# REFLECTIONS ON TRIALS IN NEPHROLOGY: LESSONS FROM THE PAST AND CHALLENGES FOR THE FUTURE



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(Thanks to Phyllis Butow, Simon Finfer, Mustafa Khasraw, Suetonia Palmer, Armando Teixeira-Pinto, Allison Tong)

# Disclosure of Interests

- Editor of Cochrane Kidney and Transplant group
- Member, Pharmaceutical Benefits Advisory Committee (Australian funder of medicines)
- Member, Medicare Services Advisory Committee (Australian funder of tests, devices, and services)
- Member, AKTN

# Why are we here? KDIGO mission

"To improve the care and outcomes of kidney disease patients worldwide through .. Clinical trials"

# THE EFFECTS OF NORMAL AS COMPARED WITH LOW HEMATOCRIT IN PATIENTS WITH CARDIAC DISEASE WHO ARE RECEIVING HEMO AND EPOETIN

ANATOLE BESARAB, M.D., W. KLINE BOLTON, M.D., JEFFREY K. BROWNE, PH.D., JOAN C. EGRIE, ALLEN R. NISSENSON, M.D., DOUGLAS M. OKAMOTO, PI

## ABSTRACT

***Background*** In patients with end-stage renal dis-ease, anemia develops as a result of erythropoietin deficiency, and recombinant human erythropoietin (epoetin) is prescribed to correct the anemia partial-ly. We examined the risks and benefits of normaliz-ing the hematocrit in patients with cardiac disease who were undergoing hemodialysis.

***Methods*** We studied 1233 patients with clinical ev-idence of congestive heart failure or ischemic heart disease who were undergoing hemodialysis: 618 pa-tients were assigned to receive increasing doses of epoetin to achieve and maintain a hematocrit of 42 percent, and 615 were assigned to receive doses of epoetin sufficient to maintain a hematocrit of 30 per-cent throughout the study. The median duration of treatment was 14 months. The primary end point was the length of time to death or a first nonfatal myo-cardial infarction.

***Results*** After 29 months, there were 183 deaths and 19 first nonfatal myocardial infarctions among the patients in the normal-hematocrit group and 150 deaths and 14 nonfatal myocardial infarctions among those in the low-hematocrit group (risk ratio for the normal-hematocrit group as compared with the low-hematocrit group, 1.3; 95 percent confidence inter-val, 0.9 to 1.9). Although the difference in event-free survival between the two groups did not reach the prespecified statistical stopping boundary, the study was halted. The causes of death in the two groups were similar. The mortality rates decreased with in-creasing hematocrit values in both groups. The pa-tients in the normal-hematocrit group had a decline in the adequacy of dialysis and received intravenous iron dextran more often than those in the low-hem-atocrit group.

***Conclusions*** In patients with clinically evident congestive heart failure or ischemic heart disease who are receiving hemodialysis, administration of epoetin to raise their hematocrit to 42 percent is not recommended. (N Engl J Med 1998;339:584-90.)



## The effects of lowering LDL cho plus ezetimibe in patients with (Study of Heart and Renal Prote placebo-controlled trial

Colin Baigent, Martin J Landray, Christina Reith, Jonathan Emberson, David Jonathan Craig, Bruce Neal, Lixin Jiang, Lai Seong Hooi, Adeera Levin, Lawren Bo Feldt-Rasmussen, Udom Krairittichai, Vuddidhej Ophascharoensuk, Beng Diederick Grobbee, Dick de Zeeuw, Carola Grönhagen-Riska, Tanaji Dasgupta Karl Wallendszus, Richard Grimm, Terje Pedersen, Jonathan Tobert, Jane Arm Michael Hill, Carol Knott, Sarah Parish, David Simpson, Peter Sleight, Alan Y

### Summary

**Background** Lowering LDL cholesterol with statin regime stroke, and the need for coronary revascularisation in peo moderate-to-severe kidney disease are uncertain. The SH combination of simvastatin plus ezetimibe in such patients

**Methods** This randomised double-blind trial included 9270 6247 not) with no known history of myocardial infarctio assigned to simvastatin 20 mg plus ezetimibe 10 mg daily ve first major atherosclerotic event (non-fatal myocardial infar arterial revascularisation procedure). All analyses were by in NCT00125593, and ISRCTN54137607.

**Findings** 4650 patients were assigned to receive simvastatin pl plus ezetimibe yielded an average LDL cholesterol differ compliance) during a median follow-up of 4·9 years and prod events (526 [11·3%] simvastatin plus ezetimibe *vs* 619 [13·4% p=0·0021). Non-significantly fewer patients allocated to simv or died from coronary heart disease (213 [4·6%] *vs* 230 [5·( significant reductions in non-haemorrhagic stroke (131 [2·8 arterial revascularisation procedures (284 [6·1%] *vs* 352 [7·6% for subgroup-specific reductions in LDL cholesterol, there w atherosclerotic events differed from the summary rate ratio similar in patients on dialysis and those who were not. The e year of treatment with this combination (9 [0·2%] *vs* 5 [0· (21 [0·5%] *vs* 18 [0·4%]), gallstones (106 [2·3%] *vs* 106 [2·3% was no significant excess of death from any non-vascular cau

**Interpretation** Reduction of LDL cholesterol with simvasta incidence of major atherosclerotic events in a wide range of

**Funding** Merck/Schering-Plough Pharmaceuticals; Australi Heart Foundation; UK Medical Research Council.

percent while receiving epoetin during the four rollment. Ninety percent of the patients receive

ORIGINAL ARTICLE

# Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

## ABSTRACT

### BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

### METHODS

We randomly assigned patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group. The key secondary composite outcome was the primary outcome plus hospitalization for unstable angina.

### RESULTS

A total of 7020 patients were treated (median observation time, 3.1 years). The primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group and in 282 of 2333 patients (12.1%) in the placebo group (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). There were no significant between-group differences in the rates of myocardial infarction or stroke, but in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). There was no significant between-group difference in the key secondary outcome (P=0.08 for superiority). Among patients receiving empagliflozin, there was an increased rate of genital infection but no increase in other adverse events.

### CONCLUSIONS

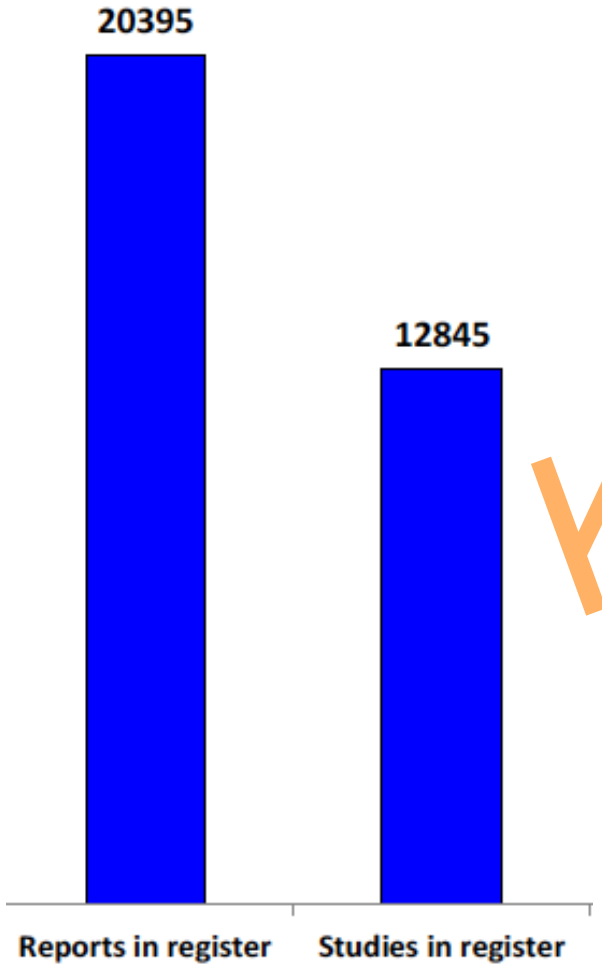
Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care. (Funded by Boehringer Ingelheim and Eli Lilly; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.)

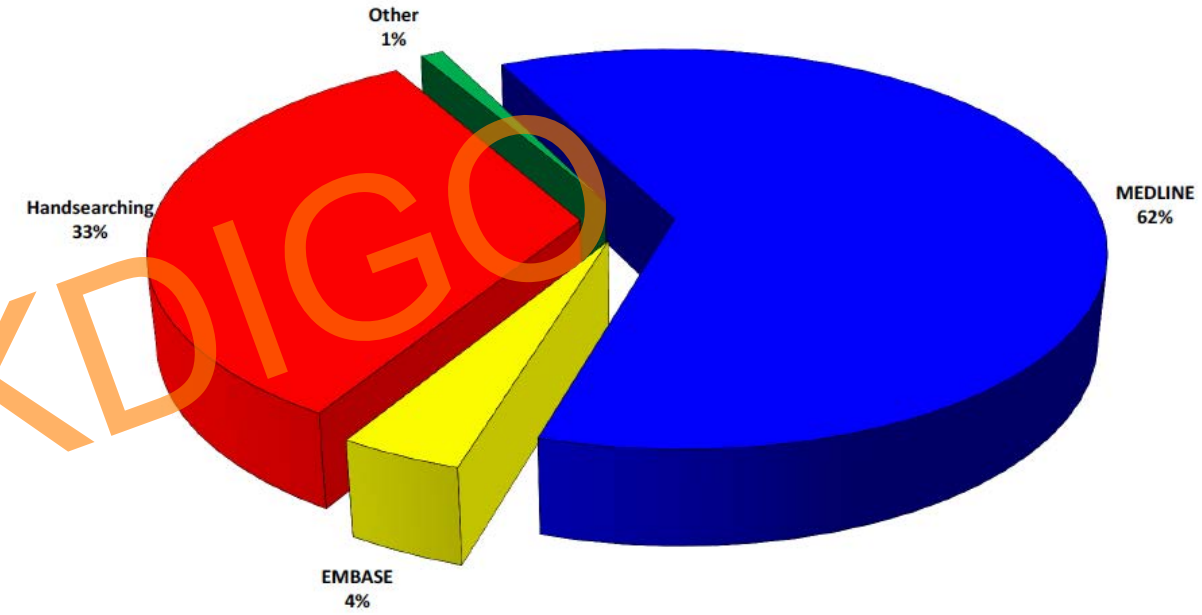
# Overview

- A snapshot of our current state
- The past: Too much waste
- The future: Cause for hope

