

Renal Replacement therapy in the ICU



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Dr. H. Sudarshan Ballal. M.D.FRCPP
Chairman – Medical Advisory Board &
Medical Director
Manipal Health Enterprises Pvt Ltd
Manipal Hospitals, Bangalore



Outline



- AKI in the ICU
- Principles of RRT
- Modes of RRT
- Indications for RRT
- Optimal timing: When to start
- Optimal modality: What Modality and Where ??
- Optimal dosing- How Much?
- Summary and Conclusions



AKI in the ICU

AKI in the ICU



- AKI is common in the ICU
- Depending on definition of AKI, up to 50-60% of patients in the ICU have AKI
- Up to 70% of these will require RRT
- Independent risk factor for mortality: 50 - 60% mortality in critically ill

AKI in the ICU

Mortality remains unchanged

CRRT-Associated Mortality in Major RCTs

Clinical Trial	Comparison	APACHE II	Endpoint	Mortality
Ronco et al (2000)	CRRT Dose	22	15-day ²	59% ³
Mehta et al (2001)	IHD vs CRRT	25.5	Hospital	66%
Augustine et al (2004)	IHD vs CRRT	-	Hospital	68%
Saudan et al (2006)	CRRT Dose	25	90-day	66% ³
Vinsonneau et al (2006)	IHD vs CRRT	25	60-day	68%
Lins et al (2008)	IHD vs CRRT	27	Hospital	58%
Tolwani et al (2008)	CRRT Dose	26	Hospital	60% ³
ATN Trial (2008)	Dialysis Dose	26.3	60-day	52.5% ⁴
RENAL Trial (2009)	CRRT Dose	~26 ¹	90-day	45%

AKI in the ICU



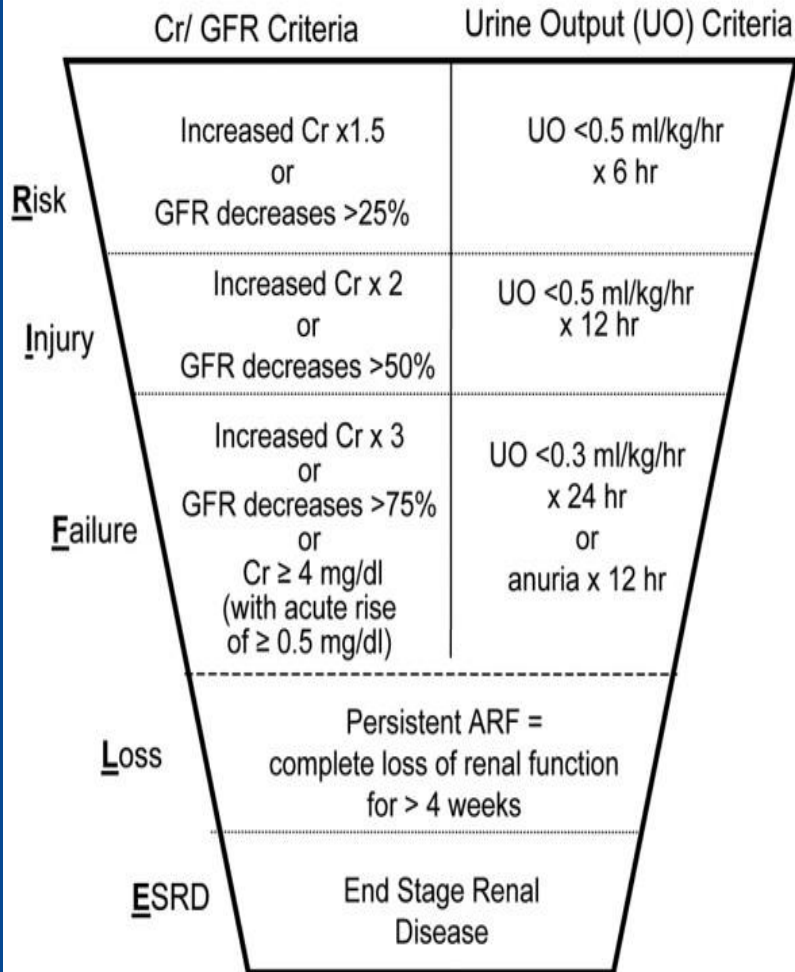
Treatment success or Treatment failure ???



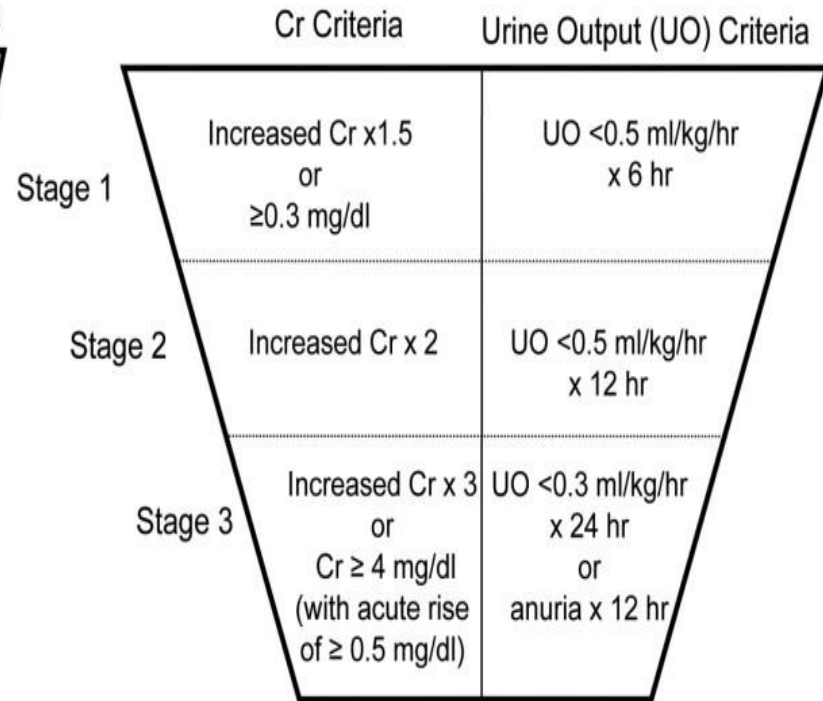
RIFLE and AKIN Classification for AKI



RIFLE



AKIN



Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT.

