

Prognostic factors for the vascular components of erectile dysfunction in patients on renal replacement therapy

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A total of 76 male patients on renal replacement therapy (RRT) were investigated. Erectile dysfunction (ED) was defined as insufficient erection during visual erotic stimulation (VES) or during sleep as measured with Rigiscan[®] and Erectimeter[®]. Data on medical history, physical examination, and laboratory variables were collected. Furthermore, penile pharmacological duplex ultrasonography (PPDU) was performed. Univariate and multivariate logistic regressions were used to determine prognostic values and to develop prognostic models. Independent prognostic factors for ED were the number of cardiovascular events, waist-hip ratio, body mass index, and acceleration time (AT) as measured with PPDU. Independent prognostic factors for an abnormal AT (> 100 ms) were number of cardiovascular events, age category, and the presence of carotid bruits. Independent prognostic factors for insufficient veno-occlusion during PPDU were number of cardiovascular events and supine diastolic blood pressure. The vascular contribution to ED in patients on RRT is substantial. Data from medical history, limited physical examination, and PPDU contribute to the prediction of the vascular contribution to ED.

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Introduction

In men on renal replacement therapy (RRT), including hemodialysis (HD), peritoneal dialysis (PD), and renal transplantation (RTx), the prevalences of sexual problems and erectile dysfunction (ED) are up to 69.8% as compared to 8.7% in the general Dutch population.¹ Taking into account the premature vascular dysfunction in these patients, it is conceivable that vascular causes substantially contribute to their ED.^{2,3}

To date, very little is known about the power of various clinical assessments such as history taking,

physical examination, and laboratory testing to predict vascular ED in men on RRT. Such knowledge may be important for several reasons. Firstly, it will contribute to the understanding of the nature of ED in these patients. This may facilitate the acceptance of ED by the patient and his partner, but it may also facilitate the development of preventive strategies. Moreover, knowledge of the specific patient profile at risk for vascular ED implies that a less comprehensive diagnostic work-up can be focused on these patients.

The aim of this study is firstly to identify patients' characteristics that predict ED, secondly to identify patients' characteristics that predict vascular dysfunction, and finally to assess the vascular contribution to ED in patients on RRT.

To reach that goal, we have comprehensively investigated 76 male patients. The investigations included vascular and nonvascular aspects of ED. For this study, patient characteristics and results of investigations with any linkage with vascular dysfunction and ED were used in the analyses. Analyses of the nonvascular aspects of ED will be described later.

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Materials and methods

Patients

A questionnaire was sent to 852 male patients with RRT consisting of either HD, PD, or RTx with a minimal follow-up of 3 months and an endogenous creatinine clearance of >25 ml/min. Furthermore, they were in a stable condition and aged between 18 and 65 y. In total, 470 (55.2%) patients answered the questionnaire, including a question on willingness to participate in further examinations. These patients were representative of the Dutch patients on RRT with regard to age distribution. A total of 76 male patients signed an informed consent for participation in the investigation. The different treatment modalities and the prevalences of ED are given in Table 1. The ethical committees of the various participating hospitals approved the study protocol.

Methods

ED is defined as an inability to initiate and maintain a penile erection sufficient for intercourse and causing personal distress.⁴ In this study, this definition was operationalized as an inability to achieve an erectile response during visual erotic stimulation (VES) or nocturnal penile tumescence (NPT) measurement.

VES was performed as previously described by Janssen *et al*.⁵ This included alternating erotic and nonerotic visual stimulation and penile vibration. Tumescence and rigidity were recorded by RigiScan[®] real-time monitoring. Cutoff values as established by Vrugink⁶ *et al* were used to define a normal and an abnormal response. Briefly, a total tumescence increase at base and tip ≥ 20 mm or a rigidity at base $\geq 50\%$ together with a rigidity at tip $\geq 30\%$ were considered as a sufficient erectile response. VES measures the entire erectile mechanism, including afferent pathways (conduction of

visual and penile sensory stimuli), central processing (labeling of stimuli and environmental conditions as sexual) and the efferent pathways as measured with NPT. Presence of VES-evoked tumescence and rigidity implies an intact erectile mechanism. Absence of VES response points to a lack of sexual stimulation, lack of labeling or a defect in the somatic pathways.

