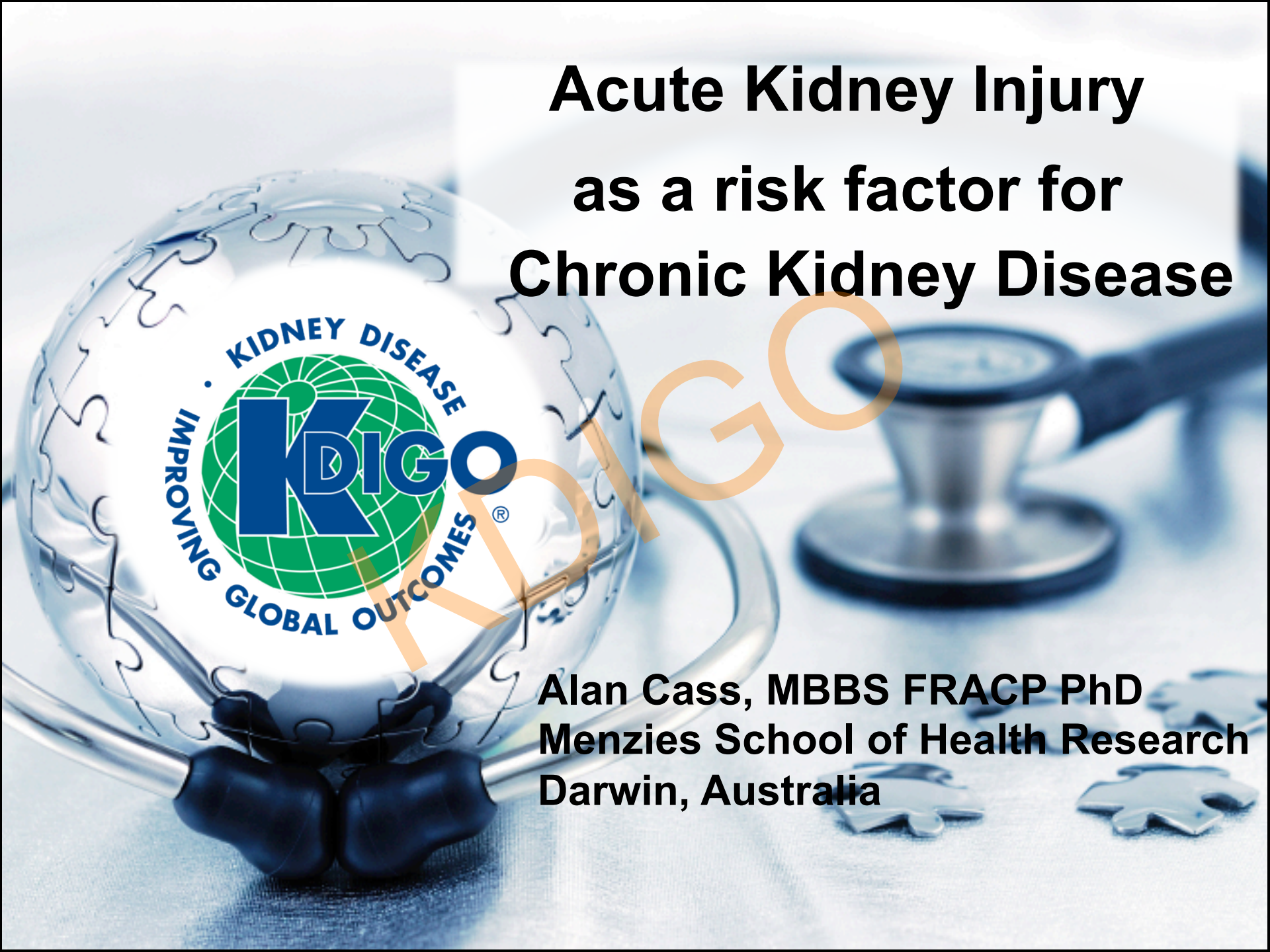
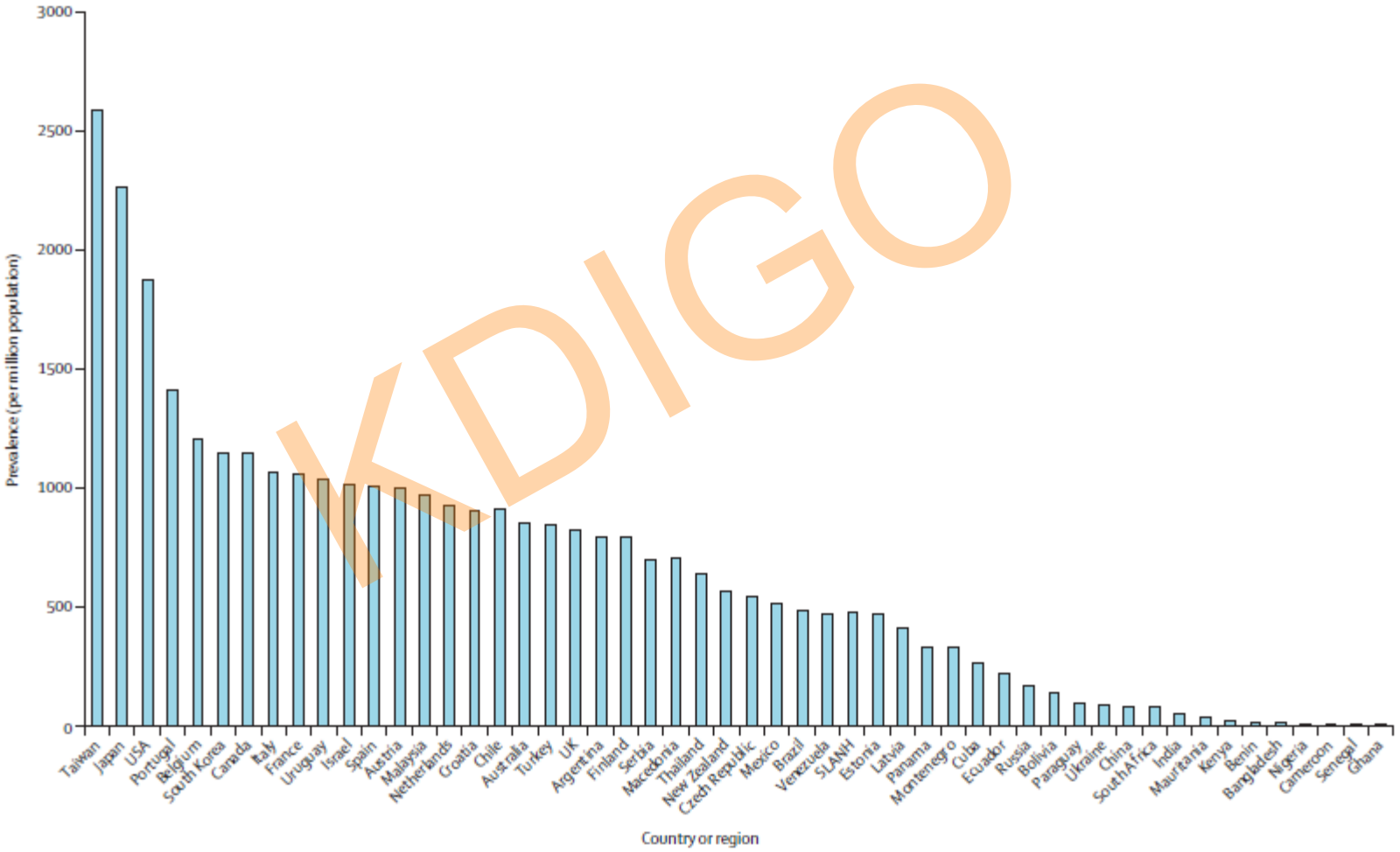
Acute Kidney Injury as a risk factor for Chronic Kidney Disease