AKI in the ICU



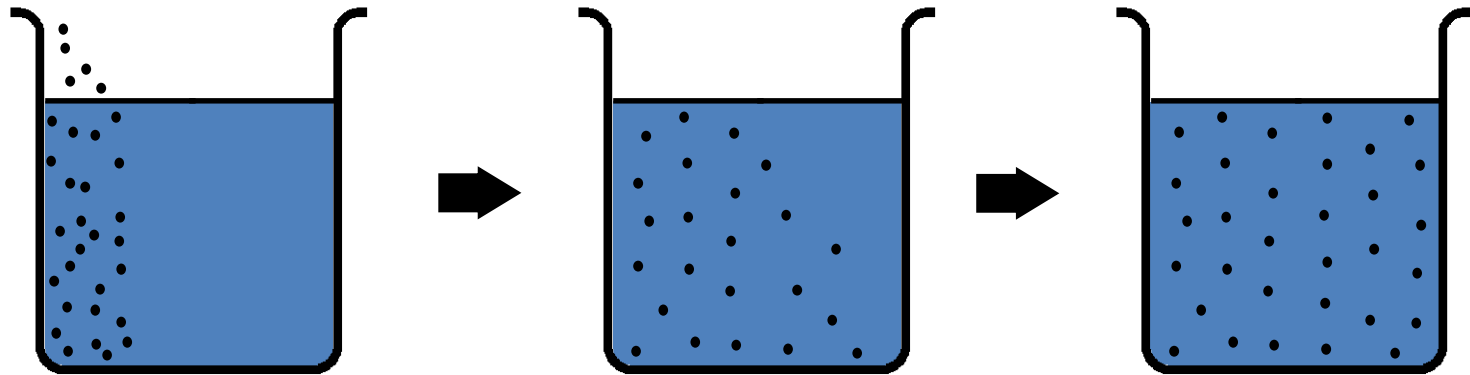
- Treatment of acute kidney injury (AKI) is principally supportive
- Renal replacement therapy (RRT) indicated in patients with severe kidney injury.
- Goal: optimization of fluid status ,maintain metabolic, nutritional & electrolyte balance
- Multiple modalities of RRT :
 - Intermittent hemodialysis (IHD),
 - Continuous Renal Replacement Therapies (CRRTs)
 - Peritoneal dialysis
 - Hybrid therapies, ie Sustained Low-Efficiency Dialysis (SLED), Renal assist device (RAD)



Principles of RRT

Diffusion

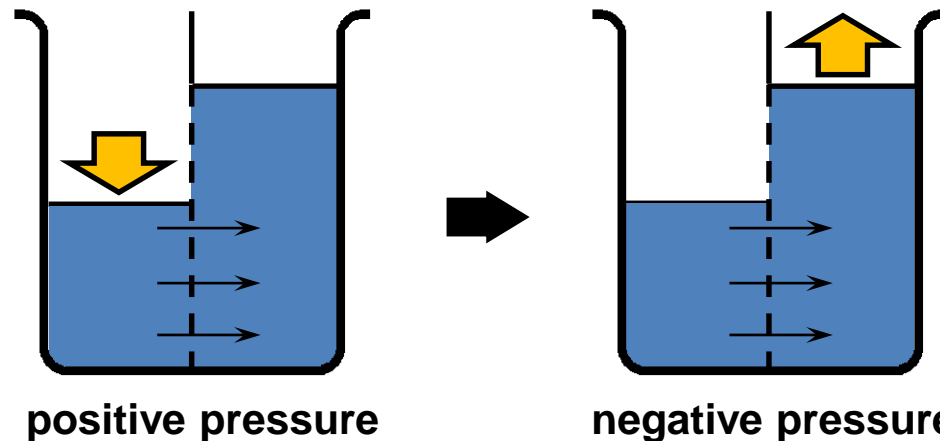
- Movement of Solutes from an area of **higher** concentration to an area of **lower** concentration
- Dialysis uses a semi permeable membrane for selected diffusion



Diffusion: The movement of solutes from a higher to a lower solute concentration area.

Ultrafiltration

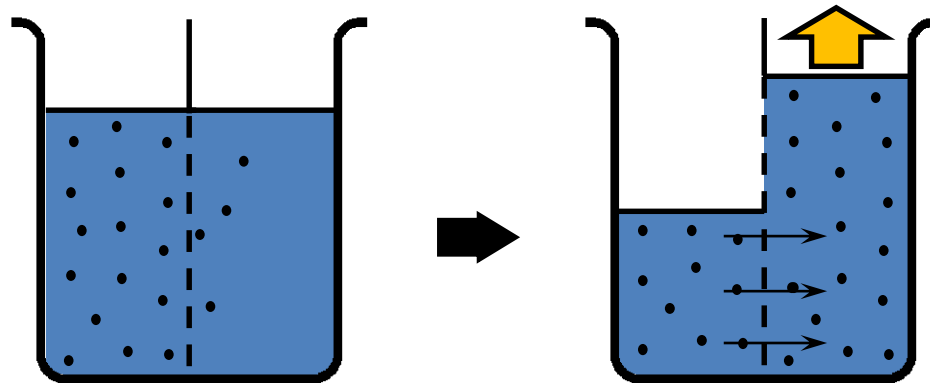
- Movement of **FLUIDS** through a membrane caused by pressure gradient
- Positive, negative and osmotic pressure from non-permeable solutes



Ultrafiltration: The movement of fluid through a membrane caused by a pressure gradient.

Convection

- Movement of **SOLUTES** with a water flow, “solvent drag”.



Convection: The movement of solutes with a water-flow, “solvent drag”, e.g., the movement of membrane-permeable solutes with ultrafiltered water.



Modes of RRT

Modes of RRT



- Intermittent hemodialysis (IHD)
- Continuous renal replacement therapy (CRRT)
- Peritoneal dialysis
- Hybrid therapies, like SLED , Renal tubule Assist device (RAD)

Intermittent hemodialysis (IHD)



- Oldest and most common technique
- Primarily diffusive treatment: blood and dialysate are circulated in countercurrent manner
 - Also some fluid removal by ultrafiltration due to pressure driving through circuit
- Best for removal of small molecules
- Typically performed 4 hours 3x/wk or daily

Continuous Renal Replacement Therapy



Defined as

- “Any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and applied for or aimed at being applied for 24 hours /day.”

Bellomo R., Ronco C., Mehta R, *Nomenclature for Continuous Renal Replacement Therapies*, AJKD, Vol 28, No. 5, Suppl 3, November 1996

