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Determinants of Acute Kidney Injury and Renal Function Decline After Endovascular Abdominal Aortic Aneurysm Repair

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WHAT THIS PAPER ADDS

This study analysed risk factors for the occurrence of acute kidney injury (AKI) and long-term renal function deterioration following endovascular aneurysm repair. Besides peri-operative complications this study identified the use of angiotensin II receptor blockers as a risk factor for AKI and the presence of renal artery stenosis as a risk factor for long-term renal function deterioration. Better understanding of these pathophysiological mechanisms could help to implement preventive strategies.

Objective/Background: Endovascular aneurysm repair (EVAR) may be associated with renal injury and more insight is needed into potential risk factors. The aim was to identify clinical, anatomical, and peri-procedural parameters as potential risk factors for the occurrence of acute kidney injury (AKI) and to evaluate chronic kidney disease (CKD) after EVAR.

Methods: A cohort of 212 consecutive patients who underwent elective EVAR for abdominal aortic aneurysm from January 2009 to October 2016 was included. A subgroup of 149 patients with 2 years follow-up was compared with a set of 135 non-operated aneurysm patients with smaller aneurysms (similar cardiovascular risk profile) to assess CKD. Primary outcomes were AKI (Acute Kidney Injury Network criteria) and CKD measured by estimated glomerular filtration rate (Kidney Disease Improving Global Outcomes guidelines). For AKI, candidate risk factors were identified by univariate and multivariate logistic regression analysis; for chronic renal function decline, risk factors were identified using Cox regression analysis.

Results: AKI occurred in 30 patients (15%). On multivariate analysis, the use of angiotensin II blocker (odds ratio [OR] 4.08, 95% confidence interval [CI] 1.38–12.07) and peri-operative complications (OR 3.12, 95% CI 1.20–8.10) were independent risk factors for AKI, whereas statin use was a protective factor (OR 0.19, 95% CI 0.07–0.52). EVAR resulted in a significant increase (23.5%) in the occurrence of CKD compared with the control group (6.7%; $p < .001$). On univariate and multivariate Cox regression the risk factors: aortic neck diameter (per mm increase) (hazard ratio [HR] 1.13, 95% CI 1.02–1.25), renal artery stenosis >50% (HR 2.24, 95% CI 1.05–4.79), and the occurrence of AKI (HR 2.19, 95% CI 0.99–4.85) were significant predictors of CKD.

Conclusion: This study identified use of angiotensin II blockers and peri-operative complications as risk factors for AKI. In addition, the problem of renal function decline after EVAR is highlighted, which indicates that prolonged protective measures (e.g., in those patients at high risk) over time are needed to improve patient outcomes.

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INTRODUCTION

The occurrence of acute kidney injury (AKI) is associated with increased morbidity and mortality after vascular interventions. It has been demonstrated that after percutaneous coronary intervention and elective coronary bypass grafting, patients with AKI have a 20 fold increased risk of post-procedure mortality.[1,2]

In open abdominal infrarenal aortic surgery, post-operative renal dysfunction is also associated with increased in hospital mortality.[3] Furthermore, other studies have documented increased long-term mortality associated with the occurrence of AKI after cardiovascular procedures.[4,5] In aneurysm treatment, studies have focused on the differences in occurrence

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of renal dysfunction between open surgery and endovascular aneurysm repair (EVAR) and it is clear that both treatment approaches carry a risk of AKI.[3,6,7] After EVAR, a wide range of AKI incidences have been reported (3—19%), depending on the criteria used. However, more recent data using the Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggested that about 15% to 20% of all EVAR patients develop AKI.[6,8,9] With a shift towards more endovascular procedures and, consequently, more re-interventions in aneurysm treatment, extra attention is being paid to the problem of EVAR related long-term renal function decline. A recent systematic review and meta-analysis on renal function after EVAR indicated that there is a significant deterioration in renal function in the follow-up period.[10] However, it is not clear whether the EVAR procedure itself or the cardiovascular risk profile of the patient and/or re-interventions is affecting long-term renal function. Compared with open aneurysm repair, EVAR is associated with fewer operative haemodynamic changes that have an impact on renal function. However, EVAR is accompanied by other potential insults to the kidneys, such as contrast material and microemboli.[11] Recent studies have described reduced renal function and poor cardiovascular reserve as significant risk factors for AKI after EVAR.[12,13] Other studies showed contradictory results with regard to whether suprarenal graft fixation might be associated with renal function decline.[9,14] In order to reduce the occurrence of AKI in endovascular aneurysm treatment more studies are needed to unravel its mechanism and elucidate specific risk factors. Moreover, additional knowledge is needed on potential decline in renal function during follow-up. Therefore, this study examined the occurrence of post-operative AKI after EVAR and evaluated risk factors associated with AKI. In addition, by using a control group of non-operated aneurysm patients, this study examined clinically relevant renal function decline during follow-up.

