# Optimizing Trial Design



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# Disclosure of Interests

Core funding:

- Medical Research Council, Cancer Research UK, British Heart Foundation

Funding for clinical trials (for which University of Oxford acts as the regulatory sponsor):

- Merck, Pfizer, Novartis

Co-principal investigator for randomized trials in kidney and cardiovascular disease

- SHARP, 3C, UK-HARP-III, THRIVE, REVEAL



Working with European and US regulators to improve clinical research regulation

- FDA Clinical Trial Transformation Initiative
- European Society of Cardiology
- Medical Research Council, Department of Health

The Clinical Trial Service Unit at University of Oxford has a staff policy of not accepting honoraria or consultancy fees:
https://www.ctsu.ox.ac.uk/about/ctsu_honoraria_25june14-1.pdf

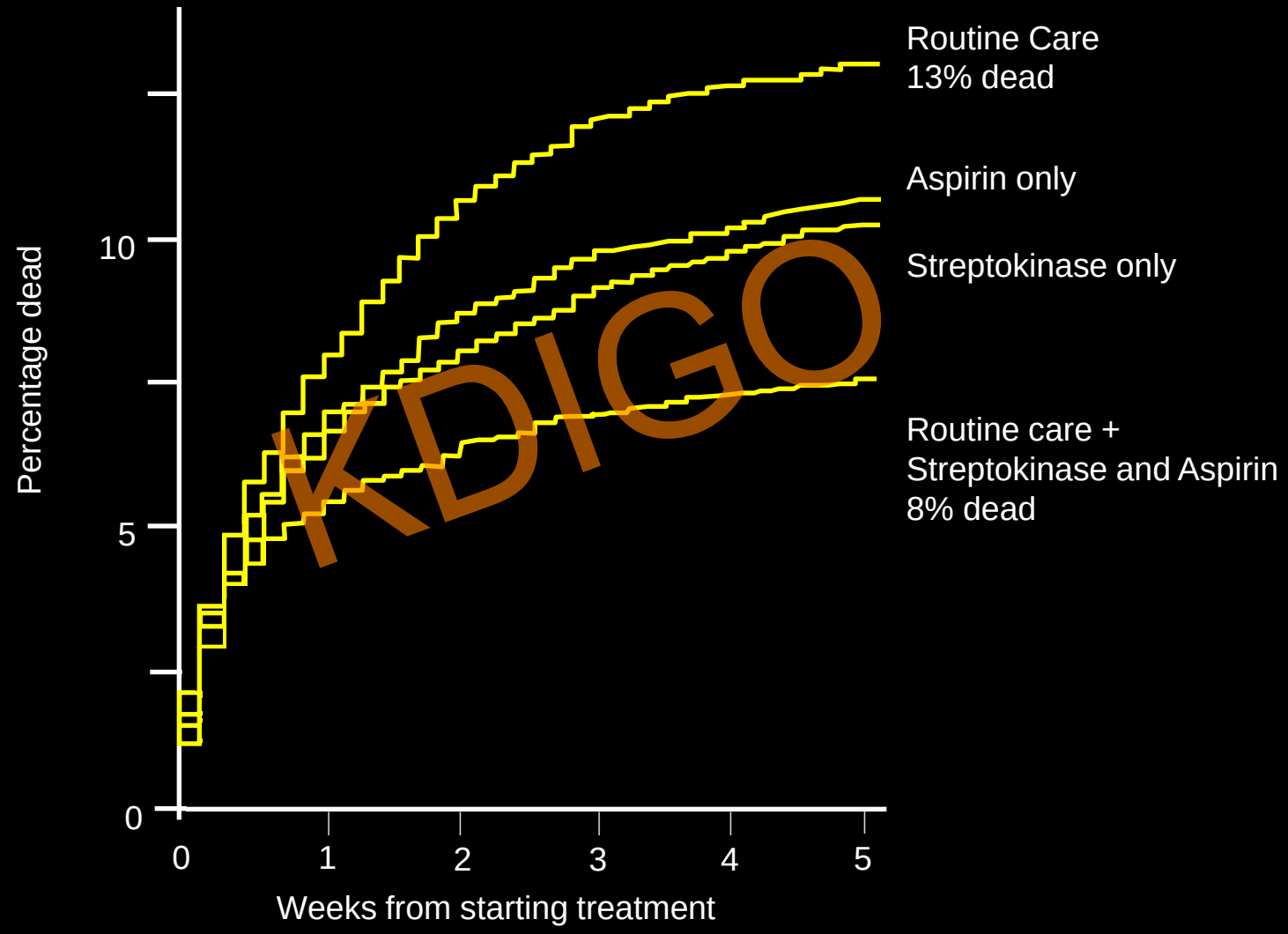
# Outline

- Introduction & key principles
- Recruitment
- Adherence
- Completeness of follow-up
- Efficacy outcomes
- Safety assessment
- Analysis

# Moderate treatment effects are important

- Many treatments have (on their own) only moderate effects
- Moderate effects can change medical practice
  - Using several treatments with moderate effects can have a dramatic effect on outcome
  - In common conditions, moderate effects can have a substantial impact on public health
- To detect moderate effects requires
  - Randomization with intention-to-treat analysis (to avoid bias)
  - Large sample size (number of outcomes) to overcome chance

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






ISIS-2 Lancet 1988

# ISIS2: Principles

"By far the most important determinant of the success of ISIS is the extent to which, in those busy hospitals where the majority of acute MI patients are actually admitted, the responsible physicians and nurses choose to enter their patients.

Hence, the extra work must be – and is – absolutely minimal."

# 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

# Key principles for high quality clinical trials

- Protect the rights, safety & wellbeing of study participants
  - appropriate ethics approval
  - safe administration & monitoring of investigational products
  - safe study procedures & investigations
- Ensure reliability of the results (for the benefit of patients)
  - detect and quantify the efficacy and safety of treatment



"Quality" in clinical trials is defined as the absence of errors that matter to decision making

i.e. have a meaningful impact on either of the above

CTTI Quality by Design Recommendations
www.ctti-clinicaltrials.org/qbd
Landray DIJ 2012
Meeker-O'Connell Clinical Trials 2016

# 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

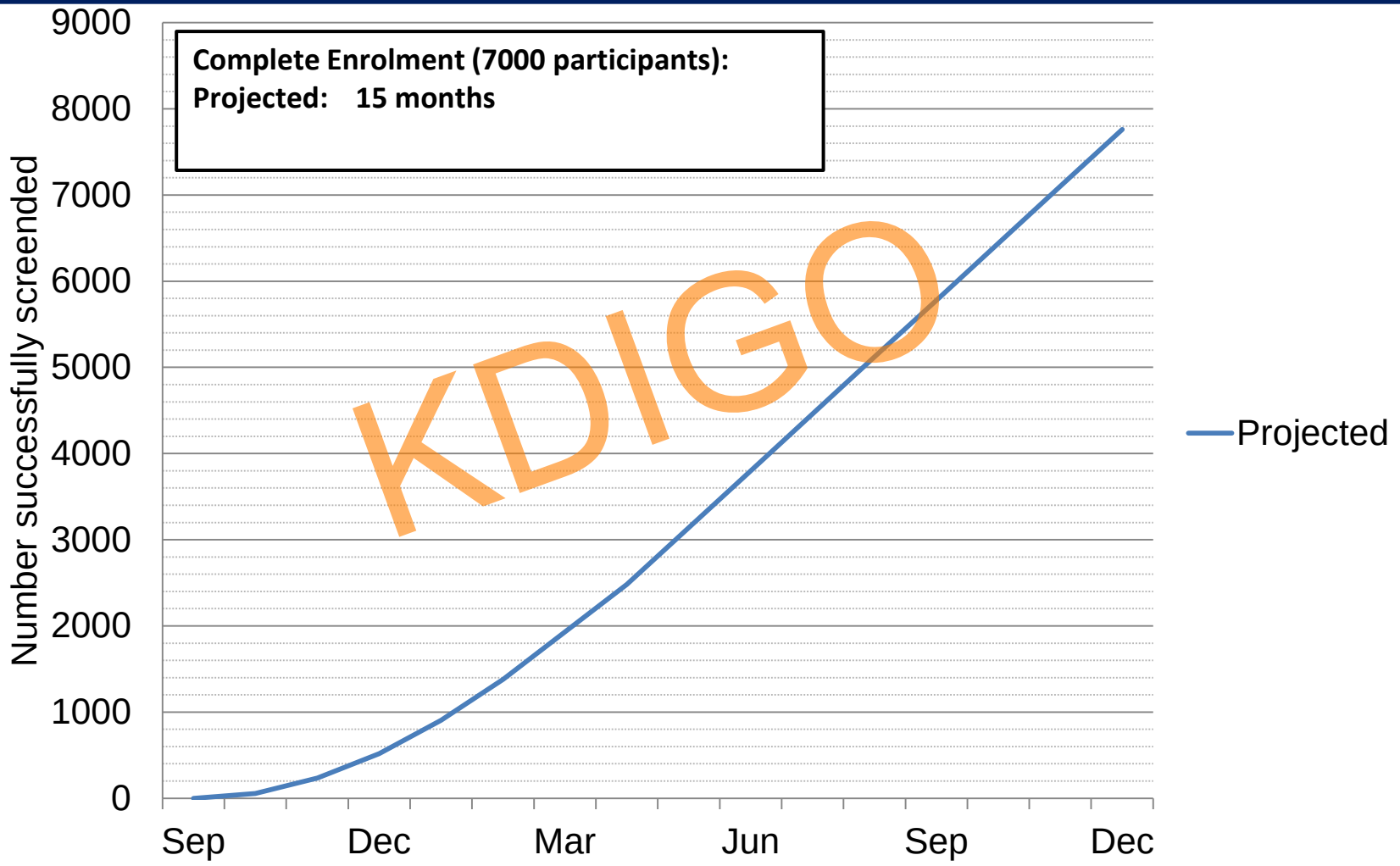
# Key features for reliable assessment of moderate treatment effects