Alan Cass, MBBS FRACP PhD
Menzies School of Health Research
Darwin, Australia

Global burden of kidney disease



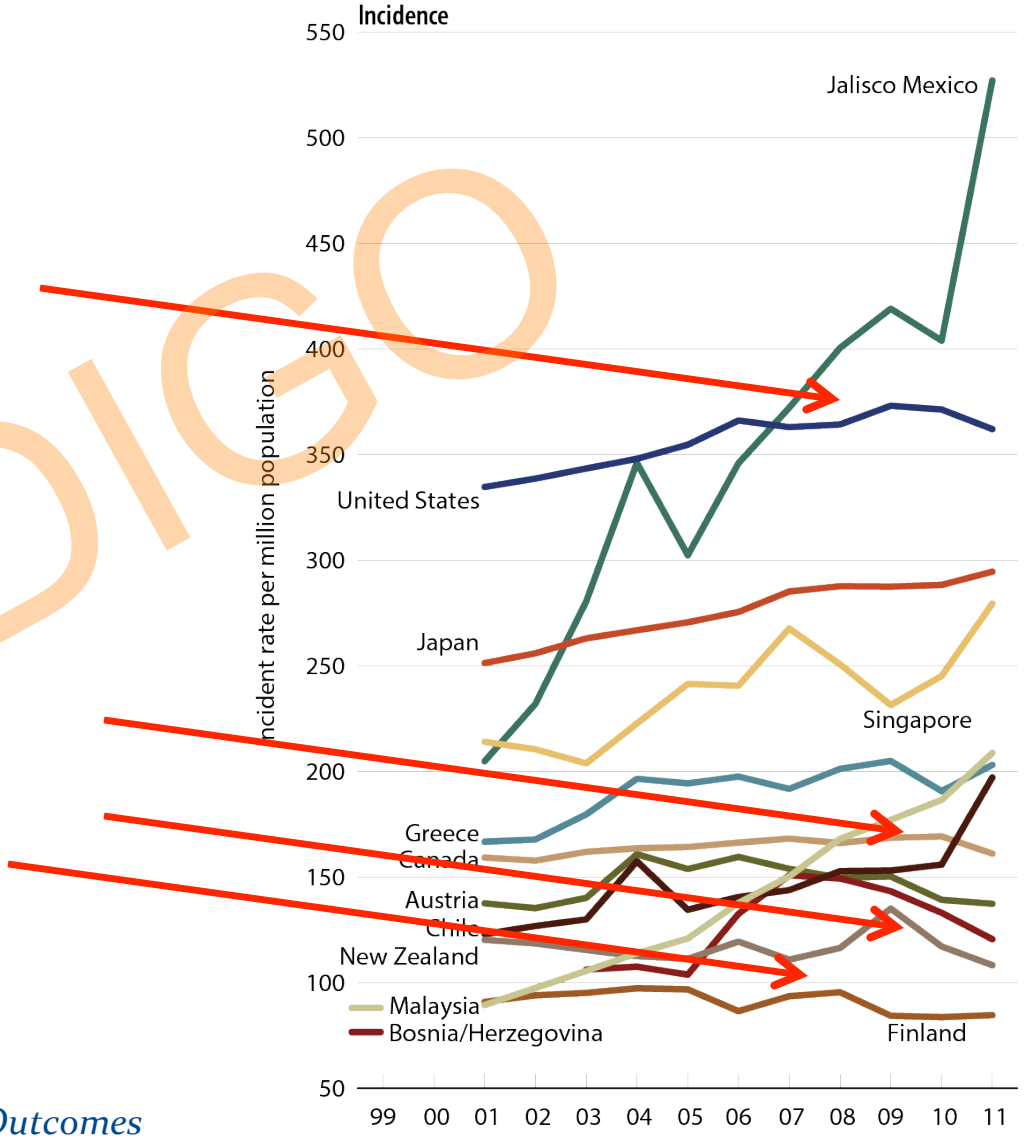
Jha et al – *Lancet* 2013

Globalization and kidney disease

White et al – *WHO Bulletin* 2008

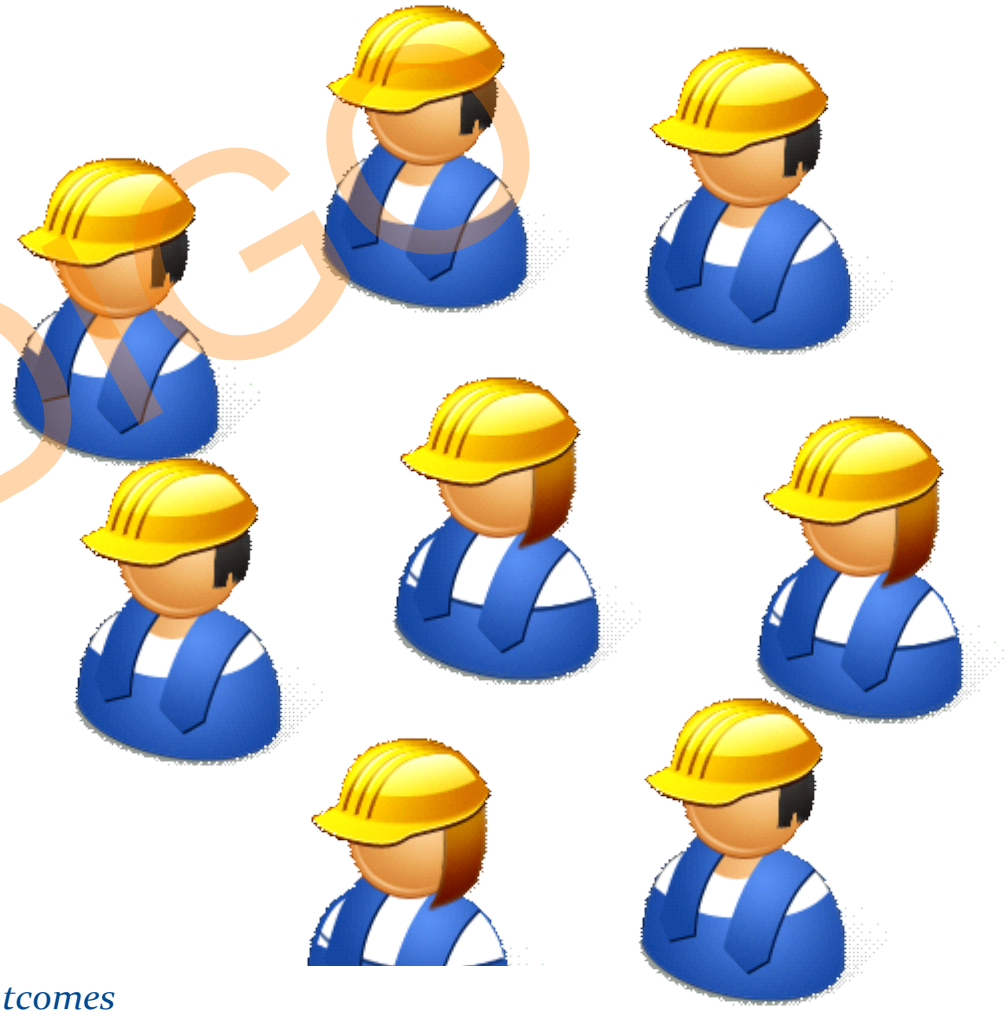
Kidney disease – winning the war?

Is incidence falling in high-income countries?