# CURRENT SNAPSHOT

# Number of RCTs in nephrology: more than you think



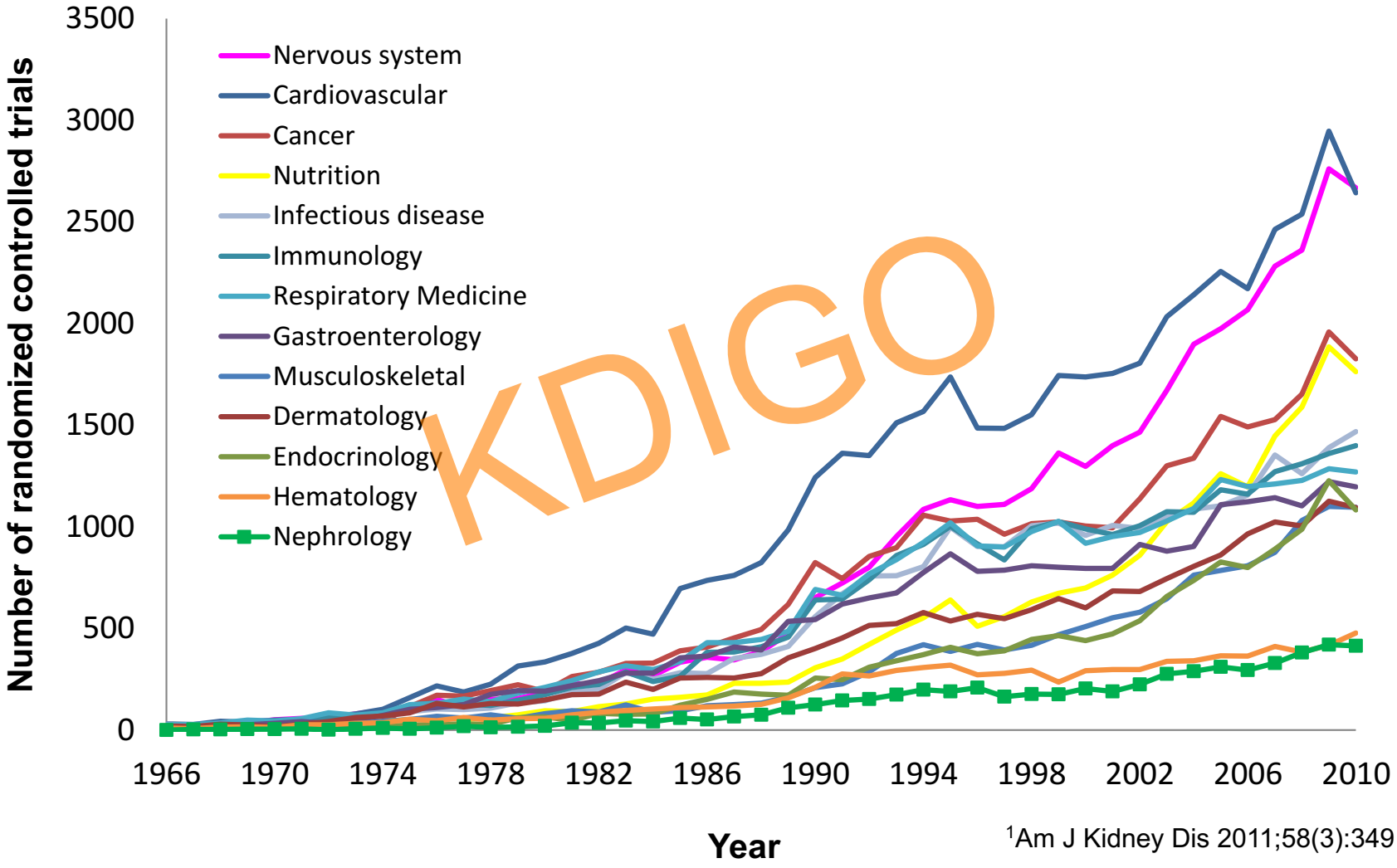





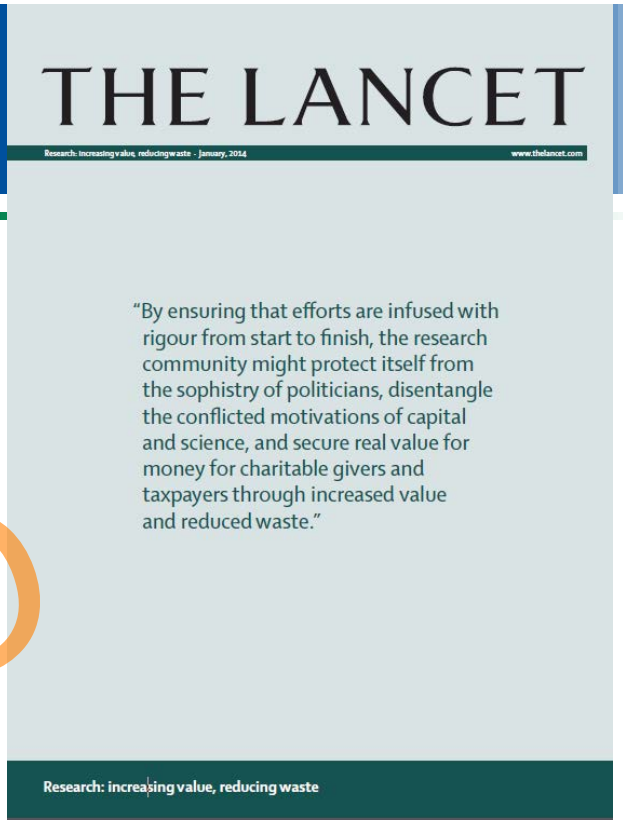

Cochrane Kidney and Transplant

Trusted evidence.
Informed decisions.
Better health.

# But not enough:
## Holders of the 'wooden spoon'




[1]Am J Kidney Dis 2011;58(3):349






# THE PAST: TOO MUCH RESEARCH WASTE

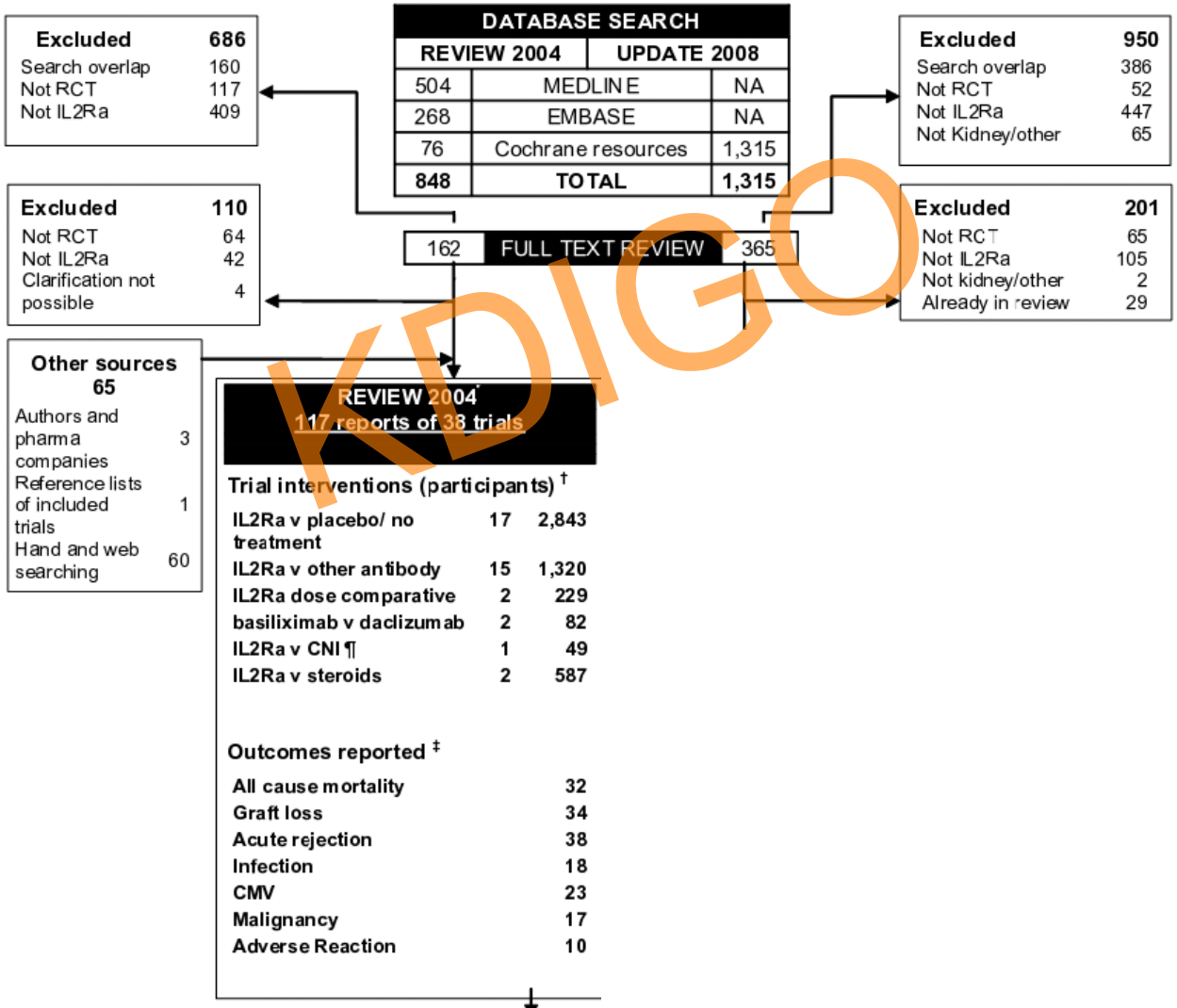
# Avoidable waste or inefficiency in biomedical research




**85% of US$240 billion in 2010**

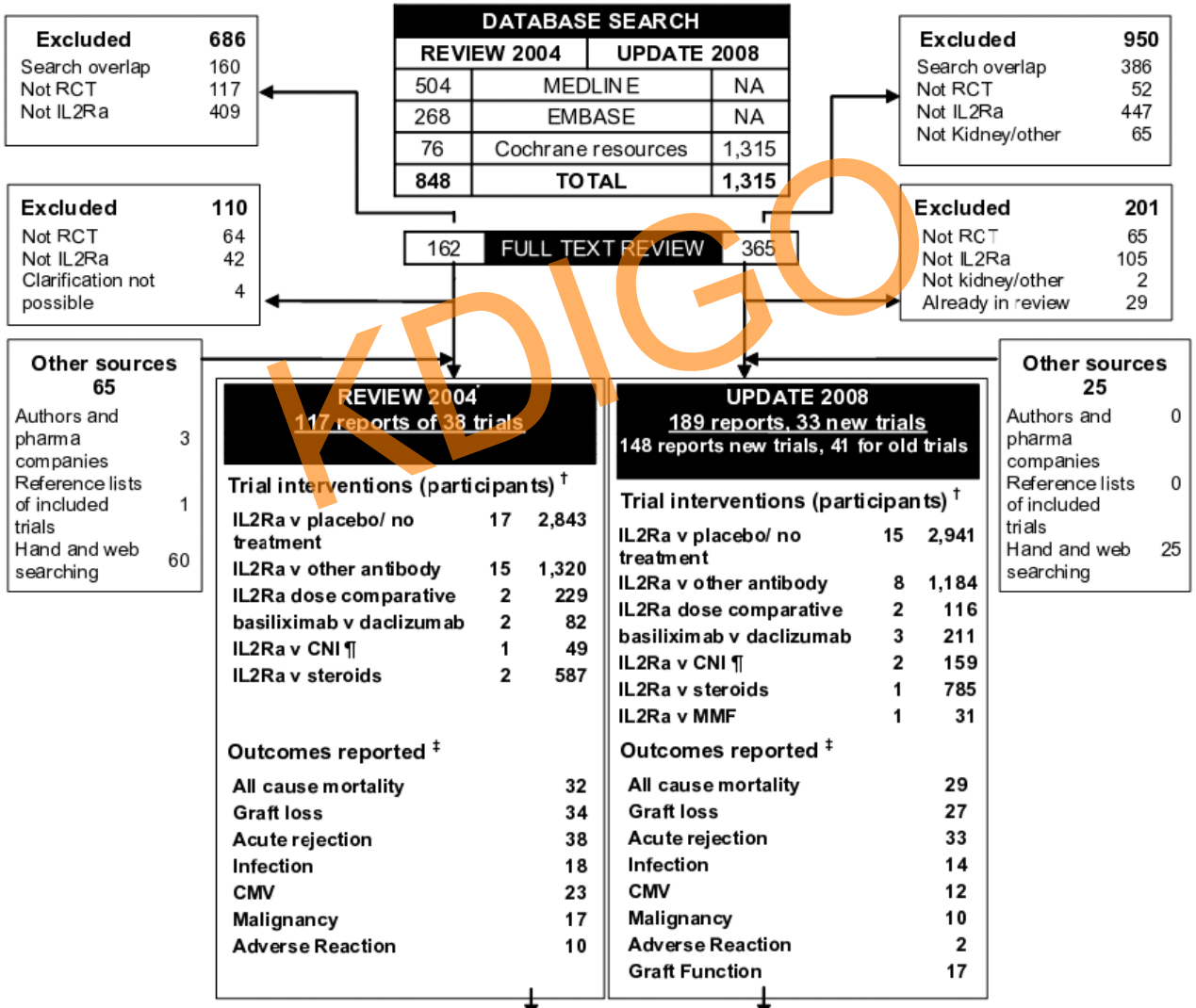
# 1. Question: already answered
## e.g. IL2RA for induction immunosuppression