- Proper randomization
  - no foreknowledge of likely treatment allocation
- Appropriate follow-up & ascertainment of study outcomes
  - meaningful treatment difference
  - unbiased (i.e. similar in all randomized arms)
  - complete for all participants
  - appropriate level of accuracy & aggregation
- Large number of relevant outcomes
  - sufficient number of participants at risk
  - sensitive and generalizable outcomes
- Unbiased analysis
  - focus on robustness of result, not precision of data points
  - comparisons with the randomized control group (except for assessing big effects on rare events)
  - avoid emphasis on subgroups and on non-randomized “on-treatment” analyses

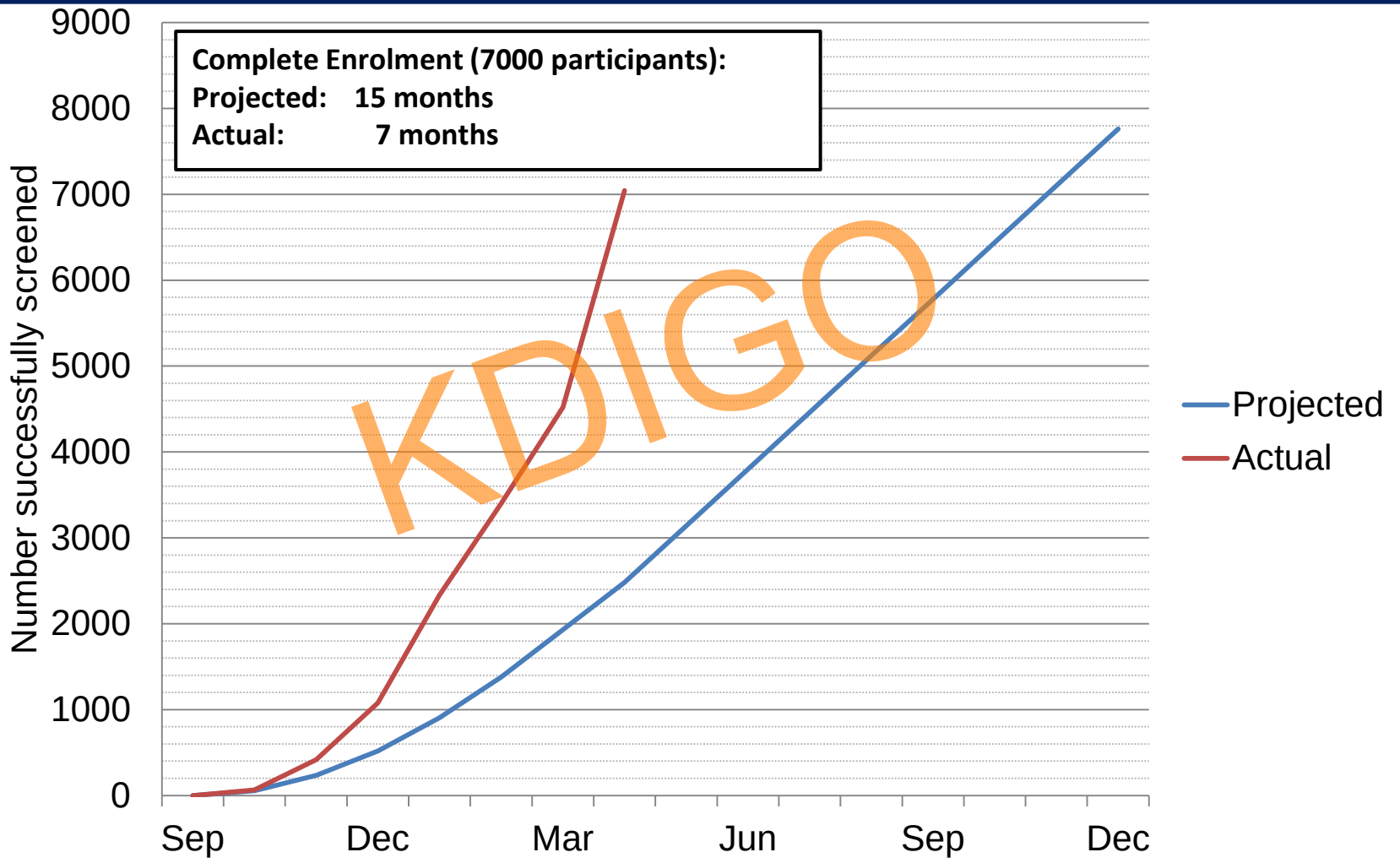
# Facilitating recruitment

- Choose a good question
  - Must be relevant & interesting to clinicians and patients
- Focus the eligibility criteria
  - INCLUSION: Identify relevant population at risk of the key outcomes
  - EXCLUSION: Protect participants rights & well-being (e.g. comorbidity)
- Use the Uncertainty Principle
  - if uncertain whether the treatment is indicated then randomize
- Ensure the procedures are feasible
  - must be streamlined and fit with routine care
  - clinicians are busy; patients are busy (and may be sick too)

