Endovascular Aneurysm Repair (EVAR) And Transcatheter Aortic Valve Repair (TAVR) associated Acute Kidney Injury

Running head: AKI in EVAR and TAVR

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Abstract

Acute kidney injury (AKI) following surgery or intervention is an important complication that may impact on mortality, morbidity, and healthcare costs. Endovascular procedures are now performed routinely for a variety of pathologies that were traditionally treated with open surgery, since randomized trials comparing endovascular and open surgery have shown at least equally good results and reduced complication and hospitalization rates with the endovascular techniques. However, endovascular procedures have been associated with increased risk of post-operative AKI, predominantly due to contrast nephrotoxicity. Over the years, endovascular techniques have progressively been applied for the treatment of complex cardiovascular pathologies, and, in recent years, nephrologists increasingly encounter patients that have developed AKI following endovascular aneurysm repair (EVAR) or transcatheter aortic valve repair (TAVR). These two procedures typically involved high-risk patients, who have several established AKI risk-factors prior to the intervention. Several studies have investigated the incidence, risk factors and natural course of AKI following EVAR and TAVR. This review summarizes current data on incidence, risk factors, pathophysiology, prognostic implications, and treatment of AKI associated with EVAR and TAVR.

Keywords: Acute Kidney Injury, EVAR, TAVR, Endovascular Repair
INTRODUCTION

The term Acute Kidney Injury (AKI) has been proposed to encompass the entire spectrum of a syndrome that ranges from minor changes in markers of renal function to requirement for renal replacement therapy.\(^1\)\(^,\)\(^2\) It represents an acute and usually reversible drop in renal function and is defined by stringent criteria, based on fluctuation in Serum Creatinine (SCr) levels and urine output. Acute kidney injury of various aetiologies is an important public health issue worldwide.\(^3\) Based on various epidemiological studies, 20% of individuals undergoing elective cardiovascular (CV) surgery or intervention may develop AKI.\(^4\)\(^,\)\(^5\) Post-operative AKI has important implications relating to subsequent mortality, morbidity, and cost.\(^4\)\(^,\)\(^6\)\(^-\)\(^8\)

Endovascular techniques have evolved greatly since their conception and are now widely applied for the correction of atheromatous and non-atheromatous lesions in various vascular beds. Recently, technological evolutions have allowed the treatment of more complex pathologies using such techniques. Endovascular aneurysm repair (EVAR) for abdominal aortic aneurysm (AAA) is now routinely performed, both as an elective and as an emergency procedure; randomized controlled trials (RCTs) have shown equally good or better results over the short and medium term compared to open surgery.\(^9\)\(^-\)\(^12\) Similarly, transcatheter aortic valve repair (TAVR) for severe aortic stenosis has recently been introduced, with promising results in RCTs involving intermediate and high-risk patients.\(^13\)\(^,\)\(^14\) However, such endovascular procedures have traditionally been associated with a significant risk of AKI development, mainly attributed to the use of contrast media, amongst other risk-factors.\(^6\)\(^,\)\(^15\) Important research efforts have been undertaken, aiming to establish appropriate preventive measures for this complication.\(^16\)\(^-\)\(^18\) Given that EVAR and, more recently, TAVR are used ever more often across the world, AKI following such procedures has become a more common occurrence for nephrologists, while several aspects of AKI related to these
procedures have been the object of research studies. This review aims to provide an up-to-date overview of the incidence, risk factors, pathophysiology, prognostic implications, and treatment of AKI associated with EVAR and TAVR.

ACUTE KIDNEY INJURY AFTER ENDOVASCULAR ABDOMINAL AORTIC ANEURYSM REPAIR

Abdominal aortic aneurysm (AAA) constitutes an important health problem and a common cardiovascular cause of death in the Western World, with prevalence rates ranging from 1.3% to 4%.\textsuperscript{19-21} Endovascular repair (EVAR), a minimally invasive alternative to the traditional open-repair, was introduced about 25 years ago and is now a first-line treatment, predominantly in the elective setting.\textsuperscript{22} EVAR involves the deployment of a stent-graft into the abdominal aorta in order to exclude the aneurysmal segment from circulation and prevent rupture. Access is usually gained through the femoral arteries, either percutaneously or after surgical exposure, and the devices are subsequently advanced and deployed using fluoroscopic control and a contrast medium, which is necessary in order to visualize the relevant anatomy.\textsuperscript{23} An iodine based non-ionic contrast medium is typically used in modern practice. The stent-grafts, in the case of an infra-renal AAA, are fixated below the renal orifices and may employ suprarenal fixation modalities, such as hooks, bare stents or barbs, which attach the device on the healthy suprarenal aortic wall, whilst allowing blood flow into the renal arteries.\textsuperscript{24} Early and medium-term outcomes of EVAR have proven similar or superior to open-repair in several randomized controlled trials (RCTs).\textsuperscript{12} However, patients undergoing EVAR are at risk of certain “technical” and device-related complications, such as endoleak, stent-graft migration and endo-graft limb occlusions, but they are also at serious risk of developing AKI. Similar to other endovascular procedures, accumulating evidence
suggests that AKI after EVAR impacts on subsequent mortality, cardiovascular morbidity, long term renal-function, length of hospital stay and associated cost.4,6,25

**Incidence**

The reported incidence of AKI after elective EVAR ranges widely from 3 to 19%; the main reason for that is the wide variability of AKI definition criteria that were used in the literature until recently.26-30 Several investigators have not included post-operative urine output in defining AKI. Furthermore, most studies used solely Serum Creatinine (SCr) changes as a marker of immediate (24-48 hours) post-operative renal dysfunction and then reported this as “AKI incidence”. Other measures previously applied include creatinine clearance or estimated glomerular filtration rate (eGFR) drop.31 The RCTs in the field of EVAR did also not report AKI incidence using contemporary acceptable definitions. Overall, immediate post-operative renal injury, using absolute SCr drop within 48 hours, has a lower incidence post- EVAR compared to open-repair in most historical series,32 whereas at least 3 studies (2 of which defined “AKI” as SCr rise> 50% and one as >30% compared to baseline) have shown increased incidence following EVAR (estimated at about 18%) than open repair (ranging from 5% to 15%).4, 6, 28, 33-35