NPT was measured with the Erectiometer[®] as described previously by Joans⁷ and confirmed by Slob.⁸ Measurements were done during three consecutive nights at home; 2 days with the yellow version and third night with the green version. Briefly, an increase of ≥ 15 mm with the yellow version or of ≥ 10 mm with the green version was considered as sufficient penile erection. NPT measures the efferent part of the somatic penile erectile mechanism, including the central and peripheral nervous, vascular, and endocrinological pathways. Afferent pathways are not involved in NPT and therefore, environmental factors have no substantial influence on NPT. Presence of sufficient nocturnal penile tumescence is considered as proof of an intact efferent part of the somatic penile erectile mechanism. Absence of sufficient nocturnal penile tumescence may point to efferent neuropathy, vasculopathy or endocrinological disturbance, but also to depression or sleep disturbances.

PPDU was performed as previously described by Meuleman, using 0.25 ml Androskat[®] (containing 3.75 mg papaverine and 0.125 mg phentolamine).⁹ Within the first 6 min after injection, at least three measurements were recorded. The measurements with the highest peak systolic velocity (PSV) was analyzed for PSV and acceleration time (AT). Recordings after 6 min were used to determine the highest resistance index (RI). The same physician (WLD) and the same vascular laboratory assistant performed all measurements. Duplex ultrasonography was performed with a color-coded ultrasound scanner (Toshiba SSA270, Tokyo, Japan), equipped with a 7.5 MHz linear array probe. The insonation angle was kept below 60° for all Doppler measurements. Penile pharmacological duplex ultrasonography allows an assessment of the arterial and veno-occlusive response to the intracavernous injection with a vasodilating agent. The arterial response, expressed as PSV and AT, is not influenced by sympathetic tone.¹⁰ In contrast, the veno-occlusive response, expressed as RI (RI = PSV/ (diastolic velocity + PSV)) can be frustrated by a sympathetic tone like anxiety.

History taking and physical examination were all performed by one investigator (WLD). In patients on PD, waist circumference was measured after drainage of the peritoneal cavity. Venous blood samples were drawn in the morning in a nonfasting condition. The original kidney disease was classified according to the classification of the Dutch Registry of Dialysis Patients in either diabetes mellitus type I

Table 1 Prevalence of ED in the different RRT groups

	Erectile dysfunction ^a	
	No n (%)	Yes n (%)
Hemodialysis (n=18)	8 (44.4)	10 (55.6)
Peritoneal dialysis (n=24)	8 (33.3)	16 (66.7)
Renal transplant (n=33)	11 (33.3)	22 (66.7)
All (n=75)	27 (36.0)	48 (64.0)

^a Absence of erection during VES or during NPT.

nephropathy, diabetes mellitus type II nephropathy, glomerulonephritis, polycystic disease, pyelonephritis, renal vascular disease excluding vasculitis, other causes, not determined or unknown.

Information about cardiovascular events was retrieved with a comorbidity questionnaire. This questionnaire asked for the presence of hypertension, angina pectoris, heart valve disturbances, heart rhythm disturbances, pulmonary edema, pericarditis, hypotension, peripheral arterial disease, need for more than two arteriovenous shunts and a cerebrovascular accident. Each condition scored 1 point and the sum score was used for the analysis.

Currently used medicines were coded according to the WHO anatomic–therapeutic–chemical classification system (ATC code).¹¹ As cardiovascular medication was considered those medicines with an ATC code starting with C. This class includes among others antihypertensives, anti arrhythmia agents, diuretics, and RAAS antagonists.

Parathyroid hormone was determined by an immunoradiometric assay (Biosource/Medgenix Diagnostics, Fleurus, Belgium). Reference values are 1.1–6.3 pmol/l. Testosterone was determined by a radioimmunoassay from Coat-A-Count (Coat-A-Count DPC, Los Angeles, USA). Reference values are >8.0 nmol/l. Hemoglobin reference values are 8.1–10.7 mmol/l. An overview of the analyzed variables is described in Table 2.

Statistical methods

The Mann–Whitney test was used to test for statistically significant differences between men with ED compared to those without ED in the case of quantitative variables and the χ^2 test was used in case of qualitative variables.

Univariate logistic regression was used to evaluate prognostic variables. The results are expressed as crude odds ratios with 95% confidence intervals (CIs).

Multivariate logistic regression with forward selection procedures was used to identify variables that contributed independently to the risk of ED. Because forward selection procedures do not identify other important variables, the *P*-values for entry into the model were considered in order to find close alternatives to the variables selected. Adjusted odds ratio with 95% CI of the final model were presented.