# Value of pre-screening and streamlined protocol



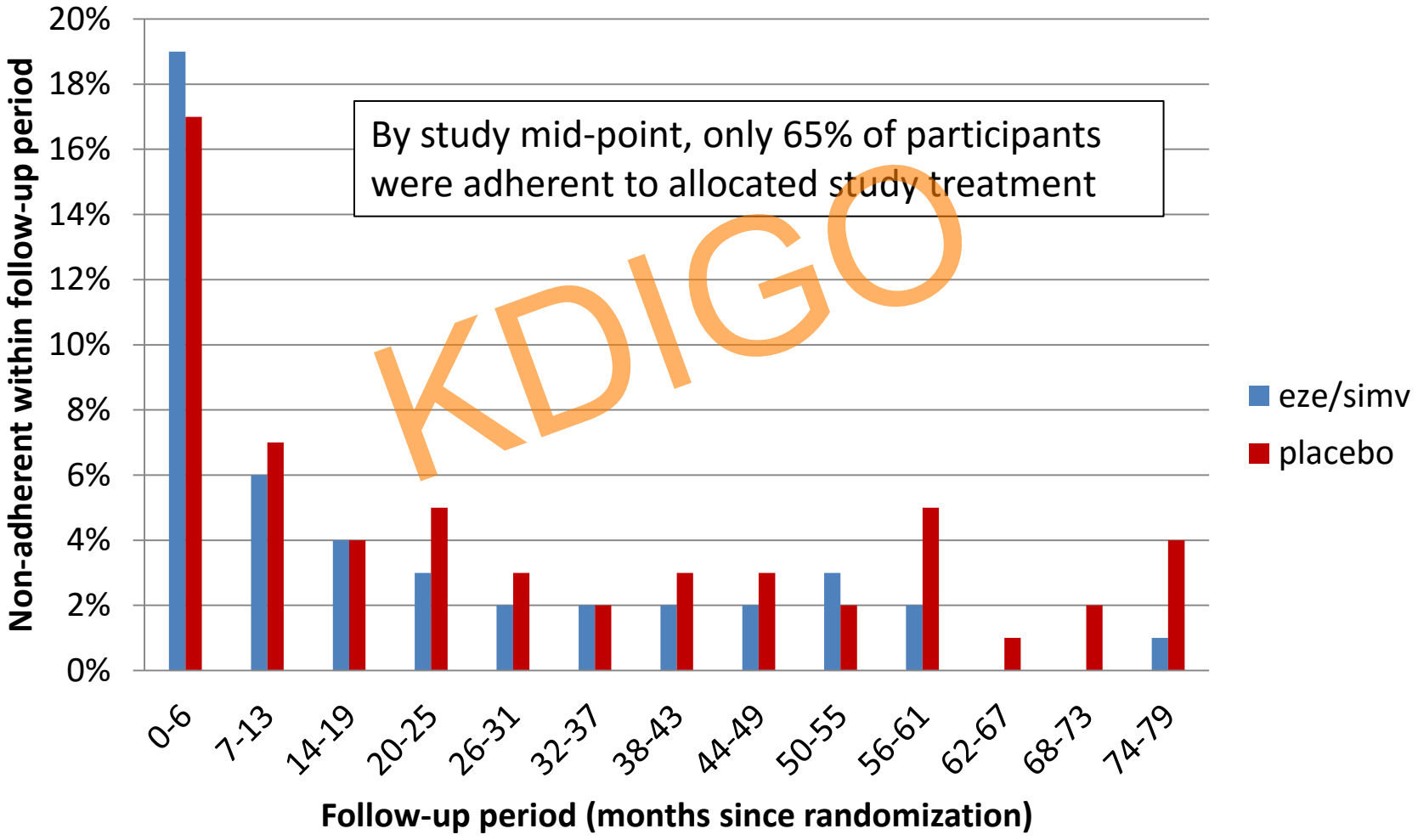
# Value of pre-screening and streamlined protocol



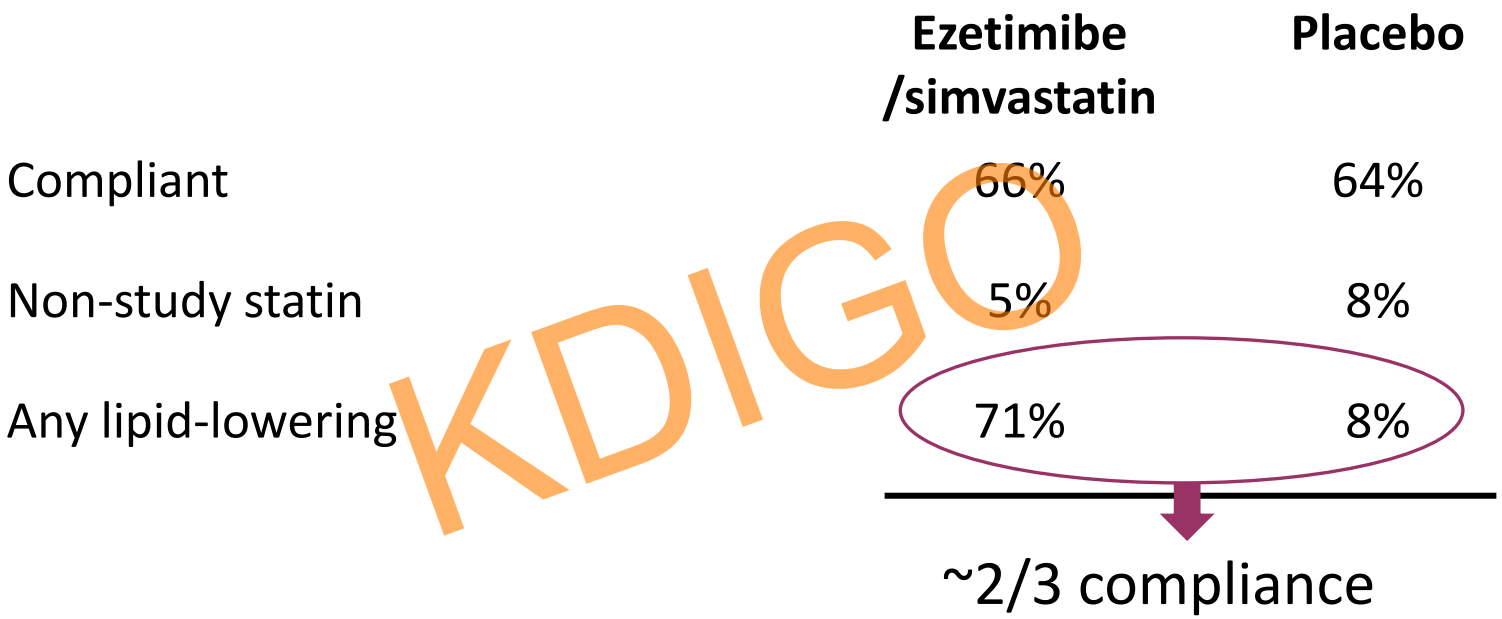
# Adherence to study treatment

- 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

# SHARP: Loss of adherence to study treatment by study period



# SHARP: Compliance and LDL-C reduction at study midpoint






LDL-C reduction of 0.84 mmol/L with 2/3 compliance, equivalent to 1.3 mmol/L with full compliance

# Impact of non-adherence

| Treatment effect on biomarker | Anticipated relative risk reduction | Active (n=4000) | Control (n=4000) | Power at p=0.01 |
|---|---|---|---|---|
| 1.0 | 20% | 480 (12.0%) | 600 (15.0%) | 91% |
| 0.7 | 14% | 516 (12.9%) | 600 (15.0%) | 54% |

# Impact of missing follow-up 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

# Missing follow-up information – common causes

- Lost contact
- “Withdrawal of consent”
- Premature site closure
- Migration
- 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

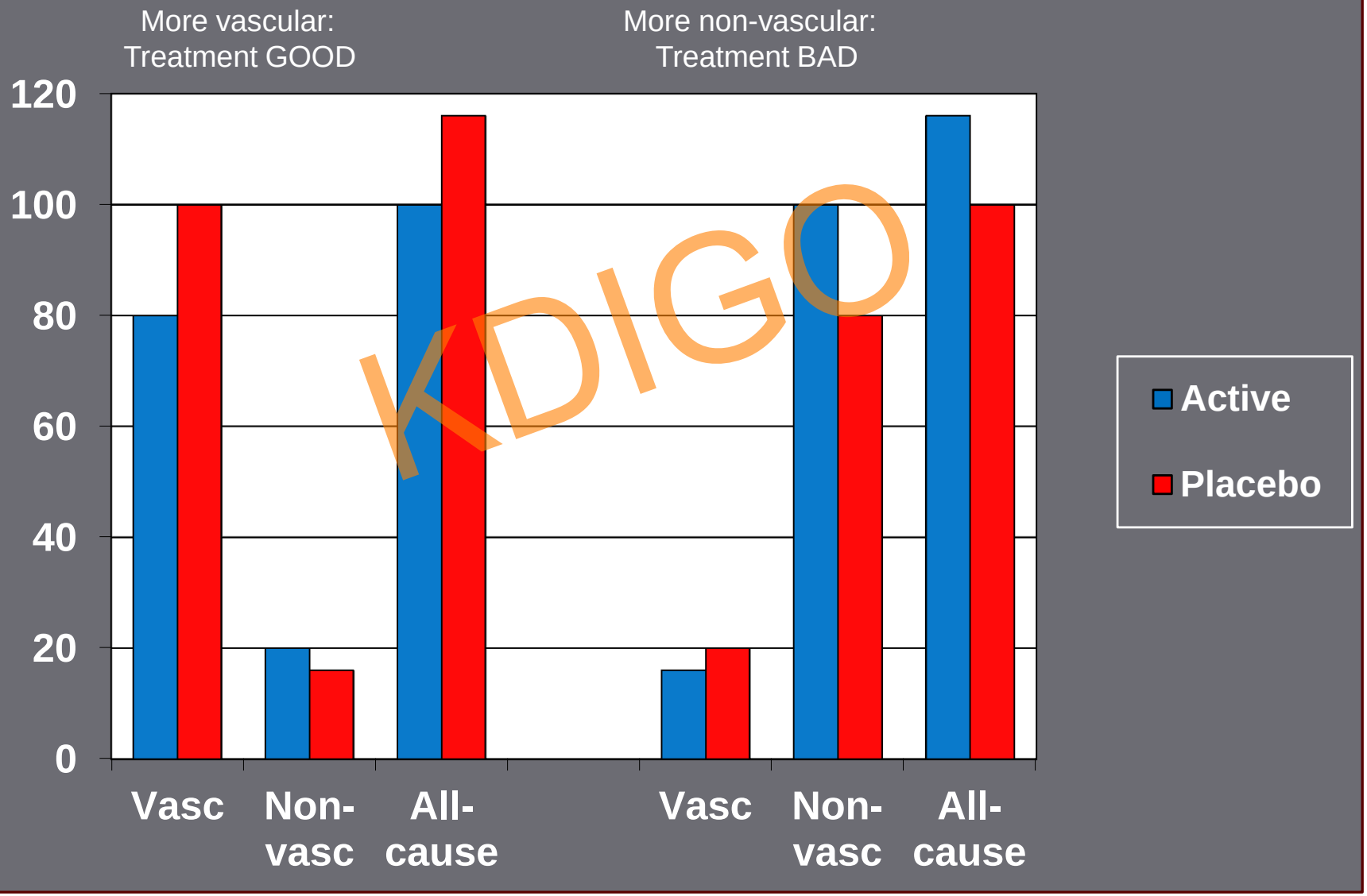
**FDA rejected possible indication for rivaroxaban in ACS patients because of concerns regarding missing data**