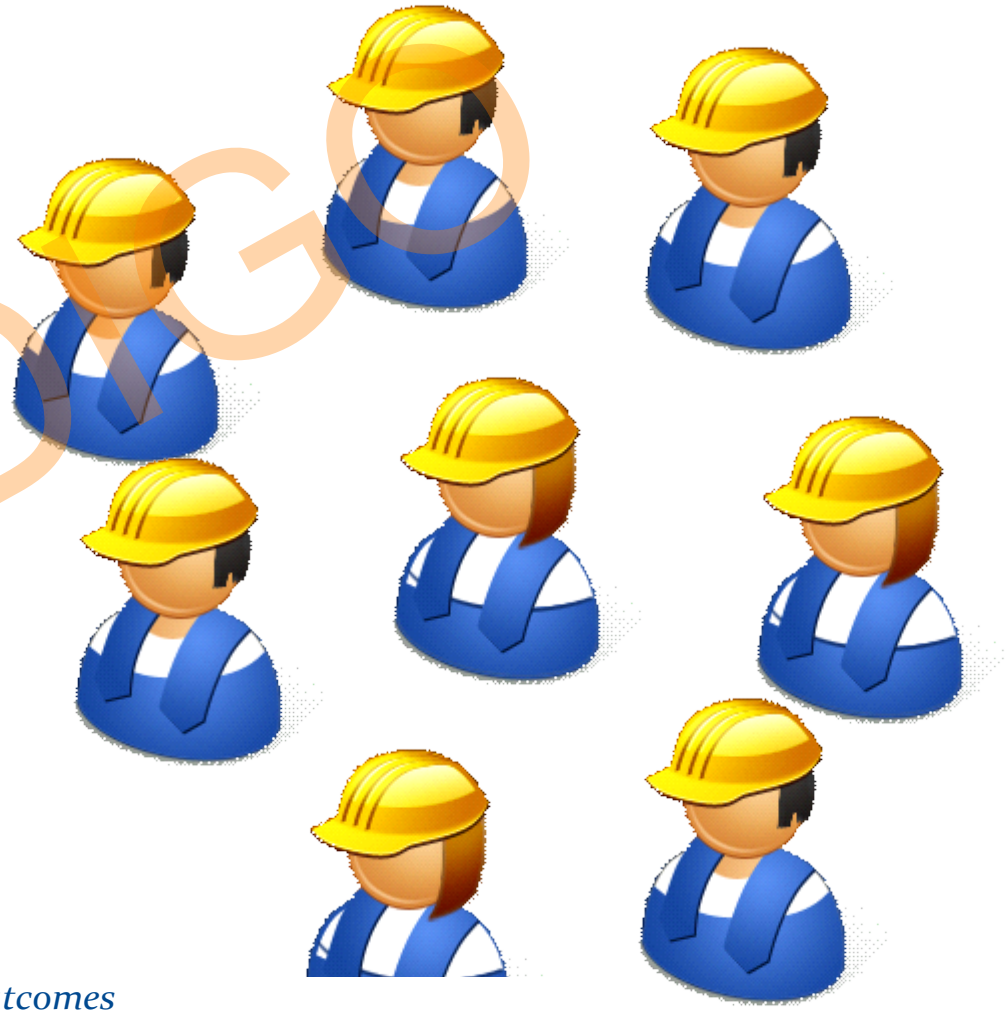
Ageing population

1970



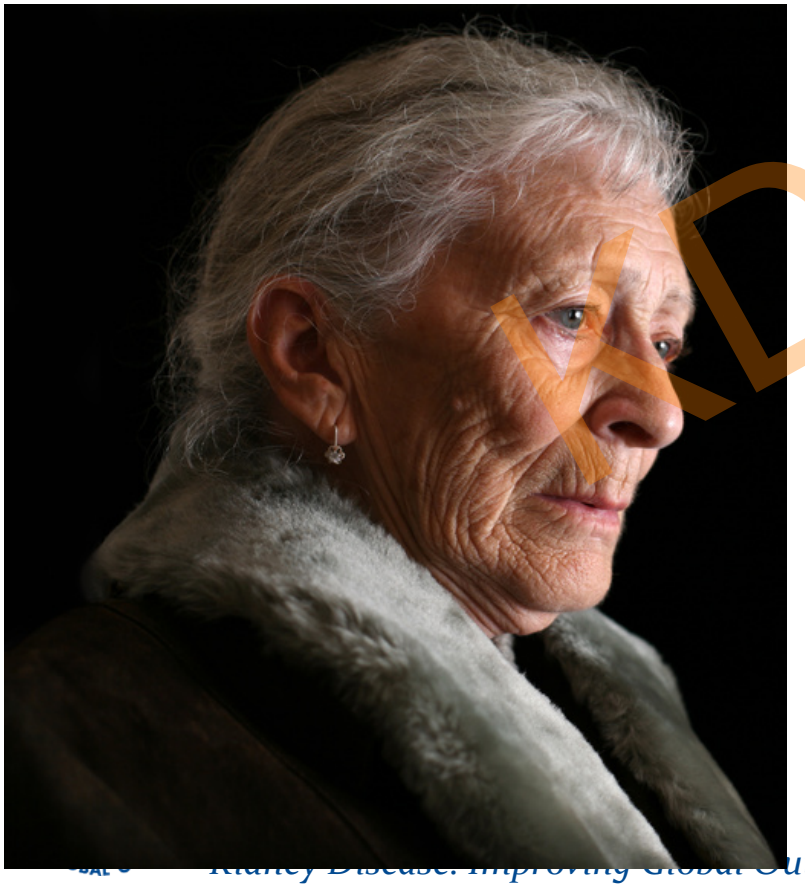
Ageing population

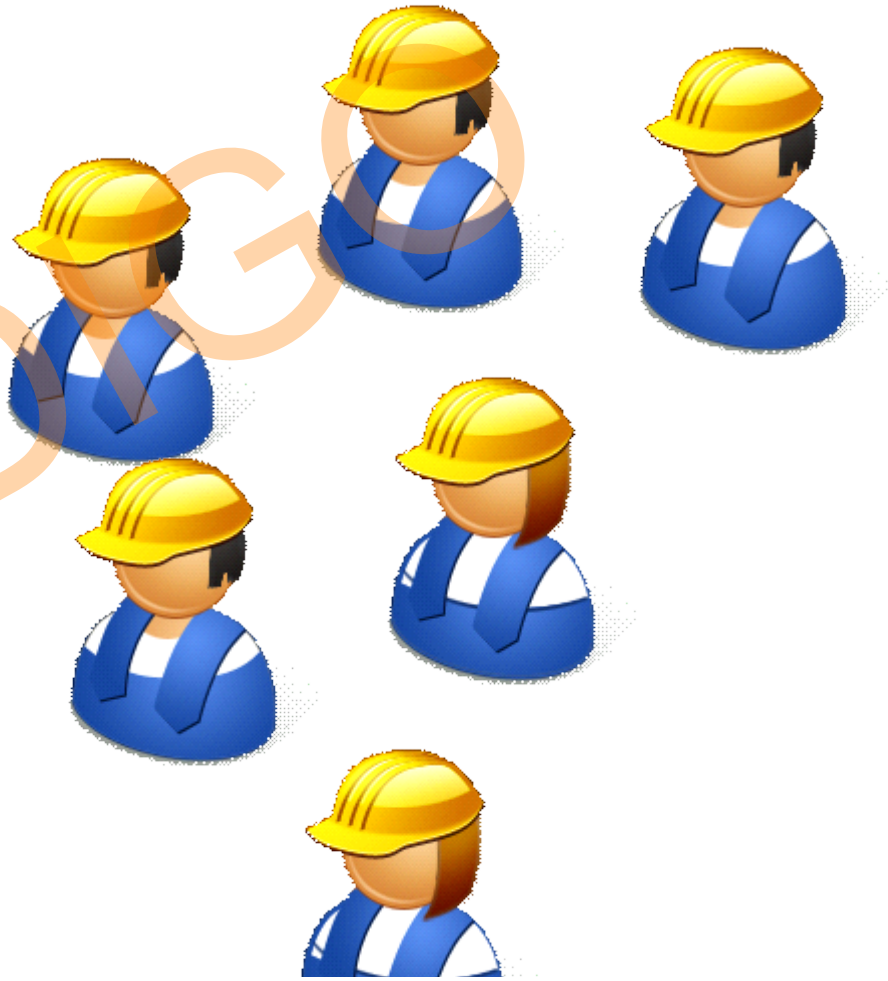
2010



Ageing population

2050





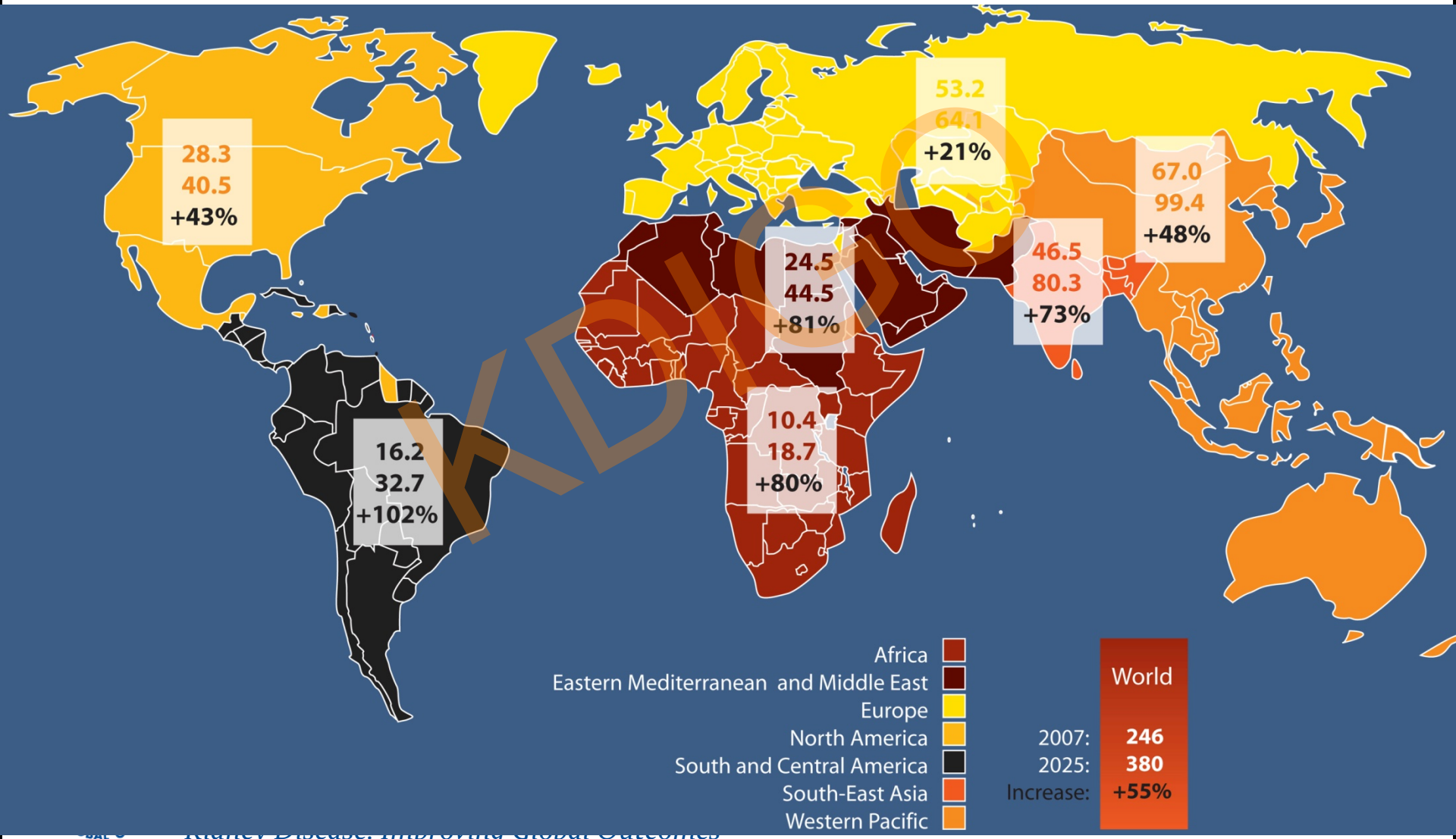
Ageing across Asia-Pacific region

2009			2050		
Country	**15-59:60+**	**Rank**	**Country**	**15-59:60+**	**Rank**
Japan	1.92	1	Japan	1.01	1
Australia	3.24	2			
USA	3.45	3			
Hong Kong	3.97	4			
Singapore	4.51	5			
S. Korea	4.51	6			
Taiwan	4.75	7			
China	5.71	8			
Vietnam	7.63	9			

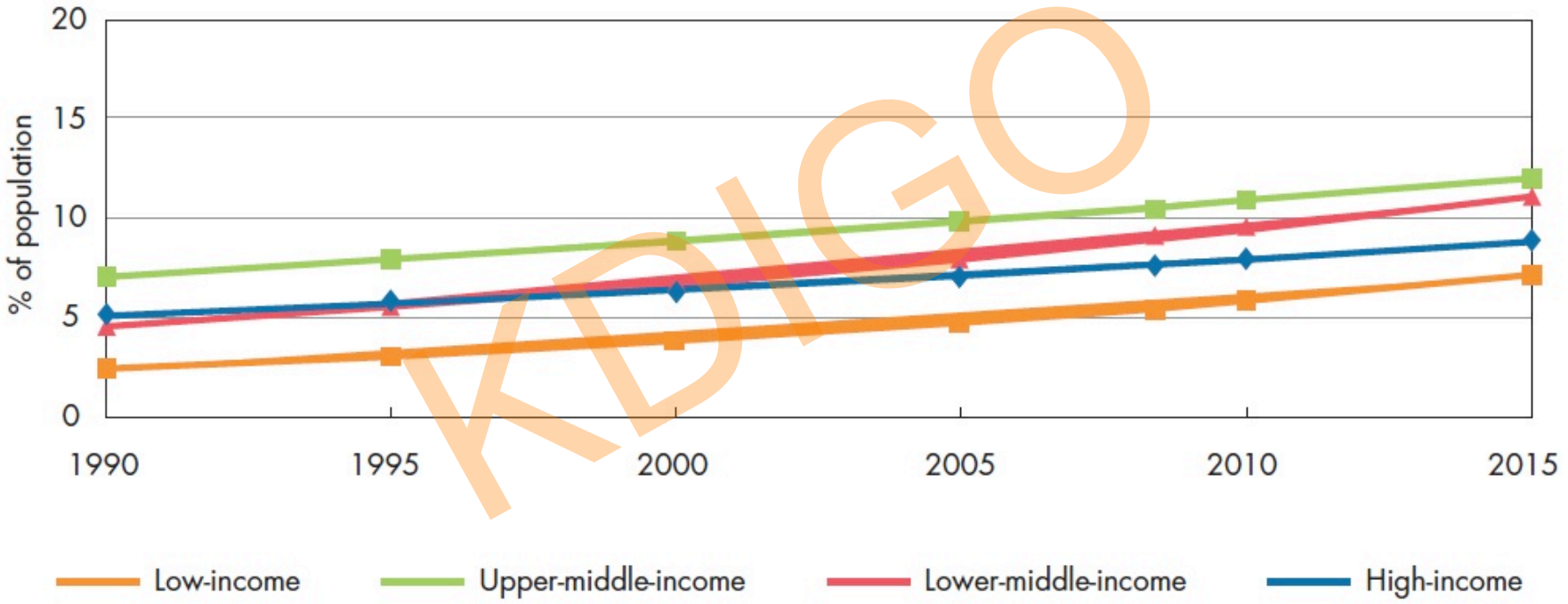
Ageing across Asia-Pacific region

2009			2050		
Country	**15-59:60+**	**Rank**	**Country**	**15-59:60+**	**Rank**
Japan	1.92	1	Japan	1.01	1
Australia	3.24	2	Taiwan	1.14	2
USA	3.45	3	S. Korea	1.17	3
Hong Kong	3.97	4	Singapore	1.24	4
Singapore	4.51	5	Hong Kong	1.25	5
S. Korea	4.51	6	China	1.73	6
Taiwan	4.75	7	Australia	1.82	7
China	5.71	8	USA	2.03	8
Vietnam	7.63	9	Vietnam	2.13	9

Increasing burden of diabetes



Coming wave of obesity in children



WHO 2010

Who is at risk of CKD?

Who is at risk of CKD?

- 1 in 3 adult Australians is at an increased risk of developing CKD.
- Adult Australians are at increased risk of developing CKD if they:
  - are 60 years or older
  - have diabetes
  - have a family history of kidney disease
  - have established cardiovascular disease
  - have high blood pressure
  - are obese (body mass index ≥ 30)
  - are a smoker
  - are of Aboriginal or Torres Strait Islander origin*

Typically previous episode of AKI not featured amongst risk factors

Kidney Health Australia 2012

KDIGO – AKI definition

2.1.1: AKI is defined as any of the following:

- Increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours; or
- Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 ml/kg/h for 6 hours

KDIGO – AKI staging/ severity

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 µmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

KDIGO – AKI causes

Table 6 | Causes of AKI: exposures and susceptibilities for non-specific AKI

Exposures	Susceptibilities
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	CKD
Cardiac surgery (especially with CPB)	Chronic diseases (heart, lung, liver)
Major noncardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anemia
Poisonous plants and animals	

Traditional concept of AKI recovery

- Pre-renal phase
- Acute kidney injury that is reversible
- Predictable and complete recovery
- No long-term sequelae

