosis.[20] Of the remaining 180 patients, complete data on clinical predictors and renal artery stenosis (outcome) were available. The predictors were defined as in the development sample except for vascular disease and smoking history (see Table 4.1 for details). Renal artery stenosis was defined as stenosis of at least 50% in lumen diameter proven by conventional intra-arterial subtraction angiography according to a panel of three radiologists. The treating physician prospectively collected data on predictors and outcome on standardized case record forms.

Data analysis

We refitted the logistic regression model in the validation sample to compare the value of the predictors for renal artery stenosis in the validation sample to that of these predictors in the development sample. To assess the validity of the published prediction rule (i.e., without refitting the regression model) in the validation sample, we studied the agreement between the predicted and observed

probabilities of stenosis ('reliability' or 'calibration'), and the ability of the model to distinguish between patients with stenosis and those without stenosis ('discrimination').[18,21] The agreement between predicted and observed probabilities was evaluated visually in a calibration plot. The U-statistic was used to test whether the agreement between predicted and observed probabilities was different from perfect agreement, i.e. a line with intercept equal to 0 and calibration slope equal to 1.[22] The agreement was also evaluated with the Hosmer-Lemeshow goodness-of-fit test.[23] The discriminative ability of the prediction rule was inspected visually by plotting the distribution of patients with stenosis and of patients without stenosis in the calibration plot. Further, we compared the predicted probabilities for the patients with and those without stenosis, and the predictions for patients with atherosclerotic stenosis and those with fibromuscular dysplasia by Student's T-test. The discriminative ability was quantified with the area under the receiver operating characteristic (ROC) curve.[24] Finally, we assessed the potential impact of the prediction rule on the decision-making process ('clinical usefulness').[21] Clinical usefulness was evaluated by calculating the sensitivity and specificity in relation to the reference test (conventional angiography) for several cut-off points of the probability of stenosis according to the prediction rule. For each cut-off point, we calculated the likelihood ratio for a positive and a negative test result, and the proportion of patients that would undergo angiography.

Results

Validation sample

The prevalence of renal artery stenosis in the development sample was similar to that in the validation sample, but the proportion of patients with stenosis caused by fibromuscular dysplasia rather than atherosclerosis was higher in the validation sample (Table 4.1). The patients in the validation sample had a higher systolic and diastolic blood pressure despite a higher amount of antihypertensive medication. Most predictors were equally prevalent in the samples, except a history of smoking, presence of vascular disease, and presence of an abdominal bruit, which were less prevalent in the validation sample.

Predictors of stenosis

The predictive value of most predictors of renal artery stenosis in the validation sample was similar to that in the development sample (Table 4.2). Presence of an abdominal bruit and presence of hypercholesterolemia, however, seemed negatively associated with stenosis in the validation sample. The odds ratios for these predictors were far from statistically significant.

Table 4.1. Clinical characteristics in the development sample and in the validation sample.

Clinical characteristic	Development sample (N=460)	Validation sample (N=180)
	Number (%) or mean ± SD	
Renal artery stenosis *	106 (23)	35 (19)
Fibromuscular dysplasia	17/106 (16)	13/35 (37)
Academic hospital	221 (48)	161 (89)
Systolic blood pressure, mm Hg	169 ± 25	183 ± 24
Diastolic blood pressure, mm Hg	105 ± 11	110 ± 13
Antihypertensive drugs, number	2 ± 1	3 ± 1
Age, years	51 ± 12	52 ± 11
Male sex	253 (55)	96 (53)
Signs/symptoms of vascular disease	165 (36) †	38 (21) ‡
Recent onset of hypertension §	162 (35)	68 (38)
History of smoking	316 (69) ‖	50 (28) ¶
Obesity **	288 (63)	134 (74)
Abdominal bruit	42 (9)	5 (3) ††
Serum creatinine, μmol/L	94 ± 27	97 ± 24
Hypercholesterolemia	142 (31) ‡‡	50 (28) §§

* stenosis of 50% or more on angiography.
† presence of one or more of the following: femoral or carotic bruit, angina pectoris, claudication, myocardial infarction, stroke, vascular surgery.
‡ presence of one or more of the following: atherosclerosis, vascular disease, angina pectoris, myocardial infarction, coronary heart disease, stroke, cerebral infarction, peripheral vascular disease, iliac stenosis, coronary artery bypass grafting.
§ onset within the last 2 years.
‖ current or former smoker.
¶ current smoker or patient who quitted smoking within the past 6 months.
** body mass index >25 kg/m^2
†† this proportion is an underestimation because presence of an abdominal bruit was not registered systematically.
‡‡ serum cholesterol >6.5 mmol/L and/or use of cholesterol-lowering drugs.
§§ serum cholesterol >6.5 mmol/L and/or use of cholesterol-lowering drugs, or described as hypercholesterolemic or hyperlipidemic.

Reliability

The agreement between the predicted probabilities and the observed frequency of stenosis is shown in Figure 4.1. The deviations from the ideal line were statistically non-significant (U-statistic, P=0.06; Hosmer-Lemeshow goodness-of-fit test, P=0.87). It appeared that the predicted probabilities of stenosis in the lower range were somewhat too low.

Table 4.2. Associations between clinical characteristics and presence of renal artery stenosis, expressed as multivariable odds ratio (95% confidence interval) in the development sample and the validation sample.

Clinical characteristic	Development sample (N=460)	Validation sample (N=180)
Age, per 10-year increase *	1.8 (1.3-2.6)	1.5 (1.0-2.5)
Male	0.4 (0.2-0.7)	0.5 (0.2-1.2)
Signs/symptoms of vascular disease	1.8 (1.0-3.3)	1.9 (0.7-5.2)
Recent onset of hypertension	1.9 (1.1-3.4)	2.1 (0.9-5.2)
Smoking †	1.6 (1.1-2.6)	2.1 (1.2-2.8)
Obesity	0.4 (0.2-0.6)	0.2 (0.1-0.6)
Abdominal bruit	5.4 (2.4-12.2)	0.7 (0.1-7.3)
Serum creatinine, per 10 μmol/L increase	1.4 (1.2-1.5)	1.2 (1.0-1.4)
Hypercholesterolemia	1.6 (1.0-2.5)	0.8 (0.3-2.2)

* Value for a non-smoking patient (value depends on smoking).
† Value for a 60-year-old patient (value depends on age).

Discriminative ability

The predicted probabilities for the patients with stenosis in the validation sample were higher (mean ± SD, 26% ± 20%) than for the patients without stenosis (13% ± 13%, P=0.001). The distributions of the predicted probabilities for the patients with and without stenosis overlapped considerably, however, as shown in the calibration plot (Figure 4.1). The predicted probabilities were 14% ± 10% for patients with fibromuscular dysplasia and 32% ± 22% for those with atherosclerotic stenosis (P=0.003). The area under the ROC curve was 0.71 (95% confidence interval, 0.61 to 0.81).

Clinical usefulness

When we intend to use the prediction rule to select patients for angiography, we need to choose a cut-off level for the predicted probability of stenosis above which angiography is performed. When angiography was performed only in patients with a probability of stenosis of 5% or higher (score >7, see Figure 3.2, Chapter 3), 144 of the 180 patients (80%) would undergo angiography while 3 of the 35 patients with a stenosis would be missed (sensitivity, 91%). The likelihood ratio for a positive test result (i.e., a predicted probability of 5% or higher) was 1.18, and for a negative test result 0.38. For the 26 patients with a stenosis who received an intervention, the sensitivity of the prediction rule was 100%. When the cut-off level was increased to 10% (score >9, see Figure 3.2, Chapter 3), the number of patients undergoing angiography would be reduced to 88 of the 180 patients (49%), but at the expense of an increased number of patients in whom

stenosis would be missed to 10 out of 35 (sensitivity, 71%). Then, the likelihood ratio for a positive test result was 1.65, and for a negative test result 0.51.

Discussion

The predicted probabilities of renal artery stenosis provided by the prediction rule were reasonably valid. The results agree with a previously published, smaller study on the validity of the rule in patients with hypertension refractory to at least two antihypertensive drugs.[25] Our study, however, gives further insight into the use of the prediction rule in daily clinical practice because the earlier study involved mainly patients at high risk of renal artery stenosis.[25] In our validation sample, the prediction rule reliably predicted the presence of stenosis, especially for patients with higher risks. The ability of the prediction rule to discriminate between patients with stenosis and those without stenosis, however, was considerably lower in the validation sample than in the development sample. The area under

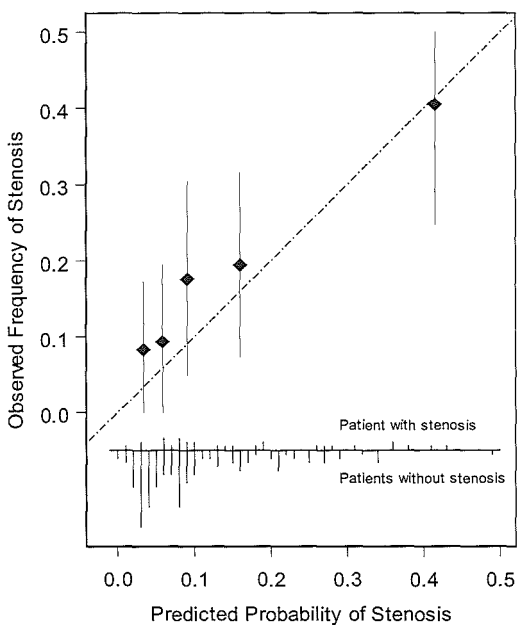

Figure 4.1. Calibration plot for 180 patients in the validation sample. Each square represents 20% of patients with similar predicted probabilities. Vertical lines represent 95% confidence intervals. At the bottom, the distribution of the predicted probabilities of renal artery stenosis is given for patients with stenosis and for those without stenosis.

the ROC curve was 0.71 in the validation sample and 0.84 in the development sample.

The patients in the validation sample had a higher blood pressure than the patients in the development sample, while more antihypertensive drugs were prescribed. This finding can be explained by the fact that the patients in the development sample were assigned to standardized and effective drug regimens, and probably complied more to the prescribed medications because they visited the hypertension clinic every two weeks to optimize the blood pressure control.[20] The patients in the validation sample reflected usual clinical practice with regard to blood pressure control and medication use. The validation sample was, therefore, more representative of the patients for whom the prediction rule was developed.

A limitation of our study was that the validation sample was not optimal for validating the prediction rule. Two predictors, smoking and vascular disease, were defined differently than in the development sample. This may have influenced their predictive value in the validation sample, although this was not apparent from the odds ratios. Another limitation of our study was the rather small sample size, which caused uncertainty in the evaluation of the rule.[26] A possible consequence of this limitation was that the odds ratios for the presence of abdominal bruit and hypercholesterolemia seemed opposite of what was expected, but with wide confidence intervals.

The proportion of patients with fibromuscular dysplasia among patients with stenosis in the validation sample (13/35 or 37%) was over twice as high as in the development sample (17/106 or 16%) and in other patient series (around 10%).[1] The high prevalence of fibromuscular dysplasia seems to be the main cause of the disappointing discriminative ability of the prediction rule in the validation sample. As in the development sample, the prediction rule discriminated less between these patients and patients without stenosis than it did between patients with atherosclerotic renal artery stenosis and patients without stenosis. This discrepancy is caused by the fact that some of the clinical characteristics in the rule are predictive of atherosclerosis rather than of fibromuscular dysplasia.[2,27] The proportions of missed diagnoses among patients with fibromuscular dysplasia (1/13, or 8%, if patients with a predicted probability of 5% or higher were referred to angiography) and among patients with atherosclerotic renal artery stenosis (2/22, or 9%), however, were similar. This is an important finding because intervention in patients with fibromuscular dysplasia is generally successful.[5,28] If the patients with fibromuscular dysplasia were left out of the validation sample, the discriminative ability of the prediction rule improved considerably, which was reflected in the increase in the area under

the ROC curve from 0.71 to 0.77. In the development sample, the area under the ROC curve also increased if patients with fibromuscular dysplasia were excluded, but only from 0.84 to 0.86. We therefore may expect that the discriminative ability of the prediction rule in most clinical settings is better than in this validation study, because the proportion of patients with fibromuscular dysplasia is generally lower.

Before applying the prediction rule, the individual physician should judge if his or her patient population is comparable to the patient sample on which the prediction rule was based. Also, the definition of the clinical predictors and stenosis should be the same. If these conditions are met, the rule will probably provide valid predictions for the probability of renal artery stenosis. In clinical practice, a conservative cut-off level for the predicted probability might be chosen above which patients are referred to angiography. In that case, the proportion of missed stenoses is acceptable. When a cut-off level of 5% was applied to our validation sample, less than 10% of the patients with stenosis were missed while the number of angiographic procedures was reduced by 20%. In the development sample, this ratio was twice as favourable. Nevertheless, the reduction of the number of angiographic procedures as found in the validation sample is worthwhile and seems about what one may expect of a prediction rule when dealing with a clinical decision problem that requires a high sensitivity.[29,30]

Presently, both computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are used more and more for the diagnosis of renal artery stenosis instead of intra-arterial angiography. Advantages include that these imaging tests are minimally invasive and seem to have a high diagnostic accuracy compared to intra-arterial angiography.[31,32] If replacement of intra-arterial angiography by one or both of these modalities proves to be justified in unselected patient series, selection of patients is still warranted because these procedures are expensive, require injection of intravenous contrast media, and their availability may be limited in some settings. Whether the prediction rule could be used validly to select patients for CTA and MRA requires further study.

Our study suggests that the prediction rule is valid in patients who were more recently treated in other settings. The prediction rule can be used reliably to select patients with drug-resistant hypertension for angiography, provided that it is used conservatively in order not to miss too many patients with stenosis. In that case, the usefulness of the prediction rule in clinical practice is limited, however, because the rule indicates only a small proportion of the patients in whom angiography should not be performed.

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5

The effect of balloon angioplasty on hypertension in atherosclerotic renal artery stenosis

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Abstract

Background: Patients with hypertension and renal artery stenosis are often treated with percutaneous transluminal renal angioplasty. However, the long-term effects of this procedure on blood pressure are not well understood.

Methods: We randomly assigned 106 patients with hypertension who had atherosclerotic renal artery stenosis (defined as a decrease in luminal diameter of 50% or more) and a serum creatinine concentration of 200 μmol/L (2.3 mg/dL) or less to undergo percutaneous transluminal renal angioplasty or to receive drug therapy. To be included, patients also had to have a diastolic blood pressure of 95 mm Hg or higher despite treatment with two antihypertensive drugs or an increase of at least 20 μmol/L (0.2 mg/dL) in the serum creatinine concentration during treatment with an angiotensin-converting enzyme inhibitor. Blood pressure, doses of antihypertensive drugs, and renal function were assessed at 3 and 12 months, and patency of the renal artery was assessed at 12 months.

Results: At baseline, the mean (± SD) systolic and diastolic blood pressures were 179 ± 25 and 104 ± 10 mm Hg, respectively, in the angioplasty group and 180 ± 23 and 103 ± 8 mm Hg, respectively, in the drug-therapy group. At 3 months, the blood pressures were similar in the two groups (169 ± 28 and 99 ± 12 mm Hg, respectively, in the 56 patients in the angioplasty group and 176 ± 31 and 101 ± 14 mm Hg, respectively, in the 50 patients in the drug-therapy group; P=0.25 for the comparison of systolic pressure and P=0.36 for the comparison of diastolic pressure between the two groups); at the time, patients in the angioplasty group were taking 2.1 ± 1.3 defined daily doses of medication and those in the drug-therapy group were taking 3.2 ± 1.5 daily doses (P<0.001). In the drug-therapy group, 22 patients underwent balloon angioplasty after 3 months because of persistent hypertension despite treatment with 3 or more drugs or because of deterioration in renal function. According to intention-to-treat analysis, at 12 months, there were no significant differences between the angioplasty and drug-therapy groups in systolic and diastolic blood pressures, daily drug doses, or renal function.

Conclusion: In the treatment of patients with hypertension and renal artery stenosis, angioplasty has little advantage over antihypertensive-drug therapy.

Introduction

Experiments conducted by Goldblatt and colleagues[1] on the effects of renal artery constriction in animals led to the recognition that renal artery stenosis may cause hypertension. Initially, surgical revascularization was the only treatment for renal artery stenosis,[2,3] but percutaneous transluminal balloon angioplasty,[4] with or without stent placement, later supplanted surgery as the preferred treatment.[5] In uncontrolled, retrospective studies of balloon angioplasty, 36% to 100% of patients with hypertension had some reduction in blood pressure, with the highest rates of response in patients with fibromuscular dysplasia,[6] but in few patients, however, was blood pressure restored to normal levels. In two small, randomized studies, the benefit of balloon angioplasty was even smaller,[7,8] suggesting that the general enthusiasm for this procedure may not be justified.

We report the results of a multicenter, randomized, controlled comparison of balloon angioplasty and antihypertensive-drug therapy for the treatment of atherosclerotic renal artery stenosis associated with hypertension and normal or mildly impaired renal function.

Patients and methods

This prospective, randomized study was conducted at 26 centers in the Netherlands between January 1993 and November 1998. The study was designed to identify patients with hypertension caused by renal artery stenosis and to evaluate their treatment. The current report focuses on the treatment phase of the study, in which 106 patients with atherosclerotic renal artery stenosis were randomly assigned to undergo balloon angioplasty of the renal artery (without stent placement) or to receive antihypertensive-drug therapy. The study was approved by the institutional review board at each participating center, and all patients provided written informed consent.

The diagnostic phase of the study involved 1205 patients, 18 to75 years old, who had been referred to the participating centers because of difficult-to-treat hypertension associated with normal or mildly impaired renal function (defined as a serum creatinine concentration of ≤200 μmol/L [2.3 mg/dL]). The diagnostic workup included a medical history, a physical examination, and laboratory studies, renography after the administration of captopril and renal angiography.[9] Patients were excluded if they had cancer, hypertension caused by a condition other than renovascular disease (e.g. renal parenchymal disease, primary aldosteronism, or hypercortisolism) or unstable coronary artery disease or heart failure, or if they were pregnant. Renal angiography was performed in 543 patients because their diastolic blood pressure, measured at three consecutive outpatient visits one to three weeks apart, was at least 95 mm Hg despite

treatment with a standardized regimen of two antihypertensive drugs or because their serum creatinine concentration on the second or third visit had risen by at least 20 μmol/L (0.2 mg/dL) during treatment with an angiotensin-converting enzyme inhibitor. Of these 543 patients, 169 were found to have ostial or nonostial renal artery stenosis (defined as a decrease in lumen diameter of ≥50%) and thus were considered candidates for the treatment phase.

Patients were excluded from the treatment phase of the study if they had any of the following: a single functioning kidney and a serum creatinine concentration greater than 150 μmol/L (1.7 mg/dL); an affected kidney that was less than 8.0 cm long, as determined by ultrasonography; total occlusion of the renal artery; an aortic aneurysm necessitating surgery; or renal artery stenosis due to fibromuscular dysplasia. For the treatment phase, 106 patients were eligible and were randomly assigned to undergo balloon angioplasty or to receive antihypertensive-drug therapy. Block randomization was used to ensure that the groups contained roughly equal numbers of patients, with stratification according to institution and several clinical variables.[10] Stratification variables were the serum creatinine concentration (<120 μmol/L [1.4 mg/dL] vs. ≥120 to 200 μmol/L), the type of antihypertensive-drug therapy received during the diagnostic phase of the study (amlodipine and atenolol vs. enalapril and hydrochlorothiazide), and the extent of renal artery stenosis (unilateral vs. bilateral). Randomization was performed by computer at the coordinating center (Erasmus University Hospital, Rotterdam), without investigators' knowledge of patients' groups at the time of assignment.

Treatment and follow-up

Patients assigned to the drug-therapy group and, if necessary, those assigned to the angioplasty group, received antihypertensive-drug therapy according to a stepwise protocol, with a target diastolic blood pressure of less than 95 mm Hg. Drug therapy consisted of the two-drug regimen the patient had been receiving during the diagnostic phase of the study; if necessary, a dose could be increased or another drug added.

Blood pressure was measured by standard sphygmomanometry every one to three months, and always at months 3 and 12, with the patient seated after a five-minute rest; three measurements were made at least one minute apart, and the values were recorded to the nearest 2 mm Hg and then averaged.[11] Three and 12 months after randomization, blood pressure was also measured with an automatic device (Datascope, Montvale, N.J.) at five-minute intervals for 60 minutes. In addition, at 3 and 12 months, serum creatinine was measured and renography was performed after the administration of captopril.[12] In both the

angioplasty group and the drug-therapy group, renal angiography was repeated at 12 months.

Patients assigned to the angioplasty group were given 300 mg of aspirin daily, starting the day before angioplasty and continuing for six months. Antihypertensive-drug therapy was discontinued on the day of the procedure to prevent hypotension and was subsequently resumed if necessary. If, after three months, the patient's diastolic pressure was 95 mm Hg or higher or the serum creatinine concentration had risen by at least 20 μmol/L, the treating physician decided whether to recommend a second balloon angioplasty, stent deployment, or bypass surgery.

Patients assigned to the drug-therapy group underwent balloon angioplasty if, after three months, their diastolic pressure was 95 mm Hg or higher despite treatment with three or more drugs or if there was evidence of progressive renovascular occlusive disease. Progressive renovascular occlusive disease was defined as an increase of at least 20 μmol/L in the serum creatinine concentration or worsening of the time-activity curve on renography; worsening was defined as a change in the time-activity curve from type 1 or 2 to type 3, 4, or 5 or a change in the curve from type 3 to type 4 or 5 (type 1 indicates minor abnormalities, type 2 delayed excretion with washout, type 3 delayed excretion without washout, type 4 renal failure with measurable uptake by the kidney, and type 5 renal failure without measurable uptake).[13] Lipid-lowering medication was prescribed for any patient who had a serum cholesterol concentration greater than 6.5 mmol/L (251 mg/dL).

Renal angiography, renography and balloon angioplasty

Angiography was performed before the beginning of the treatment phase and at 12 months by the femoral approach with the digital-subtraction technique. The images were then assessed at each participating center by the radiologist who had performed the angiography. All angiograms were subsequently evaluated by three independent radiologists, who graded the images according to the severity of stenosis, expressed in steps of 10% decrease in luminal diameter. The median value of these three grades was then calculated.