MATERIAL AND METHODS

Study population

This study was based on a retrospective analysis of a cohort of 212 consecutive patients who underwent elective EVAR for infrarenal aortic or iliac aneurysm from January 2009 to October 2016 at the HAGA Teaching Hospital, The Hague, The Netherlands. This retrospective study was approved by the local ethical committee of HAGA Hospital which issued a waiver for informed consent. Data were derived from electronic patient records, which included clinical data, imaging studies from the PACS image storage system, and laboratory values (collected as part of routine patient care). Patients treated for a ruptured abdominal aortic aneurysm, those treated with fenestrated/ branched or chimney stent grafts, and patients who were on pre-operative dialysis were excluded (Fig. 1).

Study outcomes

The primary outcome of this study was occurrence of AKI in the post-operative period. Secondary outcome was details of clinically relevant renal function decline 2 years after the procedure. AKI was defined using Acute Kidney Injury Network criteria (KDIGO; www.kdigo.org). AKI (stage 1) is present when an abrupt (in 48 hours) reduction in kidney function results in an absolute increase in serum creatinine of $\geq$ 0.3 mg/dL (26 µmol/L) or serum creatinine rise of $>$ 1.5 fold from the reference value, known to have occurred within 1week. The highest level of creatinine within this period after EVAR was used to evaluate the presence of AKI.[15,16] Increase in serum creatinine of $>$ 2—3 fold compared with baseline is classified as stage 2 and more than threefold as stage 3 AKI. The evaluation of renal function during follow-up was based on estimated glomerular filtration rate (eGFR; mL/minute/1.73 m^2). eGFR was determined using the abbreviated Modification of Diet in Renal Disease study equation.[17] Clinically relevant renal function decline was defined using the KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease (CKD); renal function is categorized in several grades, based on eGFR ($>$ 90 [G1], 60—89 [G2], 45—59 [G3a], 30—44 [G3b], 15—29 [G4], $<$ 15 [G5]). A significant decrease in eGFR is defined as a drop in GFR category accompanied by a $\geq$ 25% drop in eGFR from baseline.[18]

Study outcome assessment

Before patients underwent EVAR, eGFR was determined pre-operatively (routinely performed and in most patients prior to contrast imaging studies). Thereafter, renal function was measured several times during hospital stay (data used for AKI outcome). After hospital discharge, patients visited the clinic at regular, protocolled time intervals for follow-up. To evaluate clinically relevant renal function decline eGFR values were compared in the follow-up period (at 2 years) to pre-operative eGFR. eGFR values were also collected in a control cohort consisting of patients with a small aneurysm. This control group of patients had an aortic diameter $>$ 3 cm and was periodically examined by ultrasound at the vascular outpatient clinic. For both EVAR and control patients, serial measurements of eGFR and follow-up for at least 2 years were required to be included in these analyses (comparing clinically relevant renal function decline). Patients and controls were identified during the same period.

The EVAR procedure using stent grafts with suprarenal fixation was performed in the operating theatre, usually under general anaesthesia. All EVAR procedures were performed percutaneously with minimal blood loss and only patients with a neck length $>$ 1 cm were considered for EVAR in this series. The details of the procedure have been described previously.[19] Patients with a pre-operative eGFR $<$ 45 were routinely pre-hydrated with 1 L 0.9% NaCl over 4 hours pre-operatively. All patients received 2 L lactated Ringer's solution in the first 24 hours post-operatively.