The introduction and evolution of contemporary criteria for AKI definition [Risk Injury Failure Loss End-stage (RIFLE), Acute Kidney Injury Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO)]36 has provided a uniform basis for research efforts in the field and led to conduction of several relevant studies. Table 1 summarizes findings of studies reporting AKI incidence after elective EVAR, using contemporary AKI reporting criteria. Using AKIN and KDIGO criteria, including urine output measurements which are usually not included in similar literature, we reported on 149 patients undergoing EVAR and observed a post-operative AKI incidence of 18.8%.4 We verified this in a
subsequent study of 947 elective EVARs; using AKIN and KDIGO criteria, AKI incidence was 18%. The vast majority of patients undergoing elective EVAR who do develop AKI are typically classified as Stage 1 in these series and requirement for dialysis is rare (<1%). Two previous studies, using the AKIN and RIFLE criteria, which included 87 and 207 elective EVARs respectively, have shown an incidence of 17%. Another prior retrospective series, including 47 EVARs, showed an incidence of 14%, when using the AKIN criteria.

Fenestrated and branched (fEVAR and bEVAR) EVAR were introduced during the last decade, allowing the treatment of a wider range of aneurysmal disease of the abdominal aorta using endovascular means. These techniques involve the cannulation and stenting of aortic branches, such as the renal arteries, during EVAR in order to treat juxtarenal or suprarenal AAAs. Such aneurysms could not have otherwise been treated using endovascular means. These procedures are more complex and require more contrast than standard infrarenal EVAR. Furthermore, the renal arteries are at far higher risk of occlusion or stenosis, given that covered stents are deployed into the actual renal vasculature. In the largest series of fEVAR and bEVAR reported to date (449 patients), the rate of renal artery occlusion was 2.3% for fEVAR and 9.6% for bEVAR. We recently used the AKIN and KDIGO criteria and found an AKI incidence of 28% in a cohort of 58 patients undergoing fEVAR; we also performed a meta-analysis and found that the pooled proportions of an eGFR drop >30% were 20% [95% Confidence Interval (CI) 9% to 39%] after 30 days. Following the publication of our meta-analysis, Sailer et al. reported an AKI incidence of 28% using the AKIN criteria in 157 patients undergoing fEVAR or bEVAR and Ducasse et al. reported an incidence of 32% in a similar fEVAR population. Tran et al also reported on 110 fEVARs, with an AKI incidence of 22.7%. In all these fEVAR/bEVAR series, most patients (60%) developed stage 1 AKI; however, the percentage developing stage 2 AKI or above was indeed higher compared to the standard infrarenal EVAR series. Sailer and Tran et al have
also shown a clear association between AKI and long-term renal dysfunction in these patients.\textsuperscript{46}

Following the above, it is clear that the incidence of AKI after EVAR has previously been underestimated and true incidence is close to 15-20% in up to date series using acceptable reporting criteria.

\textit{Risk factors}

The development of AKI after any type of intervention depends on preoperative risk factors and perioperative events.\textsuperscript{1, 49} Preoperative risk-stratification is critical.\textsuperscript{50} The lack of uniformly reported AKI incidence after EVAR and the complex pathophysiology involved prohibit meaningful meta-regression using currently available data. Of note, a major limitation of studies looking at risk factors of AKI after EVAR associated AKI is the absence of objective information on the perioperative volume status of the patients. Obviously, patients with AAA have multiple co-morbidities, several of which (diabetes, smoking, hypertension, ischemic heart disease) are recognised risk factors for AKI.\textsuperscript{1, 49} We recently assessed the impact of various traditional risk-factors for AKI in a multivariate model in patients undergoing elective infra-renal EVAR using a suprarenal fixation device (almost 1,000 individuals)\textsuperscript{49} Preoperative eGFR and Chronic Kidney Disease (CKD) stage>2 were the main determinants of AKI development [Odds Ratio (OR): 1.02 (per eGFR unit decrease); 95\% CI: 1.003-1.041; \( P=0.025 \) and OR:1.28; 95\% CI: 1.249-2.531, \( P=0.001 \), respectively). It has previously been suggested that suprarenal endograft fixation (in the form of bare suprarenal stents that anchor to the healthy aorta) may be associated with amplified renal damage.\textsuperscript{51} Suprarenal fixation may impact on blood flow through the renal artery orifice and may also be the source of microemboli during device deployment or through turbulent flow; however, these assumptions have not been proven in vivo or in vitro. Furthermore, this
appears to be mostly a medium to long-term effect rather than an acute decline of renal function and a recent meta-analysis has found no significant differences in AKI between devices with and without these suprarenal fixation modalities.52

**Mechanisms of renal damage**

Several pathophysiological mechanisms are implicated in renal damage during and after elective EVAR; emergency EVAR, in the case of aneurysmal rupture, has the additional burden of hypovolemic shock leading to pre-renal AKI and, depending of the duration of hypovolemia, in ischemic acute tubular necrosis (ATN). Figure 1 summarizes the possible mechanisms of renal injury during elective EVAR. Intra-arterial administration of contrast close to the orifice of the renal arteries, during proximal stent deployment and completion angiography leads to increased vasoconstrictive forces, decreased local prostaglandin- and nitric oxide- mediated vasodilatation, a direct toxic effect on renal tubular cells with damage caused by oxygen free radicals, as well as increased intratubular pressure secondary to contrast-induced diuresis, increased urinary viscosity, and tubular obstruction, all culminating in renal medullary ischemia [development of contrast-induced nephropathy (CIN)53]. Angiography with CO₂ has been proposed but has not been widely adopted due to limitations relating to image quality and ease of use54. Patients with an AAA are likely to have a significant burden of intra-aortic mural thrombus, which may be disrupted during device deployment and other endovascular manipulations 55, leading to microembolisation in the renal vasculature and ) localised ischemia of the renal parenchyma. Severe proximal aortic neck thrombus or calcification, are currently considered as contra-indications to EVAR. Given that most contemporary devices now feature suprarenal fixation modalities, this “microembolisation” phenomenon may be amplified56. It is, however, interesting that in none of the series of patients undergoing EVAR in which we specifically reported on AKI did we
observe visible microemboli and renal infarcts 30 days after the repair on a computed tomographic angiogram (CTA)\textsuperscript{4-6, 49}. Further to the above, atherosclerotic renal artery stenosis (RAS) is common in patients with AAA\textsuperscript{57} and may be also a factor related to AKI, through increasing the likelihood of microembolisation or simply by disrupting normal renal blood perfusion during the procedure. It is also not uncommon for angiography to detect a RAS of large degree (i.e. more than 80-90\%) and the interventionist to opt to correct this simultaneously, thus increasing the total amount of contrast medium used. To the best of our knowledge, there is no study looking specifically at the interaction between EVAR-related AKI and renal artery stenosis.