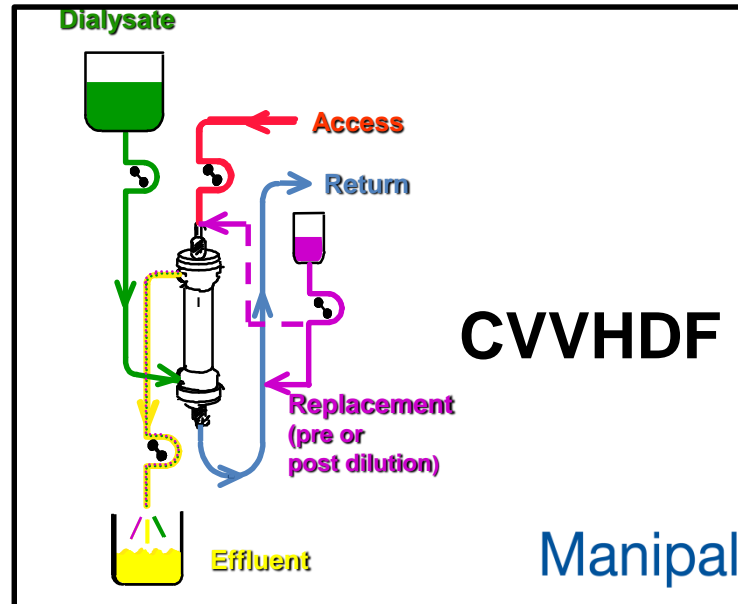
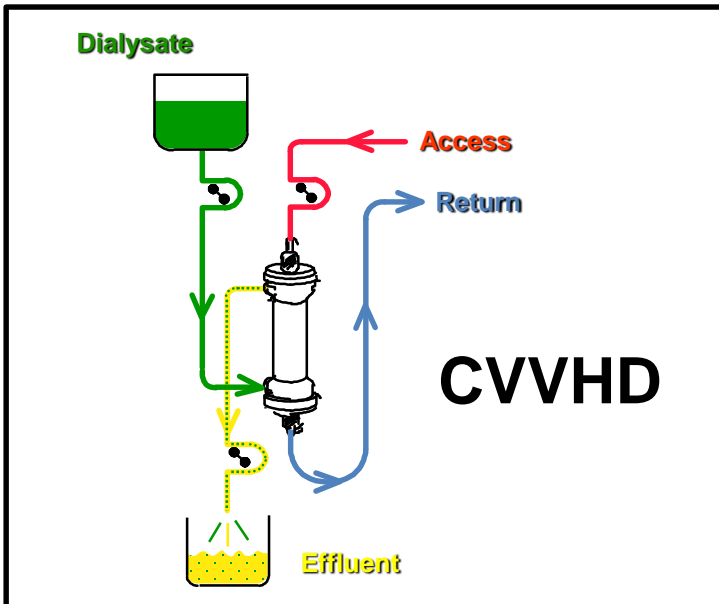
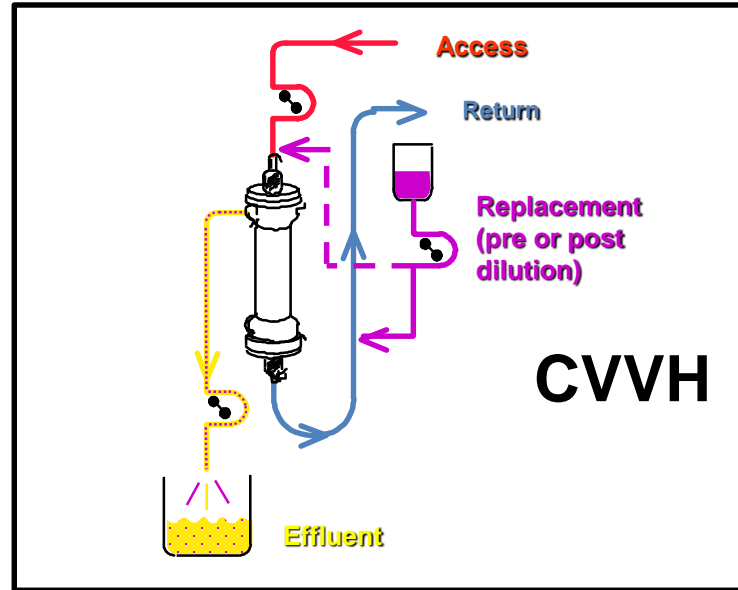
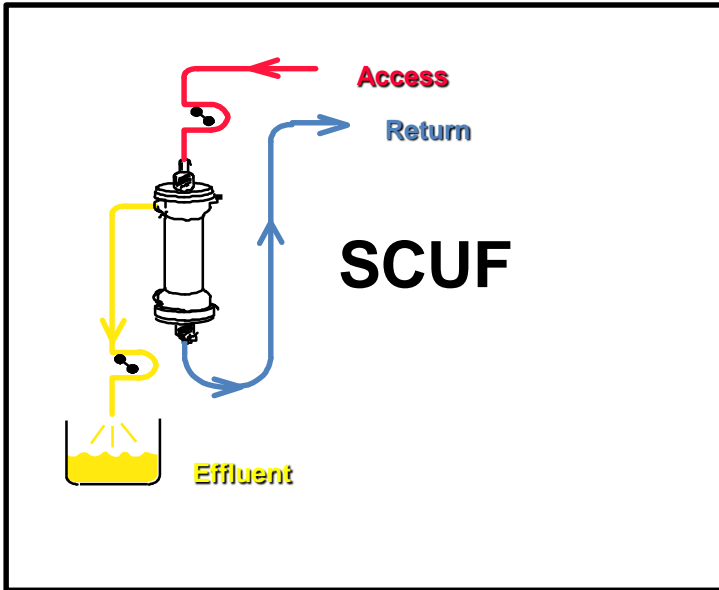
Introduction to CRRT



- Group of words
 - Continuous
 - Renal
 - Replacement
 - Therapy

- Describes a group of Therapies
 - SCUF
 - CVVH
 - CVVHD
 - CVVHDF

Summary





Sustained low-efficiency daily dialysis (SLEDD)

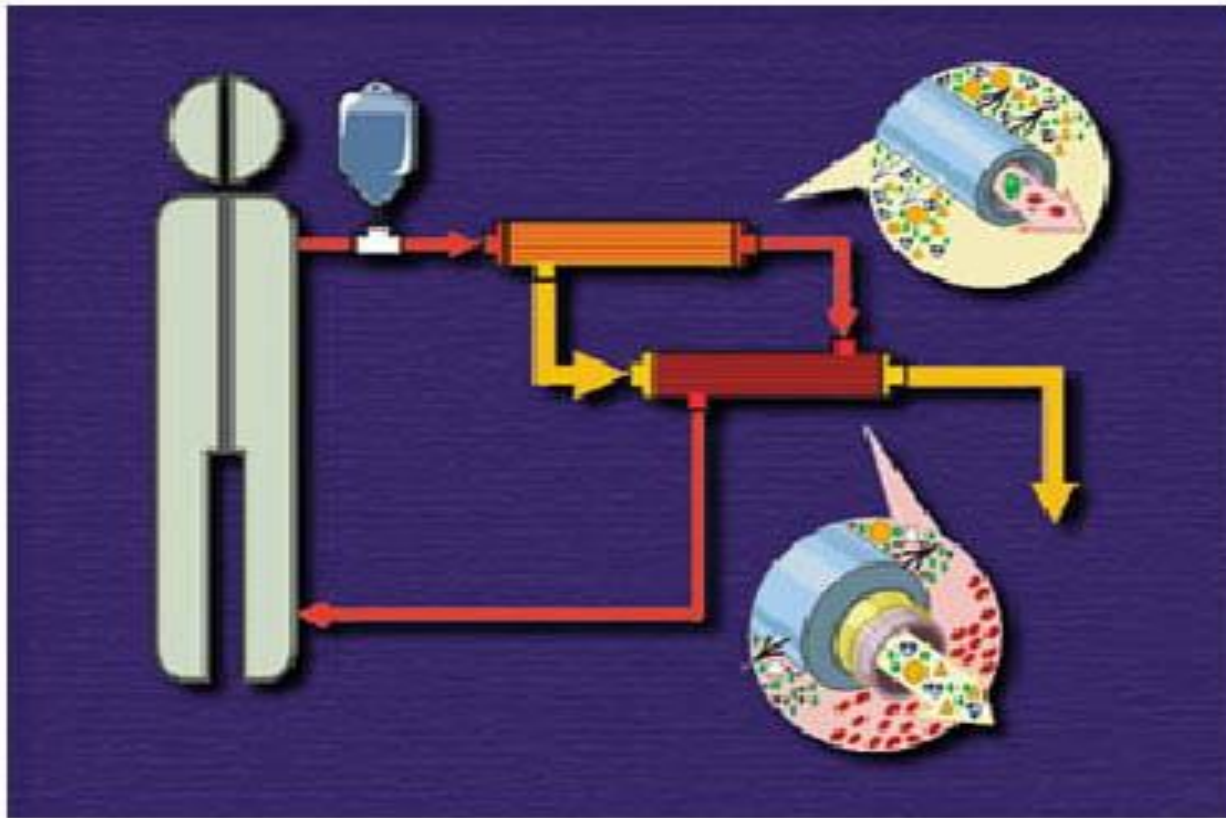
- Extended daily dialysis (EDD) or slow continuous dialysis (SCD)
- Hybrid therapy: IRRT at lower blood and dialysate flows for prolonged times (Usually ≥ 6 hrs)
- Uses conventional dialysis machines
- Flexibility of duration and intensity
- Major advantages: flexibility, reduced costs, low or absent anticoagulation

Renal Tubule Assist Device (RAD)



- Despite the ability of HD and PD to filter the blood of excess solutes and water, these therapies are **unable to mimic the normal kidney's ability to secrete vital endocrine and immunologic factors, reabsorb and metabolize.**
- A bioartificial kidney - uses a patient's own cells in an artificial structure - would fulfil functions unaddressed by current dialysis.**
- Currently under the research of Dr. David Humes is in clinical trials for ACUTE renal failure. The Renal Assist Device (RAD) hopes to carry out those functions neglected by simple hemofiltration, and improve the current mortality rate.

