



king
Karolinska intensive care nephrology group

AKI EPIDEMIOLOGY

Akut nefrologi och dialys inom intensivvården 2021

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Historical incidence, hard to describe

- *ICU-incidence: 1-70%

• G. M. Chertow, "Independent association between acute renal failure and mortality following cardiac surgery," *American Journal of Medicine*, vol. 104, no. 4, pp. 343–348, 1998.

• A. M. Escoresca Ortega, Z. Ruz De Azúa López, R. Hinojosa Pérez et al., "Kidney failure after heart transplantation," *Transplantation Proceedings*, vol. 42, no. 8, pp. 3193–3195, 2010.

- *Varying definitions=lack of consensus, from a 25% increase in creatinine to need for RRT

- "Severe AKI" – need for RRT in the ICU; around 5% of the ICU population (however, case mix dependent, in the Karolinska ICU around 10%)

• Uchino, S., et al.: Acute renal failure in critically ill patients: a multinational, multicenter study. *Jama* 2005; 294:813-8.

- The incidence has risen during the latest 20 years, from 61 to 288/100,000 (AKI) and from 4 to 27/100,000 (Severe AKI)

• Waikar, S.S., et al.: Declining mortality in patients with acute renal failure, 1988 to 2002. *J Am Soc Nephrol* 2006; 17:1143-50

- In 2012 a study reported in-hospital-AKI around 20%

• H. E. Wang, P. Muntner, G. M. Chertow, et al., "Acute kidney injury and mortality in hospitalized patients," *American Journal of Nephrology*, vol. 35, pp. 349–355, 2012.

Pathophysiology behind AKI

- Multifactorial (crush injury, bleeding shock, toxins) but....
- Severe AKI were extracted from the ICNARC CMP database of **276,326** admissions to UK ICUs from 1995 to 2004
- Severe AKI occurred in 17,326 out of 276,731 admissions (**6.3%**)
- **Sepsis was present in 47.3%** and AKI was nonoliguric in 63.9% of cases Kolhe et al Crit Care. 2008; 12(Suppl 1): S2
- B.E.S.T. Kidney study
- **29,269** patients, screened in 52 ICUs from 23 countries
- **Sepsis caused 50% of these AKI cases** Uchino S, Kellum J, Bellomo R, et al. JAMA 2005



Problem #1

Epidemiology for acute kidney injury lacked a **uniform classification model**

In a legendary study, Novis et al. found 35 separate definitions in 35 studies of AKI

Novis BK, Roizen MF, Aronson S, Thisted RA (1994) Association of preoperative risk factors with postoperative acute renal failure. Anesth Analg 78:143-149.

Problem #2

How to measure **outcome**?

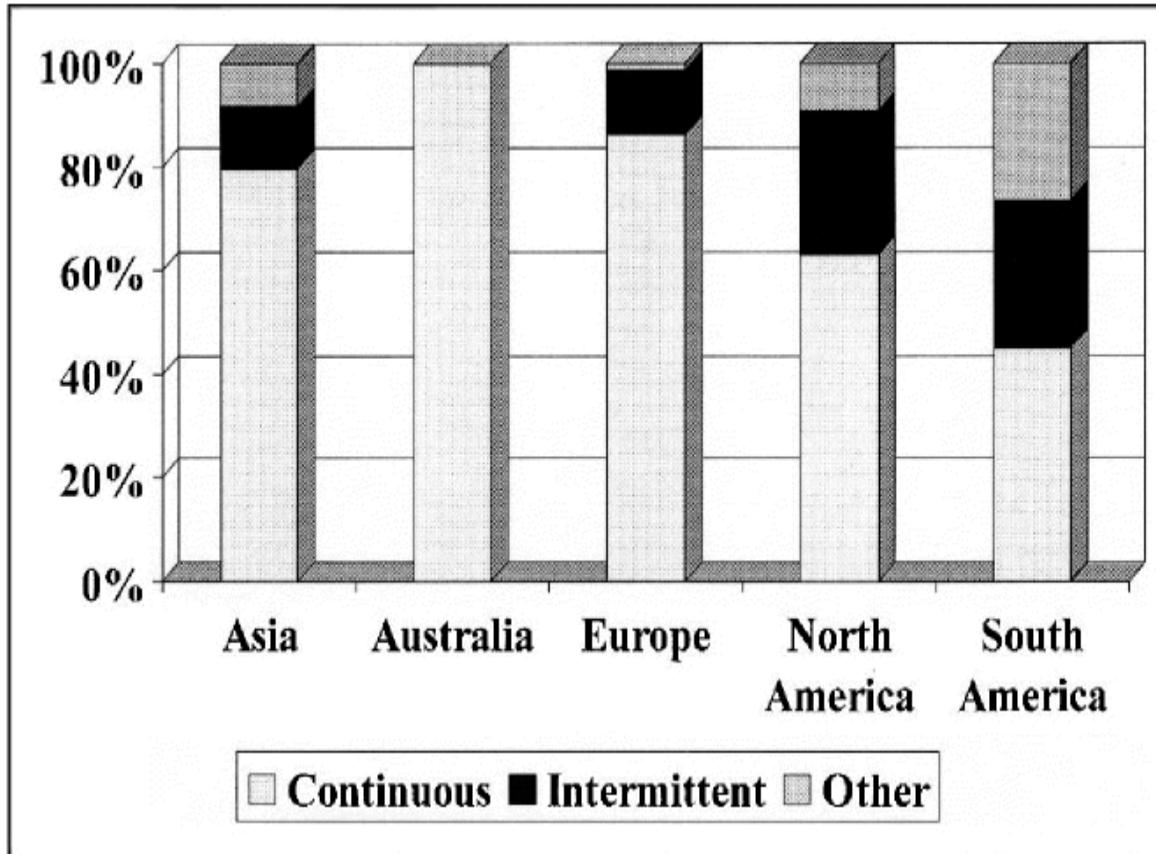
Mortality in ICU

Mortality in hospital

Mortality varies wildly in studies

Other outcome measurements, *morbidity*, renal recovery?

Problem #3



Different **forms of RRT modality** in AKI-studies

Differs across the globe

Acute Dialysis Quality Initiative II: the Vicenza conference. Bellomo, Rinaldo MD, Kellum, John A. MD, Mehta, Ravindra MD, Palevsky, Paul M. MD ++. Ronco, Claudio MD



Problem #4

Subclinical AKI? Is that a thing?

Author	no. of subjects	Single/multicenter	Patient population	AKI definition used	AKI incidence (%)	Mortality endpoint	Mortality (%)
Thakar	325,395	Multi	Mixed	RIFLE	22	ICU	10.9
Ostermann and Chang	41,972	Multi	Mixed	RIFLE	35.8	ICU Hospital	10.2 12.9
Gammelager	30,762	Multi	Mixed	RIFLE	15.6	30 days	40
Joannidis	16,784	Multi	Mixed	RIFLE	35.5	Hospital	36.4
Mandelbaum	14,524	Single	Mixed	AKIN	57	ICU Hospital	7.1 9.1
Hoste	5383	Single	Mixed	RIFLE	67.2	Hospital	13.3
Cruz	2164	Multi	Mixed	RIFLE	10.8	ICU	36.3
Samimaghram	1026	Single	Mixed	RIFLE	21.7	1 year	49
Fonseca Ruiz	794	Single	Mixed	AKIN	39.8	ICU Hospital	25.4 32.1
Piccinni.	576	Multi	Mixed	RIFLE	42.7	ICU	29
Medve and Gondos	459	Single	Mixed	AKIN	24.4	ICU Hospital	39.3 49.1
Samimaghram	235	Single	Mixed	AKIN	31.1	ICU	72.6
Yue	191	Single	Mixed	AKIN	35.5	ICU	48
Abosaif	183	Single	Mixed	RIFLE		ICU	47.5
Yegenaga	139	Single	Mixed	RIFLE	56.8	UKN	37.4
Bagshaw	120,123	Multi	Sepsis	RIFLE versus AKIN	36.1 37.1	Hospital	RIFLE: 24.2 AKIN: 24.5

Author	no. of subjects	Single/multicenter	Patient population	AKI definition used	AKI incidence (%)	Mortality endpoint	Mortality (%)
Kim	291	Single	Severe sepsis/ Septic shock	RIFLE versus AKIN	RIFLE: 62.9 AKIN: 65.6	28 days	RIFLE: 58.5 AKIN: 57.6
Lopes	182	Single	Sepsis	RIFLE	37.4	NS	37.4
Lerolle	35	Single	Septic shock	RIFLE	65.8	28 days	62.8
Coca	304	Single	Burn	RIFLE	26.6	NS	7.6
Lopes	126	Single	Burn	RIFLE	35.7	NS	17.5
Palmieri	60	Single	Burn	RIFLE	53.3	UKN	34.4
Bagshaw	9449	Multi	Trauma	RIFLE	18.1	Hospital	16.7
Costantini	571	Single	Trauma	AKIN	29.8	Hospital	15.9
Gomes	436	Single	Trauma	RIFLE	50	ICU	8.2
Lin	46	Single	ECMO	RIFLE	78	Hospital	10.8
Englberger	951	Single	Tricuspid valve surgery	RIFLE	30	30 days	5.5
Englberger	851	Single	Thoracic aortic surgery	RIFLE	17.7	30 days	1.3
Kuitunen	813	Single	Cardiac surgery	RIFLE	19.3	90 days	3.2
Kramer	668	Multi	Cardiac surgery	AKIN	Surgery: 33.7 Cath + surgery: 50.2	NS	NS
Yan	509	Single	Cardiac surgery	RIFLE	32.8	Hospital	4.3
Mariscalo	414	Multi	Aortic root repair	RIFLE	16.7	Hospital	2.7
Roh	98	Single	Thoracic aorta graft placement	RIFLE	54	30 days	5.1
Machado	817	Single	CP bypass	RIFLE	48.5	30 days	12.6
Sirvinskas	179	Single	CP bypass	RIFLE	10.6	NS	NR
O'Riordan	300	Multi	OLT	RIFLE	36.8	NS	NS

Author	no. of subjects	Single/multicenter	Patient population	AKI definition used	AKI incidence (%)	Mortality endpoint	Mortality (%)
Biagioni	144	Single	OLT versus NEAS	RIFLE	OLT: 29 NEAS: 47	ICU	OLT: 29 NEAS: 51
Guitard	97	Single	OLT	RIFLE	63.8	UKN	UKN
Medve and Gondos	295	Multi	Major noncardiac surgery	AKIN	18.1	ICU	33.3
Tallgren	69	Single	Elective infra-renal AAA surgery	RIFLE	22	Hospital	1.4
Hoste	787	Single	CIN	UKN	16.3	28 days 1 year	13.1 35.9
Lakhal	299	Single	CIN	AKIN	14	ICU	18
Rashid	139	Single	CIN	RIFLE	11.5	ICU	31
Valette	101	Single	CIN/Surgical	RIFLE versus AKIN	RIFLE: 19 AKIN: 19	ICU	RIFLE: 26.3 AKIN: 31.6 PCRS: 46.6
Chua	105	Single	ROSC following cardiac arrest	RIFLE	PRCS: 51.7 No PRCS: 6.4	ICU Hospital	No PRCS: 27.7 PCRS: 51.7 No PCRS: 34
Cholongitas	412	Single	Cirrhosis	RIFLE	50	6 weeks	61.2
Hata	376	Single	ADHF	RIFLE	73.1	Hospital	10.5
Martin-Leoches	661	Multi	H1N1	AKIN	17.7	ICU	44.1
Jung	221	Multi	H1N1	RIFLE	22.6	30 days	17.2
Nin	84	Multi	H1N1	RIFLE	51	28 days	51.2
Abdulkader	47	Single	H1N1	RIFLE	53	Hospital	19.1
Chacko	31	Single	H1N1	RIFLE	3.2	28 days	16.1

Fixing the problem (ADQI/AKIN/KDIGO, 2004/2007/2012)