In order to find a reasonable cut off value for the AT to predict ED, the condition of equal ‘costs’ of misclassification of cases and of noncases was used. This resulted in the optimal cut off value for AT, where the sum of sensitivity and specificity to predict ED is maximal. The same procedure was used to determine the cut off value for the RI. In addition, logistic regression was used to calculate

crude odds ratio of prognostic variables to identify men with AT above the threshold found. Subsequently, the most important prognostic variables were determined using forward selection procedure as mentioned above. Adjusted odds ratios with 95% CI of the final model are presented. Finally, the same procedure was used to evaluate prognostic variables to identify men with an increased RI.

Results

Patients

Patient recruitment resulted in 76 men on RRT. One patient refused the VES procedure and had a normal NPT. Since normal erectile function was defined as having both normal VES and normal NPT, this patient was excluded from the study. As a result, 75 men were included in the study. The results are described in Table 2.

The original kidney disease was diverse diabetes mellitus type I (*n* = 2), glomerulonephritis (*n* = 15), polycystic disease (*n* = 13), pyelonephritis (*n* = 11), renal vascular disease excluding vasculitis (*n* = 5), others (*n* = 21), unknown (*n* = 8).

Since PSV, in contrast with AT and RI, did not differentiate between men with and without ED, this variable was not further analyzed.

Patient characteristics and ED

The studied prognostic variables of the patients with and without ED are listed in Table 2. Statistically significant differences between patients with and without ED were noted for age, number of cardiovascular events, body mass index (BMI), waist–hip (W–H) ratio, AT, and RI.

Since the AT and the RI, as determined by the vascular function test PPDU, reflect cavernous vascular function, it is of major interest to determine their optimal cut off value for the prediction of ED. Therefore, these variables were dichotomized using logistic regression and the principle of equal costs of misclassification of ED. The optimal cut off value was 100 ms for the AT (sensitivity 0.32, specificity 0.96) and 1.00 for the RI (sensitivity 0.29, specificity 0.93).

In order to identify prognostic variables in men with ED, the crude odds ratios and 95% CIs for ED of all variables of history, physical examination, laboratory outcomes, and PPDU (Figure 1) are presented. In summary, statistically significant crude odds ratios are reported for number of cardiovascular events, age category (18–40, 41–55, 56–65), BMI category (<25, 25–28, >28), W–H ratio,

Table 2 Variables from the medical history, physical examination, laboratory analysis and PPDU of patients with or without ED

Variable	Unit\ classification	Definition\ classification	Erectile dysfunction				P
			No		Yes		
			Median (number)	Range (%)	Median (number)	Range (%)	
<i>Medical history</i>							
Age	y	Range 18–65	46.0	23–65	51.5	24–64	0.034
Duration of kidney disease	months	Since diagnosis	131	21–524	188	14–588	0.070
Pre–RRT duration	months	Between diagnosis and start any RRT	38.0	0–360	91.5	0–519	0.282
Duration RRT	months	Total duration of HD, Pd and RTx	47.0	5–282	64.5	3–288	0.356
Duration of dialysis	months	Total duration of HD and PD	30.0	5–241	28.5	3–264	0.800
Duration of RTx	months	Duration of all functioning RTx periods	0.0	0–184	12.5	0–190	0.148
Number of RTx		Number of RTx with survival >1 month	0	0–3	0	0–3	0.741
Number of cardiovascular events			1	0–4	2	0–5	0.023
Number of Cardiovascular medications			1	1–5	1	0–3	0.400
Smoking	Never		7	41.2	10	58.8	0.880
	Ever		10	34.5	19	65.5	
	Currently		10	34.5	19	65.5	
Packyears	years	Years with >20 cigarettes/day	6	0–56	11	0–68	0.079
<i>Physical examination</i>							
BMI	kg/m ²		23.2	20.0–29.6	25.0	20.8–32.9	0.001
Waist–hip ratio	cm/cm		0.96	0.83–1.07	0.99	0.87–1.12	0.013
SBP supine	mmhg		141	96–178	134	94–188	0.571
DBP supine	mmhg		84	50–108	81	62–108	0.590
HR supine	bpm		72	42–96	72	52–120	0.940
Carotid artery bruit	None		23	30.7	40	53.3	1.000
	Any		4	33.3	8	66.7	
Cardiac bruits	None		12	27.9	31	72.1	0.084
	Any		15	50.0	15	50.0	
Abdominal bruits	None		22	37.3	37	62.7	0.774
	Any		5	31.3	11	68.7	
<i>Laboratory</i>							
Parathyroid hormone	pmol/l		7.0	2.1–44	7.2	0.7–130	0.570
Testosterone	nmol/l		14.5	6.8–30	16.0	2.0–34	0.360
Hemoglobin	nmol/l		7.5	5.6–9.6	7.7	5.6–9.7	0.661
<i>PPDU</i>							
PSV	cm/s		37.0	21–82	34.5	14–91	0.191
AT	ms		64	16–120	80	40–208	0.021
Highest RI	Ratio		100.0	85–100	100.0	63–100	0.023

