Pre-operative renal function is the main predictor of Acute Kidney Injury (AKI) after Endovascular Abdominal Aortic Aneurysm Repair (EVAR)

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ABSTRACT

Background: Post-operative acute kidney injury (AKI) may occur in up to 18% of elective endovascular aneurysm repairs (EVAR) and has been associated with poor outcome; however, it is not clear which patients are at highest-risk, in order to target reno-protection effectively. We sought to determine the predictive factors of AKI after elective EVAR.

Methods: Overall, 947 patients undergoing elective EVAR between January 2000 and December 2014 were analysed, using prospectively-collected data. Postoperative AKI was defined by serum creatinine change within 48 hours, as per the Kidney Disease Improving Global Outcomes guidelines. Cardiovascular and kidney-disease risk-factors were entered in uni- and multi-variate analyses to assess influence on AKI-development.

Results: Overall, 167 (17.6%) patients developed AKI but only 2 patients required dialysis peri-operatively. At multivariate analysis, adjusted for established AKI risk-factors and parameters that differed between groups at baseline, pre-operative eGFR (as per the CKD-EPI formula) [Odds Ratio (OR): 1.02 (per unit decrease); 95% Confidence Interval (CI): 1.003-1.041; p=0.025] and chronic kidney-disease (CKD) stage > 2 (OR: 1.28; 95% CI: 1.249-2.531, p=0.001) were associated with development of AKI.

Conclusions: AKI was common after elective infra-renal EVAR and pre-operative renal function appears to be the main factor associated with AKI. Patients with a low eGFR need to be targeted with more aggressive renal protection.

Keywords: endovascular aneurysm repair (EVAR), acute kidney injury (AKI), renal function, predictive factors, estimated glomerular filtration rate (eGFR)

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INTRODUCTION

Abdominal aortic aneurysm (AAA) constitutes a serious health problem with current prevalence for men above the age of 65 ranging from 1.5% to 5% (1-3). Endovascular abdominal aortic aneurysm repair (EVAR) is now an established treatment. Early and medium-term outcomes have proven similar or superior to traditional open aneurysm repair (OAR) in randomized studies and subsequent meta-analyses (4, 5). However, those undergoing EVAR, either in the elective or emergency setting, are at risk of developing acute kidney injury (AKI), due to several reasons, including contrast-administration, blood-loss, associated comorbid-conditions, ischemia-reperfusion injury and inflammation, which we have previously discussed(6). Using up-to-date precise AKI reporting criteria that included urine output measurements, we recently documented that elective EVAR can lead to AKI in 18.8% of patients (in a cohort of 149 patients), which was associated with mortality and cardiovascular morbidity over the medium-term(7). Further to EVAR, AKI after various types of surgical or radiological intervention has been independently associated with higher morbidity, prolonged length of hospital stay, cost, short-term mortality (8-10), as well as decreased long-term survival (11-15). As a result, preventing AKI is crucial in improving outcome, especially in populations at high-risk, such as those undergoing EVAR. The predictive factors of AKI after elective EVAR are not well determined, as the randomized studies have not reported AKI-

incidence and the majority of case-series have not used a consistent AKI definition(16-20). Serum creatinine (SCr) in isolation has typically been used as a marker of immediate post-operative renal dysfunction (defined as a rise of more than 25% or 50%) and then reported as 'AKI incidence'(6, 7). Given that AKI can impact on short and longer-term outcome, it is important to establish risk-factors for AKI in EVAR in order to guide reno-protective strategies more efficiently. As a result, the aim of this study is to assess predictive factors of AKI defined using established and widely accepted (21, 22) criteria after elective EVAR in a sufficiently large cohort of patients.

METHODS

This is a study including patients undergoing elective endovascular repair (EVAR) of an infra-renal abdominal aortic aneurysm (AAA) between January 2004 and December 2014 in a tertiary referral centre for vascular disease; data were retrieved using a prospectively maintained electronic EVAR database, which includes baseline and follow-up information. Patients were eligible for repair if they had an AAA diameter >5.5 cm or an AAA <5.5 cm with a rapidly increasing sac (>1cm per year). Data for patients undergoing EVAR were entered prospectively in an electronic database at baseline and during follow-up. Patients were included in the analysis if they had a valid Serum Creatinine (SCr) measurement at 48 hours after the repair, relevant information (cardiovascular and chronic kidney disease risk-factors) available at baseline and were able to provide written informed consent. Patients with symptomatic, leaking, ruptured, infected, or inflammatory aneurysms, fenestrated EVARs, and patients with end-stage renal disease (ESRD) receiving renal replacement therapy (at baseline) were excluded. Written informed consent for the procedure and participation in a registry collecting

outcome data after surgery were obtained. This study follows departmental reporting and ethical guidance and relevant institutional ethical approvals have been obtained.