Renography was performed with use of technetium-99m-labeled mercapto-acetyltriglycine. The nuclear medicine specialists who assessed the renal renograms were asked to report the results in terms of the probability of renovascular disease (low, indeterminate, or high), according to a consensus report on the diagnosis of renovascular disease by renography.[14] Renograms judged to indicate a high or indeterminate probability of renovascular disease were considered abnormal.

Outcome measures

The primary outcome measures were the systolic and diastolic blood pressures at 3 and 12 months after randomization. The secondary outcome measures were the numbers and defined daily doses of antihypertensive drugs (one defined daily dose is the average maintenance dose per day in adults),[15] the serum creatinine concentration, the creatinine clearance according to the formula of Cockcroft and Gault,[16] the results of renography, the presence or absence of patency of the renal artery (where patency was defined as stenosis of <50%), and the incidence of complications.

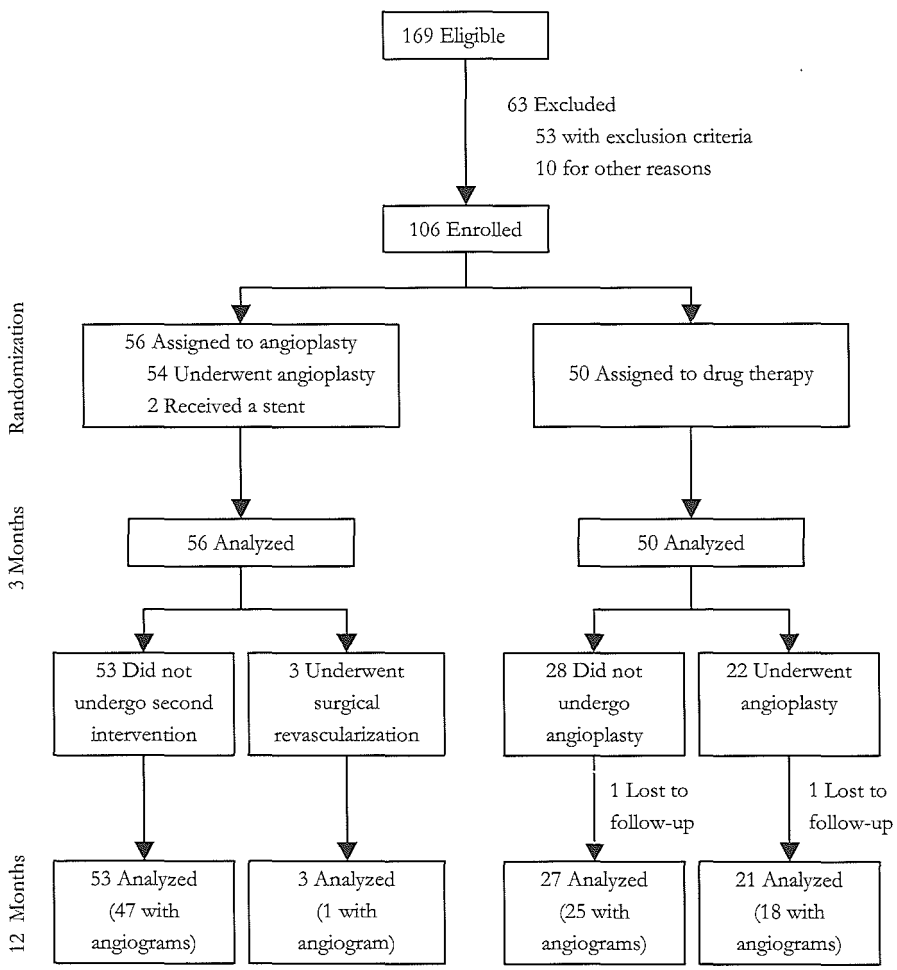

Figure 5.1. Design of the study

In a separate analysis, outcomes were assessed in terms of blood pressure responses in the two groups. In this analysis, improvement was defined as either (1) a decrease of 10 mm Hg or more in diastolic pressure with either no change or a decrease in the number of drugs or (2) a decrease in the number of drugs without a change in diastolic pressure; worsening was defined as either (1) an increase of 10 mm Hg or more in diastolic pressure with either no change or a increase in the number of drugs or (2) an increase in the number of drugs without a change in diastolic pressure; and cure of hypertension was defined as a diastolic blood pressure of less than 95 mm Hg without the use of antihypertensive drugs.

Statistical analysis

Results are given as means ± SD or as medians and ranges. Results at 12 months were analyzed according to the intention-to-treat principle. In addition, results at 3 and 12 months in the drug-therapy group were analyzed according to whether patients underwent angioplasty after three months. Two-sided comparisons between groups were made with Student's T-test or the Mann-Whitney test. Chi-squared testing was used for analysis of categorical data. A paired T-test was used to compare the blood pressure values measured at the 3-month and 12-month follow-up visits with the values measured at baseline.

Results

Of the 169 patients with renal artery stenosis, 53 were excluded on the basis of the prespecified exclusion criteria and 10 patients were excluded for other reasons (prominent aortic plaques in 2, a serum creatinine concentration >200 μmol/L in 1, lack of informed consent in 4, and withdrawal by the internist in 3). Of the remaining 106 patients, 56 were randomly assigned to balloon angioplasty and 50 to antihypertensive-drug therapy (Figure 5.1). At baseline, the blood pressure levels and doses of antihypertensive drugs (means of the values obtained at the three visits during the diagnostic phase) were similar in the two groups, as were other baseline characteristics (Table 5.1). Likewise, in the subgroup of patients with impairment of renal function related to the use of angiotensin-converting enzyme inhibitors, the blood pressure levels and drug doses in the patients randomly assigned to balloon angioplasty were similar to those in the patients assigned to antihypertensive-drug therapy.

Renal angiography

To be included in the study, patients were required to have unilateral or bilateral renal artery stenosis of at least 50%, as judged by the radiologist who had performed the angiography. In 10 of the 106 patients included (5 in the

Table 5.1. Baseline characteristics of the patients.

Variable	Angioplasty group (N=56)	Drug-therapy group (N=50)
	Number (%) or mean ± SD	
Clinical data		
Male sex	37 (66)	28 (56)
Age, years	59 ± 10	61 ± 10
Body-mass index, kg/m^2	25.4 ± 3.5	25.2 ± 3.1
Cigarette smoking		
Former or current	46 (82)	35 (70)
Pack-years among those who smoked	22 ± 14	25 ± 17
Abdominal bruit	12/56 (21)	12/48 (25)
Diabetes mellitus	3 (5)	3 (6)
Onset of hypertension <2 yr before enrollment	19 (34)	17 (34)
Blood pressure, mm Hg		
Systolic	179 ± 25	180 ± 23
Diastolic	104 ± 10	103 ± 8
Antihypertensive drugs		
No. of defined daily doses	3.3 ± 1.1	3.2 ± 1.5
No. of drugs	2.0 ± 0.8	2.0 ± 0.9
Regimen, no.		
Amlodipine and atenolol	18	13
Enalapril and hydrochlorothiazide	22	23
Other	16	14
Laboratory and angiographic data		
Serum creatinine, μmol/L		
Median	105	111
Range	61-237	43-203
Serum creatinine ≥120 μmol/L	18 (32)	21 (42)
Creatinine clearance, mL/min	67 ± 23	60 ± 24
Serum cholesterol, mmol/L	6.3 ± 1.1	6.4 ± 1.2
Serum cholesterol >6.5 mmol/L	22/56 (39)	18/45 (40)
Abnormal renogram	35/54 (65)	32/49 (65)
Stenosis		
Bilateral	13 (23)	11 (22)
<70%	12 (21)	15 (30)
Average decrease in luminal diameter, %	76 ± 20	72 ± 18
Inclusion criteria		
Hypertension resistant to standardized medication	49 (88)	38 (76)
Renal function impairment related to angiotensine-converting enzyme inhibitors *	7 (12)	12 (24)

* In the subgroup with renal function impairment related to the use of angiotensin-converting enzyme inhibitors, the systolic blood pressure was 164 ± 25mm Hg and the diastolic blood pressure 98 ± 10 mm Hg among the patients assigned to angioplasty, and the respective systolic and diastolic pressures were 160 ± 20 and 98 ± 5 mm Hg among the patients assigned to drug-therapy group; these patients were receiving 2.9 ± 0.4 and 2.9 ± 1.1 defined daily doses, respectively.

angioplasty group and 5 in the drug-therapy group), however, the stenosis was judged to be less than 50% by the panel of three independent radiologists.

Of the 56 patients in the angioplasty group, 2 received a stent in addition to undergoing angioplasty (1 because of a small aneurysm in the distal segment of the renal artery and the other because the radiologist had not adhered to the protocol). Balloon angioplasty failed for technical reasons in 3 patients with unilateral stenosis and on one side in one patient with bilateral stenosis. After 3 months, surgical revascularization was performed in 2 of the patients in whom angioplasty had failed and in one patient in the angioplasty group who had persistent hypertension (diastolic pressure, ≥95 mm Hg).

Renal angiography was repeated 12 months after balloon angioplasty in 48 of the 56 patients assigned to that group, 4 patients declined to undergo the procedure, and it was not requested for 3 of the patients in whom angioplasty had failed and for 1 of the patients who had undergone surgical revascularization. Of these 48 patients, 23 had at least 50% stenosis of the treated artery, but none had total occlusion.

Of the 50 patients in the drug-therapy group, 28 were treated exclusively with antihypertensive drugs during the 12-month follow-up period. Of the remaining 22 patients, balloon angioplasty was performed after the 3-month follow-up in 14 patients because of persistent hypertension despite treatment with three or more drugs and in 8 patients because of progressive renovascular occlusive disease (as indicated by an increase of 20 μmol/L or more in the serum creatinine concentration or worsening of the time-activity curve on renography). At the time of angioplasty, the angiograms of 3 of the 22 patients who underwent angioplasty showed total occlusion, so the procedure had to be aborted.

Renal angiography was repeated 12 months after randomization in 43 of the 50 patients initially assigned to the drug-therapy group. Angiography showed stenosis of 50% or more in 31 of the 43 patients (72%), stenosis that had progressed to total occlusion in 4 patients (9%), and stenosis of less than 50% in 8 patients. Of the 25 patients who underwent repeated angiography and who had been treated exclusively with drug therapy, 5 had an increase in stenosis of 20 percentage points or more, 16 had no change, and 4 had regression of stenosis of 20 percentage points or more.

Blood pressure

Mean systolic and diastolic blood pressure at 3 months did not differ significantly between the angioplasty and drug-therapy groups (Table 5.2). At 12 months, intention-to-treat analysis revealed no significant differences in systolic and

Table 5.2. Outcomes at 3 and 12 months in the angioplasty and drug-therapy groups.

Variable	Angioplasty group (N=56)	Drug-therapy group (N=50)	P value
	Number (%) or mean ± SD		
Outcomes 3 months after randomization			
Blood pressure, mm Hg *			
Systolic	169 ± 28	176 ± 31	0.25
Diastolic	99 ± 12	101 ± 14	0.36
Blood pressure by automatic device, mm Hg			
Systolic	160 ± 26	163 ± 27	0.61
Diastolic	89 ± 14	88 ± 13	0.73
Antihypertensive drugs			
No. of defined daily doses	2.1 ± 1.3	3.2 ± 1.5	<0.001
No. of drugs	1.9 ± 0.9	2.5 ± 1.0	0.002
Serum creatinine, μmol/L			0.05
Median	107	112	
Range	58-166	50-232	
Creatinine clearance, mL/min	70 ± 25	59 ± 23	0.03
Abnormal renogram	17/47 (36)	28/40 (70)	0.002
Outcomes 12 months after randomization			
Blood pressure, mm Hg †			
Systolic	160 ± 26	163 ± 25	0.51
Diastolic	93 ± 13	96 ± 10	0.25
Blood pressure by automatic device, mm Hg			
Systolic	152 ± 20	162 ± 27	0.07
Diastolic	84 ± 10	88 ± 13	0.13
Antihypertensive drugs			
No. of defined daily doses	2.5 ± 1.7	3.1 ± 2.3	0.10
No. of drugs	1.9 ± 0.9	2.4 ± 0.9	0.002
Serum creatinine, μmol/L			0.11
Median	104	110	
Range	52-169	50-726	
Creatinine clearance, mL/min	70 ± 24	62 ± 27	0.11
Abnormal renogram	19/53 (36)	25/44 (57)	0.04
Complications during follow-up			
Occlusion of affected artery	0	4 (8)	
Rupture of affected artery	0	0	
Increase of ≥50% in serum creatinine	1 (2)	3 (6)	
Embolization of cholesterol crystals	0	1 (2)	
Groin hematoma necessitating transfusion or surgery	1 (2)	2 (4)	
Other ‡	1 (2)	2 (4)	

* P<0.001 for the comparison with systolic and diastolic pressure at randomization in the angioplasty group; P=0.16 for the comparison with systolic pressure at randomization and P=0.13 for the comparison with diastolic pressure at randomization in the drug-therapy group.

† P=0.001 for the comparison with systolic and diastolic pressure at 3 months in the angioplasty group; P=0.001 for the comparison with systolic pressure at 3 months and P=0.002 for the comparison with diastolic pressure at 3 months in the drug-therapy group.

‡ Other complications were symptomatic hypotension at the time of angioplasty in one patient in the angioplasty group and angina pectoris in one patient and myocardial infarction in one patient in the drug-therapy group.

diastolic blood pressure between the drug-therapy group (of which 22 patients underwent balloon angioplasty after 3 months) and the angioplasty group. The doses of antihypertensive drugs used by the patients in the angioplasty group were significantly lower than those used in the drug-therapy group at 3 months, but this difference was no longer significant at 12 months. Among patients with renal function impairment related to the use of angiotensin-converting enzyme inhibitors, the blood pressure levels at 3 and 12 months were similar in the drug-therapy and angioplasty groups.

Among the patients who were randomly assigned to the drug-therapy group, the systolic and diastolic blood pressures were higher at baseline and at the 3-month follow-up visit in patients who underwent balloon angioplasty after 3 months than in those who did not (Table 5.3). Blood pressure decreased after angioplasty but was still higher at 12 months in the patients who underwent this procedure than in the patients who received drug therapy alone. The doses of drugs did not change significantly after balloon angioplasty, and at 12 months they were similar in the two subgroups.

Although there was no significant difference between groups in mean blood pressure levels, a favorable effect in the angioplasty group could be identified when outcomes were categorized according to blood pressure response, as defined in the Methods section. At 12 months, blood pressure control had improved in 38 of the 56 patients in the angioplasty group (68%) and in 18 of the 48 patients in the drug-therapy group who had complete follow-up (38%). Conversely, blood pressure control had worsened at 12 months in 5 patients in the angioplasty group (9%) and 16 patients in the drug-therapy group (33%) (P=0.002). Hypertension was considered cured at 12 months in 4 of the 56 patients in the angioplasty group (7%) and in none of the patients in the drug-therapy group.

In the 54 patients in the angioplasty group in whom balloon angioplasty was technically successful, including the 2 patients who also received a stent, neither the blood pressure levels nor the defined daily doses of antihypertensive drug at 3 and 12 months were related to the severity of renal artery stenosis at randomization; the blood pressure levels and the drug doses of the 32 patients with greater than 70% stenosis did not differ from those of the 20 patients with stenosis of 70% or less (data not shown). Blood pressure and drug doses in the angioplasty group also were not correlated with the presence or absence of stenosis of 50% or greater at 12 months: among the 26 patients (23 in whom angiography was repeated and 3 in whom angiography was not repeated and in whom there was technical failure) with at least 50% stenosis after 12 months, the

Table 5.3. Baseline characteristics and outcomes in patients in the drug-therapy group according to whether they underwent angioplasty after 3 months.

Variable	Drug therapy with angioplasty after 3 months (N=22)	Drug therapy alone (N=28)	P value
	Number (%) or mean ± SD		
Baseline characteristics			
Blood pressure, mm Hg			
Systolic	185±22	176±24	0.21
Diastolic	107±7	101±9	0.02
Antihypertensive drugs			
No. of defined daily doses	3.6±1.8	2.8±0.9	0.05
No. of drugs	2.3±1.0	1.8±0.8	0.08
Serum creatinine, μmol/L			0.56
Median	115	110	
Range	77-203	43-198	
Creatinine clearance, mL/min	55±21	63±26	0.22
Abnormal renogram	14/21 (67)	18/28 (64)	0.86
Outcomes 3 months after randomization			
Blood pressure, mm Hg			
Systolic	190±33	164±24	0.004
Diastolic	111±13	94±9	<0.001
Antihypertensive drugs			
No. of defined daily doses	3.7±1.6	2.8±1.2	0.03
No. of drugs	2.8±1.1	2.2±0.8	0.02
Serum creatinine,μmol/L			0.65
Median	105	112	
Range	66-195	50-232	
Creatinine clearance, ml/min	58±21	60±24	0.75
Abnormal renogram	10/16 (63)	18/24 (75)	0.49
Outcomes 12 months after randomization			
Blood pressure, mm Hg			
Systolic	169±25 *	159±24 †	0.16
Diastolic	102±9 *	91±9 †	<0.001
Antihypertensive drugs			
No. of defined daily doses	3.3±2.8	3.0±1.8	0.74
No. of drugs	2.5±1.1	2.4±0.8	0.81
Serum creatinine, μmol/L			0.33
Median	114	108	
Range	53-726	50-176	
Creatinine clearance, mL/min	58±26	65±27	0.42
Abnormal renograms	10/19 (53)	15/25 (60)	0.63

* P<0.001 for the comparison with systolic and diastolic pressure in this subgroup at 3 months.

† P=0.26 for the comparison with systolic pressure and P=0.32 for the comparison with diastolic pressure in this subgroup at 3 months.

mean (± SD) systolic and diastolic blood pressure were 162 ± 21 and 91 ± 11 mm Hg, respectively, during treatment with 2.3 ± 1.3 defined daily doses, as

compared with 159 ± 32 mm Hg (P=0.79) and 96 ± 16 mm Hg (P=0.14), respectively, during treatment with 2.9 ± 2.0 defined daily doses (P=0.13) among the 25 patients with less than 50% stenosis. In addition, in the angioplasty group, the presence of an abnormal renogram at entry did not predict the blood pressure level: there were no significant differences in blood pressure or defined daily doses of antihypertensive drugs between patients with a normal renogram at entry and those with an abnormal renogram.

Renal function and results of renography

At 3 months, the median serum creatinine concentration in the angioplasty group was lower and the mean creatinine clearance higher than the respective values in the drug-therapy group, but at 12 months the values of these variables were similar in the two groups, according to intention-to-treat analysis. The percentage of abnormal renograms was lower in the angioplasty group than in the drug-therapy group at both 3 and 12 months (Table 5.2).

Discussion

The aim of our study was to determine whether balloon angioplasty offers any advantage over drug therapy in the treatment of patients with hypertension associated with atherosclerotic renal artery stenosis. We found that both approaches resulted in similar decreases in blood pressure, but that angioplasty reduced the need for one additional antihypertensive drug given in its usual daily dose. Fewer drugs were used in the angioplasty group than in the drug-therapy group in part because of the design of the study, and thus this difference does not constitute proof of the efficacy of angioplasty. The blood pressure in this group might have been lower if the patients had received as many antihypertensive drugs as the patients in the drug-therapy group. In very few of the patients in the angioplasty group was hypertension cured.

Several factors may account for the limited efficacy of balloon angioplasty in our study. Angioplasty is followed by restenosis in a high proportion of patients,[17-19] which may adversely affect the blood pressure response. However, we found no difference after one year in the blood pressure response between patients with stenosis and those without stenosis. Stent placement as an adjunct to angioplasty has been reported to lower the incidence of restenosis,[20,21] but in one study the use of a stent did not result in greater improvement in blood pressure or renal function after 6 months than did angioplasty without stenting,[20] a finding consistent with our results. Whether stenting is better than balloon angioplasty, in terms of long-term control of blood pressure and improvement in renal function, is not known.

Another explanation for the disappointingly small effect of balloon angioplasty on blood pressure in our study may be the fact that a substantial number of patients in the drug-therapy group underwent balloon angioplasty after 3 months because their hypertension persisted despite treatment with 3 or more drugs or because they had signs of progressive occlusive renovascular disease. As a result, follow-up data on the effects of drug therapy alone in these patients were available only at 3 months. When the patients who had initially been assigned to the drug-therapy group but who later underwent balloon angioplasty were evaluated as a separate subgroup, it appeared that angioplasty had had a favorable effect on blood pressure. The important point is that blood pressure was not higher at 12 months in the drug-therapy group as a whole than in the angioplasty group. Therefore, our results cannot be used as an argument against the more conservative, drug-based treatment.

Our method of selecting patients may also have affected the results. Of the 106 patients, 10 (5 in each group) had stenosis of the renal artery that was judged by an independent panel of three radiologists to be less than 50%. Some investigators consider stenosis to be hemodynamically important only if the diameter is reduced by more than 60%[22,23] or by more than 70%.[13,24] However, we found no correlation between the blood pressure response and the severity of renal artery stenosis at baseline.

Our study was designed primarily to assess the influence of balloon angioplasty on the control of blood pressure, but our data also provide information about the effect of this intervention on renal function. Renal function appeared to be better in the angioplasty group than in the drug-therapy group at 3 months, but not at 12 months. The long-term effects of angioplasty on renal function remain to be determined.

We conclude that it is still prudent to restrict balloon angioplasty (with or without the use of a stent) to patients whose hypertension persists despite treatment with three or more drugs or who have progressive occlusive renovascular disease (as indicated by an increase in the serum creatinine concentration or worsening findings on the renogram).

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6

Which patients with hypertension and atherosclerotic renal artery stenosis benefit from immediate intervention?

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Abstract

Objective: To identify subgroups of patients with hypertension and atherosclerotic renal artery stenosis who may benefit from immediate intervention.

