



Planning a Clinical Trial And Critical Appraisal

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Global Kidney Academy



Outline

- **1. How to Plan testing for a new Drug**
- **2. How to critically appraise a clinical trial**
- **3. Exercises**





Clinical Trials

- **Testing a new drug**
- **Ethical Issues**
- **Liability and Indemnity**
- **Trial Design**
- **Trial Protocol**
- **Statistical analysis**



New treatment for CKD



How do you test the hypothesis that this new drug is beneficial to slow the progression of CKD?



Hierarchy of evidence		
Level of evidence	Description	No. studies
1a	Systematic review of randomised, controlled clinical trials (RCT)	0
1b	Individual randomised controlled clinical trial	0
1c	All or none	0
2a	Systematic review of cohort studies	0
2b	Individual cohort study (including low-quality RCT)	0
2c	Outcomes research	0
3a	Systematic review of case-control studies	0
3b	Individual case-control study	0
4	Case series, poor quality cohort and case-control studies and reviews	14
5	Expert opinion without explicit critical appraisal	1
Other	Letter to the editor (5), Abstract (2)	7

Requirements

- **1. Preclinical information**
- **2. Test for Safety**
- **3. Test it Works**
- **4. Show it is better than current therapies**
- **Requirements:**
 - **1. Ethical approval**
 - **2. Sponsor**
 - **3. PI who is trained in GCP**
 - **4. Protocol for RCT**
 - **5. Monitoring**



Clinical Trials

Clinical Development of a Drug

- Phase I: Tolerability (healthy volunteers)
- Phase II: Efficacy in target population
- Phase III: Efficacy and Comparison with current medication

Approval by regulatory bodies

- Phase IV: Confirmatory and post-marketing surveillance



Human Pharmacology (Phase 1)

- **First human doses – usually healthy volunteers**
- **Estimation of initial safety and tolerability**
 - **Dose range**
 - **Single and multiple doses**
- **Pharmacokinetics (PK)**
- **Pharmacodynamics (PD)**



Therapeutic Exploratory (Phase 2)

- “Proof of concept” (POC)
- Early testing of efficacy
- Narrow inclusion and exclusion criteria
- Small number of patients
- Dose and dose regimen for phase 3
- Multiple endpoints



Therapeutic Confirmatory (Phase 3)

- **To demonstrate therapeutic benefit**
- **To demonstrate safety in a large cohort**
- **Extended exposure**
- **To provide adequate basis for marketing approval**
- **Typically RCT design**
 - **Multicentre**
 - **Multinational**



Therapeutic Use (Phase 4)

- **Begins after drug approval**
- **Within the approved indications**
- **For optimising drug use**
- **SAMM (post-marketing surveillance) Safety Assessment of a Marketed Drug**
- **A type of observational study with specific rules**



Declaration of Helsinki

- Protection of patients rights
- Informed consent
- Independent approval
- Scientific/medical basis
- Appropriate risk: benefit ratio
- Subject well being takes precedence over other considerations



Clinical Trials

ICH- Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected



EU 2003

Medicine for Human Use Clinical Trial Regulations

- All clinical trials (Except non-interventional trials)
- Involving human subjects
- Involving medicinal products
- Commercial and non-commercial
- Within and outside the NHS



Principles of IH-GCP I

- Anticipated benefits to the subject, science and society justify the risks/inconveniences
- Scientifically sound, clear and detailed protocol
- Adequate pre-clinical and clinical data (pre-trial regulatory approval)
- Pre-trial Ethics Committee approval



Principles of ICH-GCP II

- Freely given consent prior to trial
- Medical care given by qualified doctor/dentist
- Suitably trained staff
- Trial supplies manufactured, handled and stored according to GMP
- Data management systems accurate
- Confidentiality of records
- Quality assurance of every aspect of the trial



Guidance Documents

The EU directives is supported by guidance documents:

- Principles of GCP
- Authorisation for a clinical trial
- Ethics committee application
- Trial master file and archiving
- Qualification of investigator
- Qualification of inspectors



- All trials require:
- **A Sponsor** who is responsible for :
 - The initiation of the study
 - The management of the study
 - Financing of the study
 - Monitoring that the trial is GCP
- **An Investigator** who is an authorised health professional, responsible for:
 - Conduct of the trial
 - The trial study team