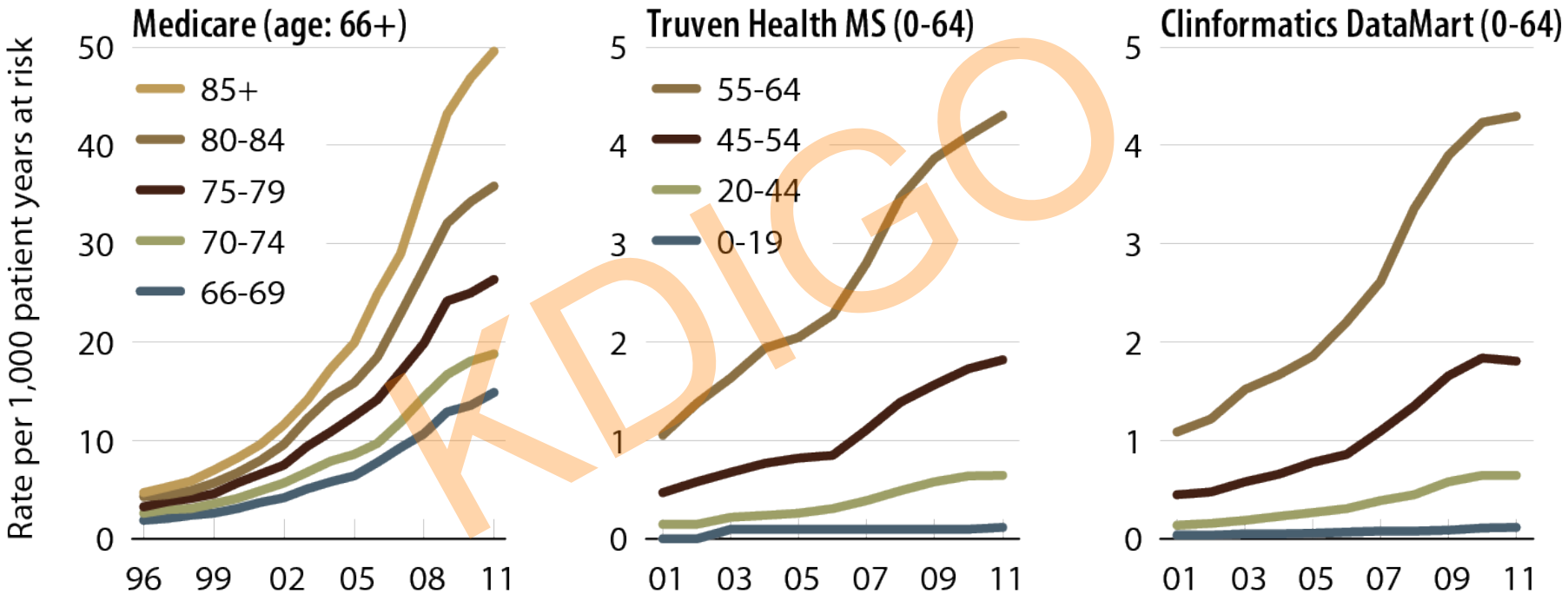
Acute Kidney Injury

- Increasing incidence, especially in hospitalized elderly patients
- Prolongs hospital stay
- Often requires ICU transfer/dialysis support
- In hospital mortality remains high

Patients with at least one recognized AKI event

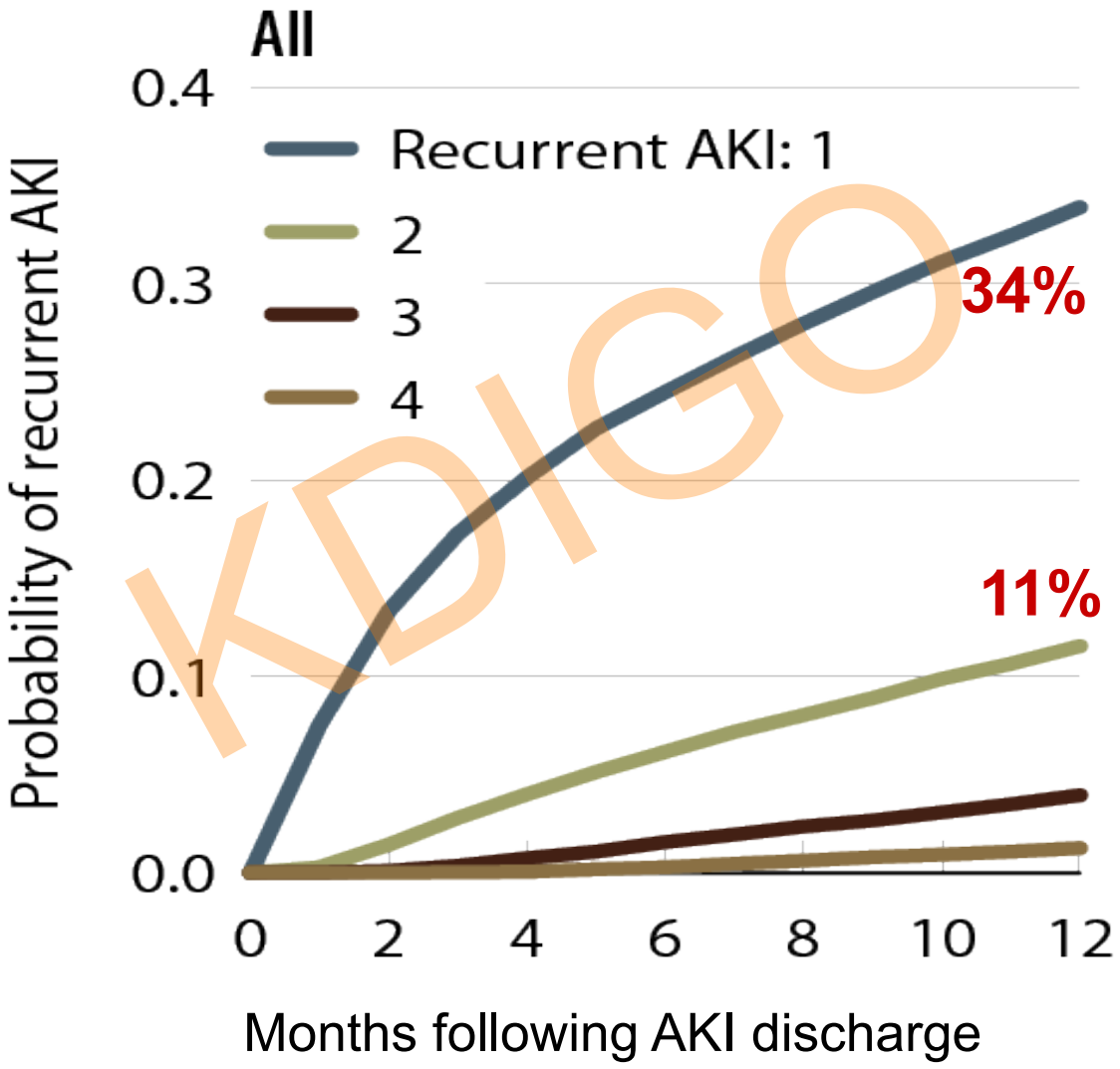
Medicare patients age 66 & older. USRDS 2013

Rate of first AKI - 2011



USRDS 2013

Probability of a recurrent AKI hospitalization in next 12 months



USRDS 2013

AKI and CKD - Interplay

- Accept that CKD is a risk factor for AKI
- Concentrate on AKI as a risk factor for CKD
- Long-term follow-up of survivors RCT of intense vs standard CRRT for severe AKI
- Is there any evidence to suggest that modality of treatment for severe AKI affects dialysis dependence in survivors?

CKD as a risk factor for AKI

Alberta Kidney Disease Network study

- 920,985 adults living in Alberta
- Followed median 35 months
- 6520 (0.7%) admitted with AKI
- Stratified by eGFR and proteinuria
- Examined risk for hospitalization with AKI

James et al – *Lancet* 2010

Risk factors for AKI admission

Reference group eGFR ≥60mLs/min/1.73m^2 and no proteinuria

- eGFR ≥60mLs/min/1.73m^2 and heavy proteinuria
  - AKI admission ARR 4.4, needing dialysis ARR 7.7
- eGFR 45.0 – 59.9 mLs/min/1.73m^2 and no proteinuria
  - AKI admission ARR 2.3, needing dialysis ARR 1.9
- eGFR 30.0 – 44.9 mLs/min/1.73m^2 and no proteinuria
  - AKI admission ARR 5.6, needing dialysis ARR 4.6
- eGFR 15.0 – 29.9 mLs/min/1.73m^2 and no proteinuria
  - AKI admission ARR 13, needing dialysis ARR 15

James et al – *Lancet* 2010

CKD after AKI – meta-analysis and SR

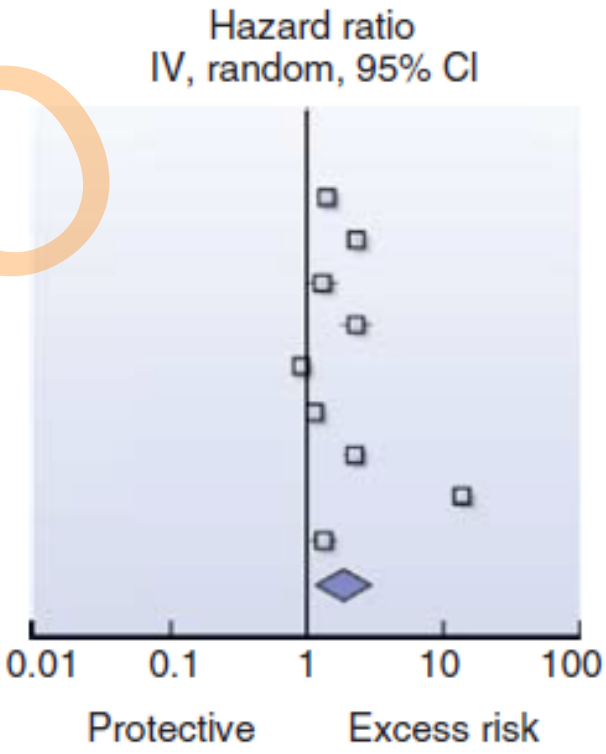
- SR comparing risk for death, CKD and ESRD in patients with and without AKI
- 13 studies with long-term renal and non-renal outcomes selected
- 11 followed more than 3,000 patients
- 1 in HIV, 2 included stem cell Tx recipients
- 8 cardiac surgery, ICU, coronary angiography, post MI, hospitalized cohort

Coca et al – *KI* 2012

Mortality after AKI

Study or subgroup	Weight (%)	Hazard ratio IV, random, 95% CI
Newsome *et al.* (14)	11.2	1.39 (1.35–1.43)
Ishani *et al.* (20)	11.2	2.38 (2.31–2.46)
Hsu *et al.* (10)	10.9	1.30 (1.03–1.64)
Lo *et al.* (11)	10.8	2.30 (1.76–2.99)
Wald *et al.* (17)	11.2	0.95 (0.89–1.02)
Choi *et al.* (12)	11.2	1.20 (1.13–1.28)
Lafrance *et al.* (18)	11.1	2.32 (2.04–2.63)
James *et al.* (16)	11.2	12.99 (12.08–13.96)
Ishani *et al.* (21)	11.1	1.38 (1.20–1.59)
Total (95% CI)	100.0	1.98 (1.26–3.11)

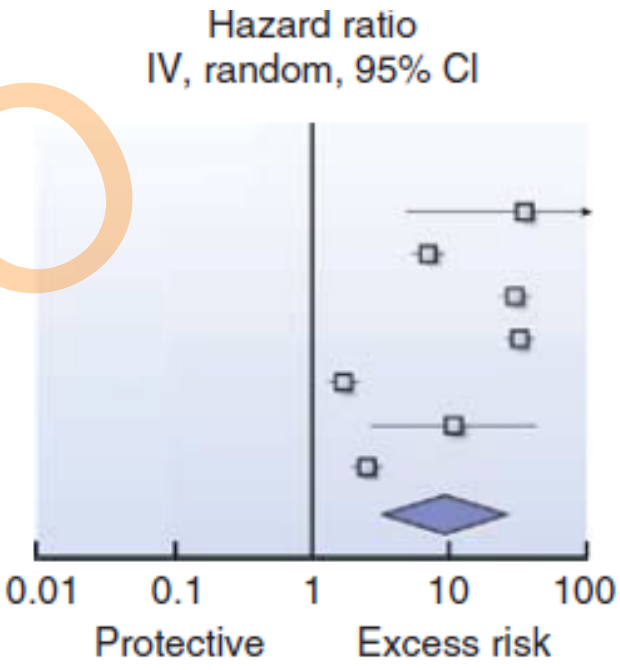
Heterogeneity: $\tau^2 = 0.47$; $\chi^2 = 4001.87$, d.f. = 8 ($P < 0.00001$); $I^2 = 100\%$. Test for overall effect: $Z = 2.96$ ($P < 0.003$)