Further mechanisms of AKI following EVAR include complications directly relating to the renal arteries, such as dissection or coverage of the arterial orifice;\textsuperscript{58} coverage of main renal artery orifices is exceptionally rare in modern practice for elective EVAR as meticulous planning and new generation software allow the operators to avoid such complications. Based on data from randomized studies, accessory renal arteries may be covered in about 5\% of elective EVAR procedures, which may result in infarction of renal parenchyma and subsequent injury\textsuperscript{35}. In our multivariate analyses, we haven’t observed a higher-rate of AKI in patients where an accessory renal artery was intentionally covered.\textsuperscript{49} Lower limb ischemia causing subsequent ischemia-reperfusion injury and muscular cell necrosis may be an additional mechanism.\textsuperscript{59} It is expected that lower limbs will be excluded from circulation for at least 60 minutes during a standard EVAR procedure; reperfusion may lead to kidney damage, through release of myoglobin and inflammatory molecules\textsuperscript{60}. Presence of an inflammatory infiltrate (the actual aneurysmal sac that is not excised such as in open-repair) and the inflammatory response subsequent to introduction of a foreign body may predispose to AKI.\textsuperscript{61} Thrombin generation, fibrinolysis, platelet and endothelial cell activity, and cytokine release appear immediately after EVAR and a third of patients may develop system
inflammatory symptoms.62, 63. Typical hypovolemia (i.e. following blood loss) that escapes correction during surgery is a factor common with other procedures. Importantly, as discussed above, patients that are typically scheduled for EVAR have a range of co-morbidities64 (i.e. older age, diabetes, pre-existing CKD) that reduce the autoregulatory capacity of the kidneys and pre-dispose to AKI after various insults.

**Association of AKI with mortality, morbidity, and long-term renal function after EVAR**

Recent data suggest that AKI is associated with both short and longer-term outcomes after EVAR. We have recently shown, in a series of 149 elective EVARs, that freedom from AKI development was associated with reduced mortality [Hazard Ratio (HR): 0.035, 95% CI: 0.005-0.240, p<0.001] and cardiovascular morbidity (HR: 0.021, 95% CI: 0.004-0.11, p<0.001) in adjusted analysis, over 33 months of follow-up.4 The majority of these patients died due to a cardiovascular (CV) event. In another cohort of 1,068 individuals undergoing AAA repair, AKI development was independently associated with increased risk of cardiovascular events (HR:1.73, 95% CI 1.06-3.39, p=0.03) during a median follow-up of 62 months (range 11-121).5 Whether AKI is the precipitating factor behind CV-events or these patients are simply more likely to have a higher burden of occult CV-morbidity is unclear. Based on these epidemiological observations, one may regard AKI at least as a marker of higher cardiovascular-risk. It is currently unknown how and if AKI pathogenically accelerates cardiovascular morbidity and mortality. To answer this, further mechanistic evidence is required.

Apart from an acute decline in renal function, EVAR may also impact on longer-term renal outcomes. We previously performed a nested case-matched analysis of 726 patients to compare long-term renal function between patients undergoing EVAR, open-repair and patients with no AAA. 65 The open-repair patients lost an average of 7.4 ml/min/1.73 m² at 5
years (95% CI: 4.8-10.6), compared with 8.2 ml/min/1.73 m² (95% CI: 6.5-10.8; P<0.001) for infrarenal-fixation EVAR, 16.9 ml/min/1.73 m² (95% CI: 13.0-21.9, P<0.001) for suprarenal-fixation EVAR, and 5.4 ml/min/1.73 m² (95% CI: 1.7-7.5; P<0.001) for patients with carotid atherosclerosis and no AAA. The decrease in eGFR was steeper during the first postoperative year in the EVAR population, indirectly suggesting an association between peri-operative renal injury and long-term decline. This decline in renal function over the 1st post-operative year is further supported by a meta-analysis which has shown that 18% of patients have developed “clinically important renal dysfunction” at 1 year (defined as rise in SCr>30% compared to baseline).66 This meta-analysis has, however, not reported AKI incidence using standardised criteria and employed suboptimal measures of renal decline over the long-term.67 In our series investigating long-term renal decline (at 5 years) after EVAR, those who did develop AKI had a trend towards greater eGFR drop in multivariate analysis (beta co-efficient, 0.04; 95% CI: 24.25 to 8.54; p=0.06).65 Following the above, it is rather clear that suprarenal EVAR is associated with renal function peri-operatively and during the 1st post-operative year and AKI, regardless of stage, is associated with a more significant long-term decline. An important issue regarding long-term renal function decline and EVAR is that younger patients are now offered EVAR routinely, more so since the introduction of nationwide AAA screening in the UK, USA and some European countries. Vascular surgeons should counsel patients about renal implications, especially since open repair seems to have a less pronounce long-term impact on renal function and does not necessitate follow-up with contrast-requiring imaging.