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

# Outcomes – principles

- Number of events, not participants, is chief determinant of power
- Composite outcomes that combine events which may involve different directions of effect are less sensitive and generalizable
- Treatment effects (hazards & benefits) may emerge at different time points
- Adjudication of study outcomes may have little impact on the reliability of results

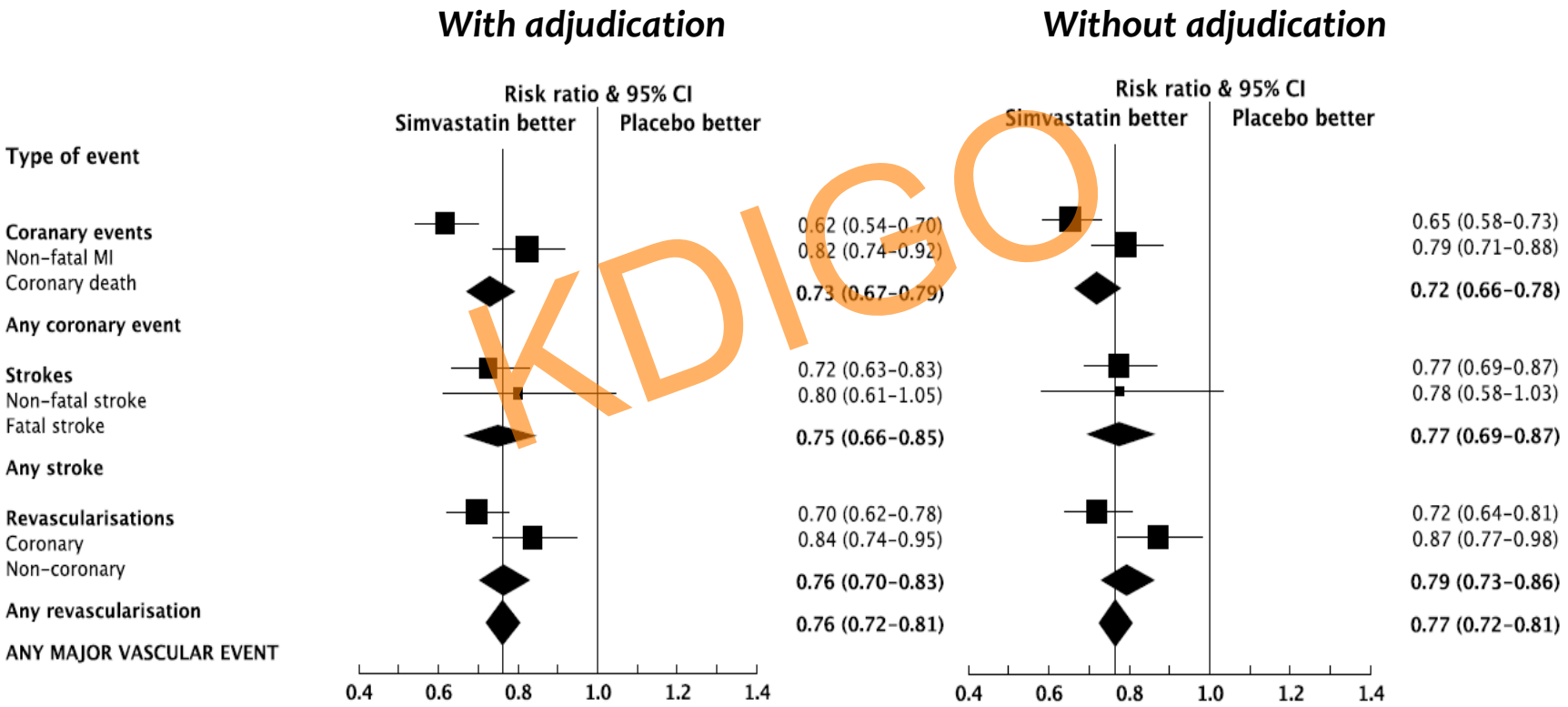
# Direction of effect on all-cause mortality depends on proportions of vascular & non-vascular death



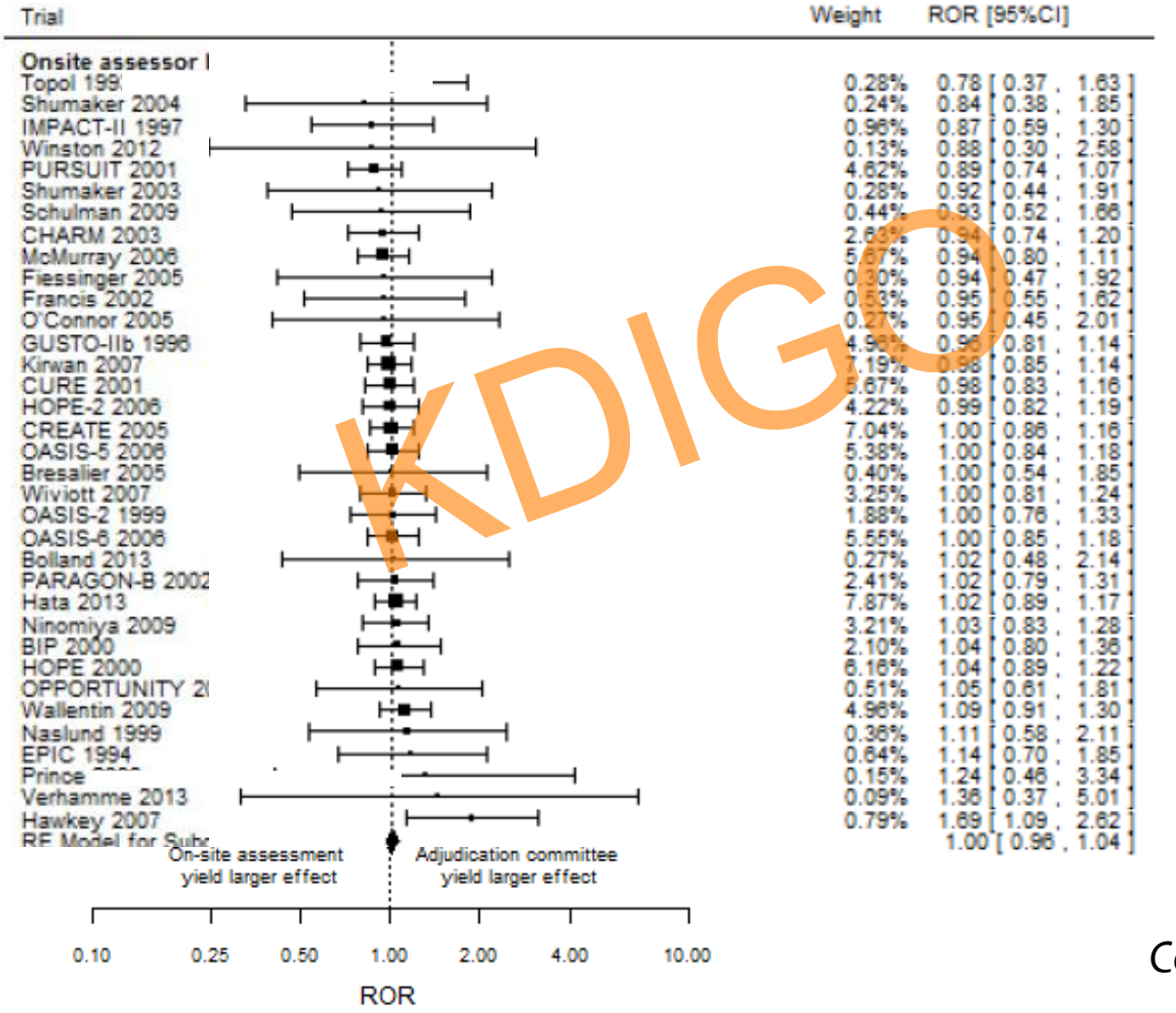
# Outcome ascertainment & adjudication:
## Minimal impact of including false events / missing real events