**Figure 1: Flow chart for identification of randomised controlled trials (RCT) for 2009 IL2Ra review update**



# 1. Question: already answered

**Figure 1: Flow chart for identification of randomised controlled trials (RCT) for 2009 IL2Ra review update**



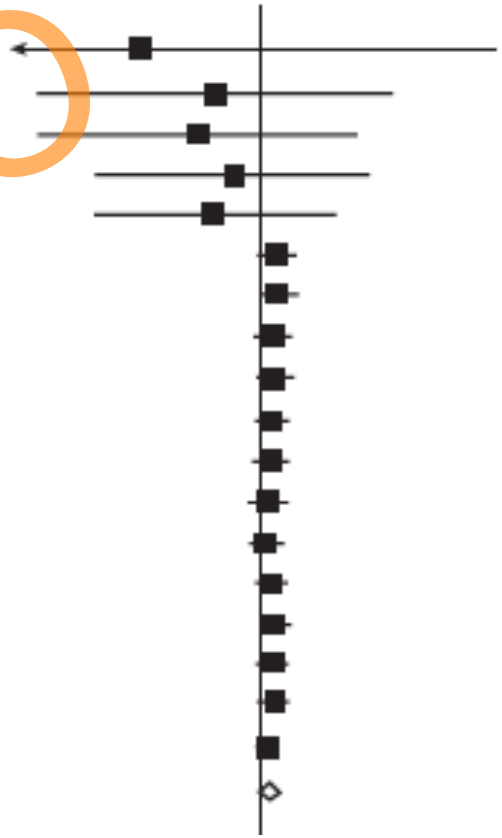
# 1. Question: already answered
# e.g. ESA therapy

## Meta-analysis: Erythropoiesis-Stimulating Agents in Patients With Chronic Kidney Disease

*Ann Intern Med.* 2010;153:23-33.

| Study, Year (Reference) | Cumulative Events, *n/N* | | Cumulative Relative Risk (95% CI) | Cumulative *P* Value |
|---|---|---|---|---|
| | Higher Hemoglobin Target | Lower Hemoglobin Target | | |
| All-cause mortality | | | | |
| Canadian EPO Study Group, 1990 (7) | 0/38 | 1/40 | 0.35 (0.01–8.35) | 0.52 |
| Bahlmann et al, 1991 (8) | 2/91 | 3/86 | 0.68 (0.13–3.52) | 0.65 |
| Revicki et al, 1995 (14) | 2/134 | 4/126 | 0.58 (0.13–2.48) | 0.46 |
| Nissenson et al, 1995 (13) | 4/212 | 5/200 | 0.80 (0.23–2.77) | 0.72 |
| Kuriyama et al, 1997 (11) | 5/254 | 7/231 | 0.67 (0.22–2.03) | 0.48 |
| Besarab et al (NHS), 1998 (22) | 188/872 | 157/846 | 1.19 (1.00–1.43) | 0.06 |
| Foley et al, 2000 (30) | 192/945 | 160/919 | 1.20 (1.00–1.43) | 0.05 |
| Furuland et al, 2003 (31) | 216/1125 | 186/1083 | 1.15 (0.97–1.36) | 0.11 |
| Roger et al, 2004 (36) | 216/1199 | 186/1161 | 1.15 (0.97–1.36) | 0.11 |
| Gouva et al, 2004 (32) | 219/1244 | 190/1204 | 1.14 (0.97–1.35) | 0.12 |
| Levin et al, 2005 (33) | 220/1318 | 193/1282 | 1.14 (0.96–1.34) | 0.14 |
| Parfrey et al, 2005 (24) | 233/1614 | 213/1582 | 1.10 (0.93–1.30) | 0.25 |
| Rossert et al, 2006 (37) | 234/1809 | 219/1777 | 1.09 (0.92–1.28) | 0.31 |
| Drüeke et al (CREATE), 2006 (29) | 265/2110 | 240/2079 | 1.12 (0.96–1.31) | 0.16 |
| Singh et al (CHOIR), 2006 (23) | 317/2825 | 276/2796 | 1.15 (1.00–1.34) | 0.05 |
| Macdougall et al, 2007 (34) | 318/2890 | 282/2928 | 1.15 (0.99–1.33) | 0.06 |
| Ciancíaruso et al, 2008 (27) | 319/2939 | 282/2974 | 1.15 (0.99–1.33) | 0.06 |
| Pfeffer et al (TREAT), 2009 (18) | 731/4951 | 677/5000 | 1.09 (0.99–1.20) | 0.07 |
| Cumulative total | 731/4951 | 677/5000 | 1.09 (0.99–1.20) | 0.07 |

Cumulative Relative Risk (95% CI)



# 1. Question: important ones not addressed

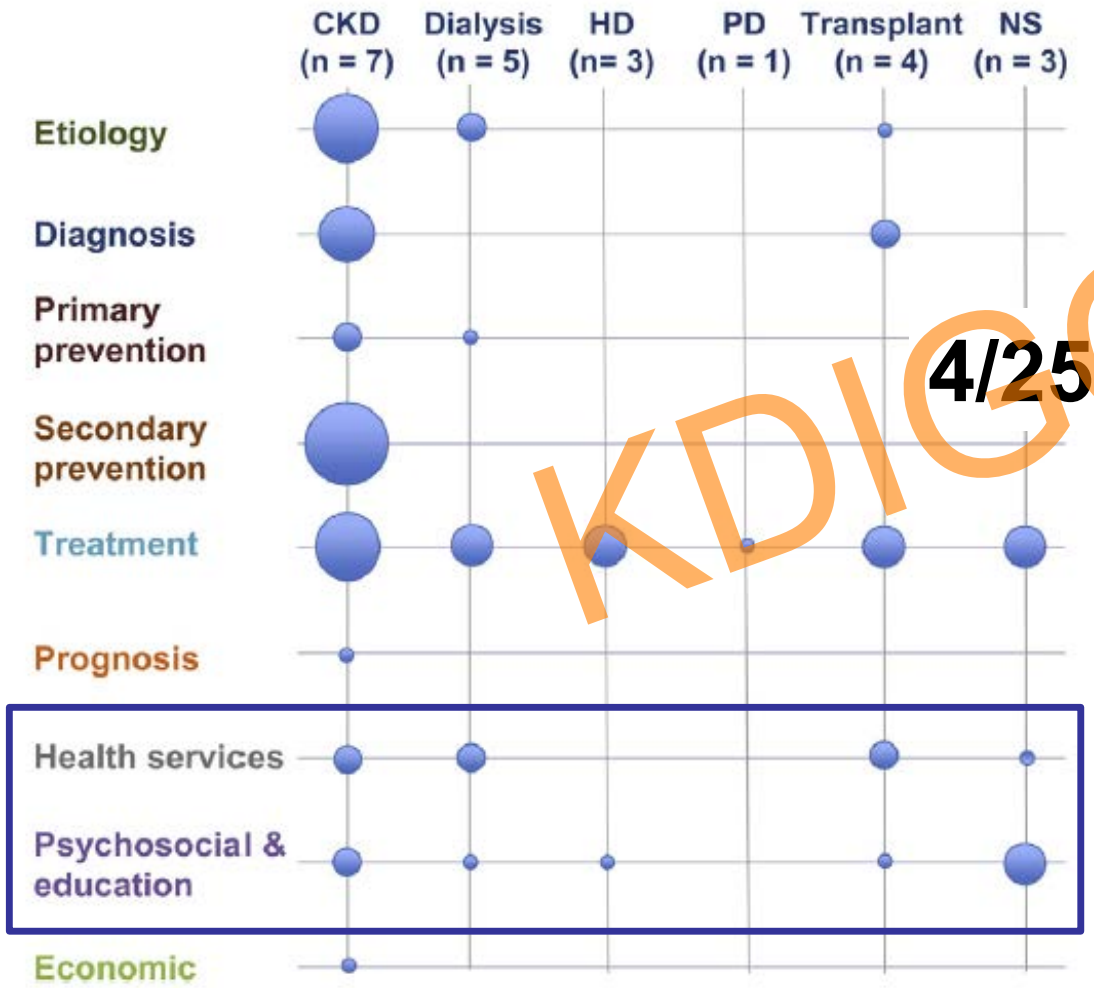



**Figure 2.** Matrix of research priorities in kidney disease. Size of the circles indicates the number (n) of studies identifying the question type as a research priority. Etiology: identify risk

