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Erythropoietin in traumatic brain injury associated acute kidney injury - A randomised controlled trial

Short title: Erythropoietin in kidney and traumatic brain injury

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Conflicts of interest:

Markus Skrifvars reports having received a research grant from GE Healthcare, travel reimbursements and lecture fees from Orion Pharma, COVIDIEN, Astellas Pharma and Axis-Shield. All other authors report that they have no conflicts of interest.

Abstract

Background

Acute kidney injury (AKI) in traumatic brain injury (TBI) is poorly understood and it is unknown if it can be attenuated using erythropoietin (EPO).

Methods

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Pre-planned analysis of patients included in the EPO-TBI (ClinicalTrials.gov NCT00987454) trial who were randomised to weekly EPO (40,000 units) or placebo (0.9% sodium chloride) subcutaneously up to three doses or until intensive care unit (ICU) discharge. Creatinine levels and urinary output (up to seven days) were categorised according to the Kidney Disease Improving Global Outcome (KDIGO) classification. Severity of TBI was categorised with the International Mission for Prognosis and Analysis of Clinical Trials in TBI.

Results

Of 3,348 screened patients, 606 were randomized and 603 were analysed. Of these, 82 (14%) patients developed AKI according to KDIGO [60 (10%) with KDIGO 1, 11 (2%) patients with KDIGO 2, and 11 (2%) patients with KDIGO 3]. Male gender (hazard ratio [HR] 4.0 95% confidence interval [CI] 1.4-11.2, p=0.008) and severity of TBI (HR 1.3 95% CI 1.1-1.4, p<0.001 for each 10% increase in risk of poor six month outcome) predicted time to AKI. KDIGO stage 1 (HR 8.8 95% CI 4.5-17, p<0.001), KDIGO stage 2 (HR 13.2 95% CI 3.9-45.2, p<0.001) and KDIGO stage 3 (HR 11.7 95% CI 3.5-39.7, p<0.005) predicted time to mortality. Erythropoietin did not influence time to AKI (HR 1.08 95% CI 0.7-1.67, p=0.73) or creatinine levels during ICU stay (p=0.09).

Conclusions

Acute kidney injury is more common in male patients and those with severe compared to moderate TBI and appears associated with worse outcome. Erythropoietin does not prevent AKI after TBI.

Key words: acute kidney injury, creatinine, critical care, erythropoietin, renal insufficiency, traumatic brain injury

Editorial Comment

Erythropoietin, as a potent hormone that the body releases in response to some forms of stress, has been tested as a potentially protective treatment substance in different clinical

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contexts. In this post-hoc subgroup analysis from an earlier trial, erythropoietin did not appear to alter risk for kidney injury in traumatic brain injury patients.

Introduction

Traumatic brain injury (TBI) is a rising global health concern affecting especially the younger population and results in both high mortality and, in many cases, life-long morbidity and considerable treatment costs [1-3]. Severely injured TBI patients require treatment in an intensive care unit (ICU) [4]. During ICU care, TBI patients are at risk of developing complications such as various degrees of organ failure [5]. One serious complication is acute kidney injury (AKI) which has been shown to occur in 18-36% of trauma patients treated in the ICU [6,7]. Severity of AKI may range from a momentary decrease in urinary output or a slight increase in a creatinine, to complete anuria and the need for renal replacement therapy [7].

Recombinant erythropoietin (EPO) has been shown to have renal protective effects in experimental studies [8-10]. The use EPO for prevention of AKI has been studied in patients undergoing cardiac surgery and following renal transplantation, but thus far the data are conflicting [11-14]. No studies have assessed the effect of EPO on kidney function in patients with trauma [15]. Accordingly, we aimed to assess the incidence and factors increasing the likelihood as well as survival association of AKI in patients with moderate to severe TBI.

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Secondarily, we studied the effect of EPO on kidney function by comparing the occurrence of AKI using the KDIGO classification and creatinine levels in patients treated with either EPO or placebo.