| | **Active** (10,000) | **Control** (10,000) | **OR** (& 95%CI) | **Z score** |
|---|---|---|---|---|
| **True events** | 800 | 1000 | 0.78 (0.71-0.86) | 4.9 |
| **Extra false events** (evenly distributed) | | | | |
| + 10% | 890 | 1090 | 0.80 (0.73-0.88) | 4.7 |
| + 20% | 980 | 1180 | 0.81 (0.74-0.89) | 4.6 |
| **Missing real events** (evenly distributed) | | | | |
| - 10% | 720 | 900 | 0.78 (0.71-0.87) | 4.7 |
| - 20% | 640 | 800 | 0.79 (0.71-0.88) | 4.4 |

# Effect of simvastatin on major vascular events: Impact of adjudication



# Effect of adjudication on estimate of treatment effect

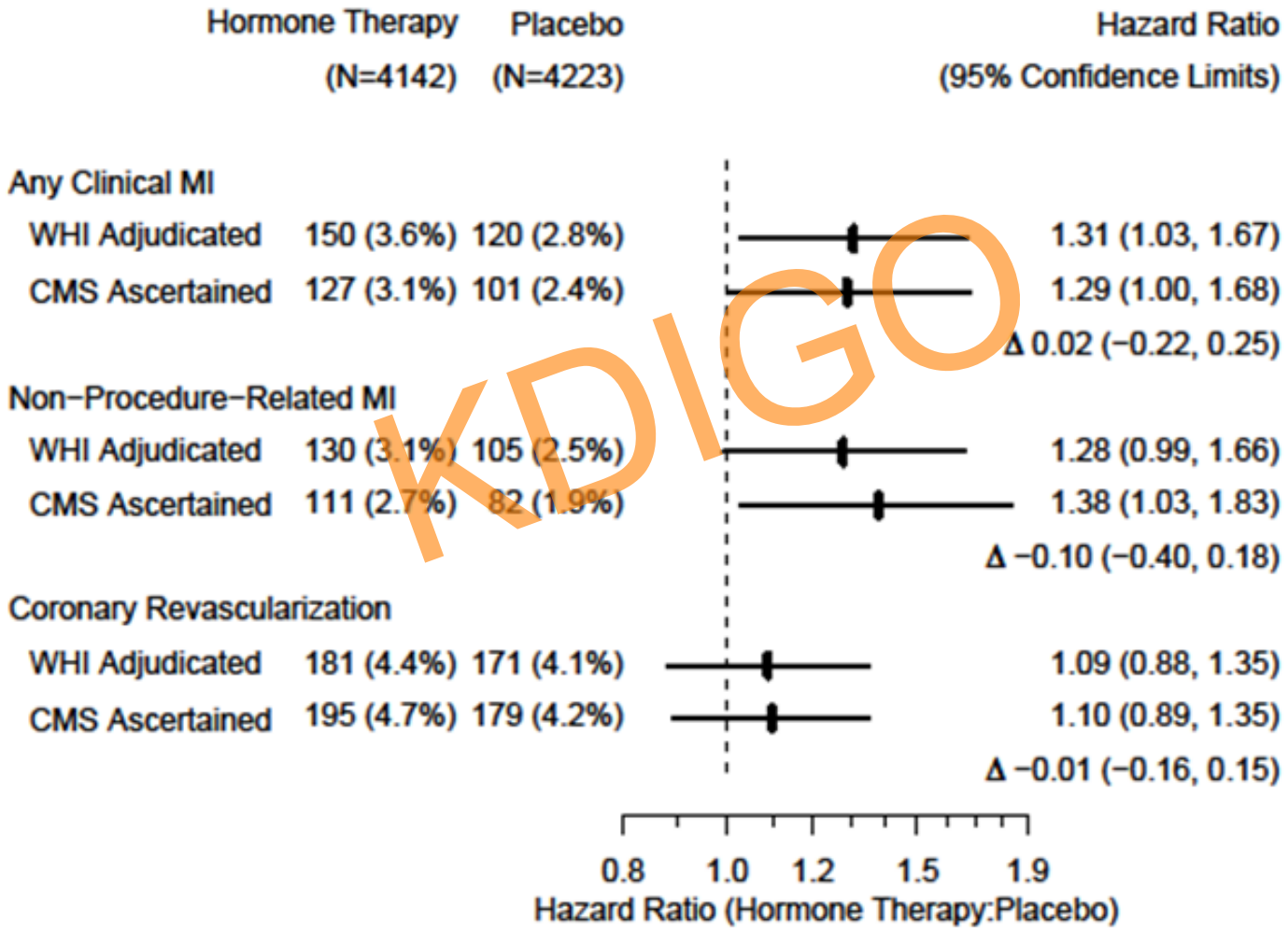





*Daikou L, Cochrane Methodology Review Group, 2016*

# Using adjudicated vs routine claims data:

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

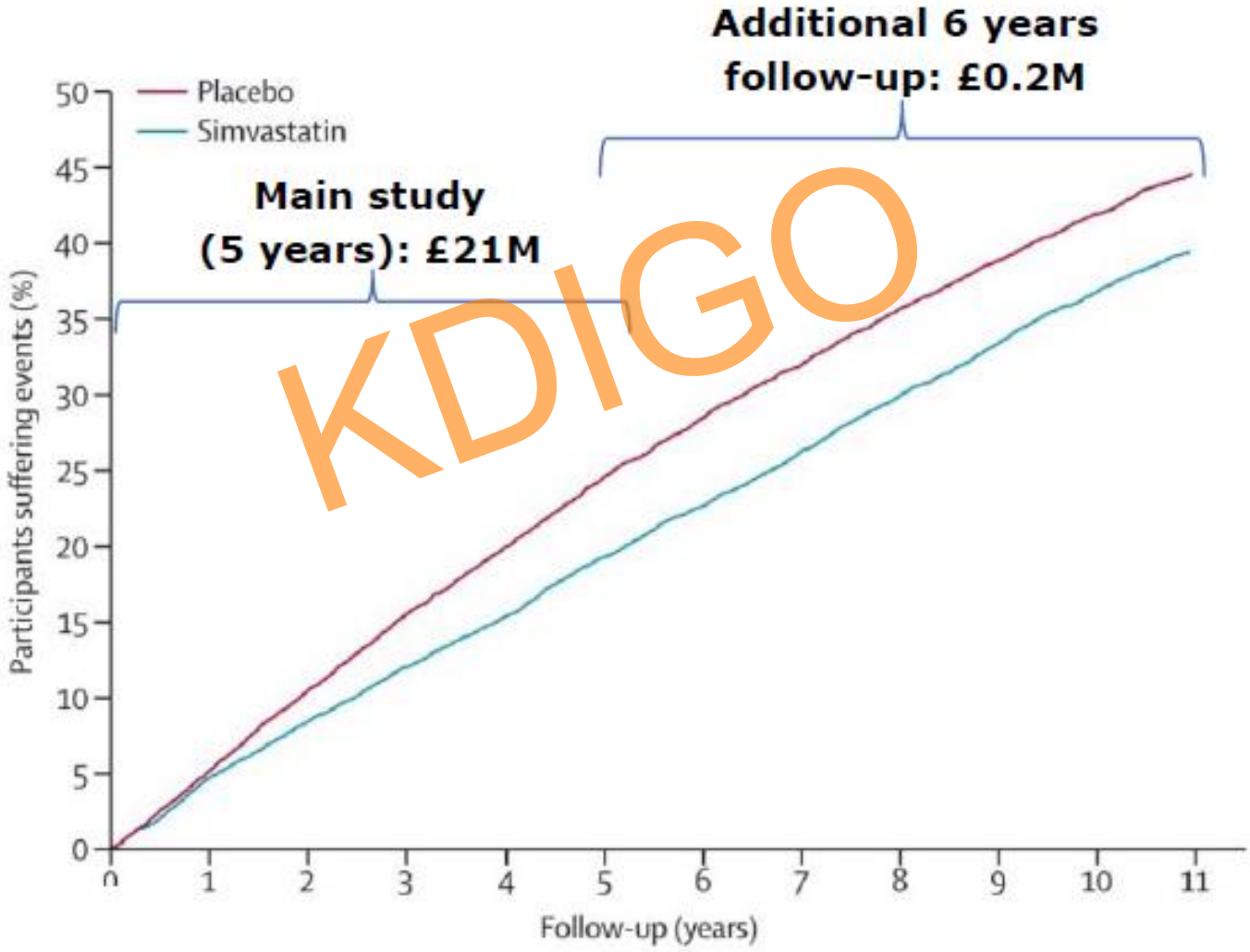





Hlatky et al. Circ Cardiovasc Qual Outcomes 2014

# Routine data to assess long-term treatment effects:
## Lowering cholesterol reduces risk of vascular events

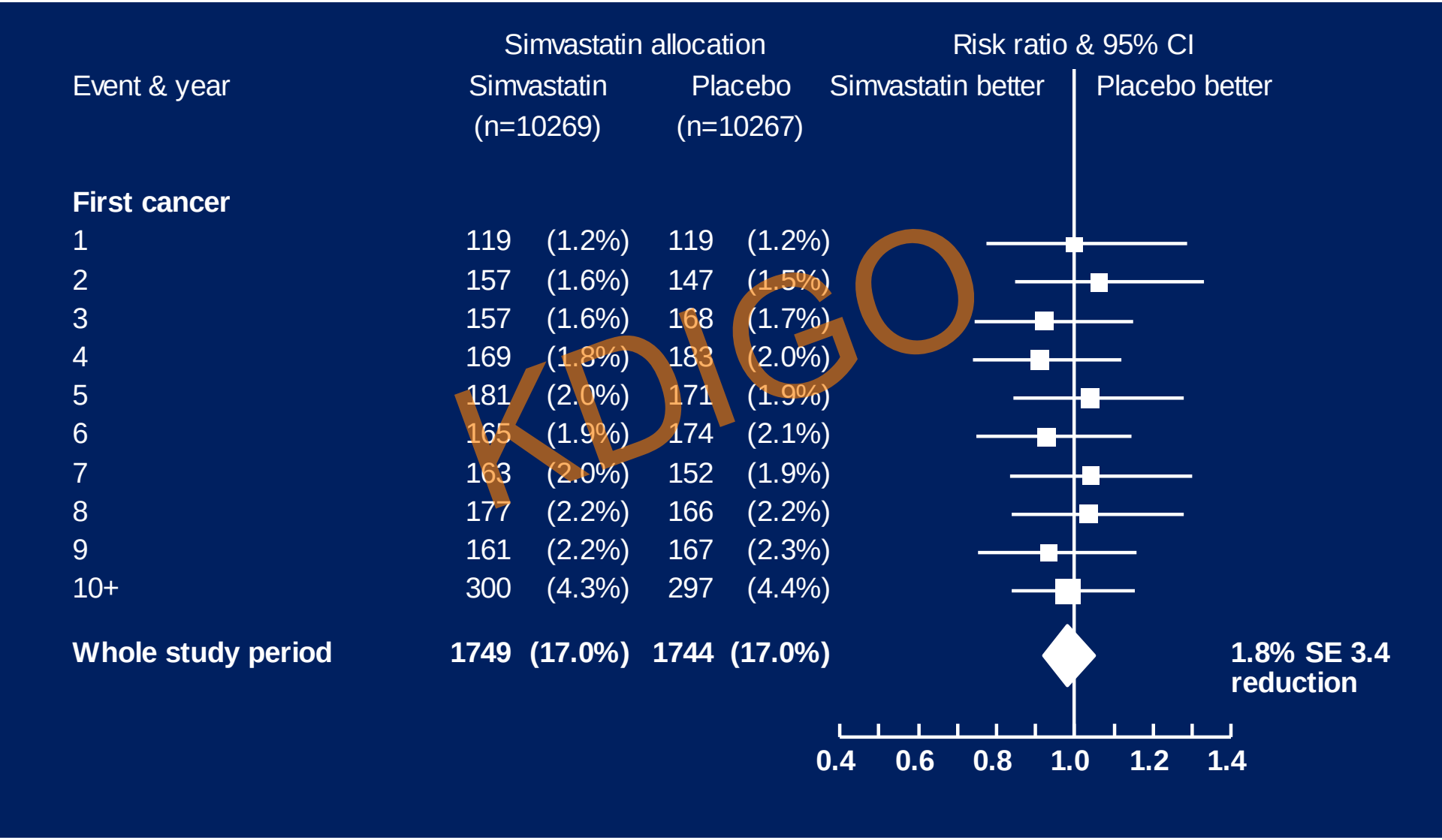
**20,536 patients randomized to simvastatin vs placebo in the Heart Protection Study**






Heart Protection Study Collaborative Group Lancet 2011

# HPS: Effects of 5 years of LDL- cholesterol statin therapy on in-trial and post-trial cancer incidence



# Assessing safety

- LARGE effects on RARE outcomes may be detected by the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARS) – with no need for randomized evidence