(Problem #1) A **uniform classification model** for AKI-AKD*

(Problem #2) An **internationally accepted outcome measurement** for AKI patients

(Problem #3) We might still need even more studies on the difference between choice of **dialysis modality**

(Problem #4) Should we do anything with **subclinical AKI**



RIFLE came first

A model for classification of AKI

Kellum JA, Levin N, Bouman C, Lameire N (2002) Developing a consensus classification system for acute renal failure. *Curr Opin Crit Care* 8:509-514

Sudden: within 1-7 days

Persistent: at least 24 hours

RIFLE/AKIN, is now validated in >500.000 patients

RIFLE

	Cr/ GFR Criteria	Urine Output (UO) Criteria
Risk	Increased Cr x1.5 or GFR decreases >25%	UO <0.5 ml/kg/hr x 6 hr
Injury	Increased Cr x 2 or GFR decreases >50%	UO <0.5 ml/kg/hr x 12 hr
Failure	Increased Cr x 3 or GFR decreases >75% or Cr ≥ 4 mg/dl (with acute rise of ≥ 0.5 mg/dl)	UO <0.3 ml/kg/hr x 24 hr or anuria x 12 hr
Loss	Persistent ARF = complete loss of renal function for > 4 weeks	
ESRD	End Stage Renal Disease	

AKIN

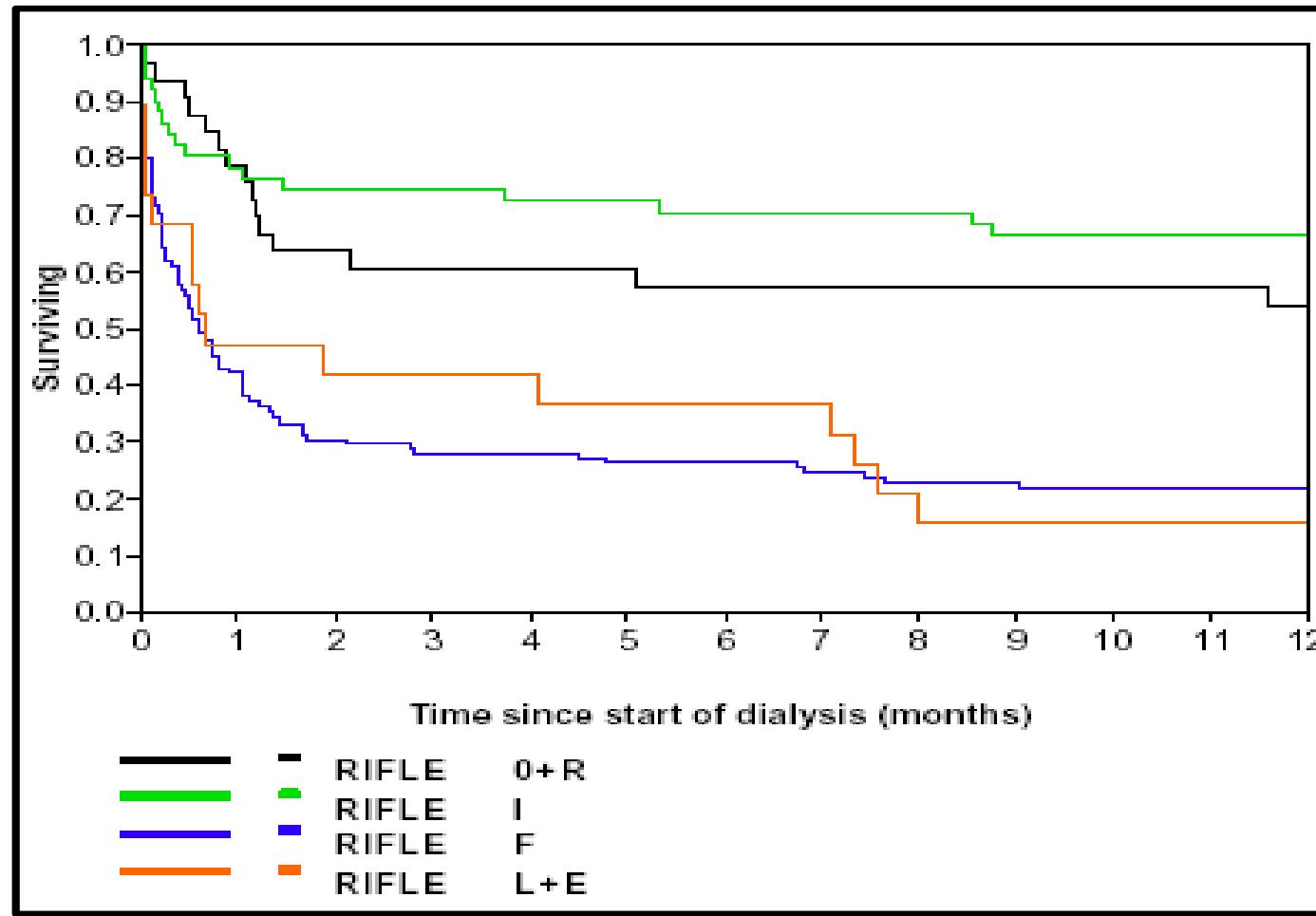
	Cr Criteria	Urine Output (UO) Criteria
Stage 1	Increased Cr x1.5 or ≥0.3 mg/dl	UO <0.5 ml/kg/hr x 6 hr
Stage 2	Increased Cr x 2	UO <0.5 ml/kg/hr x 12 hr
Stage 3	Increased Cr x 3 or Cr ≥ 4 mg/dl (with acute rise of ≥ 0.5 mg/dl)	UO <0.3 ml/kg/hr x 24 hr or anuria x 12 hr

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.

RIFLE/AKIN/KDIGO

Urine output (common to all)	KDIGO stage ^{198,199} Serum creatinine		AKIN stage Serum creatinine		RIFLE class Serum creatinine or GFR	
<0.5 mL/kg/h for 6 h	Stage 1	Increase of 1.5–1.9 times baseline or $\geq 27 \mu\text{mol/L}$ ($\geq 0.3 \text{ mg/dL}$) increase	Stage 1	Increase to $>150\text{--}200\%$ (1.5–2-fold) from baseline or $\geq 27 \mu\text{mol/L}$ ($\geq 0.3 \text{ mg/dL}$) increase	Risk	Increase in serum creatinine $\times 1.5$ or GFR decrease $>25\%$
<0.5 mL/kg/h for 12 h	Stage 2	Increase of 2–2.9 times baseline	Stage 2	Increase to $>200\text{--}300\%$ ($>2\text{--}3\text{-fold}$) from baseline	Injury	Increase in serum creatinine $\times 2$ or GFR decreased $>50\%$
<0.3 mL/kg/h for 24 h or anuria for 12h	Stage 3	Increase of >3 times baseline or increase in serum creatinine to $\geq 354 \mu\text{mol/L}$ ($\geq 4 \text{ mg/dL}$) or initiation of RRT	Stage 3	Increase to $>300\%$ ($>3\text{-fold}$) from baseline or $\geq 354 \mu\text{mol/L}$ ($\geq 4 \text{ mg/dL}$) with an acute increase of $>44 \mu\text{mol/L}$ ($>0.5 \text{ mg/dL}$) or initiation of RRT	Failure	Increase in serum creatinine $\times 3$ or serum creatinine $\geq 354 \mu\text{mol/L}$ ($>4 \text{ mg/dL}$) with an acute rise $\geq 44 \mu\text{mol/L}$ ($>0.5 \text{ mg/dL}$) or GFR decreased $>75\%$
					ESRD	ESRD >3 months

Data from Karolinska central ICU 1995-2001



Optimal follow-up time after continuous renal replacement therapy in actual renal failure patients stratified with the RIFLE criteria. [Bell M](#), [Liljestam E](#), [Granath F](#), [Fryckstedt J](#), [Ekbom A](#), [Martling CR](#). *Nephrol Dial Transplant.* 2005 Feb;20(2):354-60

Data from Karolinska central ICU 1995-2001

8152 ICU visits between 95 and 2001
223 on RRT and included in the study

ICU mortality 34.1%

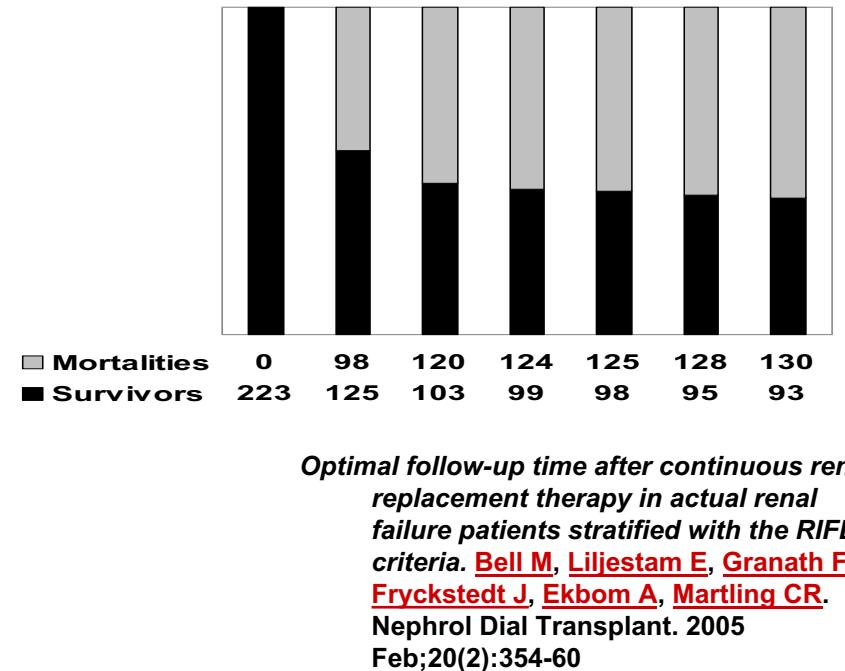
30-day mortality 43.9%

Hospital mortality 49.3%

6 month mortality 58.3%

2-month mortality 53.8%

Figure 2 Cumulative number of mortalities 30, 60, 90, 120, 150 and 180 day after CRRT start



US hospital RIFLE study

- In a US study of a cohort of **5,383 ICU patients two thirds developed AKI**

12.4% of patients had a maximum RIFLE Risk,
26.7% had maximum RIFLE Injury and
28.1% had maximum RIFLE Failure

- Patients with maximum RIFLE class R, class I and class F had **hospital mortality rates of 8.8%, 11.4% and 26.3%**, respectively, compared with 5.5% for patients without acute kidney injury

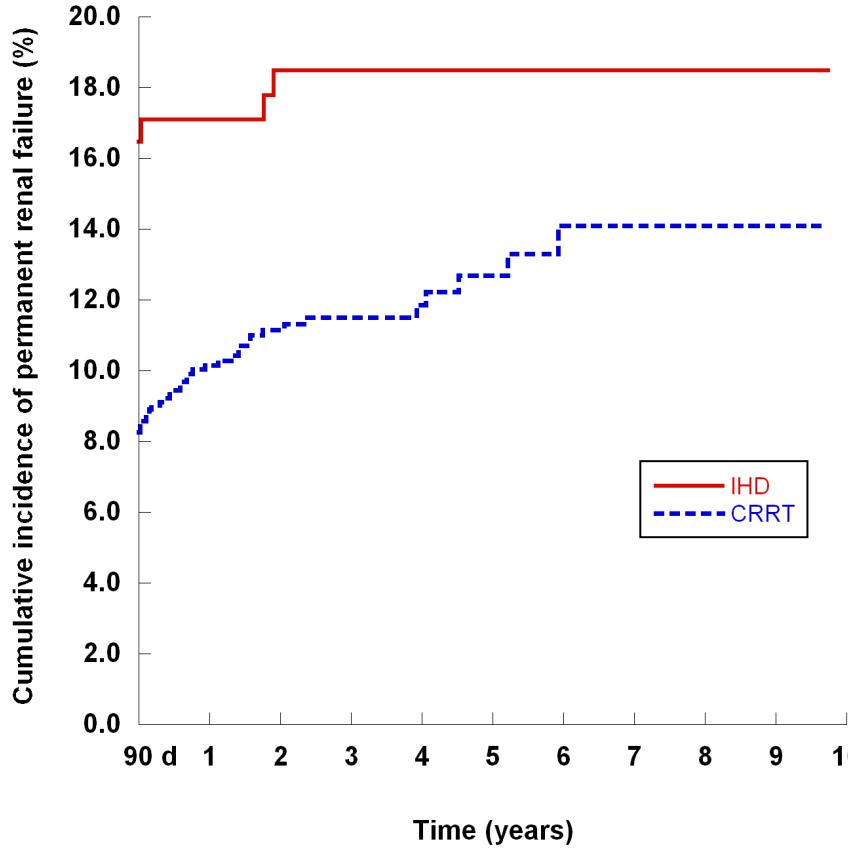
Hoste, E.A., et al.: RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006; 10:R73

