KDIGO 2017 – Paris, September 2016

# Conducting Clinical Trials in Nephrology: Controversies Conference



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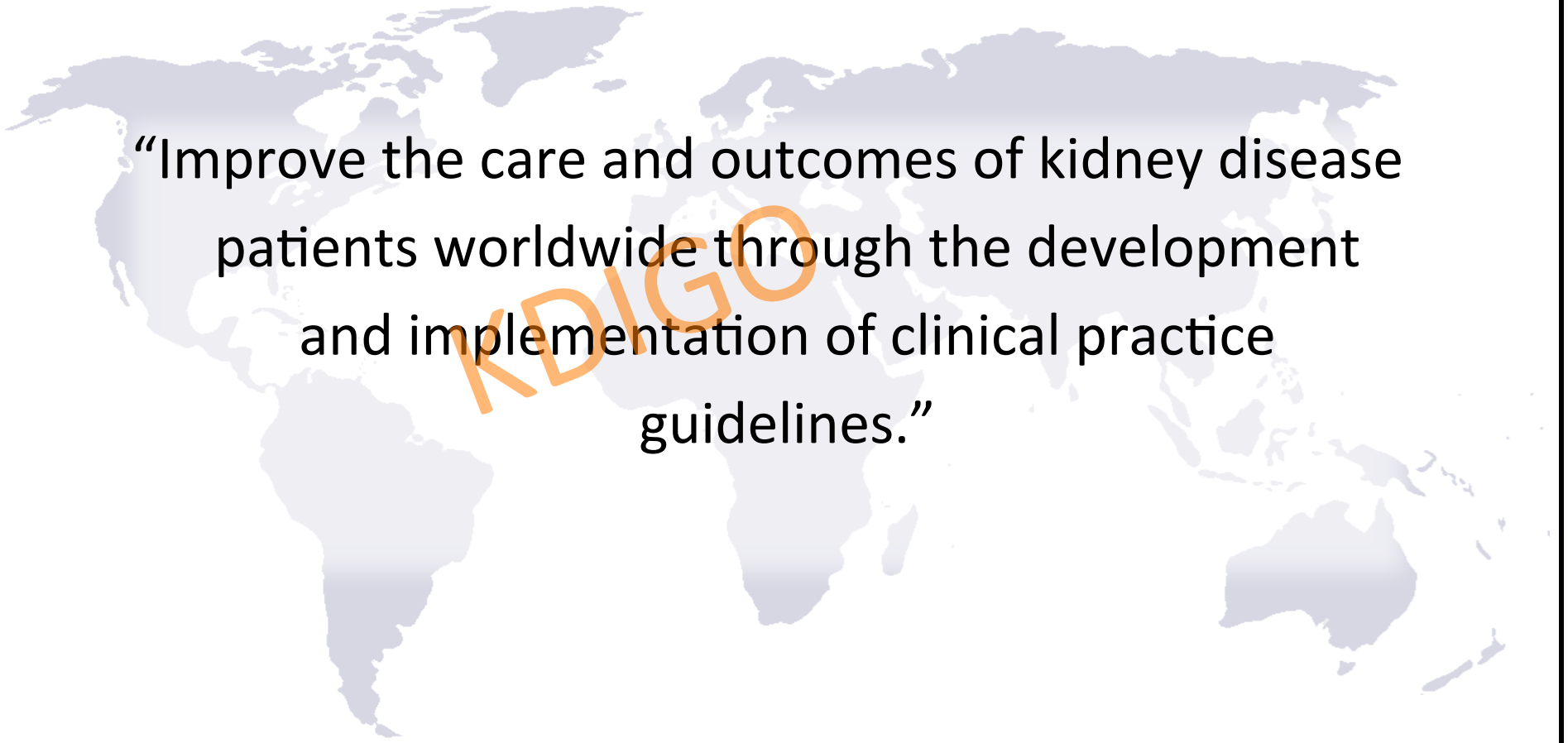
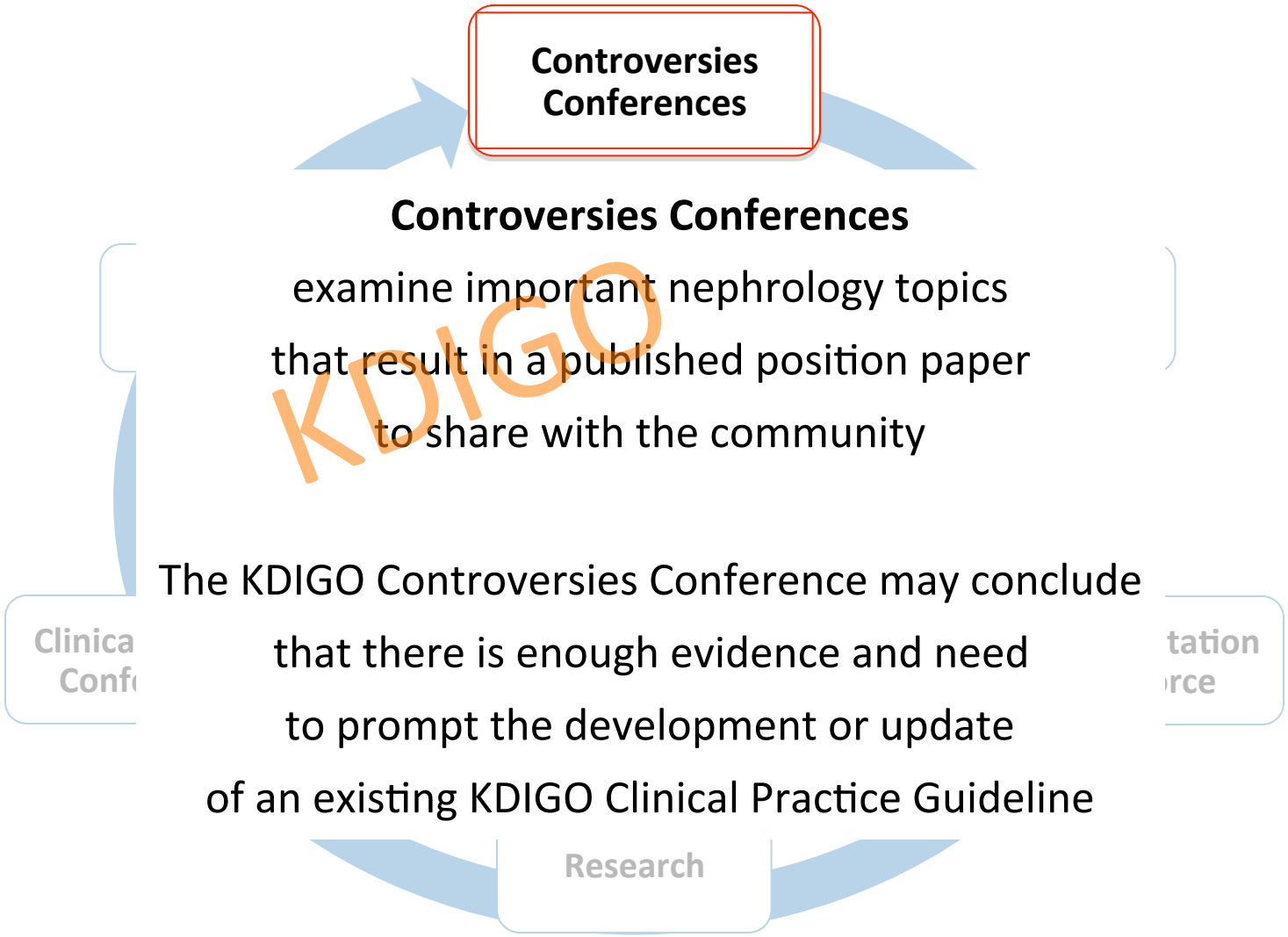
Denver, USA

# KDIGO Mission



"Improve the care and outcomes of kidney disease patients worldwide through the development and implementation of clinical practice guidelines."

# Controversies Conferences




**Controversies Conferences**

examine important nephrology topics

that result in a published position paper

to share with the community



The KDIGO Controversies Conference may conclude

that there is enough evidence and need

to prompt the development or update

of an existing KDIGO Clinical Practice Guideline

# Meeting Rationale and Objectives

- Chronic Kidney Disease is a *growing, global,* public health issue with high societal costs and high individual patient burden
- There is *very limited* reliable information to guide the care of patients with CKD
- Most randomized trials in nephrology have been too small to detect treatment effects of moderate size (15-20% reduction in major outcomes such as death or disability)
- Conducting RCT's in nephrology is challenging!
- Slides from todays presentation are from the outstanding speakers who presented at the KDIGO Controversies Conference in Paris, September 2016 including: Dr. Jonathan Craig, Dr. Leslie Inker, Dr. Michael Walsh, Dr. Vlado Perkovic and Dr. Martin Landry.
- The conference agenda and select presentations are available at http://kdigo.org/conferences/clinical-trials/
- My goal is to communicate some of the important aspects of the Controversies Conference
- Conference proceedings published in Kidney International (2017) 92, 297-305