P value for differences between men with and without ED, using the Mann–Whitney test for quantitative variables and the χ^2 test (Fisher’s exact test in case of 2 × 2 tables) for qualitative variables. RRT: renal replacement therapy, RTx: renal transplant, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, PPDU: penile pharmacological duplex ultrasonography.

AT category (< or ≥100 ms), and RI category (≥1.0 or <1.0), indicating that the vascular contribution to ED in this population is significant, since age, BMI, and W–H ratio are well known vascular risk factors. The significance of the number of cardiovascular events in the past, the long AT and RI below 1.00 as prognostic variables underline the vascular nature of ED even more.

A multivariate analysis was performed with these variables to identify those parameters that independently predict ED. The adjusted odds ratios (with

95% CI) of the variables selected for ED are shown in Table 3. The transition of an AT from below to above 100 ms and the transition to a higher BMI category substantially raise the probability of ED.

Patient characteristics and vascular dysfunction

AT is a parameter for arterial vascular function, and was identified as significant prognostic variable for

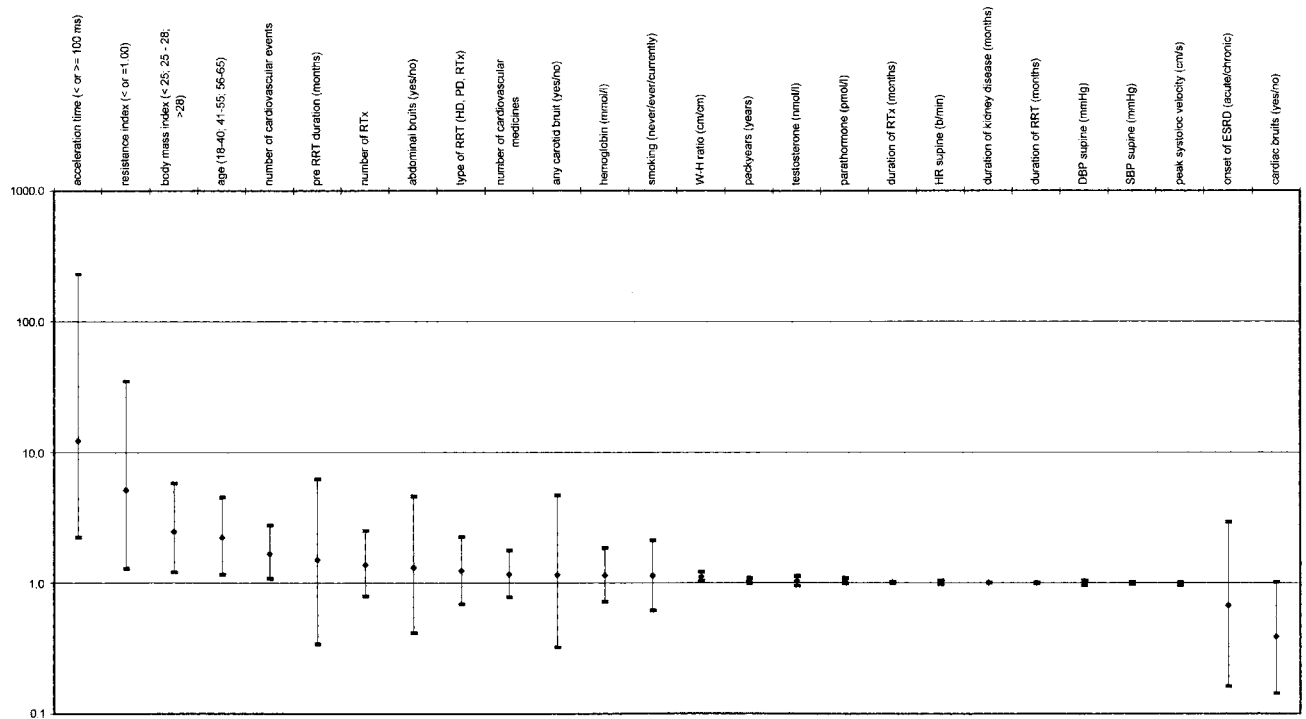


Figure 1 Crude odds ratio and 95% CI of the prognostic variables for ED.