Clinical Trials

Liability and Indemnity

Association of the British Pharmaceutical Industry (ABPI) guidelines (1988-1990):

- The sponsor to compensate for injuries
- Compensation to be quick and fair
- Provision for arbitration



Clinical Trials

Trial Design

- Ecological studies
- Case- Control studies
 - Retrospective analysis
- Cohort studies
- Randomised Prospective controlled trial (RCT)
 - Active control
 - Placebo control
 - Parallel/Cross-over



Sample size estimation

- 1. **Expected difference between groups (~20%)**
- 2. **Power (probability of NOT getting a false negative result) (80%)**
- 3. **Level of statistical difference (p value = probability that we have a False Positive) (<5%)**



Clinical Trials

Trial Protocol

- **Background**
- **Aim**
- **Inclusion and Exclusion criteria**
- **Primary/secondary end-points**
- **Parameters**
- **Documentation (CRF)**
- **Monitoring**
- **Statistical analysis**
- **Reporting**





How do you test the hypothesis that this new drug is beneficial to slow the progression of CKD?

Clinical Trial

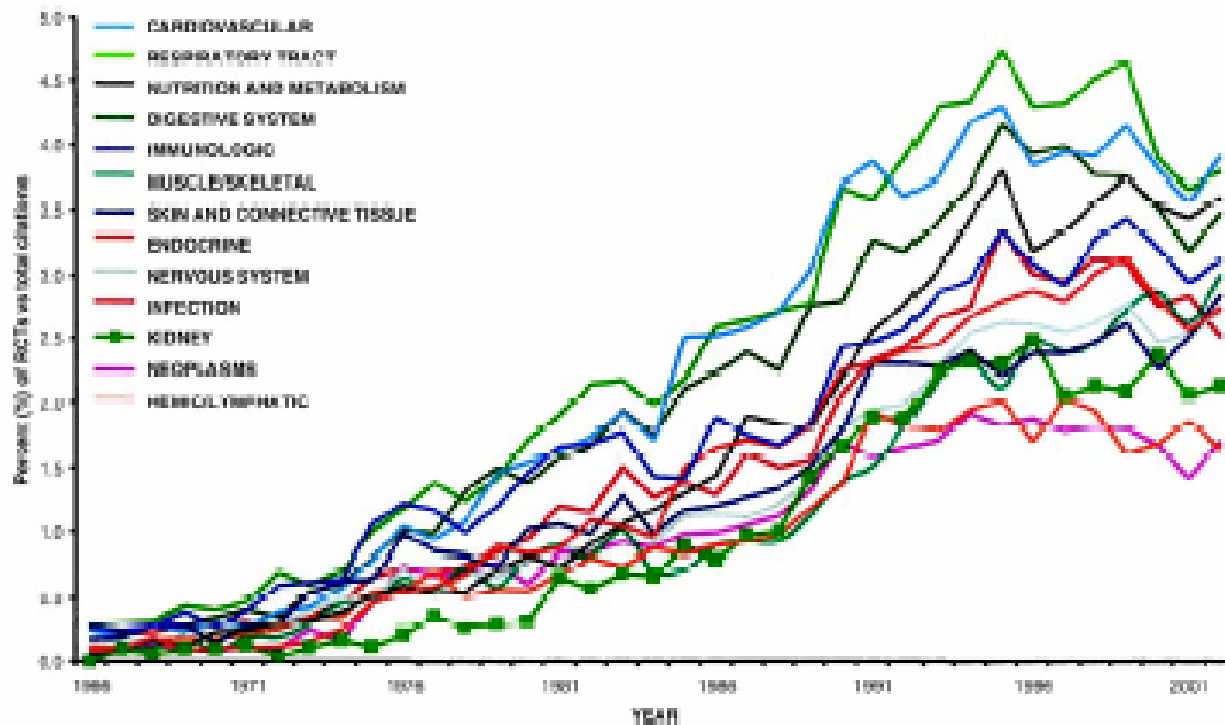
- **1. RCT**
- **2. Prospective**
- **3. Detailed protocol: primary endpoint**
- **4. Compare to best available treatment**
- **5. Adequate sample size**
- **6. Adequate Method of monitoring GFR**
- **7. Adequate Duration of follow-up**
- **8. Appropriate Analysis of the Data**
- **9. Honest Reporting of the Data**





Critical Appraisal of Clinical Trials





2. Percentage of RCT versus total citations in nephrology and 12 other specialties of internal medicine from 1966 to 2002.