CKD after AKI

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

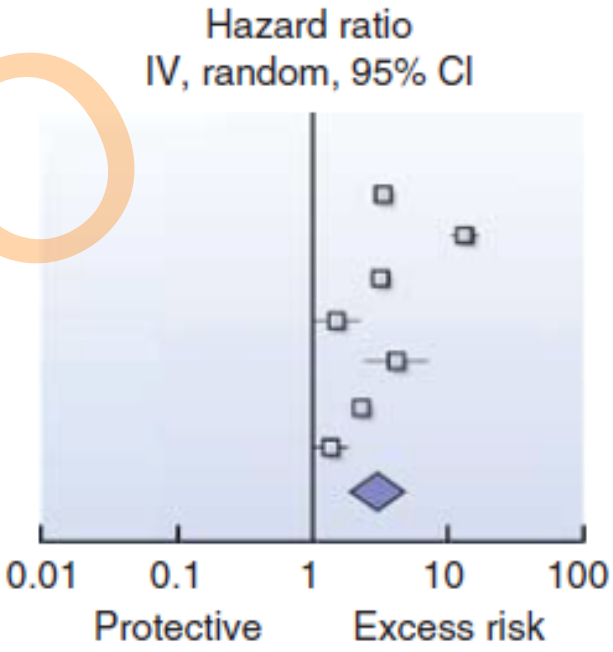
Heterogeneity: $\tau^2 = 1.87$; $\chi^2 = 446.89$, d.f. = 6 ($P < 0.00001$); $I^2 = 99\%$. Test for overall effect: $Z = 4.02$ ($P < 0.0001$)



ESKD after AKI

Study or subgroup	Weight (%)	Hazard ratio IV, random, 95% CI
Newsome *et al.* (14)	15.0	3.26 (2.87–3.70)
Ishani *et al.* (20)	14.8	12.99 (10.57–15.96)
Wald *et al.* (17)	14.9	3.22 (2.70–3.85)
Hsu *et al.* (10)	13.5	1.47 (0.95–2.28)
James *et al.* (15,23)	12.5	4.15 (2.32–7.41)
Lafrance *et al.* (18)	15.0	2.33 (2.08–2.61)
Choi *et al.* (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: $Z = 4.58$ ($P < 0.00001$)



Outcomes in CA vs HA-AKI

- Electronic record review of 15,976 patients admitted two district general hospitals in UK
- Baseline SCr established from blood tests taken 12 months prior to admission
- No baseline available in 49 and used upper limit of normal range SCr
- CA = AKI apparent on admission blood test
- HA = AKI occurred during hospitalization

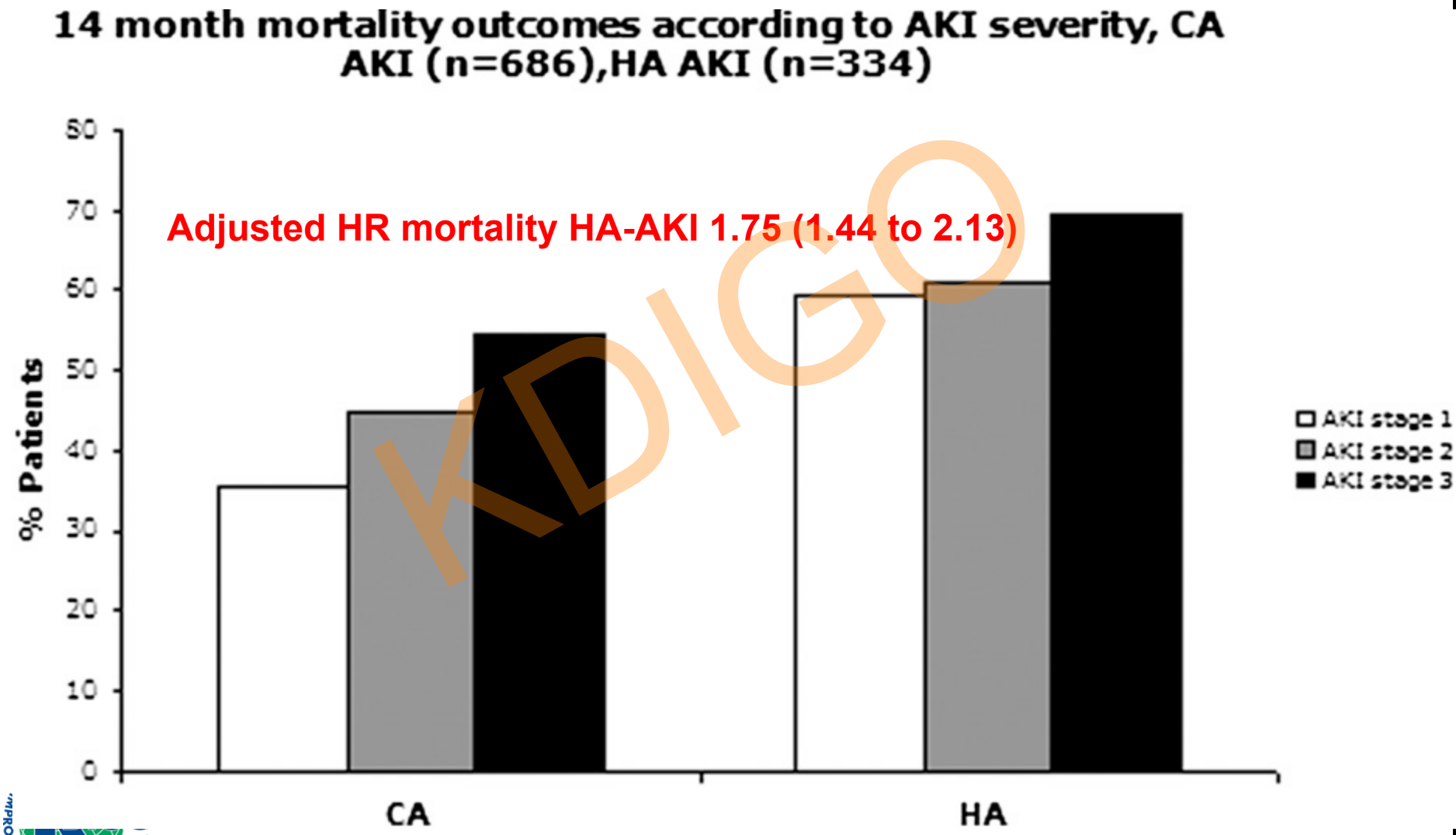
Wonnacott et al – *cJASN* 2012

Outcomes in CA vs HA-AKI

- No dedicated onsite renal service or cardiothoracic surgery
- 1020 (6.4%) admission with AKI
- 686 or approx 2/3 AKI cases were CA
- 334 or approx 1/3 were HA
- CA mean age 74.4 vs 76.8, admitted to ICU 4.7% vs 9.9%, median LOS 7 vs 15 days

Wonnacott et al – *cJASN* 2012

Mortality after AKI

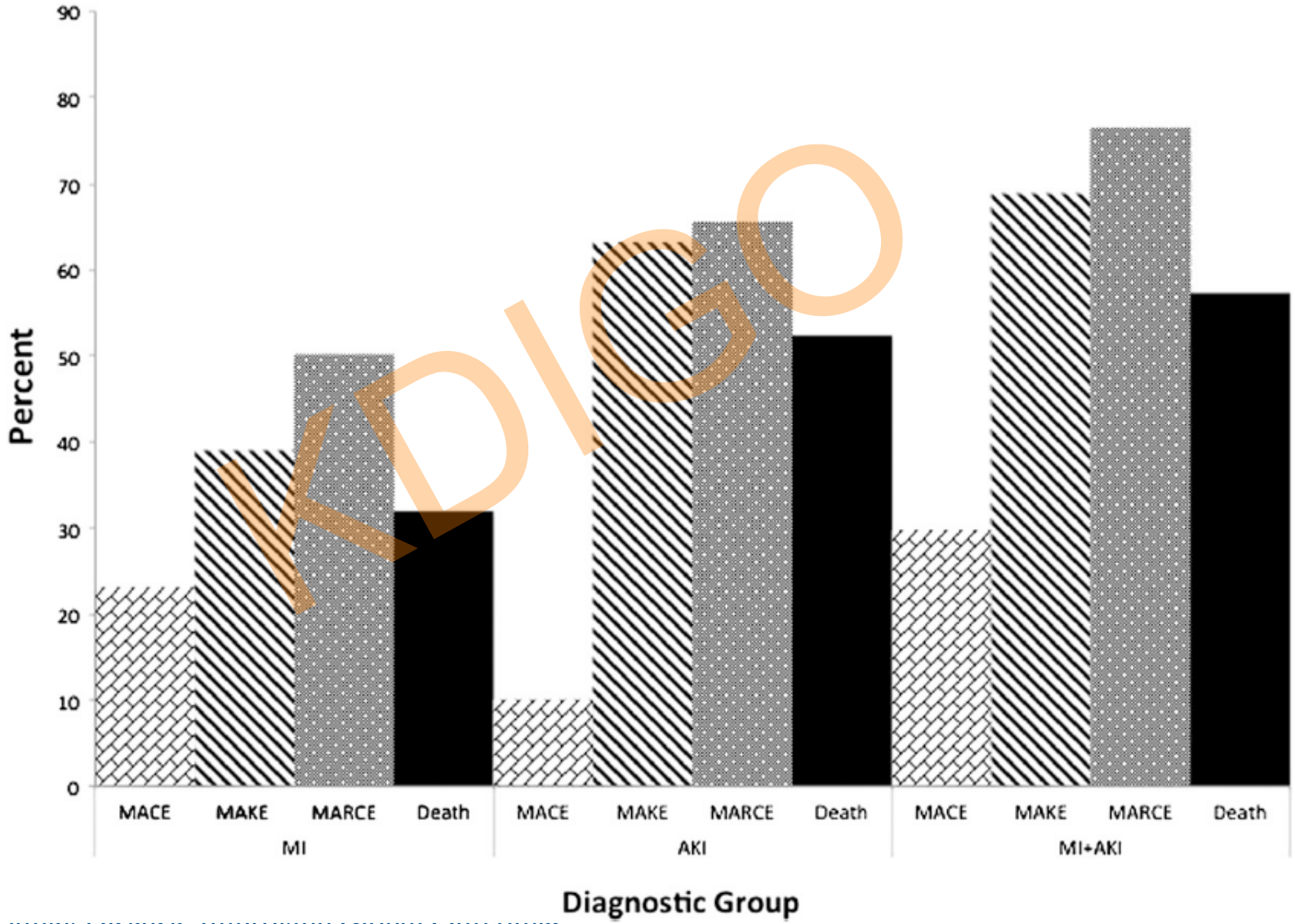


AKI - renal and CV outcomes

- Patients in VA database with discharge Dx of AKI or MI
- 36,980 patients admitted (and discharged) 1999 to 2005 analysed
- Known CKD and baseline eGFR <45mLs/min excluded
- Outcomes for people with MI, AKI, MI + AKI compared
- Median follow-up 1.4 years
- Outcomes death, kidney (dialysis, loss >25% eGFR or died), cardiac (CVA, MI or CHF admission) and combined kidney and cardiac