**AKI prevention in EVAR**

Due to the complex nature of the mechanisms contributing to renal damage during and after EVAR, prevention strategies applicable to general surgery or percutaneous
radiological interventions cannot be extra-polated for EVAR. Prevention strategies that have been studied in EVAR so far have included slow or rapid fluid administration (using various non-uniform regimes with varying results), ischemic preconditioning in a small study with a positive trend, regional anaesthesia, various pharmacological agents (with no conclusive evidence), and targeted renal therapy. Intravenous bicarbonate administration has been assessed in a prospective study with limited follow-up and a non-uniform volume expansion protocol. Overall, the aforementioned modalities have been evaluated in small under-powered studies that have not used a consistent AKI definition. Thus, randomized trials with large numbers of patients undergoing EVAR are needed to elucidate this field. Since several mechanisms are implicated in EVAR-specific renal injury, future trials should investigate a variety of protection strategies and possible interactions, possibly using complex adaptive trial designs. Given that volume expansion with isotonic intravenous fluid is the only known effective preventing strategy in procedures involving high contrast use, this should probably be the first to be investigated in EVAR-specific trials.

ACUTE KIDNEY INJURY AFTER TRANSCATHETER AORTIC VALVE REPLACEMENT

Aortic stenosis (AS) is a common cardiac valvular disease with a high prevalence in the elderly. Surgical aortic valve replacement (SAVR) is currently considered the gold standard treatment for severe symptomatic AS. Transcatheter aortic valve replacement (TAVR) was introduced in 2002 and since then has become a viable treatment option for high-risk patients with severe AS who are not suitable candidates for SAVR. Decisions to proceed with TAVR versus SAVR are based on surgical risk, need for coronary bypass grafting, and other concurrent comorbid conditions. Several trials have compared these two
modalities in high risk cardiac patients and found lower or comparable mortality rates in the TAVR group compared to the surgical group. While major vascular complications such as cardiac perforation and permanent pacemaker implantation were more frequent after TAVR, life-threatening bleeding and new onset atrial fibrillation was more common after SAVR. After 2 and 5 years of follow-up, both SAVR and TAVR had similar mortality rates. However, AKI has emerged as a major complication following TAVR and has been the focus of several recent studies.

**Incidence**

Given variable staging definitions for AKI in the intensive care unit setting, the Valve Academic Research Consortium (VARC) published criteria in 2011 to standardize definitions of clinical end points for TAVR. The Valve Academic Research Consortium (VARC) version 2 definition of AKI is based on a modified version of the AKIN classification (Figure 2). Table 2 lists all large recent studies that evaluated AKI in TAVR patients. For studies using the RIFLE criteria to report AKI, the mean incidence across studies is 22%; if the AKIN criteria are used the mean incidence across studies is 21.5%. The rate of severe AKI requiring dialysis in these studies varies widely between 0% and 10% of the procedures and 0% to 52% (mean of 17%) among all AKI episodes. The mean incidence across studies in the currently available literature for those undergoing SAVR is 33% when using the RIFLE criteria and 26% when using the AKIN criteria. In a recent meta-analysis of twelve studies including >90,000 SAVR patients and 26 studies with >6,000 TAVR patients, AKI occurred in 3.4%–43% of SAVR cases and in 3.4%–57% of TAVR cases, the wide range of incidence being due to vastly different definitions of AKI. A recent meta-analysis of RCTs and cohort-studies demonstrated that TAVR was associated with a lower AKI risk [Risk Ratio (RR) 0.35, 95% CI 0.25-0.50)] but did not find associations between TAVR and reduced risk
of severe AKI requiring dialysis (RR 0.82, 95% CI 0.38-1.79). Furthermore, in a propensity matched single center study comparing TAVR versus SAVR, no significant difference was found regarding AKI incidence (24.1% versus 29.7%; p=0.21), major adverse kidney events (2.1% versus 1.5%; p=0.70), or mortality after 6 months post-operatively (6.0% versus 8.3%; p=0.51). Another study comparing TAVR and SAVR reported similar incidence of renal injury at 1 and 5 years (5.4% in TAVR, 6.5% in SAVR at 1 year, 8.6% in TAVR and 8.5% in SAVR at 5 years).82

**Risk Factors**

Several studies have evaluated several risk factors associated with AKI development after TAVR.93, 94, 96-100 Table 3 summarizes all relevant risk factors; interestingly, these are similar to those seen in AKI post coronary artery bypass surgery (CABG).104 Older age and female gender have both been identified as strong independent risk factors.105 Pre-operative predictors of AKI include baseline serum creatinine >1.42 mg/dl [Hazard Ratio (HR) 3.7, 95% CI 1.24-11.30], pre-existing peripheral vascular disease (HR 1.48, 95% CI 1.075-2.10), higher EuroSCORE (HR 1.02, 95% CI 1.00-1.03), hypertension (HR 6.4, 95% CI 2.9-17.3), diabetes (HR 1.68, 95% CI 0.92-3.05) and prior-CABG (OR: 3.02, 95% CI 1.007-9.09).88, 93, 94, 96-100 Pre-existing chronic kidney disease (CKD) has been identified as an important risk-factor in several studies.86, 93, 99, 106 However, two studies have shown no such association85, 107 As in the case of EVAR, the absence of objective information on the volume status of the patients is a limitation of the relevant TAVR literature.

The timing the angiograms are performed relative to the TAVR procedure is also considered as a potential risk factor for AKI. Two studies noted that if contrast was given <5 days from the surgical procedure, the risk of AKI was increased independently of other factors.108, 109 A recent more detailed evaluation showed that this risk is not applicable to
patients with normal renal function. In coronary interventions, a contrast volume >100cc has been associated with AKI. Only one study has demonstrated a linear relationship between the ratio of contrast to body size and subsequent AKI in TAVR.