“The **Conviction** with which many
Nephrologists hold an opinion
varies inversely with the
Evidence...”

Ed Lewis



“The Good Old Times...”



“The Google Generation...”



ASN Kidney Daily

- **LEADING THE NEWS:**

- + **Genetic Variant In Kidney Donors Linked To Increased Likelihood Of Graft Failure...**



Clinical Trials in Nephrology

- REIN
- DCCT
- Lewis Trial
- HEMO
- TREAT



DETECTIVE

What is the evidence
Valid?
Useful?

Study Design

Study Results

Study Conclusions

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Stages in Appraisal Process

1. Skim reading
2. The Abstract/Message
3. What are the Results
4. **Validity of the study?**
5. **Utility of the study?**



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Critical appraisal of the medical literature



- **Validity:** Is the trial valid?
- **Utility:** Will the results help locally?

Is the study valid ?

Design

- **Was assignment of patients to treatment random?**
 - Need robust randomisation, no chance that treatment allocation could be guessed. Details of randomisation should be given in methodology
- **Is the study large enough?**
 - Power of study (type II error – odds of accepting null hypothesis when actually the alternative hypothesis is true)
 - Is the number too small to generate a Type I error; false positive result?
- **Were all patients who entered properly accounted for?**
 - Patients who are lost to follow up not necessarily representative of whole cohort and may therefore bias results
 - Ensure follow up complete and similar in both treatment limbs
 - ITT rather than PP analysis

Is the study valid ?

Analysis

- **Intention to treat analysis**
 - Analysing groups to which they were randomised to rather than whether received treatment
 - If participants move between groups this distorts random generation of groups and may distort result
- **Were the statistical methods appropriate?**
- **Was methods for dealing with missing information appropriate?**
- **Do results deal with whole data set or a specific subgroup?**

Appraising a Randomised Controlled Trial



Did the study ask a clearly focussed question?



Was this a randomised controlled trial?

Was it appropriately so?



Were participants appropriately allocated to intervention and control groups?

- The flip of a coin is a perfectly reasonable method of randomisation.
- Random Number Tables are good.



Are the groups well balanced?



Is there a Bias ?



Selection Bias

- **Occurs when the method of drawing the sample affects the results of the study**
 - **Was the sample typical?**
 - **Could the method of drawing the sample favour or ignore certain participants?**



Observer Bias

- **Occurs when those involved with the study* allow their knowledge of the study to affect the way observations are scored or recorded.**



Attrition Bias

- Occurs when there are important differences between the number of participants lost to follow-up in the comparison groups
- Intention to Treat analysis says that data on *all* participants should be analysed with respect to the groups to which they were initially randomised.

Follow-Up and Drop-Out

- **Patients who are lost often have different prognoses from those who are retained**
- **Researchers should check this by doing a calculation that assumes:**
 1. **Patients lost from the treatment group did badly**
 2. **Patients lost from the control group did well**
- **If the conclusions would change, then the strength of those conclusions is weakened**



Data Analysis

- **ITT = Intention to Treat = ALL included in analysis**
- **PP = Per Protocol = ONLY those who finish the study included in analysis**



Performance Bias

- Occurs when what was measured happened because of the study itself rather than the intervention.
 - Ask whether participants have been treated the same way throughout the trial (apart from the intervention)



Is the Sample size adequate?



Getting a false negative

“Saying that there is NO difference between the control and intervention in the population, and being WRONG”

(Sometimes known as a Type II Error)



Getting a false positive

“Saying that there **IS** a difference between the control and intervention in the population, and being **WRONG**”

(Sometimes known as a Type I Error)



In search of a higher Power

- The Power is expressed as a probability (between 0 and 1):
- The probability that you *won't* get a false negative.
- The higher the power, the more chance there is that *if there is* a significant difference, you *will* detect it.



More about the Power

- By convention, power is usually set at 0.8 (80%), by balancing effect size, sample size and uncertainty.
 - If:
 - the number of participants recruited is lower than planned,
 - or the effect size is different than expected,
- then the power will be lower, and the chance of getting a false negative will be *more than 20%*.



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Critical Appraisal

Process of assessing

- Validity
- Usefulness of evidence



Utility – will the results help locally?