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Methods

The EPO-TBI study was an international randomized controlled trial conducted in multiple centres in Australia, New Zealand, Saudi-Arabia, France, Finland, Ireland and Germany between May 3, 2010 and Nov 1, 2014 [16]. All patients treated in the ICU for moderate or severe TBI were screened for eligibility (Supplementary Figure 1). Patients with end-stage renal failure receiving chronic dialysis were excluded from the trial. Enrolled patients received either weekly doses of 40,000 IU of subcutaneous epoetin alfa (Eprex Janssen-Cilag Pty Ltd, Titusville, NJ, USA) or placebo (0.9% sodium chloride). The randomisation process and administration of drug has been described previously[15]. The administration of EPO continued until patients had received a maximum of three doses, or until the patients was discharged from the ICU [17,18]. A consort checklist for the reporting of the current study is included in the Supplemantary Materials. The EPO-AKI sub-study was a pre-planned study and the protocol (a part of the original EPO-AKI protocol) is included in the Supplementary Materials.

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Data collection

A web based case record form was used including detailed data on patient characteristics, injury mechanism, pre-hospital care and immediate hospital management [17]. Specifically, data enabling the calculation of the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT-TBI) risk for poor six-month outcome was included [19]. Trained assessors classified injury severity with Injury Severity Scores (ISS), Abbreviated Injury Scales (AIS) based on radiological findings and hospital notes. Serum creatinine were prospectively recorded daily until ICU discharge and urine output during the first seven days.

AKI based on the KDIGO classification

Stages of AKI according to KDIGO [20] were defined as follows:

Stage 1: A 1.5 to 1.9 fold increase in creatinine compared to the creatinine measured on hospital admission, an absolute increase > 26.5 µmol/l over 48 hours or a urinary output of less than 0.5 ml/kg/hour for 6-12 hours.

Stage 2: A 2.0 to 2.9 fold increase in creatinine compared to the creatinine measured hospital admission or a urinary output less than 0.5 ml/kg/hour for more than 12 hours.

Stage 3: A 3 fold increase in creatinine compared to creatinine measured on hospital admission, an increase in creatinine to more than 353.6 µmol/l, urinary output of less than 0.3 ml/kg/hour for more than 24 hours, anuria for more than 12 hours or initiation of renal replacement therapy.

Daily data on creatinine levels were available during the whole ICU stay and thus, in our primary analysis we used AKI KDIGO stages defined by changes in creatinine during the whole ICU stay. We also reported AKI free ICU days up to 21 days. Data on urinary output according to the KDIGO stages were only available during the first 7 days of ICU care. Therefore, in a secondary analysis, we studied early AKI, defined by changes in either creatinine or UO occurring during the first 7 days in the ICU. Renal recovery was defined as the absence of any KDIGO stage 1-3 on the day of ICU discharge or at day seven. No data on creatinine or urinary output after ICU discharge are included in the analysis.

Study outcomes

The primary outcome of the current study was the presence and timing of KDIGO stages 1-3 based on creatinine levels during the whole ICU stay. A secondary outcome was KDIGO

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stages 1-3 based on creatinine levels and urinary output during the first 7 days. Patient outcomes included ICU, hospital and six-month survival. Neurological function at six months was determined by an assessor blinded to treatment group using the Glasgow Outcome Scale extended (GOSE). The GOSE ranges from 1-8 with good outcome defined as a GOSE score of 5-8.

Sample size analysis

Prior to the study initiation it was estimated that the incidence of AKI (KDIGO 1-3 compared to no KDIGO class) would be around 9%. Given this assessment, a trial with 287 patients in each group was estimated to have an 86% power to detect a change from 9% to 3% with a two sided p-value 0.05. The EPO TBI trial enrolled 602 patients.

Statistical analysis

Categorical data are presented as counts and percentages and are compared using chi-square test. Numerical data are presented as medians and interquartile range (IQR) in parenthesis. Parametric data is compared with a Student's T test and non-parametric data with the Mann-Whitney U test (two groups) or Kruskall-Wallis test (more than two groups). Cox regression analysis was used to assess independent predictors of time to development of AKI and patient survival at six months. Covariates included in the analysis of the development of AKI included factors that had a p-value less than 0.1 in the univariate analysis. Covariates included in the mortality analysis included covariates pre-specified in our statistical analysis plan and included age, presence of hypoxia (oxygen saturation less than 90%) or hypotension (systolic blood pressure less than 90 mmHg), intracranial mass lesion, abnormal pupils (not equal or not reactive) and geographical region (Australia and New Zealand, Saudi-Arabia or Europe) [21]. The presence of KDIGO class was included as a time dependent covariate and thus included transition between KDIGO states. Kaplan-Meier curves for patients with AKI and those without were compared with a log-rank test. Creatinine levels over time were compared with a mixed model with a diagonal covariance structure, including time, treatment (EPO or placebo) and the interaction between time and treatment. Statistical analysis was performed with SPSS version 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