Study protocol

Demographics and risk-factors were recorded and stored at baseline, as listed on Table 1. Participants underwent a computed tomographic angiography (CTA) with 3-dimensional reconstruction before EVAR to assess anatomy and a multidisciplinary meeting discussion took place to assess anatomical eligibility. Blood samples at baseline were obtained prior to imaging requiring the administration of contrast in all cases. SCr measurements at 48 hours, obtained using the trust's online electronic reporting system, were used to assess incidence of AKI as per the criteria described below. A standard follow-up protocol was employed. Imaging during follow-up included plain abdominal radiography and a CTA at 6 months, 12 months, and annually thereafter, which was the standard follow-up protocol for EVAR at the time. Since July 2013 patients undergo follow-up with ultrasound imaging at the same intervals.

Endovascular repair procedures

The endovascular device deployed in each case depended on anatomy, as assessed by the multidisciplinary meeting, and availability. Suprarenal and infrarenal fixation devices were used as appropriate, following instructions for use provided by the manufacturers, regarding anatomical eligibility. None of the patients included in this series underwent a fenestrated EVAR. Procedures were performed in an operating theatre under general anaesthesia, using a non-ionic contrast agent. Prior to EVAR, the administration of contrast and non-steroidal anti-inflammatory drugs (NSAIDs) was avoided for at least 1 week. Metformin and angiotensin converting enzyme inhibitors were discontinued for 2 days, where applicable. For patients with a pre-operative eGFR>60 ml/min/1.73m^2, intravenous fluids (0.9% saline, 2mL/kg/hour) were

started on the day of the operation. Patients with an eGFR<60 units were admitted one day before and received intravenous fluids (0.9% saline, 1.5 L/24 hours) for 24 hours, until nil by mouth, when they were commenced on 0.9% saline at 2mL/kg/hour. This represents the institutional standard for pre-EVAR hydration. Urinary catheterization and hourly urine output measurements were routinely employed and patients remained catheterized until ambulatory. Intra-operative fluid management was guided by mean arterial pressure, recorded via a peripheral arterial line. The aim of fluid therapy (consisting only of crystalloid solutions) was to keep the mean arterial pressure within 80% of the baseline (before induction) for 90% of the operating time. All patients were started on aspirin and a statin pre-operatively, which continued in the peri- and post-operative period. Patients were asked to mobilise and eat and drink, as tolerated, as soon as possible after the repair and were usually discharged on day 2 or 3. Blood transfusion was given if the patient's Haemoglobin (Hb) was less than 8g/dl or if the patient had a history of cardiac disease and was symptomatic with a Hb<10g/dl.

Definitions and study outcomes

In order to define Acute Kidney Injury (AKI) incidence and classify the different stages of AKI, Serum Creatinine (SCr) measurements were taken into account at 48 hours after the repair. The following criteria were applied: "Acute Kidney Injury Network" (AKIN)(23), and "Kidney Disease Improving Global Outcomes" (KDIGO)(21, 22). As per that criteria, the diagnosis of AKI was defined as an absolute increase in SCr of more than or equal to .3 mg/dl (≥26.4 μmol/l), or a percentage increase in SCr of more than or equal to 50% (1.5-fold from baseline) at 48 hours after the completion of the procedure. This represents the patient meeting the minimum criteria for "stage 1" AKI as per the AKIN and KDIGO definitions and is in line with the current "National Institute of Health and Care Excellence" definition(24). Patients were classified into 3 different stages of AKI, according to AKIN and KDIGO criteria staging.

Stage 2 AKI was defined as 100-199% SCr rise within 48 hours and Stage 3 AKI was defined as >=200% SCr rise within 48 hours or rise to >354μmol/l with an acute rise >44μmol/l. Complications and other baseline and post-operative characteristics were defined according to the reporting standards for EVAR by Chaikof et al (25).

Statistical analysis

Analyses were performed using the Statistical Package for Social Sciences Version 21.0 (SPSS, Chicago, Ill, USA). Continuous parametric data are presented as mean value ± standard deviation (SD) and categorical data are presented as absolute values and percentages. Comparisons between the study groups were performed using the independent or paired (where applicable) samples t-test for continuous parametric variables and Pearson's chi-square test for categorical variables. A multivariate analysis was performed using binary logistic regression in order to assess the effect of important risk-factors at baseline on AKI incidence. Factors with a p value <0.20 at univariate comparison were entered in the multivariate analysis. A p value level <0.05 was considered statistically significant.