- **Can results be applied to local population?**
 - Are there differences between study and local population, must consider those participants not completing study
- **Were all clinically important outcomes considered?**
 - Consider whether other important outcomes have been highlighted or omitted
- **Are the benefits worth the harm and costs?**
 - Risk-Benefit analysis
 - Cost effectiveness



Jadad Score

- Randomisation and allocation concealment
- Blinding
- Sample size/Power
- Analysis; ITT versus PP
- Drop out and Lost to follow-up



Validity

- **RCT :** YES/NO
- **Blinded:** YES/NO
- **Randomisation detailed:** YES/NO
- **Randomisation Bias** YES/NO
- **Sample size estimation:** YES/NO
- **Drop out >25%:** YES/NO
- **ITT analysis:** YES/NO

Utility

- Applicable to my patient YES/NO
- Applicable to my country YES/NO
- Applicable to my socio-demographic environment
- Applicable to my health economics YES/NO



DETECTIVE

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Utility

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- Applicable to my health economics **YES/NO**



Lewis Study

Did you know that....

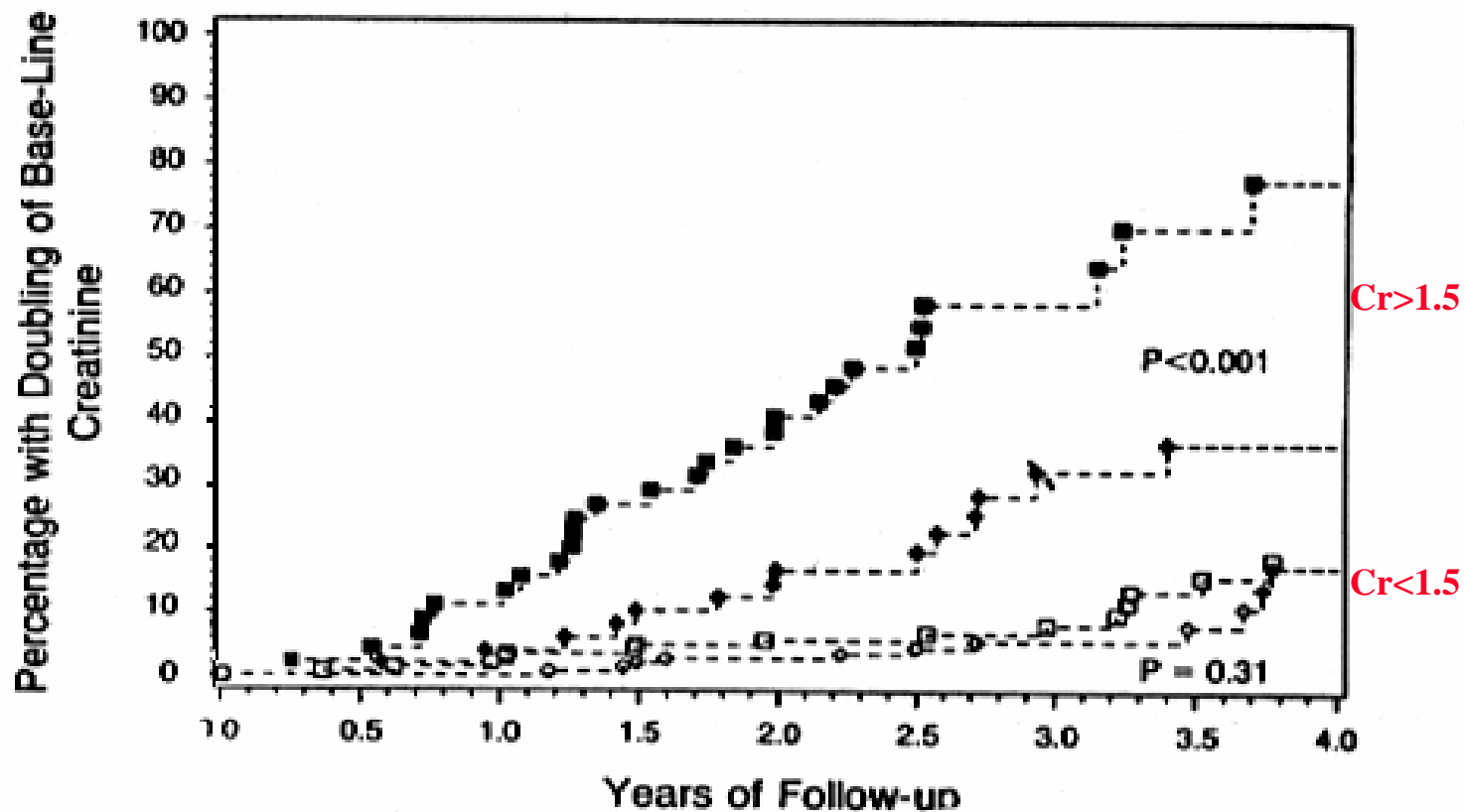


**THE EFFECT OF ANGIOTENSIN-CONVERTING-ENZYME INHIBITION ON DIABETIC
NEPHROPATHY**

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., RAYMOND P. BAIN, PH.D.,