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Ethical assessment, consent and trial registration

The EPO-TBI study was approved by ethical committees at all study sites. Informed consent was obtained from the patient´s next of kin or legal representative prior to study inclusion according to local ethical requirement. The trial was registered at ClinicalTrials.gov (NCT00987454), the Australian and New Zealand Clinical Trials Registry (ACTRN12609000827235), and European Drug Regulatory Authorities Clinical Trials (011-005235-22)

Results

Incidence of AKI during the first seven days and ICU stay

A total of 606 patients were included in the EPO-TBI trial (Fig. 1). Consent was withdrawn in three patients, therefore this analysis included a total of 603 patients. During the whole ICU stay, 82 (14%) patients developed AKI based on changes in creatinine (Fig.1). Sixty patients (10%) had a KDIGO stage of 1, 11 (2%) a KDIGO stage of 2, and 11 (2%) a KDIGO stage of 3 (Fig. 1). Median time to the highest KDIGO day was 6 days (IQR 4-9). Of the 82 patients with AKI, 59 (72%) had renal recovery prior to ICU discharge. Eight (1.3%) patients received RRT (seven during ICU stay) and of these, seven (88%) were alive at six months. The median time to initiation of RRT was 8 days (IQR 5-11) and in one patient, RRT was initiated on the day of ICU admission. During the first seven days, 210 (35%) patients developed AKI according to UO, 29 (5%) according to creatinine changes and 23 (4%) according to both creatinine and UO changes (Supplementary Fig. 1).

Admission risk factors for acute kidney injury

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There were several differences in both patient, injury and treatment characteristics between patients that developed and those who did not develop AKI during ICU stay (Supplementary Table 1). Notably, patients with AKI were more commonly of male gender; had a higher body weight and more severe brain injury (Supplementary Table 1). On Cox regression analysis, independent predictors of time to development of AKI were male gender (HR 4.0 95% CI 1.4-11.2, p=0.008), and severity of TBI according to the IMPACT model (per 10% increase in risk of poor outcome, HR 1.25 95% CI 1.1-1.4, p<0.001) (Table 1).

Risk factors for AKI on day 3

In a COX regression model for time to AKI later than day 3, excluding those who had died or developed AKI before day three, several factors were identified; Male gender (HR 7.2 95% CI 1.7-29.9, p=0.007), TBI severity (per 10% increase in risk of poor outcome HR 1.2 95% CI 1.1-1.4, p=0.007) and the use of therapeutic hypothermia on days 1-2 (HR 2.6 95% CI 1.5-4.5, p=0.001) were independently associated with time to development of AKI after day 3. The use of EPO was not associated with time to AKI (HR 0.9 95% CI 0.6-1.5, p=0.70) (Supplementary Table 2).

Association of AKI with outcome

Patients with AKI (any KDIGO stage 1-3 during their ICU stay) had a higher ICU mortality (32% compared to 6%, p<0.001), hospital mortality (33% compared to 8%, p<0.001) and six-month mortality (34% compared to 10%, p<0.001) (Supplementary Table 3). Prior to day three, 26 patients had died and 9 patients had developed AKI. Survival curves of patients who had developed AKI and where alive at day three are shown in Fig. 2. Median stay in the ICU was longer in patients with AKI (15 IQR 8-25) compared to those without AKI (12 IQR 7-20) (p=0.005). However, median hospital length of stay was not different between patients with AKI (28 IQR 11-49) and those without (25 IQR 15-43) (p=0.91) (Supplementary Table 3). Similar findings were seen in patients with AKI occurring during the first seven days (Supplementary Table 4). Good neurologic recovery defined according to the GOSE scale occurred in 31 (38%) out of 82 AKI patients compared to 299 (58%) of 514 non-AKI patients (p<0.001).

