

## **TREATING ACUTE KIDNEY INJURY USING CONTINUOUS AND INTERMITTENT RENAL REPLACEMENT THERAPY**

### **ZBRINJAVANJE AKUTNOG BUBREŽNOG ZATAJENJA KONTINUIRANIM I INTERMITENTNIM POSTUPKOM**

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**Descriptors:** Acute kidney injury – therapy; Renal replacement therapy – methods

**Summary.** Acute kidney injury (AKI) is the sudden kidney excretory function loss. Patient data of patients hospitalized on intensive care unit from 2009 to 2011 and had to undergo one sort of renal replacement therapy (RRT) – continuous or intermittent – was used. 63 patients were in this study, 46 on continuous RRT (CRRT) and 17 on intermittent RRT (IRRT). The aim was to analyze connection between RRT method and outcome, DM type 2 and outcome, malignant disease and outcome, to analyze whether there is statistically significant difference between these and other parameters (potassium, urea, creatinine, blood pressure, age, and sex). Outcome was momentary survival – whether patient did or didn't survive. Results have shown that mortality rate was higher at patients on CRRT. However, these patients were haemodynamically unstable compared to patients on IRRT.

**Deskriptori:** Akutno zatajenje bubrega – liječenje; Bubrežno nadomjestno liječenje – metode

**Sažetak.** Akutno zatajenje bubrega (AZB) nagli je gubitak ekskretorne funkcije bubrega. Analizirani su podatci bolesnika koji su bili hospitalizirani u jedinici intenzivnog liječenja od 2009. do 2011. godine, kod kojih je došlo do razvoja AZB-a i čije je stanje bilo takvo da je zahtijevalo primjenu jedne od mehaničkih metoda liječenja AZB-a – kontinuiranu ili intermitentnu. Obuhvaćena su 63 bolesnika, 46 na kontinuiranoj metodi, 17 na intermitentnoj. Cilj je bio analizirati povezanost između metode liječenja i ishoda, šećerne bolesti tipa 2 i ishoda, maligne bolesti i ishoda, analizirati postoji li statistički značajna razlika između tih i ostalih parametara (kalij, urea, kreatinin, krvni tlak, dob, spol). Ishod je bio trenutačno preživljenje – je li bolesnik preživio ili nije. Rezultati su pokazali da je stopa mortaliteta veća kod bolesnika na kontinuiranoj metodi. Ipak, ti su bolesnici bili hemodinamski nestabilniji u usporedbi s bolesnicima na intermitentnoj metodi.

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Acute kidney injury (AKI) is the sudden loss of an excretory kidney function of previously healthy kidneys which cannot be fixed through regulating an extrarenal factors.<sup>1</sup> It is most often presented with increased serum concentrations of creatinine and urea and oliguria (diuresis below 400 mL per day), although oliguria doesn't have to be present (diuresis can be 600 mL or more per day).<sup>2</sup> AKI can occur because of circulation disorders, intrinsic kidney damage or urinary tract obstruction. Therefore, it can be divided into prerenal, renal or intrarenal and postrenal kidney injury. Most common cause of acute renal injury is acute tubular necrosis.<sup>3</sup>

Prerenal kidney injury with functional oliguria is featured by reduced glomerular filtration and increased tubular reabsorption of water and salt. In prerenal AKI, tubules are not yet damaged and can react to antidiuretic hormone and aldosterone.<sup>2</sup> Therefore, urine is typically changed; osmolality is increased, urea/creatinine plasma ratio is increased and urine sodium concentration is reduced.<sup>4</sup>

Oliguria in acute tubular necrosis is featured by reduced tubular function. Urine osmolality becomes more similar to plasma osmolality and is lower than 350 mmol/kg.

Electrolytic disbalance often occurs.<sup>2</sup> Hyponatremia is caused by reduced excretion of water. Intrarenal form of AKI is featured by increased sodium concentration in the urin.<sup>5</sup> Hyperkalemia is caused by reduced potassium excretion, increased katabolism, acidosis and hypoxia. Mem-

brane potential disorders are more expressed when hyperkalemia occurs more rapid.