AND RICHARD D. ROHDE, B.S., FOR THE COLLABORATIVE STUDY GROUP*



A



Creatinine \geq 1.5 mg/dl

■ Placebo	49	44	39	32	25	15	8	4	1
◆ Captopril	53	50	46	42	37	28	17	13	3

Creatinine < 1.5 mg/dl

□ Placebo	153	140	134	129	117	84	67	41	21
◇ Captopril	154	149	144	138	130	92	65	37	21

Selection Bias

CHARACTERISTIC	CAPTOPRIL (N = 207)	PLACEBO (N = 202)	P VALUE†
Age (yr)	35±7	34±8	0.46
Male sex (%)	52	54	0.69
Race (%)			
White	91	87	0.12
Black	5	10	
Duration of diabetes (yr)	22±7	22±7	0.96
Hypertension (%)‡	75	76	0.91
Antihypertensive therapy (%)	60	59	0.84
Systolic blood pressure (mm Hg)§	137±19	140±20	0.21
Diastolic blood pressure (mm Hg)§	85±11	86±12	0.47
Mean arterial pressure (mm Hg)§	102±12	104±13	0.25
Serum creatinine (mg/dl)¶	1.3±0.4	1.3±0.4	0.54
24-Hour urinary protein excretion (mg/day)	2500±2500	3000±2600	0.02
24-Hour urinary urea nitrogen (g/day)	11±5	10±5	0.08
24-Hour creatinine clearance (ml/min)	84±46	79±35	0.50
Glycosylated hemoglobin (%)	11.8±2.8	11.6±2.8	0.75

*Plus-minus values are means ±SD.

†For categorical variables the P values were based on Fisher's exact test. The P values for continuous variables were based on the Wilcoxon test.

‡Hypertension was defined as a systolic blood pressure above 140 mm Hg or a diastolic blood pressure above 90 mm Hg.