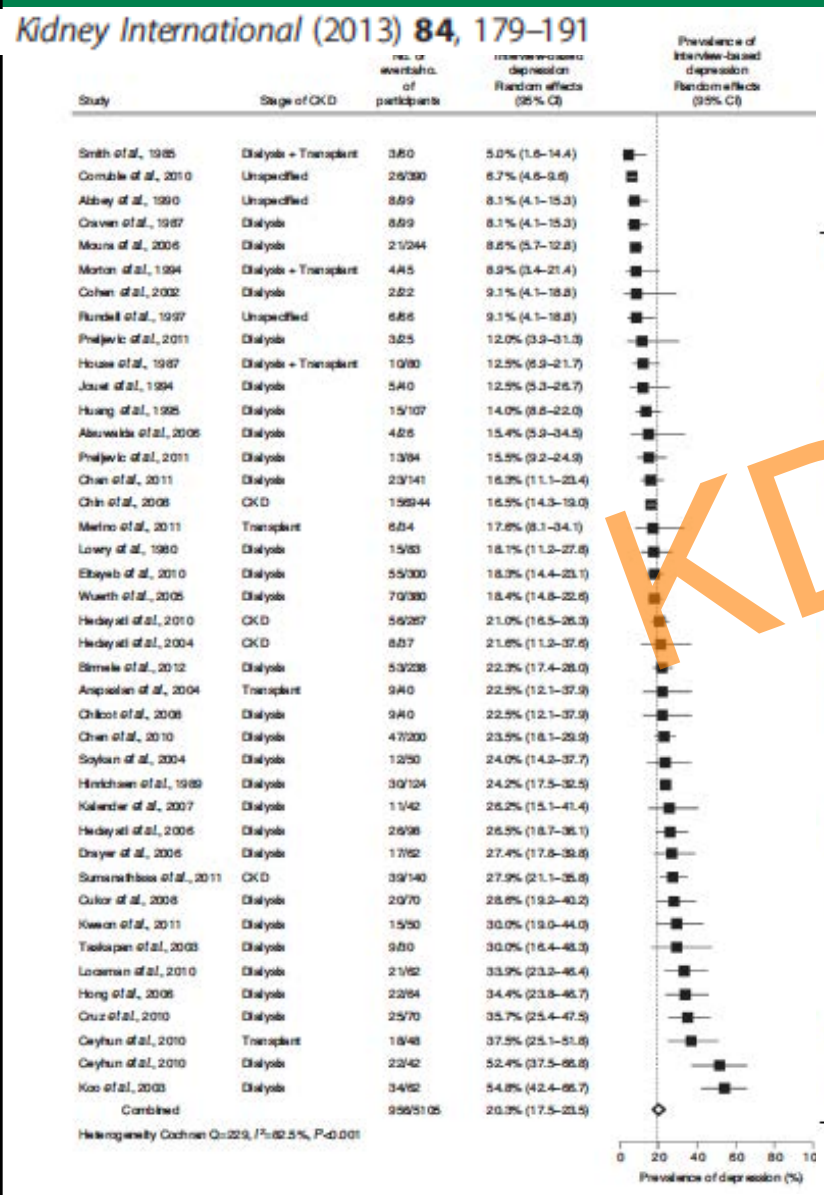


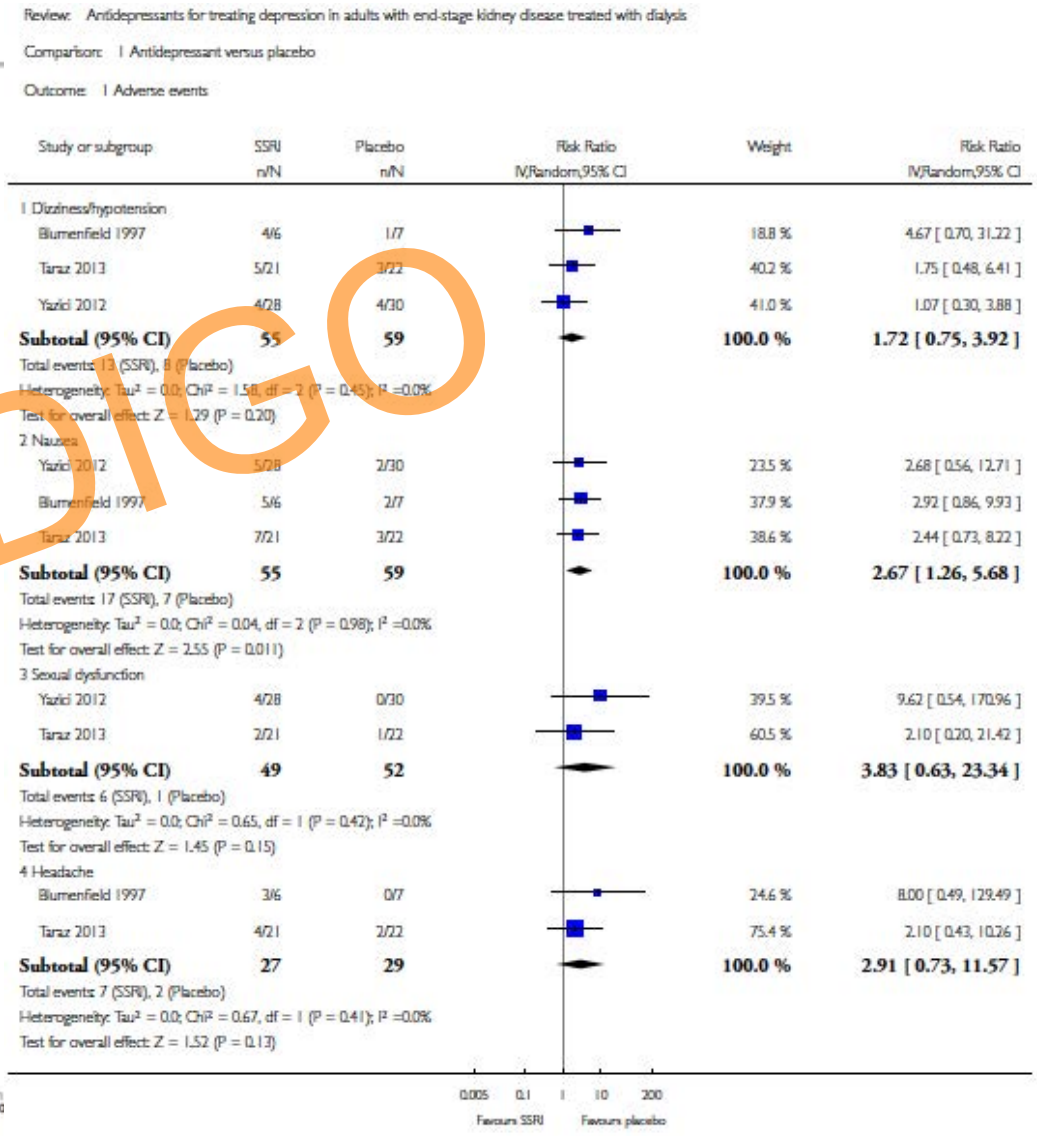
**4/25 involved patients**

*Am J Kidney Dis.* 65(5):674-683.

| | Question | Med. | IQR |
|---|---|---|---|
| 1 | How effective are lifestyle programs (diet, exercise and smoking cessation) for preventing deterioration in kidney function in patients with early CKD? | 5 | 2-10 |
| 2 | What strategies will improve don… …d donation taking different cultural groups into… | 6 | 3-13 |
| 3 | What interventions can … …ugs, lifestyle)? | 7 | 2-11 |
| 4 | What are the effec… | 7 | 4-14 |
| 5 | What can we do … …er management of s… | 8 | 4-12 |
| 6 | What strategies … | 8 | 4-13 |
| 7 | What psychologic… transition between… | 9 | 5-16 |
| 8 | How do we improve… | 10 | 5-15 |
| 9 | What are the best inter… …s of people faced with HD? | 10 | 6-16 |
| 10 | Does provision of culturally appr… …rly CKD modify acknowledgement, medication adherence, … service uptake in patients with early CKD? | 11 | 6-15 |

# 1. Question: important ones not addressed e.g. depression



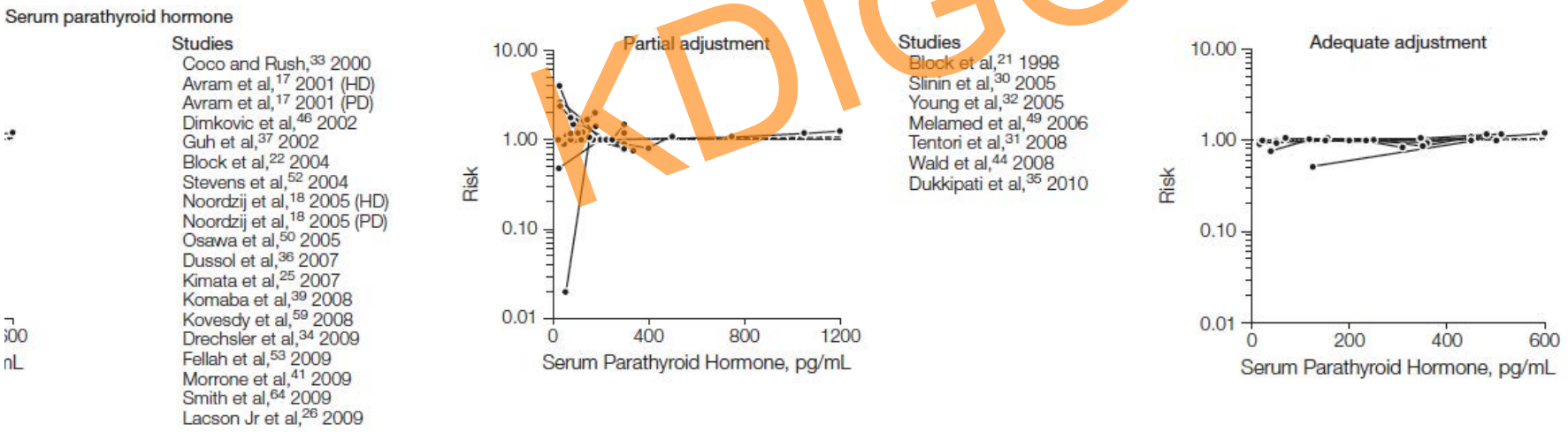
# 1. Question: not informed by a systematic review
## e.g. PTH lowering

**Serum Levels of Phosphorus, Parathyroid Hormone, and Calcium and Risks of Death and Cardiovascular Disease in Individuals With Chronic Kidney Disease**
A Systematic Review and Meta-analysis

*JAMA. 2011;305(11):1119-1127*

**Figure 2.** Risks of All-Cause Mortality Grouped According to Level of Study Adjustment for Confounding Variables

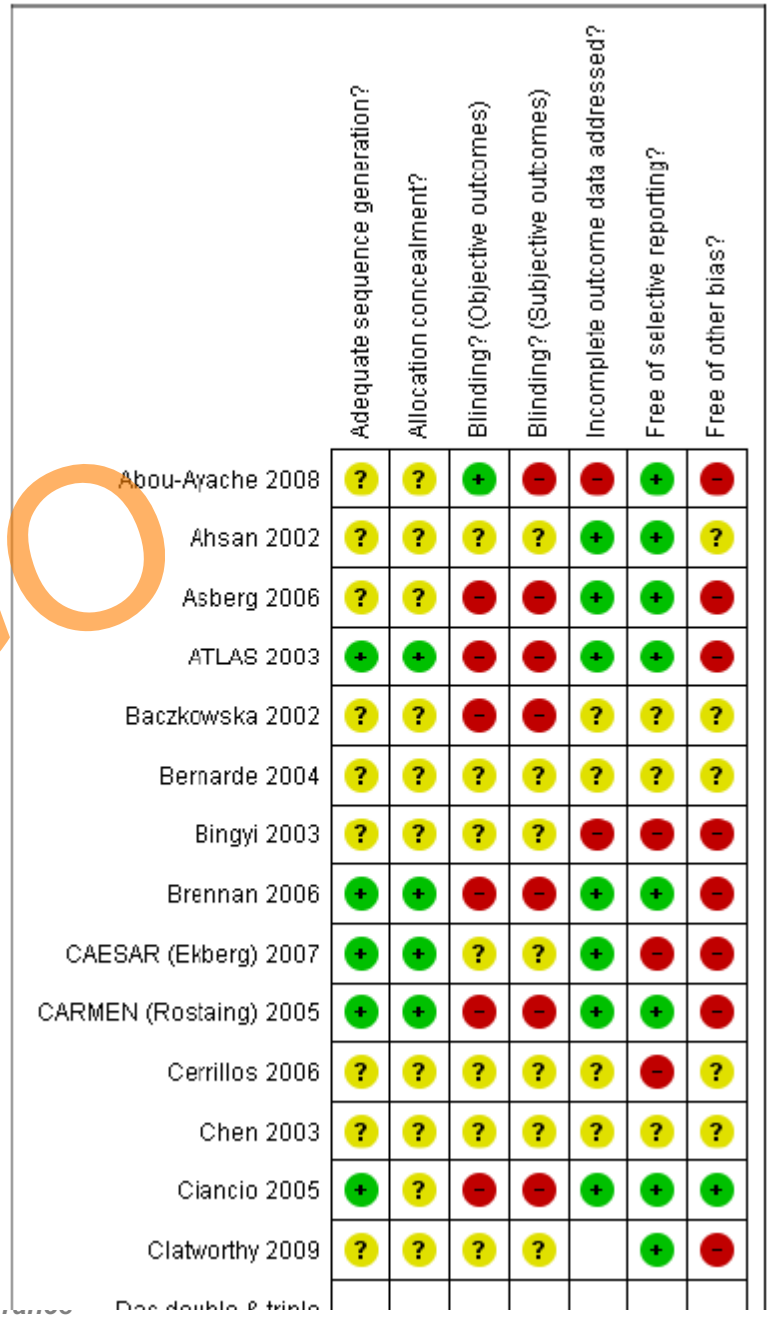




# 2. Design/reporting risk of bias

Table 2.—Odds Ratios in the Unclearly and Inadequately Concealed Trials Compared With Those in Adequately Concealed Trials*

| Level of Allocation Concealment | Ratio of Odds Ratios (95% Confidence Interval) | $\chi^2$ (*df*) | *P* |
|---|---|---|---|
| Adequate | 1.00 (referent) | | |
| Unclear | 0.67 (0.60-0.75) | 57.9 (2) | <.001 |
| Inadequate | 0.59 (0.48-0.73) | | |