In a Cox regression model including KDIGO class as a time-dependent covariate, all three KDIGO stages were related to six-month mortality (Table 2). Other significant predictors of

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increased mortality were age (HR 1.04 95% CI 1.02-1.05, p<0.001), abnormal pupils (HR 2.0 95% CI 1.2-3.3, p=0.01) while treatment with EPO (HR 0.61 95% CI 0.38-0.96, p=0.03) predicted decreased mortality. Similar findings were seen using AKI occurring during the first seven days (Supplementary Table 5).

Effect of erythropoietin on AKI

The cumulative number of patients with AKI treated with EPO and placebo in the study and over time in the ICU are shown in Fig. 1, Fig.3 and Supplementary Fig.1. In Cox regression analysis the use of EPO was not found to influence time to development of AKI during the whole ICU stay (HR 0.99 95% CI 0.96-1.03, p=0.56) or during the first seven days (HR 1.01 95% CI 0.79-1.28, p=0.96). Creatinine levels over time are shown in Supplementary Fig.3. There were no differences in creatinine values over time in patients treated with EPO compared to placebo (p=0.09) nor were there any interactions between intervention (EPO or placebo) with time (p=0.99). There was no difference in AKI free days between EPO treated patients (median 11 days, IQR 5-18) compared to placebo treated patients (median 11, IQR 5-19) (p=0.95).

Discussion

We studied the EPO-TBI trial population to assess the incidence and outcome associations of AKI in patients with TBI admitted to ICU. Moreover, we aimed to test whether EPO treatment was associated with any evidence of a renal protective effect. We found that AKI as defined by the KDIGO criteria based on creatinine levels occurred in one in seven patients. Acute kidney injury based on either urinary output or creatinine levels during the first seven days was more common and occurred in 40% of patients. All forms of AKI had an independent association with long-term mortality, but the confidence intervals were wide. Finally, the use of EPO did not provide any protection from AKI.

The incidence of AKI was comparable to previous studies conducted in patients with trauma and TBI. Eriksson and colleagues reported the development of AKI in 103 (25%) patients in a sample of 413 ICU patients admitted following trauma. In a large study involving registry data of trauma patients admitted to the ICU [7] Bagshaw and colleagues reported an AKI

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incidence rate of 18% during the first 24 hours [6]. Gomes and colleagues observed AKI in 50% of trauma patients admitted to the ICU [22]. Noteworthy is that the current study, due to its design, excluded some categories of patients in whom AKI might be even more common.

All stages of AKI were associated with a marked increase in mortality compared to patients without AKI. Previous studies including patients with all types of trauma, have shown similar findings, but data in patients with TBI have are limited [6,7,23,24]. One possible mechanism for the increase in mortality in TBI is aggravated cerebral oedema due to changes in osmolality [25]. In a recent study Siew and colleagues showed that among ICU patients with shock and respiratory failure, KDIGO stage 2 and 3 are significant risk factors for both delirium and coma (25). Interestingly, the use of RRT has been shown to be associated with a very high mortality after TBI [25]. This was not the case in the current study, as all but one of eight patients that received RRT survived.

The current study identified several known markers of increased risk of AKI including male gender. This observation may be explained by differences in weight and muscle mass between males and females: a greater increase in creatinine in males may occur without a true decrease in renal function. The current study also suggested an association between the use of therapeutic hypothermia (TH) and increased likelihood of AKI. It is possible that vasoconstriction, induced by hypothermia, reduces renal blood flow [26]. A meta-analysis including mainly patients resuscitated from cardiac arrest suggested no difference in the prevalence of AKI in between TH and normothermia [27]. On the other hand in a sub-study from the Hypothermia and Cardiac Arrest trial the use of hypothermia was associated with a delay in renal recovery [28]. The study on the use of early induction of TH in TBI by Clifton and colleagues showed no difference in creatinine levels between groups but did show an increased use of intravenous fluids with TH [29].