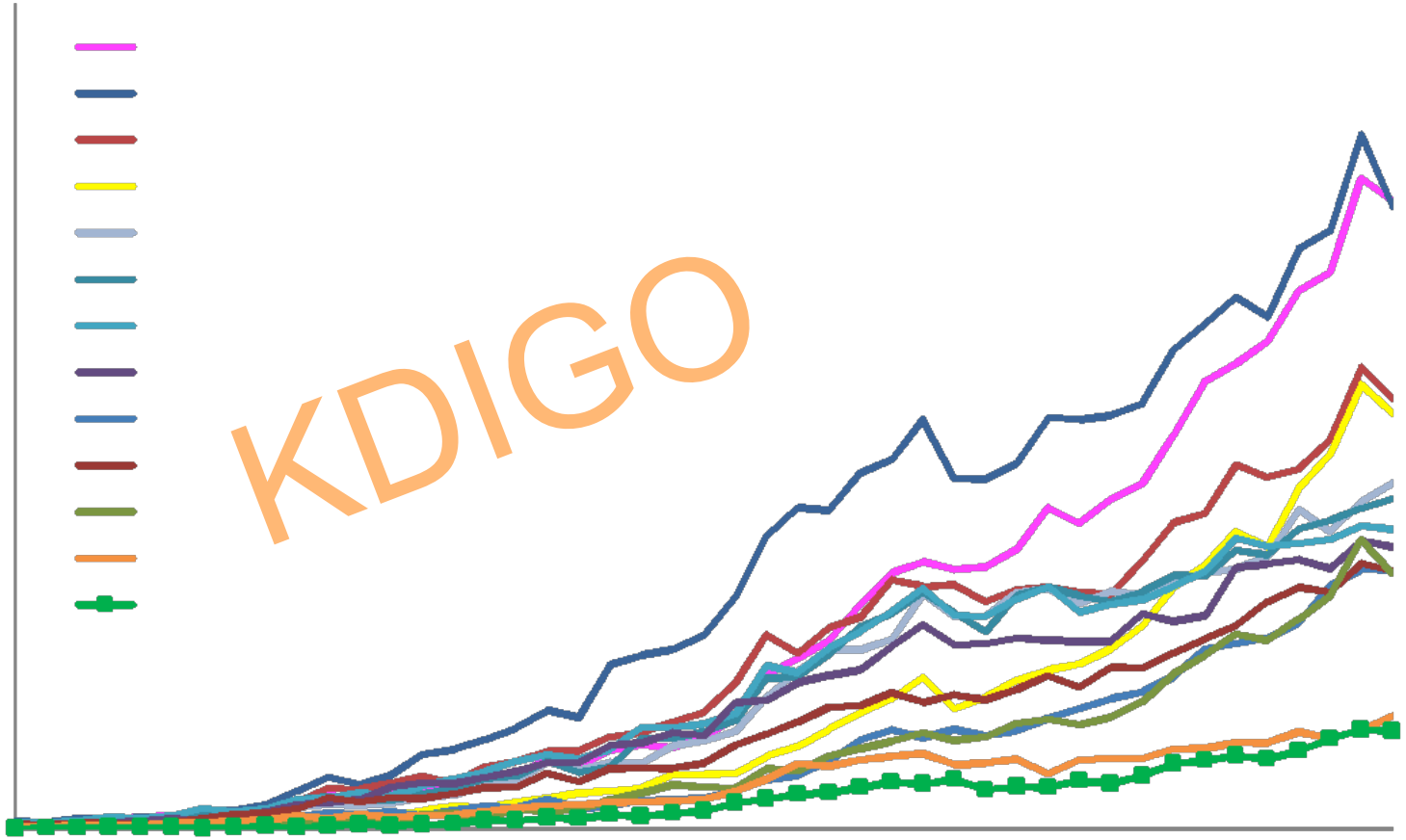
# OVERVIEW

- Clinical trial Design
- Outcomes for clinical trials in nephrology: Renal and Non-Renal
- Conduct of clinical trials



- 4 KEY components of high quality RCT's
  - **Adequate** number of patients enrolled (to ensure adequate number of outcomes)
  - **Adherence** to assigned study treatment
  - **Ascertainment** of outcomes fully
  - **Analysis** is statistically appropriate

# Clinical Trials in Nephrology




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

# 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, PH

## ABSTRACT

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

***Methods*** We studied 1233 patients with clinical evidence of congestive heart failure or ischemic heart disease who were undergoing hemodialysis: 618 patients 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 percent 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 myocardial 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 interval, 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 increasing hematocrit values in both groups. The patients 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-hematocrit 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, Lisán Jiang, Lai Seong Hooi, Adeera Levin, Lawren Bo Feldt-Rasmussen, Udom Krairitthichai, 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 [5·0 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 received



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.

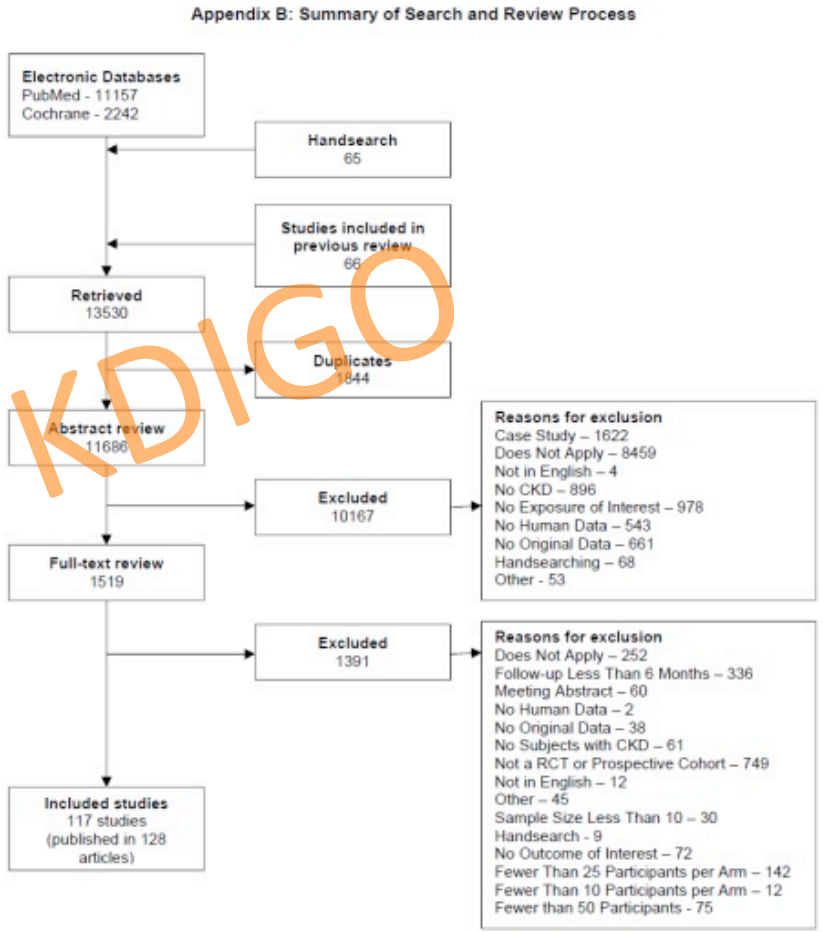
### RESULTS

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.)