Risk factors

Candidate risk factors for the development of AKI and clinically relevant renal function decline included patient

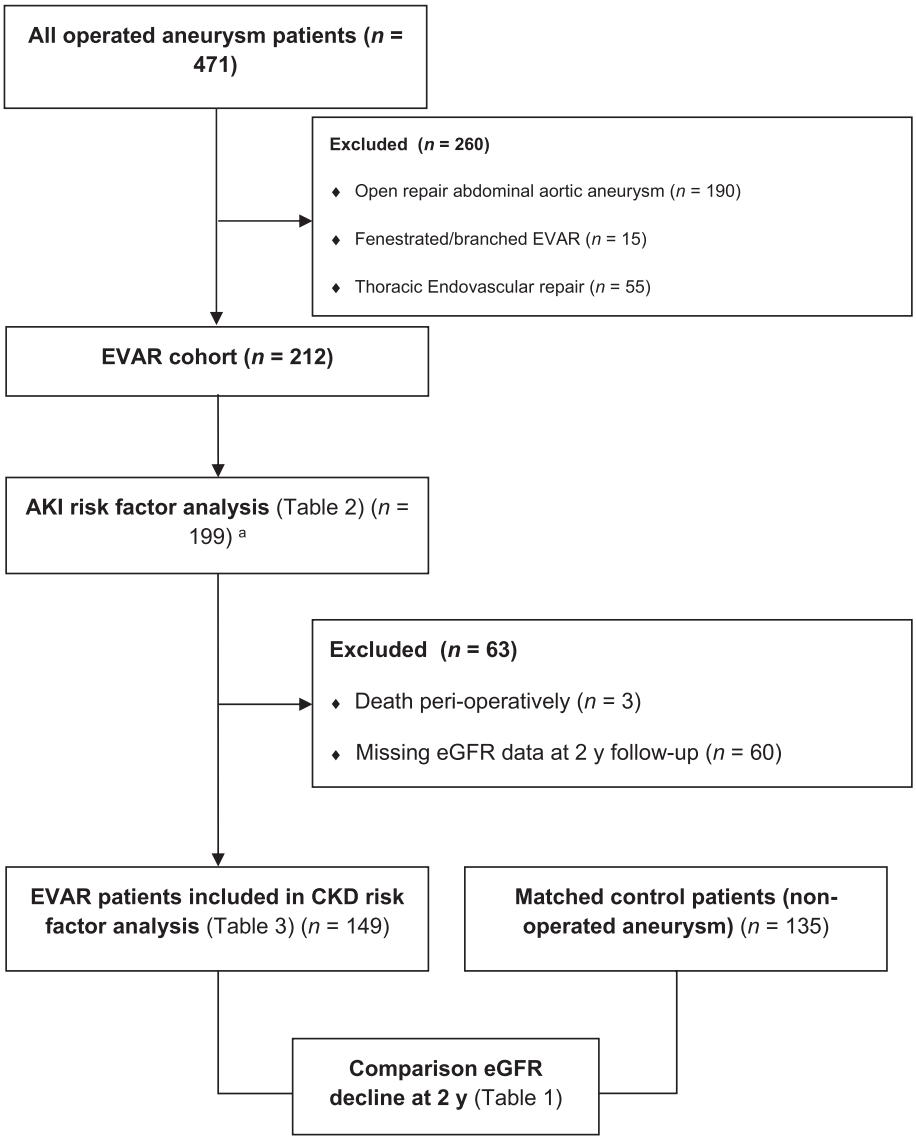


Figure 1. Flowchart of endovascular aneurysm repair patients included in acute kidney injury and chronic kidney disease analyses. *Note*. eGFR = estimated glomerular filtration rate. [a] Thirteen patients did not have adequate kreatinine measurements and were excluded from the AKI analysis. However, as baseline data were available these patients could be included in the CKD analysis.

demographics, comorbidities (hypertension, diabetes mellitus, heart failure, coronary disease, cerebrovascular disease, peripheral arterial occlusive disease), anatomical (neck diameter, renal artery stenosis, suprarenal thrombus, coverage of accessory renal artery), and operative variables (operating time, contrast volume, complications during surgery). Post-operative variables (number contrast administrations, presence of endoleak, re-intervention) were considered for the long-term renal function decline. These variables were pre-specified and based on clinical importance and current knowledge of potential risk factors for AKI and renal function decline in general.