Methods: In the DRASTIC study, patients with hypertension, significant atherosclerotic renal artery stenosis, and a normal or mildly impaired renal function were randomized between immediate balloon angioplasty (PTRA; N=56) and drug therapy followed by angioplasty after 3 months, if needed (Med-PTRA; N=50). In this secondary analysis of the data, changes in the renal function and blood pressure after 1 year were studied by analysis of covariance in the following subgroups: patients with positive captopril-renin challenge test, abnormal captopril renogram, recently developed hypertension, bilateral stenosis, and severe stenosis.

Results: We found a benefit of immediate angioplasty only for patients with bilateral stenosis. Their creatinine clearance had decreased (mean ± SD: -4.2 ± 13.5 mL/min) in the Med-PTRA group, whereas it had improved substantially (+10.0 ± 15.7 mL/min) in the PTRA group (P=0.02). For patients with unilateral stenosis, the change in creatinine clearance did not differ between PTRA and Med-PTRA (+4.3 ± 15.5 mL/min and +1.3 ± 12.5 mL/min, respectively). The patients with bilateral stenosis also seemed to benefit most from immediate intervention with regard to blood pressure control. None of the other subgroups had a clear benefit of immediate intervention regarding renal function or blood pressure control.

Conclusions: Intervention should not be postponed in patients with bilateral stenosis, even if renal function is normal. Other hypertensive patients with atherosclerotic renal artery disease could initially well be treated by aggressive multidrug therapy alone unless hypertension persists or renal function deteriorates.

Introduction

Renal artery stenosis can lead to secondary hypertension and renal failure, and is caused by atherosclerosis in approximately 90% of the patients.[1,2] The optimal treatment for patients with atherosclerotic renal artery stenosis and hypertension without chronic renal insufficiency is still unclear. Three randomized trials, one described in Chapter 5 and two other trials,[3,4] compared balloon angioplasty with conservative treatment. These trials showed that blood pressure was not significantly better controlled after balloon angioplasty, although less antihypertensive medication was needed. A meta-analysis combining these trials also did not show a clear benefit of angioplasty.[5] Furthermore, it is unclear whether invasive treatment offers an advantage over conservative treatment for prevention of renal failure in patients with stable renal function.[6,7] In a randomized trial comparing angioplasty with additional stent placement and angioplasty alone, additional stent placement did not improve the clinical outcomes after 6 months despite a higher rate of technical success and a lower rate of restenosis.[8]

Since invasive treatment is costly and not without risk,[9,10] one may propose that it is sensible to treat nonazotemic patients with atherosclerotic renal artery stenosis and hypertension by aggressive drug therapy and to perform an intervention only if the hypertension persists or if the renal function deteriorates. Some subgroups of patients may benefit from immediate intervention, however, either because they are likely to have a favorable response to intervention or because they are at risk for rapid deterioration of renal function. We explored this assumption by studying the changes in blood pressure and renal function after 1 year of treatment in patients who were randomized between immediate balloon angioplasty and drug therapy followed by angioplasty if hypertension persisted or renal function deteriorated in the DRASTIC study.[11]

Patients and methods

Study population

Patients participated in a prospective randomized study that was designed to identify patients with renal artery stenosis and to evaluate their treatment (the DRASTIC study).[11] Patients had been referred because of difficult-to-treat hypertension associated with normal or mildly impaired renal function (defined as a serum creatinine concentration of 200 μmol/L [2.3 mg/dL] or less). The patients in the present analysis were from the therapeutic phase of the study, which was described in detail in Chapter 5. In total, 106 patients with atherosclerotic renal artery stenosis of 50% of lumen diameter or more according

to intra-arterial digital subtraction angiography were randomized between two treatment strategies: immediate balloon angioplasty (PTRA, N=56) and drug therapy followed by balloon angioplasty after 3 months, if needed (Med-PTRA, N=50). In accordance with the study protocol, 22 of the 50 patients in the Med-PTRA group underwent angioplasty after 3 months because of persistent hypertension (diastolic blood pressure of 95 mm Hg or higher) despite treatment with three or more drugs (N=14), or because of progressive renal failure (as indicated by an increase in the serum creatinine concentration of 20 μmol/L [0.23 mg/dL] or more, or worsening of the time-activity curve on captopril renography; N=8). All patients gave written informed consent. Blood pressure and renal function after 1 year did not differ significantly between the randomized groups (Table 5.2, Chapter 5).

Clinical data

In the present study, the clinical outcomes were change in diastolic blood pressure and change in creatinine clearance from baseline (before randomization) to 1 year. The baseline blood pressure was defined as the average of office blood pressure readings at three consecutive visits, and the blood pressure after 1 year was defined as the average of all available office blood pressure readings measured between 9 and 12 months after randomization (average two visits, range 1-4 visits). At each visit, the blood pressure was measured three times using a standard sphygmomanometer in sitting position after 5 minutes rest. The creatinine clearance at baseline and after 1 year were calculated according to the Cockcroft formula.[12] Data on diastolic blood pressure and creatinine clearance after 1 year were available for 103 and 102 patients, respectively.

As a rule, the results of subgroup analyses should be interpreted with caution.[13,14] To improve the credibility of our analyses, a limited number of subgroups were selected on the basis of clinical plausibility. We studied three subgroups of patients with a supposedly good response to intervention: those with positive captopril-renin challenge test[15,16] (1-hour plasma renin ≥50 μU/mL; this cutoff represents the optimal value for identifying renal artery stenosis in our study group),[17] those with abnormal renogram after stimulation with captopril,[18] and those with recently developed hypertension (within the last 2 years).[19,20] Two subgroups of patients with a supposed risk for rapid disease progression were studied: those with bilateral stenosis (≥50% of lumen diameter on both sides), and those with severe stenosis (≥80% of lumen diameter).[21,22] Subgroup data were available for all patients except for the captopril-renin challenge test and captopril renography. These tests were not performed in 28 patients and in three patients, respectively, for logistic reasons.

Statistical analysis

We applied analysis of covariance to study the change in diastolic blood pressure in the subgroup of patients with a positive captopril-renin challenge test. The blood pressure at baseline was included as a covariate in the analysis to adjust for its correlation with the blood pressure level after 1 year.[23] Mathematically, the analysis of treatment effect according to change in outcome with the baseline value as covariate is equivalent to the more standard analysis of outcome with the baseline value as covariate. To study whether the difference, if any, in the effect of the treatment strategies on blood pressure was similar for patients with a positive and a negative test captopril-renin challenge test, an interaction term of treatment strategy (PTRA or Med-PTRA) with captopril-renin challenge test (positive or negative) was tested in an analysis of covariance using all patients.[14] Again, diastolic blood pressure at baseline was included as a covariate. Similar analyses were performed to study the effect of treatment on diastolic blood pressure for the other patient subgroups, and to study the effect of treatment on renal function in all patient subgroups. In the latter analyses, the change in creatinine clearance from baseline to 1 year was used as the dependent variable (outcome), and the creatinine clearance at baseline was included as a covariate. P values <0.05 were considered statistically significant.

Table 6.1. Baseline characteristics of the patients.

Characteristic	PTRA (N=56)	Med-PTRA (N=50)
	Number (%) or mean ± SD	
Male sex	37 (66)	28 (56)
Age, years	59 ± 10	61 ± 10
Blood pressure, mm Hg		
Systolic	179 ± 25	180 ± 23
Diastolic	104 ± 10	103 ± 8
Antihypertensive drugs, number	2.0 ± 0.8	2.0 ± 0.9
Creatinine clearance, mL/min	67 ± 23	60 ± 24
Abnormal captopril test	35/45 (78)	26/33 (79)
Abnormal renogram	35/54 (65)	32/49 (65)
Recent hypertension	19 (34)	17 (34)
Bilateral stenosis	13 (23)	11 (22)
Severe stenosis	38 (68)	26 (52)

Table 6.2. Diastolic blood pressure at baseline and change in diastolic blood pressure (in mm Hg) after 3 and 12 months of treatment (mean ± SD) in subgroups of patients, separately for the PTRA group and for the Med-PTRA group.

Characteristic	No. of patients without missing data		Baseline level	
	PTRA	Med-PTRA	PTRA	Med-PTRA
Positive captopril test				
Yes	35	24	105 ± 9	105 ± 10
No	10	7	107 ± 13	104 ± 5
Abnormal renogram				
Yes	35	31	105 ± 9	102 ± 7
No	19	15	105 ± 11	106 ± 11
Recent hypertension				
Yes	19	15	104 ± 6	101 ± 8
No	37	32	105 ± 11	104 ± 9
Bilateral stenosis				
Yes	13	10	105 ± 9	100 ± 5
No	43	37	105 ± 10	104 ± 9
Severe stenosis				
Yes	38	24	103 ± 8	102 ± 7
No	18	23	108 ± 12	105 ± 10

Results

The patients in the PTRA group and in the Med-PTRA group did not differ with respect to sex, age, blood pressure, number of drugs and creatinine clearance at baseline (Table 6.1). Also, the proportions of patients with positive captopril-renin challenge test, with an abnormal renogram, with recently developed hypertension, with bilateral stenosis, and with severe stenosis were similar in these groups. The distribution of these characteristics was similar for the 66 patients with complete data (data not shown).

Baseline levels and outcomes after 3 months

The diastolic blood pressure levels at baseline of patients with a positive captopril-renin challenge test, with an abnormal renogram, with recently developed hypertension, with bilateral stenosis, or with severe stenosis were fairly comparable to those of patients without the respective characteristic (Table 6.2). Patients with bilateral stenosis had a lower baseline creatinine clearance on

Table 6.2 (continued).

Characteristic	Change from baseline to 3 months		Change from baseline to 12 months	
	PTRA	Med-PTRA*	PTRA	Med-PTRA†
Positive captopril test				
Yes	-6.4 ± 10	-2.5 ± 11	-12 ± 9.6	-7.6 ± 11
No	-3.7 ± 5.4	+3.6 ± 6.9	-10 ± 17	-4.1 ± 8.0
Abnormal renogram				
Yes	-7.0 ± 12	-3.1 ± 9.6	-12 ± 12	-6.9 ± 9.8
No	-5.6 ± 7.2	-1.6 ± 12	-11 ± 12	-7.9 ± 9.8
Recent hypertension				
Yes	-8.8 ± 11	-3.6 ± 10	-15 ± 8.8	-8.5 ± 9.5
No	-4.6 ± 10	-2.1 ± 10	-9.9 ± 12	-6.6 ± 9.7
Bilateral stenosis				
Yes	-5.9 ± 11	+1.1 ± 11	-12 ± 11	-4.0 ± 8.5
No	-6.0 ± 10	-3.6 ± 10	-11 ± 11	-8.1 ± 9.8
Severe stenosis				
Yes	-5.5 ± 11	-0.1 ± 10	-12 ± 11	-6.8 ± 10
No	-7.0 ± 10	-5.1 ± 9.8	-11 ± 13	-7.6 ± 9.3

* Clinical outcome after drug therapy only.

† Clinical outcome after drug therapy followed by angioplasty after 3 months, if needed.

average than those with unilateral stenosis (Table 6.3; P<0.0001). Also, the average baseline creatinine clearance was lower in patients with severe stenosis compared to patients with moderate stenosis (P=0.02). The baseline creatinine clearance levels were equal for the patients in the other subgroups.

Three months after randomization, the improvement in blood pressure (Table 6.2) and in creatinine clearance (Table 6.3) tended to be larger in the PTRA group. At that point in time, all patients in the Med-PTRA group had been treated by drug therapy only. In accordance with the study protocol, a number of patients in the Med-PTRA group received angioplasty after 3 months because of persistent hypertension or deterioration of renal function: 13/26 (50%) and 5/7 (71%) of patients with positive and negative captopril-renin challenge test, respectively; 14/32 (44%) and 7/17 (41%) of patients with an abnormal and a normal renogram, respectively; 7/17 (41%) and 15/33 (46%) of patients with recent and longer existing hypertension, respectively; 6/11 (55%) and 16/39 (41%) of patients with bilateral and unilateral stenosis, respectively; and 15/26

Table 6.3. Creatinine clearance at baseline and change in creatinine clearance (in mL/min) after 3 and 12 months of treatment (mean ± SD) in subgroups of patients, separately for the PTRA group and for the Med-PTRA group.

Characteristic	No. of patients without missing data		Baseline level	
	PTRA	Med-PTRA	PTRA	Med-PTRA
Positive captopril test				
Yes	34	26	69 ± 22	57 ± 23
No	10	7	68 ± 29	68 ± 18
Abnormal renogram				
Yes	34	31	65 ± 22	56 ± 24
No	19	15	69 ± 24	65 ± 23
Recent hypertension				
Yes	19	14	78 ± 16	55 ± 17
No	36	33	61 ± 23	61 ± 27
Bilateral stenosis				
Yes	13	11	53 ± 18	42 ± 15
No	42	36	71 ± 22	65 ± 24
Severe stenosis				
Yes	37	25	63 ± 21	52 ± 17
No	18	22	73 ± 24	67 ± 29

(58%) and 7/24 (29%) of patients with severe and moderate stenosis, respectively. These differences were not statistically significant except for the difference between the patients with severe stenosis and those with moderate stenosis (P=0.04).

Outcomes after 1 year

Blood pressure

After 1 year, the diastolic blood pressure had decreased on average in both treatment groups. The drop in blood pressure level in the PTRA group seemed somewhat larger than in the Med-PTRA group: 11.6 ± 11.3 mm Hg and 7.2 ± 9.6 mm Hg (mean ± SD). This difference was not statistically significant after adjustment for blood pressure at baseline, however (P=0.06). The apparent benefit in the PTRA group was largest in the patients with bilateral stenosis

Table 6.3 (continued).

Characteristic	Change from baseline to 3 months		Change from baseline to 12 months	
	PTRA	Med-PTRA*	PTRA	Med-PTRA†
Positive captopril test				
Yes	+6.1 ± 14	+1.2 ± 11	+5.1 ± 16	+3.0 ± 18
No	-1.4 ± 6.8	+5.7 ± 2.9	+0.5 ± 9.0	+4.8 ± 9.6
Abnormal renogram				
Yes	+4.6 ± 12	+0.3 ± 9.7	+3.6 ± 16	+0.5 ± 14
No	+4.9 ± 13	+0.2 ± 8.2	+3.8 ± 10	+6.6 ± 18
Recent hypertension				
Yes	+2.8 ± 15	+4.6 ± 9.3	+3.7 ± 16	+6.0 ± 17
No	+4.9 ± 11	-1.3 ± 8.7	+3.2 ± 13	+0.7 ± 15
Bilateral stenosis				
Yes	+9.5 ± 17	-0.4 ± 7.4	+10.0 ± 16 ‡§	-4.2 ± 14
No	+2.4 ± 9.4	+0.7 ± 9.8	+1.3 ± 13	+4.3 ± 16
Severe stenosis				
Yes	+4.2 ± 13	+1.6 ± 9.8	+3.0 ± 16	+1.9 ± 17
No	+4.3 ± 8.6	-0.9 ± 8.4	+4.1 ± 8.3	+2.8 ± 14

* Clinical outcome after drug therapy only.
† Clinical outcome after drug therapy followed by angioplasty after 3 months, if needed.
‡ P=0.03 for PTRA vs. Med-PTRA in patients with bilateral stenosis.
§ P=0.007 for interaction of treatment arm (PTRA or Med-PTRA) and bilateral stenosis (yes or no) (see Patients and methods)

(Table 6.2): 12.2 ± 11.3 mm Hg for patients in the PTRA group and 4.0 ± 8.5 mm Hg for patients in the Med-PTRA group (P=0.07). The benefit of PTRA over Med-PTRA within this subgroup seemed higher than for patients with unilateral stenosis, but was not statistically significant (interaction, P=0.46). For the other subgroups (patients with a positive captopril-renin challenge test, patients with an abnormal renogram, patients with recent hypertension, and patients with severe stenosis), the differences between PTRA and Med-PTRA were smaller and also not statistically significant.

Renal function

After 1 year, the creatinine clearance had somewhat increased on average in both treatment groups: 2.3 ± 15.4 mL/min and 3.4 ± 13.7 mL/min. This difference was not statistically significant after adjustment for the creatinine clearance at

baseline (P=0.51). In all subgroups but one, the average creatinine clearance was stable or had increased after 1 year (Table 6.3). The creatinine clearance of patients with bilateral stenosis who were randomized for Med-PTRA, had decreased by -4.2 ± 13.5 mL/min. This occurred despite the fact that six of these 11 patients underwent angioplasty after 3 months of follow-up. On the other hand, the creatinine clearance of the patients with bilateral stenosis who were randomized for PTRA, had improved substantially after one year by +10.0 ± 15.7 mL/min (P=0.03). For patients with unilateral stenosis, the average creatinine clearance had improved somewhat in both treatment groups (+1.3 ± 12.5 mL/min in the angioplasty group and +4.3 ± 15.5 mL/min in the drug therapy group). The difference in treatment effect on renal function between the patients with bilateral stenosis and those with unilateral stenosis was statistically significant (interaction term, P=0.007). For none of the other subgroups, a clear difference between the PTRA group and the Med-PTRA group was found.

Discussion

Our main finding was that patients with atherosclerotic bilateral stenosis had an evident benefit of immediate intervention compared to drug therapy followed by intervention after 3 months, if needed. These patients had a normal or mildly impaired renal function at study entry. After 1 year of follow-up, their renal function had improved if intervention had taken place immediately after the diagnosis, whereas it had deteriorated if intervention had been performed after 3 months in case of persistent hypertension or a decline in renal function. This finding is consistent with the studies reporting that patients with bilateral stenosis have an increased risk of progressive renal dysfunction.[21,22] The patients with bilateral stenosis also seemed to benefit most from immediate intervention with regard to blood pressure control.

We did not find any other subgroup with a clear benefit of immediate intervention, either with regard to blood pressure control or with regard to preservation of renal function. A serious limitation of our study, however, was the lack of statistical power for detecting small differences in treatment effects per subgroup.[14] Our study should therefore be regarded as exploratory. Nevertheless, this is the only study reporting on treatment effects in these subgroups of patients with atherosclerotic renal artery stenosis so far. Another prospective study to confirm these results may not be feasible, given the large numbers of patients needed per subgroup to reach statistical significance.

The results of the treatment strategies with regard to preservation of renal function may have been influenced in a number of ways. First, the assessment of renal function with the creatinine clearance according to the Cockcroft formula

was rather crude. Unfortunately, no other data were available by which the renal function could have been assessed more accurately. Also, the use of ACE inhibitors, AT1 antagonists and diuretics could have affected the renal function, especially in patients with bilateral stenosis. Whereas AT1 antagonists were not used at all, ACE inhibitors and diuretics were used by comparable proportions of the patients in the treatment groups and were used only in low dosages. Patients with bilateral disease benefited by immediate intervention whereas they used ACE inhibitors twice as often as the patients with bilateral disease who were allocated to medication.

A benefit of immediate intervention for preservation of renal function may have been hidden for the subgroups of patients with a positive captopril-renin challenge test, with an abnormal renogram, and with recently developed hypertension. The patients with these characteristics, who were allocated to initial medication, had a relatively worse renal function at baseline, and, consequently, could have gained more from treatment than the patients who were allocated to immediate intervention. However, the actual benefit in renal function after 1 year seemed larger in the patients who received medication only in the subgroup with recent hypertension.

Another limitation was that the treatment strategies in this study did not include renal artery stent placement. Stent placement is superior to angioplasty alone on theoretical grounds. Until now, only one randomized study was published that compared stent placement with angioplasty alone.[8] Although this study reported superior vessel patency and a lower restenosis rate after stent placement, the clinical outcomes after stent placement were similar to those after angioplasty alone. The follow-up in this study was limited to 6 months, however. Based on the available evidence of this randomized study, we suppose that our conclusions would have been similar if additional stent placement would have been included in both treatment arms.

Percutaneous intervention can successfully control blood pressure in patients with renovascular (i.e., renin-dependent) hypertension.[24] Reviews of medical therapy for renovascular hypertension have shown, however, that modern antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers, can achieve adequate blood pressure control in a large proportion of patients with renovascular hypertension.[25] Renovascular hypertension is supposed to be more likely in patients in whom the plasma renin activity is increased after stimulation with captopril (captopril-renin challenge test),[15] in patients with an abnormal renogram after stimulation with captopril,[19] and in patients with recently developed hypertension.[19,20] In these subgroups, immediate intervention did not have an apparent benefit over

restricting intervention to those patients in whom hypertension persisted or renal function declined after 3 months of drug therapy. This benefit, if any, is small and probably does not outweigh the risks of complications and cost of intervention for patients in whom blood pressure can be controlled medically.

Successful intervention may preserve or even restore the renal function in patients with atherosclerotic renal artery stenosis whose renal function is already deteriorating.[26-30] For patients with a normal or mildly impaired renal function, however, it is unclear if and when intervention should be performed to prevent progressive renal failure, because the rate of progressive narrowing of the renal artery and the associated rate of progressive renal failure is generally slow.[31] Our study shows that intervention should not be postponed in patients with bilateral stenosis, even if their renal function is not impaired as yet. This result is in agreement with a prospective study on disease progression, showing that renal survival was lowest in patients with bilateral stenosis, especially in case of an occluded renal artery on one side.[21] Severe unilateral stenosis, on the other hand, did not seem to justify immediate intervention in our study. Although severe stenoses are more likely to progress than less advanced lesions,[31] renal insufficiency develops mainly in patients in whom the entire renal mass is affected.[25] Even in patients with severe stenosis, bilateral disease is present in a minority of cases (in our sample, 34%). Stenosis could be expected to develop in the contralateral kidney, however, although this process is unpredictable and may take a long time.[32]

In conclusion, intervention should be performed immediately in hypertensive patients with atherosclerotic renal artery stenosis and a normal or mildly impaired renal function if bilateral disease is diagnosed. In the remaining patients, aggressive drug therapy followed by intervention in a selection of patients after 3 months is a sensible treatment strategy. In this way, unnecessary interventions can be avoided in a considerable number of patients. Clinicians should be wary of disease progression, however, especially in patients with severe unilateral disease.