Despite multiple animal studies suggesting positive effects on the kidney, we did not find that EPO protected patients from AKI [30]. The use of EPO in animal models has been shown to decrease the extent of ischemia reperfusion injury, reduce the incidence of contrast induced nephropathy and alleviate inflammation [8-10,31]. The proposed protective mechanisms include reduction of apoptotic cell death by several mechanisms[32,33]. In the ischemic kindey EPO enhances tissue regeneration, and neovascularisation[34,35]. EPO also supresses the synthesis of TNF-alpha and interleukin-2 inflammatory markers which may part in the development of AKI[33]. In smaller clinical trials EPO has been shown to alleviate

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early AKI after coronary artery bypass grafting[36]. Thus in trauma patients EPO could the expected to have some protective effects within 24-48 hours after injury. Despite experimental and evidence, a lack in positive effects on renal function has been shown in patients undergoing kidney transplantation and in the current study, in TBI patients with trauma[15]. It needs to be noted that the renal endpoints we studied i.e. KDIGO although relevant, may be too crude to detect smaller changes in renal function. All in all our finding corroborate that human AKI is much more complex than in experimental AKI.

Study strengths and limitations

The current study has a number of strengths. Centres from different health systems participated and therefore our results are likely to be generalizable. We also had detailed data on severity of traumatic brain injury and were able to adjust for that in the analysis.

Nonetheless several limitations need to be kept in mind. The study did not include data specific medical conditions such as hypertension, diabetes mellitus or chronic kidney disease that may influence the development of AKI. In addition, the study did not include data on the use of medications, maintenance fluids, myoglobin levels, or therapies that might have influenced renal function. We only had data on urinary output during the first seven days. The UO data only included whether any of the KDIGO UO criteria occurred during the first seven days and did not include hourly or total diuresis. The study only includes short-term data on kidney function and thus we cannot comment of long term effects of EPO on kidney function. Finally, as the main sample size calculation was based on an assumed change in neurologically intact survivors at six months between the EPO and placebo groups, this sub-study may be underpowered to detect clinically meaningful differences the more severe forms of AKI such as the need for RRT in TBI patients.

Conclusion

Within this RCT including patients with moderate to severe TBI, AKI was independently associated with mortality. We identified several factors associated with increasing the risk of AKI including increasing patient weight, male gender, more severe TBI, more severe admission illness severity, and the use of therapeutic hypothermia. Contrary to our hypothesis and despite compelling animal evidence, the use of EPO did not attenuate renal injury in this population.

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Authors contributions: The current post-hoc analysis was planned by MS, EM, JM, MB, CF, AN, DJC and RB. MS, EM, MB, CF, JP, AN, LL, JD, OH, SH, YA, CM, DJC, RB were a part of the

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EPO-TBI study. MS take responsibility of the integrity of the data and drafted the first version of the manuscript. All authors have read and critically contributed to the final draft.

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Table 1 Multivariable analysis of admission factors related to development of time to acute kidney injury in patients with traumatic brain injury included in the erythropoietin in traumatic brain injury trial

Variable	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI	p-value
Patient weight	1.01 (1.001-1.02)	0.03	1.01 (0.99-1.02)	0.32
Male gender	3.99 (1.46-10.89)	0.007	4.02 (1.44-11.23)	0.008
Injury mechanism:				
Motorcycle accident	1.67 (0.94-2.97)	0.08	1.72 (0.95-3.11)	0.07
Pedestrian accident	1.44 (0.78-2.66)	0.24	1.67 (0.89-3.13)	0.11
TBI severity according to IMPACT risk of poor outcome (per 10%)	1.19 (1.07-1.33)	0.002	1.24 (1.10-1.40)	<0.001

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APACHE II score	1.01 (0.98-1.04)	0.47	0.99 (0.96-1.03)	0.56

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Table 2 Independent predictors of mortality in patients included in the erythropoietin in traumatic brain injury trial including time to development and severity of acute kidney injury.

Variable	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI	p-value

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Age	1.03 (1.02-1.05)	<0.001	1.04 (1.02-1.05)	<0.001
Hypotension	1.15 (0.72-1.84)	0.52	1.06 (0.65-1.75)	0.81
Hypoxia	1.31 (0.78-2.23)	0.31	1.44 (0.83-2.5)	0.20
No intracranial mass lesion	0.72 (0.43-1.23)	0.23	0.77 (0.45-1.3)	0.33
Pupils abnormal (not equal, non-reactive)	2.20 (1.37-3.52)	0.001	2.00 (1.21-3.3)	0.01
Region (Saudi-Arabia reference)				0.30
Australia and New Zealand	0.82 (0.53-1.28)	0.39	0.71 (0.22-2.32)	
Europe	1.05 (0.63-1.77)	0.84	0.57 (0.16-2.00)	
Moderate TBI	0.7 (0.4-1.22)	0.21	0.68 (0.38-1.2)	0.19
Acute Kidney Injury[1]				<0.001
KDIGO 1	8.61 (4.52-16.42)	<0.001	8.76 (4.51-16.99)	
KDIGO 2	14.24 (4.36-46.56)	<0.001	13.22 (3.87-45.16)	
KDIGO 3	8.61 (2.7-27.48)	<0.001	11.72 (3.46-39.68)	
Treatment with EPO	0.65 (0.41-1.02)	0.06	0.61 (0.38-0.96)	0.03

[1] The reference category is no AKI (Absence of KDIGO 1-3).