AKI and morbidity

In our first study, we found 5 out of 118 on chronic HD (**4,2%**)*

Optimal follow-up time after continuous renal replacement therapy in actual renal failure patients stratified with the RIFLE criteria. Bell M, Liljestam E, Granath F, Fryckstedt J, Ekbom A, Martling CR.
Nephrol Dial Transplant. 2005 Feb;20(2):354-60

AKI and morbidity, SWING, data from Sweden 95-04



Intensive Care Med (2007) 33:773–780
DOI 10.1007/s00134-007-0590-6

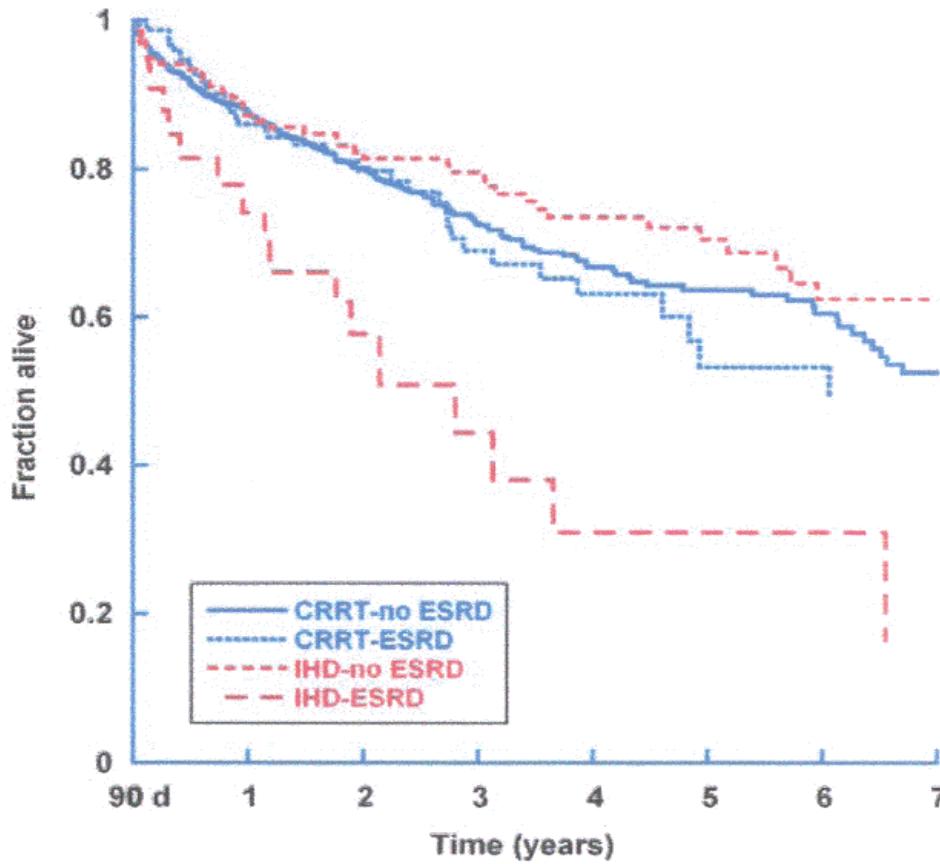
ORIGINAL

Max Bell
SWING
Peter Grankvist
Staffan Sjöholm
Anders Ekblom
Clas-Roland Martling

Continuous renal replacement therapy
is associated with less chronic renal failure
than intermittent haemodialysis after acute
renal failure

- 2202 patients, 32 ICUs, 1995-2004
- 1102 patients alive at 90 days
- **Significant difference in chronic dialysis dependence at 90 days:**
CRRT 8%, IHD 17%
- **Adjusted odds ratio for IHD was 2.6 (1.5-4.3)**

AKI and morbidity+mortality, SWING, data from Sweden 95-04



Intensive Care Med (2007) 33:773–780
DOI 10.1007/s00134-007-0590-6

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Continuous renal replacement therapy
is associated with less chronic renal failure
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renal failure

- 2202 patients, 32 ICUs, 1995-2004
- 1102 patients alive at 90 days
- **Survival rate was significantly lower in patients treated with HD for AKI compared to CRRT-treated patients**



AKI, morbidity+mortality, Swedish data 2005-2011

Rimes-Stigare et al. *Critical Care* (2015) 19:383
DOI 10.1186/s13054-015-1101-8



RESEARCH

Open Access

Long-term mortality and risk factors for development of end-stage renal disease in critically ill patients with and without chronic kidney disease

Claire Rimes-Stigare^{1,2*}, Paolo Frumento³, Matteo Bottai³, Johan Mårtensson^{1,4}, Claes-Roland Martling^{1,2} and Max Bell^{1,2}



RESEARCH

Open Access

Evolution of chronic renal impairment and long-term mortality after de novo acute kidney injury in the critically ill; a Swedish multi-centre cohort study

Claire Rimes-Stigare^{1,2*}, Paolo Frumento³, Matteo Bottai³, Johan Mårtensson^{2,4}, Claes-Roland Martling^{1,2}, Sten M Walther^{5,6}, Göran Karlström⁷ and Max Bell^{1,2}

Methods

Swedish Intensive care Register (SIR)

SIR → All first admissions for adult patients

2005 & 2010 =140,161 patients

Cross-matched with:

Swedish cause of death register → all cause mortality

Outpatient and inpatient registries → Co-morbidities & post ICU
Chronic kidney disease (CKD)

The Swedish renal register → End-stage renal disease (ESRD)



Patient groups

No renal disease pre/peri ICU (Control group)

AKI (de novo)

CKD

Acute on Chronic (AoC)

ESRD

Crude mortality at one and five years

Group	Mortality probability (%)	
	1 year	5 year
No renal disease	24.6	39.1
AKI	48.7	61.8
Chronic only	47.7	71.3
Acute on Chronic	54.3	68.2
ESRD	40.3	62.9

Multivariable regression analysis of risk of death

Group	N	Crude MRR (95% CI)	Adjusted MRR# (95% CI)
No renal disease	92509	1	1
AKI	5273	2.87 (2.76-2.97)	1.15 (1.09-1.21)
Chronic only	3194	2.99 (2.86-3.13)	1.26 (1.17-1.36)
Acute on Chronic	998	3.53 (3.26-3.33)	1.38 (1.24-1.54)
ESRD	1389	2.08 (1.94-2.23)	1.46 (1.29-1.67)

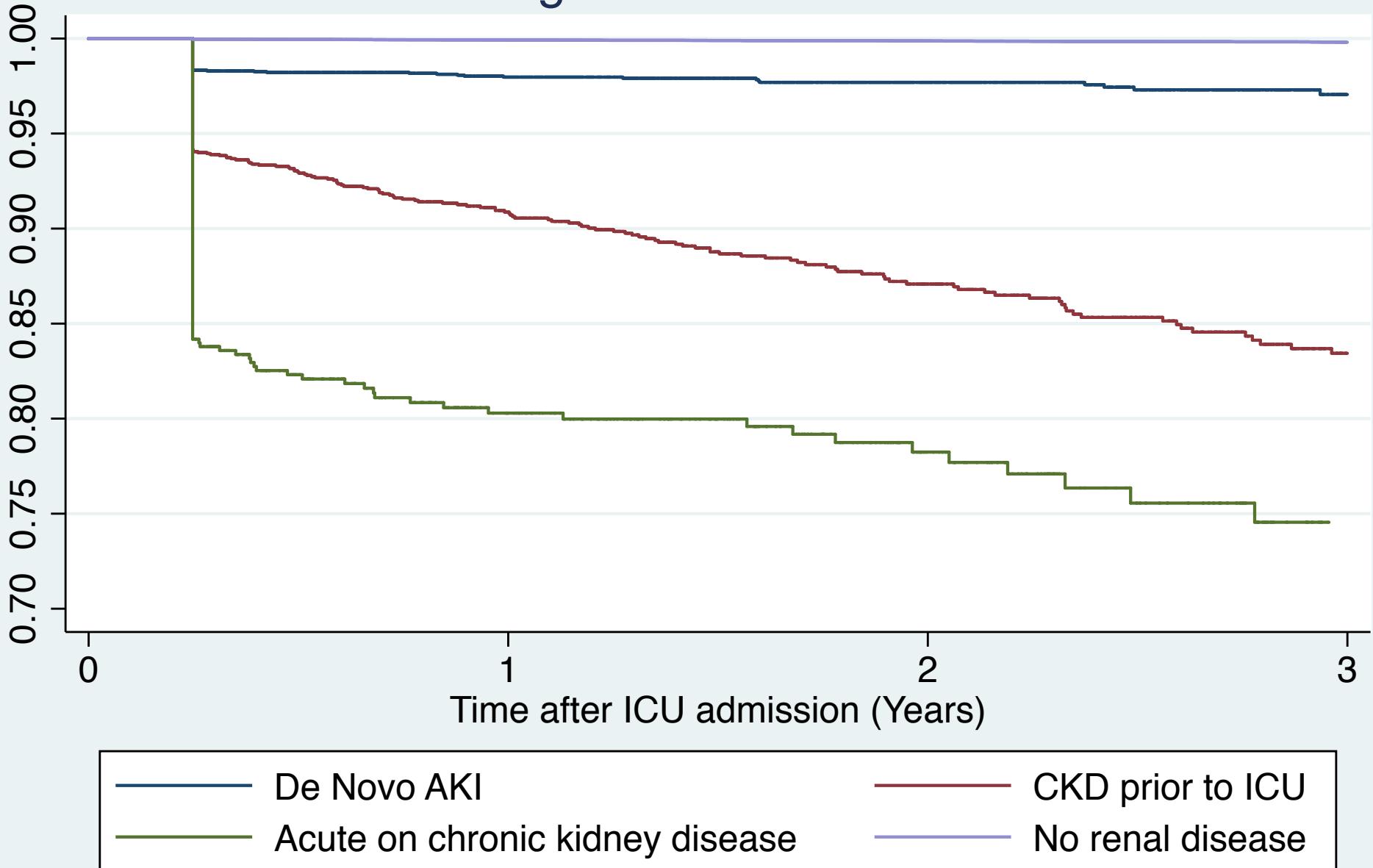
Crude estimates of likelihood of developing ESRD

Group	Probability of ESRD (%)	
	1 year	5 year
No renal disease	0.08	0.30
AKI	2.03	3.88
Chronic only	9.13	21.09
Acute on chronic	19.71	25.45

Multivariable regression for risk of developing ESRD.

Group	Patients (N)	Events (N)	Person years	IR event/ 1000 person year (CI)	Crude IRR (95% CI)	Adjusted IRR * (CI)
No renal disease	92509	116	1.7×10^5	0.7 (0.6-0.8)	1	1
AKI	5273	65	5.2×10^3	12.5 (9.8-16)	18.6 (13.7-25.2)	24.1 (13.9-42.0)
Chronic only	3194	237	3.4×10^3	69 (61.1-78.8)	103 (82.5-128.6)	96.4 (59.7-155.6)
Acute on Chronic	998	111	803.1	138.2 (114.7-166.5)	205.1 (158.1-266.1)	259 (156.9-429.1)

Kaplan Meier estimates of time to development of ESRD according to renal disease status.