Acidosis occurs due to reduced hydrogen ions excretion. Their concentration is further increased by sulphate, phosphate and organic anions which are released through cell katabolism.

Reduced renal excretory function leads to cummulation of nitrogenous waste products, urea and creatinine, in blood. This state is called azotemia. Creatinine concentration increase depends on state of muscle katabolism and is very expressed in AKI caused by rhabdomyolysis.

Cardiovascular system is compromised due to hypervolaemia and water and salt retention.<sup>6</sup> Hyperkalemia can cause arrhythmia.

Neurological disorders include central and peripheral nervous system and are caused by uremic toxins, electrolytic disbalances and metabolic acidosis.<sup>2</sup>

Treating AKI can be done in two ways, using renal replacement therapy (RRT) or using drug treatment.

RRT includes haemodialysis and haemofiltration. Haemodialysis is a process where patient's blood is pumped through an array of membranes. This method is known as

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intermittent RRT. Through those membranes, blood comes into contact with dialysate which flows in the opposite direction of blood. Because of diffusion and concentration gradient, plasma components change.

Haemodialysis is adjusted in order to get efficient excretion of nitrogenous waste products and to avoid hypervolaemia between the procedures. Average height adult is undergone to procedure usually three times a week four to five hours per procedure.<sup>7</sup> Twice a week dialysis is to be performed only if patient has sufficient renal function.

Table 1. Patient age  
Tablica 1. Dob bolesnika

	Method / Metoda					
	CRRT		IRRT			
	Median Srednja	Min.	Max. Maks.	Median Srednja	Min.	Max. Maks.
Age (years) Dob (godine)	68.00	30.00	89.00	62.00	18.00	89.00

Table 2. Sex and distribution by method  
Tablica 2. Spol i distribucija prema metodi

		Sex / Spol		Total Ukupno	
		Male Muški	Female Ženski		
Method Metoda	CRRT	N	30	16	46
		% of method % metode	65.2%	34.8%	100.0%
		% of total % ukupnog	47.6%	25.4%	73.0%
	IRRT	N	10	7	17
		% of method % metode	58.8%	41.2%	100.0%
		% of total % ukupnog	15.9%	11.1%	27.0%
Total Ukupno	N	40	23	63	
	% of method % metode	63.5%	36.5%	100.0%	
	% of total % ukupnog	63.5%	36.5%	100.0%	

Table 3. Outcome comparison between methods  
Tablica 3. Usporedba ishoda između metoda

		Outcome / Ishod		Total Ukupno	
		Survived Preživjeli	Died Umri		
Method Metoda	CRRT	N	22	24	46
		% of method % metode	47.8%	52.2%	100.0%
		% of total % ukupnog	34.9%	38.1%	73.0%
	IRRT	N	14	3	17
		% of method % metode	82.4%	17.6%	100.0%
		% of total % ukupnog	22.2%	4.8%	27.0%
Total	N	36	27	63	
	% of method % metode	57.1%	42.9%	100.0%	
	% of total % ukupnog	57.1%	42.9%	100.0%	

All the patients who undergo dialysis also undergo an anticoagulant therapy, most often heparin, since blood clots in contact with artificial surfaces.

Main complication of the procedure is hypotension. Insufficient fluid and volume replacement, excessive fluid removal, venous tone disturbances, autonomous neuropathy and left ventricle insufficiency can contribute to its occurrence.

Haemofiltration means removing plasma water and its dissolved components (potassium, sodium, urea, creatinine) by using convective flow through »high-flux« semipermeable membrane and replacing it with components that fit to individual patient. This method is known as continuous RRT.