# NEED FOR HIGH QUALITY RCT



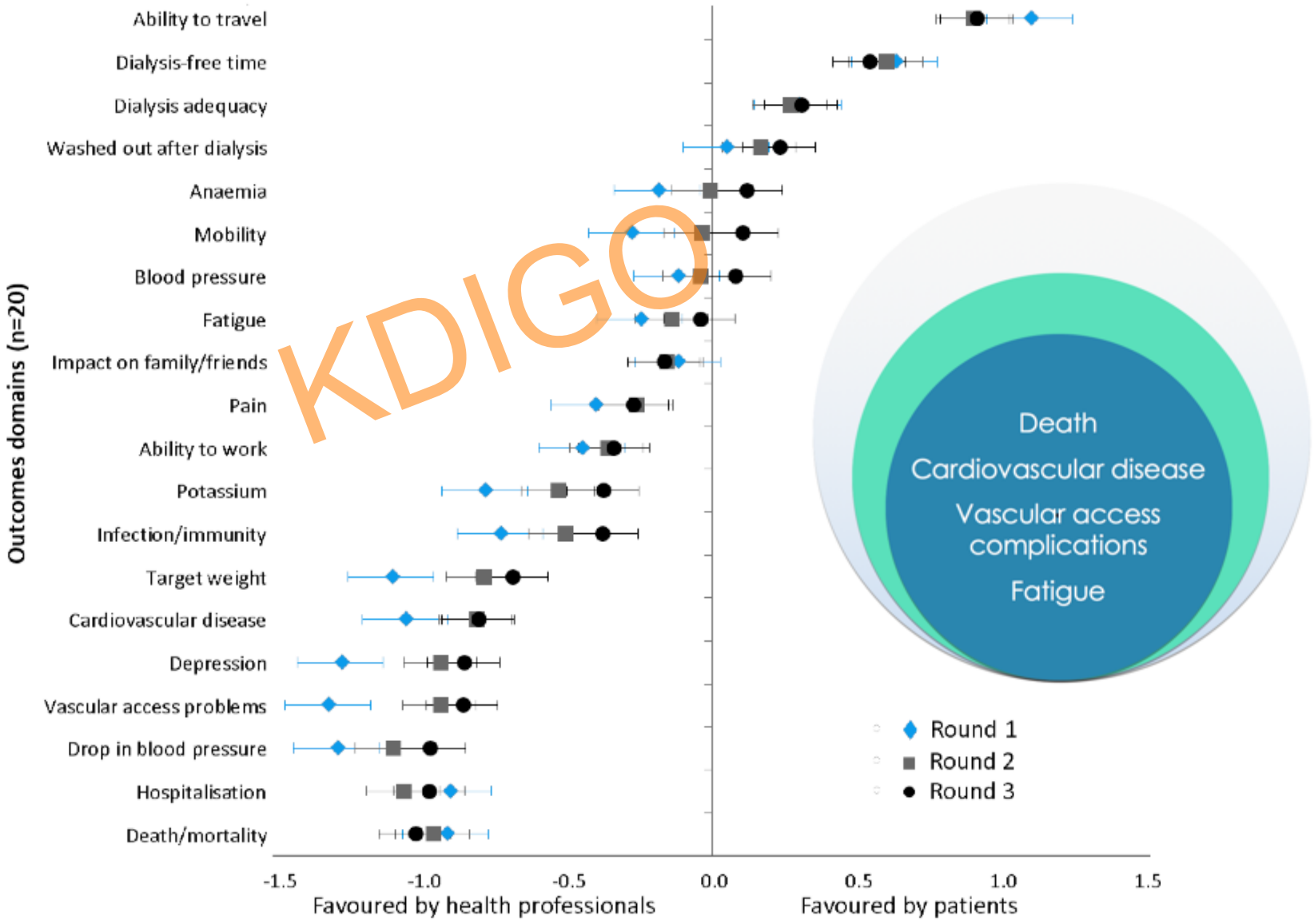
# Trial Design Common Issues

- Question already answered (e.g. ESA)
- Important questions not addressed – not important to CONSUMERS
  - SONG
- Trial population too narrow
  - Eligibility criteria must be practical and BROAD
  - Exclusion criteria should be based only on specific safety concerns
- Wrong outcome (e.g. all-cause mortality)
- Lack of Equipoise
  - Guideline committee must avoid making recommendations with weak evidence and should state explicitly where placebo controlled trials are needed

# Consumers improve trials by:

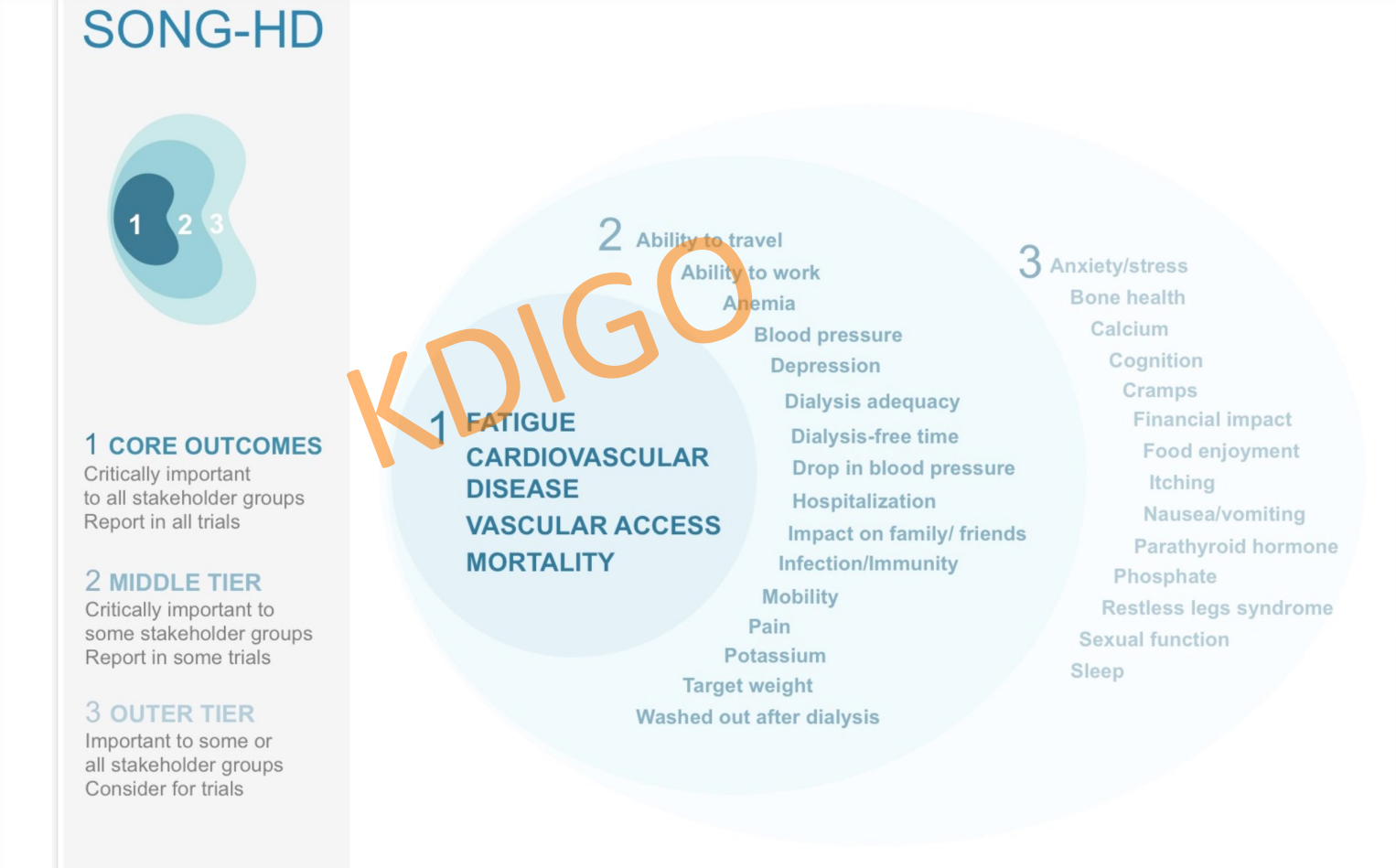
- Identifying and prioritising topics
  - Stevens, 2003
- Getting trials funded
  - Terry, 2007
- Improving information sheets and consent forms
  - Marsden & Bradburn, 2004
- Ensuring outcome measures are relevant and feasible
  - Ali, 2006
- Increasing trial recruitment and identifying trials likely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

# Patients-professionals differences

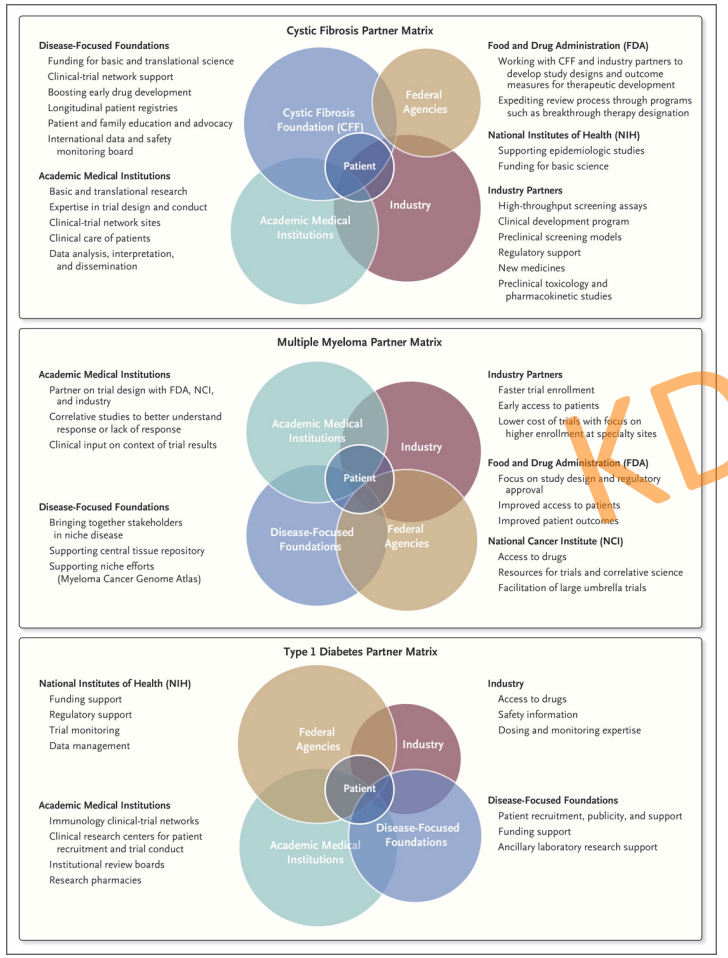


# STANDARDIZED OUTCOMES IN NEPHROLOGY

## HTTP://SONGINITIATIVE.ORG



# Collaboration-Who Knew it Was Such a Good Idea?






- A word on ‘Academia’
- - Entire career in private practice and clinical research
- - Principal Investigator on 97+ clinical trials
- - Collaborator with global academic centers, pharmaceutical partners all over world
- Workgroup Member- KDIGO MBD 2009, 2017