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Fig.1 Flow chart of patients included in the EPO-TBI trial and the development of various stages of acute kidney injury based on changes in creatinine during ICU stay.

Fig.2 Survival curves in 599 (excluding deaths prior to day 3) traumatic brain injury patients treated in the intensive care unit indexed by the development of acute kidney injury before day 3 based on creatinine and urinary output.

Fig.3 The timing and cumulative cases of acute kidney in injury in patients treated with erythropoietin or placebo in the erythropoietin in traumatic brain injury trial.

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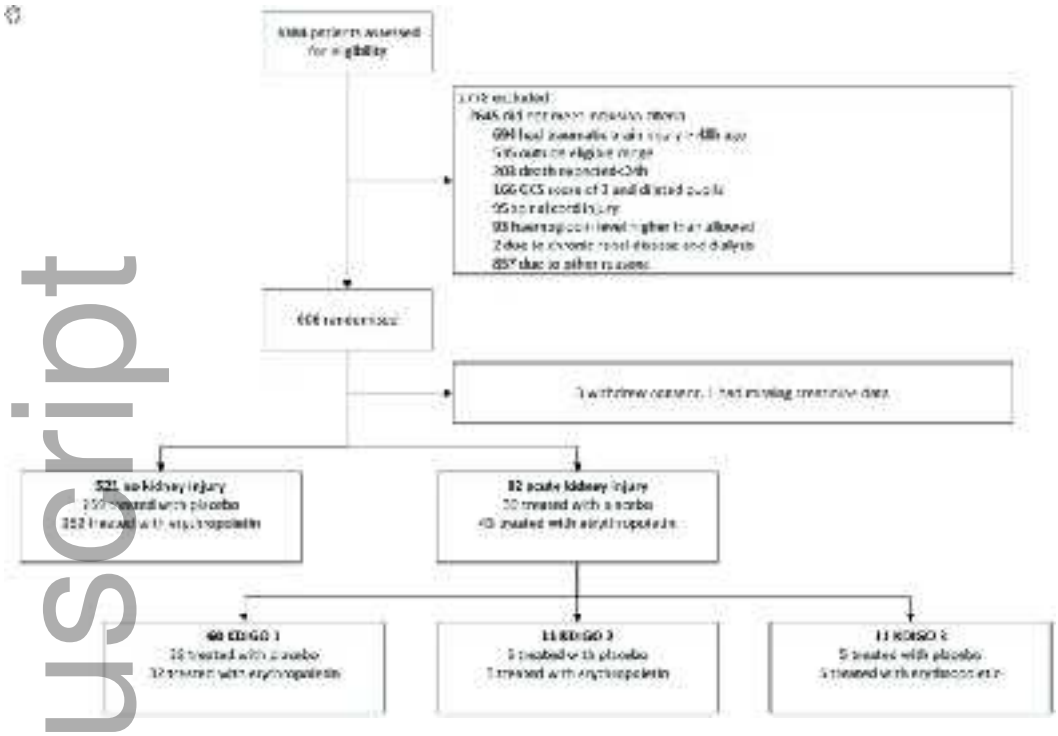