Chawla et al – *cJASN* 2014

Mortality after AKI

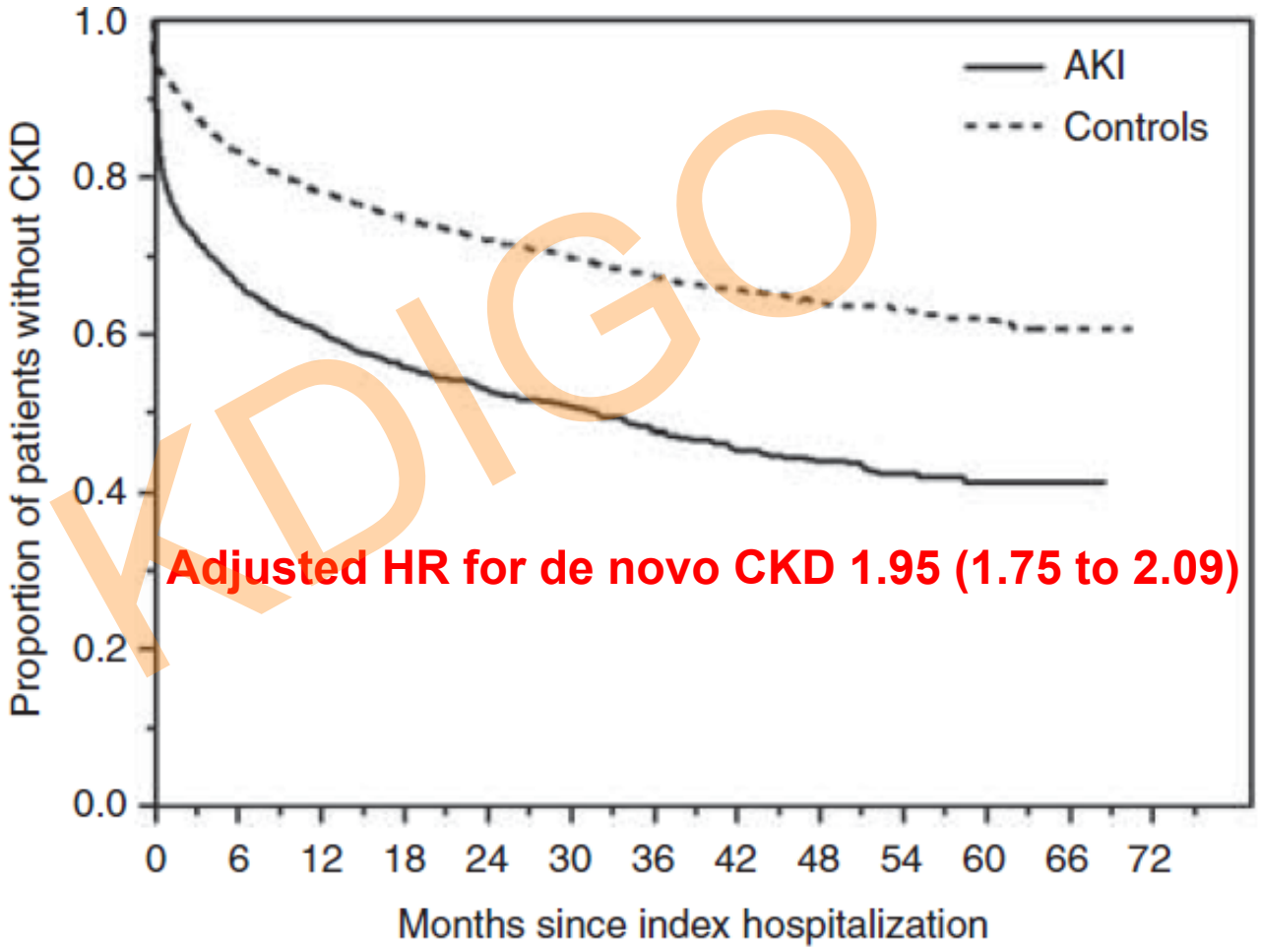


Poor outcomes with reversible AKI?

- Propensity matched cohort study of patients admitted to a US medical center
- Excluded patients with eGFR < 60 in preceding 12 months, known CKD or receiving RRT
- "Recovery" of renal function defined as eGFR of at least 90% of baseline within 90 days of AKI
- Cohort 1610 with reversible AKI
- Median follow-up 3.3 years
- De novo CKD = occurrence of two eGFR measures <60mLs/min/1.73m^2 separated 90 days

Bucaloiu et al – *KI* 2012

De novo CKD after “reversible” AKI



Renal 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*

Renal Study

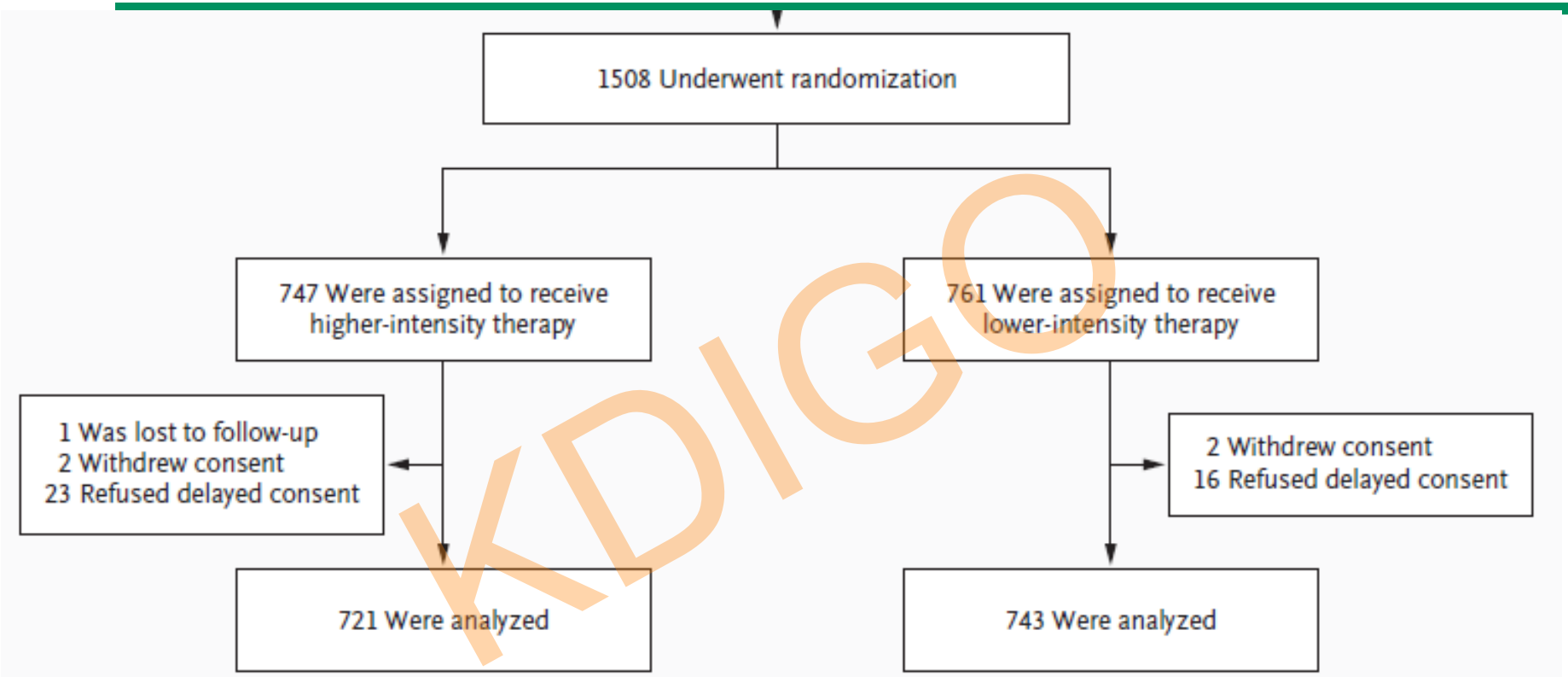


Figure 1. Numbers of Patients Enrolled in the Study, Randomly Assigned to a Treatment Group, and Included in the Analysis.

Renal Study

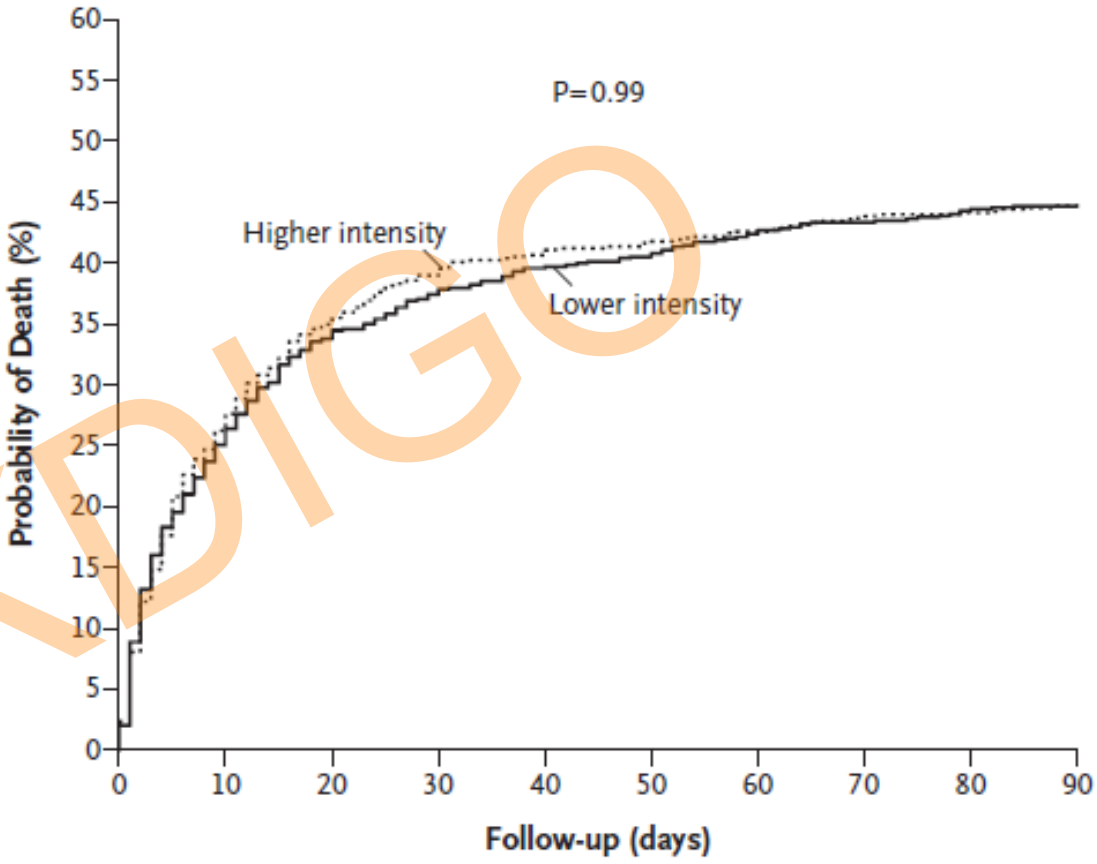


Figure 2. Kaplan–Meier Estimates of the Probability of Death.

Mortality at 28 days was similar in the higher-intensity and lower-intensity treatment groups (38.5% and 36.9%, respectively), and mortality at 90 days was the same (44.7%) in both groups.