Renal Tubule Assist Device (RAD)



Light micrograph of a hematoxylin and eosin stained section of a hollow fiber with a confluent monolayer of porcine renal proximal tubule cells along the inner surface of the fiber.

Renal Assist Device' reduces risk of death from acute kidney failure

*Cell-filled device temporarily replaces renal tubule **function***

AMERICAN SOCIETY OF NEPHROLOGY

- 40 of 58 patients with AKI were randomly assigned to treatment with the RAD, in addition to standard renal replacement therapy.
- Outcomes were **significantly better** for AKI patients treated with the RAD. After one month, 33 percent of patients in the RAD group had died, compared to 61 percent of those treated with renal replacement therapy only.
- Patients who received the RAD were also more likely to be alive after six months. The **risk of death was about 50 percent lower in the RAD group.**
- Patients in the **RAD group also had a shorter time to return of kidney function.** Overall, kidney function recovered in 53 percent of patients with RAD, compared to 28 percent without RAD. In both groups, about 20 percent of patients survived but never recovered kidney function, requiring chronic dialysis.



Indications for RRT

Indications for RRT

1. Renal Replacement :

Acute management of life-threatening complications of AKI:

- **A:** Metabolic acidosis (pH less than 7.1)
- **E:** Electrolytes -- Hyperkalemia (K >6.5 meq/L) or rapidly rising K)
- **I:** Ingestion -- Certain alcohol and drug intoxications
- **O:** Refractory fluid overload
- **U:** Uremia, ie. pericarditis, neuropathy, decline in mental status

2. Renal Support: RRT even before any of the complications arise



Timing of initiation of RRT



Timing of CRRT

- This is a very important issue and traditionally dialysis is started when standard indications for dialysis like volume overload or solute removal become necessary.
- However recent data suggests that early initiation of CRRT improves patient outcome

Timing of RRT Initiation: Effect on Outcome

Payen et al, Crit Care 2008

Table 5

Characteristics of patients with acute renal failure, stratified by time of initiation of renal replacement therapy (RRT)

Characteristic	Early RRT n = 213	Late RRT n = 65	P value
Age	62.3 ± 15.5	64.6 ± 15.0	0.30
Male gender	126 (59.4)	44 (68.8)	0.18
SAPS II	49.7 ± 17.5	45.3 ± 18	0.04
SOFA score	9.2 ± 4.1	8.2 ± 3.5	0.04
Mechanical ventilation	166 (77.9)	61 (93.8)	<0.01
Type of admission			
Medical	87 (40.8)	38 (58.5)	0.01
Surgical	126 (59.2)	27 (41.5)	0.01
Urine output, L/24 hours	0.18 (0.03–0.50)	0.47 (0.09–1.74)	<0.001
Creatinine, mg/dL	3.99 (2.57–6.17)	3.29 (2.10–5.00)	0.06
ICU stay, days	6.1 (2.5–14.8)	12.2 (8.0–26.5)	<0.001
Hospital stay, days	25.0 (8.0–46.0)	27.0 (17.0–45.0)	0.10
ICU mortality, number (percentage)	84 (39.4)	40 (61.5)	<0.01
60-day mortality, number (percentage)	94 (44.8)	42 (64.6)	<0.01

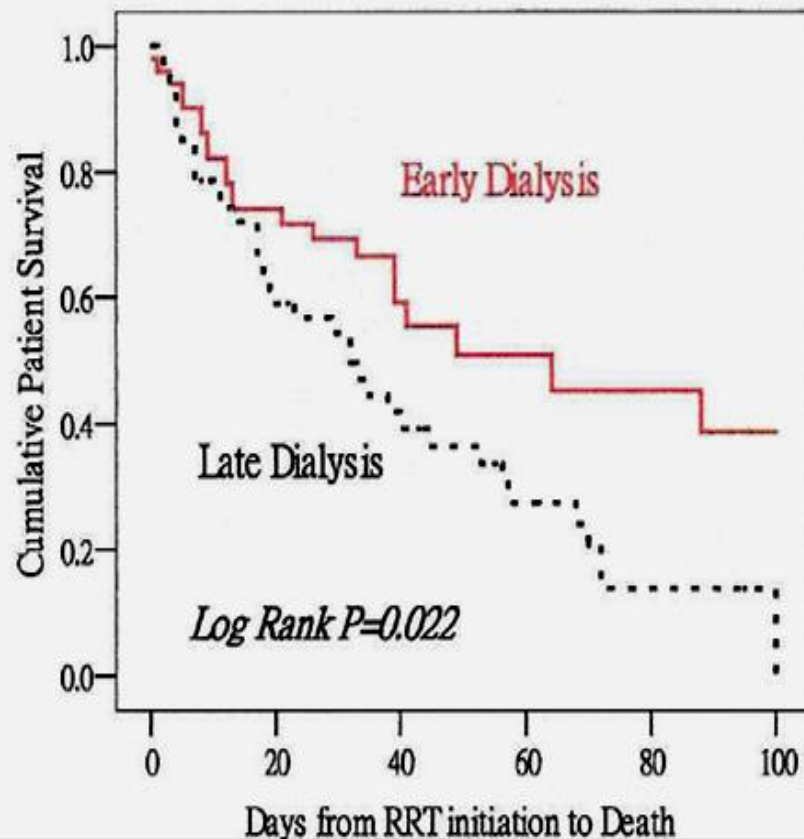
Data represent mean ± standard deviation, number (percentage), or median (interquartile range). ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II; SOFA, sequential organ failure assessment.

Early vs Late RRT Initiation According to RIFLE

Shiao et al, Crit Care 2010



Figure 2





Optimum Modality

Continuous

VS

Intermittent dialysis

Continuous vs Intermittent dialysis



- Ongoing debate
- Theoretical benefits to both
- At least 7 RCTs and 3 meta-analyses have not demonstrated difference in outcome
 - Meta analysis of 9 randomized trials: No effect on mortality (OR 0.99) or recovery to RRT independence (OR 0.76). Bagshaw et al *Crit Care Med* 2008, 36:610-617
 - Suggestion that continuous RRT had fewer episodes of hemodynamic instability and better control of fluid balance
- May be preferable in specific subpopulations

Pro-continuous RRT



- **Better preservation of cardiovascular function** and maintenance of hemodynamic stability
- **Prevents the surge in intracranial pressure** associated with intermittent therapies- hence useful in neurosurgical patient and acute liver failure.
- **Effective in clearance of middle molecules**
- **Useful in removal of immunomodulatory substances** in sepsis like endotoxin, interleukin-1, etc
- **Permits protein rich nutritional support** with a neutral nitrogen balance preventing protein malnutrition
- **Clinical benefits**
 - ? Better survival
 - ? Better renal recovery



Pro-continuous RRT

- **Specific patient populations who may benefit from CRRT**
 - Hemodynamic instability
 - Combined acute renal and hepatic failure
 - Improved CV instability and intracranial pressure
 - Acute brain injury
 - Decreased cerebral edema



Pro-intermittent RRT

- **Practicality and flexibility**
 - Uses same machines as chronic HD
 - Multiple pts per day
 - Easier to mobilize pts
- **Less expensive than CRRT (by about ½)**
- **Fewer bleeding complications**
 - CRRT requires continuous anticoagulation
- **Less filter clotting**
- **Superior solute clearance**, more rapid removal of toxins (due to higher flows)



Pro-intermittent RRT

- **Specific patient populations benefitting from IRRT:**
 - High bleeding risk
 - ie. after recent surgery
 - Acute treatment of hyperkalemia, rhabdomyolysis, poisoning, tumor lysis syndrome



Is SLEDD the answer?