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7

Reproducibility and validity of quality of life measurements in hypertensive patients on stable medication

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Abstract

Objective: The reproducibility and validity of a hypertension-specific questionnaire and a generic health questionnaire (the MOS Short-form General Health Survey) were evaluated for measuring the quality of life in a randomized controlled trial comparing balloon angioplasty and long-term medication in patients with hypertension and renal artery stenosis.

Methods: The health questionnaires were filled out by 97 patients with hypertension on stable medication. The reproducibility of the questionnaires was assessed by intraclass correlation coefficients (ICCs). Pearson's correlation coefficients were calculated between the scales of the questionnaires to evaluate the validity.

Results: Medication had been changed to eliminate side effects in an earlier phase of treatment. Only 7% of the patients reported non-compliance with the medication regime. Most patients suffered from physical symptoms, but the impact of long-term antihypertensive medication on the quality of life was not substantial. The reproducibility was good for most scales (ICC >0.70), except for the role and social functioning scales. All correlations between the scales of the questionnaires were statistically significant and no contradictory correlations were found.

Conclusion: The health questionnaires together form a reproducible and valid instrument for measuring the quality of life of hypertensive patients on stable medication.

Introduction

The quality of life of patients on antihypertensive medication is affected by side-effects of antihypertensive drugs and may also be impaired by concomitant diseases and by labelling the patient with a diagnosis of hypertension.[1-5] The diagnosis and treatment of hypertension can affect both physical and psychological well-being and influence work performance and leisure activities.[6] In clinical trials on treatment of hypertension the quality of life is an important treatment outcome, because side-effects of treatment may endanger the patient's compliance to the prescribed medication regimen.[2,3,7]

The quality of life is one of the treatment outcomes in an ongoing randomized multicenter trial in the Netherlands, comparing the effects of balloon angioplasty of the renal artery and long-term antihypertensive medication after 1 year in patients with hypertension and renal artery stenosis (the 'Dutch Renal Artery Stenosis Intervention Cooperative' or 'DRASTIC' study).[8] As in regular clinical practice, the medication is changed in case of side-effects before intake in the trial. Therefore, the quality of life of these patients on stable medication is believed to be less impaired than that of patients participating in clinical trials studying the treatment results and side effects of new antihypertensive drugs.

In the DRASTIC study physical symptoms associated with a high blood pressure or antihypertensive treatment and the effect of treatment on lifestyle are measured by means of a hypertension-specific questionnaire developed by Bulpitt, hereafter called the Hypertension Questionnaire.[9] This questionnaire has been used in several trials comparing treatment results and side-effects of antihypertensive drugs.[10] The MOS Short-form General Health Survey[11] is used to measure in a concise way the psychological well-being and health perceptions as well as other relevant aspects of quality of life that may be affected by treatment and long-term complications of hypertension.

Versions of these questionnaires in the Dutch language are validated in a population of ambulant hypertensive patients on stable antihypertensive medication. The following questions are addressed: What is the quality of life of patients with hypertension on stable medication? Are the questionnaires a valid method for measuring quality of life in these patients? And how reproducible are the questionnaires when used in this patient group?

Patients and methods

Study population

The questionnaires were filled out by 101 consecutive visiting patients treated for hypertension at the outpatient clinic of the Department of Internal Medicine of the Rotterdam University Hospital. New patients were not included. The majority of

patients had essential hypertension, whereas less than a quarter suffered from renovascular hypertension. Patients with other forms of secondary hypertension were not included. Four patients were excluded because they did not use stable antihypertensive medication. All data were collected at the outpatient clinic of the hospital. After the patient had filled out the questionnaires, the medication was recorded and the sitting blood pressure was measured three times with a standard sphygmomanometer. The mean of the blood pressure measurements was used for statistical analysis. Patients were scheduled to return within two weeks for a second study visit. Ninety-five patients returned after an average interval of 16 ± 16 days (mean ± SD) between visits.

Quality of life measurement

The Hypertension Questionnaire[9] contains a checklist of 30 items on physical symptoms attributed to hypertension or to side effects of antihypertensive drugs (Appendix A). This list was extended with eight other potential side effects of antihypertensive drugs commonly used in our hospital (questions marked with '*' in Appendix A). The symptom complaint rate was calculated as the number of positively scored symptoms divided by the total number of non-missing symptom items. A question on compliance to the prescribed medication was included. Another 15 questions cover the patient's perception of the effects of antihypertensive treatment on lifestyle. States of disability are calculated from the scores on both sections of the questionnaire in a health index ranging from 0 (death) to 1 (perfect health)[9,12]. The questionnaire was translated into Dutch by three clinicians of our hospital. Differences between translations were settled in agreement.

The MOS Short-form General Health Survey (or MOS Survey)[11] is a 20-item generic health questionnaire measuring quality of life on 6 scales: physical functioning (6 items), role functioning (2 items), social functioning (1 item), psychological well-being and health perceptions (both 5 items), and pain (1 item) (Appendix B). The instrument was translated into Dutch by two independent translators and differences between translations were settled in agreement.[13,14] To enable the measurement of levels of impairment, the items covering physical functioning and role functioning were limited to the past month. Since the influence of hypertension and antihypertensive medication on psychological well-being has been stressed,[6] the psychological well-being scale was extended with three items concerning irritability, anxiety and listlessness (questions marked with '*' in Appendix B). For each scale, a score between 0 and 100 was calculated. High scores reflect better health, except for the pain scale where a high score indicates more pain.[11]

Data analysis

Apart from the symptom complaint rate, scores on the health scales were calculated only if all items of the scale were filled out. To study whether the symptom complaint rate was related to the blood pressure, the number of prescribed antihypertensive drugs or the patient's age, Pearson's product-moment correlation coefficients were computed. The symptom complaint rate was also compared between patients using specific types of antihypertensive drugs and patients not using these drugs and between male and female patients by Student's T-tests. These patient characteristics were combined in a multiple linear regression model with the symptom complaint rate as the outcome variable. Factors influencing psychological well-being were studied in a similar way. Statistical testing was two-sided with a significance level of 5%.

The internal consistency of the multi-item scales of the MOS Survey was determined with Cronbach's α-coefficient. An α-coefficient of 0.70 or higher was considered sufficient for assessments on a group level.[15]

The reproducibility was assessed by the intraclass correlation coefficient (ICC) in a subgroup of 71 patients who used exactly the same medication on both study visits (test-retest group).[16] The ICC is preferable to Pearson's correlation coefficient, since the ICC also takes into account systematic differences between measurements.[17] It is important to check for systematic differences when assessing the reproducibility of health status measures, because systematic changes in health status measures are known to occur as a learning effect or as an effect of participating in a study.[16] For measuring attitudes like quality of life estimations on a group level, ICCs of 0.70 or higher are considered to be adequate.[18]

Since there is no gold standard for quality of life measurement, the validity of the questionnaires was judged by studying relations between the scales of the questionnaires (convergent validity).[18,19] These relations were assessed by Pearson's correlation coefficients.

Results

Patient characteristics

Ninety-seven patients filled out the questionnaires on the first study visit. Half of the patient group was male and the age was 57 $\pm$ 11 years (mean $\pm$ SD). The systolic blood pressure (SBP) was 162 $\pm$ 27 mm Hg and the diastolic blood pressure (DBP) 97 $\pm$ 14 mm Hg. Most of the patients used two to five different kinds of antihypertensive drugs. Monotherapy was prescribed to only one quarter of the patients. Various kinds of drugs were prescribed: ACE inhibitors (in 62% of patients), diuretics (in 49%), calcium antagonists (in 46%), β-adrenoreceptor antagonists (in 35%), and centrally acting drugs (in 2%). Seven percent of the

Table 7.1. Quality of life: scores on the Hypertension Questionnaire at the first study visit.

Health scale	Score		No. of patients
Mean complaint rate ± SD [scored range]	28% ± 18%	[0-76%]	97
Mean health index ± SD [scored range]	0.87 ± 0.13	[0.63-1.00]	80
Health state			80
Perfect health	2%		2
Minor dissatisfaction	49%		39
Discomfort	9%		7
Minor disability	10%		8
Major disability	19%		15
Disablement	11%		9
Confined to the house or worse	0%		0

patients reported they had failed to take the prescribed dose because of perceived side effects in the past month. This proportion did not differ between patients on monotherapy and patients on a polydrug regimen (χ^2-test, P=0.94).

At the second study visit the blood pressure was virtually unchanged (change in SBP 1.1 ± 18.5 mm Hg and change in DBP 0.7 ± 11.8 mm Hg) in the 71 patients who used the same medication at both study visits (test-retest group). This group did not differ from the total group of 97 patients with respect to gender, age, blood pressure and medication.

Quality of life measurement

Hypertension Questionnaire

All but two patients reported one or more symptoms mentioned in the questionnaire (8 ± 5 symptoms). The most common symptoms were flushing of face and neck (in 52% of patients), light-headedness or faintness (in 51%), sleepiness during the day (in 45%), blurring of vision (in 42%), and headaches (in 40%). The mean symptom complaint rate was 28% ± 18% (Table 7.1).

The symptom complaint rate was weakly correlated with the DBP (correlation coefficient=0.20, P=0.03). No significant correlations were found with the SBP, the number of antihypertensive drugs, or the patient's age. The symptom complaint rate of patients using ACE inhibitors, diuretics, calcium antagonists, or β-adrenoreceptor antagonists did not differ from that of patients who did not use that specific type of antihypertensive drug. Female patients scored a higher complaint rate than male patients (31% and 24% on average; Student's T-test, P=0.04). In a multiple regression model, only 5% of the variance of the symptom complaint rate

Table 7.2. Quality of life: scores on the scales of the MOS Survey at the first study visit.

Scale	Items (N)	Patients (N)	Score (mean± SD)	Scored range	α
Physical functioning	6	88	58 ± 32	0-100	0.81
Role functioning	2	93	72 ± 44	0-100	0.92
Social functioning	1	92	83 ± 22	20-100	-
Psychological well-being	8	93	72 ± 19	23-100	0.89
Health perceptions	8	87	60 ± 23	5-100	0.84
Pain	1	92	34 ± 32	0-100	-

was accounted for by age, gender, blood pressure, and medication. Analogous to the univariate results, only gender had a statistically significant regression coefficient, whereas the other variables did not correlate significantly with the symptom complaint rate.

Eleven percent of the patients were unemployed for medical reasons, 21% were unable to go to work or do usual jobs in and around the house for more than three days in the past month, and 26% stated that their hypertension or its treatment interfered with their hobbies or life. Although the health index was high (0.87 ± 0.13), only 2 patients enjoyed perfect health (Table 7.1).

MOS Survey

The 6 scales of the MOS Survey were completed by more than 90% of the patients. The majority of patients scored in ranges reflecting good health, but patients scored over a wide range on all scales (Table 7.2). All multi-item scales, measuring physical and role functioning, psychological well-being and health perceptions, had α-coefficients above 0.80. The patients scored 72 ± 19 on the psychological well-being scale. Psychological well-being scores were not related to the patient's blood pressure, medication, age, or gender.

Reproducibility

The reproducibility between the study visits was assessed in the test-retest group of 71 patients (Table 7.3). The ICC was 0.88 for the symptom complaint rate and 0.76 for the health index of the Hypertension Questionnaire. Of the scales of the MOS Survey, psychological well-being and health perceptions had the highest ICC (0.88 and 0.81, respectively), followed by the scales measuring physical

Table 7.3. Reproducibility and validity of the health scales.

	CR	HI	PF	RF	SF	PWB	HP	Pain
Complaint rate (CR) *	*0.88*							
Health index (HI) *	0.59	*0.76*						
Physical functioning (PF) †	-0.69	-0.54	*0.76*					
Role functioning (RF) †	-0.45	-0.62	0.46	*0.57*				
Social functioning (SF) †	-0.63	-0.58	0.64	0.45	*0.63*			
Psychological well-being (PWB) †	-0.43	-0.48	0.42	0.36	0.42	*0.88*		
Health perceptions (HP) †	-0.64	-0.51	0.56	0.44	0.50	0.54	*0.81*	
Pain †	0.57	0.23	-0.28	-0.31	-0.34	-0.37	-0.36	*0.69*

The intraclass correlation coefficients on the diagonal are estimates for the reproducibility of the health scales. The product-moment correlation coefficients off the diagonal are estimates for the convergent validity between health scales.

* Scale of the Hypertension Questionnaire.

† Scale of the MOS Survey.

functioning (ICC=0.76) and pain (ICC=0.69). For the social and role functioning scales, low ICCs were found (0.63 and 0.57, respectively).

Validity

Correlations between the health scales of the questionnaires were all statistically significant. The absolute correlation coefficients were between 0.23 and 0.69 (Table 7.3). The symptom complaint rate of the Hypertension Questionnaire was negatively correlated with the scores on the MOS scales measuring psychological well-being scale and health perceptions (correlation coefficient = -0.43 and -0.64 respectively, $P<0.0001$).The scales within the questionnaires also correlated significantly and no contradictory correlations were found.

Discussion

In this study, the quality of life of a group of consecutive visiting hypertensive patients of an outpatient university clinic was measured. The patients were aware of their high blood pressure and used long-term antihypertensive medication. The majority of the patients used two or more different kinds of antihypertensive drugs. Patients with polydrug treatment may be somewhat over represented due to the clinical setting, but this makes the study population very suitable to evaluate the impact of antihypertensive drug treatment on the quality of life. Only 7% of the patients reported non-compliance with the prescribed medication regimen because of perceived side-effects. Since the compliance was not objectively verified, the non-compliance rate may be underestimated due to patients giving socially desirable

answers. Nevertheless, we assume that the compliance had been enhanced by previously changing the medication because of perceived side effects.

By inducing physical complaints, antihypertensive treatment can have a negative impact on the quality of life of patients with hypertension.[6,7] In this patient group, however, the number of physical symptoms did not differ between various drug regimens. These results confirm the finding of other studies that the number of physical complaints does not differ between various treatment regimens after elimination of intolerable side effects.[7,20] Furthermore, the reported non-compliance rate did not vary between patients on monotherapy and patients using more than one type of drug. As mentioned in the literature, the blood pressure and gender were related to the number of physical complaints, but no relation with age was found.[1,7,19] The medication, blood pressure, gender, and age together accounted for only a small part of the variation in the symptom complaint rate of these patients on long-term antihypertensive medication. Since most of the physical complaints listed in the questionnaire are not specific for hypertension, conditions other than hypertension may account for much of the unexplained variation.[5,6]

The relationship between hypertension and psychological well-being has been studied from different viewpoints.[4-7] In this study, variation in psychological well-being scores between patients cannot be explained by labelling or self-selection, as patients were aware of their high blood pressure before entering the study. Differences in psychological well-being scores were not explained by the medication. Effects of medication on specific psychological features could nevertheless be obscured, because these aspects of psychological well-being were not measured on separate scales.[6,21] The most plausible explanation for differences in psychological well-being scores is the presence or absence of co-morbidity,[5] since the psychological well-being was negatively associated with the number of physical complaints.

Although no clinically relevant change in quality of life due to medication is expected in clinical trials involving hypertensive patients on stable medication, the quality of life still is an important outcome measure in these trials. Decreases in quality of life may be expected due to complications of invasive treatment. Furthermore, the occurrence of long-term complications of hypertension, like coronary heart disease and stroke, may differ between treatment strategies after follow-up, leading to considerable differences in the quality of life between study groups.[5,10]

The reproducibility of the health scales was studied in a subgroup of 71 patients who used exactly the same medication on both study visits. Their quality of life was assumed to be stable over the two study visits. For the majority of these patients, the interval between the study visits exceeded one week. We therefore

assume that most of them were not able to duplicate their answers to the questionnaires by memory. The reproducibility of most health scales was satisfactory, although that of the role and social functioning scales was not as good. The underlying health concepts of these two scales harbour different aspects, which are covered in only two items and one item, respectively. Therefore, these scales may lack specificity.

Because no gold standard for quality of life is available, the convergent validity of the health questionnaires was assessed by calculating correlation coefficients between the health scales. High correlations cannot be expected between various scales, because they address different dimensions of quality of life. No contradictory correlations were found between the health scales and all correlations were statistically significant. We therefore provisionally conclude that the health questionnaires used in this study render a valid representation of the quality of life in patients with hypertension on long-term medication.

We conclude that the two health questionnaires together form a valid and reproducible instrument for measuring the quality of life in hypertension, which can be used to detect clinically relevant changes in quality of life caused by hypertension itself or by complications of therapy.

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8

The effect of treatment on health-related quality of life in patients with hypertension and renal artery stenosis

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Abstract

Background: The quality of life in patients with hypertension is considered to be impaired mainly by side effects of antihypertensive-drug therapy. Because balloon angioplasty for renal artery stenosis has a medication-sparing effect, it may lead to an improvement in quality of life. The objective of the study was to compare the effect of antihypertensive-drug therapy and balloon angioplasty on quality of life in patients with hypertension and renal artery stenosis.

Methods: We compared the quality of life in 56 patients randomized to balloon angioplasty to that in 50 patients randomized to antihypertensive-drug therapy after 3 and 12 months of follow-up. Quality of life was measured using a questionnaire on physical symptoms associated with hypertension and antihypertensive drugs, and two generic health questionnaires (MOS Survey and EuroQol instrument).

Results: After follow-up, the patients who underwent angioplasty used less antihypertensive drugs than the patients who were treated with antihypertensive drugs only (mean ± SD, 2.5 ± 1.0 versus 1.9 ± 0.9 drugs after 3 months, P=0.002). They reported similar physical complaints, however, and a similar quality of life. The results after 12 months of follow-up were the same.

Conclusion: For patients with hypertension and renal artery stenosis, the decrease in antihypertensive medication after intervention is too small to lead to a detectable improvement in quality of life.

Introduction

Health-related quality of life is often studied as an outcome of clinical research.[1] Treatment of a clinical condition may improve the quality of life in patients, but it may also decrease the quality of life due to side effects or complications. Hypertension, especially in the mild to moderate stages, generally is an asymptomatic condition. Treatment of hypertension with antihypertensive drugs, however, can have side effects that impair quality of life.[2,3] Physical complaints such as headache, dizziness, nausea, drowsiness, diarrhea, and impotence are commonly acknowledged side effects of antihypertensive drugs.[4] Also, some of these drugs have been associated with psychological side effects, such as depression.[2]

The objective of this study was to assess the effect of treatment on the quality of life in patients with hypertension and renal artery stenosis. We compared the quality of life in patients with atherosclerotic renal artery stenosis who were treated with or without balloon angioplasty. Angioplasty can lead to improvement or even cure of hypertension.[5] As a consequence, patients who benefit by intervention may need less or even no antihypertensive drugs after the procedure, and may therefore be expected to experience an improvement in their quality of life.

Patients and methods

Patients

We compared the quality of life in patients who participated in the therapeutic phase of the 'DRASTIC' study.[6] In this phase of the study, which was described in detail in Chapter 5, 106 patients were included with drug-resistant hypertension (defined as diastolic blood pressure of 95 mm Hg or more despite a standardized regimen of 2 antihypertensive drugs on three consecutive visits) and angiographically proven atherosclerotic renal artery stenosis of 50% or more.[7] The patients were randomly allocated to balloon angioplasty (N=56) or to increased antihypertensive-drug therapy (N=50).

Quality of life

Quality of life was measured before randomization and after 3 and 12 months of follow-up, using three questionnaires. The first questionnaire was a questionnaire for recording physical symptoms associated with hypertension or antihypertensive treatment and the effect of treatment on lifestyle.[8] The second questionnaire was a validated Dutch version of the 'MOS Short-form General Health Survey' (MOS Survey).[9,10] This generic health questionnaire measures six dimensions of quality of life: physical functioning, role functioning, social functioning, psychological well-

being, health perceptions, and pain. Scores on these scales range between 0 and 100, with higher scores reflecting a better health. Dutch versions of these two questionnaires were validated in Chapter 7. The third questionnaire was a validated Dutch version of the 'EuroQol' instrument.[11] This generic health questionnaire measures the ability to walk, the ability to perform daily activities, depression, anxiety, and pain on a 3-point scale. The scores on these aspects of quality of life are combined to describe general health status, which can be linked to a preference (utility) for the health status obtained from the general population.[12,13] The utilities range between 0 (worst imaginable health status) and 100 (best imaginable health status).

Data analysis

We used regression analysis to compare the quality of life between the patients randomized to angioplasty or drug therapy after 3 and 12 months of follow-up. In the analyses, the scores at 3 or at 12 months were used as the dependent variable, and treatment group (angioplasty or medication) as the independent variable. Quality of life scores before randomization were entered as a covariate into the regression models to correct for baseline differences between the treatment groups. Comparisons over time within patient groups were tested with the paired Student's T-test.

Results

The treatment groups were comparable with regard to age and sex, and with regard to blood pressure and antihypertensive medication at the time of randomization (see Table 5.1, Chapter 5). After 3 months of follow-up, the treatment groups had similar blood pressure levels, but the patients in the drug-therapy group used more antihypertensive drugs than the patients in the angioplasty group (mean $\pm$ SD, 2.5 $\pm$ 1.0 and 1.9 $\pm$ 0.9 drugs, respectively; P=0.002). According to the study protocol, 22 of the 50 patients in the drug-therapy arm of the trial received angioplasty during the remaining follow-up period of another 9 months, either because of inadequate blood pressure control or because of a decline in renal function. At the end of the study, the blood pressure levels of the treatment groups were similar. The drug use in the drug-therapy group was higher than in the angioplasty group (2.4 $\pm$ 0.9 and 1.9 $\pm$ 0.9 drugs, respectively; P=0.002).

The quality of life before randomization was comparable between the treatment groups (Table 8.1). After 3 months of follow-up, the number of physical complaints in the angioplasty group seemed to have decreased more than in the drug-therapy group, but the difference was not statistically significant

Table 8.1. Scores on the physical symptoms list, EuroQol index, and six scales of the MOS Survey for patients randomized to balloon angioplasty (N=56) and drug therapy (N=50) measured before randomization ('T0') and changes in scores after 3 and 12 months of follow-up ('T3-T0' and 'T12-T0', respectively). Higher scores reflect better health, except for physical symptoms. (Differences in) scores are expressed as mean±SD. Data on physical symptoms were complete. Data on quality of life scales were missing for 28% to 50% of the patients.