RESULTS

A total of 947 patients undergoing elective endovascular infra-renal AAA repair were included (mean age: 71 ± 8 years; 70 females, 7%; Table 1). None of the procedures were immediately converted to open repair and all aneurysms were successfully excluded. A total of 167 patients developed AKI as per the definition used in the analysis (17.6%). Of these, most developed stage 1 AKI (145 patients, 87%), 19 (11%) developed stage 2 AKI and 3 (1.7%) developed stage 3 AKI. Two patients who developed stage 3 AKI required short-term renal replacement therapy but both patients had recovery of their renal function and did not require life-long

dialysis. On univariate analysis, those with and without AKI differed significantly (at baseline) with regard to history of stroke ($p<0.001$), peripheral arterial disease ($p=0.005$), diabetes ($p=0.02$), urea ($p=0.003$) and pre-operative renal function (estimated using eGFR as per the CKD-EPI formula, $p=0.002$) – as summarized on Table 1. The amount of contrast did not differ significantly for those with or without AKI (112±28 versus 117±19 ml, $p=0.12$) and the rate of patients receive inotropic support during the procedure or in the immediate post-procedural period was not different either (3% versus 4%, $p=0.84$). None of the patients had an intra-procedural cardiac event or prolonged period of hypotension. No renal artery associated complications occurred intra-operatively or within the peri-operative period and none of the patients underwent renal artery angioplasty as an adjunctive procedure to their EVAR. A total of 428 patients (68 of which had previously developed AKI) had a CT scan available at 30 days after the repair, none of which demonstrated any radiological evidence of renal infarction. Table 2 summarizes stages of CKD for those with and without AKI at baseline; 90% of patients who did develop AKI were clustered above stage 1 whilst 25% of patients without AKI were at CKD stage 1 pre-operatively ($p<0.001$).

Multivariate analysis (Tables 3 and 4), adjusted for age, sex, history of stroke, hypertensions, diabetes, peripheral arterial disease, AAA diameter, statin use, urea, eGFR and Chronic Kidney Disease (CKD) stage > 2, revealed that pre-operative eGFR (as per the CKD-EPI formula) [OR: 1.02 (per unit decrease); 95% CI: 1.003-1.041; $p=0.025$] was associated with development of post-operative AKI. This translates to a 2% higher chance of AKI per unit decrease in eGFR prior to surgery. Those who were above CKD stage 2 were also more likely to develop AKI with an Odds Ratio (OR) of 1.28; 95% Confidence Interval (CI): 1.269-2.531 ($p=0.001$).

DISCUSSION

This analysis suggests that pre-operative renal function is the main predictor of Acute Kidney Injury (AKI) after elective Endovascular Aneurysm Repair (EVAR). Surgeons and intervenionalists should therefore target this group of patients with appropriate more aggressive renoprotection peri-operatively.

Acute kidney injury can lead to increased mortality, morbidity, and a rise increase in healthcare costs after various types of surgery and radiological intervention(6, 26, 27). A recent study involving 10,518 patients undergoing various types of major surgery suggested that long-term survival was significantly worse among patients with AKI and was proportional to the peri-operative drop in SCr with an adjusted hazard ratio of 1.57 (95% CI: 1.40-1.75) compared with patients without AKI ($P < .001$), even for those with complete recovery of renal function (28). In a small series of elective EVARs we recently documented an incidence of 18% using stringent criteria (the "Acute Kidney Injury Network" and "Kidney Disease Improving Global Outcomes" criteria) to report AKI after elective EVAR (including urine output measurements for 48 hours) and development of AKI was associated with both morbidity and mortality over the medium term(7). In that analysis of AKI-incidence after EVAR, we found that only hypercholesterolaemia was marginally associated with AKI development; however, the population of only 149 patients in that report does not allow accurate determination of predictive factors due to type-2 error(7). Previous studies reporting on renal decline immediately after elective EVAR have not used consistent definitions of renal injury, as we reported in a systematic literature review(6), therefore it is difficult to analyse available data in a meta-analytical manner to assess the impact of AKI on outcome after EVAR. However, there is a plethora of evidence suggesting that pre-operative and post-operative renal dysfunction after EVAR, using various different definitions, is associated with both mortality and

morbidity(29, 30). The scope of the current analysis was not to associate EVAR-related AKI with outcome, as we have recently reported on this association(7).