States of AKI where patients had to undergo RRT have mortality of 50 to 60%,<sup>8</sup> although according to some authors, it can be as high as 90%.<sup>9</sup>

Drug therapy includes volume replacement and diuretics, which can treat non-severe AKI. Still, careless volume replacement can cause pulmonary oedema, hypoxia, and need for mechanical ventilation.<sup>10</sup>

Table 4. Association between diagnosis of DM type 2 and outcome  
Tablica 4. Povezanost između dijagnoze DM tip 2 i ishoda

		DM		Total Ukupno	
		Yes Da	No Ne		
Method Metoda	CRRT	N	9	37	46
		% of method % metode	19.6%	80.4%	100.0%
		% of total % ukupnog	14.3%	58.7%	73.0%
	IRRT	N	3	14	17
		% of method % metode	17.6%	82.4%	100.0%
		% of total % ukupnog	4.8%	22.2%	27.0%
Total Ukupno	N	12	51	63	
	% of method % metode	19.0%	81.0%	100.0%	
	% of total % ukupnog	19.0%	81.0%	100.0%	

Table 5. Association between malignant disease and outcome  
Tablica 5. Povezanost između zloćudne bolesti i ishoda

		Malignant disease Zloćudna bolest		Total Ukupno	
		Yes/Da	No/Ne		
Method Metoda	CRRT	N	5	41	46
		% of method % metode	10.9%	89.1%	100.0%
		% of total % ukupnog	7.9%	65.1%	73.0%
	IRRT	N	3	14	17
		% of method % metode	17.6%	82.4%	100.0%
		% of total % ukupnog	4.8%	22.2%	27.0%
Total Ukupno	N	8	55	63	
	% of method % metode	12.7%	87.3%	100.0%	
	% of total % ukupnog	12.7%	87.3%	100.0%	

Table 6. Other parameters  
Tablica 6. Ostali parametri

	Method Metoda	N	Parameter value Vrijednost parametra	SD	T	p
Systolic pressure Sistolički tlak (mmHg)	CRRT	46	113.02	27.09	-2.829	0.006
	IRRT	17	135.41	29.98		
Diastolic pressure Dijastolički tlak (mmHg)	CRRT	46	56.04	16.49	-4.390	<0.001
	IRRT	17	77.24	18.35		
Potassium (mmol/L)	CRRT	46	5.00	1.49	1.120	0.267
	IRRT	17	4.55	1.18		
Urea (mmol/L)	CRRT	46	32.41	20.93	0.213	0.832
	IRRT	17	31.26	11.14		
Creatinine Kreatinin ( $\mu$ mol/L)	CRRT	46	505.54	364.57	-1.676	0.099
	IRRT	17	676.53	344.79		

Table 7. Correlation coefficients  
Tablica 7. Koeficijenti korelacije

Method Metoda	Outcome Ishod	Sex Spol	Malignant disease Zloćudna bolest	DM
r	0.310	0.059	-0.090	0.022
P	0.014	0.646	0.481	0.866
N	63	63	63	63