Intra-operative factors consistently shown to be independently associated with AKI in several studies include a transapical approach for TAVR and need for red blood cell (RBC) transfusion. Small observational studies, and a recent large cohort-study confirmed that TAVR via a transapical approach is associated with 4.7-9.3 times higher risk for AKI when compared to the transfemoral approach. Patients who undergo a transapical approach usually have severe atherosclerotic disease that precludes them from transfemoral access. This was elegantly shown by Thongprayoon et al; in patients undergoing the transapical approach for TAVR, PVD was more prevalent than those undergoing transfemoral approach (73% vs 44%; p<0.001). Patients with advanced PVD have a larger atherosclerotic burden that puts them at a higher risk of distal embolic events from the dislodgement of the plaque to the kidney during instrumentation of the aorta. An alternative explanation might be that since general anesthesia is needed during the transapical approach, this may be associated with higher rates of hemodynamic or nephrotoxic insult to the kidney but this hypothesis has not been specifically examined. Need for transfusion, severe anemia and life threatening bleeding have been shown in several studies to have an independent association with AKI after TAVR. Barbash et al. demonstrated that patients receiving RBC transfusion had a higher risk of AKI (HR 3.74, 95% CI 1.36-10.3). Nuis et al. also showed that transfusion of multiple units of RBCs in <24 hours was an independent risk factor (HR 3.05, 95% CI 1.24-7.53), but potential triggers of blood transfusion such as baseline anemia, bleeding-vascular complications, and perioperative blood loss were not. Overall, while the comorbidities or complications defining the need for blood transfusions (i.e. blood loss, advanced heart failure accompanied with anemia etc.) may be the factors responsible for
AKI, the above data suggest that transfusions per se may be involved. Post-operative risk factors for AKI are dependent on operative and perioperative causes such as hypotension and other drug related injuries. Specifically, post-operative thrombocytopenia (over 4-fold increase), leukocytosis, aortic regurgitation and need for intra-aortic balloon pump use, have all been noted to be associated with AKI development.84, 100, 112, 114

Mechanisms of renal damage

No specific studies have looked at the mechanism of renal injury in TAVR but certain hypothesis exists in the literature (Figure 3). The kidney is susceptible to hemodynamic injury with TAVR, similar to CABG or SAVR.104 Multiple ischemic insults can lead to cellular ischemia and acute tubular necrosis (ATN). Hypotension from bleeding, sepsis, heart-failure, and rapid ventricular pacing can lead to decreased renal perfusion and renal ischemic insults. Vasoconstriction from contrast medium can add to the pre-renal insult and toxic ATN. As discussed above, anemia and RBC transfusion were associated with a higher risk of AKI.100 Although this can reflect an association of underlying factors (i.e. blood loss, heart failure etc.), with AKI, anemia per se can lead to reduced oxygen delivery to the tissue and enhance oxidative stress as native erythrocytes, impair platelet function and create a pro-inflammatory state and endothelial damage.115-117 Transfusion of several units of stored RBCs can lead to direct renal injury due to reduced deformability and increased aggregability of preserved RBCs 118 and/or higher concentration of free hemoglobin and iron which could be also toxic to the kidneys.119 Finally, atherosclerosis is common in the majority of patients undergoing TAVR.112 Calcification of the aorta and use of a transapical approach can put the patient at risk of distal cholesterol emboli to the renal vascular bed especially during catheter manipulation in the aorta.
Association of AKI with mortality, morbidity and long-term renal function after TAVR

In several studies, AKI has been associated with increased short and long-term mortality in patients undergoing TAVR. In the TAVR literature (summarized in Table 4), 30-day mortality rates ranged from 6.6 to 44%. At 1 year, mortality ranged from 20-70% with a mean of 41%. In previous studies, when patients that developed AKI were compared to those that didn’t the 30-day and 1-year mortality was significantly higher in those with AKI. Patients requiring renal replacement therapy (RRT) after TAVR had on average a 3-fold increase in 30-day mortality and a 3.3-fold increase in 1-year mortality as compared with patients with AKI of lower severity. In a recent meta-analysis of randomized controlled trials in TAVR, there was no association between TAVR and reduced risks of short term mortality (<1 year, RR 0.84, 95% CI 0.56-1.26); patients that developed AKI following TAVR stayed 1.5 to 2 fold longer in hospital than patients without AKI. A recent study looked at incidence, causes and predictors of early (≤30 days) and late unplanned hospital re-admissions after TAVR; CKD (p=0.013) was found to be associated with late unplanned re-admission after TAVR. Further to the above, a meta-analysis suggested that 30-day mortality was 7.8%-29% for patients with AKI following TAVR and 5.5%-46% for those with AKI after SAVR, the rates being 2-16 times higher than in patients without AKI after the procedure.

With regards to renal function following TAVR in general, in an interesting study Voigtländer et al divided patients into three groups based on their GFR prior to the TAVR (GFR ≥60 (normal), 30–59 (moderate CKD), and <30 mL/min/1.73 m² (severe CKD), and demonstrated a modest increase in GFR in the moderately impaired renal function group and a significant increase in GFR in those with severe CKD. There was no significant change in eGFR after TAVR in patients with normal renal function. Patients who experienced an increase in GFR after TAVR by more than 22% had improved survival rate (p=0.0068),
whereas a decrease in GFR by more than 15% was associated with decreased survival (p=0.0051). Another study showed improvement of eGFR at one month following TAVR in patients with pre-existing CKD\textsuperscript{39}. It is therefore possible that renal function can improve in some cases following TAVR due to the improvement in cardiac performance and renal perfusion following correction of valvular disease. Whether patients of intermediate risk but with a degree of renal dysfunction should be predisposed to TAVR over SAVR is a question to be answered in larger prospective clinical trials.

**AKI prevention in TAVR**

No trials have studied any specific prevention and treatment strategies in TAVR associated AKI. Besides using RRT when indicated, the most important preventive strategy seems to be optimizing renal perfusion prior to the procedure. Using pre-operative volume expansion before contrast administration may help minimize contrast-related injury; other modalities such as use of bicarbonate or statins could be helpful\textsuperscript{16, 72, 76} but they have not been specifically studied in TAVR related AKI prevention.

One study using the RenalGuard system suggests possibly a strategy to prevent TAVR associated AKI. The RenalGuard system is a device capable of delivering precise amounts of intravenous fluids which matches the volume of urine produced by the patient.\textsuperscript{121} A single center, open-label randomized trial evaluated use of furosemide-induced diuresis with matched intravenous isotonic fluid administration using the RenalGuard in 112 patients undergoing TAVR. The AKI rate was lower in the RenalGuard group (3% versus 14%, p=0.014).\textsuperscript{121} No patient required dialysis and there were no significant differences in terms of mortality, cardiac and cerebral events, and hospitalization at 30 days.