Table 3 Adjusted odds ratios (and 95% CIs) for ED, AT ≥ 100 ms, and RI < 1.0, using multiple logistic regression with forward selection procedure on all relevant variables

	ED	AT ≥ 100 ms	RI < 1.0
AT: < or ≥ 100 ms	7.7 (1.1–156.0) 3.5	NA	—
BMI category: < 25, 25–28, > 28	1.5–10.3 1.9	— 1.6	— 1.6
Number of cardiovascular events	(1.1–3.8) 1.1	(1.0–2.1)	(1.0–2.7)
Waist-H ratio	(1.0–1.3)	4.5	—
Age category: 18–40, 41–55, 56–65	—	(1.6–16.9) 5.5	—
Carotid bruit: yes/no	—	1.1–32.8	1.1
DBP supine (per mmHg)	—	—	(1.0–1.1)

NA: not applicable; —: not selected in forward procedure.

ED. Therefore, it is of interest to determine whether the above-mentioned prognostic variables for ED are related to AT as well. This might elucidate whether the impact of the prognostic variables

for ED goes by arterial insufficiency as indicated by an AT > 100 ms. The crude odds ratios of these variables for AT category (< or ≥ 100 ms) are shown in Figure 2. Number of packyears, age category,

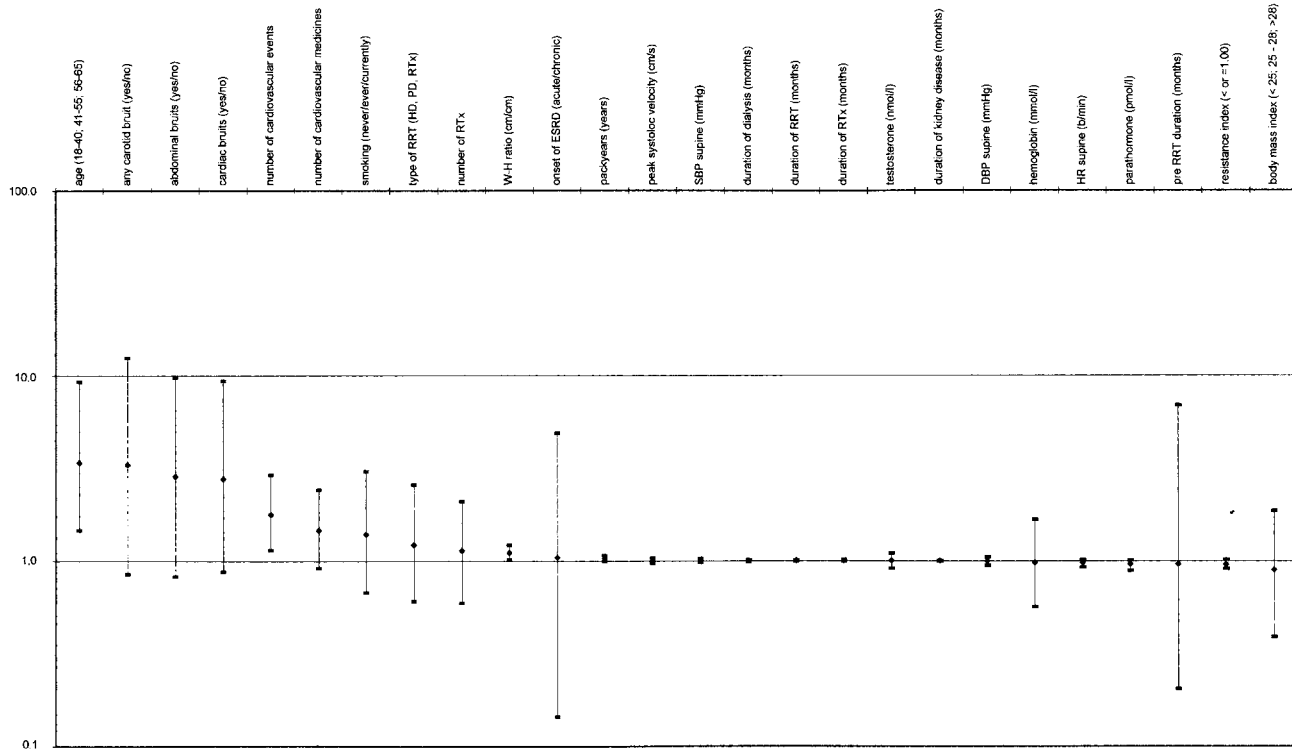


Figure 2 Crude odds ratio and 95% CI of the prognostic variables for AT ≥ 100 ms.

number of cardiovascular events, and W–H ratio were statistically significant related to the AT category.

RI is the PPDU parameter for veno-occlusive function. Without proper veno-occlusion, implying an RI of < 1.0 , rigidity may be suboptimal and ED may result. As for AT, the RI is significantly related to ED. Figure 3 shows the crude odds ratios of these variables for RI < 1.0 . Statistically significant crude odds ratios are reported for number of cardiovascular medicines, number of cardiovascular events, and supine DBP after 10 min of rest.