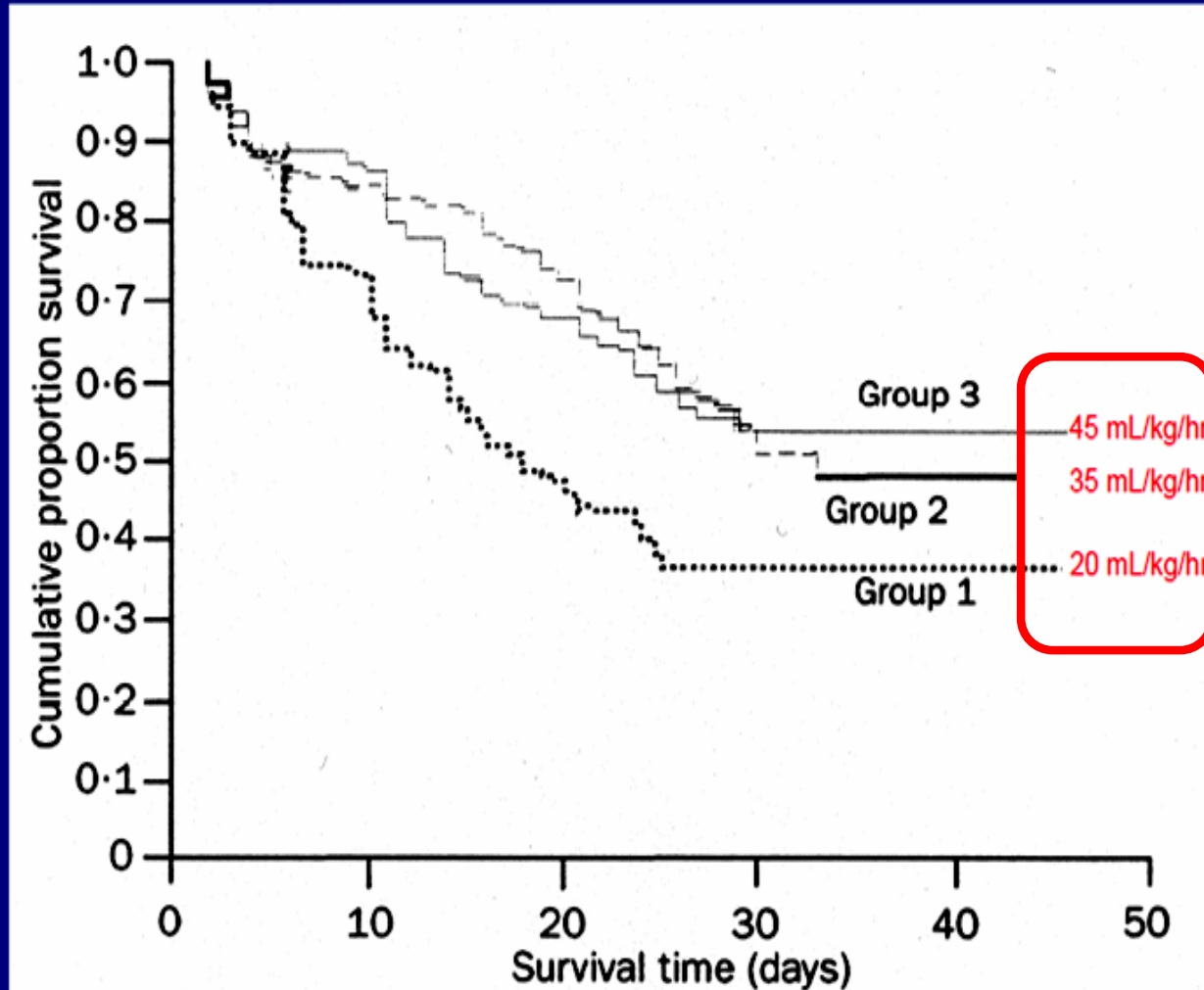
- Hybrid therapy with flexibility of duration and intensity
- SLEDD vs CRRT
- Major advantages: flexibility, reduced costs, low or absent anticoagulation
- Similar adequacy and hemodynamics
 - One small study showed slightly higher acidosis and lower BP (Baldwin et al 2007)
 - VA/NIH ATN trial (Palevsky et al; NEJM 2008) suggests similar outcomes as CRRT and IRRT.
 - Extended Daily Dialysis Versus Continuous Renal Replacement Therapy for Acute Kidney Injury: A Meta-analysis: Am J kidney Dis 2015 Aug;66(2):322-30: **EDD is associated with similar outcomes to CRRT in RCTs**