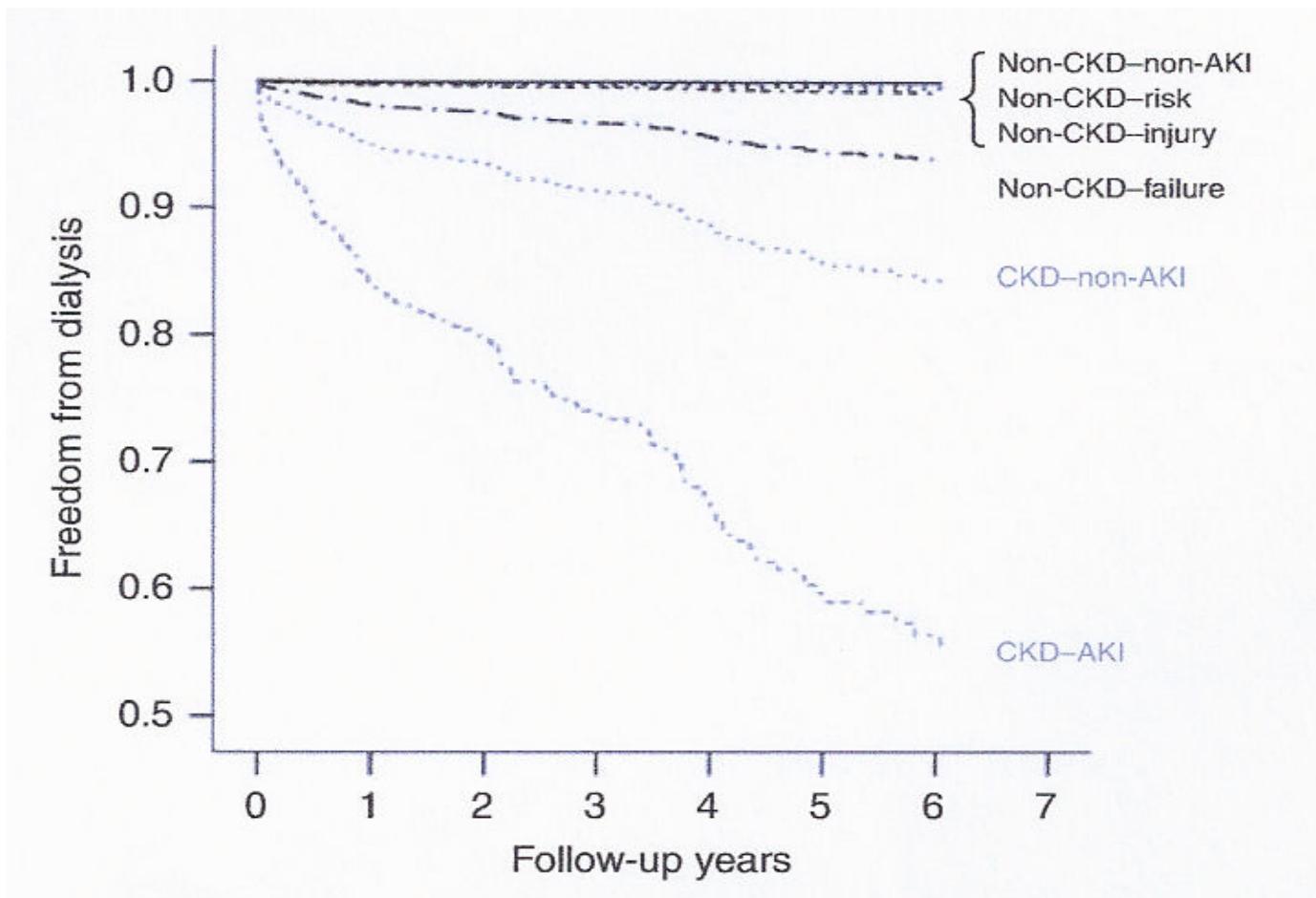
Competing risks model: risk of ESRD in 1yr ICU survivors by polynomial multivariable logistic regression analysis

Covariate	Relative risk ratio * (95% CI)	P value
Female gender	1.12(0.48-2.63)	0.787
Congestive heart failure	0.091 (0.011-0.690)	*0.020
Admission serum potassium high (>4.59)	4.6 (1.30-16.40)	*0.018
AKI	30.4 (5.98-154)	<0.001
CKD	265.7 (55.1-1280)	<0.001
AoC	356.6 (69.9-1811)	<0.001

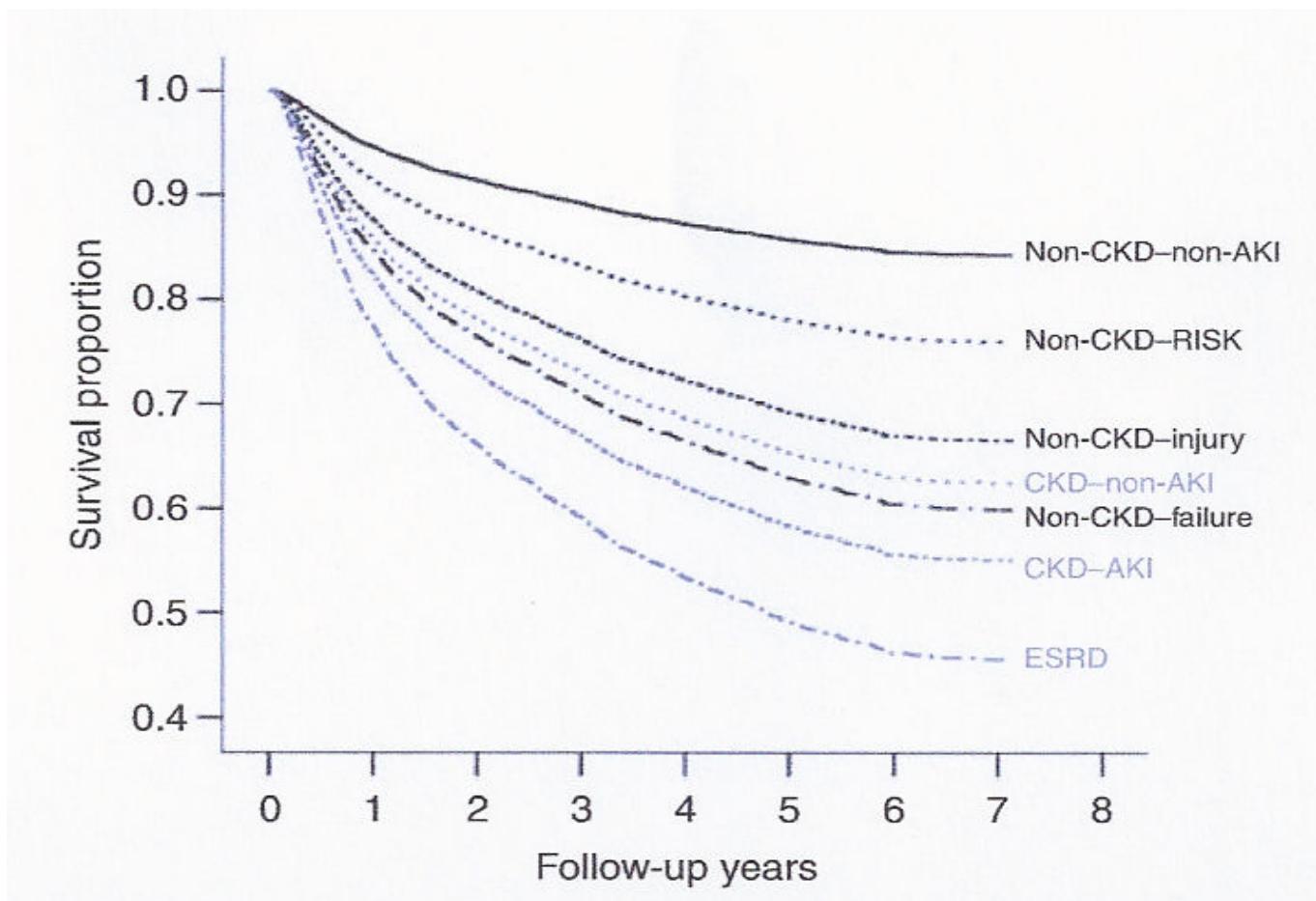
Reference category = Male, no comorbidity (according to Charlson index), admission potassium (3.9-4.59), no renal disease.

*Risk relative to reference category.

AKI and morbidity ESRD after AKI



Long term outcome, stratified by CKD/AKI



Risk for ESRD two years after discharge from hospital

Baseline CKD

yes	25.11	6.82 (6.05 to 7.67)
no	2.60	1.00

AKI

yes	43.35	6.74 (5.90 to 7.71)
no	4.10	1.00

AKI and CKD

both AKI and CKD	79.45	41.19 (34.58 to 49.08)
AKI only	24.52	13.00 (10.57 to 15.99)
CKD only	19.88	8.43 (7.39 to 9.61)
no AKI or CKD	2.08	1.00

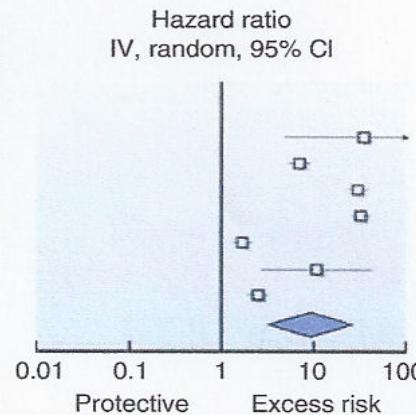
^aObtained using Cox proportional models with adjustment for age, gender, race, diabetes, and hypertension.

CKD and ESRD after AKI, systematic review

a

Study or subgroup	Weight (%)	Hazard ratio IV, random, 95% CI
Weiss <i>et al.</i> (13)	10.0	32.79 (4.30–249.77)
Amdur <i>et al.</i> (22)	15.5	6.64 (5.05–8.74)
Lo <i>et al.</i> (11)	15.5	28.08 (21.01–37.53)
James <i>et al.</i> (16)	15.6	29.99 (24.32–36.99)
James <i>et al.</i> (15,23)	15.5	1.60 (1.20–2.14)
Ando <i>et al.</i> (19)	12.4	9.91 (2.48–39.63)
Ishani <i>et al.</i> (21)	15.6	2.33 (1.83–2.96)
Total (95% CI)	100.0	8.82 (3.05–25.48)

Heterogeneity: $\tau^2 = 1.87$; $\chi^2 = 446.89$, d.f. = 6 ($P < 0.00001$);
 $I^2 = 99\%$. Test for overall effect: $Z = 4.02$ ($P < 0.0001$)

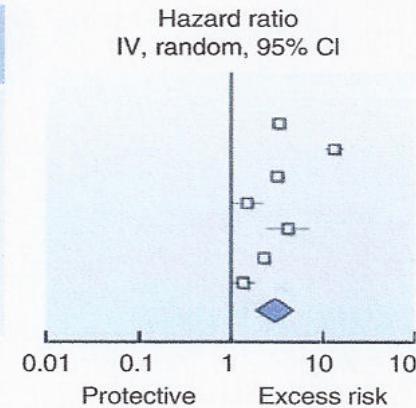


CKD

b

Study or subgroup	Weight (%)	Hazard ratio IV, random, 95% CI
Newsome <i>et al.</i> (14)	15.0	3.26 (2.87–3.70)
Ishani <i>et al.</i> (20)	14.8	12.99 (10.57–15.96)
Wald <i>et al.</i> (17)	14.9	3.22 (2.70–3.85)
Hsu <i>et al.</i> (10)	13.5	1.47 (0.95–2.28)
James <i>et al.</i> (15,23)	12.5	4.15 (2.32–7.41)
Lafrance <i>et al.</i> (18)	15.0	2.33 (2.08–2.61)
Choi <i>et al.</i> (12)	14.4	1.37 (1.02–1.84)
Total (95% CI)	100.0	3.10 (1.91–5.03)

Heterogeneity: $\tau^2 = 0.40$; $\chi^2 = 252.85$, d.f. = 6 ($P < 0.00001$);
 $I^2 = 98\%$. Test for overall effect: $Z = 4.58$ ($P < 0.00001$)



ESRD

ESRD after AKI, B.E.S.T.