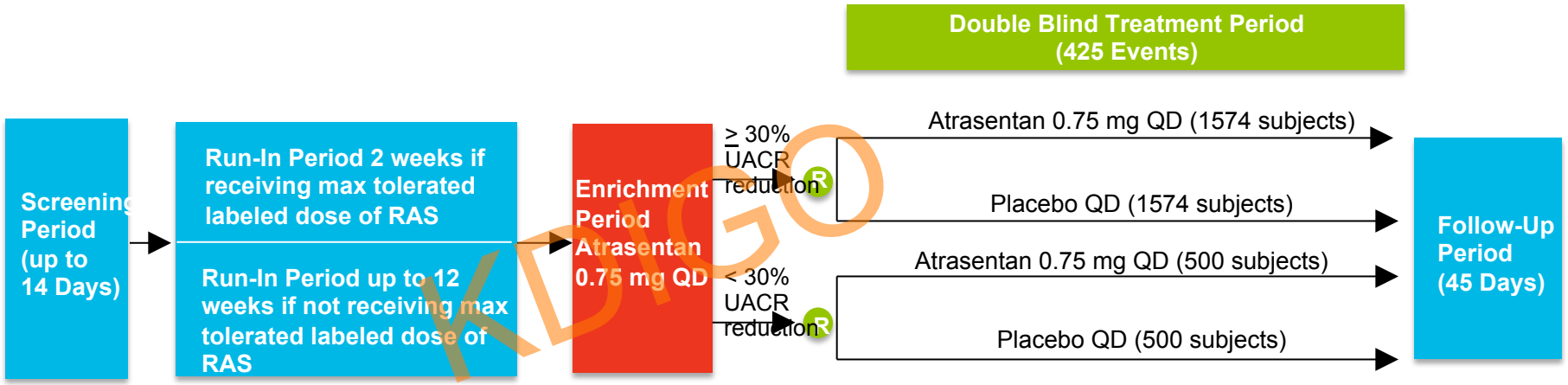
# Strategies to Improve Trial Conduct

- Streamline the process of data collection by assessing a LIMITED number of critical data elements
- Maximize adherence and minimize loss to follow-up
- Improve the efficiency AND APPROPRIATENESS of trial monitoring- consider central risk-based statistical processes
- Rationalizing safety monitoring and pharmacovigilance activity with more focus on review of randomized aggregate data by un-blinded DSMB
- Make sure adjudication methods focus on events in which adjudication which materially influence interpretation

# Objectives, Hurdles and Suggestions for Trial Design

- Answer an important question
  (many treatments already in use without reliable evidence)
- Uncertainty principle –if uncertain, randomize!
- Use routine databases to pre-screen; avoid unnecessary exclusions
- Run in; Enrichment to minimize non-adherence
- SIMPLE CRF's – avoid complex definitions of outcomes
- Realistic effect size (15%); Event driven with minimum duration
- Account for non-adherence
- Rarely is total mortality best
- Allow flexibility in nontrial Rx
- Streamline data collection to fit with routine care for team/patient
- Identify primary/secondary/ exploratory analyses up-front

# Enrichment



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# Impact of errors on the reliability of results

## Accurate DATA ≠ Reliable RESULT

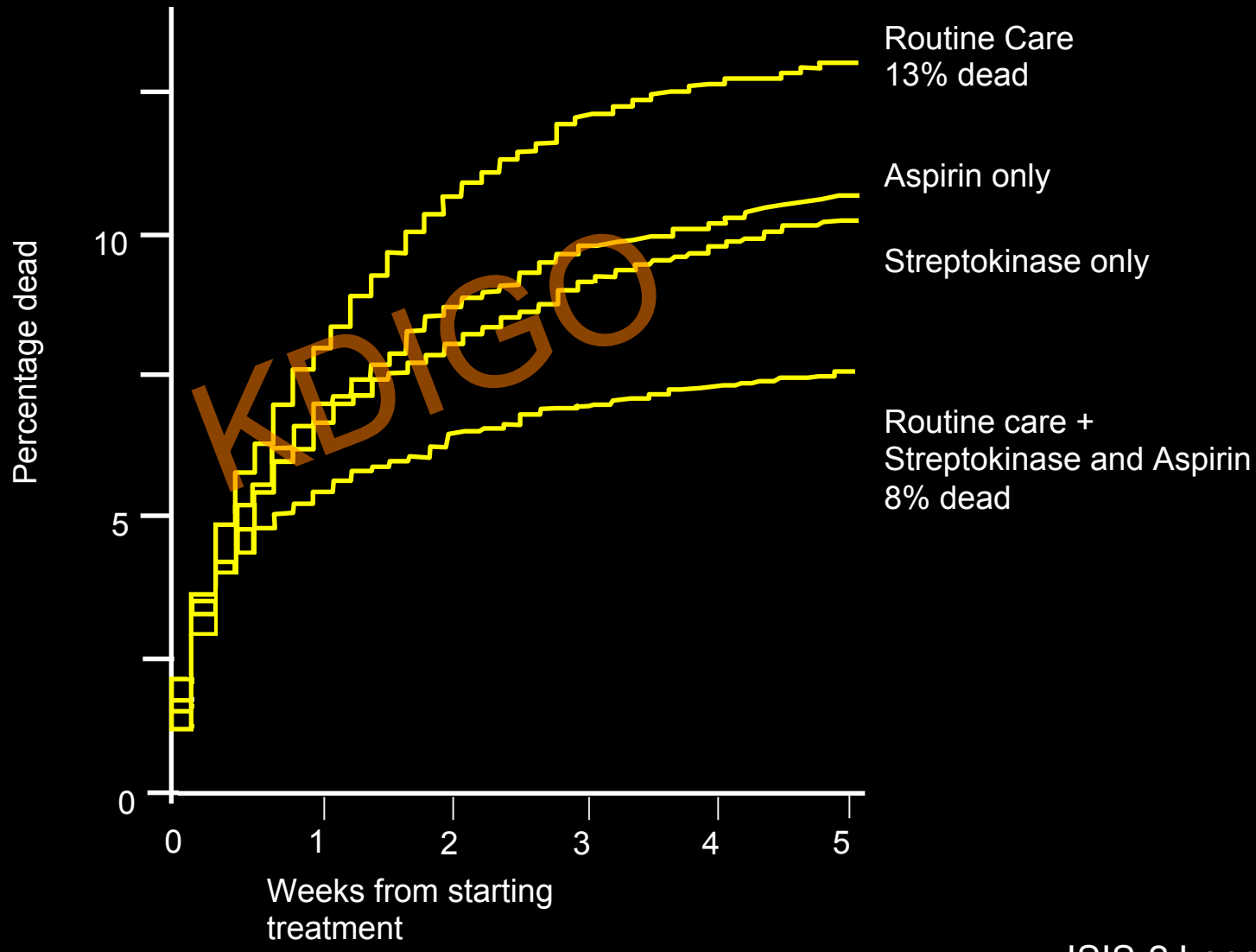
- **Random Errors**
  - add noise -> reduces power -> minimizes a difference
  - does not bias the result in any direction
- **Systematic Errors**
  - add bias -> lead towards a particular decision
  - direction & extent difficult to assess



**Large *randomized* trials (appropriately analysed) are remarkably resistant to small random errors in the data**

Data do not need to be perfect!

# Second International Study of Infarct Survival (ISIS-2)






ISIS-2 Lancet 1988

# ISIS2: Protocol & procedures

- Eligibility
  - Signs or symptoms suggestive of definite or suspected acute myocardial infarction
  - <24 hours since onset of episode of pain that led to admission
  - No *clear* contra-indication to, or indication for, immediate streptokinase or aspirin, *in the view of the responsible physician*
- Randomization
  - By telephone - 9 questions plus site and patient identifiers
- Follow-up data collection
  - Discharge form
  - Pre-randomization ECG

**PATIENT IDENTIFIERS** (Please PRINT):
(for central monitoring of certified causes of death)

Hospital: .....

Surname/Family name: .....

All given name(s): .....

Date of birth: day: ...../ month: ...../ year: .....

Address: .....

.....

.....

Maiden name: .....
(if available)

Family doctor: .....
(if available)

# ISIS 2

Second International Study of Infarct Survival
NOTIFICATION OF DISCHARGE OR PRIOR DEATH

OR: PATIENT STICKER,
IF **ALL** DETAILS PROVIDED

**TICK** ✓ **PRE-TREATMENT CHARACTERISTICS**

- ☐ Female
- ☐ Previous myocardial infarction
- ☐ Previous diabetes

**TICK** ✓ **ANY DEVIATIONS FROM TRIAL TREATMENT**

- ☐ **STREPTOKINASE/PLACEBO** infusion interrupted, or not given
- ☐ **ASPIRIN/PLACEBO** calender pack interrupted, or not given

**TICK** ✓ **APPARENT SIDE-EFFECTS OF STREPTOKINASE/PLACEBO INFUSION**

- ☐ Significant hypotension during, or just after, infusion
- ☐ Anaphylactic shock
- ☐ Rigor
- ☐ Rash
- ☐ Other (specify, eg. respiratory distress) .....

**TICK** ✓ **MAIN EVENTS (FATAL OR NOT) AFTER RANDOMISATION, AND ENTER DATE (FIRST) OCCURRED**

day / month / year

- ☐ "Major" bleed (transfused) ...../...../..... and site(s).....
- ☐ "Minor" bleed (not transfused) ...../...../.....
- ☐ Cardiac rupture ...../...../.....
- ☐ Reinfarction ...../...../.....
- ☐ Ventricular fibrillation ...../...../.....
- ☐ Other cardiac arrest ...../...../.....
- ☐ Stroke, probable cerebral haemorrhage ...../...../..... Likely residual disability (if alive):
- ☐ Stroke, infarct or unknown type ...../...../..... ☐ Non-significant/ ☐ Moderate/ ☐ Severe
- ☐ Discharge alive from hospital ...../...../.....
- ☐ Death in hospital ...../...../..... and underlying cause, if **not** cardiac:
  .....