Optimal dosing of CRRT

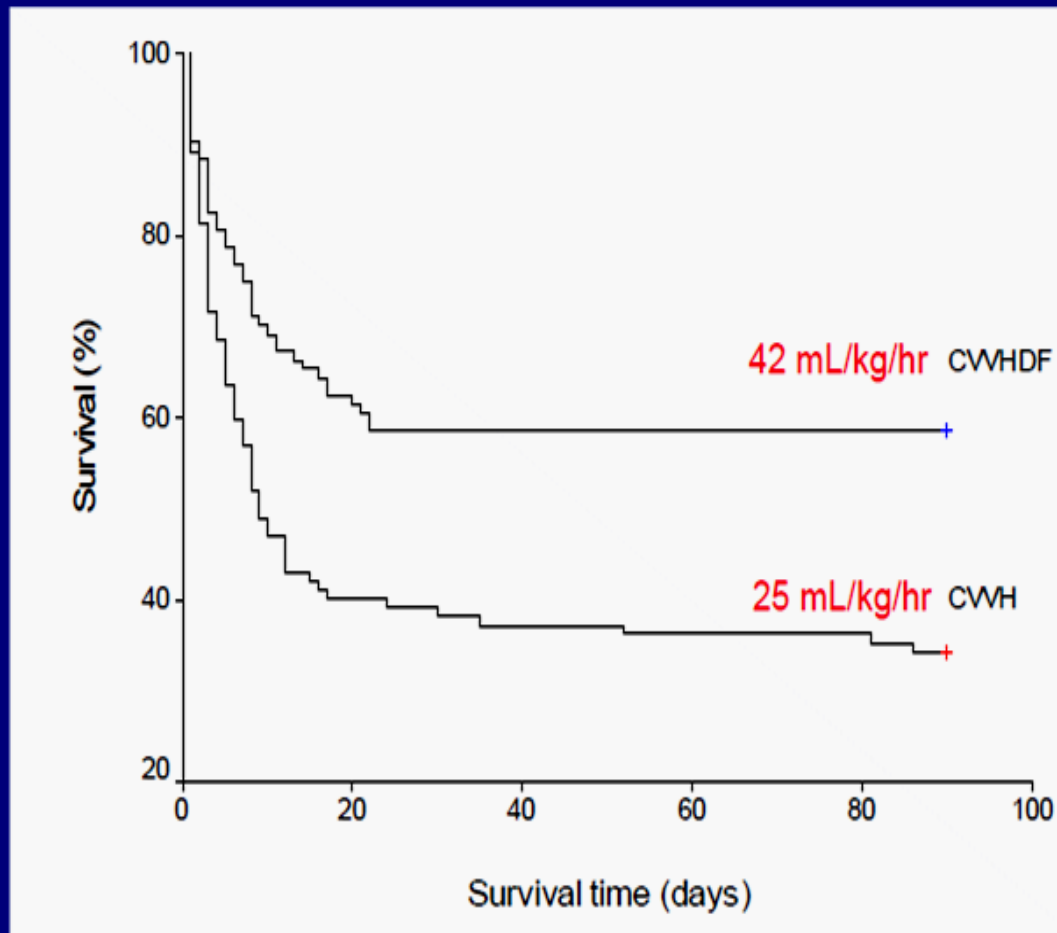
Survival in CVVH Dose Study

Ronco et al., Lancet 2000



Survival in Pre-Dilution CVVH vs CVVHDF

Saudan et al, Kidney Int 2006





The NEW ENGLAND JOURNAL *of* MEDICINE

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VOL. 359 NO. 1

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network*

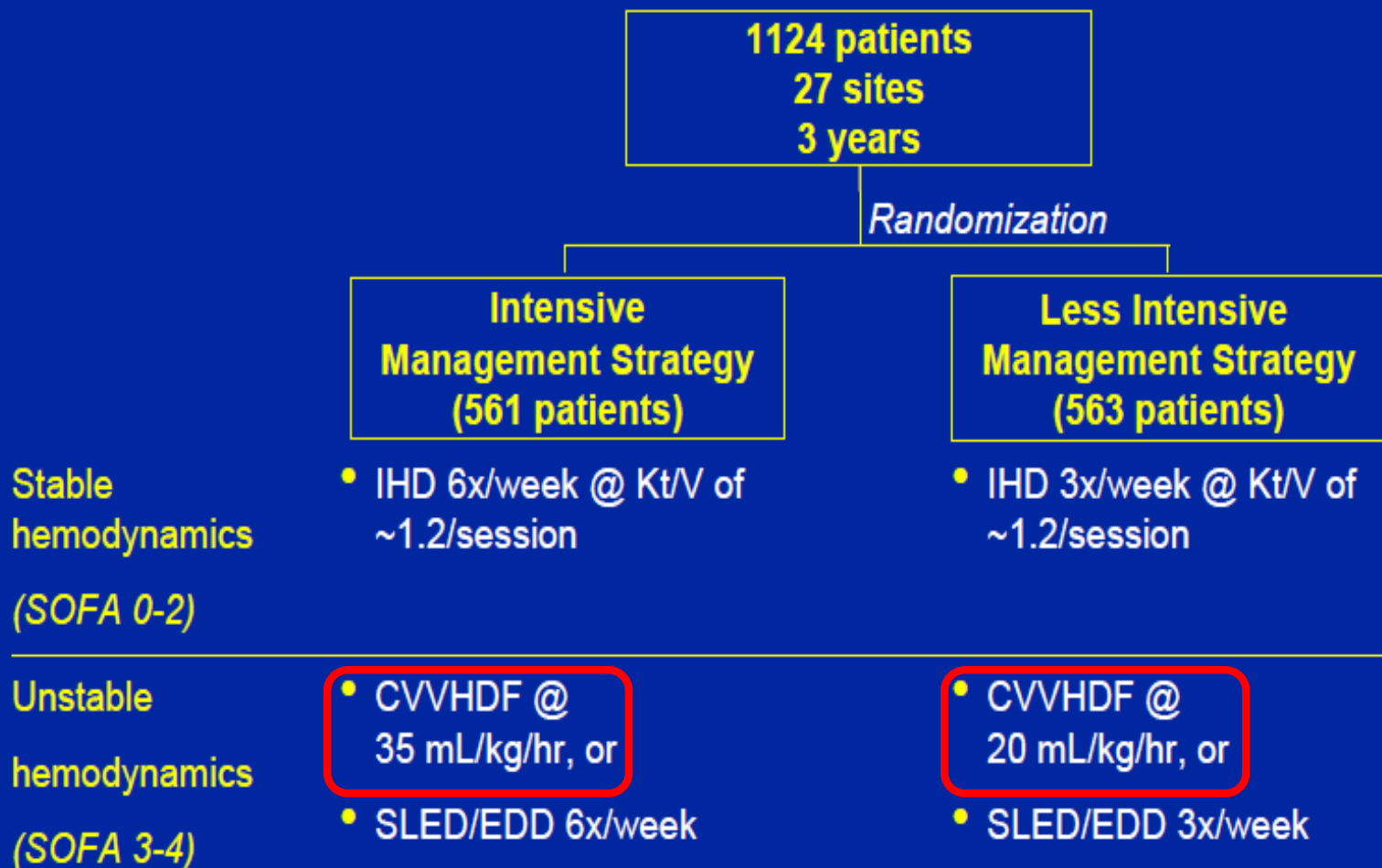
CONCLUSIONS

Intensive renal support in critically ill patients with acute kidney injury did not decrease mortality, improve recovery of kidney function, or reduce the rate of nonrenal organ failure as compared with less-intensive therapy involving a defined dose of intermittent hemodialysis three times per week and continuous renal-replacement therapy at 20 ml per kilogram per hour. (ClinicalTrials.gov number, NCT00076219.)