Questionnaire	Angioplasty group			Drug-therapy group		
	T0	T3-T0	T12-T0	T0	T3-T0	T12-T0
Physical symptoms	6.8±5.8	-3.4±6.8	-2.2±6.2	5.9±6.9	-1.1±6.9	-1.0±8.4
MOS Survey						
Physical functioning	52±29	10±26	2±24	48±33	5±19	11±20
Role functioning	57±49	17±53	21±49	56±48	21±35	17±49
Social functioning	80±25	11±25	-2±26	73±34	0±22	13±33
Psychological well-being	68±16	7±11	8±12	72±16	2±11	3±9
Health perceptions	50±24	6±18	7±20	49±28	7±17	9±19
Pain	69±35	8±31	6±37	60±37	10±17	7±27
EuroQol index						
Overall well-being	80±16	9±15	6±13	80±19	8±11	7±14

(P=0.09). After 12 months, the patients in both groups reported a similar number of physical complaints. For the generic questionnaires (EuroQol index and scales of the MOS Survey), the average scores after 3 and 12 months of follow-up were similar to the baseline measurement or had improved in both treatment groups (Table 8.1). No differences between the treatment groups in change in these quality of life scores after follow-up could be demonstrated after correction for the baseline scores (P>0.10), except for the MOS-social functioning scale. The difference in change in scores on the latter scale was borderline significant at both 3 and 12 months (P=0.06), but at 3 months the angioplasty group had the better scores, and at 12 months the drug-therapy group.

Discussion

The quality of life in patients with hypertension is considered to be impaired mainly by side effects of antihypertensive drug treatment.[2,3] We hypothesized to find an improvement in quality of life for patients with hypertension and renal

artery stenosis who were treated by percutaneous intervention (balloon angioplasty) compared to patients who received antihypertensive-drug therapy only, because the patients who were treated by angioplasty needed less or even no drug therapy after intervention (Chapter 5). The patients in the angioplasty group did seem to have less physical complaints after 3 months of follow-up, but the difference was too small to be confirmed statistically. We also expected but did not find an improvement of the generic health measures in the angioplasty group compared to the drug-therapy group. Apparently, the decrease in medication due to intervention, which amounted to less than 1 drug on average, was too small to lead to a meaningful and detectable improvement in the measures of quality of life that were used in our study.

In a large community-based population, it was found that patients with hypertension who used less antihypertensive medication reported a better health status.[14] Our data, however, did not confirm this finding. At baseline, the number of antihypertensive drugs was not statistically significantly associated with any of the quality of life scales, probably because there was little variation in the number of prescribed drugs. Although the patients in our study used up to 5 different antihypertensive drugs at the same time, the majority used 2 or 3 drugs (59% and 24% of the patients, respectively).

The comparison between the quality of life in the groups with and without percutaneous intervention after 3 months was straightforward. The comparison between the treatment groups after 12 months of follow-up, however, was complicated by the fact that after 3 months of follow-up nearly half of the patients in the drug-therapy group underwent angioplasty because of unsatisfactory blood pressure control or a decline of renal function. So, the comparison at 12 months was not one between patients with or without percutaneous intervention. The patients who were allocated to drug therapy but underwent angioplasty during follow-up, were clinically worse off at baseline with respect to blood pressure and medication use (Table 5.3, Chapter 5). These patients also seemed to be somewhat worse off with regard to the number of reported physical complaints and general health status, although this could not be confirmed statistically due to the small number of patients with non-missing data in each group (data not shown).

Patients with hypertension have a lower appreciation for their general health than persons of the same age without hypertension.[14] In a community-based population, the persons with hypertension valued their general health status as 83 (95% confidence interval, 81-85) on a scale from 0 (lowest valuation) to 100 (highest valuation).[14] The average valuation of general health in our group of hypertensive patients as measured by the EuroQol index at baseline was 80 (95%

confidence interval, 76-84). This estimation must be appreciated as somewhat low, because we used valuations for the health states descriptions given by the general public, which are generally lower than those of the patients themselves. The improvement of the valuation of the general health status in our study group after follow-up was not statistically significant. We do not have a clear explanation for such an improvement other than that of a study effect.

In conclusion, the medication sparing effect of intervention in patients with hypertension and renal artery stenosis is too small to lead to a meaningful improvement in quality of life for these patients.

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9

Cost-effectiveness of treatment strategies for hypertensive patients with renal artery stenosis on CTA or MRA

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In preparation

Abstract

Background: The objective of the study was to compare the cost-effectiveness of various treatment strategies for patients with drug-resistant hypertension without severe renal failure, who have findings suggestive of significant renal artery stenosis on CTA or MRA.

Methods: Clinical decision analysis was used to compare antihypertensive medication (reference strategy) to six strategies involving confirmation of renal artery stenosis by intra-arterial angiography and percutaneous intervention. Intervention for atherosclerotic renal artery stenosis consisted of percutaneous transluminal angioplasty (PTA) with or without selective stent placement, or primary stent placement. Our multi-state transition (Markov) model combined individual patient data and data from the literature to weigh short-term complications and cost of percutaneous intervention against long-term risks and cost of hypertension and renal insufficiency. The model simulated the quality-adjusted life expectancy, lifetime costs and incremental cost-effectiveness ratios for 60-year-old men (base-case analysis).

Results: In the base-case analysis, medication yielded the lowest effectiveness (9.33 QALYs) and highest cost (€107,200). Compared to medication, quality-adjusted life expectancy increased by 72 to 75 days if PTA was performed without stent placement, and by 108 to 112 days if selective or direct stent placement was performed. For some age groups, PTA with selective stent placement was the most effective and least costly strategy. For other age groups, it was more cost-effective to treat with medication first and to perform intra-arterial procedures only if blood pressure control failed or renal function deteriorated. The differences in cost and effectiveness between these strategies were very small. The results were sensitive to variation in the risk of end-stage renal disease.

Conclusions: For patients with drug-resistant hypertension and findings suggestive of renal artery stenosis on CTA or MRA, the cost-effectiveness of performing direct angiography and subsequent intervention is comparable with that of starting with medication first. If an intervention is performed, atherosclerotic stenosis should be treated with PTA followed by stent placement in the same session if the PTA procedure fails.

Introduction

Renal artery stenosis is the most frequent cause of secondary hypertension and an increasingly important cause of end-stage renal disease.[1] Patients are generally evaluated for the presence of renal artery stenosis if they have drug-resistant hypertension or progressive renal failure. The definite diagnosis is based on intra-arterial angiography, which is a relatively costly imaging technique and has a risk of morbidity and mortality. Non-invasive imaging techniques such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are commonly used to select patients for intra-arterial angiography. According to a meta-analysis,[2] the sensitivity and specificity of CTA and gadolinium-enhanced MRA for finding significant renal artery stenosis on intra-arterial angiography are more than 90%.

Percutaneous transluminal angioplasty (PTA) with or without stent placement is an effective therapy for restoring renal artery patency.[3] However, for the majority of patients with renal artery stenosis, namely those with stenosis caused by atherosclerosis,[1] the optimal treatment strategy is still uncertain. In a meta-analysis of the results of the study described in Chapter 5 and two other randomized controlled trials comparing PTA to medical treatment,[4,5] the benefit of PTA with respect to blood pressure control was small.[6] In our study, there was some indication that PTA was beneficial for preserving renal function (Chapter 5). Also, the advantage of additional stent placement is still unclear. In a randomized trial comparing stent placement to PTA, stent placement led to superior vessel patency but not to better blood pressure control or better preservation of renal function.[7] In these randomized studies, long-term complications of hypertension and progressive renal failure were not measured and costs were not taken into account.

Purpose of this study was to compare the cost-effectiveness of various treatment strategies for patients with drug-resistant hypertension without severe renal failure, who have findings suggestive of significant renal artery stenosis on CTA or MRA.

Patients and methods

A decision analytic model was developed to compare the costs, effectiveness and cost-effectiveness of seven treatment strategies for patients with drug-resistant hypertension (defined as diastolic blood pressure >95 mm Hg while using 2 antihypertensive drugs) and findings suggestive of significant renal artery stenosis (>50%) on CTA or MRA. Patients with severe renal failure (defined as a serum creatinine concentration >200 μmol/L) were not considered for the analysis because their condition requires an intervention without delay.[8]

The model combined self-collected data and data from the literature on short-term and long-term risks, benefits, and costs to predict quality-adjusted life expectancy, lifetime costs, and incremental cost-effectiveness (CE) ratios. For the sake of simplification, several assumptions were made (see below). The model was programmed in DATA Pro Treeage Release 7 (Treeage Software, Inc., Williamstown, MA).

Model and modelling assumptions

Treatment strategies

In the reference strategy, all patients were treated with aggressive antihypertensive medication without any form of revascularization (strategy Med). The other six strategies involved intra-arterial angiography followed, if a stenosis was present, by percutaneous intervention in the same session. Intervention for patients with stenosis due to fibromuscular dysplasia was always PTA without stent placement.[9,10] Atherosclerotic stenoses were treated with PTA without stent placement (strategy PTA), PTA with stent placement only in case of elastic recoil immediately after dilation (strategy PTA-SelectiveStent) or direct stent placement (strategy Stent). In the other three strategies involving intervention, the initial therapy was antihypertensive medication, and intra-arterial angiography and intervention were only performed if a clinical indication for intervention was present (strategies Med-PTA, Med-PTA-SelectiveStent, and Med-Stent). The criteria for a clinical indication for intervention were inadequate blood pressure control (defined as diastolic blood pressure >95 mm Hg using three drugs, or >100 mm Hg using two drugs) or renal failure (defined as serum creatinine concentration >150 μmol/L or an increase in serum creatinine concentration >20 μmol/L).

After an intervention, patients received antihypertensive medication if blood pressure control was inadequate. For every patient with renal artery stenosis, a maximum of two interventions were modelled.

Model

We developed a multistate transition (Markov) model to simulate patients who were followed over time and to estimate the prognosis resulting from each treatment strategy.[11] Patients moved among a limited number of predefined health states, starting in one of three health states reflecting blood pressure level and renal function 3 months after intervention or antihypertensive medication. 'Clinical success' was defined as diastolic blood pressure <90 mm Hg and serum creatinine <150 μmol/L. 'Clinical improvement' was defined as diastolic blood pressure 90-110 mm Hg and serum creatinine <150 μmol/L. 'Clinical failure' was

defined as diastolic blood pressure >110 mm Hg and/or serum creatinine >150 μmol/L.

Patients were at risk for cardiovascular disease (stroke and myocardial infarction) and for end-stage renal disease, which was assumed to necessitate dialysis therapy for the remaining lifetime. After these events, the quality of life was reduced and the mortality risk was increased. Percutaneous intervention involved a procedure-related mortality risk, and a procedure-related risk of stroke, end-stage renal disease and other major complications. The benefits of percutaneous intervention involved better blood pressure control and better preserved renal function, which decreased the risk of cardiovascular disease and end-stage renal disease.

Data sources and data assumptions

In the model, the predictive value of a positive CTA or MRA in the group of patients with drug-resistant hypertension was 83%.[2,12] In 80% of the patients with stenosis, atherosclerosis was the underlying cause.[1,12]

Model estimates on treatment outcomes and costs were based on the data of two large prospective studies on diagnosis and treatment of renal artery stenosis in the Netherlands, the 'DRASTIC' study and the 'RADISH' study.[13] Model estimates concerning percutaneous intervention, and risks of cardiovascular complications and end-stage renal disease were based on data from the literature. Key parameters are given in Table 9.1 (probabilities and rates) and in Table 9.2 (utilities and costs).

Intervention

Technical failure of a procedure was assumed to occur if the stenosis could not be passed with the catheter or in case of elastic recoil when the vessel was dilated and no stent was placed. So, stent placement resulted in a higher technical success rate than PTA.[14] If technically successful, however, the clinical outcomes after stent placement and after PTA were similar.[7] We assumed that a second procedure would not be attempted if a procedure failed technically. The nature and rate of complications of PTA and stent placement were the same.[7,14] Also, the risks and benefits of first and second interventions were assumed not to differ.

Morbidity and mortality

The risk of cardiovascular complications (stroke and myocardial infarction) and, for patients without a significant stenosis, the risk of end-stage renal disease were assumed to depend on the diastolic blood pressure level.[15,16] For patients with a

Table 9.1. Rates and probabilities.

Variable	Base case (Range)	References
Stenosis		
% In patients with drug-resistant hypertension	0.20 (0.17-0.24)	12
Sensitivity of MRA/CTA	0.95 (0.80-1)	2
Specificity of MRA/CTA	0.95 (0.80-1)	2
% Stenosis due to fibromuscular dysplasia	0.16 (0.09-0.23)	12
Intra-arterial angiography		
Mortality	0.0003 (0.0002-0.0004)	28
Chronic renal failure *	0.0002 (0-0.0004)	29
Stroke	0.0012 (0.0003-0.0035)	30
Major complication (other than the above) †	0.013 (0.004-0.030)	13
Intervention		
Mortality	0.01 (0-0.02)	14
Chronic renal failure *	0.003 (0.0003-0.0107)	31
Stroke	0.0044 (0.0009-0.0129)	31
Major complication (other than the above) †	0.088 (0.072-0.106)	32
Technical success of		
PTA		
in patients with atherosclerotic stenosis	0.77 (0.68-0.86)	14
in patients with fibromuscular dysplasia	0.94 (0.89-0.98)	33, 34, 35
Stent placement	0.98 (0.95-1.0)	14
Treatment results after medical therapy ‡		
Successful §	0.10 (0.03-0.22)	DRASTIC database
Improved ‖	0.66 (0.51-0.79)	DRASTIC database
Failed ¶	0.24 (0.13-0.38)	DRASTIC database
Indication for intervention **		
After 3 months	0.61 (0.42-0.77)	DRASTIC database
After 12 months	0.70 (0.50-0.86)	DRASTIC database
Treatment results after intervention ‡		
Successful §	0.18 (0.09-0.31)	DRASTIC database
Improved ‖	0.66 (0.51-0.78)	DRASTIC database
Failed ¶	0.16 (0.08-0.28)	DRASTIC database
Indication for intervention after 12 months **	0.27 (0.13-0.46)	DRASTIC database

* It was assumed that one third of the severe reactions to the use of contrast media reactions would result in chronic renal failure.

† Including branch renal artery injury (2.2%), main renal artery damage (2.4%), puncture site injury (2.3%), embolization (1.1%), nephrectomy (0.3%), and other major complication (0.5%).

‡ For patients with atherosclerotic renal artery stenosis, after 3 months of follow-up.

§ Diastolic blood pressure <90 mm Hg and serum creatinine <150 μmol/L.

‖ Diastolic blood pressure 90-110 mm Hg and serum creatinine <150 μmol/L.

¶ Diastolic blood pressure >110 mm Hg and/or serum creatinine >150 μmol/L.

** Defined as inadequate blood pressure control (diastolic blood pressure >95 mm Hg on 3 antihypertensive drugs or >100 mm Hg on 2 drugs) and/or failure of renal function (serum creatinine >150 μmol/L or increase of serum creatinine of >20 μmol/L).

Table 9.1 (continued).

Variable	Base case (Range)	References
Events		
Stroke (annual risk)		
Diastolic blood pressure <90 mm Hg	0.0011 (0.0008-0.0015)	15
Diastolic blood pressure 90-110 mm Hg	0.0025 (0.0018-0.0034)	15
Diastolic blood pressure >110 mm Hg	0.0101 (0.0064-0.0150)	15
Myocardial infarction (annual risk)		
Diastolic blood pressure <90 mm Hg	0.0044 (0.0037-0.0051)	15
Diastolic blood pressure 90-110 mm Hg	0.0095 (0.0080-0.0112)	15
Diastolic blood pressure >110 mm Hg	0.0136 (0.0093-0.0192)	15
End-stage renal disease (annual risk)		
Diastolic blood pressure < 90 mm Hg	0.00011 (0.00003-0.00028)	16
Diastolic blood pressure 90-110 mm Hg	0.00051 (0.00030-0.00082)	16
Diastolic blood pressure > 110 mm Hg	0.00122 (0.00087-0.00166)	16
For stenosis patients, before intervention	0.027 (0.010-0.062)	17
For stenosis patients, after intervention	0.0016 (0.0003-0.0045)	36

significant stenosis, the risk of end-stage renal disease was increased, especially if percutaneous intervention was not performed.[17] The risk of cardiovascular complications and the associated mortality risks were increased after a previous cardiovascular event and in case of chronic dialysis therapy. If cardiovascular events and chronic renal failure did not occur, the mortality risk was equal to that of standard life tables of the Dutch general population according to age and sex.

Quality of life

The quality of life of the patients in the model was assumed not to depend on the type or the amount of antihypertensive medication (Chapter 8). Temporary quality of life adjustments were made to take into account the diminished quality of life as a result of undergoing an intra-arterial procedure, and during the first year after myocardial infarction. The quality of life was decreased permanently for patients on chronic dialysis therapy and after stroke.

Costs

Estimates for costs of percutaneous interventions and of medical treatment were based on detailed cost calculations performed in the RADISH study.[13] Estimates for costs of complications of intervention and costs of long-term complications were based on the literature. Patients who suffered from major stroke, were assumed to be admitted into a nursing home for their remaining lifetime. Costs were expressed in 2000 Euros (€1 = US$1.20).

Table 9.2. Health related quality of life values and costs.

Variable	Base case (Range)	References
Quality of life		
Antihypertensive-drug therapy	0.85 (0.80-0.90)	DRASTIC database
Duration of experienced discomfort (days)		
Intra-arterial angiography	0.94 (0-2)	13
PTA (with or without stent placement)	5.34 (1-10)	13
Disutility from invasive procedure during the days of experienced discomfort	0.56 (0.4-0.8)	13
After myocardial infarction (for 1 year)	0.72 (0.6-0.8)	37
After major stroke	0.37 (0.33-0.41)	38
On dialysis therapy	0.45 (0.43-0.56)	39
Costs (in 2000 Euros)		
Antihypertensive medication (annual cost)		
DBP <90 mm Hg	3,487 (2,441-4,533)	13
DBP ≥90 mm Hg	3,693 (2,585-4,801)	13
Intra-arterial angiography *	1,359 (951-1,767)	13
PTA †		
for fibromuscular dysplasia	2,717 (1,902-3,532)	13
for atherosclerotic renal artery stenosis	2,762 (1,933-3,591)	13
Stent placement †	4,778 (3,345-6,211)	13
Complications of intra-arterial procedures		
Procedure-related mortality	2,416 (1,691-3,141)	40
Other major complications ‡	704 (493-915)	40
Treatment after stroke	11,281 (7,897-14,665)	41
Treatment after myocardial infarction	5,000 (3,500-6,500)	40, 42
Start dialysis therapy	7,686 (5,380-9,992)	43
Nursing home (annual cost)	52,509 (36,756-68,262)	40
Dialysis therapy (annual cost)	62,020 (43,414-80,626)	43

* Including one night of hospital admission.
† Weighted average for unilateral and bilateral procedures.
‡ Assumed to involve two extra days of hospitalization.

Cost-effectiveness analysis

Effectiveness was measured as quality-adjusted life-years (QALY's).[18] With regard to cost-effectiveness, the analysis took the perspective of the Dutch health care system and included hospital costs and physician costs for medical treatment, percutaneous intervention, and long-term complications (cardiovascular events, nursing home, end-stage renal disease, and dialysis therapy). Future years and costs were discounted at an annual rate of 3%.[19]

A strategy was considered superior by dominance if it was more effective and cost-saving compared to another strategy.[18] If a strategy was more effective but also more expensive than another strategy, the incremental CE ratio was calculated by dividing the additional cost of the strategy by its additional

effectiveness. In the Netherlands, the threshold incremental CE ratio is somewhere between €33,000/QALY (i.e., the incremental CE ratio for heart transplantation, which was considered acceptable)[20] and €54,000/QALY (i.e. the incremental CE ratio for lung transplantation, which was not considered acceptable)[21]. In this study, incremental CE ratios below €50,000/QALY were considered acceptable.

In the base-case analysis, the remaining lifetime of a 60-year-old male patient was simulated 100,000 times (first-order Monte Carlo simulation). We also studied the effect of age and sex on the outcome of the model. Furthermore, the effect of the uncertainty in the key parameters (Tables 9.1 and 9.2) was explored by varying the estimates over plausible ranges in one-way and two-way sensitivity analyses. Plausible ranges for probabilities, rates and utilities consisted of 95% confidence intervals. Plausible ranges for costs were expressed as the base-case estimate plus or minus 30%.

Results

Base-case analysis

The quality-adjusted life expectancy for the reference strategy consisting of treatment with antihypertensive medication only (strategy Med) was 9.33 QALY's (Table 9.3). Compared to medication only, the strategies involving PTA without stent placement (strategies Med-PTA and PTA) increased the quality-adjusted life expectancy by 72 and 75 quality-adjusted days, respectively. The strategies involving stent placement (strategies Med-PTA-SelectiveStent, Med-Stent, PTA-SelectiveStent, and Stent) increased the quality-adjusted life expectancy by 108 to 112 quality-adjusted days. The lifetime costs of the strategies ranged from €100,200 for the strategy PTA-SelectiveStent to €107,200 for the medication only strategy (strategy Med). The strategy PTA-SelectiveStent was superior by dominance, which means that it had a larger (or equal) effectiveness and a lower cost than the other six strategies. The differences between the strategies involving stent placement, however, were small.

Analysis for age and sex

The outcome of the model was sensitive to variation in the patient's age. Varying age, the preferred strategy was either PTA-SelectiveStent or Med-PTA-SelectiveStent, but the differences in both effectiveness and costs were very small (maximally 10 quality-adjusted days and less than €1000) for both male and female patients (Table 9.4).

Table 9.3. Cost (Euros), effectiveness (QALY's), and incremental CE ratios of treatment strategies for 60-year-old male patients with drug-resistant hypertension and findings suggestive of renal artery stenosis on MRA or CTA.

Treatment strategy	Cost (Euros)	Effectiveness (QALY's)	Incremental CE ratio
Med	107,200	9.329	Dominated *
Med-PTA	101,600	9.527	Dominated *
PTA	102,100	9.534	Dominated *
Med-Stent	102,200	9.626	Dominated *
Med-PTA-SelectiveStent	100,300	9.626	Dominated *
Stent	102,200	9.636	Dominated *
PTA-SelectiveStent	100,200	9.636	-

* More expensive and less effective than another treatment strategy.