**TICK** ✓ **TREATMENT IN HOSPITAL**

- ☐ Steroids prior to streptokinase/placebo infusion
- ☐ Subcutaneous heparin
- ☐ Intravenous heparin
- ☐ Oral anticoagulant
- ☐ Intravenous beta-blocker
- ☐ Non-trial aspirin
- ☐ Other anti-platelet agent(s)

**TICK** ✓ **DRUGS ON DISCHARGE**

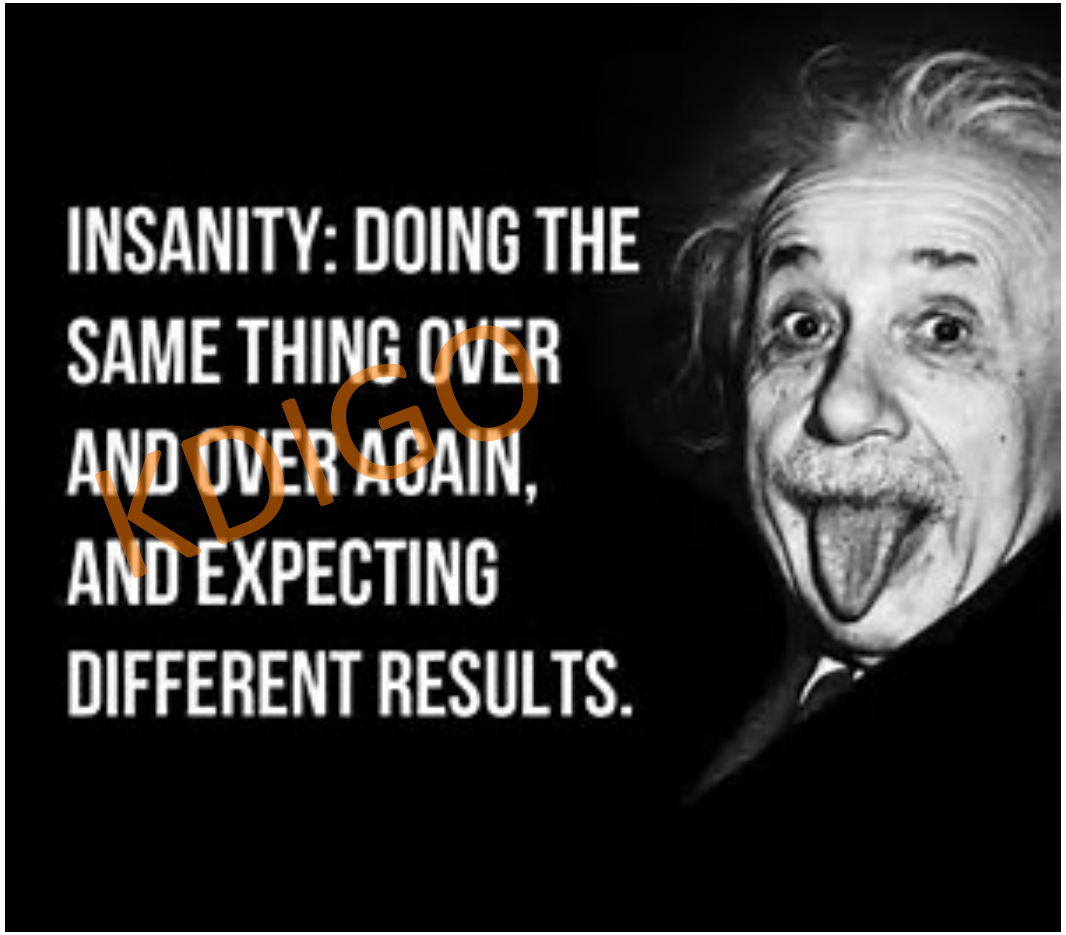
- ☐ Oral anticoagulant
- ☐ Non-trial aspirin
- ☐ Other anti-platelet agent(s)
- ☐ Beta-blocker

**NAME OF PERSON COMPLETING FORM** (please PRINT): .....

PLEASE SEND: — TOP COPY OF THIS FORM (retain bottom green copy)
— AND PRE-RANDOMISATION ECG (original or good photocopy)
TO: ISIS-2, FREEPOST, OXFORD OX2 6BR, UK (no stamp required within UK)

THANK YOU VERY MUCH

# Have a Willingness to Change 'How It's Done'



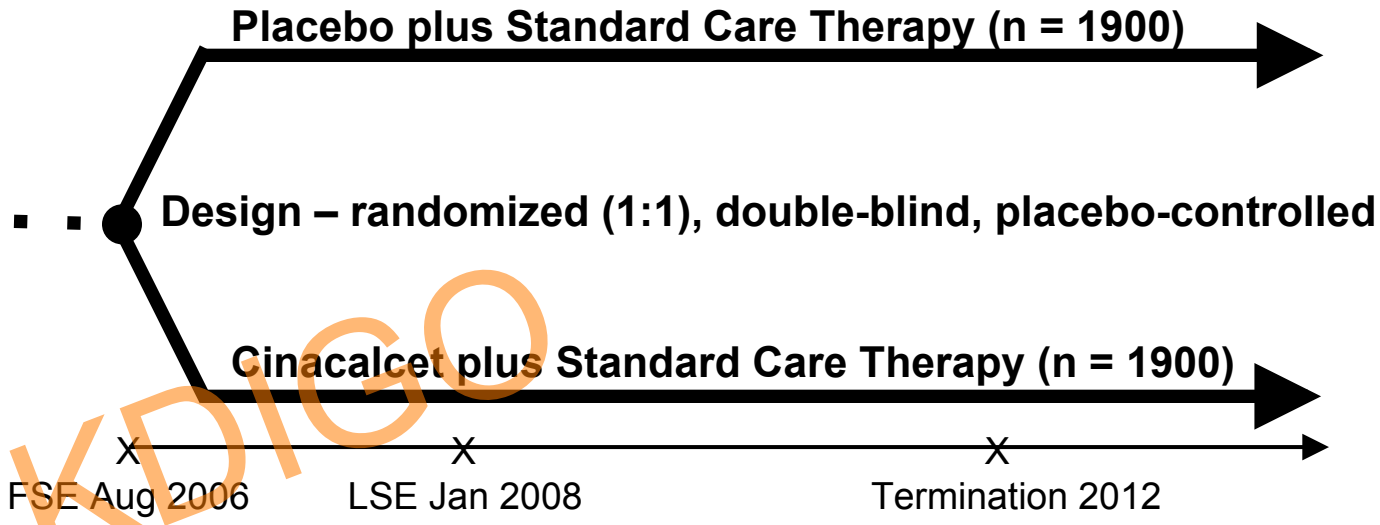
# Adherence to study treatment

- Clinical need always overrides research idealism
- Non-adherence
  - Active group stops active treatment
  - Active group starts other treatment (e.g. effective comparator)
  - Control group starts active treatment (unusual in IND studies)
- Impact on results
  - less difference between randomized groups
  - conservative for superiority assessments
  - counter-conservative for non-inferiority / safety assessments

# EVOLVE™

**Study Population**

- Adult
- Hemodialysis
- iPTH ≥ 300 pg/mL
- Ca ≥ 8.4 mg/dL
- Ca x P ≥ 45 $mg^2/dL^2$






**Primary Endpoint**

Time to composite event:
- All-cause mortality
- Myocardial infarction
- Hospitalization for unstable angina
- Heart failure
- Peripheral vascular event

**Secondary Endpoints**

- Clinical bone fracture
- Parathyroidectomy
- Cardiovascular mortality
- Stroke
- Individual components of primary endpoint

**Standard Care Therapy Includes Flexible use of:**

- Vitamin D sterols
- Phosphate binders

FSE = first subject enrolled; LSE = last subject enrolled.

Chertow GM, et al. *Clin J Am Soc Nephrol.* 2007;2:898-905.