Forward stepwise selection procedure using only the variables with a statistically significant crude odds ratio was performed to identify those variables that are sufficient to predict independently the AT ($< \text{ or } \geq 100$ ms) and the RI ($< \text{ or } \leq 1.00$), respectively. Table 3 shows the adjusted odds ratios for AT and RI. The number of cardiovascular events, the age category and the presence of any carotid bruit contribute independently to the prediction of the presence of an AT ≥ 100 ms. The number of cardiovascular events and the supine DBP contributed independently to the prediction of the presence of an RI < 1.0 .

Vascular contribution to ED

In general, having identified a prognostic model for the vascular contribution to ED, increased AT and

abnormal RI, it is also of interest to study the discriminatory power of these models. The discriminatory power of the prognostic models (for the vascular contribution to ED, increased AT, and abnormal RI, respectively) is visualized in Figure 4 and further quantified in Table 4. From both the maximal (vertical) distance from the $y = x$ line and the AUC it can be concluded that these three models are satisfactory with regard to the discriminatory power. This implies that, for example, the application of the number of cardiovascular events, BMI category, W–H ratio, and AT category to predict ED, without having measured VES and NPT, results in an *a priori* chance with a sensitivity of 0.66 and a specificity of 0.88. The prediction of an AT ≥ 100 ms, without having performed a PPDU, from the number of cardiovascular events, age category, and the presence of any carotid bruit results in an *a priori* chance with a sensitivity of 0.69 and a specificity of 0.84.

Discussion

Our results indicate that patients on RRT with ED, as determined by VES and NPT, were significantly older, have suffered from more cardiovascular events, had a higher BMI and W–H ratio, a longer AT and a lower RI. Moreover, this group showed a tendency to a longer duration of their kidney disease