Endovascular aneurysm repair can lead to AKI via several different mechanisms: contrast administration (31) (contrast administration leads to increased vaso-constrictive forces, decreased local prostaglandin and nitric oxide mediated vasodilatation in the tubule, a direct toxic effect on renal tubular cells, increased oxygen consumption in the kidney, increased intratubular pressure secondary to increased diuresis, increased urinary viscosity, and tubular obstruction, all culminating in renal medullary ischaemia), renal microembolisation during device deployment and other endovascular manipulations (32), complications directly relating to the renal arteries, such as dissection or coverage of the arterial orifice (33), lower limb ischaemia and the subsequent ischaemia-reperfusion syndrome(34), hypovolaemia, the presence of an inflammatory infiltrate (the actual aneurysmal sac that is not excised such as in open aneurysm repair)(35), dehydration, and the presence of pre-morbid cardiovascular risk-factors(36). Further to the acute and transient post-operative decline in renal function, another important observation is that EVAR can lead up to a 6 unit decrease in eGFR per annum, which is significantly more pronounced than the estimated loss of renal function compared to the general population, as we have previously shown(37). This later loss in renal function can lead to further cardiovascular morbidity over the long term. As a result, it is important to identify patients at high-risk of AKI prior to EVAR and target renoprotection accordingly.

In this analysis, none of the patients with available cross sectional imaging in the first post-operative month had evidence of renal emboli or cortical ischaemia. Also, none of the main renal arteries were covered and only a small number of accessory renal arteries were covered (no difference between those with or without AKI, as summarized on Table 1). Multivariate analysis, adjusted for several factors known to be associated with renal damage, showed that eGFR is the main factor associated with development of AKI (OR: .963; 95% CI: .947-.979;

p<.001). We have used the most recent and precise formula to calculate eGFR in our cohort, the Chronic Kidney Disease Epidemiology equation(38), which is novel in the EVAR literature. This has been shown to be superior to previous GFR estimates in patients with cardiovascular disease(38). We have not included serum creatinine in our multivariate analyses, as it underestimates renal dysfunction – especially in older populations with a significant cardiovascular burden, as we have previously discussed(6, 29, 39).

Regarding prevention of AKI in EVAR, unfortunately there are no adequately powered randomized studies investigating relevant strategies. Hydration is traditionally considered as an effective way of preventing AKI in various interventions (6). This is because it provides volume expansion and protects the tubule from the ischaemic and oxidative insult of contrast. However, because EVAR-related AKI is multifactorial, hydration alone cannot address all precipitating factors and the relatively high rate of AKI in this series, despite attempts to hydrate these patients pre-operatively, confirms that. Prevention strategies that have been studied in EVAR to some extent include slow or rapid hydration using various non-uniform regimes with variable results(40), ischaemic preconditioning in a small study (41), regional anaesthesia(42, 43), and various pharmacological agents(6)–with no conclusive evidence. All the aforementioned modalities have been assessed in small under-powered studies that have not used a consistent definition of AKI and have not attempted to investigate the exact mechanism of each renoprotective modality. Bicarbonate hydration has also been recently assessed in a small prospective study that included 34 recruits (44). It is clear that adequately powered randomized studies are urgently required.

This report has certain limitations that need to be mentioned. Firstly, it represents a retrospective analysis, even though data were collected prospectively using an electronic EVAR database. Additionally, the criteria used to report AKI did not include urine output as it is difficult to precisely document urine output over 48 hours in a large population; however,

we have previously reported AKI incidence in EVAR using precise urine output recording in a smaller population and the incidence is almost identical (7). Even though none of the patients had adverse proximal neck anatomy, the exact lengths are not available for comparisons between those with and without AKI. Despite these, we have included several risk-factors for renal damage in our adjusted analyses and used the most precise estimate of GFR.

Overall, this analysis provides strong evidence that pre-operative renal function is the main precipitating factor leading to AKI in patients undergoing EVAR. Renoprotection should be applied more aggressively in this population, especially in those at CKD stage above 2 prior to the intervention, to prevent acute kidney injury which may lead to adverse events.

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Tables and Figures

Table 1: Baseline characteristics for those with and without acute kidney injury (AKI).