Renal Study

Table 3. Primary and Secondary Outcomes.*

Outcome	Higher-Intensity CRRT	Lower-Intensity CRRT	Odds Ratio	P Value†
Death — no./total no. (%)				
By day 90	322/721 (44.7)	332/743 (44.7)	1.00 (0.81–1.23)	0.99
By day 28	278/722 (38.5)	274/743 (36.9)	1.07 (0.87–1.32)	0.52
Place of death — no./total no. (%)				
ICU	251/722 (34.8)	254/743 (34.2)	1.026 (0.827–1.273)	0.81
Hospital ward	68/722 (9.4)	76/743 (10.2)	0.913 (0.647–1.288)	0.60
Outside hospital, after discharge	3/722 (0.4)	2/743 (0.3)	1.546 (0.258–9.279)	0.63
RRT dependence among survivors				
At day 28	64/443 (14.4)	57/469 (12.2)	1.22 (0.83–1.79)	0.31
At day 90	27/399 (6.8)	18/411 (4.4)	1.59 (0.86–2.92)	0.14
No. of days of RRT, from randomization to day 90	13.0±20.8	11.5±18.0	—	0.14

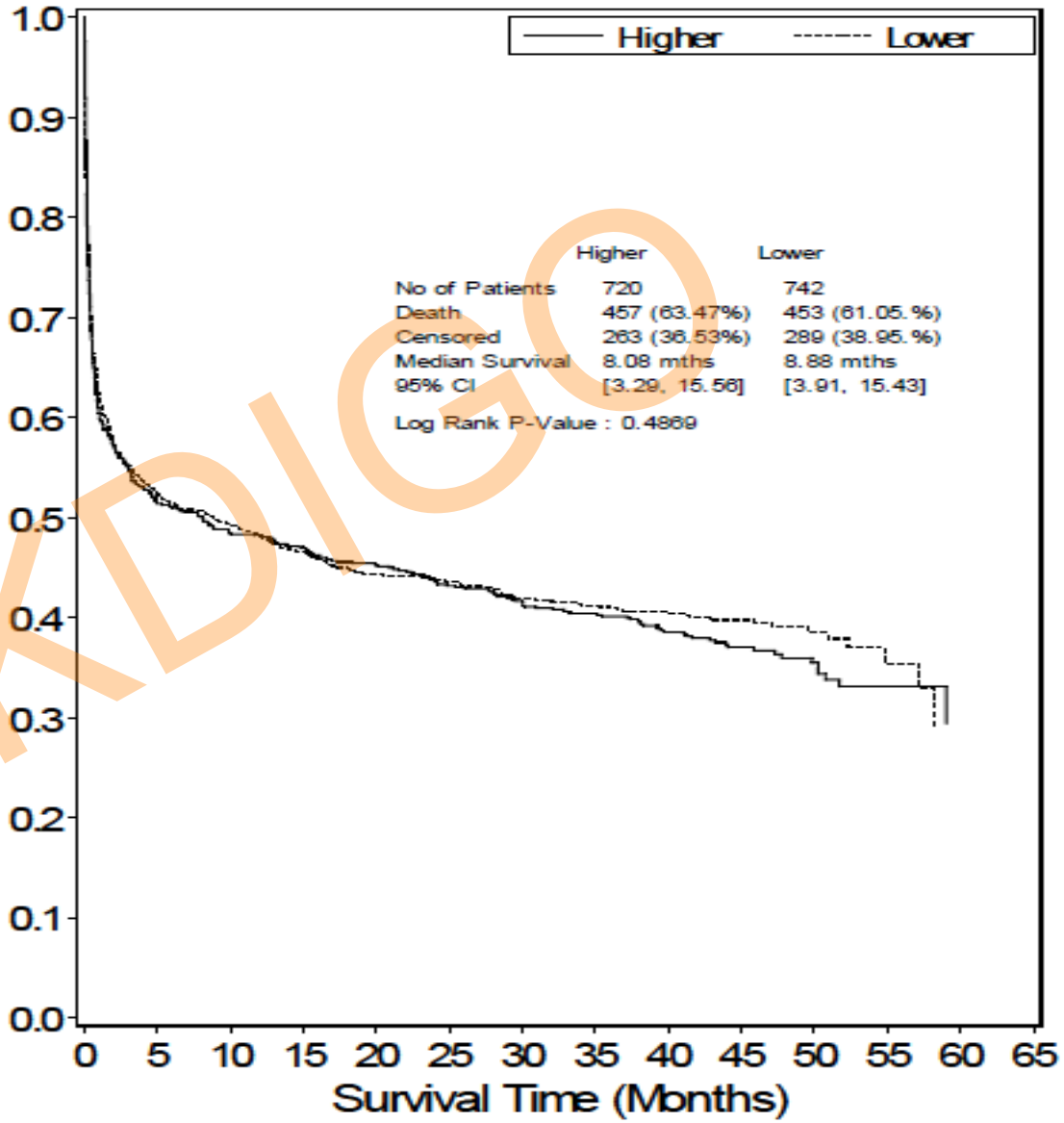
Post-RENAL Study

- Extended follow-up of survivors from 90 days to 4 years
- Primary and secondary outcomes – death and commencement RRT – ascertained for 1464 (97%) of original participants at median of 43.9 months
- Tertiary outcomes assessed in 350 participants included eGFR and spot ACR

More than 40% of participants seen at follow-up had micro or macroalbuminuria

Gallagher et al – *PLoS Med* 2014

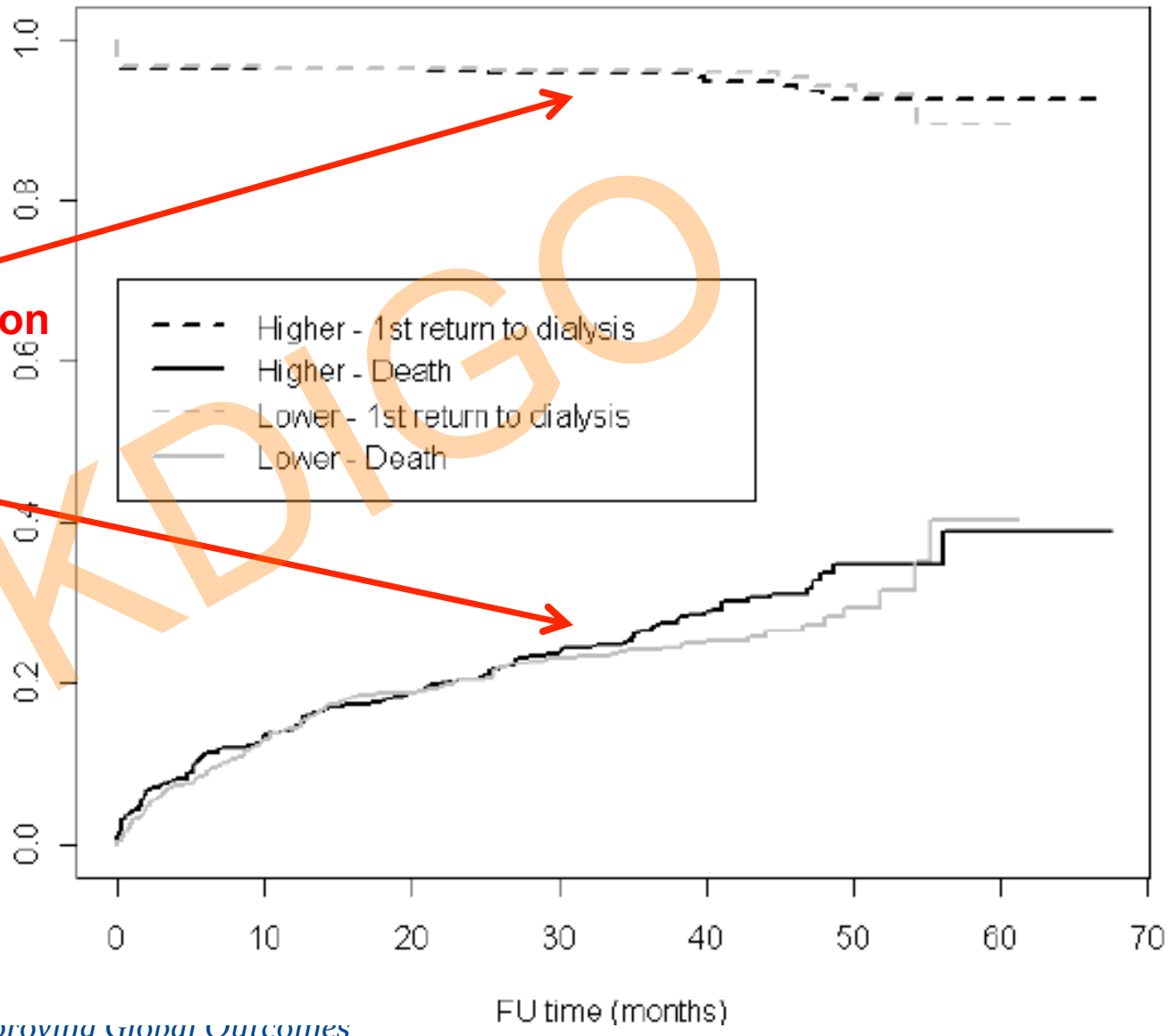
Mortality



Death and dialysis after Day 90

Low rates progression to ESKD

Ongoing high death rate



Modality and renal recovery

Intensive Care Med (2013) 39:987–997
DOI 10.1007/s00134-013-2864-5

SYSTEMATIC REVIEW

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

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

Modality and renal recovery

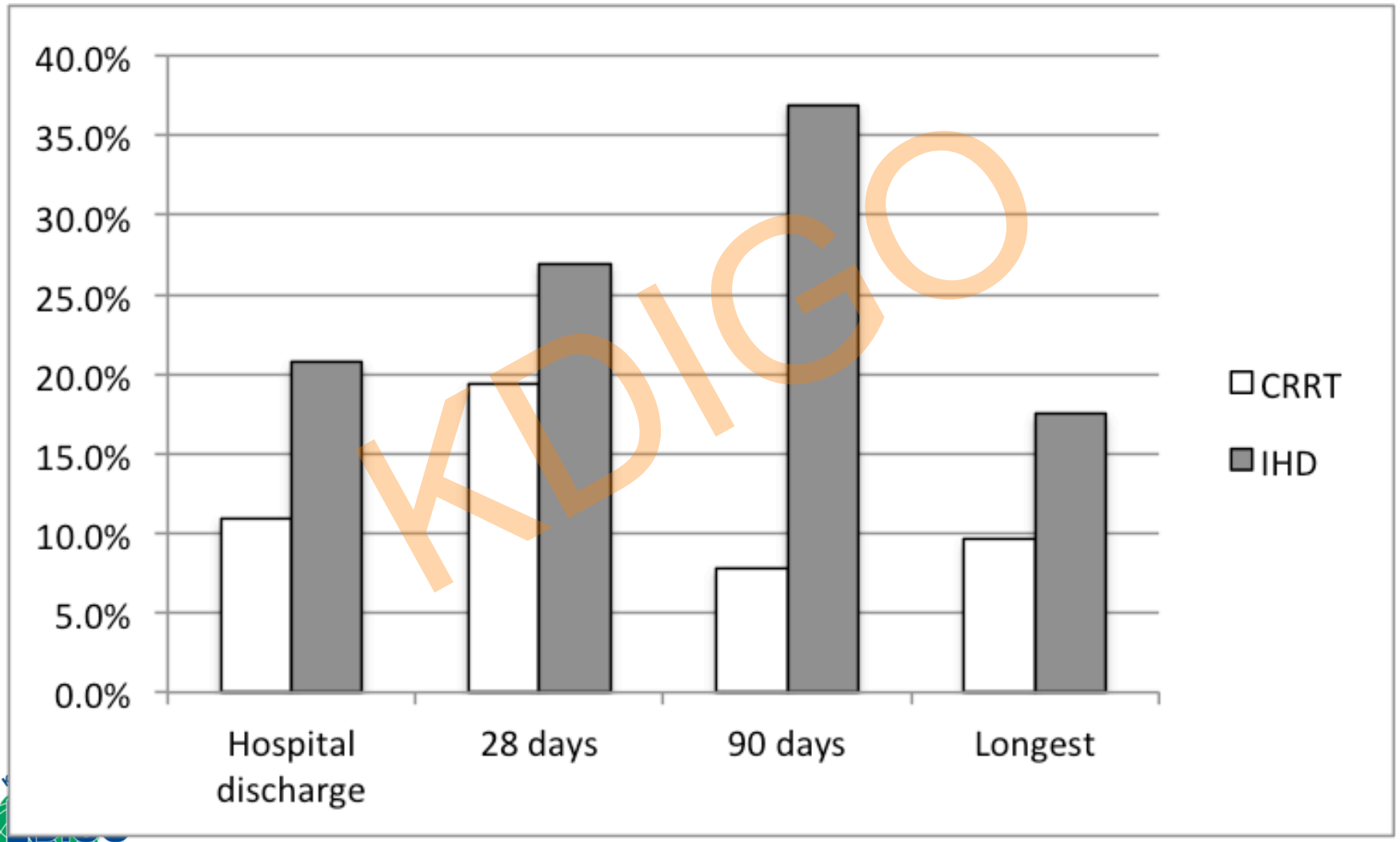
OBJECTIVES: To compare recovery to RRT independence in AKI survivors according to initial RRT modality.