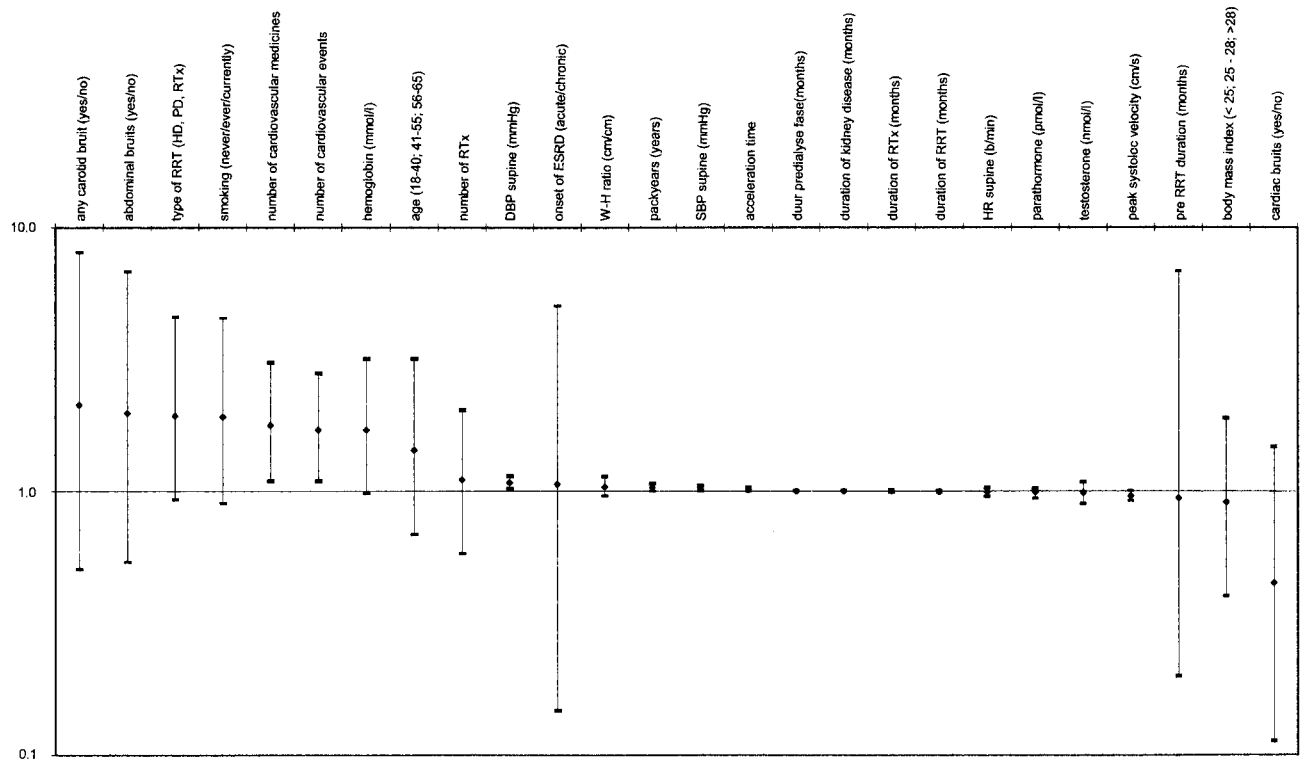


Figure 3 Crude odds ratio and 95% CI of the prognostic variables for RI < 1.00.

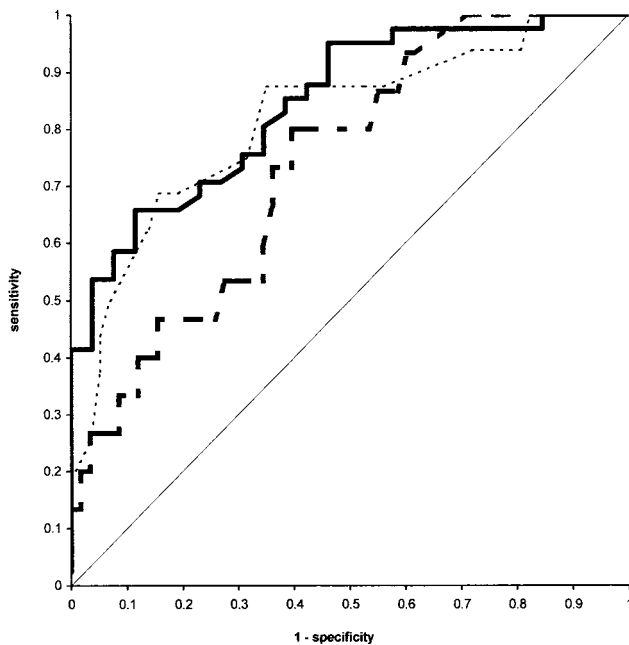


Figure 4 ROC curves presenting the discriminatory power as distance between ROC curve and the $x = y$ line, of the prognostic models of ED (solid line), increased AT (thin dashed line), and decreased RI (thick dashed line).

Table 4 ROC curves for the prediction of ED, acceleration time (< or ≥ 100 ms) and resistance index (≤ 1.00) by using the independent variables listed in Table 3

	Sensitivity	Specificity
ED	0.66	0.88
AT	0.69	0.84
RI	0.80	0.60

cardiovascular events, BMI category, $W-H$ ratio, and AT are independent risk factors for ED. The number of cardiovascular events as independent risk factor for ED points to a vascular contribution of ED. Apparently, the penis is not protected from systemic cardiovascular disease, as already suggested in patients with hypertension.¹² BMI category as independent risk factor for ED is intriguing. Indeed, obesity is considered as an independent risk factor for cardiovascular disease.¹³ However, its independency from AT suggests another type of contribution to ED than by atherosclerosis. The follow-up study of the Massachusetts Male Aging Study (MMAS) also revealed obesity (BMI > 30) as a risk factor for ED, but weight reduction during the follow-up period (average follow-up 8.8 y) did unfortunately not convert this risk.¹⁴ The $W-H$ ratio as prognostic factor for ED is surprising, because of its independency from the AT and BMI. Waist and hip circumferences affect risk factors for cardiovascular disease and identify patients at increased risk for