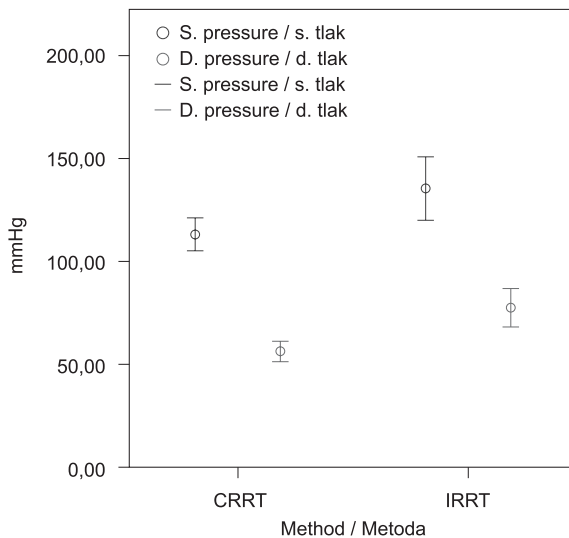


Figure 1. Blood pressure range

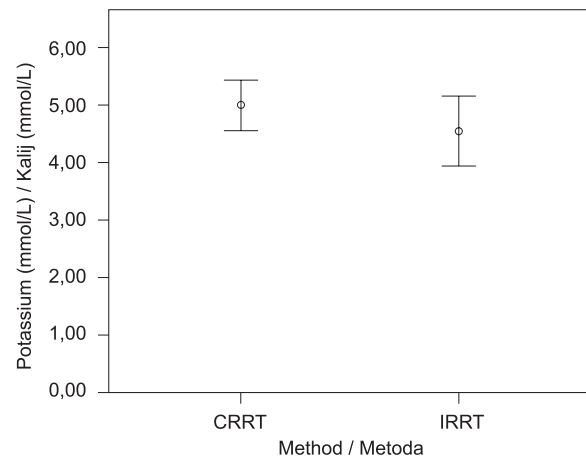
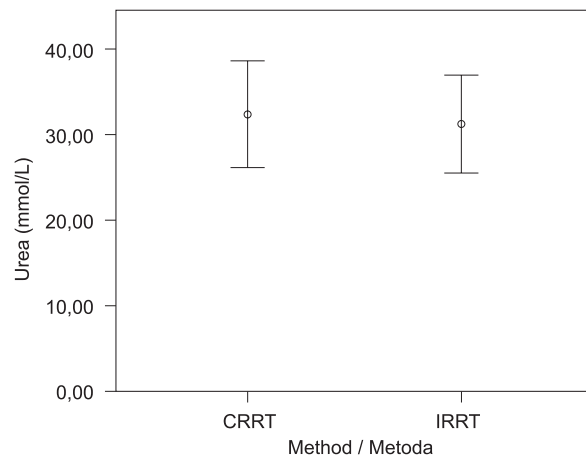
Slika 1. Raspon vrijednosti krvnog tlaka kod pacijenata

Therapy also depends on which level an injury has occurred.<sup>11</sup>

At prerenal AKI, rapid volume replacement is indicated since the kidneys are insufficiently perfused. As prerenal kidney injury can occur in combination with renal, patient should be closely monitored.

If the kidney injury occurred on the intrarenal level, patient should be kept alive until kidney recover spontaneously.

Postrenal kidney injury is most often treated surgically, by removing the obstruction.

Figure 2. Serum potassium concentration range  
Slika 2. Raspon koncentracija kalija u serumu pacijenataFigure 3. Serum urea concentration range  
Slika 3. Raspon koncentracija uree u serumu pacijenata

The aim of this study was to analyze association between RRT method and outcome, between existence of DM type 2 and outcome, between existence of malignant disease and outcome, to analyze whether there is statistically significant difference between these parameters and to analyze if there

is statistically significant difference between other parameters (potassium, urea, creatinine, blood pressure, age, and sex). Outcome was momentary survival – whether patient did or didn't survive.

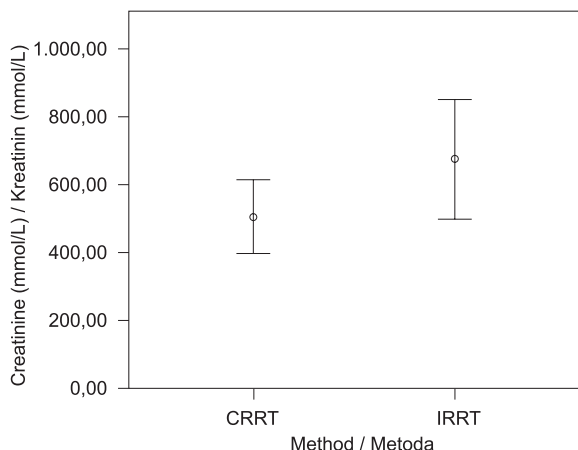


Figure 4. Serum creatinine concentration range  
Slika 4. Raspon koncentracija kreatinina u serumu pacijenata

**Patients and methods**

In this retrospective study, made on Clinical Hospital Centre Zagreb, patient histories data of those patients who were hospitalized on intensive care unit of Clinical Hospital Centre Zagreb from 2009 to 2011 and had to undergo one sort of RRT – continuous (CRRT) or intermittent (IRRT) – was used. Altogether there were 63 patients in this study, 46 on CRRT (group 1), 17 on IRRT (group 2). Data taken for the analysis were potassium, creatinine and urea serum concentrations and systolic and diastolic blood pressure at the moment prior to the start of RRT. Age, sex, AKI etiology, history of diabetes mellitus type 2 (DM type 2) and malignant disease were also obtained.