DATA SOURCES: We searched MEDLINE and EMBASE for the keywords “renal replacement therapy” and “acute kidney injury” and their equivalents.

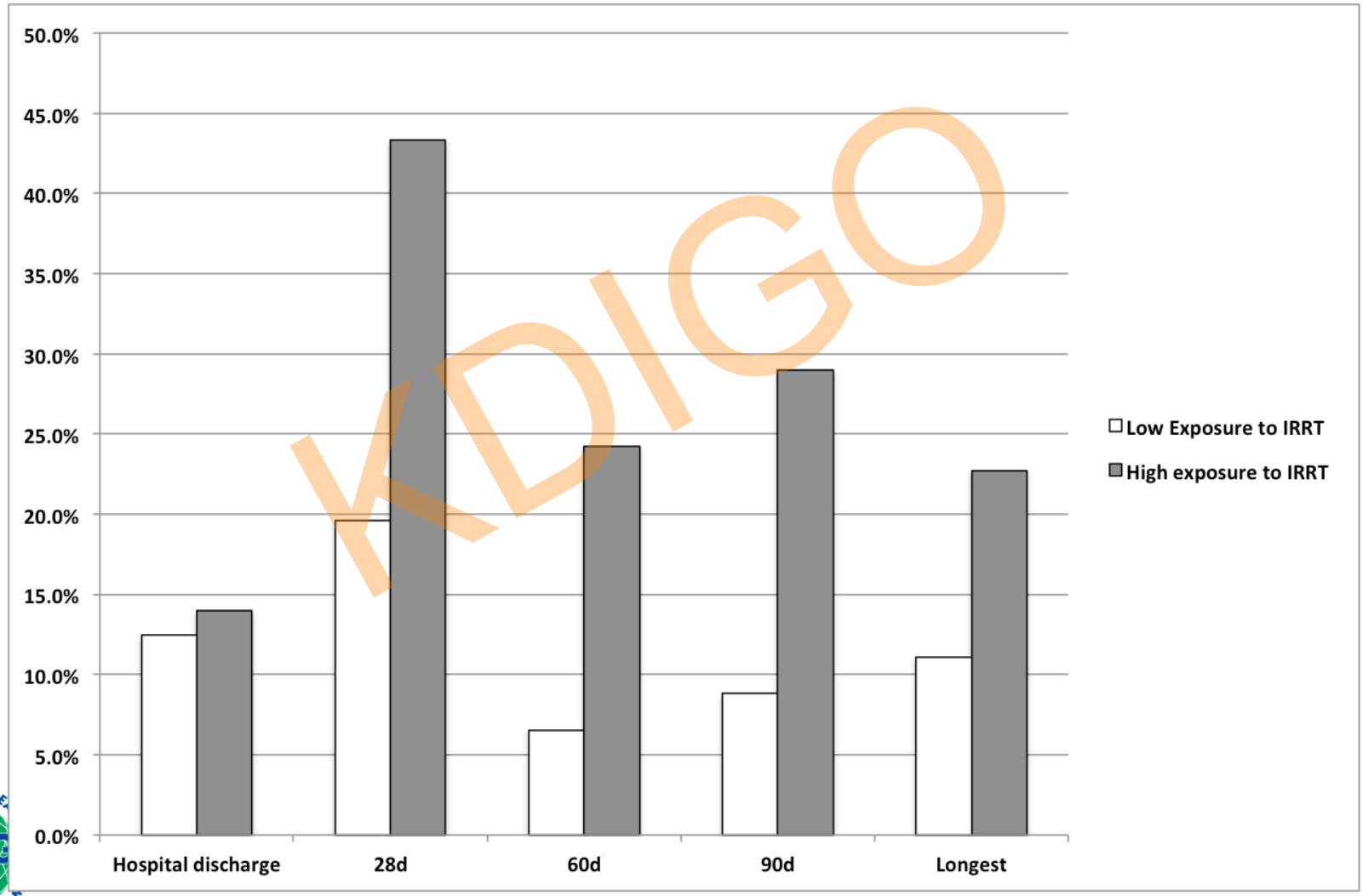
STUDY SELECTION: We retrieved all English language studies (2000 to 2010) reporting renal recovery to RRT independence after adult AKI.

DATA EXTRACTION: Two authors independently assessed study quality and extracted data. We used pooled analyses and the chi-square test for comparison. We performed sensitivity analyses with stratification by study type, size, pre-morbid chronic kidney disease, and illness severity. Secondarily, studies were pooled into Low (<50% exposed) or High-exposure (>50% exposed) according to the percentage of patients exposed to intermittent RRT (IRRT) (essentially intermittent HD).

Dialysis dependence in AKI survivors

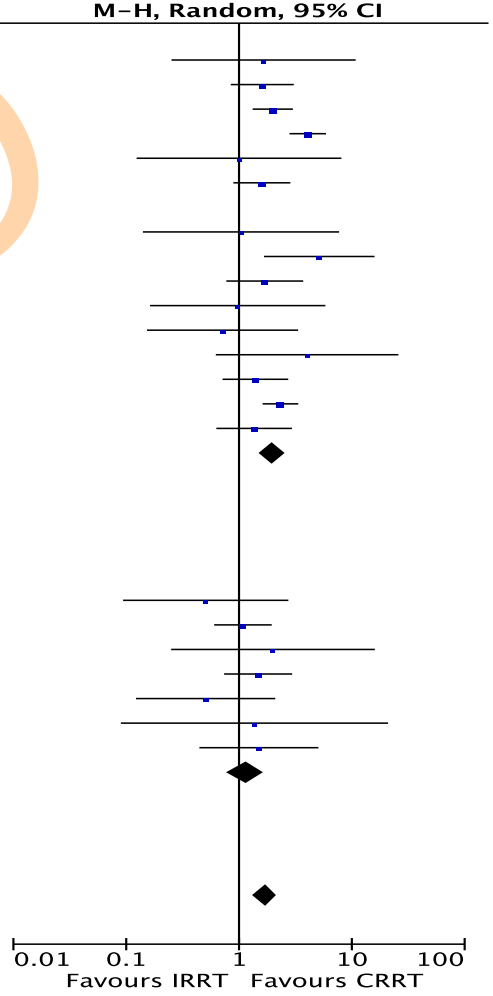


Dialysis dependence in AKI survivors



Dialysis dependence in AKI survivors

Study or Subgroup	IRRT Events	IRRT Total	CRRT Events	CRRT Total	Weight	Risk Ratio M–H, Random, 95% CI
1.1.1 Observational						
Andrikos	1	4	5	33	1.5%	1.65 [0.25, 10.81]
Bagshaw 2006	15	42	12	54	7.0%	1.61 [0.84, 3.06]
Bell 2007	26	158	78	944	9.8%	1.99 [1.32, 3.00]
CartinCeba 2009	256	555	26	229	10.3%	4.06 [2.80, 5.90]
Chang 2004	4	44	1	11	1.3%	1.00 [0.12, 8.08]
Elsevier 2010	37	175	13	98	7.7%	1.59 [0.89, 2.85]
Garcia–Fernandes 2011	0	16	0	55		Not estimable
Gonwa 2001	1	6	4	25	1.4%	1.04 [0.14, 7.71]
Jacka 2005	9	14	3	24	3.5%	5.14 [1.66, 15.89]
Lin 2009	11	54	10	83	5.7%	1.69 [0.77, 3.71]
Lins 2006	9	37	1	4	1.6%	0.97 [0.16, 5.83]
Marshall 2012	5	56	2	16	2.1%	0.71 [0.15, 3.34]
Park 2005	37	83	1	9	1.5%	4.01 [0.62, 25.86]
Swartz 2005	24	110	10	64	6.7%	1.40 [0.71, 2.73]
Uchino 2007	37	110	52	360	10.5%	2.33 [1.62, 3.35]
Waldrop 2005	7	12	6	14	5.8%	1.36 [0.63, 2.94]
Subtotal (95% CI)		**1476**		**2023**	**76.4%**	**1.99 [1.53, 2.59]**
Total events	479		224			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 24.14$, df = 14 (P = 0.04); $I^2 = 42\%$						
Test for overall effect: Z = 5.14 (P < 0.00001)						
1.1.2 RCT						
Abe	2	25	3	19	1.8%	0.51 [0.09, 2.74]
Augustine	8	12	8	13	7.6%	1.08 [0.60, 1.95]
Kumar 2004	3	12	1	8	1.3%	2.00 [0.25, 15.99]
Lins 2009	15	60	11	65	6.5%	1.48 [0.74, 2.96]
Mehta	3	43	4	29	2.4%	0.51 [0.12, 2.09]
Uehlinger	1	27	1	37	0.8%	1.37 [0.09, 20.95]
Vinsonneau	6	61	4	61	3.1%	1.50 [0.45, 5.05]
Subtotal (95% CI)		**240**		**232**	**23.6%**	**1.15 [0.78, 1.68]**
Total events	38		32			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.20$, df = 6 (P = 0.78); $I^2 = 0\%$						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**1716**		**2255**	**100.0%**	**1.73 [1.35, 2.20]**
Total events	517		256			
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 37.19$, df = 21 (P = 0.02); $I^2 = 44\%$						
Test for overall effect: Z = 4.36 (P < 0.0001)						
Test for subgroup differences: $Chi^2 = 5.45$, df = 1 (P = 0.02), $I^2 = 81.7\%$						



Summary

- AKI is common
- CKD is a risk factor for AKI
- AKI is a risk factor for development of CKD, progression to ESKD and death
- Need to identify high-risk patients - elderly, diabetes, people with CKD, undergoing major surgery
- Need to improve clinical follow-up after hospital discharge
- Further research necessary to examine whether modality of dialysis for severe AKI affects long-term dialysis dependence