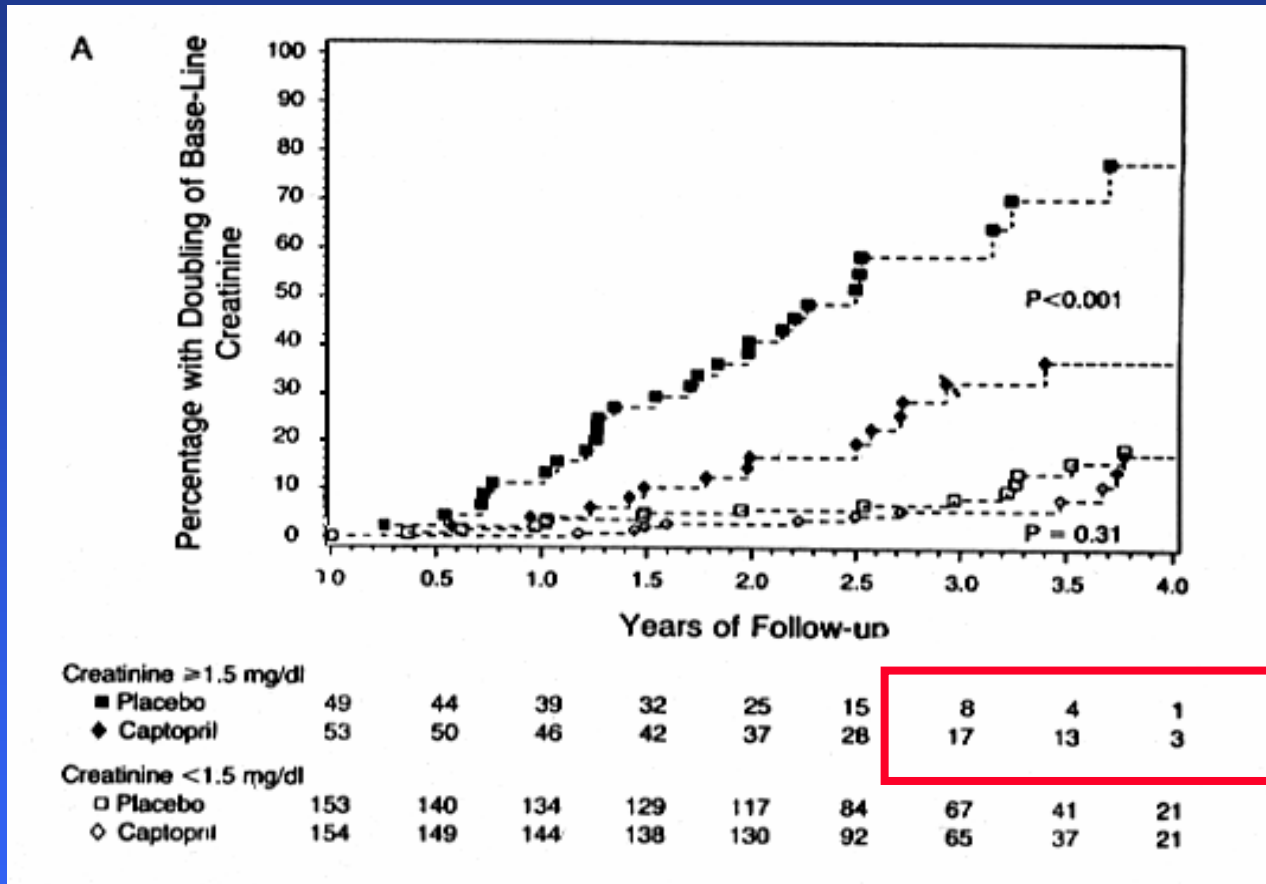
§Blood pressure was measured in seated, resting patients during an office visit.

¶To convert serum creatinine values to micromoles per liter, multiply by 88.4.

||To convert urinary urea nitrogen values to millimoles per day, multiply by 35.7.

**14/16
Black
Nephrotics
Assigned
PLACEBO!**

Attrition Bias



LEWIS: Is the trial VALID?

Was this a randomised controlled trial?

Was the randomisation blinded?

Are the groups well balanced? NO

Is there a Bias? YES

Is the Sample size adequate? NO High drop out

How was the analysis conducted?



Lewis: Validity

- RCT : YES/NO
- Blinded: YES/NO
- Randomisation detailed: YES/NO
- Randomisation Bias YES/NO
- Sample size estimation: YES/NO
- Drop out >25%: YES/NO
- ITT analysis: YES/NO