Sensitivity analyses

The strategy PTA-SelectiveStent remained superior by dominance when we varied most of the key parameters in the model (Tables 9.1 and 9.2) across their plausible ranges, or had an incremental CE ratio of less than €15,000/QALY compared to strategy Med-PTA-SelectiveStent. The model outcome was sensitive, however, to changes in the risk of end-stage renal disease for patients with stenosis before intervention. Med-PTA-SelectiveStent was more cost-effective than PTA-SelectiveStent if the annual risk of end-stage renal disease was 2% or lower. The differences between the two strategies were small, however, for all plausible values, both with regard to effectiveness (difference maximally 10 quality-adjusted days) and lifetime costs (difference less than €1000). We found similar results when both the risks of end-stage renal disease before and after intervention were varied simultaneously in a two-way sensitivity analysis.

Discussion

On the basis of the best estimates for the model parameters, the most cost-effective treatment strategy for our base-case, a 60-year-old male patient with findings suggestive of significant renal artery stenosis on CTA or MRA, was to perform intra-arterial angiography and, if the presence of a stenosis was confirmed, to perform a percutaneous intervention in the same session. Our results suggested that patients with atherosclerotic renal artery stenosis should preferably receive a stent only if PTA fails. For other age groups, however, it was more cost-effective to start with antihypertensive medication, and to perform the

Table 9.4. Cost (Euros) and effectiveness (QALY's) for the treatment strategies PTA-SelectiveStent and Med-PTA-SelectiveStent and the difference in cost (Euros) and effectiveness (quality-adjusted days) between the two strategies, for male and female patients of different ages.

Males	PTA-SelectiveStent		Med-PTA-SelectiveStent		Difference in *	
Age	Cost (Euros)	Effectiveness (QALY's)	Cost (Euros)	Effectiveness (QALY's)	Cost (Euros)	Effectiveness (days) †
40	142,900	13.507	142,700	13.521	+200	-5
50	125,300	11.890	125,200	11.902	+100	-4
60	100,200	9.636	100,300	9.626	-100	+4
70	70,700	6.946	70,400	6.954	+300	-2
80	41,900	4.352	42,700	4.352	-800	0

Females	PTA-SelectiveStent		Med-PTA-SelectiveStent		Difference in *	
Age	Cost (Euros)	Effectiveness (QALY's)	Cost (Euros)	Effectiveness (QALY's)	Cost (Euros)	Effectiveness (days) †
40	149,700	14.143	149,800	14.114	-100	+10
50	135,600	12.898	135,400	12.900	+200	0
60	115,200	11.044	115,500	11.073	-300	-10
70	87,800	8.513	87,000	8.514	+800	0
80	53,000	5.441	52,800	5.448	+200	-2

* Strategy PTA-SelectiveStent compared to strategy Med-PTA-SelectiveStent.
† Adjusted for quality of life.

intra-arterial procedure only if blood pressure was inadequately controlled or if renal function deteriorated. The discrepancies in the outcomes of the model between age groups were probably due to the fact that the differences in both cost and effectiveness between these strategies were very small.

We studied whether the outcome of the model was sensitive to the uncertainty in the key parameters in our model. As in the base-case analysis, the treatment strategy of direct intervention with selective stent placement was the most effective and least expensive strategy in most of the sensitivity analyses, or had an incremental CE ratio well within the ranges of what society generally is willing to pay. For low values of the risk of end-stage renal disease, however, it was more cost-effective to start with antihypertensive medication, but again the differences in costs and effectiveness were very small.

A limitation of our analysis was that the treatment strategies were not modeled separately for patients with unilateral disease and patients with bilateral disease for lack of data on model parameters for these subgroups. Ideally, this distinction is made because the risk of progressive renal failure seems to be determined primarily by the presence of unilateral or bilateral stenosis.[22] As found in our trial (Chapter 6) and in other studies,[8] patients with bilateral stenosis are at risk for rapid deterioration of renal function and should receive invasive treatment without delay, even if their renal function is not impaired as yet. These observations are consistent with our results. In the base-case analysis, the optimal strategy was to perform an intervention in all patients with a stenosis. This result was sensitive, however, to uncertainty in the risk of end-stage renal disease before intervention. If the value for the risk of end-stage renal disease was low, which is probably the case for patients with unilateral stenosis, the optimal strategy was to treat medically first, and to perform an intervention only in patients with inadequate blood pressure control or progressive renal failure.

Several assumptions were made in our analysis. The most important one was that we assumed that stent placement has a higher technical success rate compared to PTA alone but that, if technically successful, these procedures lead to similar clinical outcomes. It is well-established that stent placement is superior to PTA with respect to immediate vessel patency and, to a lesser extent, prevention of late restenosis.[14,23] Nevertheless, stent placement does not seem to improve the short-term clinical outcomes compared to PTA.[7] Also, the relation between vessel patency and clinical outcomes after intervention in the short-term has not been established.[24] In the long-term, however, stent placement may preserve renal function better than PTA due to a lower rate of restenosis, but data to support this theory are not available. Although our analysis was conservative with respect to the benefit of stent placement, the treatment strategies involving stent placement were more effective than the strategies involving PTA only. In our model, stent placement increased the effectiveness by more than one month compared to PTA. If, in fact, stent placement is not only superior to PTA with respect to the technical success rate but also with respect to the prevention of end-stage renal disease in the long-term, the preference for stent placement over PTA is strengthened.

Another consequence of our assumption on the limited benefit of stent placement was that the strategies involving direct stent placement (e.g., strategy Stent) differed from the strategies involving selective stent placement (e.g., strategy PTA-SelectiveStent) only with respect to costs but not with respect to effectiveness. The additional cost of stent placement for every patient with a stenosis amounted to €2000 for direct stent placement compared to selective

stent placement. If our assumption does not hold and stent placement not only improves the technical success rate but also the long-term clinical outcomes of technically successful procedures, then direct stent placement in all patients with renal artery stenosis could be the most cost-effective strategy.

In hypertensive patients with atherosclerotic renal artery stenosis, the benefit of PTA on blood pressure control is disappointing.[6] Moreover, intra-arterial procedures carry a risk of serious complications.[14,25] For this reason, we included three treatment strategies in our model in which intra-arterial procedures were not performed in every patient, but only if a clinical indication for intervention was present. A clinical indication was assumed to be present if the blood pressure was inadequately controlled or if the renal function was severely impaired or had deteriorated. Compared with these strategies, the benefit of the strategies involving intra-arterial procedures in all the patients was small. For instance, immediate stent placement was only 4 quality-adjusted days more effective and €30 less expensive compared with initial medical therapy.

At present, there is no standard approach for the treatment of hypertensive patients with atherosclerotic renal artery stenosis. Whereas some clinicians feel that every stenosis should be treated,[26] the wait-and-see approach has also been advocated for certain patient groups.[23,27] Our analysis indicates that for patients with drug-resistant hypertension and findings suggestive of significant renal artery stenosis on CTA or MRA, the cost-effectiveness of direct angiography and intervention is comparable to that of treating medically first and performing an intra-arterial procedure only if blood pressure control fails or renal function deteriorates. If an intervention is performed, atherosclerotic renal artery stenosis should be treated with PTA followed by stent placement in the same session if the PTA procedure fails.

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10

General discussion

The aim of the studies in this thesis was to contribute to the optimization of diagnosis and treatment of renal artery stenosis. The research questions on diagnosis were:

- What is the interobserver agreement of captopril renography for the detection of renal artery stenosis?
- What is the value of clinical characteristics for predicting the probability of renal artery stenosis in patients suspected of this condition?

The research questions concerning treatment were:

- Are the clinical outcomes for patients with hypertension and atherosclerotic renal artery stenosis after balloon angioplasty better than those after drug therapy?
- What is the cost-effectiveness of different treatment strategies for patients with hypertension and atherosclerotic renal artery stenosis?

In this chapter, the findings of the studies are summarized and discussed. Then, the state of the art is presented. Finally, conclusions are drawn and recommendations for further research are given.

Study findings

Diagnosis of renal artery stenosis

Renography

At the begin of our studies in the early 1990's, intra-arterial digital subtraction angiography was commonly used as reference standard to determine presence of renal artery stenosis. Renography was used as a screening test to select patients for angiography. The diagnostic accuracy of renography was variably described between studies, however, with sensitivity ranging between 70% and 100%, and specificity ranging between 60% and 100%.[1-4] In Chapter 2 of this thesis, interobserver agreement in the judgment of renographic parameters was studied in 658 renograms obtained with the use of ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) after challenge with captopril to examine whether this was a possible explanation for variation in the diagnostic accuracy. We found considerable variation between observers in their judgment of the renographic parameters. Some parameters could be assessed reliably with high agreement, e.g. the pattern of the time-activity curves, but others could not, e.g. cortical retention. The overall judgment on presence of renal artery stenosis was reliable, but the interpretation of the renograms was difficult when pelvic retention was suspected and when bilateral stenosis was present.

We conclude from these findings that there is considerable interobserver variability in the judgment of captopril renography. The interobserver variability in clinical practice is probably larger than what we found, because the three

observers in our study had a broad experience and discussed their scoring method beforehand. Also, the renograms in our study were made in a research setting, which makes it more likely that the patient preparation and renographic procedure were performed in a more careful and standardized manner than in a routine hospital setting.[5] The interobserver variability in the judgment of captopril renography may have contributed to the variation in diagnostic accuracy of renography for finding renal artery stenosis.

Other causes for this variation in diagnostic accuracy of renography have been proposed as well. These refer to the differences between studies regarding patient selection, choice of radiopharmaceutical, the way renography is performed (with or without captopril challenge, or in a two-step procedure), diagnostic criteria, and choice of reference standard (angiography or clinical response to successful intervention).[4-8] We can comment on two of these other causes for variation in diagnostic accuracy on the basis of our research. With regard to diagnostic criteria, we studied the value of the separate renographic parameters for predicting presence of renal artery stenosis on angiography. As described in Chapter 2, the relative importance of the renographic parameters for predicting presence of stenosis was virtually the same for the three nuclear medicine physicians in our study. Beside the judgment of the separate renographic parameters, the physicians also gave their overall judgment on presence or absence of stenosis. Although no specific diagnostic criteria were defined for this assessment, the sensitivity and specificity of the overall judgment was comparable between the three physicians (65-70% and 84-94%, respectively, for finding renal artery stenosis of 80% or more on angiography). In a logistic regression model, the separate renographic parameters had no additional value in predicting presence of stenosis when the overall judgment was already taken into account (unpublished data). Apparently, the physicians had integrated the available information on the renographic parameters to form their overall judgment. From this we may conclude that the use of prespecified diagnostic criteria does not necessarily diminish the variation in diagnostic accuracy.

It has been argued that the usefulness of renography is underestimated if angiography is used as reference. After all, on the basis of the angiographic images no distinction can be made between stenoses that are responsive to successful intervention and those that are not.[8,9] For this reason, it has been proposed that renography should be used not to select hypertensive patients for angiography, but to select hypertensive patients with anatomically proven stenosis for intervention.[5] In our treatment trial, which was described in Chapter 5, however, we did not find evidence that the response to intervention can be predicted on the basis of renography. Blood pressure levels after angioplasty were

the same for patients with an abnormal and with a normal renogram before treatment.[10]

We believe that renography is not a useful screening test to select patients with hypertension for further diagnostic workup or for decisions on treatment, because the diagnostic accuracy is disappointing. In addition, the test is complex with regard to both the procedure and the interpretation, is costly, and is difficult to standardize.

Prediction rule

In Chapter 3 of this thesis, a prediction rule for renal artery stenosis was introduced. After a literature study, we selected nine clinical characteristics indicative of renal artery stenosis, which were included as predictors in a multivariable logistic regression model to predict the probability of stenosis. To facilitate the use of the model in clinical practice, a prediction rule was constructed. In the prediction rule, each clinical characteristic is assigned a score. These scores can be added into a sum score that, through the logistic formula, corresponds with a predicted probability of stenosis. The predicted probabilities and their 95% confidence intervals can also be read from a graph. The prediction rule was reliable and discriminated well between patients with and without stenosis (area under the ROC curve, 0.84). The rule can support the selection of patients for renal angiography. For example, if angiography had performed only in patients whose predicted probability of stenosis was 10% or more, the number of patients undergoing angiography would have been reduced to 61%. However, 1 of every 10 stenoses would have been missed (sensitivity, 90%). If a cutoff level of 30% was chosen, the sensitivity and specificity were comparable to those of renography (68% and 87%, respectively).

A limitation of the prediction rule was that it did not discriminate well between patients without stenosis and patients with stenosis due to fibromuscular dysplasia. Atherosclerotic renal artery stenosis and fibromuscular dysplasia share some risk factors such as presence of an abdominal bruit and a short duration of the hypertension. In addition, atherosclerotic renal artery stenosis has several other distinct risk factors such as vascular disease and smoking. Additional risk factors for fibromuscular dysplasia, on the other hand, are limited to sex and age.[11-13] Patients with fibromuscular dysplasia are therefore identified less easily. However, if a conservative cutoff level for the predicted probability of stenosis (5%) was chosen above which patients would have been referred for angiography, every patient with fibromuscular dysplasia in our study would have been identified. Even so, further diagnostic workup should be performed in young female patients with drug-resistant hypertension even if the prediction rule

predicts a low probability of stenosis, particularly because fibromuscular dysplasia is amenable to angioplasty.

Some risk factors for stenosis were not included in the prediction rule. For instance, race was dropped from the multivariable regression model. This was done for statistical reasons, because the study population consisted mainly of Caucasian patients. Renovascular hypertension is known to be rare in black hypertensive patients.[14] In our study population, black ethnicity was indeed associated with a low risk of stenosis (univariable odds ratio, 0.1). Physicians should take this into consideration when they consider performing angiography in black patients with hypertension even if the prediction rule predicts a high probability of stenosis.

The predictions of the rule were valid for the patients that were used for its development ('apparent validity'). The predicted probabilities agreed well with the observed probabilities (goodness-of-fit test, P=0.79) and the rule discriminated well between patients with stenosis and those without stenosis (area under the ROC curve, 0.84). Most of the patients (422/460) were selected for the development sample because they had drug-resistant hypertension. The remaining 38 patients were included because their serum creatinine concentration increased during ACE-inhibitor therapy. Renal function impairment on ACE-inhibitor therapy is a strong risk factor for renal artery stenosis in hypertensive patients.[15] This was reflected by the fact that the predicted probabilities of stenosis for patients with this characteristic were higher than for the patients with drug-resistant hypertension (mean ± SD, 45% ± 34% and 21% ± 20%, respectively). Therefore, a rise in creatinine concentration during ACE inhibitor therapy in patients with hypertension may justify immediate referral to renal angiography.[10] It might have been more appropriate to develop the prediction rule only for patients with drug-resistant hypertension. The development sample consisted mainly of patients with drug-resistant hypertension, however. Therefore, the prediction rule was also valid for this subgroup. As expected, the predicted probabilities agreed well with the observed probabilities (goodness-of-fit test, P=0.99), and the discriminative value of the prediction rule was only slightly lower than in the entire study population (area under the ROC curve, 0.82).

We internally validated the prediction rule by bootstrapping techniques to assess the validity of the prediction rule in similar patients. Bootstrap samples were drawn from the original sample with replacement. The model development procedure (selection of predictors, estimation of logistic regression coefficients) was followed in each bootstrap sample. The resulting logistic regression models were tested in the original sample. This test indicates the expected optimism in

Table 10.1. Summary of the results on the discriminative ability of the prediction rule in de development sample and in the validation sample.

	Development Sample (N=460)	Validation Sample (N=180)
Predicted probability of stenosis in patients, mean ± SD:		
without renal artery stenosis (n)	15 ± 16 (354)	13 ± 13 (145)
with renal artery stenosis (n)	49 ± 29 (106)	26 ± 20 (35)
with atherosclerotic stenosis (% of n with stenosis)	52 ± 29 (84)	32 ± 22 (63)
with fibromuscular dysplasia (% of n with stenosis)	34 ± 26 (16)	14 ± 10 (37)
Area under the ROC curve (95% confidence interval)	0.84 (0.79-0.89)	0.71 (0.61-0.81)

performance when the original model is applied in patients similar to those in the development sample.

We also validated the rule in separate participating hospitals. The discriminative ability of the prediction rule for most hospitals was similar to that of the entire development sample, although some had only a small number of patients.

Finally, we studied the validity of the prediction rule in 180 patients who were treated recently in other hospitals. This study was described in Chapter 4. The predictions of the rule in this validation sample were reliable (goodness-of-fit test, P=0.87), but the discriminative ability was disappointing (area under the ROC curve, 0.71; Table 10.1). This was partly to be expected, because prediction rules often do not perform as good as in patients of other settings.[16] In the case of our prediction rule, however, there are several reasons that may have contributed to the disappointing discriminative ability. First, the definitions of vascular disease and smoking differed between the development sample and the validation sample. Second, we verified from the medical records of the patients from one hospital that abdominal bruits were underreported in the validation sample. This meant that the prevalence of some risk factors was underestimated in the validation study, which lowered the discriminative ability of the prediction rule. Third, the proportion of patients with stenosis due to fibromuscular dysplasia was unusually high in the validation sample (i.e., over twice as high as expected).[17] Since the predictions were lower for these patients than for the patients with atherosclerotic stenosis (Table 10.1), the overrepresentation of these patients in the validation sample decreased the discriminative ability of the prediction rule.

In our attempt to develop a valid prediction rule for renal artery stenosis, we have complied with accepted methodological standards for constructing such a tool as best we could.[18] Furthermore, we validated the rule internally and externally.[19] A limitation of our external validation, however, was that the validation sample was relatively small. This is a common problem in validation studies.[20] Further studies are therefore required for more firm conclusions on the validity and usefulness of the prediction rule. Until its validity is demonstrated more convincingly, the rule should be used with a conservative cutoff value and can reliably exclude a only small proportion of patients from angiography.

Treatment of renal artery stenosis

Balloon angioplasty versus drug therapy

The Chapters 5 through 8 of the thesis described the findings of a randomized controlled trial comparing clinical outcomes of 106 patients with atherosclerotic renal artery stenosis of 50% or more on angiography, who were randomly allocated to balloon angioplasty (N=56) or drug therapy (N=50). Inclusion criteria were hypertension resistant to a standardized regimen of two antihypertensive drugs or a rise in serum creatinine during treatment with an ACE inhibitor. All patients had a normal or mildly impaired renal function. The outcome measures of the trial were blood pressure (primary outcome), antihypertensive medication, and renal function (Chapters 5 and 6), and quality of life (Chapters 7 and 8). The outcomes were evaluated after 3 and 12 months of follow-up. To comply with the concern that untreated renal artery stenosis may lead to irreversible renal failure, the design of the trial was pragmatic. The study protocol allowed that the patients who were allocated to medication, could receive angioplasty after 3 months if the blood pressure control was inadequate or if the renal function deteriorated.

Effect on blood pressure

Blood pressure levels in the balloon angioplasty group after 3 months were not significantly lower than in the drug-therapy group (Chapter 5): 169 ± 28/99 ± 12 and 176 ± 31/101 ± 14, respectively (P=0.25 for systolic blood pressure and P=0.36 for diastolic blood pressure). The patients in the angioplasty group used less antihypertensive medication. The blood pressure lowering capacity of angioplasty was that of approximately 1 defined daily dose of medication, which corresponds with the daily average maintenance dose of one drug.[21] Although the blood pressure levels at baseline did not differ between the treatment groups, it would have been more proper to adjust for the baseline values in the analysis.[22] When we corrected for the blood pressure levels at baseline, the differences

between the treatment groups after 3 months again were not statistically significant (P=0.14 for systolic blood pressure and P=0.09 for diastolic blood pressure).

The power of our study to detect a small benefit of angioplasty was low because of the relatively small sample size. After publication of the findings, the results after 3 months in the DRASTIC trial were combined with the data of two smaller randomized trials[23,24] in two separate meta-analyses.[25,26] These other trials compared blood pressure and renal function after 6 months of follow-up in 55 and 49 patients with hypertension and atherosclerotic renal artery stenosis, who were allocated to drug therapy or to angioplasty (in one trial with or without stent placement). Both meta-analyses showed a modest but statistically significant positive effect of angioplasty on blood pressure. Compared to the drug-therapy group, the average reduction in blood pressure in the angioplasty group was 6.3 mm Hg (95% confidence interval, 0.8-11.7 mm Hg) larger for systolic blood pressure, and 3.3 mm Hg (95% confidence interval, 0.4-6.2 mm Hg) for diastolic blood pressure.[25] So, the short-term advantage of balloon angioplasty with respect to blood pressure control in patients with hypertension and atherosclerotic renal artery stenosis is small at most. It is questionable, however, whether the actual effect of angioplasty on blood pressure is clinically relevant, and not yet known whether the effect is sustained over a longer period of time.

In our trial, we were not able to evaluate the effect of drug therapy in the long term because the study protocol allowed angioplasty to be performed in the medication group after 3 months. Of the 50 patients assigned to drug therapy, 22 underwent angioplasty during follow-up because of persistent hypertension or loss of renal function. The comparison between the angioplasty group and drug-therapy group after 12 months was in fact a comparison between the treatment strategies of immediate angioplasty and of initial drug therapy followed by angioplasty if necessary. After 12 months, the blood pressure levels did not differ between the treatment strategies. This was also the case after correction for the blood pressure levels at baseline (P=0.51 for systolic blood pressure and P=0.06 for diastolic blood pressure). The medication-sparing effect of angioplasty was less evident after 12 months. With respect to blood pressure control in the long term, our results argue in favor of the more conservative treatment strategy of aggressive drug treatment and proceeding to angioplasty only if hypertension persists or renal function declines.