Presence of hypertension or diabetes was defined based on the use of antihypertensive medication or use of insulin and/or antidiabetic agents respectively (current medication use was extracted from the pre-operative screening form filled in by the anaesthetist). Classification of patients with heart failure was based on clear documentation by a cardiologist of this condition in the electronic patient record and usually consisted of previous admissions for heart failure, chronic medical treatment for this condition, and participation in an outpatient heart failure program. Presence of coronary disease was defined by previous coronary intervention/coronary artery bypass graft or a history of myocardial infarction and medical treatment for coronary artery disease. Cerebrovascular disease was defined by a history of transient ischaemic attack or a cerebrovascular accident. Patients with peripheral artery disease had a history of intermittent claudication, critical limb ischaemia, or were treated by endovascular intervention, bypass, or amputation for this condition.

Renal artery stenosis was defined as a $>$ 50% stenosis in one of the renal arteries as observed on the procedural angiogram. Significant aortic thrombus was defined as $>$ 5 mm thick and $>$ 25% circumference thrombus mass from the coeliac trunk to above the renal arteries.[20] Operative

complications were defined by (i) access site problem (conversion to open groin after percutaneous approach owing to bleeding or occlusion); (ii) inadvertent coverage of main renal artery requiring renal artery stenting; and (iii) primary type I endoleak requiring additional procedure. The number of contrast imaging studies using iodinated contrast material, such as computed tomography angiography and angiogram, in the follow-up period until the 2 year eGFR measurement was scored. Re-intervention in the follow-up period included bypass surgery for iliac limb occlusion and endovascular treatment of endoleaks.

Statistical analysis

Demographic and baseline data were summarized as mean ± SD or proportions, as appropriate. Odds ratio (OR) with 95% confidence interval (95% CI) for developing AKI for all risk factors was calculated using univariate logistic regression. A multivariate logistic regression was performed to adjust for potential confounders. Risk factors for clinically relevant renal function decline at 2 years were identified by performing a Cox regression analysis. Start of follow-up was defined as the date of surgery; patients were followed until the end of follow-up, i.e., the occurrence of renal function decline, loss to follow-up, or death, whichever occurred first.

To compare renal function decline between EVAR and control patients, mean eGFR decline was calculated for the EVAR and control groups. The EVAR and control groups were compared on baseline characteristics using an unpaired *t*-test (for continuous data) and a chi-square test for categorical variables.

The mean difference in eGFR decline between groups was estimated using an unpaired *t*-test. In addition, linear regression was performed to adjust for age, sex, baseline eGFR, follow-up time in months, aorta diameter, and use of medication. All analyses were performed using SPSS Statistics for Windows version 23.0 (IBM, Armonk, NY, USA) and STATA/SE version 14.0 (StataCorp, College Station, TX, USA).

RESULTS

Study population

A cohort of 212 EVAR patients (42 females) aged 75 ± 8 years were included in the analyses for developing AKI. From this cohort, a group of 149 patients who had a follow-up of at least 2 years with eGFR measurements (or were lost to follow-up in between) were included for evaluation of clinically relevant renal function decline. Patients who died peri-operatively ($n = 3$) and patients with missing data for eGFR measurements owing to insufficient follow-up ($n = 60$) were excluded (Fig. 1). The control group (non-operated aneurysm patients) consisted of 135 patients (Table 1).

Table 1. Patient demographics: endovascular aneurysm repair (EVAR) cohort versus control cohort.

Demographics	EVAR ($n = 149$)	Control ($n = 135$) [a]	*p*
Mean ± SD age (y)	75.4 ± 7.9	74.7 ± 7.8	.44
Male sex	116 (77.9)	113 (83.7)	0.21
Mean ± SD aorta diameter (cm)	5.9 ± 1.0	4.0 ± 0.6	< .001
Mean ± SD follow-up time (mo)	23.3 ± 4.5	25.7 ± 4.2	< .001
Mean ± SD baseline GFR (mL/min)	67.7 ± 21.2	69.5 ± 22.0	.50
Comorbidities			
Hypertension	109 (73.2)	96/134 (71.6)	.78
Diabetes mellitus	34 (22.8)	23 (17.0)	.22
Heart failure	13 (8.7)	9/134 (6.7)	.53
CVA/TIA	21 (14.1)	25/134 (18.7)	.30
Peripheral arterial occlusive disease	26 (17.4)	31/134 (23.1)	.23
Medication			
Carbasalate calcium	113 (75.8)	86/134 (64.2)	.03
Statin	112 (75.2)	96/134 (71.6)	.50
ACE inhibitor	39 (26.2)	47/134 (35.1)	.10
Angiotensin receptor blockers	38 (25.5)	28/134 (20.9)	.36
β blocker	77 (51.7)	40/134 (29.9)	< .001
GFR decline at 2 y			
Cliniically relevant renal function decline	35 (23.5)	9 (6.7)	< .001
Mean ± SD absolute GFR decline (mL/min)	−8.8 ± 13.1	−1.6 ± 12.0	
Mean absolute GFR decline difference (95% CI) b	−7.25 (-10.24 to −4.26)		
Adjusted for baseline GFR	−7.41 (−10.38 to −4.44)		
+ Adjusted for age and sex	−7.78 (−10.78 to −4.80)		
+ Adjusted for follow-up time	−8.27 (−11.36 to −5.17)		
+ Adjusted for aorta diameter	−9.57 (−14.32 to −4.82)		
+ Adjusted for β blocker or casbasalate calsium	−9.28 (−14.08 to −4.47)		