- Detection of MODERATE hazards of COMMON outcomes requires comparisons that are both RANDOMIZED and CONTROLLED – and are best monitored by a Data Monitoring Committee

# SUSARs reported in THRIVE trial of 25,000 patients randomized to 5 years of niacin vs placebo

| Category | Niacin | Placebo |
|---|---|---|
| New onset diabetes | 6 | 4 |
| Hepatobiliary | 5 | 2 |
| Skin | 0 | 2 |
| Renal | 0 | 1 |
| **Total** | **11** | **9** |

# THRIVE trial: Previously unidentified adverse effects of niacin (despite 50 years of use and regulatory pharmacovigilance)

| Serious Adverse Event | Niacin (12,838) | Placebo (12,835) | Risk ratio (95% CI) |
|---|---|---|---|
| **Infection** | | | |
| Lower respiratory | 4.3% | 3.7% | 1.17 (1.03-1.32) |
| Urinary tract | 0.9% | 0.8% | 1.07 (0.82-1.39) |
| Abdominal/gastrointestinal | 0.6% | 0.5% | 1.26 (0.91-1.75) |
| Skin | 0.5% | 0.3% | 1.66 (1.14-2.43) |
| Other | 2.4% | 1.7% | 1.38 (1.16-1.63) |
| **Any infection SAE** | **1031 (8.0%)** | **853 (6.6%)** | **1.22 (1.12-1.34)** |
| **Bleeding** | | | |
| Gastrointestinal | 0.8% | 0.6% | 1.53 (1.14-2.05) |
| Intracranial | 1.1% | 0.9% | 1.17 (0.92-1.50) |
| Other | 0.6% | 0.4% | 1.66 (1.18-2.34) |
| **Any bleeding SAE** | **326 (2.5%)** | **238 (1.9%)** | **1.38 (1.17-1.62)** |

# Reliable analysis

- Intention-to-treat

- Avoid sub-group analyses that are
  - underpowered,
  - determined by factors recorded post-randomization
  - data derived