AMGEN

# Anatomy of a MCT

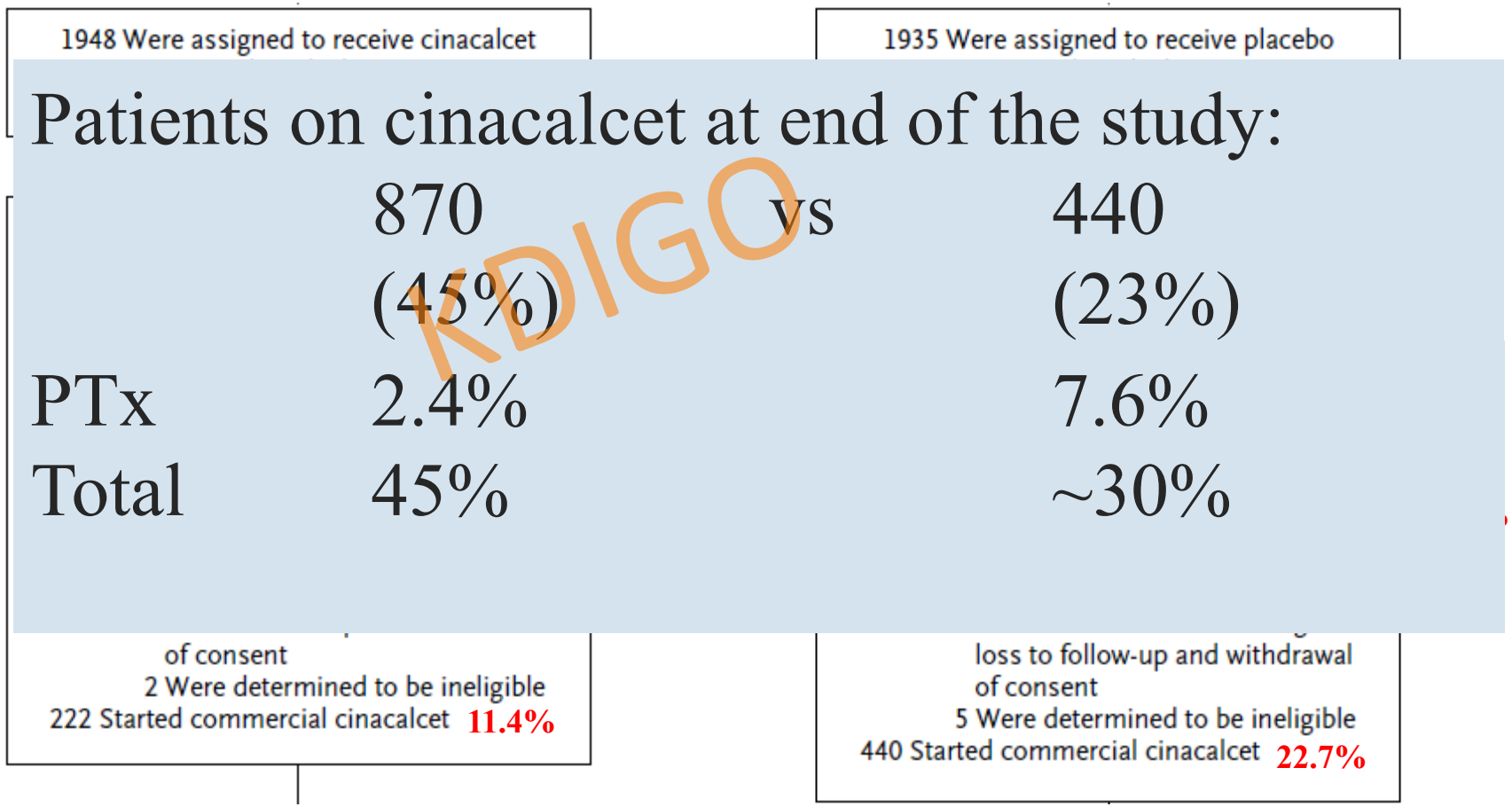
| | EVOLVE | TREAT | RED-HF |
|---|---|---|---|
| Population | Dialysis | CKD-ND, Type II Diabetic | Heart Failure |
| Subjects Enrolled | 3883 | 4038 | 2278 |
| Sites Participating | 458 | 623 | 619 |
| Countries Participating | 22 | 24 | 32 |
| Study Duration (years) | 5.5 | 5 | 6.25 |
| CRF pages* | 1,320,077 | 791,000 | 540,000 |
| Unique CRF pages /subject | 148 | 178 | 217 |
| Queries | 800,741 | 116,000 | 50,802 |
| Potential Endpoints Reported | 6,657 | 4200 | 3000 |
| Type of Investigational Product | Tablet | Injection | Injection |
| Doses of IP administered | 3,748,241 | 140,535 | 61,921 |



* EVOLVE collected data in an electronic data capture system via eCRF
TREAT and RED-HF used paper case report forms for data collection

# Adherence: the EVOLVE trial

## The impact of drop-in and drop-out




Patients on cinacalcet at end of the study:

| | | | |
|---|---|---|---|
| | 870 | vs | 440 |
| | (45%) | | (23%) |
| PTx | 2.4% | | 7.6% |
| Total | 45% | | ~30% |





Chertow *et al*, NEJM 2012

# Primary Composite Endpoint: Sensitivity Analyses

| Analysis Type | Placebo (N=1935) | Cinacalcet (N=1948) | HR (95% CI) | p-value |
|---|---|---|---|---|
| ITT | 952 (49.2) | 938 (48.2) | 0.93 (0.85, 1.02) | 0.112 |
| Lag Censoring (6 mos) | 658 (34.0) | 638 (32.8) | 0.85 (0.76, 0.95) | 0.003 |
| Censor at PTX | 911 (47.1) | 916 (47.0) | 0.90 (0.82, 0.99) | 0.031 |
| Censor at KTX | 907 (46.9) | 891 (45.7) | 0.90 (0.82, 0.99) | 0.029 |
| Censor at Commercial Cinacalcet Use | 818 (42.3) | 870 (44.7) | 0.90 (0.82, 0.99) | 0.032 |
| Censor at PTX or Commercial Cinacalcet Use | 786 (40.6) | 854 (43.8) | 0.87 (0.79, 0.96) | 0.006 |
| Censor at PTX, Commercial Cinacalcet, or KTX | 748 (38.7) | 812 (41.7) | 0.84 (0.76, 0.93) | <0.001 |

# Missing Information

- Clinical
  - Lack of information on key efficacy endpoints
  - Lack of information on potential safety issues
- Statistical
  - Random: loss of power, underestimate of difference
  - Systematic bias: unable to determine presence, direction or extent of any signal



- Lost contact
- "Withdrawal of consent"
- Premature site closure
- Inappropriate protocol / procedures
  - stop follow-up after treatment discontinuation or primary event
  - per-protocol analyses

# Impact of loss to follow-up on reliability and interpretation of results (ATLAS trial)

- Inclusion criteria: Acute coronary syndrome
- Sample size: 15,526
- Intervention: Twice daily rivaroxaban 2.5 mg vs 5 mg vs placebo

| | Rivaroxaban | Placebo | P |
|---|---|---|---|
| CV death, MI or stroke | 8.9% | 10.7% | 0.008 |
| Non-CABG major bleeding | 2.1% | 0.6% | <0.001 |
| Intra-cranial bleeding | 0.6% | 0.2% | 0.009 |
| Fatal bleeding | 0.3% | 0.2% | 0.66 |



**BUT**

- 15.5% premature discontinuations
  - including 8.3% withdrew consent with vital status unknown in 86% of these
- Differential missingness for primary endpoint
  - 12.4% rivaroxaban vs 11% placebo

**FDA rejected possible indication for rivaroxaban in ACS patients because of concerns regarding missing data**

Mega et al N Engl J Med 2012; 366:9-19
Schulz & Grimes *Lancet*. 2002;359:781-785

# GFR Decline as an Endpoint for Clinical Trials in CKD: A Scientific Workshop Sponsored by the National Kidney Foundation and the US Food and Drug Administration



Andrew S Levey (Chair), Josef Coresh, Norman Stockbridge, Aliza Thompson, Edmund Lewis, Kerry Willis, Dick de Zeeuw, Alfred Cheung, John Lawrence, Kunihiro Matsushita, Lesley Inker, Tom Greene

*Levey et al AJKD 2015 FDA-NKF Dec 2012 Workshop report*

National Kidney Foundation

FDA

# Current state of CKD Progression Endpoints

- Kidney failure is a hard clinical outcome of interest, but is late and earlier stages of disease are also associated with substantial morbidity
- GFR decline is on the path to kidney failure; a sufficiently large change in GFR, defined as halving of GFR (2XSCr), is accepted as a clinical endpoint for the progression to kidney failure, but is also a late event in CKD and takes a long time to develop
- Consequently, trials are restricted to patients with late stage or rapidly progressive disease
- Treatments for earlier stages of disease may not be effective at later stages, thus use of currently used endpoints may miss the opportunity to identify effective treatments at earlier stages

# RENAL OUTCOME RECOMMENDATION

**Table 2 | Suggested outcomes in measuring kidney disease status in randomized trials**

| | Progression of CKD | |
|---|---|---|
| CKD stage | Slow | Rapid[a] |
| Early stage: CKD G1-G3a (eGFR ≥45 ml/min per 1.73 $m^2$) | • Slope of mGFR or eGFR or<br>• Surrogate outcome[b] or<br>• Combinations of outcomes | 30%–40% decline in eGFR using repeat measurements to rule out transient acute effects[c] |
| Late stage: CKD G3b-G5 (eGFR <45 ml/min per 1.73 $m^2$) | End-stage kidney disease or 30%–40% decline in eGFR[c] | End-stage kidney disease or doubling of serum creatinine level (or 40%–57% decline in eGFR)[c] |



CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate.

[a]For example, in patients with macroalbuminuria.

[b]Surrogates may include measures of activity of disease (e.g., in lupus nephritis) or kidney structure (e.g., in adult polycystic kidney disease).

[c]The added value of eGFRs outside the routine study visit schedule has not yet been demonstrated and they may be unnecessary.

# Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of CKD:

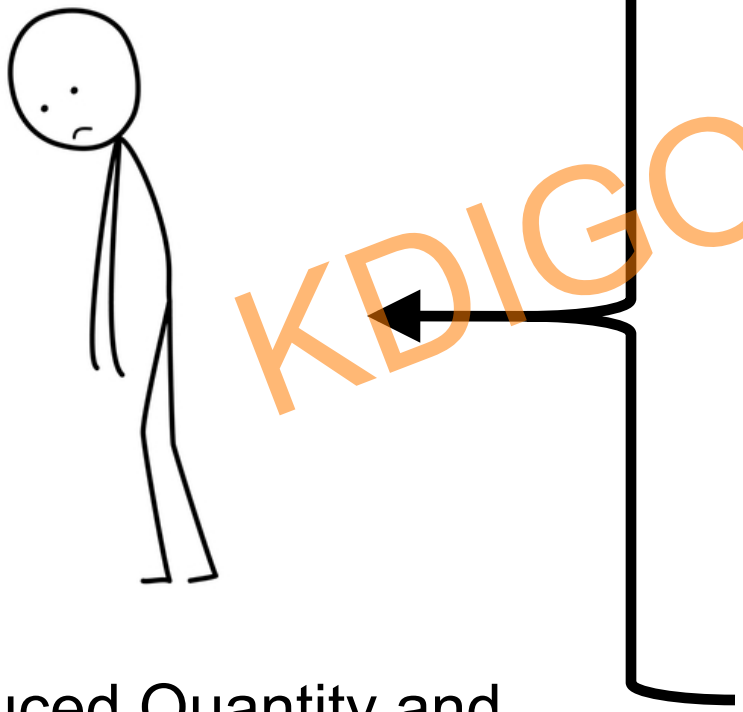
- A Scientific Workshop Sponsored by the National Kidney Foundation, US Food and Drug Administration and European Medicines Agencies
- **Planning underway for March 2018**



- Albuminuria may be an appropriate endpoint in the setting of structural damage or if there is evidence that effects of treatment are durable
  - Prevention of macroalbuminuria, remission to microalbuminuria, pre-determined quantitative change

# Why non-renal outcomes?

CKD / ESRD / Transplant /
Autoimmune kidney disease





- Anemia
- Arrhythmia
- Coronary disease
- Heart failure
- Infections
- Mineral bone disease
- Relapses of autoimmune disease
- Strokes
- Uremia and side effects

Reduced Quantity and
Quality of Life

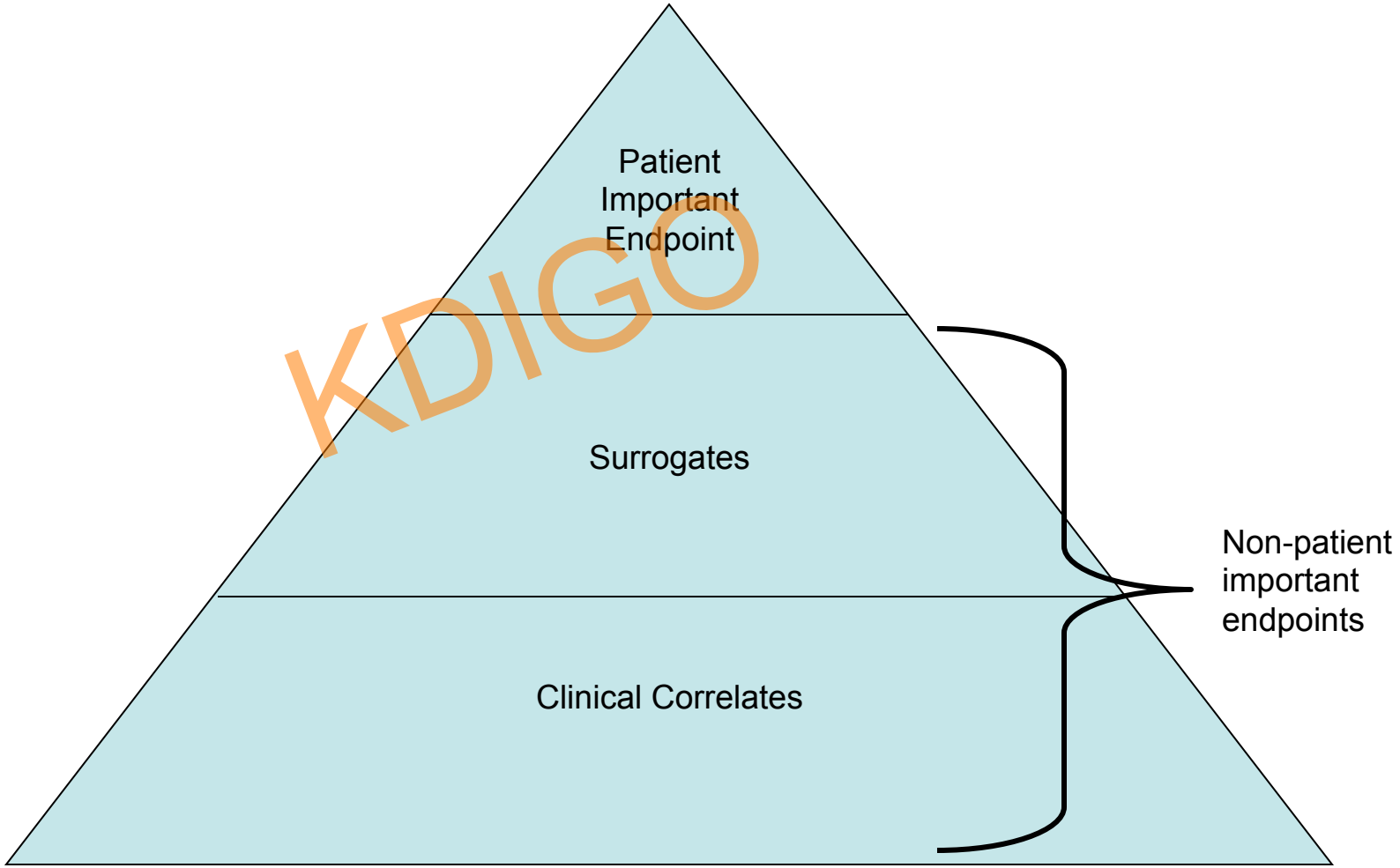
# Definitions

- Patient Important Outcome
  - Variable that reflects how the patient feels functions or survives (something meaningful to patients)
- Surrogate Outcome:
  - Variable which predicts clinical benefit (or harm) based on epidemiologic, therapeutic or scientific evidence
- Biomarkers and correlates:
  - Associated with the clinical endpoint but does not necessarily modify predictably with intervention

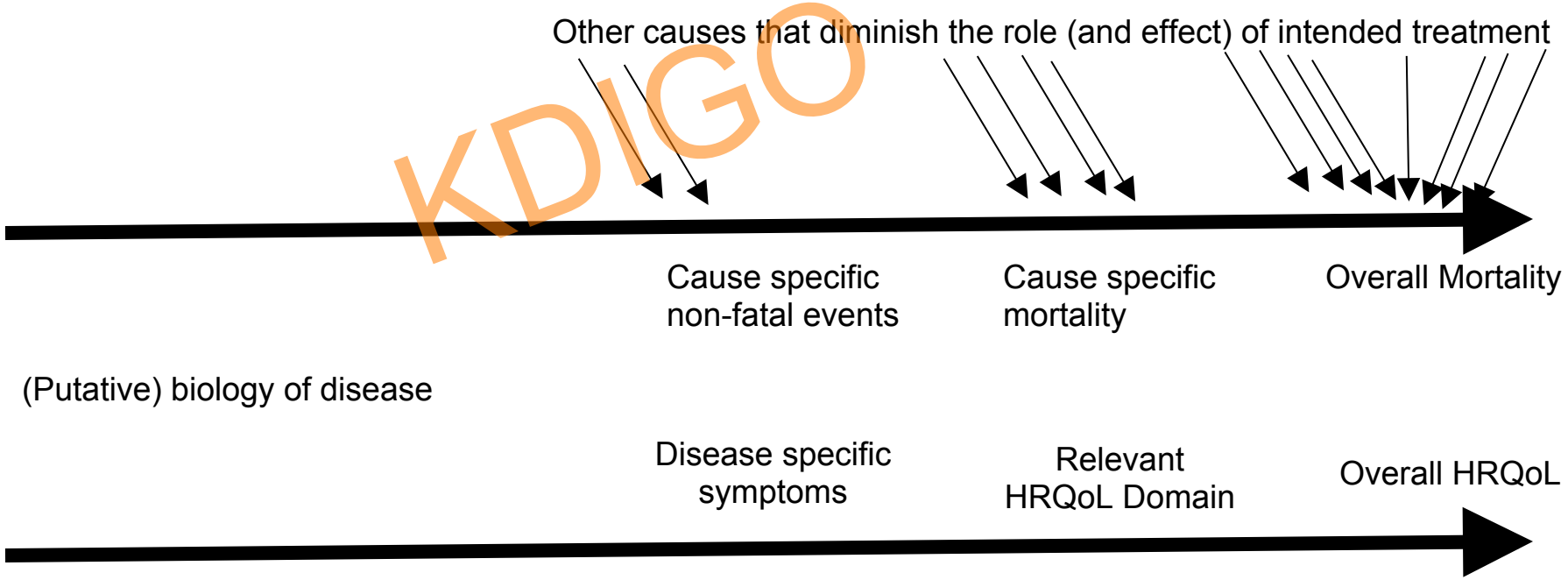


Biomarker Definition Working Group. *Clin Pharmacol Ther*. 2001.