To limit contrast exposure, non-contrast annular sizing techniques such as cardiac MRI and 3-dimensional trans-esophageal echocardiography can be used to get a precise
estimate of the valve size. In addition, limited contrast computed tomographic (CT) scanning can be performed with contrast infusion via a pigtail catheter placed in the descending aorta to provide an assessment of the vasculature prior to performing TAVR through a transfemoral approach. Arrigo et al.\textsuperscript{122} avoided performing a pre-operative CT in a study with 5 patients and planned the TAVR based on echocardiography, aortography and the amount of calcification present together with the patient’s weight and height. Only a single contrast injection was used to ensure correct positioning of the pigtail catheter at the level of the annulus. The device was successfully placed in all patients with no major complications and a median dose of 8ml (4-9ml) of contrast.\textsuperscript{122} Four of the 5 patients had improved renal function after the intervention compared to baseline. Thus, limiting contrast might help in preventing renal injury but this hasn’t been studied in a randomized controlled fashion and high-risk patients. In addition, the accurate assessment of the aortic annulus and ilio-femoral axis are best obtained using contrast agents. Employing a 48-hour interval between the last contrast-based study and TAVR, may also limit the amount of contrast injury.\textsuperscript{88} Furthermore, a restrictive blood transfusion strategy may decrease AKI incidence.\textsuperscript{123} Technical improvement in TAVR through the use of smaller delivery systems and embolic protection devices could also be helpful.\textsuperscript{124} Overall, as in the case EVAR, complex protocols may be needed to fully delineate the optimal prevention strategies for AKI in patients undergoing TAVR. However, the first step for future research could be investigating strategies that were tested in other endovascular procedures, i.e. studies on contrast load or osmolality, timing of contrast studies, volume expansion or holding diuretic strategies, use of bicarbonate solutions or NAC.
**TAVR in dialysis patients**

End-stage renal disease (ESRD) is a significant predictor of operative mortality compared to patients with normal GFR (OR 4.8, p<0.0001).\(^{125}\) Data on ESRD patients undergoing TAVR is slowly emerging. In a case-series, Rau et al.\(^{126}\) compared 10 patients on dialysis with 116 CKD patients (not on dialysis) undergoing TAVR. Even though the dialysis patients were younger (72.3 versus 82.0 years, p<0.01), their hospital-stay was longer (21.8 versus 12.1 days, p=0.01). Overall 30-day mortality was 3.17%, with no deaths among dialysis patients. Six-month survival rates were similar in both groups. The same group compared a set of ESRD patients that underwent TAVR to patients having SAVR;\(^{126}\) Patients in the surgical group tended to stay longer in hospital (29.5 days versus 22.5 days, p=0.35). Szerlip et al.\(^{127}\) performed a large multicenter retrospective study on the outcomes of TAVR in a national cohort of ESRD patients and found that ESRD patients who underwent TAVR were at high-risk for mortality (6-month mortality was 26%) with the rest of outcomes not substantially better than SAVR.\(^{127}\) The procedural complications in this study are comparable to a study including dialysis patients who underwent SAVR or SAVR with CABG.\(^{127}\) Operative mortality was 14%, similar to 19% in ESRD patients getting a SAVR.\(^{127}\) Both Rau et al. and Szerlip et al. reported a 6-month survival of 74-80% in TAVR patients on dialysis. In summary, patients with ESRD who undergo TAVR are at high-risk for morbidity and mortality, however, TAVR seems to be at least as safe and effective as SAVR in patients undergoing AV repair.

**ROLE OF THE NEPHROLOGIST IN PREVENTION AND MANAGEMENT OF AKI FROM EVAR AND TAVR**
Although currently no specific studies have assessed the impact of nephrology involvement for prevention and management of EVAR- or TAVR- associated AKI, it could be hypothesized that nephrologists could play a very important role in improving the relevant outcomes. As practice patterns vary widely in different parts of the world and in most sites nephrologists are involved only after AKI is established, in large centers that perform EVARs or TAVRs, a multi-specialty team approach could be employed to include a nephrologist in the patient selection meetings and in cases of high-risk patients to offer a full nephrology consultation prior to surgery. In the absence of specific risk stratification tools for these procedures, the role of the nephrologist is first to identify patients at risk based on common (age, CKD, diabetes, smoking etc.) and more specific (anemia, heart failure, anatomy of renal arteries etc.) risk factors, to optimize critical concomitant treatments (i.e. RAAS blockers, diuretics) before surgery or even advise against proceeding with EVAR or TAVR when the anticipated benefits are fewer than the risks. There is some evidence that stopping RAAS blockers and diuretics for a 48 hour period pre- and post-operatively may limit the nephrotoxic impact of contrast and such practice is suggested by various relevant governing bodies, such as the National Institute for Clinical Excellence (NICE). The role of the nephrologist can be also critical in developing or standardizing clinical protocols against specific risk factors (i.e. contrast-induced injury) according to current knowledge and, of course, in individualizing critical preventive measures (i.e. fluid administration, changes in concomitant treatment) for each patient during the critical period immediately before, but also after surgery when information from the procedure itself is available. Finally, nephrologists should play a central part in actual management of patients with early AKI and in those requiring renal replacement therapy (including the selection of the most appropriate method and its details), as well as in ensuring a proper point of outpatient care for those
patients that did not develop AKI during the usually short hospitalization, but are in high-risk for short-, medium- or long-term decline of renal function.