# Dangers of "subgroup analysis": Aspirin for acute myocardial infarction

| History of Prior MI | Aspirin (8587) | Placebo (8600) | Significance |
|---|---|---|---|
| Yes | 15.1% | 14.8% | n.s. |
| No | 8.2% | 11.1% | <0.000 000 1 |
| Overall | 9.4% | 11.8% | <0.000 001 |

# Dangers of “subgroup analysis”: Aspirin for acute myocardial infarction

| Astrological Birth Sign | Aspirin (8587) | Placebo (8600) | Significance |
|---|---|---|---|
| Gemini/Libra | 11.1% | 10.2% | n.s. |
| All others | 9.0% | 12.1% | <0.000 000 1 |
| Overall | 9.4% | 11.8% | <0.000 001 |

# Effect of ezetimibe on cancer incidence

| | SEAS (hypothesis generating) | | |
|---|---|---|---|
| | Active | Control | p |
| Number randomized | 944 | 929 | |
| Total person years | 3810 | 3826 | |
| **Any cancer** | **101** | **65** | **0.006** |
| | **2.7% pa** | **1.7% pa** | |



Peto et al. *NEJM* 2008; 359: 1357-66

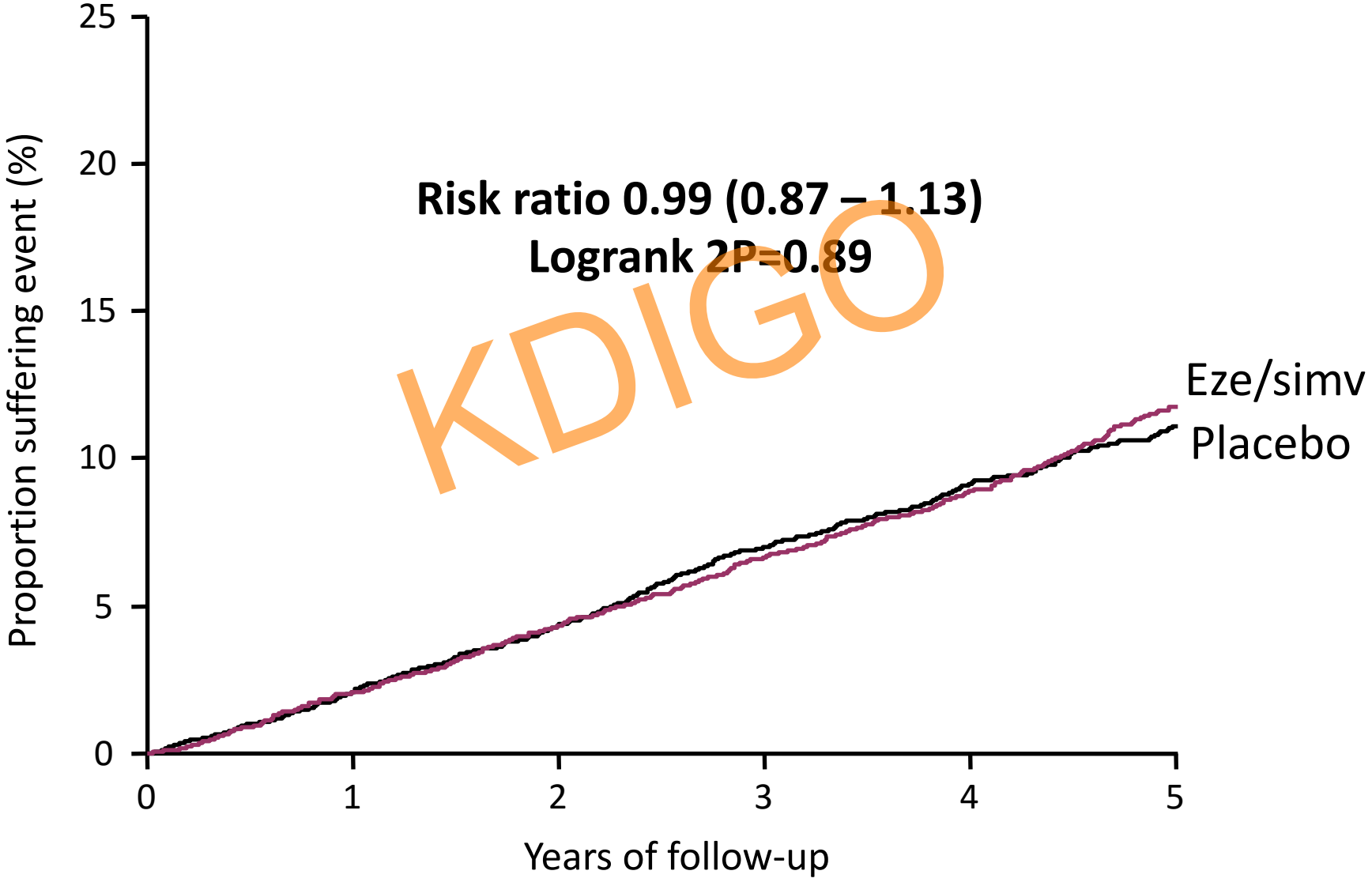
# Effect of ezetimibe on cancer incidence

| | SEAS (hypothesis generating) | | | SHARP/IMPROVE-IT (hypothesis testing) | | |
|---|---|---|---|---|---|---|
| | Active | Control | p | Active | Control | p |
| Number randomized | 944 | 929 | | 10,319 | 10,298 | |
| Total person years | 3810 | 3826 | | 18,246 | 18,255 | |
| **Any cancer** | **101** | **65** | **0.006** | **313** | **326** | **0.61** |
| | **2.7% pa** | **1.7% pa** | | **1.7% pa** | **1.8% pa** | |