Excluded from this study were patients with chronic renal failure which was not in exacerbation, patients with terminal state malignant disease and patients who died within 24 hours upon admission.

The aim of this study was to analyze the association between RRT method and outcome (methods comparison), to analyze if there is outcome difference when patient was diagnosed with DM type 2, to analyze if there is outcome difference when patient was diagnosed with malignant disease, to analyze if there is statistically significant difference between other parameters (potassium, urea, creatinine, blood

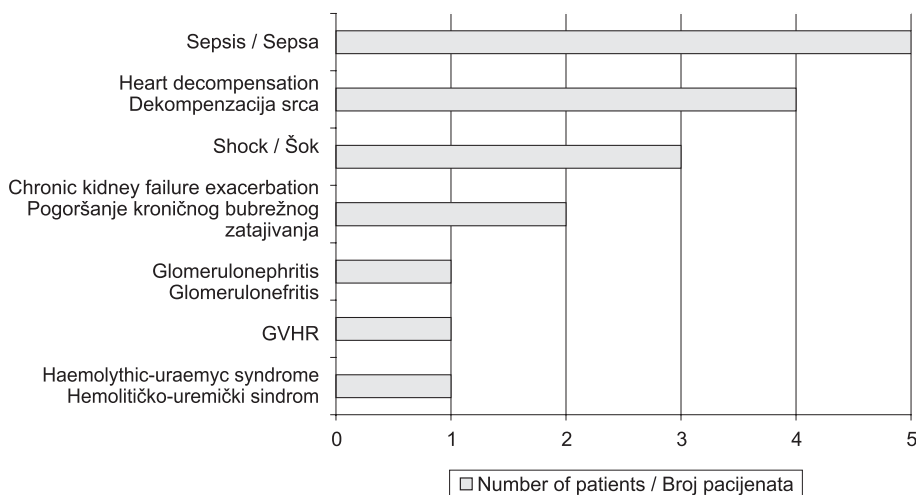


Figure 5. Kidney injury etiology at patients on CRRT. GVHR: Graft versus host reaction

Slika 5. Etiologija bubrežnog zatajenja kod pacijenata na kontinuiranoj metodi. GVHR: Graft versus host reaction

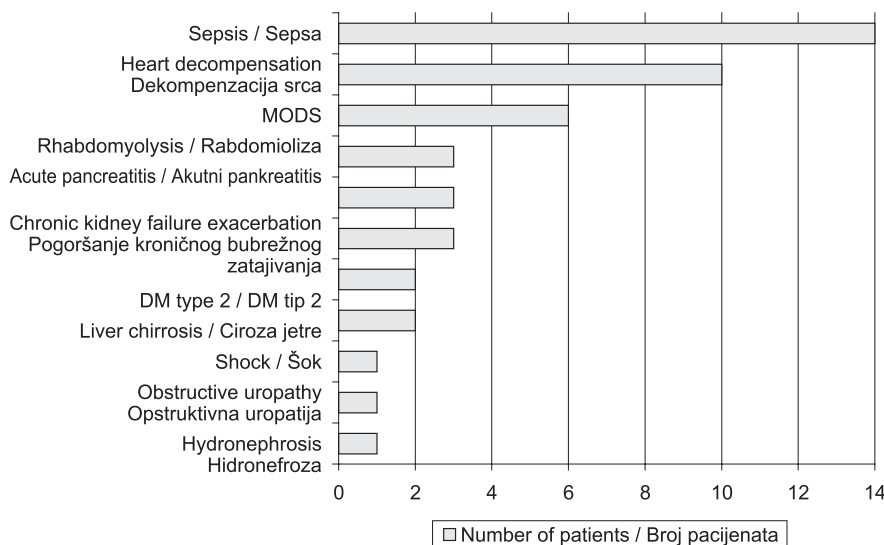


Figure 6. Kidney injury etiology at patients on IRRT. MODS: Multiple organ dysfunction syndrome

Slika 6. Etiologija bubrežnog zatajenja kod pacijenata na intermitentnoj metodi. MODS: Multiple organ dysfunction syndrome

pressure, age, sex). Outcome was momentary survival – whether patient did or did not survive.