Note. Data are *n* (%) unless otherwise indicated. GFR = glomerular filtration rate; CVA = cerebrovascular accident; TIA = transient ischaemic attack; ACE = angiotensin converting enzyme; CI = confidence interval. [a] Some risk factor data were missing for 1 patient in the control group. [b] Between-group difference (EVAR vs. control group).

AKI

The occurrence of AKI could not be determined in 13 cases owing to missing post-operative creatinine values. AKI was observed in 30/199 patients (15%). Twenty-seven patients had stage 1 AKI and in only three patients (1.5%) was there a more than doubling of post-operative serum creatinine (stage 2, 3).

The analysis of risk factors for the occurrence of AKI is presented in Table 2. Pre-operative creatinine, complication during operation, the presence of suprarenal thrombus, and the non-use use of statins or of angiotensin (AT) II blockers (pre-operatively) were associated with AKI in the univariate analyses. After adjustment for several confounders (as listed below Table 2) in the multivariate logistic regression analyses, the effect of complications during operation and the use of AT II blockers and statins remained associated with AKI with ORs of 3.12 (95% CI 1.20—8.10), 4.08 (95% CI 1.38—12.07), and 0.19 (0.07—0.52), respectively (Table 2).

Renal function decline at 2 years

EVAR patients had a similar pre-operative eGFR (67.7 ± 21.2 mL/minute) to the control group (69.5 ± 22.0 mL/minute) ($p = .50$). Almost all patient demographics and comorbidities were comparable between the EVAR and control group except for aortic diameter (5.9 cm vs. 4.0 cm; $p < .001$) and follow-up time in months (mean difference 2.4 months; $p < .001$). The number of patients and controls using statins, angiotensin converting enzyme (ACE) inhibitors (ACEi), or AT II blockers was comparable, and there was only a significant difference for the number of beta blocker and carbasalate calcium users between groups (Table 1).

The eGFR dropped by 8.8 ± 13.1 mL/minute in the EVAR group versus 1.6 ± 12.0 mL/minute in the control group (mean difference 7.25, 95% CI −10.24 to 4.26; $p < .001$). This difference gradually increased up to 9.28 mL/minute (95% CI −14.08 to −4.47) when baseline eGFR, age, sex, follow-up time, aorta diameter, and medication use were adjusted for (Table 1).

The occurrence of clinically relevant renal function decline was significantly more prevalent in the EVAR group ($n = 35/149$; 23.5%) compared with the control group ($n = 9/135$; 6.7% [$p < .001$]). Risk factors for clinically relevant renal function decline in the EVAR group included the presence of renal artery stenosis (hazard ratio [HR] 2.24, 95% CI 1.05—4.79), higher pre-operative aortic neck diameter (per mm increase; HR 1.13, 95% CI 1.02—1.25), and the occurrence of AKI (HR 2.19, 95% CI 0.99—4.85) as important risk factors in the multivariate Cox regression (Table 3).