Peto et al. *NEJM* 2008; 359: 1357-66

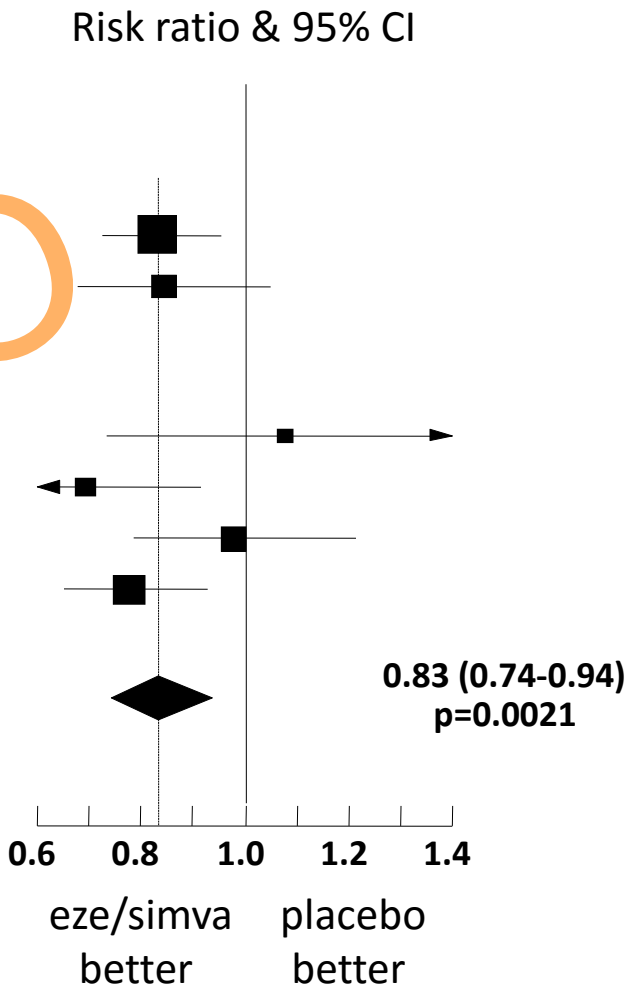
# SHARP: Cancer incidence



# SHARP: Effect of Ezetimibe/simvastatin on Major Atherosclerotic Events

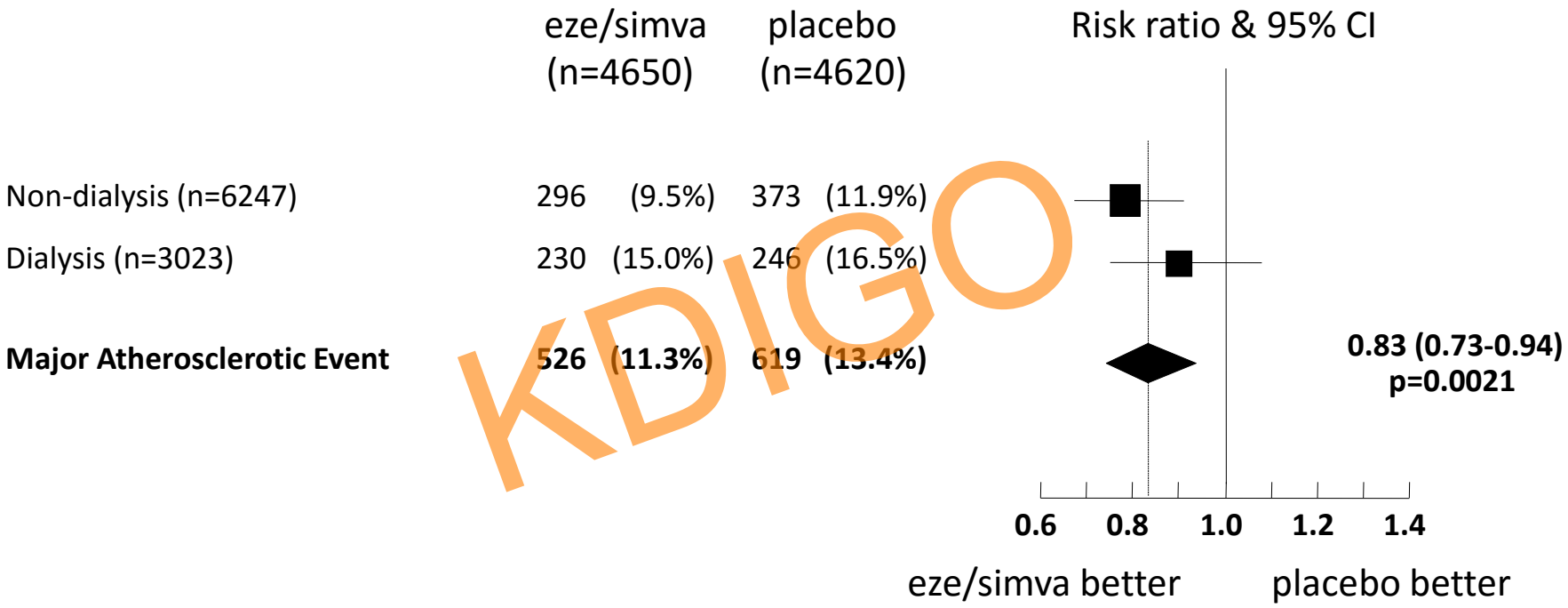
| | eze/simva (n=4650) | | placebo (n=4620) | |
|---|---|---|---|---|
| **Sex** | | | | |
| Male | 376 | (12.9%) | 445 | (15.4%) |
| Female | 150 | (8.6%) | 174 | (10.0%) |
| **Age at randomization (years)** | | | | |
| 40-49 | 56 | (5.8%) | 50 | (5.5%) |
| 50-59 | 85 | (7.3%) | 119 | (10.4%) |
| 60-69 | 163 | (13.3%) | 171 | (13.7%) |
| 70+ | 222 | (17.1%) | 279 | (21.2%) |
| **Major Atherosclerotic Event** | **526** | **(11.3%)** | **619** | **(13.4%)** |






No significant heterogeneity:
(i) by sex (p=0.9)
(ii) by age (p=0.44)

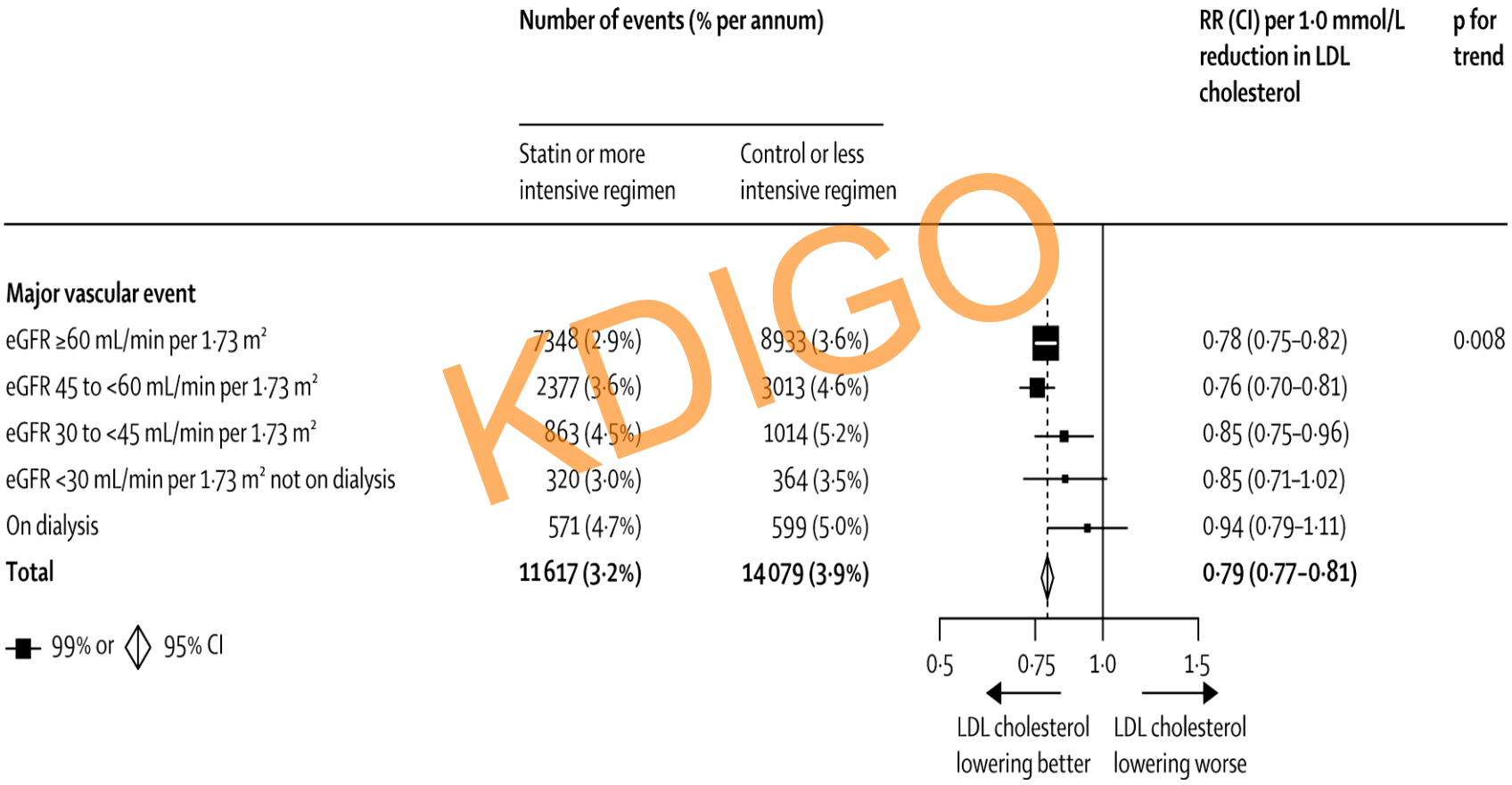
# SHARP: Effect of Ezetimibe/simvastatin on Major Atherosclerotic Events






Heterogeneity test between non-dialysis and dialysis patients: p=0.25

# Effect of LDL-lowering on major vascular events






CTT: Lancet Diabetes Endocrin 2016

# Summary: Key features for reliable assessment of moderate treatment effects

- Proper randomization
  - no foreknowledge of likely treatment allocation
- Relevant outcomes
  - sufficient number of participants at risk
  - sufficient numbers of outcomes
- Appropriate follow-up & ascertainment of study outcomes
  - meaningful treatment difference
  - unbiased (i.e. similar in all randomized arms)
  - complete for all participants
  - appropriate level of accuracy & aggregation
- Unbiased analysis
  - focus on robustness of result, not precision of data points
  - comparisons with the randomized control group (except for assessing big effects on rare events)
  - avoid emphasis on subgroups and on non-randomized “on-treatment” analyses