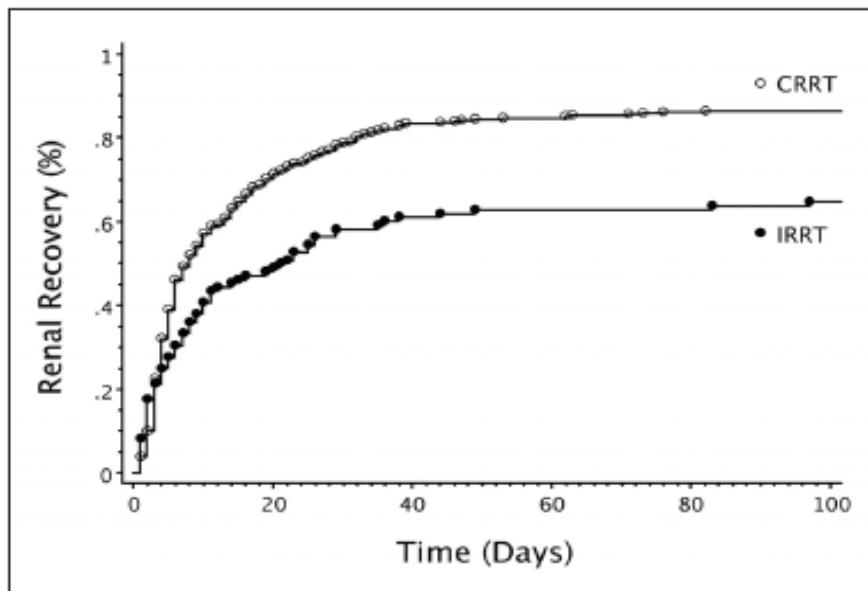
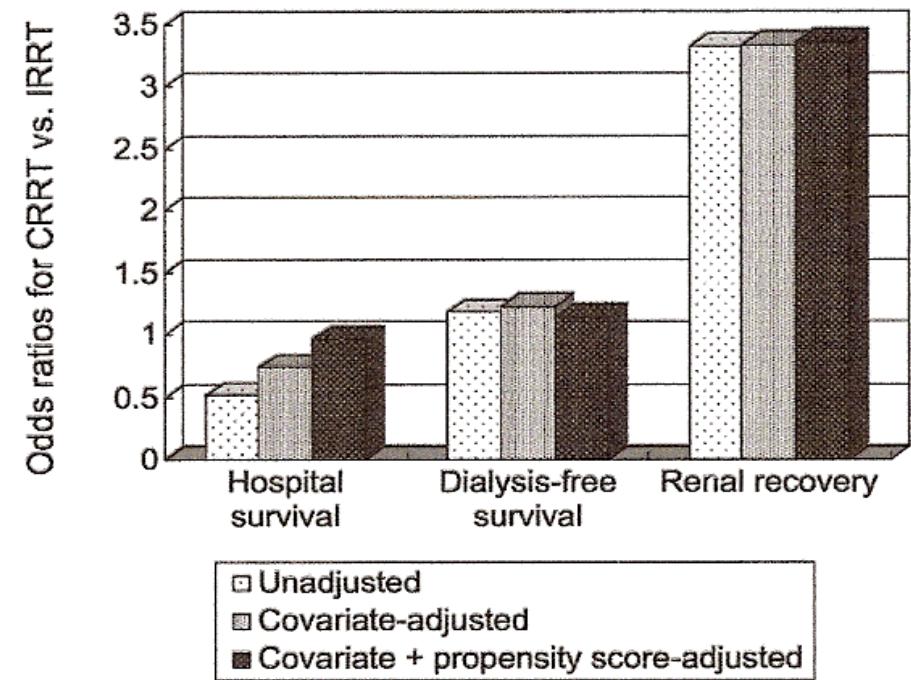
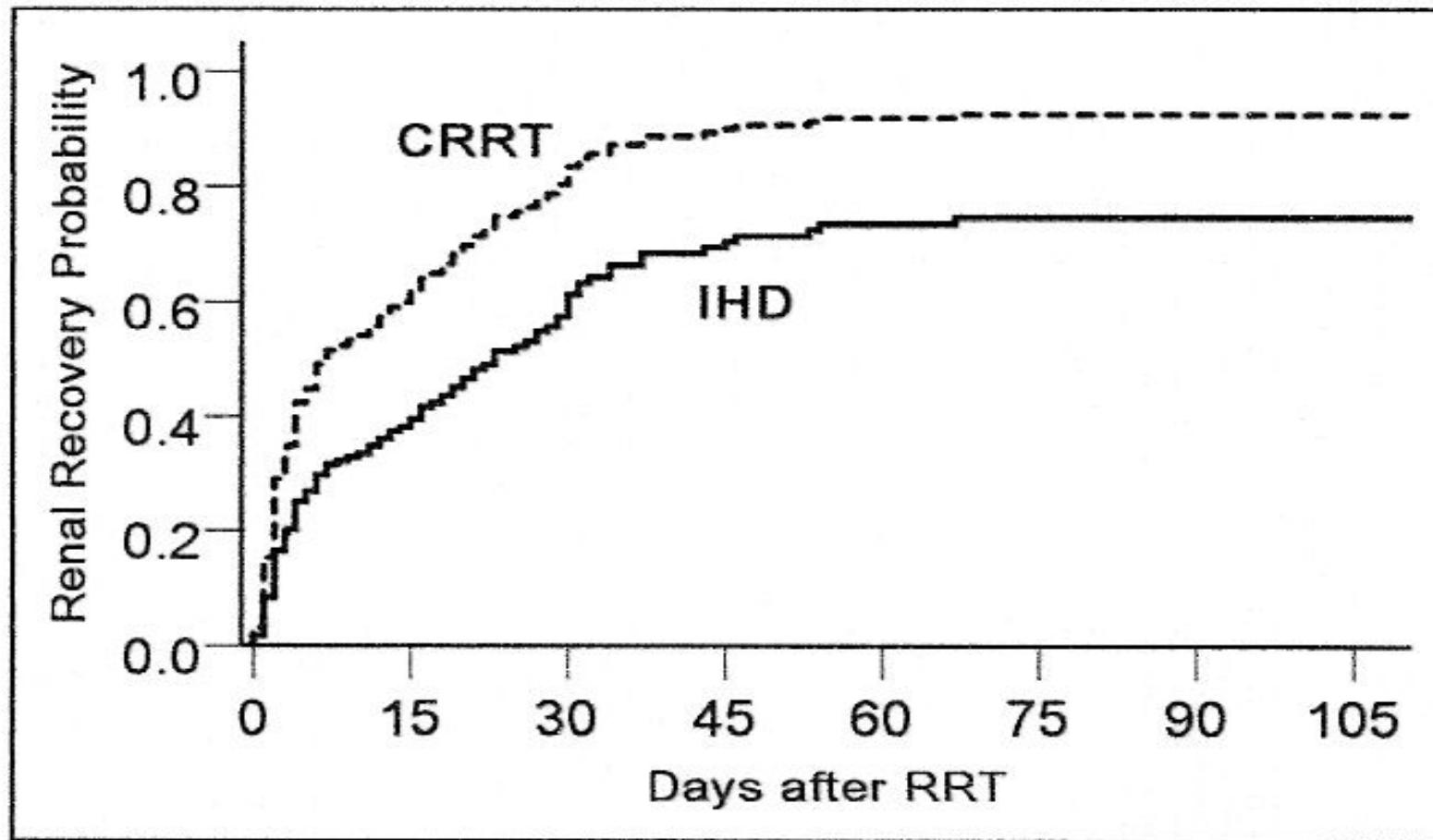


Fig. 1 - Renal recovery at hospital discharge as a function of initial dialysis modality in the BEST Kidney study (22). CRRT: continuous renal replacement therapy; IRRT: intermittent renal replacement therapy.



22. Uchino S, Bellomo R, Kellum JA, Morimatsu H, Morgera S, Schetz MR, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-Van Straaten HM, Ronco C; Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators Writing Committee. Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury. *Int J Artif Organs* 2007; 30: 281-92.

ESRD after postoperative AKI



The 90-day mortality and the subsequent renal recovery in critically ill surgical patients requiring acute renal replacement therapy.
Lin YF et al. Am J Surg. 2009 Sep;198(3):325-3

**RENAL RECOVERY IN SURVIVORS OF SEVERE ACUTE KIDNEY INJURY,
THE IMPACT OF RENAL REPLACEMENT THERAPY MODALITY**

Antoine G. Schneider^{1,2}, Sean M. Bagshaw³, Neil J. Glassford¹, R. Bellomo^{1,2}

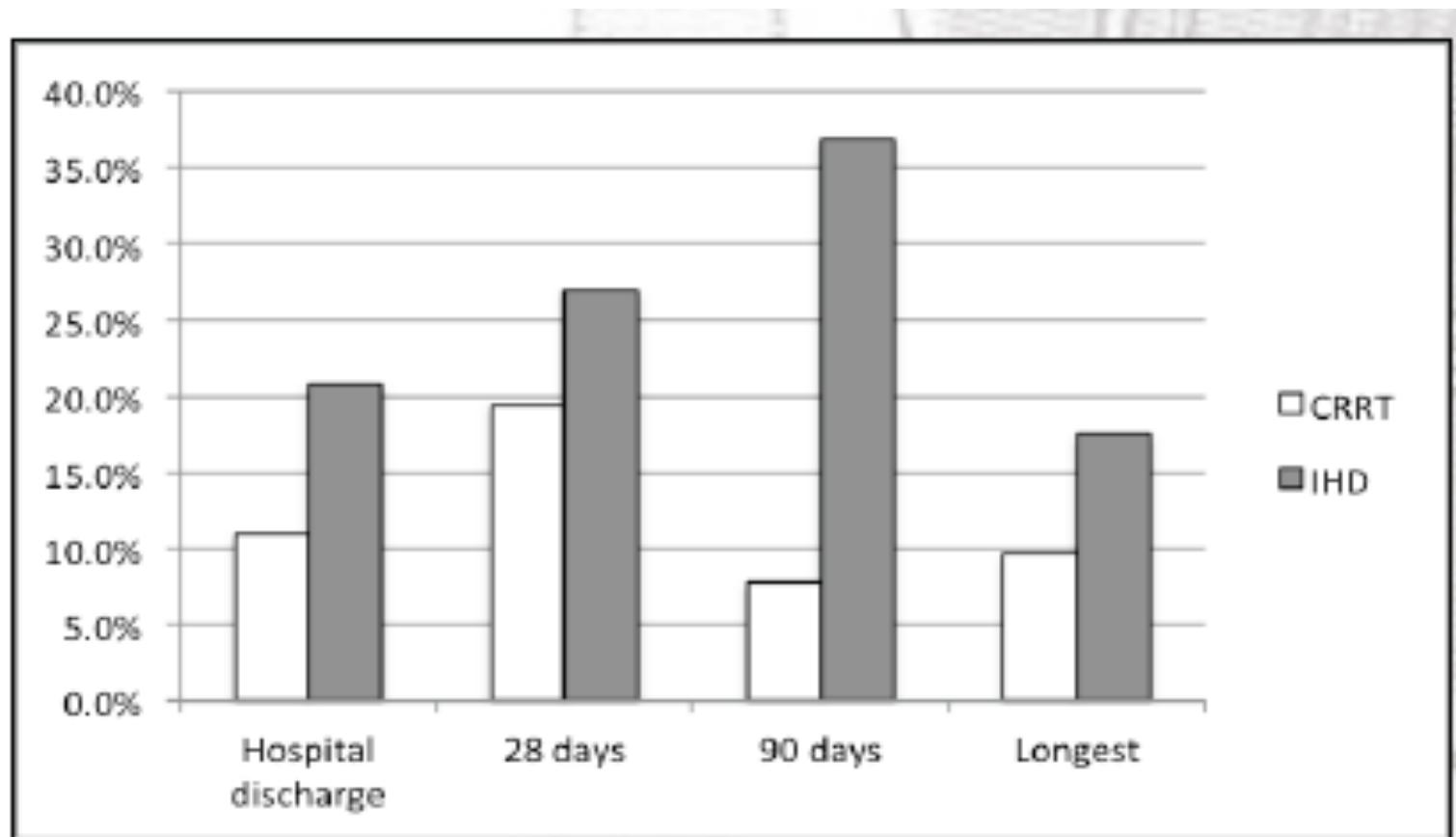


Fig. 2: Rate of RRT dependence in acute kidney injury survivors according to initial RRT modality