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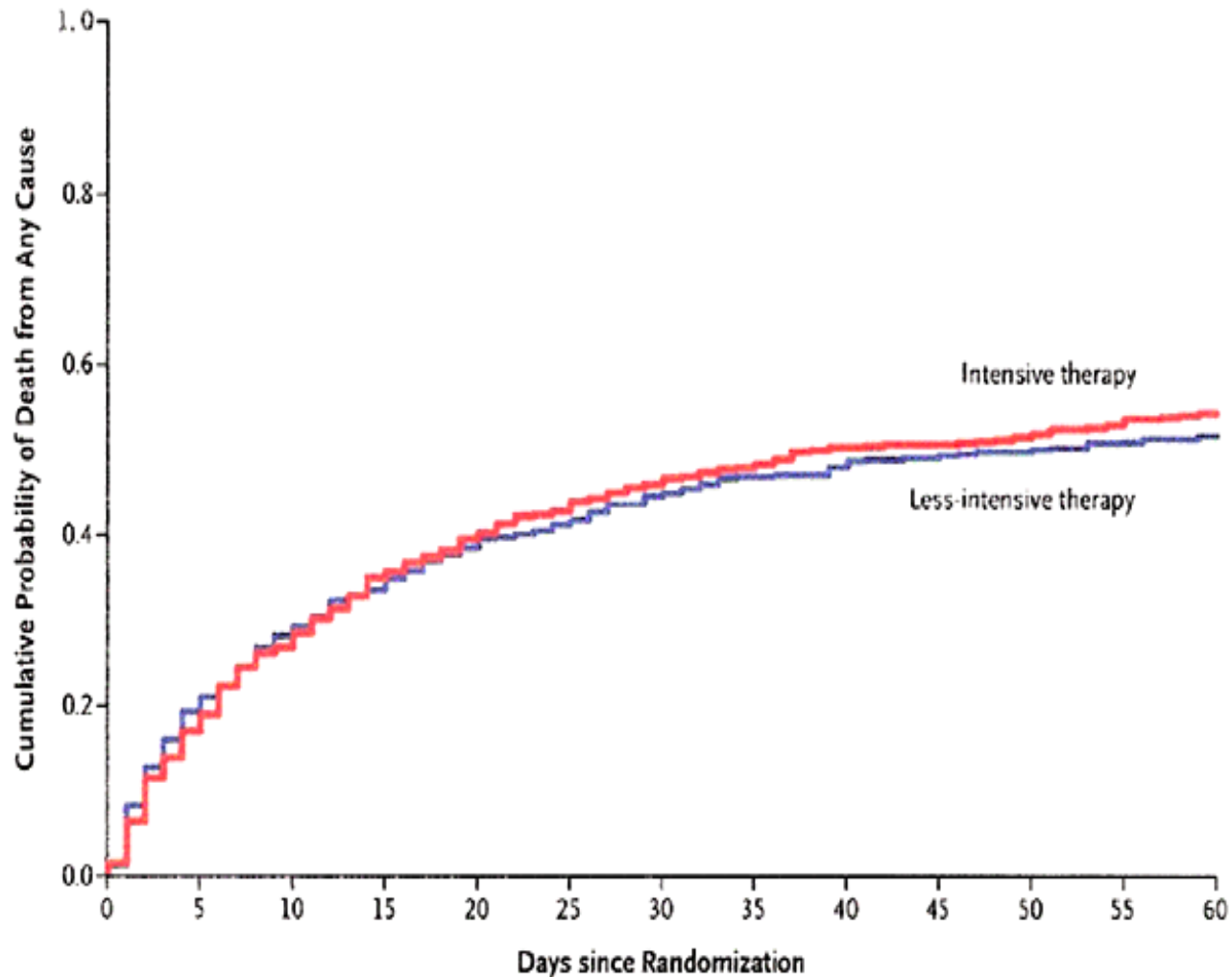
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VA/NIH Acute Renal Failure Trial Network (ATN) Study



ATN Study: Primary Outcome

VA/NIH Trial Group, NEJM 2008





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Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

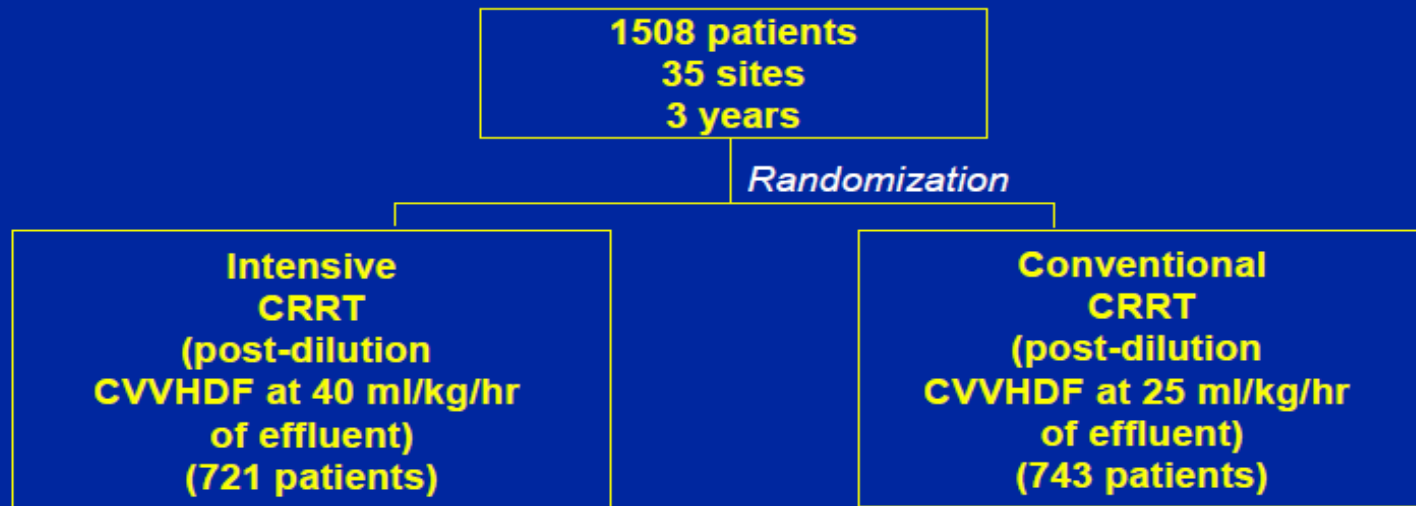
CONCLUSIONS

In critically ill patients with acute kidney injury, treatment with higher-intensity continuous renal-replacement therapy did not reduce mortality at 90 days. (ClinicalTrials.gov number, NCT00221013.)

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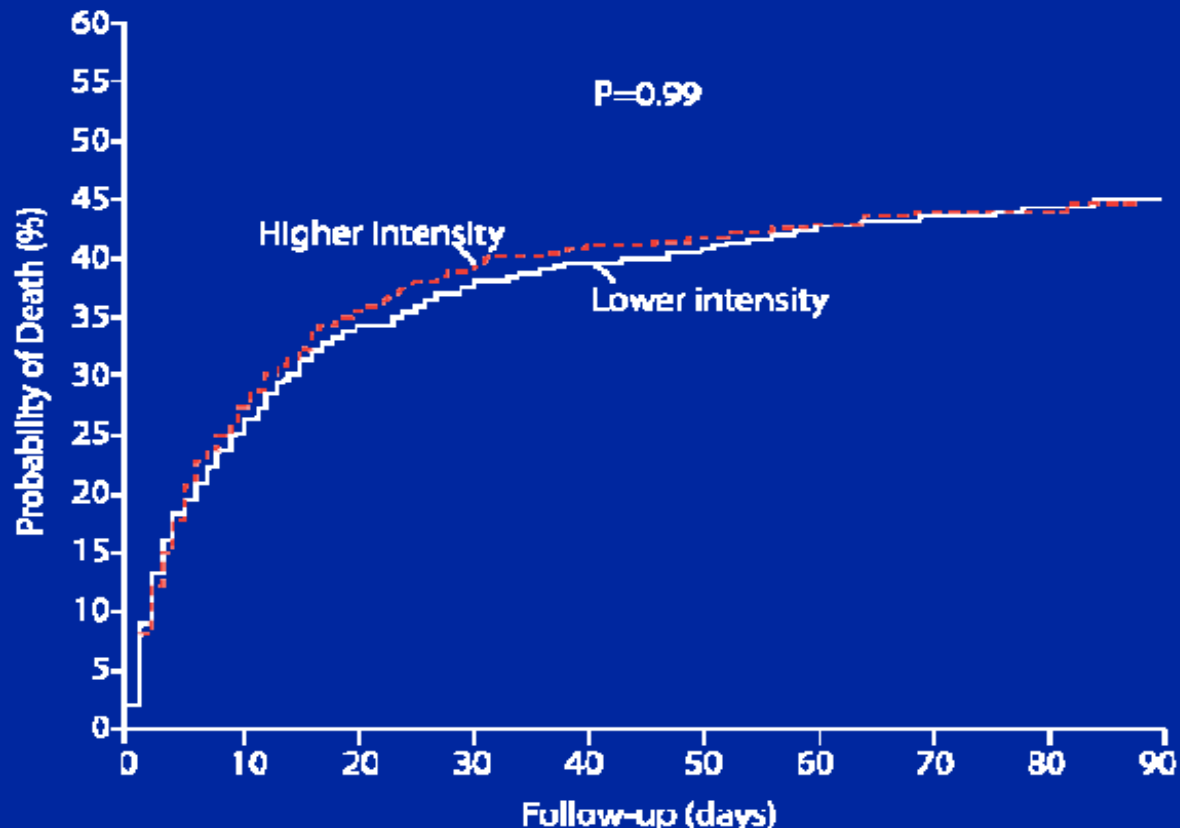
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R.E.N.A.L. Trial