Variable	No AKI	AKI	*p*
N	780	167	-
Age, years	**71 ± 8**	**72 ± 7**	**0.2**
Male sex	7%	7%	0.8

Smoking	76%	76%	0.9
Hypertension	66%	72%	0.16
Cholesterolaemia	29%	31%	0.4
Stroke	**7%**	**16%**	**<0.001**
MI	19%	21%	0.5
PAD	**15%**	**28%**	**0.005**
Diabetes	**13%**	**32%**	**0.02**
AAA Diameter, cm	**7.4 ± 1.9**	**6.8 ± 1.7**	**0.1**
Statin use	**53%**	**61%**	**0.1**
Antiplatelet use	97%	98%	0.9
Supra-renal EVAR device fixation*	78%	82%	0.25
Contrast medium, ml	112±28	117±19	0.48
Transfusion peri-operatively	4.4%	6%	0.42
Serum Creatinine	1.08 ± .46	1.10 ± .30	0.5
Urea, mmol/l	**4.6 ± 2.2**	**5.4 ± 2.6**	**0.003**
Hb, g/dL	13.2 ± 1.7	13.1 ± 1.8	0.7
CKD stage > 2	**28.2%**	**41.3%**	**0.001**
eGFR, ml/kg/1.73 m^2	**73 ± 21**	**67 ± 16**	**0.002**

COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; CABG = coronary artery bypass; AF = atrial fibrillation; PAD = peripheral artery disease; Hb = haemoglobin; AAA = abdominal aortic aneurysm; TIA = transient ischaemic attack

*Suprarenal fixation in the form of a bare stent to provide additional support – none of the aneurysms were supra- or juxta-renal in this series.

Table 2: Chronic Kidney Disease (CKD) stages (at baseline) for those with and without Acute Kidney Injury (AKI)

CKD stage	No-AKI	AKI	*%*
1	201	17	*7.8*
2	359	81	*18.4*
3	207	63	*23.3*
4	13	6	*31.6*

Chi square: 23.284, p<0.001

Table 3: Multivariate analysis regarding predictors of development of Acute Kidney Injury (AKI) after Endovascular Aneurysm Repair (EVAR)

Variable	p	OR	95% CI	
Age	0.114	0.972	0.937	1.007
Male sex	0.255	1.690	0.685	4.171
Hypertension	0.292	1.436	0.732	2.818
Stroke	0.241	1.641	0.717	3.757
PAD	0.107	1.668	0.895	3.110
Diabetes	0.501	1.242	0.661	2.332
AAA Diameter (per cm)	0.589	0.951	0.791	1.142

Statin use	0.614	0.871	0.508	1.491
Urea (baseline) per unit increase	0.597	0.970	0.867	1.085
eGFR (baseline) per unit decrease	0.025	1.022	1.003	1.041
CKD stage > 2 at baseline	0.001	1.282	1.249	2.531

PAD = peripheral arterial disease; eGFR = estimated glomerular filtration rate (CKD-EPI formula); OR = odds ratio; CI = confidence interval; CKD = chronic kidney disease

Table 4: Univariate and multivariate analysis Odds Ratios (ORs) for the variables of interest

Variable	**Univariate OR**	*p*	**Multivariate OR**	*p*
Age, years	**1.01**	**0.2**	0.97	0.12
Male sex	**1.04**	**0.8**	1.69	0.26
Smoking	1.01	0.9	-	-
Hypertension	**1.29**	**0.16**	1.44	0.29
Cholesterolaemia	1.17	0.4	-	-
Stroke	**2.58**	**0.001**	1.64	0.24
MI	1.15	0.5	-	-

PAD	**2.16**	**0.005**	1.67	0.11
Diabetes	**1.69**	**0.02**	1.24	0.50
AAA Diameter, cm	**1.05**	**0.1**	0.95	0.59
Statin use	**1.39**	**0.1**	0.87	0.61
Antiplatelet use	0.98	0.9	-	-
Supra-renal EVAR device fixation*	1.30	0.25	**-**	**-**
Contrast medium, ml	0.94	0.48	-	-
Transfusion peri-operatively	0.72	0.42	-	-
Serum Creatinine (per unit increase)	1.12	0.5	-	-
Urea (per unit increase)	**1.14**	**0.003**	0.97	0.60
Hb, g/dL	0.97	0.7	-	-
eGFR (per unit decrease)	**1.88**	**0.03**	**1.02**	**0.03**
CKD stage>2 at baseline	**1.79**	**0.001**	**1.28**	**0.001**

PAD = peripheral arterial disease; eGFR = estimated glomerular filtration rate (CKD-EPI formula); OR = odds ratio; CI = confidence interval; CKD = chronic kidney disease