**RENAL RECOVERY IN SURVIVORS OF SEVERE ACUTE KIDNEY INJURY,
THE IMPACT OF RENAL REPLACEMENT THERAPY MODALITY**

Antoine G. Schneider^{1,2}, Sean M. Bagshaw³, Neil J. Glassford¹, R. Bellomo^{1,2}

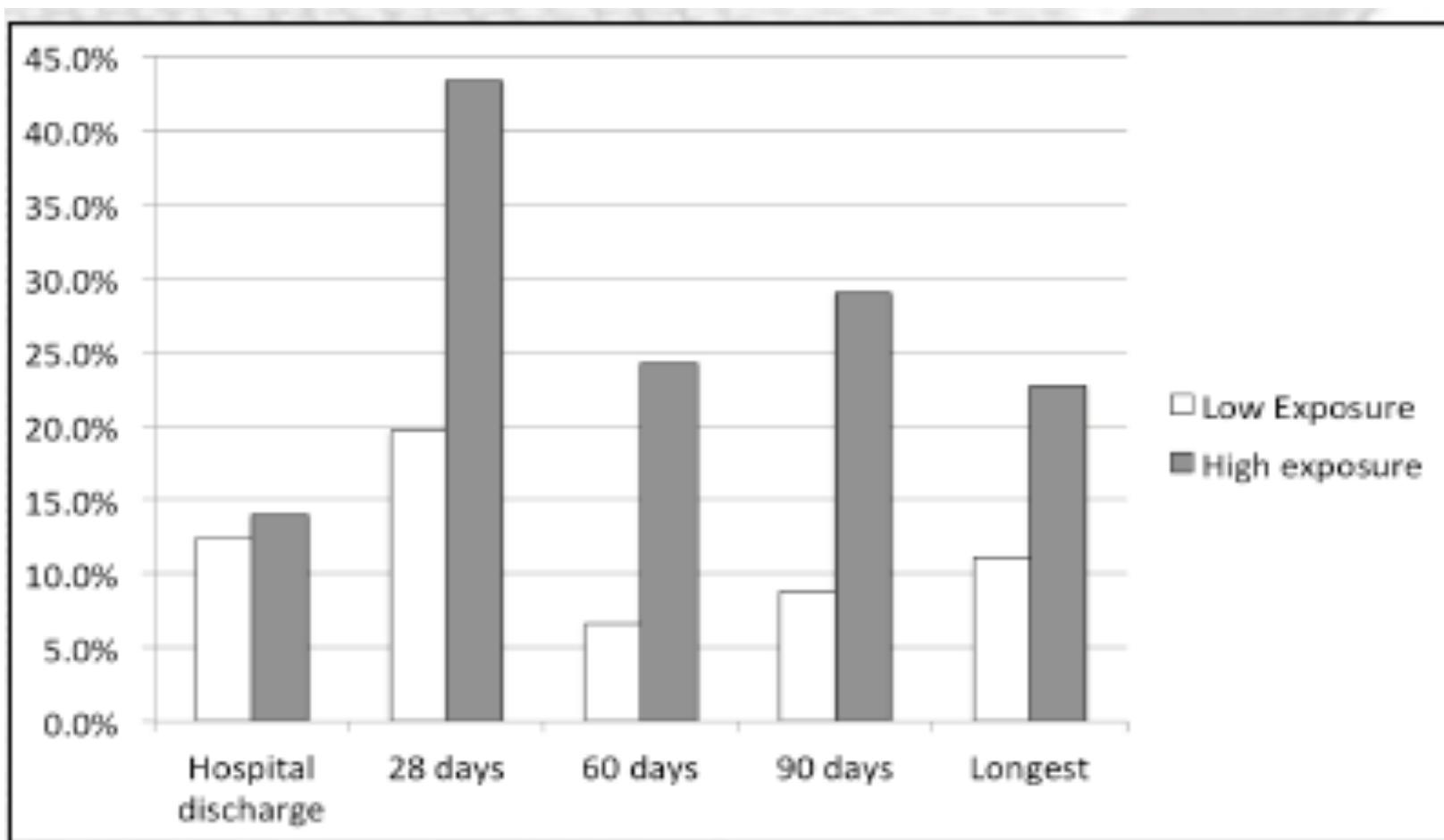


Fig. 3: Rate of RRT dependence in acute kidney injury survivors according to exposure to intermittent renal replacement therapy (IRRT).

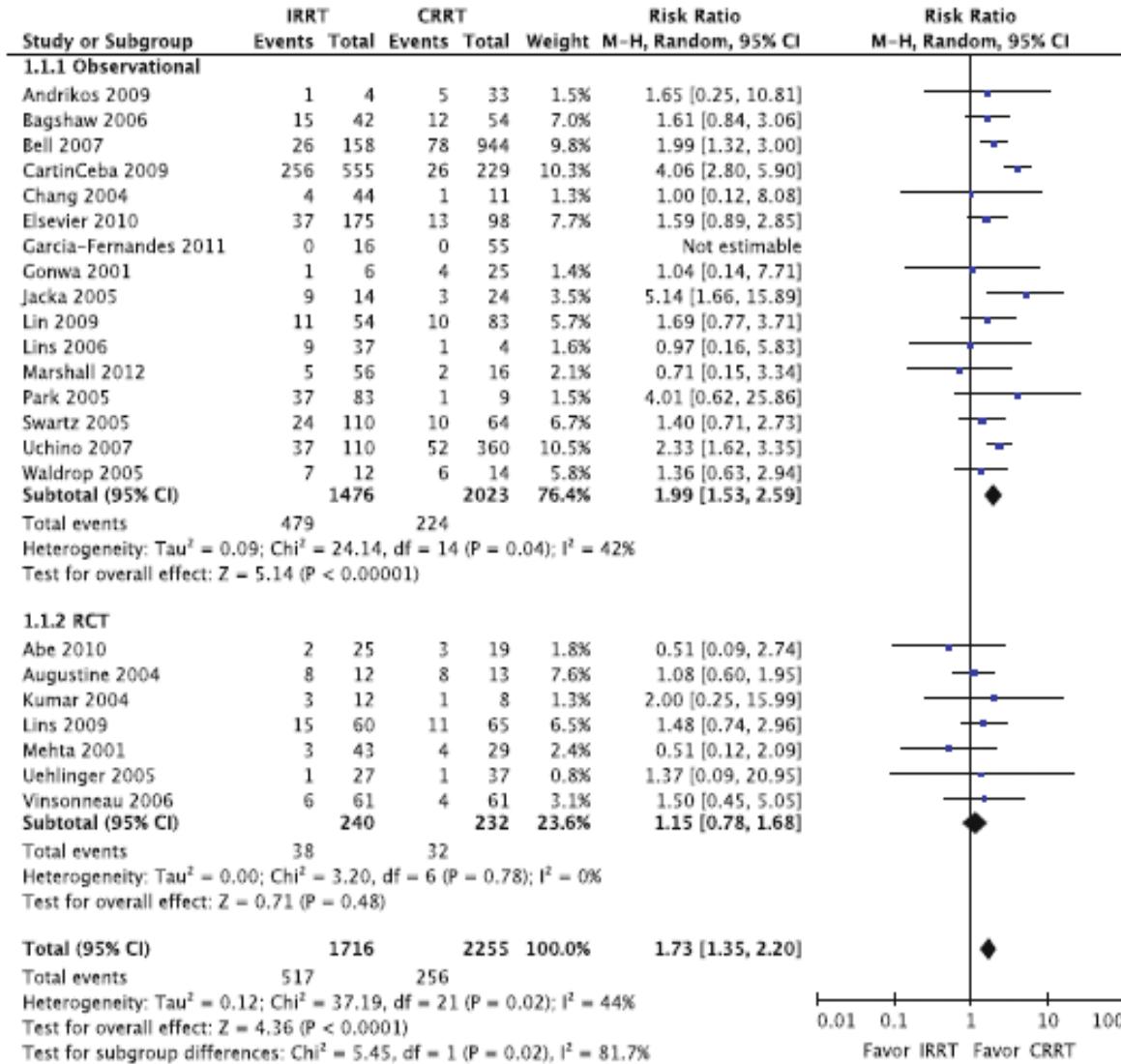


Fig. 2 Forest plot for dialysis dependence among survivors. Stratified by study design. M-H Mantel-Haenszel

[Intensive Care Med.](#) 2013 Jun;39(6):987-97.

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

Schneider AG, Bellomo R, Bagshaw SM, Glassford NJ, Lo S, Jun M, Cass A, Gallagher M.



VA/NIH Acute Renal Failure Trial Network study

The NEW ENGLAND
JOURNAL of MEDICINE

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

The VA/NIH Acute Renal Failure Trial Network*

ABSTRACT

BACKGROUND

The optimal intensity of renal-replacement therapy in critically ill patients with acute kidney injury is controversial.

METHODS

We randomly assigned critically ill patients with acute kidney injury and failure of at least one nonrenal organ or sepsis to receive intensive or less intensive renal-replacement therapy. The primary end point was death from any cause by day 60. In both study groups, hemodynamically stable patients underwent intermittent hemodialysis, and hemodynamically unstable patients underwent continuous venovenous hemodiafiltration or sustained low-efficiency dialysis. Patients receiving the intensive treatment strategy underwent intermittent hemodialysis and sustained low-efficiency dialysis six times per week and continuous venovenous hemodiafiltration at 35 ml per kilogram of body weight per hour; for patients receiving the less-intensive treatment strategy, the corresponding treatments were provided thrice weekly and at 20 ml per kilogram per hour.

The members of the writing committee (Paul M. Palevsky, M.D., Jane Hongyuan Zhang, Ph.D., Theresa Z. O'Connor, Ph.D., Glenn M. Chertow, M.D., M.P.H., Susan T. Crowley, M.D., Devasmita Choudhury, M.D., Kevin Finkel, M.D., John A. Kellum, M.D., Emil Paganini, M.D., Roland M.H. Schein, M.D., Mark W. Smith, Ph.D., Kathleen M. Swanson, M.S., R.Ph., B. Taylor Thompson, M.D., Anitha Vijayan, M.D., Suzanne Watnick, M.D., Robert A. Star, M.D., and Peter Peduzzi, Ph.D.) of the Veterans Affairs/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network assume responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Palevsky at 7E123 (111F-U), VA Pittsburgh Healthcare System, University Dr., Pittsburgh, PA 15240, or at palevsky@pitt.edu.



The RENAL Replacement Therapy study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

OCTOBER 22, 2009

VOL. 361 NO. 17

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*

ABSTRACT

BACKGROUND

The optimal intensity of continuous renal-replacement therapy remains unclear. We conducted a multicenter, randomized trial to compare the effect of this therapy, delivered at two different levels of intensity, on 90-day mortality among critically ill patients with acute kidney injury.