DISCUSSION

This work corroborates other published studies that EVAR may be associated with an important effect on renal function. Together with other published series that used established criteria to define AKI, it can be stated that about 15% to 20% of EVAR patients develop AKI in the immediate post-operative period.[6,9,12,13] The clinical impact of AKI, as defined by the current propagated guidelines, following EVAR has not been well documented and deserves further study. The study of Saratzis *et al.* looked at mortality during follow-up as a secondary outcome and found that there was a mortality of 32.1% in the AKI group ($p < .001$) after a mean follow-up period of 33 months.[6]

It can be argued that multiple factors play a causal role in renal injury after EVAR, but the exact role of these potential factors has not been clearly elucidated.[11,21] Better understanding of the mechanisms of AKI in EVAR could provide more insight into preventive strategies. For this reason the present study considered clinical, anatomical, and peri-operative factors to comprehensively evaluate potential risk factors for the occurrence of AKI. A recent study by Saratzis *et al.* of a cohort of 947 patients undergoing elective EVAR demonstrated that reduced pre-operative renal function was the main factor associated with AKI.[12] Although pre-operative increased creatinine levels appeared to play a role in the present cohort, this was not found for renal function based on eGFR. It can only be speculated that routine pre-operative nephrological consultation and pre-operative hydration in patients with lower eGFR may have blunted the effect of decreased renal function in the present series. However, a recent randomised study looking at the effectiveness of hydration in patients at risk of contrast induced nephropathy (patients with an eGFR of 30—59 mL/minute) undergoing an elective procedure requiring iodinated contrast administration did not find a difference between intravenous 0.9% NaCl hydration versus no hydration.[22] Thus, the potential benefit of hydration in patients with reduced kidney function undergoing EVAR is not clear and should be further evaluated.

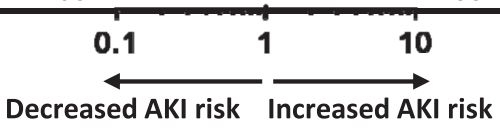
In evaluating potential risk factors for EVAR associated AKI, the present study found several important independent factors that have not been described previously: pre-operative use of AT II blockers and peri-operative complications. In addition, the pre-operative use of statins appeared to be a protective factor. Operative complications, as described in the study protocol, can affect renal function in several ways, including, for example, peri-operative hypotension due to bleeding,[23] and more pronounced peri-renal manipulation in treating a type I endoleak or additional renal stenting.

The potential negative effect of AT II blockers on short-term kidney function has been described previously in the coronary setting. Rim *et al.* reported a propensity matched study looking at the effect of renin—angiotensin—aldosterone system blockade on AKI in patients who underwent coronary angiography.[24] This study used the same AKI criteria as the present study and in 1322 propensity matched patients found that ACEi/angiotensin receptor blocker (ARB) recipients had a significantly increased risk of AKI (11.4% vs. 6.3%). The investigators showed that use of ACEi/ARBs was an independent risk factor for AKI occurrence associated with coronary angiography.

In concordance with the finding that AT II blocker and not ACEi was associated with AKI, Peng *et al.* reported a

Table 2. Risk factor analysis of the development of acute kidney failure (AKI) after endovascular aneurysm repair.

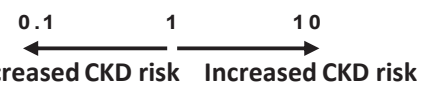
Baseline	OR	95% CI	*p*
Age (y)	1.05	1.00 – 1.11	.06
Male sex	0.60	0.30 – 1.50	.30
Serum creatinine per µmol/L increase	1.01	1.00 – 1.02	.03
Kidney function			
GFR continuous per mL/min increase	0.98	0.96 – 1.00	.10
GFR < 60 mL/min	1.93	0.87 – 4.27	.10
Pre- and peri-operative			
Contrast volume per mL increase	1.01	1.00 – 1.02	.06
Complication during operation	3.02	1.22 – 7.46	.02
Renal artery stenosis	2.42	0.96 – 6.10	.06
Thrombus (suprarenal)	3.17	1.28 – 7.88	.01
Total intervention time per min increase	1.01	1.00 – 1.02	.06
Accessory renal artery coverage	1.79	0.60 – 5.30	.30
Diameter aorta per cm increase	1.13	0.78 – 1.65	.52
Diameter neck aneurysm per mm increase	0.99	0.88 – 1.13	.93
Comorbidities			
Hypertension	1.54	0.59 – 4.01	.38
Diabetes mellitus	1.07	0.40 – 2.83	.89
Heart failure	1.45	0.38 – 5.49	.58
Coronary disease	0.69	0.30 – 1.56	.37
Stroke	0.93	0.30 – 2.90	.90
Peripheral arterial occlusive disease	1.10	0.39 – 3.13	.86
Medication			
Carbasalate calcium	0.87	0.37 – 2.04	.75
Statin	0.32	0.14 – 0.72	.01
ACE inhibitor	0.36	0.12 – 1.07	.067
Angiotensin receptor blockers	3.83	1.71 – 8.58	< .01
β blocker	0.60	0.30 – 1.40	.23
Adjusted analysis	**OR_{adj}**		
Complication during operation a	3.12	1.20 – 8.10	.02
Renal artery stenosis b	1.97	0.75 – 5.20	.17
Thrombus (suprarenal) c	2.59	0.95 – 7.06	.06
Statin d	0.19	0.07 – 0.52	< .01
ACE inhibitor e	0.73	0.20 – 2.72	.64
Angiotensin receptor blockers f	4.08	1.38 – 12.07	.01