# Evidence Hierarchy



# Balancing biological effects with unequivocally patient-important effects



# All-Cause Mortality: 'Noise'

- Assume:
  - 10/100 per year death rate
    - 50% CV deaths = 5/100 per year
      - 50% of CV death due to MBD = 2.5/100 per year
        - » Intervention reduces MBD death rate 50% = 1.25/100 deaths per year avoided
          - RRR on MBD = 50%
          - RRR on all cause death = 12.5%



- All-cause death outcome
  - Control group = 10 events per 100 patient years
  - Treatment group = 8.75 events per 100 patient years
  - Alpha 0.05, power 80%
  - 17,070 participants
    - Total 1,280 events

# Cardiovascular Mortality

- CV death outcome
  - Control group = 2.5 events per 100 patient years
  - Treatment group = 1.25 events per 100 patient years
  - Alpha 0.05, power 80%
  - 3,700 participants
    - Total of 70 events



- All-cause mortality is rarely an appropriate outcome in kidney trials
- Composite outcomes should be comprised of events likely to be influenced by the treatment and not just common events

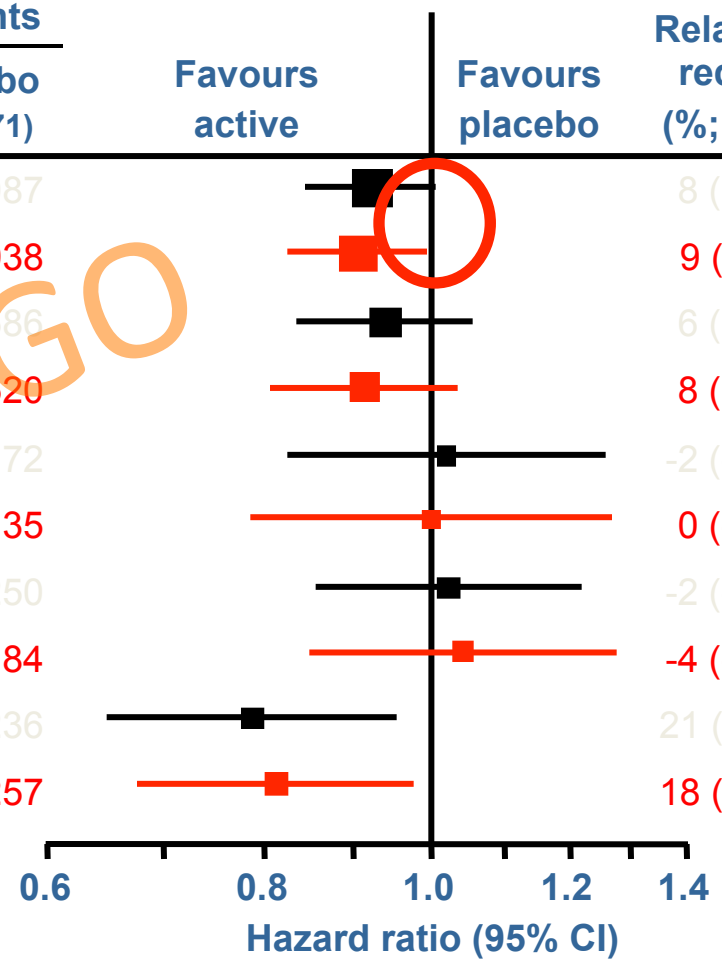
# Endpoint adjudication in kidney disease

- What is the impact of endpoint adjudication on renal outcomes?
- Is there value in adjudicating biochemical measures?
- Is confirmation important?
- Can we streamline the process?

# ADVANCE endpoint adjudication

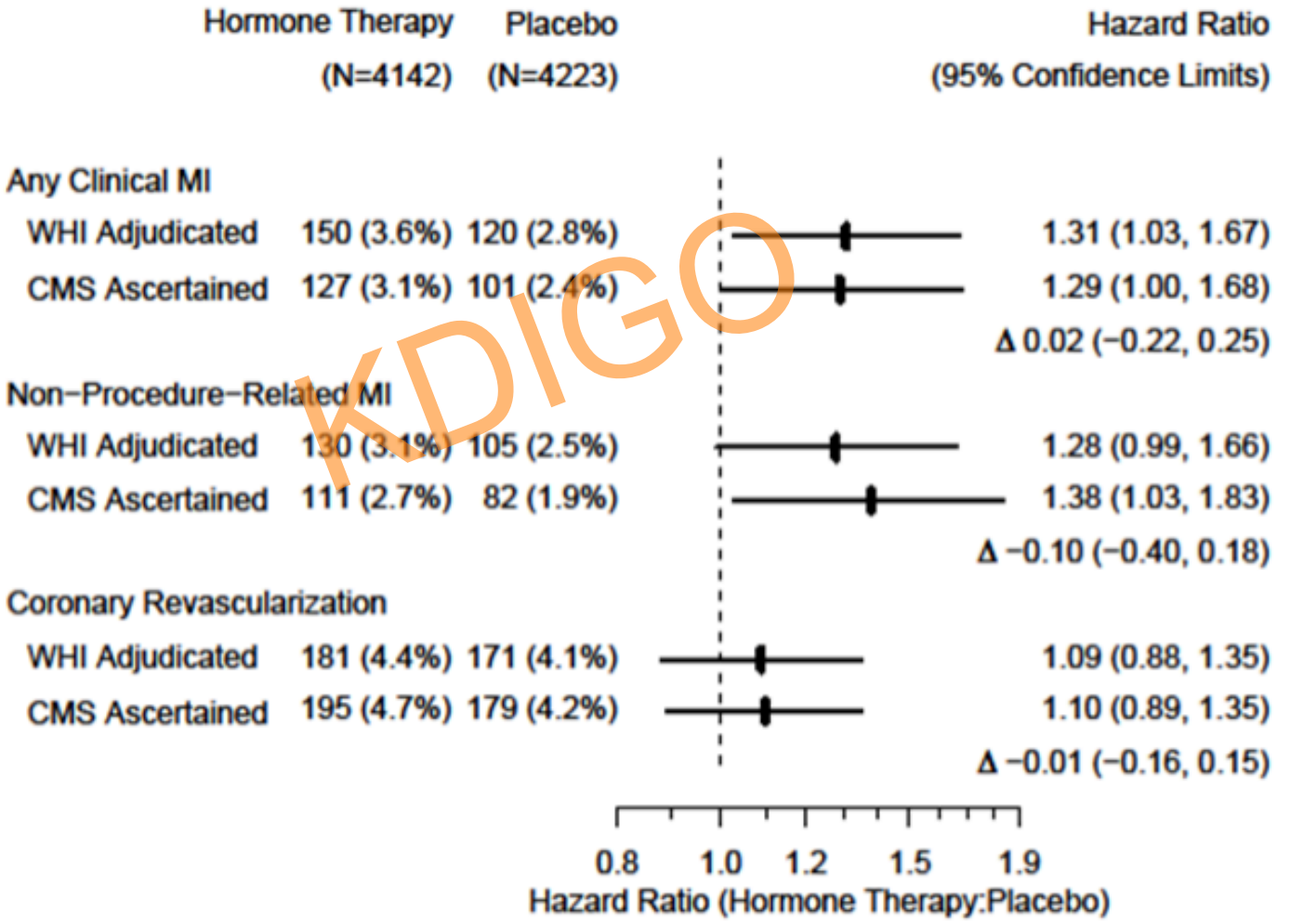
## Conclusion: 'no discernable impact'

| Endpoint | Adjudi-cation | Number of events: Active (n=5569) | Number of events: Placebo (n=5571) | Relative risk reduction (%; 95% CI) | *P* homog |
|---|---|---|---|---|---|
| Combined macro + micro | Invest. | 1018 | 1087 | 8 ( -1 to 15) | 0.70 |
| | EPAC | 861 | 938 | 9 ( 0 to 17) | |
| Major macro-vascular | Invest. | 557 | 586 | 6 ( -6 to 16) | 0.66 |
| | EPAC | 480 | 520 | 8 ( -4 to 19) | |
| Nonfatal MI | Invest. | 147 | 172 | -2 (-26 to 17) | 0.87 |
| | EPAC | 136 | 135 | 0 (-27 to 21) | |
| Nonfatal stroke | Invest. | 258 | 250 | -2 (-22 to 14) | 0.86 |
| | EPAC | 193 | 184 | -4 (-28 to 15) | |
| CV death | Invest. | 188 | 236 | 21 ( 4 to 35) | 0.74 |
| | EPAC | 211 | 257 | 18 ( 2 to 32) | |



# Adjudicated vs routine claims data:

## Effect of HRT on cardiac events in Women's Health Initiative






Hlatky et al. Circ Cardiovasc Qual Outcomes 2014

# KEEPING IT (TOO)SIMPLE: TRIALS ARE RARELY ONLY 'POSITIVE' OR 'NEGATIVE'

**Table 1. Questions to Ask When the Primary Outcome Fails.**

| |
|---|
| Is there some indication of potential benefit? |
| Was the trial underpowered? |
| Was the primary outcome appropriate (or accurately defined)? |
| Was the population appropriate? |
| Was the treatment regimen appropriate? |
| Were there deficiencies in trial conduct? |
| Is a claim of noninferiority of value? |
| Do subgroup findings elicit positive signals? |
| Do secondary outcomes reveal positive findings? |
| Can alternative analyses help? |
| Does more positive external evidence exist? |
| Is there a strong biologic rationale that favors the treatment? |


Paradigm shift
KDIGO

# SUMMARY

- Unquestionable need for more, higher quality, RCT's in nephrology
- Nephrologists MUST have equipoise and apply the 'uncertainty' principle!
- We must place a higher emphasis on outcomes meaningful to patients – SONG-
- SIMPLIFY and STREAMLINE the design of RCT's and keep in mind the essential components (adequate sample size, adherence, ascertainment of outcomes, analysis using appropriate ITT methods)