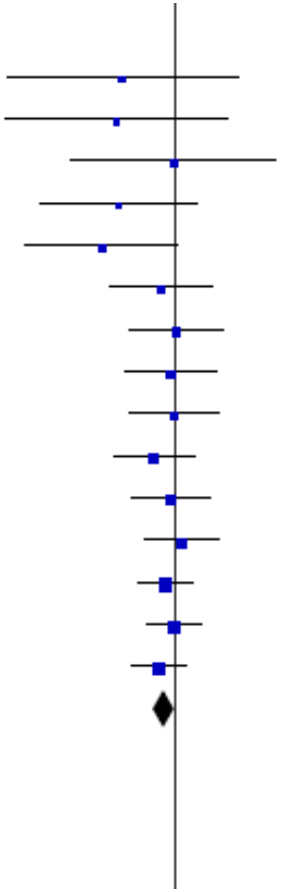


# 3. Too small e.g. IL2A

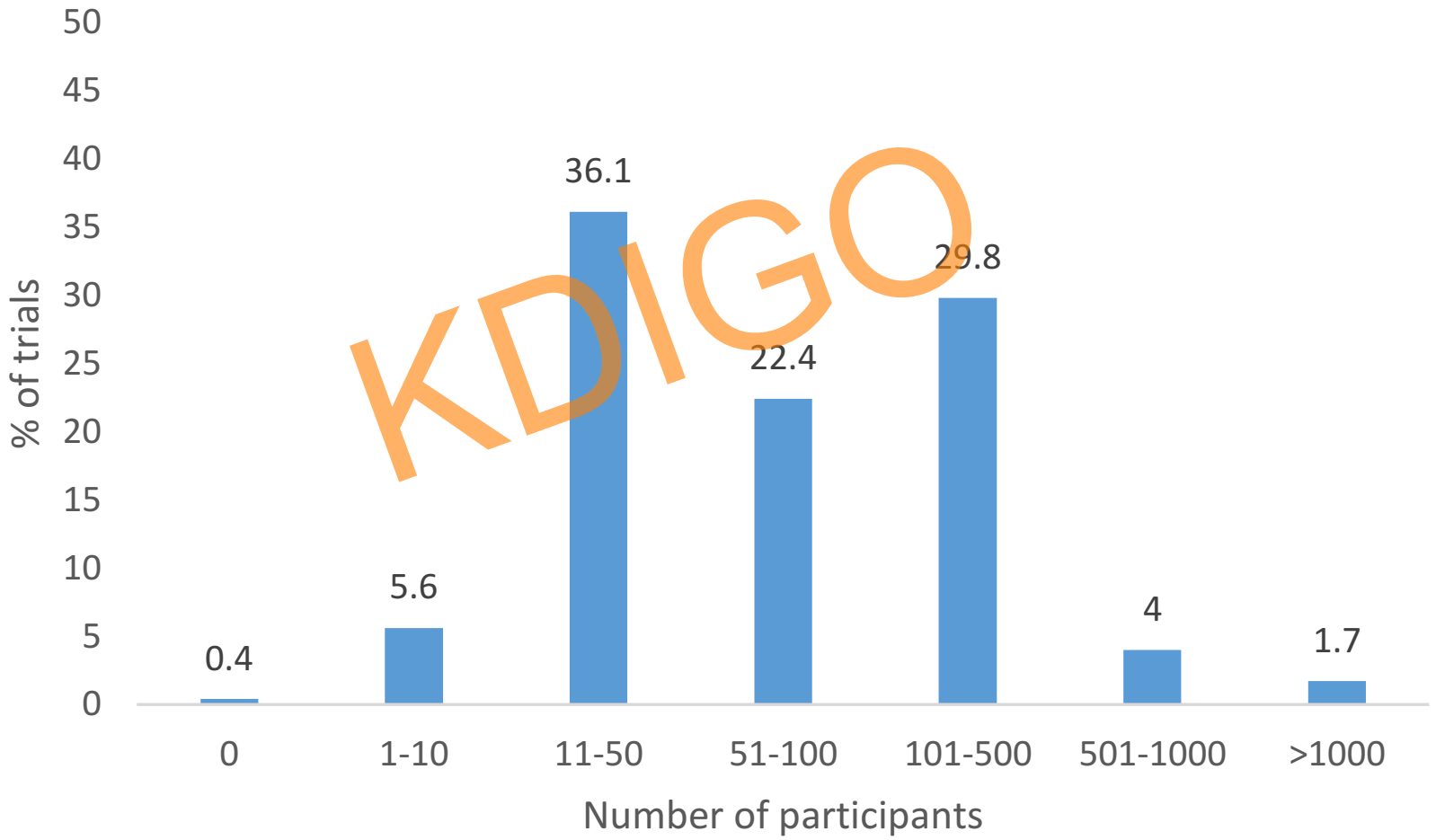
| 1.3.2 6 months | | | | | | |
|---|---|---|---|---|---|---|
| Pisani 2001 | 0 | 19 | 1 | 13 | 0.9% | 0.23 [0.01, 5.32] |
| Sheashaa 2003 | 0 | 50 | 2 | 50 | 1.0% | 0.20 [0.01, 4.06] |
| Tonshoff 2006 | 1 | 100 | 1 | 93 | 1.1% | 0.93 [0.06, 14.66] |
| Fangmann 2004 | 1 | 59 | 5 | 62 | 1.9% | 0.21 [0.03, 1.75] |
| Daclizumab triple 98 | 1 | 126 | 8 | 134 | 2.0% | 0.13 [0.02, 1.05] |
| Davies/Lawen 2000 | 3 | 59 | 5 | 64 | 4.5% | 0.65 [0.16, 2.61] |
| Gelens 2006 | 3 | 18 | 6 | 36 | 5.4% | 1.00 [0.28, 3.54] |
| Parrott 2005 | 4 | 52 | 5 | 56 | 5.4% | 0.86 [0.24, 3.04] |
| Grenda 2006 | 5 | 99 | 5 | 93 | 5.9% | 0.94 [0.28, 3.14] |
| Kahan 1999 | 5 | 168 | 9 | 167 | 7.5% | 0.55 [0.19, 1.61] |
| de Boccardo 2002 | 6 | 151 | 7 | 151 | 7.6% | 0.86 [0.29, 2.49] |
| Kirkman 1991 | 7 | 40 | 6 | 40 | 8.6% | 1.17 [0.43, 3.17] |
| Ponticelli 2001 | 11 | 168 | 15 | 172 | 15.4% | 0.75 [0.36, 1.59] |
| Daclizumab double 99 | 13 | 141 | 13 | 134 | 16.1% | 0.95 [0.46, 1.98] |
| Nashan 1997 | 11 | 168 | 18 | 172 | 16.7% | 0.63 [0.30, 1.28] |
| **Subtotal (95% CI)** | | **1418** | | **1437** | **100.0%** | **0.74 [0.55, 0.99]** |
| Total events | 71 | | 106 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 7.71, df = 14 (P = 0.90); I² = 0%

Test for overall effect: Z = 2.03 (P = 0.04)