Note. OR = odds ratio; CI = confidence interval; GFR = glomerular filtration rate; ACE = angiotensin converting enzyme. [a] OR adjusted for age and sex. [b] OR adjusted for age, sex, coronary disease, and diabetes mellitus. [c] OR adjusted for age, sex, renal artery stenosis, and carbasalate calcium. [d] OR adjusted for age, sex, hypertension, coronary disease, ACE inhibitor, and angiotensin receptor blocker. [e] OR adjusted for age, sex, hypertension, coronary disease, angiotensin receptor blocker. [f]OR adjusted for age, sex, hypertension, coronary disease, and ACE inhibitor.

Table 3. Risk factor analysis of renal function decline after endovasculair aneurysm repair (EVAR).

Baseline	HR	95% CI	p
Age (y)	1.02	0.97 – 1.06	.53
Male sex	1.16	0.50 – 2.65	.73
GFR per mL/min increase	0.99	0.98 – 1.01	.47
AKI after EVAR	2.35	1.09 – 5.07	.03
Pre- and peri-operative			
Diameter aorta per cm increase	1.00	1.02 – 1.11	.01
Thrombus SR	1.92	0.90 – 4.09	.09
Diameter neck per mm increase	1.13	1.02 – 1.25	.02
Renal artery stenosis	2.38	1.17 – 4.88	.02
Accessory renal artery coverage	1.70	0.71 – 4.11	.24
Endoleak	Not estimable	–	.70
Re-intervention	1.47	0.61 – 3.55	.39
Number contrast administrations	0.91	0.73 – 1.15	.44
Comorbidities			
Hypertension	1.63	0.71 – 3.74	.25
Diabetes mellitus	1.13	0.53 – 2.42	.75
Coronary disease	0.61	0.31 – 1.22	.16
Heart failure	2.67	1.11 – 6.45	.03
Stroke	0.56	0.17 – 1.82	.33
Peripheral arterial occlusive disease	1.02	0.42 – 2.46	.97
Adjusted analysis			
AKI after EVAR a	2.19	0.99 – 4.85	.05
Diameter neck b	1.13	1.02 – 1.25	.02
Renal artery stenosis c	2.24	1.05 – 4.79	.04



Note. HR = hazard ratio; CI = confidence interval; GFR = glomerular filtration rate; AKI = acute kidney injury; SR = ??; CKD = chronic kidney disease. [a] HR adjusted for age, sex, renal artery stenosis, thrombus. [b] HR adjusted for age and sex.[c]HR adjusted for age, sex, hypertension, thrombus, and diabetes mellitus.

prospective study with 401 patients, including a meta-analysis of 14 qualifying trials.[25] There was an overall 1.28 fold increased risk of contrast induced AKI in patients taking ACEi or ARBs. However, subgroup analysis identified a significantly increased risk of contrast induced AKI in patients taking ARBs (OR 3.31) compared with patients taking ACEIs (OR 0.86). Considering that other studies have also demonstrated a protective effect of renin—angiotensin system inhibitors on AKI,[26] it is clear that more studies are needed to clarify the published discrepancies and to further explore the effect of AT II blockers in the EVAR setting.

Although statin use has been shown to protect renal function in open aneurysm repair with suprarenal clamping,[27] this has not been described before in the EVAR setting. However, there is a great body of research in this field in the coronary intervention setting, demonstrating a protective effect.[28] It is clear that more data are needed to further delineate the effect of statins in AKI prevention following EVAR.