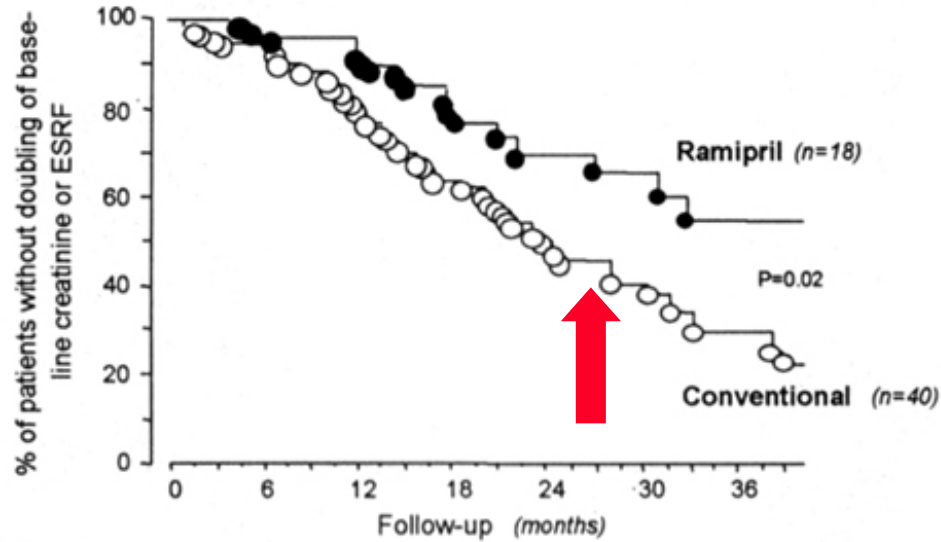
+ Difference in BP

REIN Study

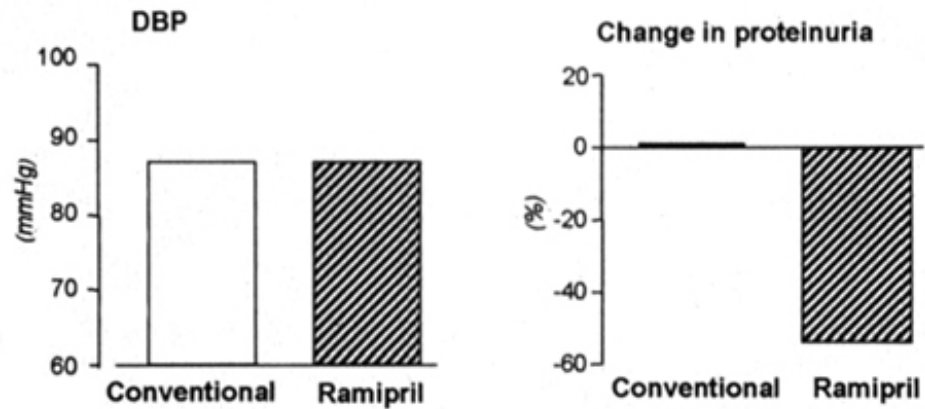
Did you know that....



REIN



UNBLINDED?!



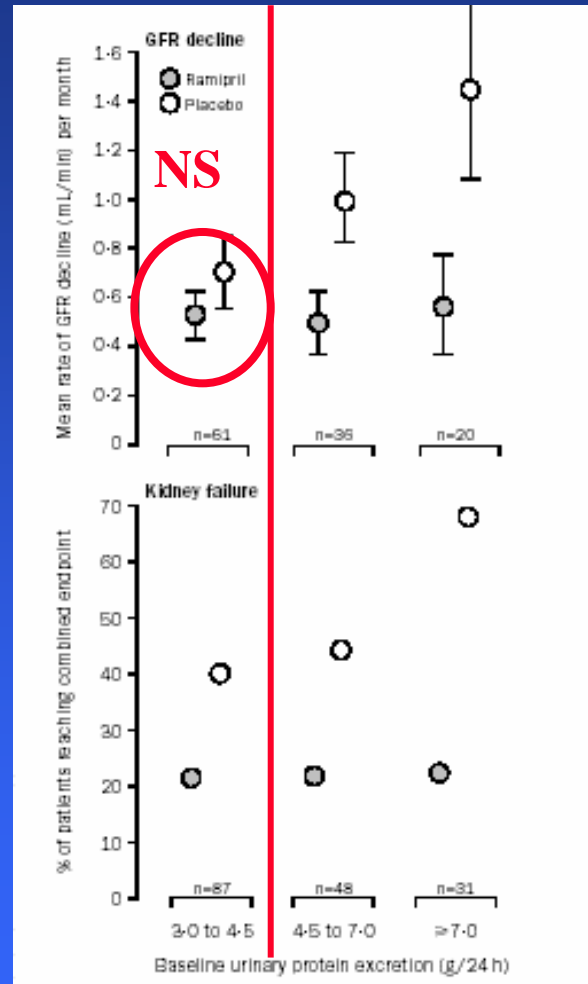
GISEN Group, Lancet, 1997

Ruggenti et al,
1997

Variable	Ramipril (n=78)	Placebo (n=88)	p*
Mean (SD) age in years	48.9 (13.6)	49.7 (13.6)	0.76
Sex			
Male	66 (85%)	64 (73%)	0.06
Female	12 (15%)	24 (27%)	
Renal disease (number of patients)			
Glomerular	50 (64%)	53 (60%)	0.93
Interstitial, polycystic	4 (5%)	5 (6%)	
Other, unknown	24 (31%)	30 (34%)	
Mean (SD) renal-function indicators			
GFR (mL/min per 1.73 m ²)	40.2 (19.0)	37.4 (17.5)	0.35
Creatinine clearance (mL/min per 1.73 m ²)	47.3 (21.7)	43.7 (20.4)	0.24
Serum creatinine (μmol/L)†	212 (88)	212 (88)	0.48
Urinary protein excretion (g/24 h)‡	5.6 (2.8)	5.1 (2.0)	0.38
Urinary urea nitrogen excretion (mmol/24 h)§	357 (343)	328 (143)	0.26
Urinary sodium excretion (mmol/24 h)	211.2 (161.2)	198.9 (92.8)	0.65



REIN



No Effect of Rate of Progression!!!