CONCLUSIONS
EVAR and TAVR are two complex endovascular procedures that have been increasingly used to treat abdominal aortic aneurysm and aortic valve stenosis in recent years. EVAR in particular is the current treatment of choice for elective correction of aortic aneurysms. However, the incidence of AKI after EVAR and TAVR is significant and development of AKI is associated with future mortality, morbidity and progression of kidney disease. Various mechanisms for AKI may be involved in each of these two procedures. Knowledge of these mechanisms is important to develop preventive strategies. Continued risk assessment of patients and reporting AKI with standardized definitions may enable the future performance of clinical trials on interventions aiming to minimize the incidence of AKI and improve the morbidity and mortality related to these procedures. Until then, a close collaboration of vascular surgeons, cardiologists and nephrologists can improve the quality of usual care and the understanding of AKI development after these endovascular procedures for the benefit of our patients.
FIGURE LEGENDS

Figure 1: Mechanisms of renal injury during Endovascular Aneurysm Repair (EVAR)

Figure 2: Valve Academic Research Consortium-2 definition of AKI based on Acute Kidney Injury Network criteria (VARC-2). (SCr: serum creatinine; AKI: acute kidney injury)

Figure 3: Mechanisms of renal injury during Transcatheter Aortic Valve Replacement (TAVR)
**TABLES**

**Table 1**: Incidence of Acute Kidney Injury (AKI) in elective infra-renal Endovascular Aneurysm Repair (EVAR) using standardised AKI reporting criteria

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type</th>
<th>Date</th>
<th>n EVAR</th>
<th>AKI criterion</th>
<th>AKI incidence</th>
<th>n AKI</th>
<th>n AKI stage &gt; 2</th>
<th>Dialysis</th>
<th>Urine output available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirgakis KM^{37}</td>
<td>Retrospective</td>
<td>2014</td>
<td>87</td>
<td>AKIN</td>
<td>17%</td>
<td>15</td>
<td>None</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Ueta K^{39}</td>
<td>Prospective</td>
<td>2014</td>
<td>47</td>
<td>AKIN</td>
<td>14%</td>
<td>6</td>
<td>Stage 2: 1</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Pisimisis GT^{38}</td>
<td>Retrospective</td>
<td>2013</td>
<td>208</td>
<td>RIFLE AKIN &amp; KDIGO</td>
<td>17%</td>
<td>36</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Saratzis A^{4}</td>
<td>Prospective</td>
<td>2015</td>
<td>149</td>
<td>KDIGO</td>
<td>19%</td>
<td>28</td>
<td>Stage 2: 3</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Saratzis A^{49}</td>
<td>Retrospective</td>
<td>2015</td>
<td>484</td>
<td>AKIN</td>
<td>12%</td>
<td>58</td>
<td>NA</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Saratzis A^{5}</td>
<td>Retrospective</td>
<td>2015</td>
<td>947</td>
<td>KDIGO Aneurysm Score</td>
<td>18%</td>
<td>167</td>
<td>Stage 2: 12; 3: 2</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Castagno C^{129}</td>
<td>Retrospective</td>
<td>2016</td>
<td>146</td>
<td>AKIN</td>
<td>5.5%</td>
<td>8</td>
<td>NA</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Obata Y^{130}</td>
<td>Prospective</td>
<td>2016</td>
<td>95</td>
<td>AKIN</td>
<td>9.4%</td>
<td>9</td>
<td>Stage 2: 1</td>
<td>None</td>
<td>No</td>
</tr>
</tbody>
</table>

AKI: Acute Kidney Injury  
AKIN: Acute Kidney Injury Network Criteria  
RIFLE: Risk, Injury, Failure, Loss, End-Stage Renal Disease Acute Dialysis Quality Initiative Criteria  
KDIGO: Kidney Disease Improving Global Outcomes Criteria  
NA: Not Available
**Table 2:** Acute Kidney Injury (AKI) incidence and need for dialysis in cohort studies of Transcatheter Aortic Valve Replacement (TAVR)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type</th>
<th>Date</th>
<th>n TVAR</th>
<th>AKI criterion</th>
<th>AKI incidence</th>
<th>n AKI</th>
<th>Dialysis</th>
<th>Urine output available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arreger et al</td>
<td>Retrospective</td>
<td>2009</td>
<td>54</td>
<td>RIFLE</td>
<td>28%</td>
<td>15</td>
<td>4</td>
<td>No</td>
</tr>
<tr>
<td>Bagur et al</td>
<td>Retrospective</td>
<td>2010</td>
<td>213</td>
<td>RFILE</td>
<td>11%</td>
<td>25</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>Sinning et al</td>
<td>Prospective</td>
<td>2010</td>
<td>77</td>
<td>AKIN</td>
<td>25%</td>
<td>20</td>
<td>8</td>
<td>No</td>
</tr>
<tr>
<td>Elhmidi et al</td>
<td>Prospective</td>
<td>2011</td>
<td>234</td>
<td>RIFLE</td>
<td>20%</td>
<td>46</td>
<td>24</td>
<td>No</td>
</tr>
<tr>
<td>Nuis et al</td>
<td>Prospective</td>
<td>2012</td>
<td>975</td>
<td>AKIN</td>
<td>20%</td>
<td>206</td>
<td>31</td>
<td>Yes</td>
</tr>
<tr>
<td>Nuis et al</td>
<td>Prospective</td>
<td>2011</td>
<td>118</td>
<td>AKIN</td>
<td>19%</td>
<td>22</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Barbash et al</td>
<td>Retrospective</td>
<td>2012</td>
<td>165</td>
<td>AKIN</td>
<td>15%</td>
<td>24</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>Alassar et al</td>
<td>Prospective</td>
<td>2012</td>
<td>81</td>
<td>AKIN</td>
<td>12%</td>
<td>10</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>Gebauer et al</td>
<td>Prospective</td>
<td>2012</td>
<td>140</td>
<td>AKIN</td>
<td>20%</td>
<td>28</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>Kong et al</td>
<td>Retrospective</td>
<td>2012</td>
<td>52</td>
<td>RIFLE</td>
<td>29%</td>
<td>15</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>Genereux et al</td>
<td>Prospective</td>
<td>2013</td>
<td>218</td>
<td>AKIN</td>
<td>8.3%</td>
<td>18</td>
<td>9</td>
<td>Yes</td>
</tr>
<tr>
<td>Saia et al</td>
<td>Prospective</td>
<td>2013</td>
<td>102</td>
<td>AKIN</td>
<td>41%</td>
<td>42</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>Yamamoto et al</td>
<td>Prospective</td>
<td>2013</td>
<td>415</td>
<td>AKIN</td>
<td>15%</td>
<td>63</td>
<td>4</td>
<td>No</td>
</tr>
<tr>
<td>Crowhurst et al</td>
<td>Prospective</td>
<td>2016</td>
<td>209</td>
<td>AKIN</td>
<td>39%</td>
<td>82</td>
<td>5</td>
<td>No</td>
</tr>
<tr>
<td>Tongaprayoon C et al</td>
<td>Retrospective</td>
<td>2016</td>
<td>386</td>
<td>KDIGO</td>
<td>28%</td>
<td>106</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>Aalaei-Andabili et al</td>
<td>Retrospective</td>
<td>2016</td>
<td>290</td>
<td>AKIN</td>
<td>25%</td>
<td>65</td>
<td>12</td>
<td>No</td>
</tr>
<tr>
<td>Arsalan et al</td>
<td>Retrospective</td>
<td>2016</td>
<td>384</td>
<td>AKIN</td>
<td>37.5%</td>
<td>144</td>
<td>12</td>
<td>Yes</td>
</tr>
<tr>
<td>Konigstein et al</td>
<td>Prospective</td>
<td>2016</td>
<td>422</td>
<td>AKIN</td>
<td>15.6%</td>
<td>66</td>
<td>0</td>
<td>Yes</td>
</tr>
</tbody>
</table>
AKIN: Acute Kidney Injury Network Criteria
RIFLE: Risk, Injury, Failure, Loss, End-Stage Renal Disease Acute Dialysis Quality Initiative Criteria
KDIGO: Kidney Disease Improving Global Outcomes Criteria
**Table 3:** Risk factors for Transcatheter Aortic Valve Replacement (TAVR) associated renal injury