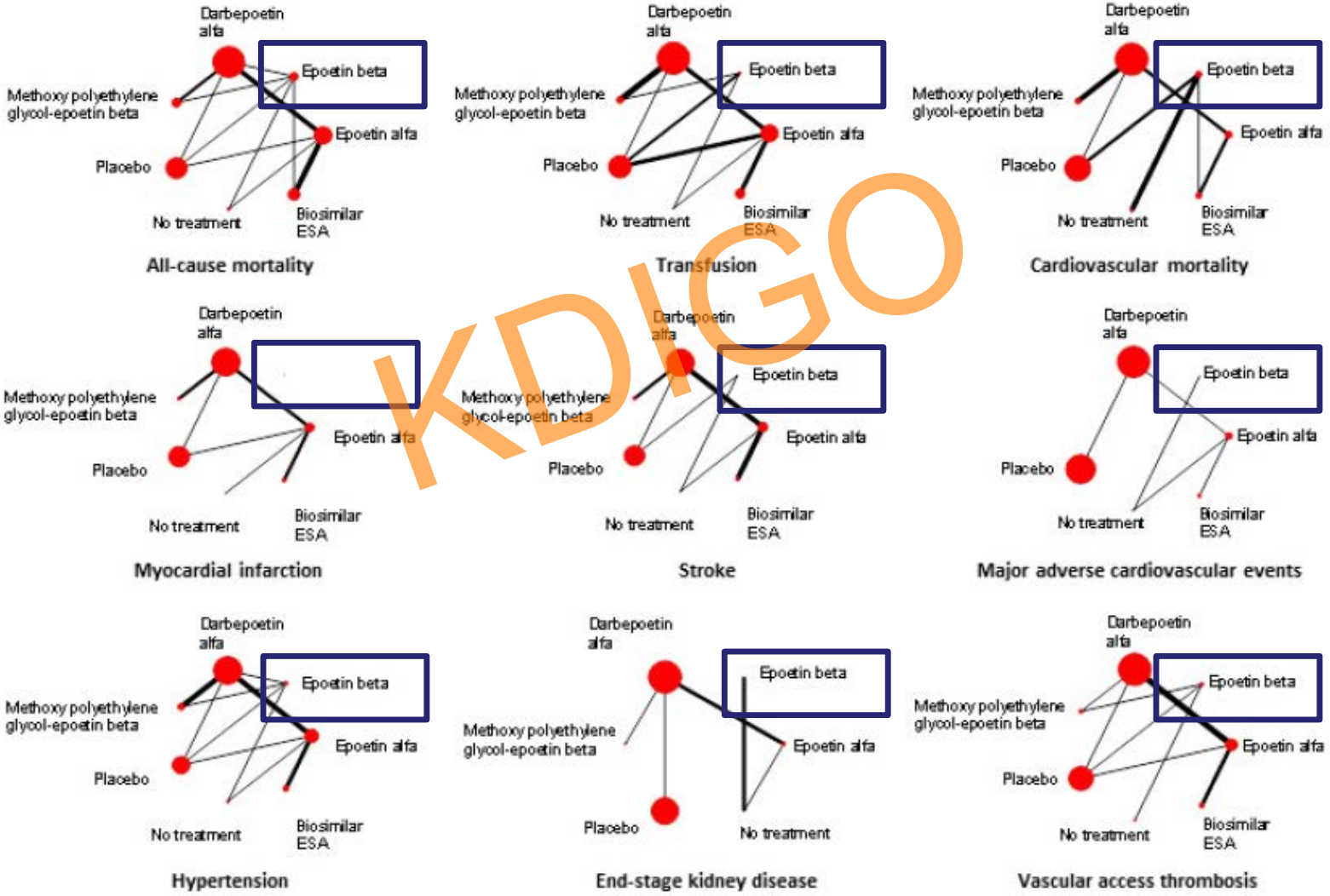
# 3. Too small






[2]AJKD 2014;63(5):771

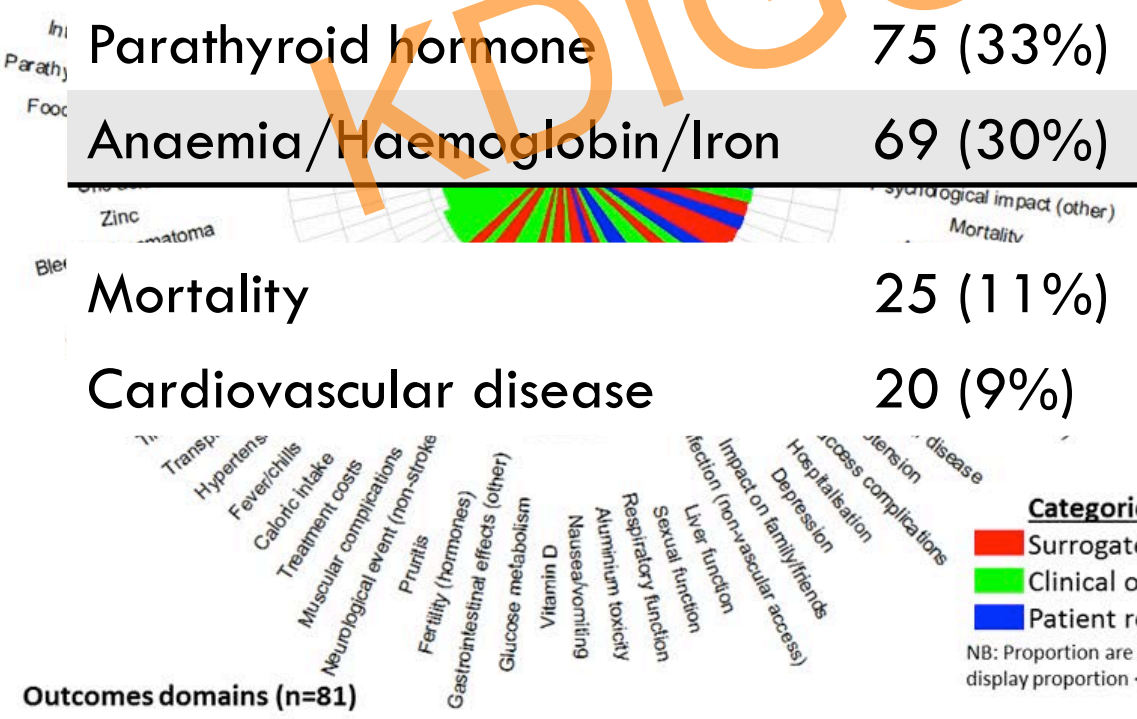
# 4. Wrong comparator e.g ESAs



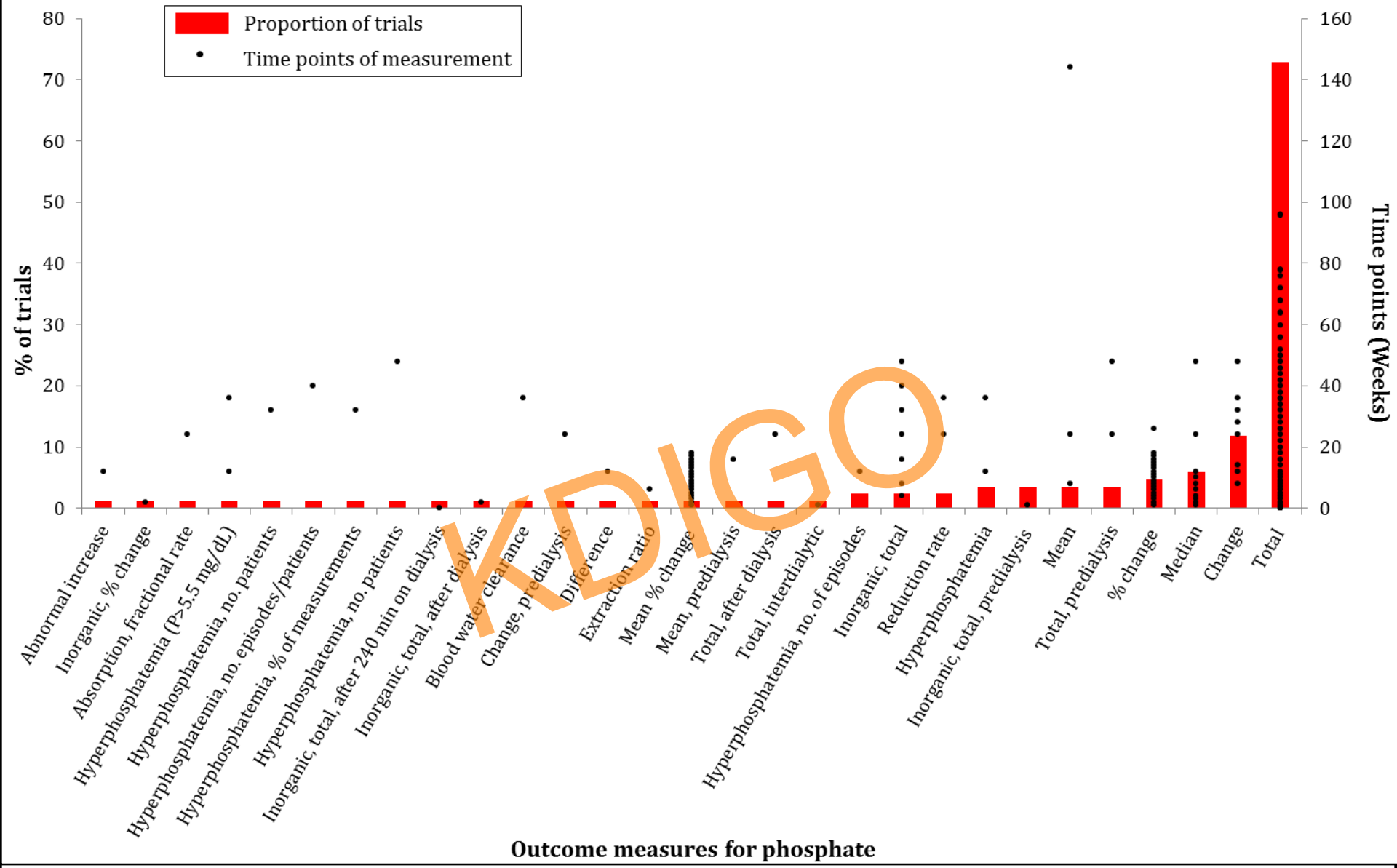
# 5. Outcomes: inconsistent, low importance, biased reporting

| Outcome | N (%) |
|---|---|
| Serum phosphate | 85 (37%) |
| Serum calcium | 77 (34%) |
| Inflammatory markers/oxidative stress | 76 (33%) |
| Parathyroid hormone | 75 (33%) |
| Anaemia/Haemoglobin/Iron | 69 (30%) |
| Mortality | 25 (11%) |
| Cardiovascular disease | 20 (9%) |





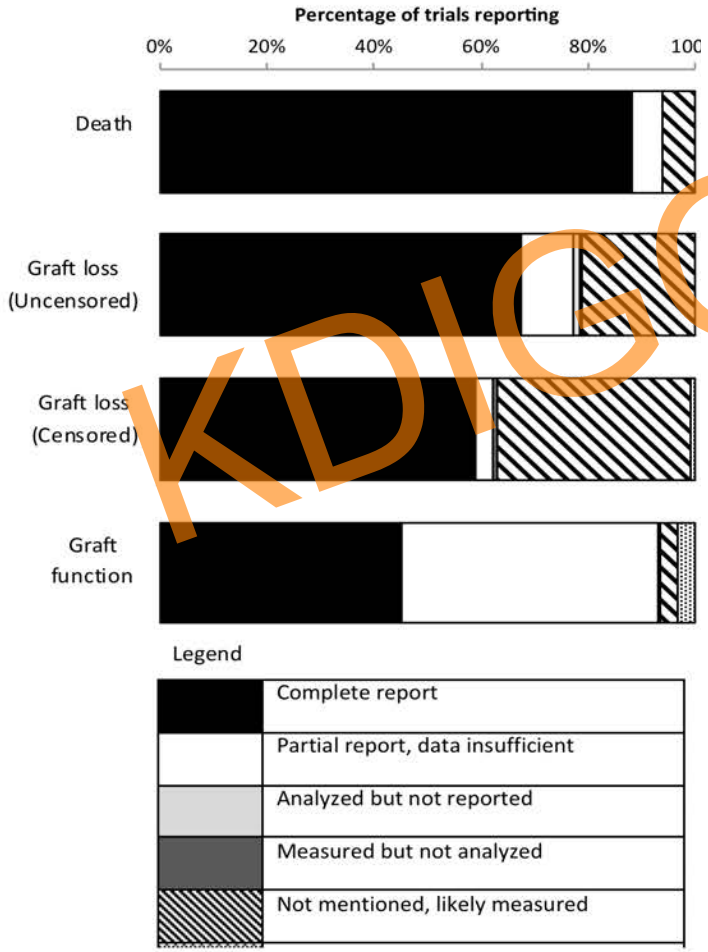

**220 HD trials**


Proportion of trials
Time points of measurement
% of trials
Time points (Weeks)
0
10
20
30
40
50
60
70
80
0
20
40
60
80
100
120
140
160
Abnormal increase
Inorganic, % change
Absorption, fractional rate
Hyperphosphatemia (P>5.5 mg/dL)
Hyperphosphatemia, no. patients
Hyperphosphatemia, no. episodes/patients
Hyperphosphatemia, % of measurements
Hyperphosphatemia, no. patients
Inorganic, total, after 240 min on dialysis
Inorganic, total, after dialysis
Blood water clearance
Change, predialysis
Difference
Extraction ratio
Mean % change
Mean, predialysis
Total, after dialysis
Total, interdialytic
Hyperphosphatemia, no. of episodes
Inorganic, total
Reduction rate
Hyperphosphatemia
Inorganic, total, predialysis
Mean
Total, predialysis
% change
Median
Change
Total
Outcome measures for phosphate

# 5. Outcomes reporting bias

## eg Immunosuppressive agents in kidney transplant recipients

**Figure 2.** Completeness of reporting of core outcomes amongst included trial reports



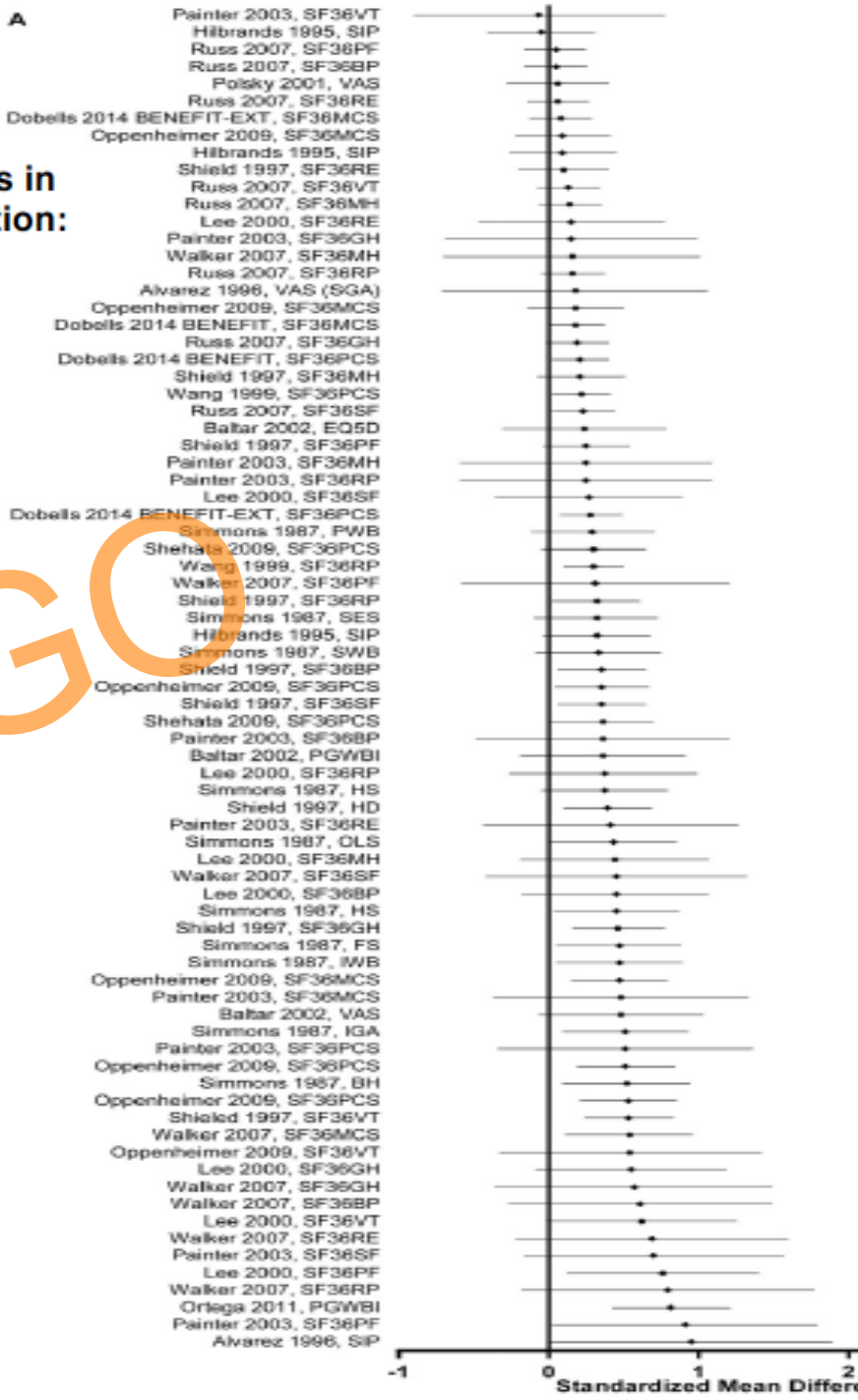
AJKD

Howell et al 2016

# The Consistency and Reporting of Quality-of-Life Outcomes in Trials of Immunosuppressive Agents in Kidney Transplantation: A Systematic Review and Meta-analysis

- 41 reports
- 23 trials (n=4549)

| Instrument | No. of Trials |
|---|---|
| **Generic instruments** | |
| PGWBI | 2 |
| SF-36 | 10 |
| SIP | 2 |
| EQ-5D[a] | 1 |
| EQ-5D[a] VAS | 1 |
| VAS–general health | 2 |
| Welzel-Kohnen color scale | 1 |
| Health thermometer | 2 |
| **Disease-specific (kidney transplantation)** | |
| KTQ | 2 |
| VAS–impact of disease | 1 |
| **Symptom-specific instruments** | |
| VAS–impact of symptom | 2 |
| ABS | 1 |
| CES-D | 1 |
| FSE | 1 |
| BPA | 1 |
| MHI | 1 |
| Study specific | 2 |
| GSRS | 5 |
| GIQLI | 4 |
| MTSOSDS | 2 |
| Memphis Survey | 1 |
| OTE | 2 |