Renal artery stenosis is considered to be hemodynamically significant when the degree of stenosis is at least 60%[27,28] or 70%.[1,8] The disappointing effect of angioplasty on blood pressure cannot be explained, however, by the fact that we had also included patients with stenosis between 50% and 70%. In our

angioplasty group, blood pressure control was not associated with severity of stenosis at baseline. This finding was supported by the fact that blood pressure control after angioplasty was similar for the patients with an abnormal renogram and the patients with a normal renogram at baseline. Another possible explanation for the disappointing effect of angioplasty on blood pressure control was that restenosis had occurred in nearly half of the patients who underwent angioplasty. One could argue that additional stent placement in the angioplasty group would have improved the blood pressure response to intervention, because stent insertion has been shown to improve vessel patency.[29] This argument does not seem to apply, however, because restenosis was not associated with the blood pressure response after 12 months. These data were referred to in Chapter 5, but were presented in detail in another publication.[10] The absence of an association between vessel patency and blood pressure response was also found in another Dutch study comparing angioplasty with and without stent placement.[29]

In Chapter 6, we evaluated the possible benefit of immediate angioplasty as opposed to performing angioplasty only in case of inadequate blood pressure control or deterioration of renal function in five subgroups of patients. These subgroups concerned patients with a supposedly good response to intervention (patients with a positive captopril-renin challenge test, an abnormal captopril renogram, and recently developed hypertension), and patients with a supposed risk for rapid disease progression (patients with bilateral stenosis, and severe stenosis). As a rule, secondary analyses for subgroup effects should be interpreted with caution, because these analyses are usually not included beforehand in the study design and lack statistical power.[30,31] For this reason, we restricted the number of subgroups before the analysis. The choice of subgroups for analysis was dictated by the assumed benefit of angioplasty in the specific patient groups. Indeed, a lack of power to detect small but relevant differences between the treatment strategies within the subgroups was a major limitation of our subgroup analysis. The patients with bilateral stenosis seemed to benefit from immediate angioplasty in terms of diastolic blood pressure compared to the patients with unilateral stenosis, but the difference in blood pressure change was not statistically significant.

Effect on renal function

Balloon angioplasty is considered useful for preserving and even re-establishing renal function in patients with renal artery stenosis.[32-36] However, there is a lack of randomized studies comparing renal function of patients treated with or without angioplasty. Although the DRASTIC study was designed to evaluate the effect of treatment on blood pressure, we also compared the patients randomized

for angioplasty and for drug therapy with respect to the serum creatinine levels and the creatinine clearance as rough indicators for the glomerular filtration rate (Chapter 5). Both the serum creatinine level and creatinine clearance were better in the angioplasty group after 3 months. The benefit remained present after correction for the baseline values (unpublished data). After 12 months, when nearly half of the drug-therapy group had received angioplasty, the renal function in the two groups was similar. These findings seem to confirm that angioplasty may be useful to preserve renal function. It is still unknown, however, whether this effect might be sustained in the long term.

In the subgroup analysis described in Chapter 6, the patients with bilateral stenosis who received immediate angioplasty had an evident benefit compared to similar patients who were assigned to initial drug therapy. The creatinine clearance had improved substantially after 12 months in the first group (+10.0 ± 15.7 mL/min), whereas it had decreased somewhat in the latter group (-4.2 ± 13.5 mL/min; P=0.03). For patients with unilateral stenosis, the change in creatinine clearance did not differ between the treatment strategies. The difference in treatment effect was statistically significant between the patients with bilateral stenosis and those with unilateral stenosis (test for interaction,[31] P=0.007). Our results justify that intervention is not delayed in patients with bilateral stenosis even if the renal function is not severely compromised as yet. Whether this effect is real and can be maintained in the long term, however, is unknown.[37] Stent placement may be helpful in this respect, although the benefit of stent placement over angioplasty was not established in a randomized comparison.[29]

Effect on quality of life

In Chapter 7, we studied the reproducibility and validity of a Dutch version of a questionnaire measuring quality of life in patients with hypertension[38] and of a generic quality of life questionnaire (the MOS Short-form General Health Survey)[39] in patients with hypertension on stable medication. The reproducibility and validity of the questionnaires were considered satisfactory. In Chapter 8, we compared the angioplasty group and the drug-therapy group in our study regarding physical symptoms associated with hypertension or antihypertensive treatment and more general dimensions of quality of life. Because quality of life in patients with hypertension is considered to be impaired mainly by side effects of antihypertensive-drug therapy and because angioplasty has a medication-sparing effect, we expected to find that the patients in the angioplasty group experienced a better quality of life after follow-up. This was, however, not the case. The difference in medication between the treatment groups (1.9 ± 0.9 drugs in the

angioplasty group and 2.5 ± 1.0 drugs in the drug-therapy group) was too small to lead to a difference in the number of physical complaints let alone to a difference in scores on the more general dimensions of quality of life. In fact, we did not find an association between the number of antihypertensive drugs and any of the quality of life measures in the study. This was probably due to the fact that the medication in the study group was modified in case of serious side effects. From these results it is apparent that quality of life considerations do not justify the choice of angioplasty over drug therapy.

Cost-effectiveness of treatment strategies for renal artery stenosis

In the Chapters 5 through 8, we studied the effect of angioplasty on blood pressure and renal function in patients with drug-resistant hypertension and atherosclerotic renal artery stenosis up to one year. In Chapter 9, we also wanted to take the long-term effects of treatment and costs into account to study the optimal treatment strategy for these patients. There is considerable uncertainty regarding the long-term effects of intervention, however, because the data are scarce and come from non-randomized studies and different patient populations. The cost of treatment has been estimated only in the short term.[40] Furthermore, we wanted to study stent placement as a treatment option for renal artery stenosis.

In Chapter 9, we combined patient data from our own study and data from the literature in a decision analytic model to weigh short-term complications and cost of percutaneous intervention against long-term risks and cost of hypertension and renal insufficiency.[41] To make the strategies compatible with current clinical practice, the model included patients who had drug-resistant hypertension and findings of renal artery stenosis on computed tomography angiography (CTA) or magnetic resonance angiography (MRA). The model simulated the quality-adjusted life expectancy, lifetime costs and incremental cost-effectiveness ratios for a large cohort of patients. It compared treatment strategies involving percutaneous intervention (balloon angioplasty and direct or selective stent placement) to a reference strategy of antihypertensive medication only. The strategies involving intervention differed for the patients with atherosclerotic renal artery stenosis. Treatment for patients with fibromuscular dysplasia was always balloon angioplasty.[42]

Medication only yielded the lowest effectiveness (9.33 QALYs) and the highest cost (€107,200). Angioplasty increased the effectiveness by about 75 days, and direct or selective stent placement increased the effectiveness by about 110 days. The lifetime costs of the treatment strategies involving intervention did not differ much (between €100.200 and €102.200). For some age groups, angioplasty

with selective stent placement was the most effective and least costly strategy. For other age groups, it was more cost-effective to treat with medication first and to perform intra-arterial procedures only if blood pressure control failed or renal function deteriorated. The differences in cost and effectiveness between these two strategies were very small.

Decision analytic models have several limitations. First, these models make simplifying assumptions in order to keep the model tractable. In our model, for instance, the effects of treatment on blood pressure and renal function were combined and categorized in three levels. In reality, these effects are more subtle and probably interrelated.[43] The assumptions we made in the model, however, applied to all treatment strategies. This enabled us to compare the strategies all the same.

Another limitation of decision analytic models is that the input of such models is generally obtained from different sources. The incidence rates for cardiovascular complications of hypertension in our model, for instance, were not obtained from a study on patients with hypertension and renal artery stenosis, but from a community-based study.[44] So, it is questionable whether these incidence rates apply to the patients in our model. Extensive sensitivity analyses were performed to explore the uncertainty of the key parameters in our model. These analyses showed that the model outcomes were rather robust. Only for different values of the risk of end-stage renal disease, it was uncertain whether it was more cost-effective to perform angioplasty with selective stent placement in all the patients with atherosclerotic renal artery stenosis, or to perform this procedure only in case of inadequate blood pressure control or progressive renal failure. The differences in costs and effectiveness, however, were small.

In general, decision analysis can be a useful tool if risks and costs in the short term and the long term have to be weighed, especially if these risks and costs are uncertain.[41] Decision analytic models can be used to explore which additional information is needed most to make better evidence-based decisions in clinical practice. This, in turn, suggests important clinical research. With respect to the treatment of atherosclerotic renal artery stenosis, our model suggested that it is cost-effective to perform intra-arterial angiography in every patient with renal artery stenosis on CTA or MRA, with subsequent intervention if the presence of stenosis is confirmed. For patients with atherosclerotic stenosis, stent placement seems more cost-effective than angioplasty alone. More information on the long-term risks of renal artery stenosis is needed, however, especially on which patients are at risk for progressive renal failure, and for which patients intervention offers a sustained benefit.

State of the art

Since the start of our studies in the early 1990's, changes have taken place in the diagnostic approach and treatment of renal artery stenosis. We believe that our studies contributed to some of these changes. The main developments are commented on in the following sections.

Diagnostic approach of renal artery stenosis

Diagnostic tests for renal artery stenosis can roughly be subdivided into imaging tests showing the presence and degree of stenosis and tests that identify hemodynamically significant stenosis. With respect to imaging tests, intra-arterial angiography is replaced more and more by less invasive imaging techniques such as MRA or CTA, although these tests have disadvantages such as a risk of nephrotoxicity (CTA) and high cost (MRA).[45] In a sample of unselected patients who received diagnostic workup for renal artery stenosis in recent years in three Dutch hospitals, the final diagnosis was made by conventional angiography in only 4%. Instead of angiography, CTA was performed in 92%, and MRA in 4% of the patients (unpublished data). Although a recent meta-analysis involving a small number of published studies suggested that the diagnostic performance of CTA and gadolinium-enhanced MRA compared to conventional angiography was excellent,[46] there is insufficient evidence as yet to replace conventional angiography by CTA or MRA as the reference standard for the diagnosis of renal artery stenosis.

With respect to tests for identifying hemodynamically significant stenosis, renography is performed less frequently for the detection of renal artery stenosis in patients with hypertension in the Netherlands. In our recent sample of unselected patients receiving diagnostic workup for renal artery stenosis, renography was performed for this purpose in only 12% of the patients (unpublished data). Other proposed tests, such as the captopril renin challenge test and renal vein renin measurements, do not qualify for use as a screening test for renal artery stenosis because they are not sufficiently accurate.[10,47,48] At present, color doppler ultrasonography seems the most promising test for predicting the response to revascularization.[45,49]

In recent guidelines, for the diagnosis of renal artery stenosis,[42] seven indications for intra-arterial angiography for the evaluation of renal artery stenosis are formulated. These indications are based on findings of non-invasive vascular imaging, patient characteristics such as onset of hypertension and age, and signs of loss of renal function.

Therapeutic approach of renal artery stenosis

Balloon angioplasty is generally considered the most appropriate treatment for patients with hypertension and stenosis due to fibromuscular dysplasia.[17,42,50,51] For hypertensive patients with atherosclerotic renal artery stenosis, however, considerable controversy still exists. In these patients, intervention often reduces but rarely eliminates the need for antihypertensive medication, and can lead to atheroembolization if widespread atherosclerotic plaques are present.[51] It remains difficult to predict which of these patients will have a favourable response to intervention with respect to blood pressure control. The lack of data on the results of intervention in the long term adds to the uncertainty.

On the basis of our trial and those of others,[23,24] the general tendency to perform an intervention in all patients seems to be shifting towards a more conservative approach in which aggressive medical treatment is started first.[17,37,42,51,52] Medical treatment should aim for blood pressure control and prevention of cardiovascular complications. For that reason, it should not only include antihypertensive drugs but also lipid lowering agents and antiplatelet agents. Patients who are treated medically should also be monitored carefully for disease progression.[17,37,51]

According to recent guidelines,[42] an intervention is indicated if hypertension is likely to be cured (e.g., in young patients), is refractory to medication or accelerated or malignant, or if renal function deteriorates. Other indications are recurrent 'flash' pulmonary oedema and unstable angina.[42] Furthermore, an intervention should be performed in patients with bilateral stenosis or with unilateral stenosis with a solitary functioning kidney (e.g. after nephrectomy or in case of occlusion of the renal artery in the contralateral kidney).[53]

The benefit of stent placement over angioplasty in patients with atherosclerotic renal artery stenosis remains a debated issue. Although stent placement has a higher technical success rate and lower rate of restenosis,[29,54,55] the superiority of stents over angioplasty in terms of blood pressure has not been demonstrated.[29] The benefit of stents with respect to preservation of renal function, especially in the long term, still has to be determined.[29,37] Recent guidelines state that stent placement is indicated for atherosclerotic stenosis located in the ostium of the renal artery and in case of a failed angioplasty procedure or restenosis after a initially successful angioplasty procedure.[42] Contraindications for stent placement have also been formulated, however, such as presence of sepsis or inelastic stenosis.[42]

Conclusions

Conclusions with regard to the diagnosis of renal artery stenosis:

- The interobserver agreement of captopril renography for the detection of renal artery stenosis varies considerably and depends on the renographic parameters that are used as diagnostic criteria. This, together with the complexity of the test, makes renography unsuitable as a screening test to select hypertensive patients for further diagnostic workup.
- Clinical characteristics are of value for predicting the probability of renal artery stenosis in patients with drug-resistant hypertension. Combined into a prediction rule for renal artery stenosis, they can be used reliably to select hypertensive patients for angiography. If used with a conservative cutoff value, the prediction rule can exclude a small proportion of the patients from angiography.

Conclusions with regard to treatment of renal artery stenosis:

- In patients with hypertension and atherosclerotic renal artery stenosis without severe renal failure, the blood pressure lowering effect of balloon angioplasty is not relevantly better than that of drug therapy, but angioplasty has a small medication-sparing effect. Balloon angioplasty seems to preserve renal function in the short term, especially in patients with bilateral stenosis.
- Based on the available data on short-term and long-term costs and effects of treatment, it is cost-effective to perform intra-arterial angiography and intervention in hypertensive patients without severe renal failure who have findings of renal artery stenosis on CTA or MRA. Patients with atherosclerotic renal artery stenosis should preferably be treated with angioplasty followed by stent placement in the same session if the angioplasty procedure fails.

Recommendations

- Diagnostic workup for renal artery stenosis is indicated for patients with drug-resistant hypertension. The prediction rule for renal artery stenosis should be integrated in the diagnostic workup of patients suspected of renal artery stenosis. A conservative cutoff level for the predicted probability of stenosis (<5%) should be adhered to below which patients are excluded from further workup. The rule should be validated more extensively, before a more lenient cutoff value can be reliably used. The value of the combination of the prediction rule with CTA or MRA might be studied to select patients for intra-arterial angiography and intervention more efficiently.

- Given the available evidence, patients with drug-resistant hypertension and substantial atherosclerotic renal artery stenosis (50% or more in lumen diameter) should receive an intervention. Large prospective randomized trials are needed, however, to compare the costs and effects of different treatment strategies with angioplasty and direct or selective stent placement. These trials should focus on the effect of treatment on renal function, particularly in the long term.
- More research is needed to find methods for identifying patients who are likely to benefit from intervention. Besides the development of complex clinical methods, such as intra-arterial pressure measurements to find criteria for hemodynamically significant stenosis, epidemiological data could be used to find predictors of a successful response to intervention.

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Summary

This thesis describes studies on diagnosis and treatment of renal artery stenosis in patients with drug-resistant hypertension. In Chapter 1, the clinical problem of renal artery stenosis is discussed. Renal artery stenosis, a narrowing of the renal artery, is a potential cause of secondary hypertension. For this reason, it is important to diagnose a stenosis, so that treatment can be initiated. Treatment of patients with hypertension and renal artery stenosis may potentially prevent cardiovascular complications and renal insufficiency. The research questions on diagnosis concerned (1) the interobserver agreement of captopril renography for the detection of renal artery stenosis, and (2) the value of clinical characteristics for predicting the probability of stenosis in patients with drug-resistant hypertension. The research questions on treatment concerned (1) the comparison of clinical outcomes after balloon angioplasty versus drug therapy for patients with drug-resistant hypertension and atherosclerotic renal artery stenosis, and (2) the cost-effectiveness of several treatment strategies in this patient group.

Diagnosis of renal artery stenosis

Diagnostic testing for renal artery stenosis is common in hypertensive patients with difficult-to-treat hypertension. Given the low prevalence of stenosis in these patients together with the invasiveness of the current reference test, digital subtraction angiography, selection of patients for angiography is desirable by means of a non-invasive diagnostic test. The Chapters 2 through 4 of the thesis describe studies on such tests for renal artery stenosis.

In Chapter 2, the interobserver agreement of captopril renography is evaluated. We found considerable variation between observers in their judgment of renographic parameters. Some parameters could be assessed reliably with high agreement, e.g. pattern of the time-activity curves, but others were difficult to assess, e.g. cortical retention. We concluded that interobserver variability offers one of several explanations for differences in the diagnostic test performance of captopril renography that are found between studies.

In Chapter 3, another way of selecting hypertensive patients for angiography is introduced. We developed a clinical prediction rule on the basis of readily available, clinical characteristics to predict the probability of renal artery stenosis in patients with drug-resistant hypertension. The prediction rule was reliable and discriminated well between patients with and without stenosis, although patients with stenosis due to fibromuscular dysplasia were less well identified than patients

with atherosclerotic renal artery stenosis. The diagnostic accuracy of the rule was comparable to that of renography.

Before the prediction rule can reliably be used in clinical practice, it has to be validated in another clinical setting. Chapter 4 describes such an external validation study. The predicted probabilities of stenosis for the patients in the validation sample again agreed well with the observed probabilities, but the ability to discriminate between patients with and without stenosis was disappointing compared to that in the development sample. In part, this was due to the unusually high prevalence of patients with fibromuscular dysplasia in the validation sample, who can be identified less well by the prediction rule. Even in this patient sample, where the discriminative ability was underestimated, the prediction rule had some clinical usefulness: if only patients with predicted probabilities of stenosis of 5% or more were referred for renal angiography, the number of referrals was reduced by 20%, while less than 10% of the patients with a stenosis were missed. We concluded that the prediction rule is a useful tool to quantify the probability of renal artery stenosis. The rule is an alternative for renography in the selection of hypertensive patients for angiography. If the prediction rule is used with a conservative cutoff value, patients can be excluded reliably from further diagnostic workup for renal artery stenosis.

Treatment of renal artery stenosis

Balloon angioplasty is often performed to lower blood pressure in hypertensive patients with renal artery stenosis. For the majority of the patients, i.e. patients with stenosis on the basis of atherosclerosis, however, the long-term effect of angioplasty on blood pressure is uncertain. The Chapters 5 through 8 describe the findings of a randomized controlled trial comparing clinical outcomes of 106 patients with atherosclerotic renal artery stenosis who were randomly allocated to balloon angioplasty (N=56) or to drug therapy (N=50). Inclusion criteria were hypertension resistant to a standardized regimen of two antihypertensive drugs or a rise in serum creatinine during treatment with an ACE inhibitor, and an otherwise normal or mildly impaired renal function. In accordance with the study protocol, 22 of the 50 patients in the drug-therapy group underwent angioplasty after 3 months, because of persistent hypertension or deterioration of renal function. We found no statistically significant differences in blood pressure at 3 months and at 12 months (Chapter 5). The patients in the drug-therapy group however used significantly more antihypertensive medication at 3 months. Renal function at 3 months in the angioplasty group was improved compared to the drug-therapy group, but was similar after 12 months of follow-up. We concluded that angioplasty had little advantage over drug therapy with regard to blood

pressure control. There was some evidence, however, that angioplasty was beneficial for preserving renal function.

In Chapter 6, a secondary analysis of the trial data was performed to identify subgroups of patients who might benefit from angioplasty compared to initial medication (followed by angioplasty if needed, after three months). Changes in blood pressure and renal function after 1 year were studied for patients with a positive captopril-renin challenge test, with an abnormal captopril renogram, with recently developed hypertension, with bilateral stenosis, and with severe stenosis. Patients with bilateral stenosis benefited more from immediate angioplasty with regard to preservation of renal function and, to a lesser extent, with regard to blood pressure control. So, with the exception of patients with bilateral stenosis, intervention can be postponed until hypertension persists despite increased medication or until renal function deteriorates.

Chapters 7 and 8 discuss the quality of life of patients with hypertension. In Chapter 7, we evaluated the reproducibility and validity of a Dutch questionnaire on physical symptoms associated with hypertension and antihypertensive drugs and of a generic health questionnaire (the MOS Survey) in hypertensive patients on stable medication. The reproducibility and validity were considered satisfactory. In Chapter 8, we evaluated whether the medication-sparing effect of angioplasty in our randomized trial led to an improved quality of life. The patients in the angioplasty group did not report less physical complaints, or a better quality of life than the patients in the drug-therapy group. Evidently, angioplasty had no advantage over drug therapy regarding the patients' quality of life.

In Chapter 9, we developed a decision analytic model to assess the cost-effectiveness of seven treatment strategies for patients with drug-resistant hypertension without severe renal failure, who have findings suggestive of significant renal artery stenosis on CTA or MRA. In the model, the short-term complications and cost of percutaneous interventions (balloon angioplasty with or without stent placement) were weighed against the long-term risks and cost of hypertension (myocardial infarction, stroke) and renal dysfunction (end-stage renal disease). The treatment strategies that included only angioplasty increased the quality-adjusted life expectancy by more than 70 days and decreased cost compared to treatment with medication only. The treatment strategies that included stent placement increased the life expectancy more than 100 days and were similarly cost saving. Immediate intervention had no evident benefit over performing intra-arterial procedures only if blood pressure control failed or renal function deteriorated.

The thesis is concluded with a general discussion on the findings of the presented studies (Chapter 10). This final chapter also gives recommendations on further diagnostic and therapeutic research.