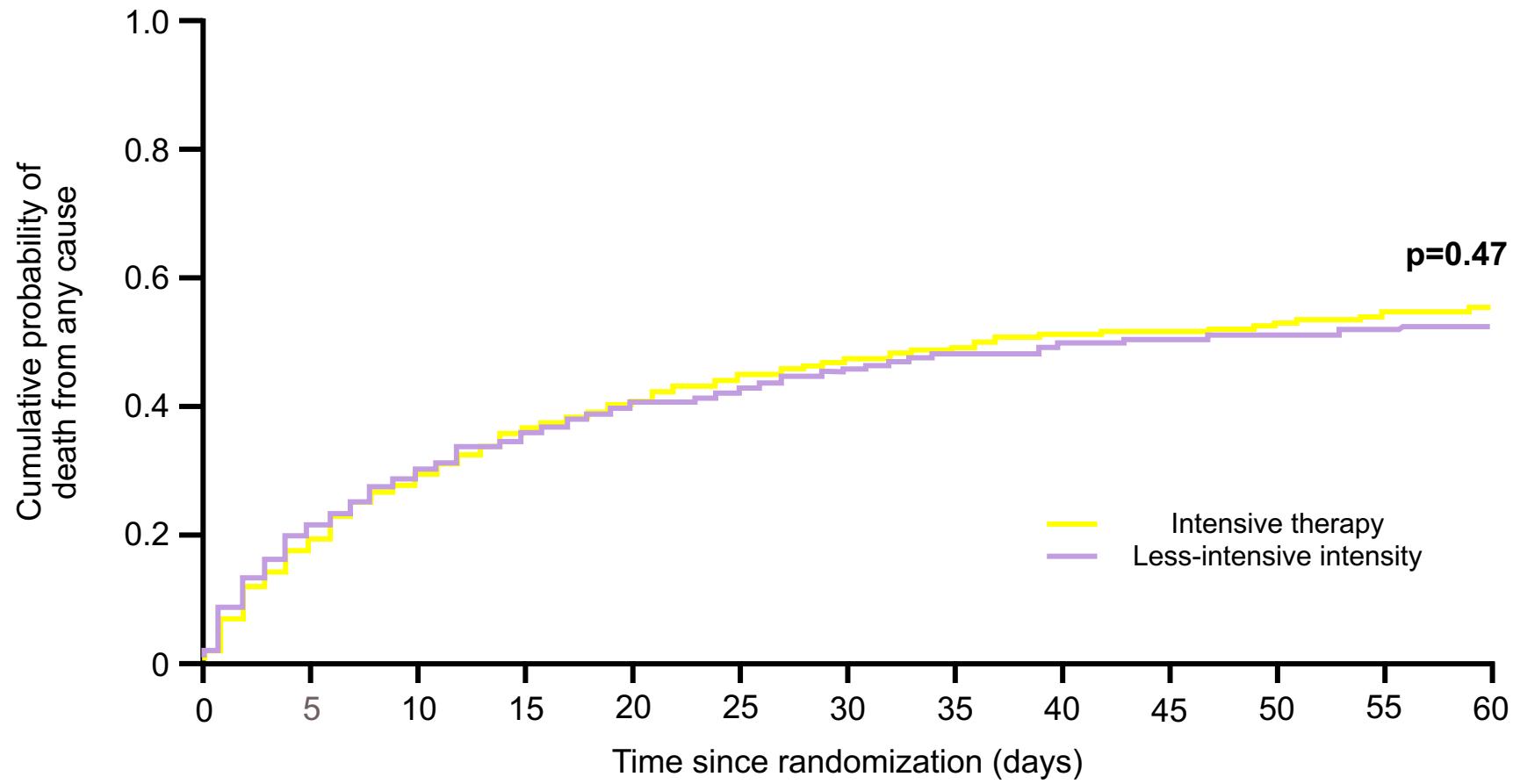
METHODS

We randomly assigned critically ill adults with acute kidney injury to continuous renal-replacement therapy in the form of postdilution continuous venovenous hemodiafiltration with an effluent flow of either 40 ml per kilogram of body weight per hour (higher intensity) or 25 ml per kilogram per hour (lower intensity). The primary outcome measure was death within 90 days after randomization.

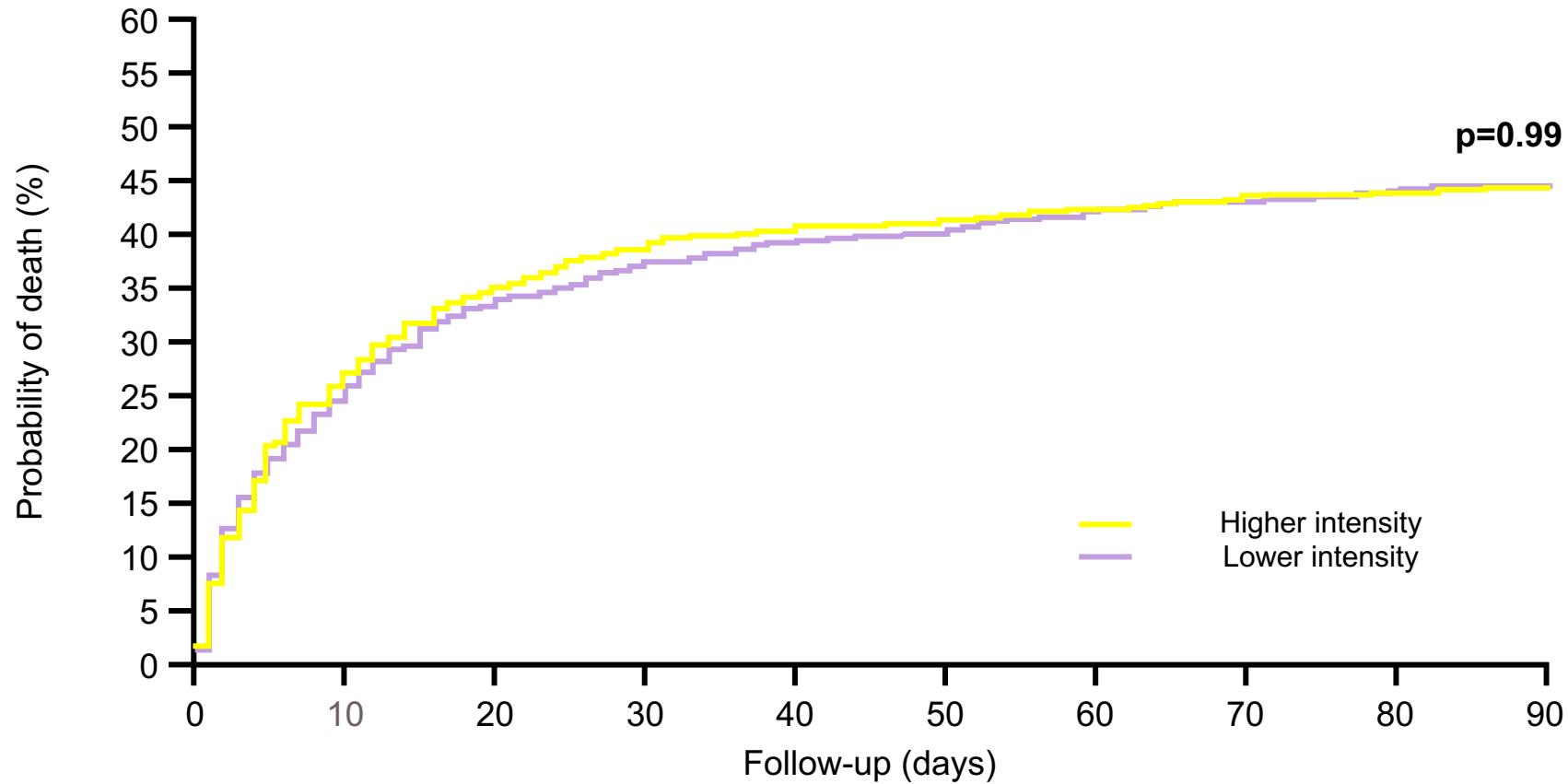
The Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group and the George Institute for International Health. The members of the Writing Committee for the RENAL Replacement Therapy Study (Rinaldo Bellomo, M.D., Alan Cass, M.D., Ph.D., Louise Cole, M.D., Ph.D., Simon Finfer, M.D., Martin Gallagher, M.D., Serigne Lo, Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., John Myburgh, M.D., Ph.D., Robyn Norton, M.D., Ph.D., M.P.H., Carlos Scheinkestel, M.D., and Steve Su, Ph.D.) take re-



VA/NIH study: RRT intensity and mortality



RENAL study: RRT intensity and mortality



RENAL & VA/NIH: Baseline differences

	RENAL ¹	VA/NIH ²
Enrolled	1,508	1,124
Mean age (years)	64.5	59.7
Male (%)	64.6	70.6
Mean weight (kg)	80.6	84.1
Sepsis (%)	49.5	63
Pre-randomisation dialysis (%)	0	64.3
ICU days before randomisation	2.1	6.7
Vasopressors at randomisation (%)	47.5	54.7
Total SOFA score	7.55	7.40
Ventilation (%)	73.9	80.6

RENAL & VA/NIH: Clinical outcomes

	RENAL ¹	VA/NIH ²
Mortality day 90 (%)	44.7	
Mortality day 60 (%)		52.5
Duration RRT (days)	12.2	?
Hospital length of stay (days)	25.2	?
*RRT dependence @ day 28 (%)	13.3	45.2
*RRT dependence @ day 60 (%)		24.6
*RRT dependence @ day 90 (%)	5.6	

Differences in IHD use!!!

VA/NIH study¹

Total of 5,077 IHD sessions in 1,124 patients

- Overall number of IHD sessions per patient = 4.8
- Number of isolated ultrafiltration sessions = 259
 - Daily fluid balance during RRT = +128 mL/day (first 14 days of study)
 - SLEDD sessions = 299

RENAL study²

Total of 3,432 IHD sessions in 1,508 patients

- Overall number of IHD sessions per patients = 2.3
- Number of isolated ultrafiltration sessions = 0
 - Daily fluid balance during RRT = -20 mL/day (during study treatment)
 - SLEDD session = ??

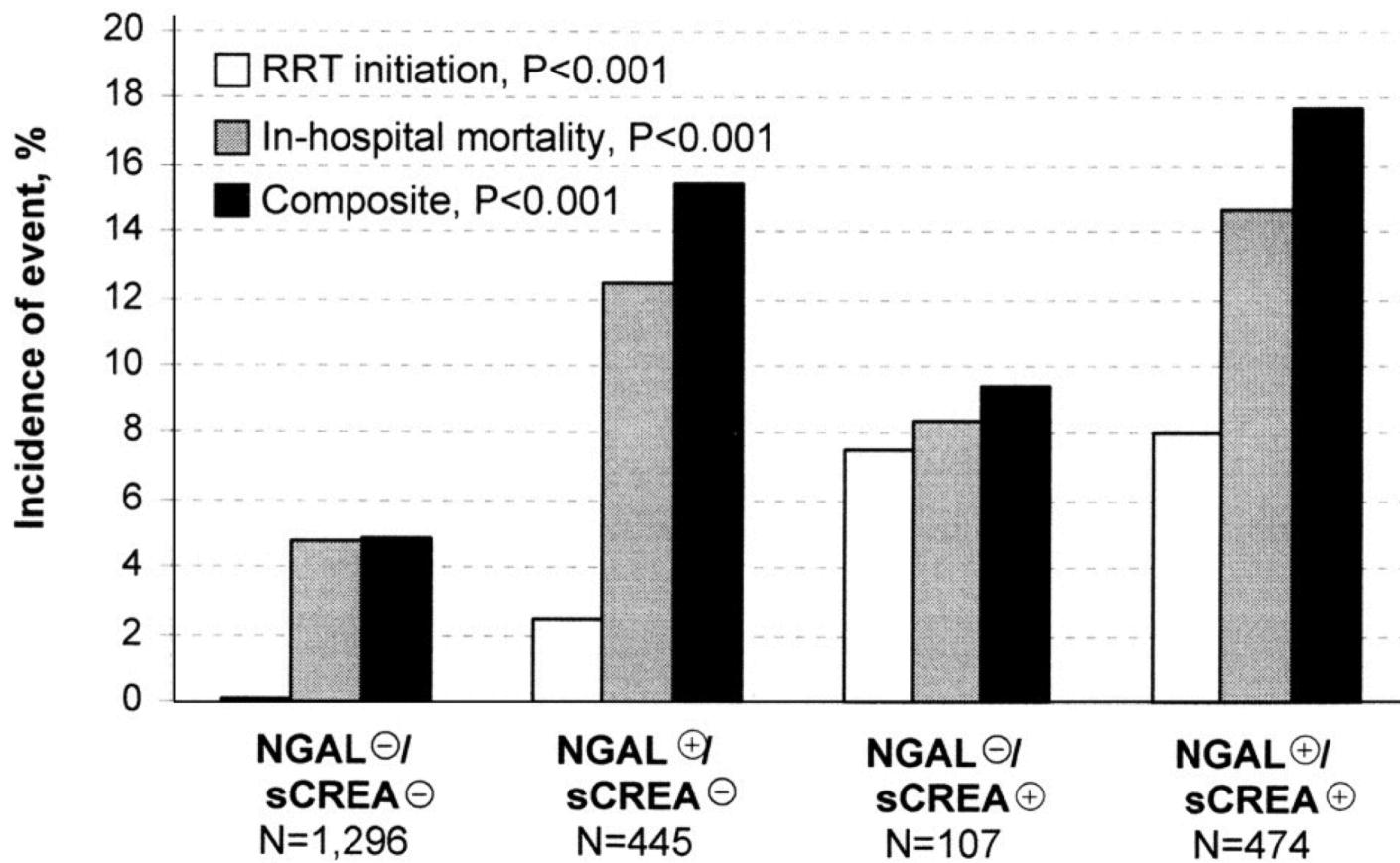
More than twice the amount of intermittent dialysis