Paradigm shift
KDIGO

Paradigm shift: Integrate trials and routine clinical care

# THE FUTURE: CAUSE FOR HOPE

# The future: more, better, more relevant trials

1. Culture change: evidence savvy community*
2. Consumer engagement*
3. Informed by systematic reviews of trials and observational studies
4. Multi-disciplinary & multi-speciality
5. Core outcomes*
6. Novel designs*
7. Larger, more effective, networks of networks*
8. More effective knowledge transfer


KDIGO
THE
PERFECT STORM

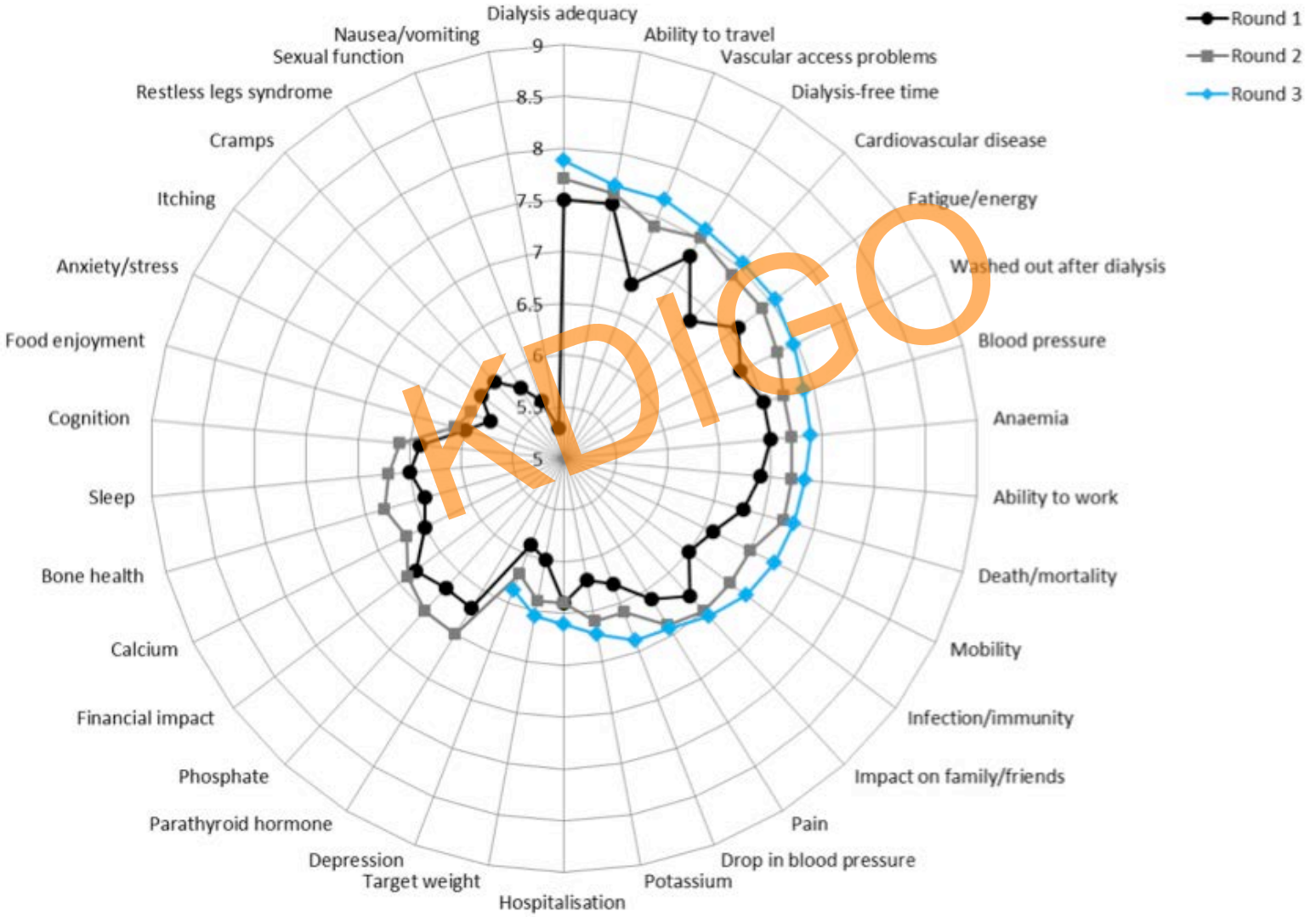
# The comparator: observational studies used for causal inference

- The 'Perfect Storm' for bias
  - POWER: Low type II error (random error)
    - Large routinely collected registries (DOPPS, ERA, ANZDATA, USRDS…)
    - Frequent end points
  - PLACE: High type I error (systematic error)
    - Confounders not measured, misclassified or incompletely adjusted for
    - Multiplicity of analysis (within and across registries)

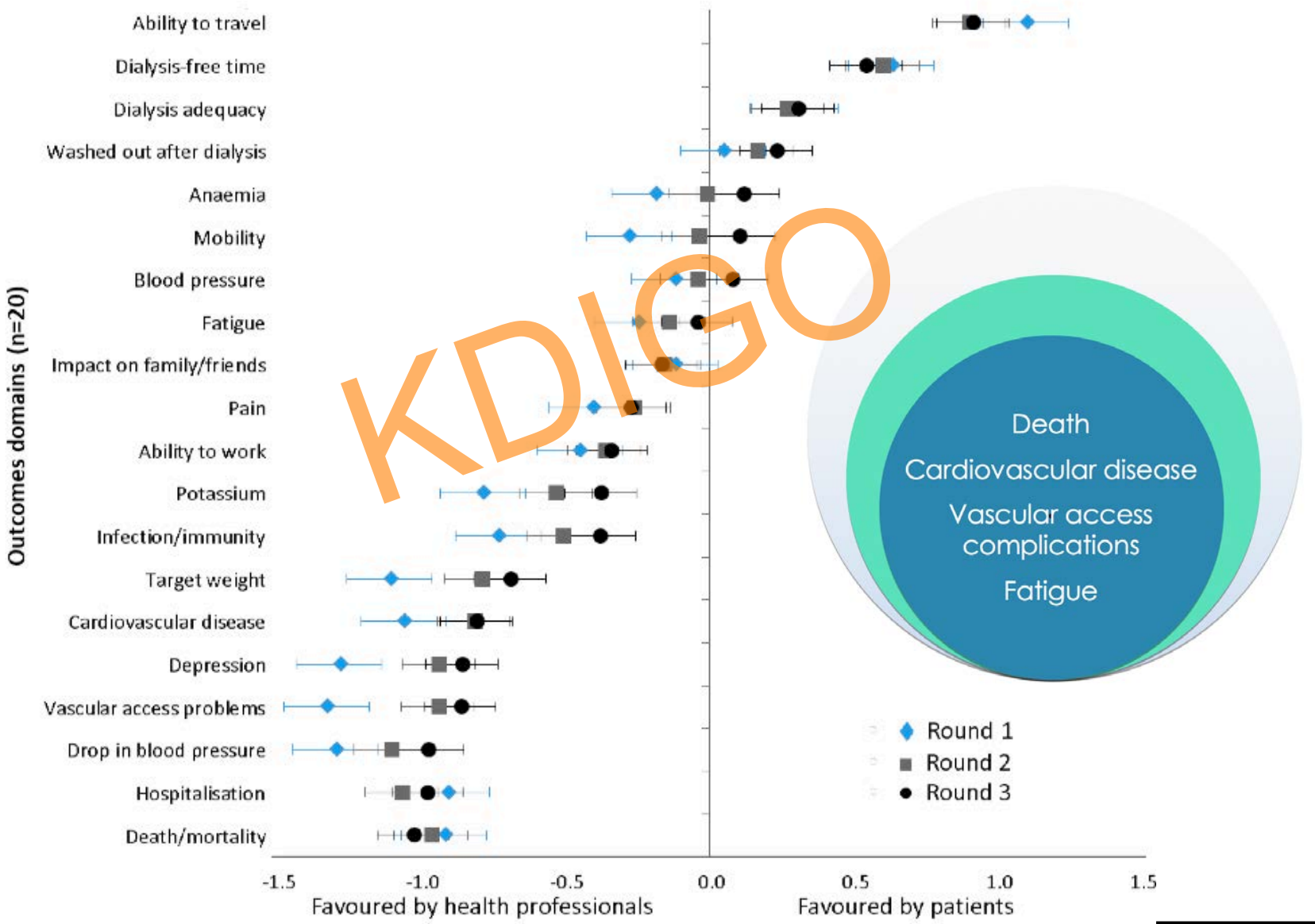
# Consumers improve trials by:

- Identifying and prioritising topics
  - Stevens, 2003
- Getting trials funded
  - Terry, 2007
- Improving information sheets and consent forms
  - Marsden & Bradburn, 2004
- Ensuring outcome measures are relevant and feasible
  - Ali, 2006
- Increasing trial recruitment and identifying trials likely to recruit poorly
  - Terry, 2007
- Understanding the results of trials
  - Hanley, 2001

# Core outcomes: patients' delphi rating for HD trials' outcomes



# Patients-professionals differences



# Novel designs: registry, adaptive, mendelian…

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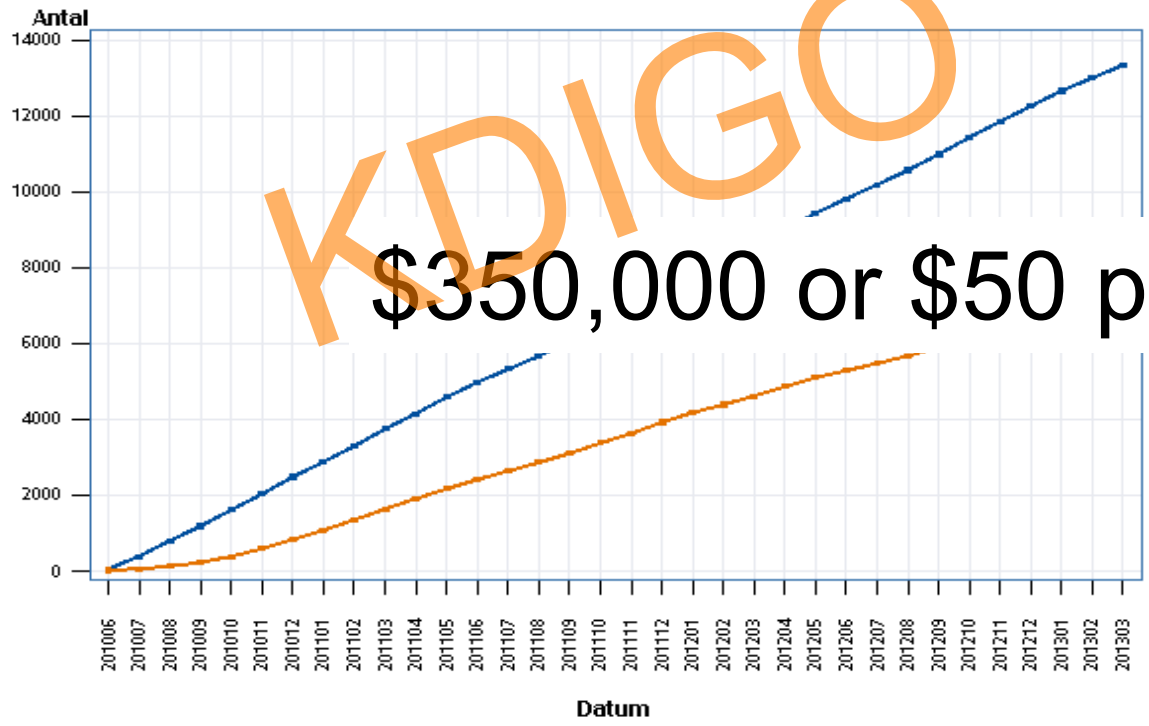
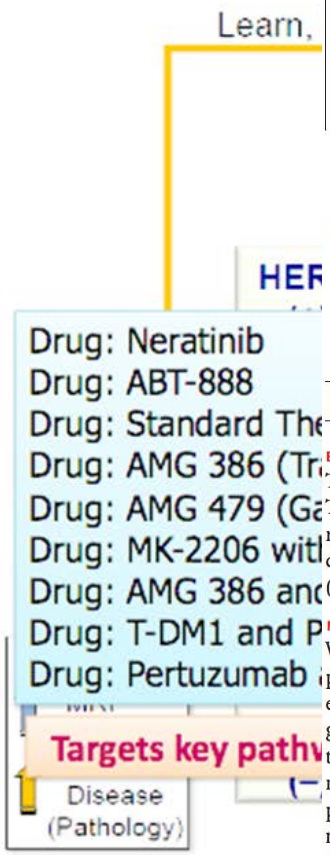