Mortality Outcomes in RENAL

Bellomo et al, NEJM 2009





CONVINT TRIAL

Schefold *et al. Critical Care* 2014, **18**:R11
<http://ccforum.com/content/18/1/R11>



RESEARCH

Open Access

The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomized controlled trial

Joerg C Schefold^{1*}, Stephan von Haehling², Rene Pschowski^{1,3}, Thorsten Onno Bender¹, Cathrin Berkmann¹, Sophie Briegel¹, Dietrich Hasper¹ and Achim Jörres¹

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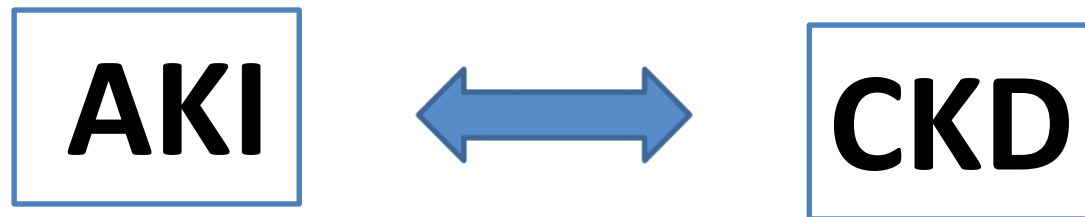
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CONVINT TRIAL



- **CONVINT TRIAL** -Single-center prospective RCT including 252 critically ill patients with dialysis-dependent ARF . Patients were randomized to receive either daily IHD or CVVH.
- The primary outcome measure was survival at 14 days .Secondary outcome measures included 30-day,ICU and intra hospital mortality, as well as course of disease severity/biomarkers and need for organ-support therapy.
- **Results:** Survival rates at 14 days after RRT were 39.5% (IHD) versus 43.9% (CVVH).14-day-, 30-day, and all-cause intra hospital mortality rates were not different between the two groups (all $P > 0.5$).
- **Conclusions:** **No statistically significant differences** was observed between the treatment modalities regarding mortality, renal-related outcome measures, or survival at 14 days after RRT.

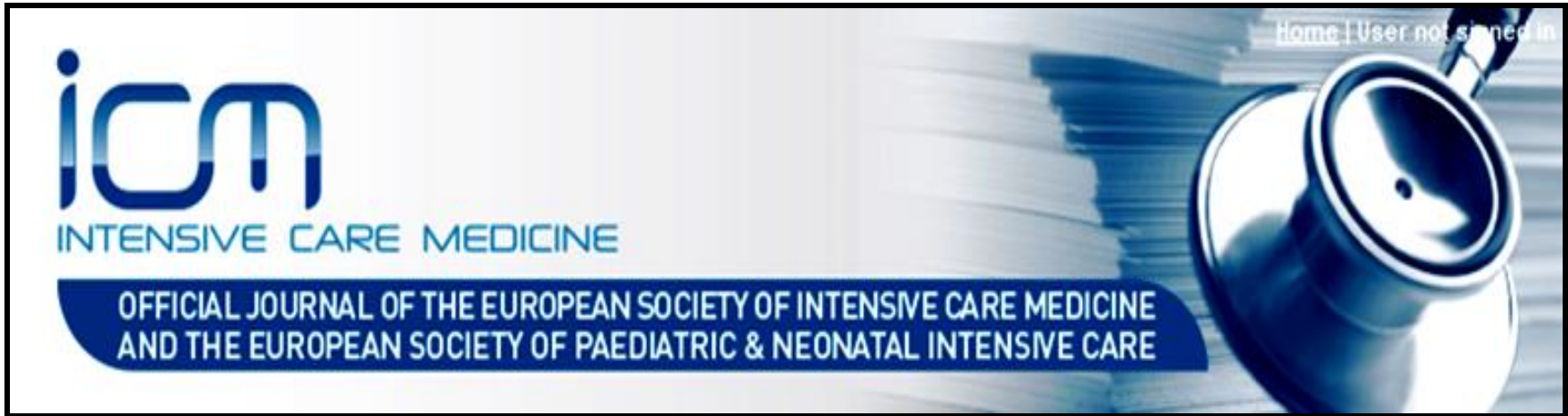
AKI and CKD - Interplay





CRRT AND DIALYSIS DEPENDENCY AFTER ACUTE KIDNEY INJURY

DOES CRRT Offers Better Acute Kidney Injury Outcomes????



Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis

Antoine G. Schneider| Rinaldo Bellomo| Sean M. Bagshaw| Neil J. Glassford| Serigne Lo| Min Jun| Alan Cass| Martin Gallagher

Systematic Review

Volume 39, Issue 6 / June , 2013

Pages 987 - 997

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Does CRRT Offers Better Acute Kidney Injury Outcomes???



- Patients with AKI treated with IRRT rather than (CRRT) may be more likely to become dialysis dependent.
- A systematic review and meta-analysis of 23 studies including 7 (RCTs) with 472 patients and 16 observational studies with 3,499 patients concluded that **Overall, initial treatment with IRRT was associated with a 1.7 times increased relative risk for dialysis dependence compared with CRRT.**
- Pooled analyses of the RCTs demonstrated **no significant difference in dialysis dependent rates** between the modalities, but **pooled analyses of the observational studies showed that patients who initially received IRRT had a twofold increased risk of dialysis dependence** compared with CRRT.

Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis

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Summary & Conclusions

SUMMARY

- Recent multicenter RCTs have failed to confirm earlier trials suggesting benefit of higher CRRT dose in critically ill
- Several differences exist among the various CRRT dose/outcome trials ,effluent dose ,convective contribution , dilution mode and timing of initiation
- A “One size fits All” approach makes it very difficult to establish a standard CRRT modality and dose in an individual patient

SUMMARY

- May be its time to say good bye to any more CRRT- high dose versus low dose ; CRRT versus IHD trials because hundreds of studies, including multicentre RCT's, meta-analysis have not shown a clear benefit of one over the other
- The choice of RRT in the critically ill is best left to the clinicians handling these patients depending on the condition of the patients, infrastructure, expertise and funds available in a given situation.



Suggested Reading

- Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury :The VA/NIH Acute Renal Failure Trial Network. **N Engl J Med 2008; 359:7-20**
- Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients:The RENAL Replacement Therapy Study Investigators **N Engl J Med 2009; 361:1627-1638**
- A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis : Karvellas et al. **Critical Care 2011, 15:R72**
- Dialysis: Results of RENAL—what is the optimal CRRT target dose? John A. Kellum & Claudio Ronco: **Nature Reviews Nephrology 6, 191-192 (April 2010)**
- The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomized controlled trial. Schefold JC, von Haehlin et al **Crit Care. 2014 Jan 10;18(1):R11.**
- Extended Daily Dialysis Versus Continuous Renal Replacement Therapy for Acute Kidney Injury: A Meta-analysis. **Am J Kidney Dis :2015 Aug;66(2):322-30**



Thank You

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