The other important finding of the present study is that EVAR was associated with a significant increase in clinically relevant renal function decline at 2 years (23.5%) as compared with untreated aneurysm patients (6.7%). The possibility of EVAR associated deterioration in kidney function has recently been emphasized. Karthikesalingam *et al*. analysed the literature on renal function after EVAR and reported in a systematic review and meta-analysis that, overall there is significant reduction in GFR in the follow-up

period.[10] Surprisingly, a study on renal function based on the UK EVAR trials reported limited renal function decline over time.[29] This study used a multilevel modelling of eGFR, measured annually over an average of 3.6 years and included 1194 patients enrolled in the EVAR trials to compare renal function in patients managed by open or endovascular repair. The mean rate of change in eGFR was around −1 mL/minute/1.73 m^2 per year. Most studies, as reported in the systematic review of Karthikesalingam *et al.*,[10] evaluated renal function decline to compare EVAR with open aneurysm repair,[30] or to compare infrarenal with suprarenal fixation.[9,14] In order to more precisely assess whether EVAR and subsequent contrast administrations affect long-term renal function, a control group of untreated aneurysm patients with a similar cardiovascular risk profile was included. Aneurysm patients are older and have a high burden of cardiovascular comorbidities with common prevalence of hypertension. Thus, it could be speculated that this group of patients is at increased risk of renal function decline over time. In this regard, it should be noted that ageing by itself is associated with a decline in GFR and in the age group of 70–80 years a slope of 1.49 mL/ minute decrease per year has been described.[31] In addition, to study the occurrence of clinically important renal function decline, with the inherent variability of creatinine when interpreting change in eGFR, the KDIGO clinical practice guidelines were used to define renal function deterioration.[13]

Interestingly, as was shown in the UK EVAR renal function study,[29] larger aortic neck diameter emerged as a significant risk factor for renal function decline. Whether this effect is mediated by increased probability of subsequent graft related complications for larger necks is unknown. There was also an indication for an effect of renal artery stenosis and the occurrence of AKI as risk factors for subsequent renal function decline. The presence of significant renal artery stenosis as a potential risk factor for renal function decline after EVAR has not been described previously. In the CORAL study (effect of renal stenting), which defined progressive renal insufficiency as a reduction from baseline of 30% in the eGFR at 2 years, about 15% of patients reached this primary outcome. This adverse renal outcome could not be prevented by renal artery stenting.[32] Although the present patient data are not compared with the study population of the CORAL investigation, a similar magnitude of renal function decline with a pronounced effect in patients with renal artery stenosis was found. The mechanism of this finding is unclear and merits further evaluation. Although stent grafts with suprarenal fixation have not consistently been shown to affect renal function versus stent grafts without suprarenal fixation,[9,14] the impact of the struts on an atherosclerotic stenotic renal artery has not been thoroughly examined. Based on the present findings it can be argued that patients at risk of renal function deterioration should be monitored more closely and would require nephrological consultation to evaluate means to protect the kidney.[33] These aspects are not routinely employed in aneurysm practice today and highlight the importance of the current findings.

Some limitations need to be addressed. First, the limited number of patients in the present study population reduced the power. For AKI analysis, multiple candidate risk factors were selected of which five resulted in an association with AKI (baseline creatinine, complications during operation, presence of a suprarenal thrombus, not using statins, or use of an AT II blocker). Because multiple risk factors were tested with a limited sample size, it is possible that a false positive risk factor was found. However, as a sensitivity analysis, several multivariate analyses were performed to adjust for important confounders, after which only renal artery stenosis was not associated with AKI and all other risk factors remained associated. This does not rule out that there was residual confounding, which may have biased the results. Second, using a cohort study it is hard to prove a causal relationship for the development of both AKI and clinically relevant renal function decline (because of confounding by indication). Nevertheless, it has been shown that, for example, patients on AT II blockers are at risk of developing AKI, whereas further research is necessary to prove causality. Therefore, it is believed that the present results give guidance in identifying patients at high risk of developing both AKI and clinically relevant renal function decline.

CONCLUSION

This study identified the use of an AT II blocker and perioperative complications as important risk factors for the occurrence of EVAR associated AKI. This finding could help to implement preventive measures to reduce AKI, which should be addressed in further studies. Furthermore, as compared with a control group of untreated aneurysm patients, the problem of renal function decline after EVAR is highlighted. Patients with renal artery stenosis and AKI following EVAR were shown to be at high risk of developing chronic renal function decline, which indicates that in these patients protective measures for a longer period of time are needed.

CONFLICTS OF INTEREST

None.

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