$350,000 or $50 per patient

# Novel designs: registry, adaptive, mendelian…




The NEW ENGLAND JOURNAL of MEDICINE

Adapt

J.W. Park, M.
A. DeMichele
C. Isaacs, R
J.E. Lang
J. Lyan

BACKGROUND
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METHODS
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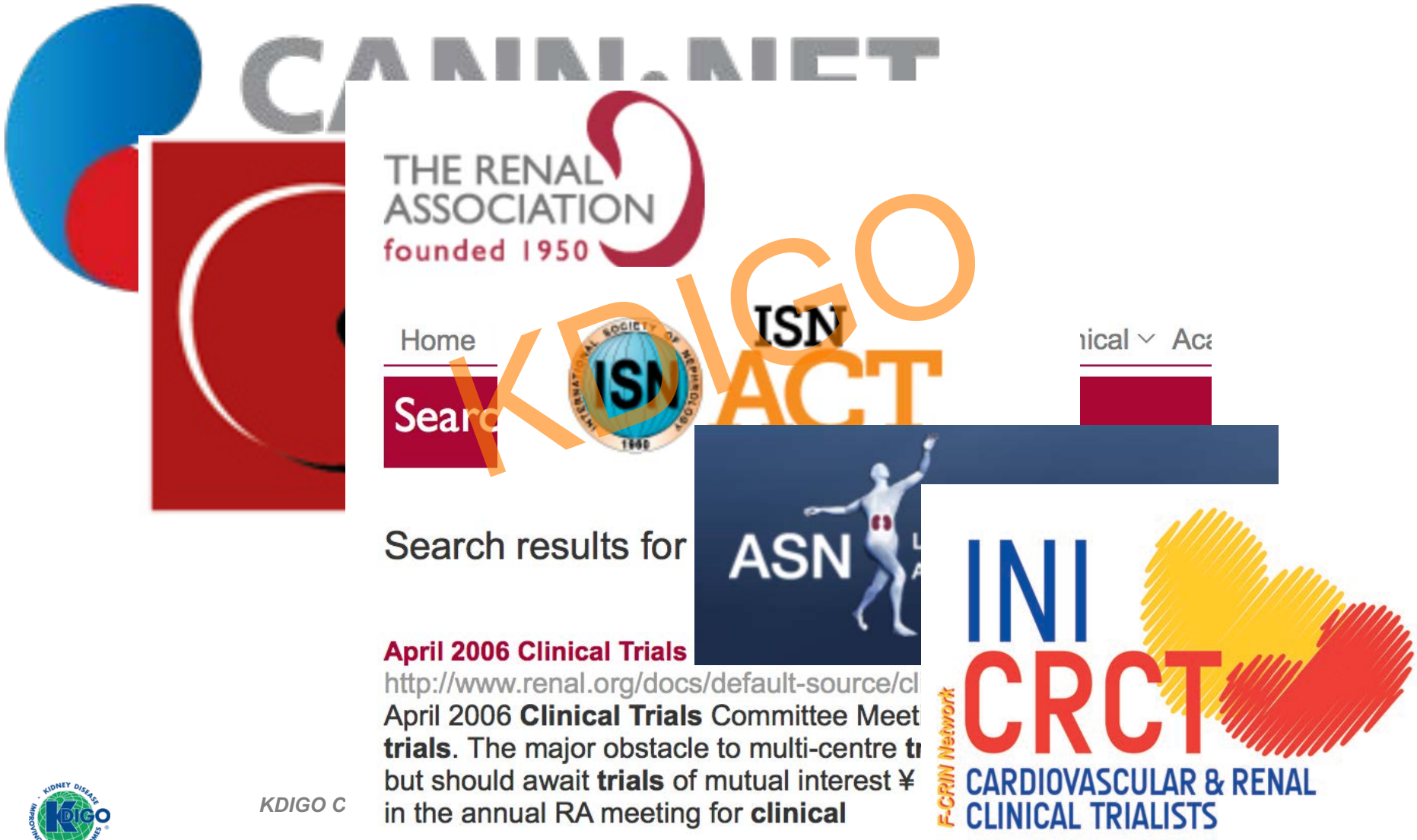
point was pathological complete response. Volume changes on serial magnetic resonance imaging were used to assess the likelihood of such a response in each patient. Adaptive assignment to experimental groups within each disease subtype was based on Bayesian probabilities of the superiority of the treatment over control. Enrollment in the experimental group was stopped when the 85% Bayesian predictive probability of success in a confirmatory phase 3 trial of neoadjuvant therapy reached a prespecified threshold for any biomarker signature ("graduation"). Enrollment was stopped for futility if the probability fell to below 10% for every biomarker signature.

**Table 2. Final Posterior and Predictive Probabilities of Neratinib Efficacy with Regard to 10 Biomarker Signatures.**

| Biomarker Signature | Estimated Rate of Pathological Complete Response (95% Probability Interval) | | Probability of Neratinib Being Superior to Control | Predictive Probability of Success in Phase 3 Trial |
|---|---|---|---|---|
| | Neratinib | Control | | |
| | *percent* | | | |
| Any | 33 (24–40) | 23 (14–33) | 93 | 48 |
| Hormone-receptor positive | 23 (13–33) | 16 (6–28) | 81 | 40 |
| Hormone-receptor negative | 44 (30–55) | 31 (17–45) | 92 | 58 |
| HER2 positive | 39 (28–51) | 23 (8–38) | 95 | 73 |
| HER2 negative | 28 (15–37) | 24 (13–35) | 69 | 25 |
| High-risk category 2 on 70-gene profile* | 48 (30–60) | 29 (11–48) | 93 | 72 |
| HER2 positive, hormone-receptor positive | 30 (18–44) | 17 (3–32) | 91 | 65 |
| HER2 positive, hormone-receptor negative | 56 (37–73) | 33 (11–54) | 95 | 79 |
| HER2 negative, hormone-receptor positive | 14 (3–25) | 16 (5–27) | 42 | 14 |
| HER2 negative, hormone-receptor negative | 38 (22–50) | 31 (15–46) | 77 | 40 |

N Engl J Med 2016;375:11-22.
DOI: 10.1056/NEJMoa1513750

# Networks of networks



# Australia-NZ Intensive Care Triallists Collaboration

SINCE 1994 CTG ENDORSED AND SUPPORTED STUDIES HAVE RANDOMISED OVER 43,000 PATIENTS INTO CLINICAL TRIALS AND INCLUDED MORE THAN 25,000 PATIENTS IN OBSERVATIONAL STUDIES

RECEIVED OVER $80 MILLION IN TOTAL RESEARCH FUNDING

PUBLISHED 148 PEER REVIEWED PUBLICATIONS, INCLUDING 10 PAPERS IN THE NEW ENGLAND JOURNAL OF MEDICINE WITH A $h$-INDEX of 38

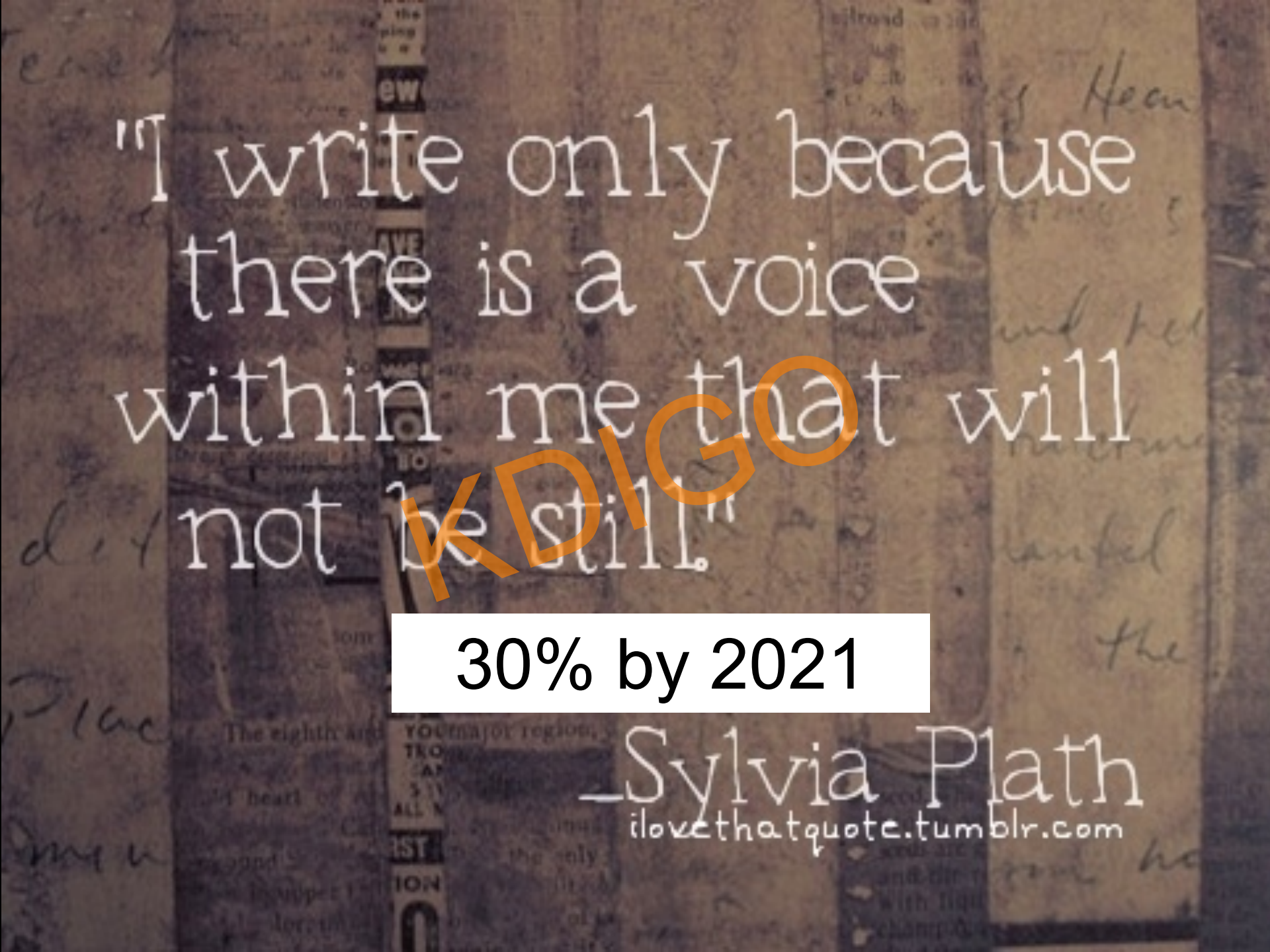
IN 2014-2015 THERE WERE 68 ADULT AND PAEDIATRIC MEMBER INTENSIVE CARE UNITS ACROSS AUSTRALIA AND NEW ZEALAND

WITH OVER 700 CLINICIANS & RESEARCHERS CURRENTLY SUBSCRIBED TO THE CTG MAILING LIST

PARTICIPATING IN 39 ACTIVE STUDIES

# Overview

- A snapshot of our current state
- The past: Too much waste
- The future: Cause for hope


"I write only because there is a voice within me that will not be still."
KDIGO
30% by 2021
_Sylvia Plath
ilovethatquote.tumblr.com