<table>
<thead>
<tr>
<th>Pre-operative</th>
<th>Intra-operative</th>
<th>Post-operative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Kidney Disease</td>
<td>Anemia/Bleeding</td>
<td>Post procedure leukocyte count</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>RBC transfusion</td>
<td>&gt;12g/L for &gt;2 days</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Trans apical approach</td>
<td>Post-operative aortic regurgitation</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td>Post-operative thrombocytopenia</td>
</tr>
<tr>
<td>Older Age</td>
<td></td>
<td>Life-threatening bleeding</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td>Need for intra-aortic balloon pump use</td>
</tr>
<tr>
<td>Ejection Fraction &lt;40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Logistic EuroSCORE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast load &gt;100ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of prior CABG</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RBC: Red Blood Cell  
euroSCORE: European System for Cardiac Operative Risk Evaluation  
CABG: Coronary Artery Bypass Grafting
<table>
<thead>
<tr>
<th>Reference</th>
<th>Date</th>
<th>Length of stay with vs without AKI (days)</th>
<th>Mortality with vs without AKI at 30 days</th>
<th>Mortality with vs without AKI at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arreger et al</td>
<td>2009</td>
<td>18 vs. 11</td>
<td>13.3% vs 0%</td>
<td>NA</td>
</tr>
<tr>
<td>Bagur et al</td>
<td>2010</td>
<td>9 vs. 6</td>
<td>28% vs 7.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Sinning et al</td>
<td>2010</td>
<td>NA</td>
<td>HR 5 for death</td>
<td>70% vs 26%</td>
</tr>
<tr>
<td>Elhmidi et al</td>
<td>2011</td>
<td>12 vs 9</td>
<td>15.2% vs 7.7%</td>
<td>NA</td>
</tr>
<tr>
<td>Nuis et al</td>
<td>2012</td>
<td>13 vs 10</td>
<td>15% vs 4%</td>
<td>20% vs 14%</td>
</tr>
<tr>
<td>Nuis et al</td>
<td>2011</td>
<td>17 vs 9</td>
<td>23% vs 4%</td>
<td>55% vs 22%</td>
</tr>
<tr>
<td>Barbash et al</td>
<td>2012</td>
<td>NA</td>
<td>29% vs 7%</td>
<td>NA</td>
</tr>
<tr>
<td>Alassar et al</td>
<td>2012</td>
<td>NA</td>
<td>No difference</td>
<td>22% vs 13%</td>
</tr>
<tr>
<td>Gebauer et al</td>
<td>2012</td>
<td>20 vs 15</td>
<td>29% vs 7%</td>
<td>43% vs 18%</td>
</tr>
<tr>
<td>Kong et al</td>
<td>2012</td>
<td>10 vs 5</td>
<td>13.5% vs 3.8%</td>
<td>27% vs.2.7%</td>
</tr>
<tr>
<td>Genereux et al</td>
<td>2013</td>
<td>11 vs 8</td>
<td>44% vs 3%</td>
<td>NA</td>
</tr>
<tr>
<td>Saia et al</td>
<td>2013</td>
<td>NA</td>
<td>NA</td>
<td>No difference (12%)</td>
</tr>
<tr>
<td>Yamamoto et al</td>
<td>2013</td>
<td>10 vs 9</td>
<td>15% vs 4%</td>
<td>48% vs 16%</td>
</tr>
<tr>
<td>Crowhurst et al</td>
<td>2016</td>
<td>12 vs 8</td>
<td>9% vs 3%</td>
<td>NA</td>
</tr>
<tr>
<td>Tongaprayoon C et al</td>
<td>2016</td>
<td>8.9 vs 6.2</td>
<td>6.6% vs 1.4%</td>
<td>23% vs 15% at 6 months</td>
</tr>
<tr>
<td>Aalaei-Andanili et al</td>
<td>2016</td>
<td>10.56 vs 6.01</td>
<td>15.38% vs 0.5%</td>
<td>66% survival vs 89% survival</td>
</tr>
<tr>
<td>Arsalan et al</td>
<td>2016</td>
<td>NA</td>
<td>NA</td>
<td>Survival was 59.2% without AKI, 43.4% Stage 1, 27.8% for Stage 2 and 25.4% for Stage 3</td>
</tr>
<tr>
<td>Konigstein et al</td>
<td>2016</td>
<td>NA</td>
<td>8% vs 2.0%</td>
<td>31% vs 19%</td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>----</td>
<td>------------</td>
<td>------------</td>
</tr>
</tbody>
</table>

HR: Hazard Ratio  
NA: Not Available
REFERENCES