($P = 0.07$ Mann-Whitney test) and to having smoked more packyears ($P = 0.08$ Mann-Whitney test). The selection procedures elucidated that the number of

cardiovascular disease.^{15,16} The influence of the *W-H* ratio on ED could be largely of vascular origin, but is apparently not covered by arterial insufficiency alone. AT category as independent risk factor for ED underlines the vascular contribution to ED in patients on RRT. Since a prolonged AT reflects proximal arteriosclerosis, it may include variables that promote arteriosclerosis. Interestingly, the type of onset of renal failure (acute or chronic), the duration of the kidney disease (pre-RRT, RRT, kidney disease, RTx), smoking (never, ever, currently), age category or the presence of any carotid bruit did not predict ED.

Penile vascular insufficiency has been divided into arterial and veno-occlusive insufficiency. Patients with arterial insufficiency, defined as AT ≥ 100 ms, were significantly older, had more cardiovascular events, and had a higher number of packyears and *W-H* ratio. Our analyses demonstrate that AT better correlates with ED than PSV. This is a remarkable result, since PSV has been considered until now as the best parameter to identify arterial penile insufficiency.⁵ Multivariate analysis revealed age category, the number of cardiovascular events and the presence of any carotid bruit as independent prognostic variables for an increased AT. Age as independent prognostic variable for prolonged AT is not surprising. The incidence of arteriosclerotic lesions proximal to the penile vascular body will rise with age, and these proximal stenoses will cause flattening of the blood velocity wave, and thereby increase the AT. Variables that promote proximal stenoses may be included in age as independent prognostic variable. The number of cardiovascular events, including hypertension, angina pectoris, heart valve disturbances, heart rhythm disturbances, pulmonary edema, pericarditis, hypotension, peripheral arterial disease, need for more than two arteriovenous shunts or a cerebrovascular accident, reflect symptomatic cardiovascular disease, although not necessarily from arteriosclerotic origin. Its correlation with penile arterial insufficiency and its independency from age are conceivable. The presence of any carotid bruit as independent prognostic factor for prolonged AT deserves attention. The predictive value of carotid bruits for carotid arteriosclerotic lesions is at least questionable.^{17,18} However, the carotid intima-media thickness is considered as independent predictor for cardiovascular death in patients on HD or PD, and is associated with left ventricular hypertrophy.¹⁹

Apparently, the *W-H* ratio, the number of packyears, and the onset (acute or chronic) and the duration of the kidney disease (pre-RRT, RRT, kidney disease, RTx) did not predict a prolonged AT.

Patients with veno-occlusive insufficiency, defined as RI < 1.0 during PPDU, had significantly more cardiovascular events, used more cardiovascular medicines, and had a higher diastolic blood pressure in supine position after 10 min rest. Multi-

variate analysis revealed that the number of cardiovascular events and the diastolic blood pressure are independent prognostic variables for veno-occlusive insufficiency. The number of cardiovascular events as independent prognostic factor for veno-occlusive insufficiency may reflect insufficient arterial filling as expression of proximal arteriosclerotic lesions resulting in an insufficient pressure gradient for veno-occlusion. The higher the diastolic blood pressure, the greater the *a priori* chance for veno-occlusive dysfunction. The mechanism behind the relationship between veno-occlusive dysfunction and higher blood pressure remains to be elucidated.

Conclusions

In patients on RRT, the *a priori* probability of ED can be estimated by the number of cardiovascular events in the past, BMI category, *W-H* ratio, and AT during PPDU. Moreover, the *a priori* probability of penile arterial insufficiency can be estimated by age category, the number of cardiovascular events and the presence of any carotid bruit. The *a priori* probability of veno-occlusive dysfunction can be estimated by the number of cardiovascular events and the diastolic blood pressure. The clinical consequences of these results are that a medical history taking, a limited physical examination, and a PPDU can predict the presence of ED and vascular contribution.

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