Samenvatting

Dit proefschrift beschrijft een aantal studies naar de diagnostiek en behandeling van nierarteriestenose bij patiënten met therapieresistente hypertensie. In Hoofdstuk 1 wordt het klinische probleem nierarteriestenose besproken. Nierarteriestenose, een vernauwing van de nierslagader, is een mogelijke oorzaak van secundaire hypertensie. Het is om deze reden belangrijk om vast te stellen dat een stenose aanwezig is zodat een behandeling kan worden ingesteld. Behandeling van patiënten met hypertensie en nierarteriestenose kan mogelijk voorkomen dat cardiovasculaire complicaties optreden en dat nierinsufficiëntie ontstaat. De vraagstellingen van het onderzoek over diagnostiek betroffen (1) de mate van overeenkomst in de beoordeling van captopril renografie tussen beoordelaars voor het vaststellen van nierarteriestenose, en (2) de waarde van klinische patiëntkenmerken voor het voorspellen van de kans op nierarteriestenose bij patiënten met therapieresistente hypertensie. De vraagstellingen over behandeling betroffen (1) de vergelijking van klinische uitkomsten na ballon-angioplastiek en na medicatie bij patiënten met therapieresistente hypertensie en atherosclerotische nierarteriestenose, en (2) de vergelijking van de kosten-effectiviteit van verschillende behandelingsstrategieën voor deze groep patiënten.

Diagnostiek van nierarteriestenose

Het is gebruikelijk om diagnostiek naar nierarteriestenose te verrichten bij patiënten met moeilijk behandelbare hypertensie. Vanwege de lage prevalentie van nierarteriestenose in deze groep patiënten en het invasieve karakter van de huidige gouden standaard test, de digitale subtractie-angiografie, is selectie van patiënten voor angiografie gewenst door middel van een niet-invasieve diagnostische test. De hoofdstukken 2, 3 en 4 van het proefschrift beschrijven studies naar zulke testen voor nierarteriestenose.

In Hoofdstuk 2 wordt de mate van overeenkomst tussen beoordelaars in de beoordeling van captopril renografie bestudeerd. We vonden aanzienlijke variatie in de beoordelingen van de renografische parameters. Voor sommige parameters werd een hoge overeenkomst in beoordeling vastgesteld, zoals voor het patroon van de tijd-activiteitscurve, maar andere parameters, zoals corticale retentie, waren moeilijk te beoordelen. We concludeerden dat verschillen in de beoordeling van renografische parameters een verklaring zijn voor de verschillen in de diagnostische waarde van captopril renografie die in de literatuur zijn gerapporteerd.

In Hoofdstuk 3 wordt een andere manier geïntroduceerd voor het selecteren van patiënten met hypertensie voor angiografie. We ontwikkelden een klinische predictieregel op basis van direct beschikbare klinische kenmerken om de kans op nierarteriestenose te voorspellen voor patiënten met therapieresistente hypertensie. De predictieregel was betrouwbaar en maakte goed onderscheid tussen patiënten met en zonder stenose. Patiënten met nierarteriestenose veroorzaakt door fibromusculaire dysplasie werden door de predictieregel echter minder goed geïdentificeerd dan patiënten met nierarteriestenose veroorzaakt door atherosclerose. De predictieregel werd intern gevalideerd. De diagnostische nauwkeurigheid van de predictieregel bleek vergelijkbaar te zijn met die van renografie.

Voordat de predictieregel betrouwbaar kan worden gebruikt in de klinische praktijk, moet deze worden gevalideerd in een andere klinische setting. Hoofdstuk 4 beschrijft een dergelijke externe validatiestudie. De voorspelde kansen op stenose voor de patiënten in de validatiesteekproef kwamen opnieuw goed overeen met de waargenomen kansen, maar het vermogen van de predictieregel om onderscheid te maken tussen patiënten met en zonder stenose was teleurstellend vergeleken met dat in de steekproef waarin de regel ontwikkeld was. Dit kon deels worden toegeschreven aan de ongewoon hoge prevalentie van patiënten met fibromusculaire dysplasie in de validatiesteekproef, aangezien deze patiënten door de predictieregel minder goed kunnen worden geïdentificeerd. Echter, zelfs in deze steekproef, waarin het onderscheidend vermogen van de regel werd onderschat, was de predictieregel enigszins bruikbaar: als alleen patiënten met een voorspelde kans op stenose van 5% of meer werden doorverwezen voor angiografie, werd het aantal verwijzingen gereduceerd met 20%, terwijl minder dan 10% van de patiënten met een stenose werd gemist. De conclusie luidt dat de klinische predictieregel een bruikbaar middel is om de kans op nierarteriestenose te kwantificeren. De regel is een alternatief voor renografie bij de selectie van patiënten met hypertensie voor angiografie. Onder de voorwaarde dat een conservatief afkappunt wordt gekozen, kan de predictieregel betrouwbaar worden gebruikt om bij een deel van de patiënten af te zien van verdere diagnostiek naar de aanwezigheid van nierarteriestenose.

Behandeling van nierarteriestenose

Ballonangioplastiek wordt vaak toegepast bij patiënten met nierarteriestenose voor de behandeling van hypertensie. Voor de overgrote meerderheid van de patiënten, namelijk voor hen bij wie de stenose veroorzaakt is door atherosclerose, is het effect van ballonangioplastiek op de bloeddruk op de lange termijn echter onzeker. In de hoofdstukken 5 tot en met 8 van dit proefschrift

worden de bevindingen beschreven van een gerandomiseerde studie waarin de klinische uitkomsten werden vergeleken van 106 patiënten met atherosclerotische nierarteriestenose die op basis van het toeval waren toegewezen aan ballonangioplastiek (N=56) of aan antihypertensieve medicatie (N=50). De inclusiecriteria waren hypertensie ondanks behandeling met twee anti-hypertensieve geneesmiddelen of een toename van de serum creatinine concentratie tijdens behandeling met een ACE remmer, en verder een normale of licht gestoorde nierfunctie. In overeenstemming met het studieprotocol ondergingen 22 van de 50 patiënten in de medicatiegroep na 3 maanden alsnog ballonangioplastiek vanwege persisterende hoge bloeddruk of vanwege een verslechtering van de nierfunctie. We vonden geen statistisch significante verschillen in bloeddruk na 3 maanden en na 12 maanden follow-up (Hoofdstuk 5). De patiënten in de medicatiegroep gebruikten echter significant meer antihypertensieve medicatie na 3 maanden follow-up. De nierfunctie van de patiënten in de angioplastiekgroep was na 3 maanden verbeterd ten opzichte van de medicatiegroep, maar was vergelijkbaar na 12 maanden follow-up. We concludeerden dat ballonangioplastiek slechts een klein voordeel biedt ten opzichte van medicatie wat betreft de behandeling van hypertensie. Er waren echter wel aanwijzingen dat ballonangioplastiek meerwaarde heeft voor het behoud van de nierfunctie.

Hoofdstuk 6 beschrijft een secundaire analyse van deze gegevens voor het identificeren van subgroepen van patiënten die mogelijk voordeel hebben van ballonangioplastiek ten opzichte van initiële medicatie met, indien nodig, angioplastiek na 3 maanden. Veranderingen in bloeddruk en nierfunctie na 1 jaar werden bestudeerd voor patiënten met een positieve captopril test, met een abnormaal captopril renogram, met recent ontstane hypertensie, met bilaterale stenose, en met ernstige stenose. Patiënten met bilaterale stenose hadden voordeel van onmiddellijke ballonangioplastiek wat betreft het behoud van de nierfunctie en, in mindere mate, wat betreft bloeddrukcontrole. Met uitzondering van patiënten met bilaterale stenose kan interventie dus worden uitgesteld totdat blijkt dat de bloeddruk niet gecontroleerd kan worden met meer medicatie of totdat de nierfunctie verslechtert.

In de hoofdstukken 7 en 8 werd de kwaliteit van leven van patiënten met hypertensie bestudeerd. In Hoofdstuk 7 evalueerden we de reproduceerbaarheid en de validiteit van een Nederlandstalige vragenlijst over lichamelijke klachten die geassocieerd worden met hypertensie en antihypertensieve geneesmiddelen en van een vragenlijst voor het meten van de algemene gezondheidstoestand (de MOS-20 vragenlijst) bij patiënten met hypertensie die behandeld werden met stabiele medicatie. We oordeelden dat de reproduceerbaarheid en validiteit van

deze vragenlijsten voldoende waren. In Hoofdstuk 8 werd bestudeerd of het medicatiesparende effect van ballonangioplastiek in onze gerandomiseerde studie leidde tot een verbetering van de kwaliteit van leven. De patiënten in de angioplastiekgroep rapporteerden noch een lager aantal lichamelijke klachten, noch een betere kwaliteit van leven vergeleken met de medicatiegroep. Klaarblijkelijk bood ballonangioplastiek geen voordeel boven medicatie wat betreft de kwaliteit van leven van de patiënten.

In Hoofdstuk 9 werd de kosten-effectiviteit berekend van zeven behandelingsstrategieën voor patiënten met moeilijk behandelbare hypertensie zonder nierfalen, bij wie een significante nierarteriestenose wordt vermoed op grond van CTA of MRA. In deze studie werd gebruik gemaakt van een besliskundig model. In het model werden de complicaties en kosten van percutane interventies (ballonangioplastiek met of zonder stentplaatsing) op de korte termijn afgewogen tegen de risico's en kosten van hypertensie op de lange termijn (myocard infarct en CVA) en van progressieve nierfunctieverslechtering (terminale nierinsufficiëntie). De behandelingsstrategieën met alleen ballon-angioplastiek verhoogden de voor kwaliteit gecorrigeerde levensverwachting met meer dan 70 dagen en gingen gepaard met met een kostenbesparing vergeleken met een behandeling met alleen medicatie. De behandelingsstrategieën met stentplaatsing verhoogden de levensverwachting met meer dan 100 dagen en leidden tot een vergelijkbare kostenbesparing. Onmiddellijke interventie had geen duidelijk voordeel boven het alleen verrichten van intra-arteriële procedures ingeval van persisterende hypertensie of nierfunctieverslechtering.

Het proefschrift wordt afgesloten met een discussie van de bevindingen van de beschreven studies (Hoofdstuk 10). In dit laatste hoofdstuk worden ook aanbevelingen gedaan voor verder onderzoek op het terrein van de diagnostiek en behandeling van nierarteriestenose.

Appendix A. Hypertension Questionnaire – Dutch version

Questions marked with '*' have been added to the original questionnaire.

Het is de bedoeling dat u per vraag één antwoordcategorie omcirkelt of een getal invult.

1.	Heeft u zich de laatste maand wel eens licht in het hoofd, of duizelig gevoeld ? *Indien met nee beantwoord, verder gaan met vraag 4.*	Ja / Nee
2.	Treedt deze lichthoofdigheid of duizeligheid alleen op als u rechtop staat ?	Ja / Nee
3.	Hoeveel uur per dag had u last van lichthoofdigheid of duizeligheid in de laatste maand ?	minder dan 1 uur 1-2 uur meer dan 2 uur
4.	Heeft u zich de laatste maand overdag vaak slaperig gevoeld ?	Ja / Nee
5.	Hoeveel uur slaapt u gewoonlijk per 24 uur ?	___ uur
6.	Heeft u de laatste maand last gehad van een zwak gevoel in de benen ?	Ja / Nee
7.	Heeft u de laatste maand weleens bemerkt wazig te zien ?	Ja / Nee
8.	Wordt u kortademig als u met mensen van uw eigen leeftijd op vlak terrein een wandeling maakt ?	Ja / Nee
9.	Heeft u aan het eind van de dag gezwollen enkels ?	Ja / Nee

10. Vergeleken met mensen van uw eigen leeftijd, loopt u dan:

langzamer	
sneller	
ongeveer even snel	

11. Hoe vaak heeft u gewoonlijk ontlasting ?
(in 1 van beide hokjes een getal invullen)

maal per dag	
of maal per week	

12. Is uw ontlasting vaak breiig of vloeibaar ? Ja | Nee

13. Had u de laatste maand vaak last van verstopping ? Ja | Nee

14. Hoe vaak staat u gemiddeld 's nachts op om te plassen ?

0 keer	
1 keer	
2 keer	
meer dan 2 keer	

15. Heeft u de laatste maand last gehad van een droge mond ? Ja | Nee
Indien met nee beantwoord, verder gaan met vraag 17.

16. Ondervindt u hinder van een droge mond bij het spreken of eten ? Ja | Nee

17. Heeft u de laatste maand last gehad van een nare smaak in de mond ? Ja | Nee

18.* Heeft u de laatste maand last gehad van smaakverlies ? Ja | Nee

19. Heeft u de laatste maand last gehad van een verstopte of lopende neus ? Ja | Nee

20. Heeft u de laatste maand last gehad van een prikkelhoest ? Ja | Nee

21. Vergeleken met mensen van uw eigen leeftijd, is uw concentratievermogen dan:

beter dan het gemiddelde	
gemiddeld	
slechter dan het gemiddelde	

22.	Heeft u de laatste maand last gehad van erg warm worden of van roodheid in het gezicht ?	Ja	Nee
23.	Heeft u de laatste maand last gehad van nachtmerries ?	Ja	Nee
24.	Heeft u zich de laatste maand vaak misselijk gevoeld of moeten braken ?	Ja	Nee
25.	Heeft u de laatste maand last gehad van huiduitslag ?	Ja	Nee
26.	Heeft u de laatste maand last gehad van jeuk ?	Ja	Nee
27.	Heeft u last van "dode vingers" bij koud weer ? *Indien met nee beantwoord, verder gaan met vraag 29.*	Ja	Nee
28.	Zo ja, worden uw vingers daarna pijnlijk ?	Ja	Nee
29.*	Heeft u de laatste maand last gehad van koude handen en voeten ?	Ja	Nee
30.*	Heeft u zich de laatste maand vaak kouwelijk of rillerig gevoeld ?	Ja	Nee
31.	Heeft u de laatste maand last gehad van hoofdpijn ? *Indien met nee beantwoord, verder gaan met vraag 34.*	Ja	Nee

32. Zo ja, hoe vaak treedt hoofdpijn bij u op?

1 of meerdere malen per dag	
1-6x per week	
minder dan 1x per week	

33. Op welk moment van de dag treedt deze hoofdpijn op ?

bij het opstaan	
overdag, maar niet bij het opstaan	
in de avond	

34.* Heeft u de laatste maand last gehad van droge, pijnlijke ogen ? Ja | Nee

35.* Heeft u de laatste maand last gehad van hartkloppingen ? Ja | Nee

36.* Heeft u de laatste maand spierkrampen gehad ? Ja | Nee

37.* Heeft u de laatste maand gewrichtsklachten gehad ? Ja | Nee

38.* Heeft u de laatste maand last gehad van benauwdheid of kortademigheid? Ja | Nee

39.* Heeft u de laatste maand tabletten laten staan vanwege bijwerkingen ? Ja | Nee

De volgende vragen gaan over uw sexuele leven. Wij weten dat deze informatie erg persoonlijk is. Toch zijn we in alle aspecten van uw welbevinden geïnteresseerd en we zouden het op prijs stellen als u de vragen wilt beantwoorden. We willen nogmaals benadrukken dat de door u gegeven informatie vertrouwelijk behandeld wordt.

40. Is uw interesse in sex de laatste tijd

verminderd	
hetzelfde of groter	

41. Heeft u sexuele gemeenschap ? Ja | Nee

Indien met nee beantwoord, verder gaan met vraag 42.

Indien met ja beantwoord, verder gaan met vraag 43.

42. Is de reden dat u geen gemeenschap heeft op een of andere manier gerelateerd aan uw gezondheid ? Ja | Nee

Ga verder met vraag 44.

43. Hoe vaak heeft u gemeenschap ?

(graag 1 hokje invullen)

aantal malen per week	
aantal malen per maand	
aantal malen per jaar	

Aanvullende vragen voor mannen:

44. Heeft u problemen met de erectie ?

Ja	Nee

45. Heeft u problemen met de zaadlozing ?

Ja	Nee

De volgende vragen hebben betrekking op uw dagelijkse activiteiten.

46. Kruis het antwoord aan dat het beste uw beroep beschrijft:

in loondienst	
zelfstandig werkzaam	
niet in loondienst, maar werkzaam in de huishouding of belast met de verzorging van familieleden	
werkloos (om niet-medische reden)	
arbeidsongeschikt (AAW/WAO)	
gepensioneerd	

47. Als u in loondienst bent of zelfstandige bent, hoeveel dagen heeft u de laatste maand wegens ziekte niet kunnen werken ? *(graag het aantal dagen invullen)*

48. Heeft uw gezondheid u in de laatste maand belemmerd om uw normale werkzaamheden in huis of in de tuin uit te voeren ?

Ja	Nee

Indien met nee beantwoord, verder gaan met vraag 50.

49. Hoeveel dagen heeft u in de laatste maand door ziekte deze werkzaamheden in huis of in de tuin niet kunnen uitvoeren ?

50. Heeft u hobbies ?

Ja	Nee

Indien met nee beantwoord, verder gaan met vraag 53.

51. Zo ja, wat zijn uw hobbies ?

_____

_____

52. Vormt uw gezondheidstoestand de laatste tijd een belemmering bij het uitoefenen van uw hobbies ?

Ja	Nee

53. Vormt uw gezondheidstoestand nog op andere manieren een belemmering in uw dagelijks leven ?

Ja	Nee

54. Zo ja, op welke manier ?

_____

_____

Appendix B. MOS Survey – Dutch version

Questions marked with '*' have been added to the original questionnaire.

Wilt u bij iedere vraag 1 antwoordmogelijkheid aankruisen.
Als u een vraag niet precies kunt beantwoorden, geef dan het best mogelijke antwoord

1. Hoe is in het algemeen uw gezondheid ?

	Uitstekend
	Erg goed
	Goed
	Redelijk
	Slecht

De volgende vragen gaan over eventuele beperkingen ten gevolge van uw gezondheid.
Heeft uw gezondheidstoestand u de afgelopen maand beperkt in een van de volgende activiteiten ?

	Beperkt in:	**Ja, ernstig beperkt**	**Ja, een beetje beperkt**	**Nee, helemaal niet beperkt**
2.	.. zeer inspannende activiteiten zoals optillen van zware voorwerpen, hardlopen, of deelname aan inspannende sporten.....	☐	☐	☐
3.	.. wat minder inspannende activiteiten zoals een tafel verplaatsen, boodschappen dragen.....	☐	☐	☐
4.	.. een heuvel oplopen of enkele trappen lopen.....	☐	☐	☐
5.	.. buigen, tillen, of bukken.....	☐	☐	☐
6.	.. een blokje om lopen.....	☐	☐	☐
7.	.. eten, aankleden, douchen of een bad nemen of naar het toilet gaan.....	☐	☐	☐

8. Heeft u de afgelopen maand vanwege uw gezondheid uw werk niet kunnen doen of huishoudelijke karweitjes niet kunnen doen ?

	Ja
	Af en toe
	Nee

9. Heeft u de afgelopen maand vanwege uw gezondheid *bepaalde werkzaamheden* niet kunnen doen ?

	Ja
	Af en toe
	Nee

10. Hoe vaak heeft uw gezondheid u de afgelopen maand beperkt in uw sociale activiteiten (zoals op bezoek gaan bij vrienden of naaste familie) ?

	Altijd
	Heel vaak
	Redelijk vaak
	Soms
	Bijna nooit
	Nooit

11. Heeft u de afgelopen maand lichamelijke pijn gehad ?

	Geen pijn
	Zeer lichte pijn
	Lichte pijn
	Matige pijn
	Hevige pijn

Hieronder staan vragen over hoe u zich de afgelopen maand heeft gevoeld.
Kruis telkens het antwoord aan dat het meest op u van toepassing is.

Hoe vaak in de afgelopen maand	Altijd	Heel vaak	Redelijk vaak	Soms	Bijna nooit	Nooit
12. .. bent u erg nerveus geweest ?.....	☐	☐	☐	☐	☐	☐
13. .. heeft u zich kalm en rustig gevoeld ?.....	☐	☐	☐	☐	☐	☐
14. .. heeft u zich neerslachtig en somber gevoeld ?.....	☐	☐	☐	☐	☐	☐
15. .. heeft u zich gelukkig gevoeld ?....	☐	☐	☐	☐	☐	☐
16. .. heeft u zich zo somber gevoeld dat niets u kon opvrolijken ?.....	☐	☐	☐	☐	☐	☐
17.* .. was u snel geïrriteerd ?.....	☐	☐	☐	☐	☐	☐
18.* .. heeft u zich angstig gevoeld ?.....	☐	☐	☐	☐	☐	☐
19.* .. heeft u zich lusteloos gevoeld ?....	☐	☐	☐	☐	☐	☐

Tot slot willen we u nog een paar andere vragen over uw gezondheid stellen.
Kruis hieronder het antwoord aan dat het best uw situatie weergeeft.

		Absoluut waar	Grotendeels waar	Ben er niet zeker van	Grotendeels niet waar	Beslist niet waar
20.	Ik ben een beetje ziek.....	☐	☐	☐	☐	☐
21.	Ik ben zo gezond als ieder ander die ik ken.....	☐	☐	☐	☐	☐
22.	Mijn gezondheid is uitstekend.....	☐	☐	☐	☐	☐
23.	Ik voel me de laatste tijd slecht.....	☐	☐	☐	☐	☐

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Curriculum vitae

Pieta Krijnen werd geboren op 24 januari 1965 in Den Haag. Ze behaalde in 1984 haar VWO diploma aan het Eerste Vrijzinnig Christelijk Lyceum in Den Haag. Na het afsluiten van haar studie Gezondheidswetenschappen aan de Katholieke Universiteit Nijmegen in 1989 werkte ze als statistisch medewerker bij de afdeling Volksgezondheid van de GG&GD in Amsterdam. Van 1992 tot medio 2004 was ze verbonden aan het Centrum voor Klinische Besliskunde, afdeling Maatschappelijke Gezondheidszorg van de Erasmus Universiteit Rotterdam (later: Erasmus MC, Universitair Medisch Centrum Rotterdam). Tijdens deze periode was ze als epidemioloog betrokken bij een aantal grootschalige studies op verschillende klinische terreinen. Het onderzoek dat is beschreven in dit proefschrift, is een uitvloeisel van een van deze studies. Daarnaast ondersteunde ze vanaf 1998 de wetenschapsadviescommissie van het Erasmus MC. Sinds augustus 2004 is ze hoofd van de afdeling Kankerregistratie van het Integraal Kankercentrum West (IKW).
Pieta Krijnen is getrouwd met Edo Didden. Samen hebben ze twee dochters, Roos en Veerle.

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