Is IHD nephrotoxic?

- IHD is associated with hypotension (as seen in ATN¹)
- Hypotension may cause renal injury
- Biopsy evidence of fresh ischaemia in the 1970s when IHD was done for AKI
- Fresh ischaemic injury = delayed recovery
- Fluid balance more positive in ATN
- Positive FB = organ oedema = perhaps kidney oedema
- Kidney oedema = delayed recovery

Do we have other evidence?

Subclinical AKI



Subclinical AKI, in plain writing

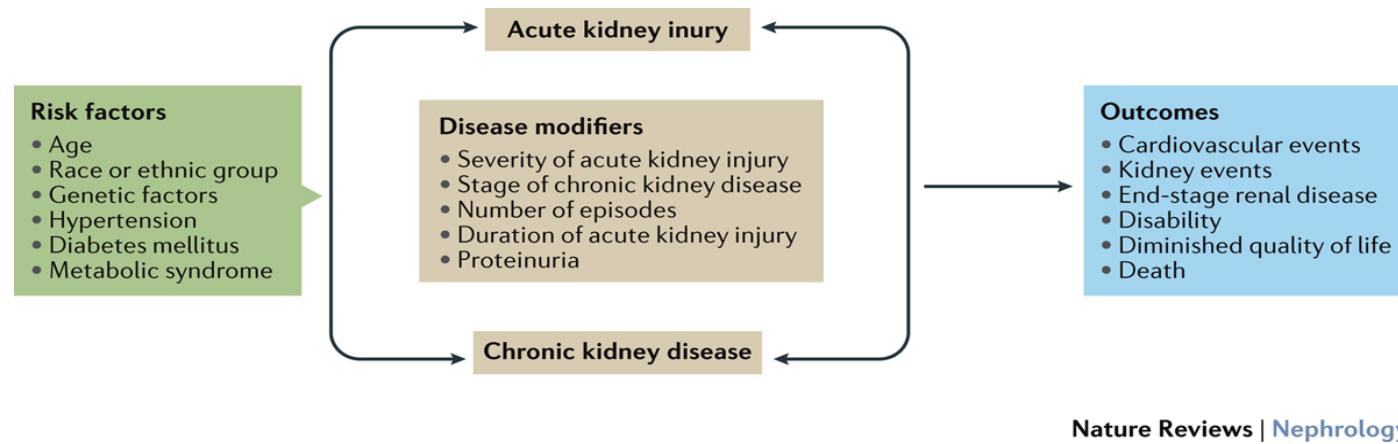
Entities of acute kidney injury syndrome

- A. No AKI (RIFLE-negative and biomarker-negative)
- B. AKI with filtration dysfunction (RIFLE/AKIN/KDIGO-positive)
- C. AKI with tubular damage (biomarker-positive) = ‘subclinical AKI’
- D. AKI with tubular damage (biomarker-positive) *and* filtration dysfunction (RIFLE/AKIN/KDIGO-positive)

AKD; acute kidney disease

Oh no. Another definition...

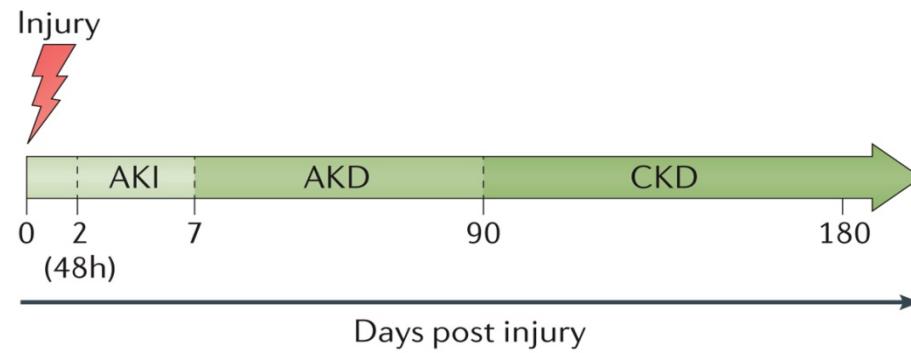
Figure 1 Acute kidney injury and chronic kidney disease



Nature Reviews | Nephrology

Modified from Acute Dialysis Quality Initiative 16; www.adqi.org.

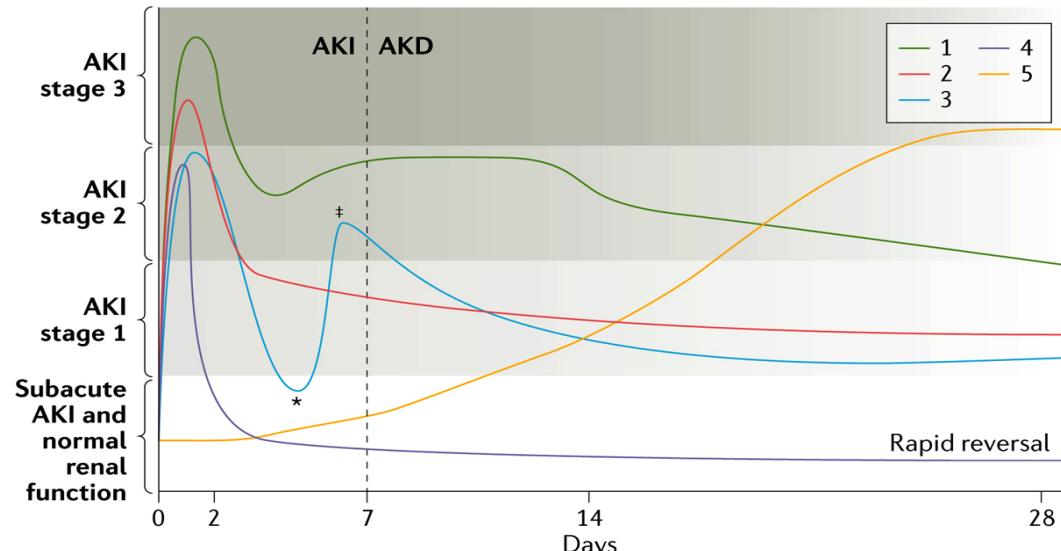
Figure 2 The continuum of acute kidney injury (AKI), acute kidney disease (AKD) and chronic kidney disease (CKD)



Nature Reviews | Nephrology

Modified from Acute Dialysis Quality Initiative 16; www.adqi.org.

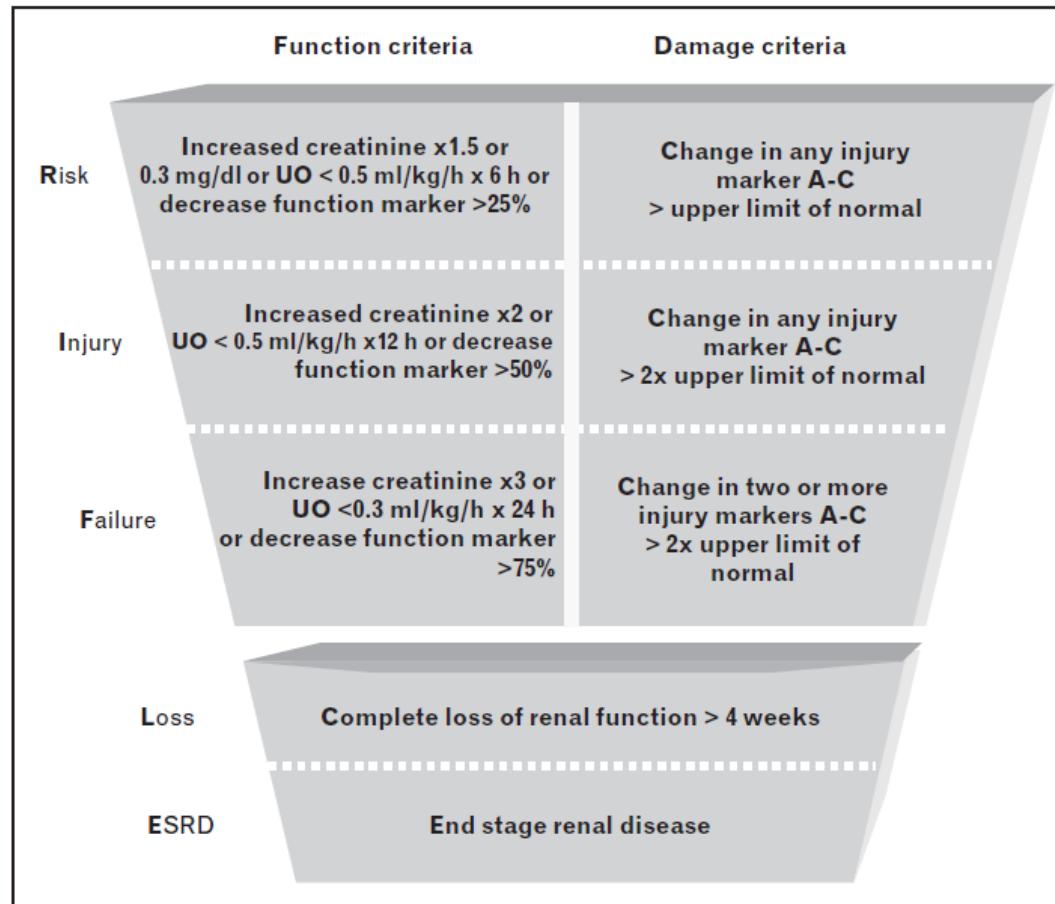
Figure 3 Hypothetical trajectories of acute kidney disease (AKD)



Nature Reviews | Nephrology

Modified from Acute Dialysis Quality Initiative 16; www.adqi.org.

Future classification models(?)



Take home messages

Incidence of AKI is on the rise, mortality is still high

New data shows that AKI increases the risk of (**AKD and**) chronic kidney injury, including the risk for progression to life long dialysis dependence

The risk for progression to life long dialysis dependence is extra high in acute on chronic kidney injury

The risk for progression to life long dialysis dependence seems to be associated with choice of modality during the ICU stay

AKI, and the grade of AKI, is associated with increased mortality

Novel markers will probably change how we look at the incidence – and treatment – of AKI