Data was analyzed by statistical procedures for testing differences and correlations using SPSS 17 (IBM, Somers, New York) and MedCalc Software 12.2.1 (Mariakerke, Belgium).

Normal distribution of continuous variable was when diaphragmatic and rounded distribution was less than 1. Distribution regularity was checked using Smirnov-Kolmogorov test. Nominal parameters were shown in form of groups and ratios. Student T-test was used to determine the differences between two independent samples of regular distribution. Mann-Whitney U-test was used to determine differences between two independent samples of irregular distribution.  $\chi^2$ -test was used to determine differences between proportions between two independent samples. Spearman  $\rho$ -test for nonparametrical analysis was used to determine correlation between samples. Statistical significance was accepted with  $p < 0.05$ .

### Results

Table 1. There was no age difference, groups were comparable ( $Z = -1.410$ ;  $p = 0.159$ ).

Table 2. There was no statistically significant difference between sex ( $\chi^2 = 0.219$ ;  $p = 0.640$ ).

Table 3. There is statistically significant difference between correlation of method and outcome. Mortality rate was higher at patients who underwent CRRT. ( $\chi^2 = 6.041$ ,  $p = 0.014$ ; OR = 5.09 (95% CI 1.288 – 20.128),  $p = 0.020$ ).

Table 4. There was no association between diagnosis of DM type 2 and RRT outcome ( $\chi^2 = 0.03$ ;  $p = 0.863$ ).

Table 5. There was no association between diagnosis of malignant disease and RRT outcome ( $\chi^2 = 0.514$ ;  $p = 0.473$ ).

Table 6. There is statistically significant difference between systolic and diastolic pressure between the two patient groups.

Table 7. The only correlation was between outcome and method with small correlation coefficient ( $r$ ). The more often CRRT was used, the more often patient outcome was lethal.

Figure 1. Blood pressure range. S. pressure: Systolic pressure. D. pressure: Diastolic pressure.

Figure 2. Serum potassium concentration range.

Figure 3. Serum urea concentration range.

Figure 4. Serum creatinine concentration range.

Figure 5. Kidney injury etiology at patients on CRRT. GVHR: Graft versus host reaction.

Figure 6. Kidney injury etiology at patients on IRRT. MODS: Multiple organ dysfunction syndrome.

### Discussion

AKI is clinical state characterized by rapid kidney function deterioration, which is determined by measuring the excreted urine and serum concentrations of urea and creatinine. It occurs at 10 to 23% of patients hospitalized on intensive care unit.<sup>9</sup>

CRRT and IRRT are efficient and safe treatment. Theoretical advantages of CRRT are better haemodynamic stability and easier fluid removal.<sup>12</sup> Prolonged duration of AKI or necessity for RRT application are connected with bad prognosis.

AKI is mostly, but not always, reversible and lasts seven days to three weeks.<sup>13</sup> It can last longer if the cause is intrarenal, if acute tubular necrosis occurred or if patient is in

sepsis.<sup>14</sup> States of AKI where patients had to undergo RRT have mortality of 50 to 60%,<sup>8</sup> although according to some authors, it can be as high as 90%.<sup>9</sup>

According to current data from most studies about comparing RRT, there are no differences when it comes to patient survival.<sup>9,12,15–18</sup>

In this study, correlation between outcome and method with not significant correlation coefficient was determined, or, the more often CRRT was used, the more often patient outcome was lethal. There was statistically significant difference among the two groups of patients in systolic and diastolic blood pressure. Both blood pressure values were lower in group 1 (CRRT) than in group 2 (IRRT). A conclusion can be drawn that patients in group 1 were haemodynamically more unstable and therefore had the higher risk for lethal outcome. Should all the patients from group 1 who had diastolic blood pressure lower than 60 mmHg be excluded from the group, number of patients in both groups would have been the same, seventeen, and only six patients in group 1 would have had a lethal outcome.