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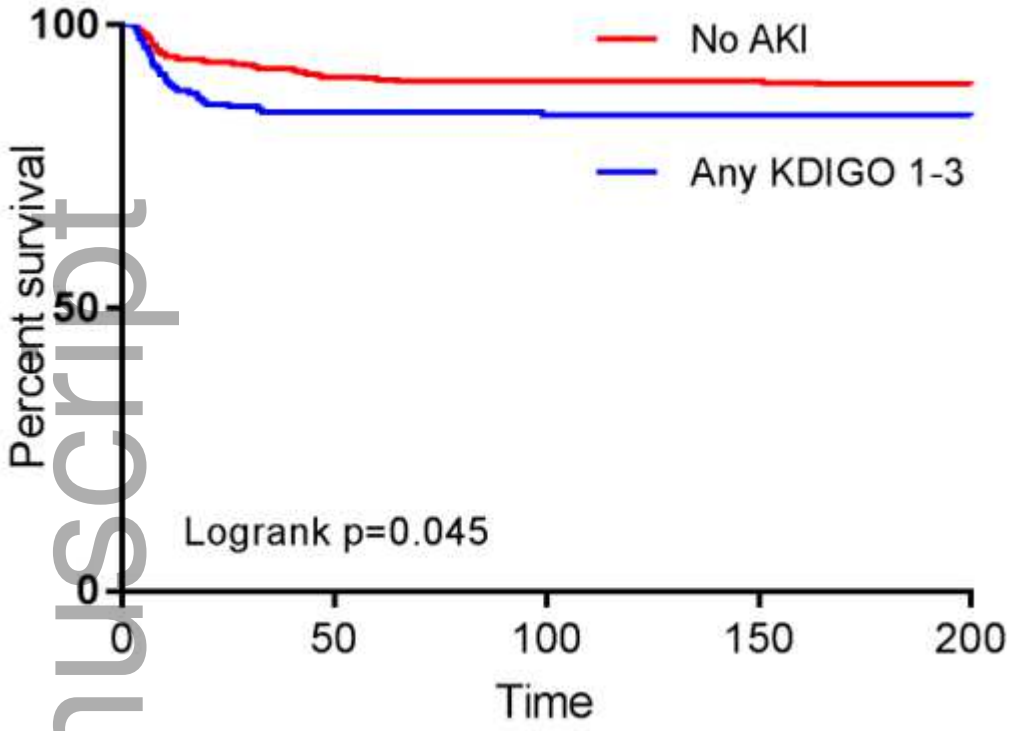

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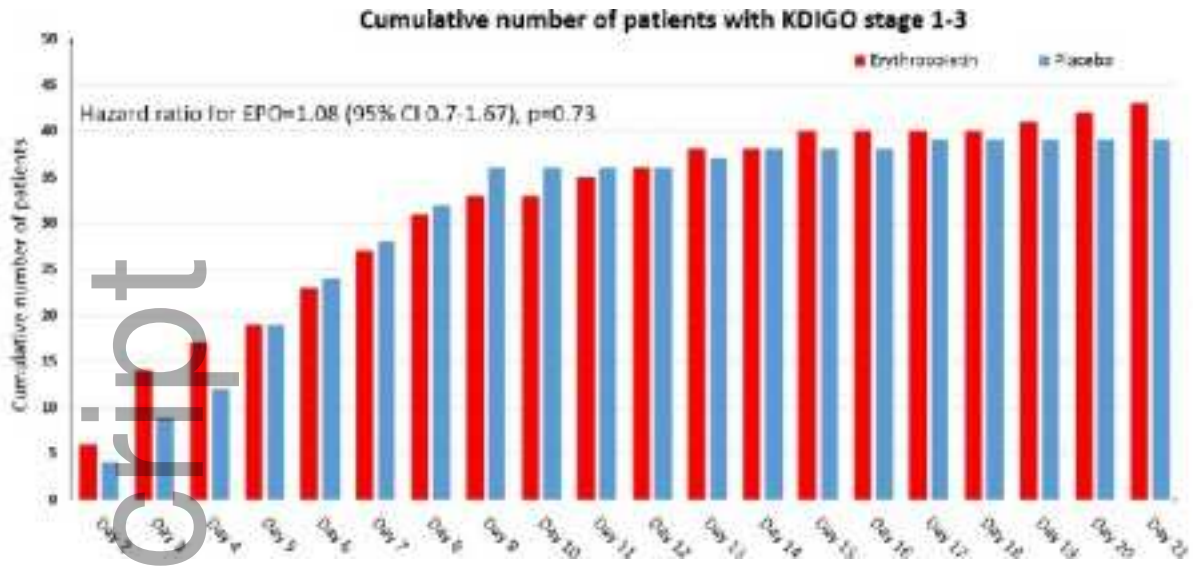

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