Statistically significant difference between age and sex between the two groups of patients was not observed in this study. Differences between potassium, urea and creatinine serum concentrations prior to the start of RRT were not statistically significant between the two groups of patients. Correlation between diagnosis of DM type 2 or malignant disease and RRT outcome was not observed.

Swartz et al. came to similar conclusions in their study. According to them, higher patient mortality on CRRT was connected with disease severity, not with the choice of RRT as such.<sup>19</sup>

One group of authors established a hypothesis that patients who underwent CRRT could have some not yet detected morbidity.<sup>15</sup>

One of the criteria for comparison were costs of the procedure. Farese et al. came to conclusion that CRRT is more expensive compared to IRRT and that hospital personnel have to spend more time next to patient when patient is on CRRT.<sup>20</sup>

What could affect data in this study is how data were collected. It didn't run all that well as many patient histories of potential candidates were unable to be found. Furthermore, number of patients on IRRT is almost three times less compared to ones who were on CRRT.

### Conclusion

Results have shown that mortality rate was higher at patients who were on CRRT (group 1). But, it was also shown that these patients were haemodynamically unstable compared to patients who were on IRRT (group 2). Since there was no statistically significant difference between other parameters – serum potassium, urea and creatinine – it suggests that in order to compare the two methods more accurately, only patients with similar haemodynamic status should be enrolled in the study.

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Članak »Treating acute kidney injury using continuous and intermittent renal replacement therapy« napisan je na temelju rezultata rada koji su objavljeni kao poster na 7. međunarodnom kongresu mladih liječnika i studenata medicine ZIMS 2012, a koji je održan od 14. do 17. studenoga 2012. u Zagrebu u prostorijama HLZ-a. Znanstveni odbor kongresa koji je organizirala studentska sekcija HLZ-a, predložio je uredničkom odboru »Liječničkog vjesnika« objavljivanje cjelovitog teksta, a nakon pozitivnih recenzija članak je prihvaćen za publiciranje. Budući da je tekst izvorno upućen znanstvenom odboru na engleskom jeziku, urednički je odbor odlučio da tekst ostane u izvornom obliku na kojem je napisan.

Mentor rada bio je prof. dr. sc. Vladimir Gašparović iz Klinike za unutrašnje bolesti Medicinskog fakulteta KBC-a Zagreb, a doc. dr. sc. Radovan Radonić pomogao je autoru savjetima tijekom pisanja.

Urednički odbor »Liječničkog vjesnika« čestita autoru na trudu i vrijednom radu te mu želi puno uspjeha u daljnjem stručnom i znanstvenom razvoju i radu.



## Vijesti News

HRVATSKI LIJEČNIČKI ZBOR  
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### DEVETI HRVATSKI KONGRES O ATEROSKLEROZI s međunarodnim sudjelovanjem

**u Rovinju, hotel Lone od 9. do 11. svibnja 2013. godine**

*Glavne teme Kongresa:* Epidemiologija koronarne i cerebrovaskularne bolesti; dislipidemije u odraslih i djece i njihovo liječenje; šećerna bolest, pretilost i metabolički sindrom; arterijska hipertenzija; upala i ateroskleroza; prehrana i rizik ateroskleroze; način života i kardiovaskularne bolesti; estrogeni, menopauza i hormonsko nadomjesno liječenje; zatajenje srca; angiografija, ultrazvuk, CT, MR u procjeni ateroskleroze; nuklearna kardiologija; perkutana angioplastika, stentovi itd.; antiagregacijsko i trombolitičko liječenje; kirurško liječenje ateroskleroze koronarnih arterija; kirurško liječenje ateroskleroze perifernih žila; ateroskleroza i cerebrovaskularna bolest.

**Krajnji rok za primitak sažetaka je 15. ožujak 2013. godine.**

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