	Δ GFR (mL/min/1.73 m ² per month)			ESRF		
	Overall	Ramipril	Conventional	Overall	Ramipril	Conventional
Overall	0.26±0.05	0.26±0.07	0.26±0.07	24/85 (28%)	7/39 (18%)	17/46 (37%)†
Proteinuria <1.5 g/24 h	0.17±0.06	0.21±0.07	0.12±0.09	9/45 (20%)	4/22 (18%)	5/23 (22%)
Proteinuria ≥1.5 g/24 h	0.36±0.08*	0.31±0.13	0.40±0.10‡	15/40 (38%)	3/17 (18%)	12/23 (52%)§

Data are mean (SE) or number of events/patients (%). *p<0.05; †p=0.03 vs proteinuria <1.5 g/24 h; ‡p=0.04; §p<0.05 vs ramipril.

Table 2: Rate of GFR decline and incidence of ESRF in patients with basal GFR of 45 mL/min or less

REIN : Is the trial VALID?

Was this a randomised controlled trial?

Was the randomisation blinded? NO

Are the groups well balanced?

Is there a Bias ? YES/Observer

Is the Sample size adequate? NO/High Drop out rate

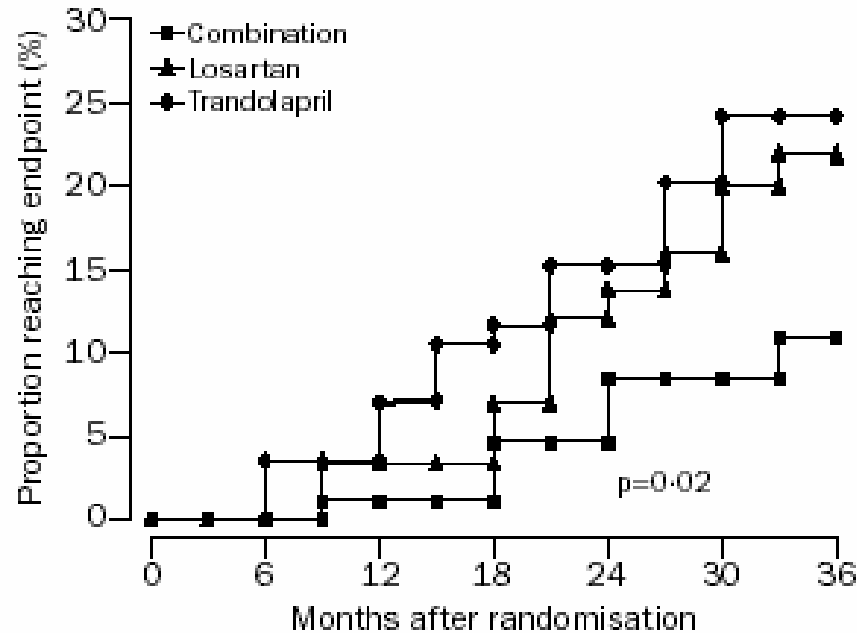
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COOPERATE



Number at risk		0	6	12	18	24	30	36
Losartan	89	88	84	79	65	59	47	
Trandolapril	86	85	83	75	72	63	58	
Combination	88	87	86	83	76	73	67	

Figure 2: Proportion of patients reaching endpoint

Letter of Concern

The number and seriousness of the inconsistencies found in the Nakao paper led us to wonder whether it is possible that this is only a case of extremely sloppy reporting or a hint towards more severe problems with the data. In fact we excluded the COOPERATE trial from our meta-analysis¹ on the basis of the implausibility of the data and internal inconsistencies and we mentioned the reason for excluding the study in our review.

We suggest that, on the basis of the information provided above, a further look into this trial is warranted.



Kunz et al, 2008



THE LANCET

Retraction – Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomized controlled trial

- An investigation committee concluded that it was not possible to prove the authenticity of the data
- The conclusions mean that the paper must be retracted from the published record



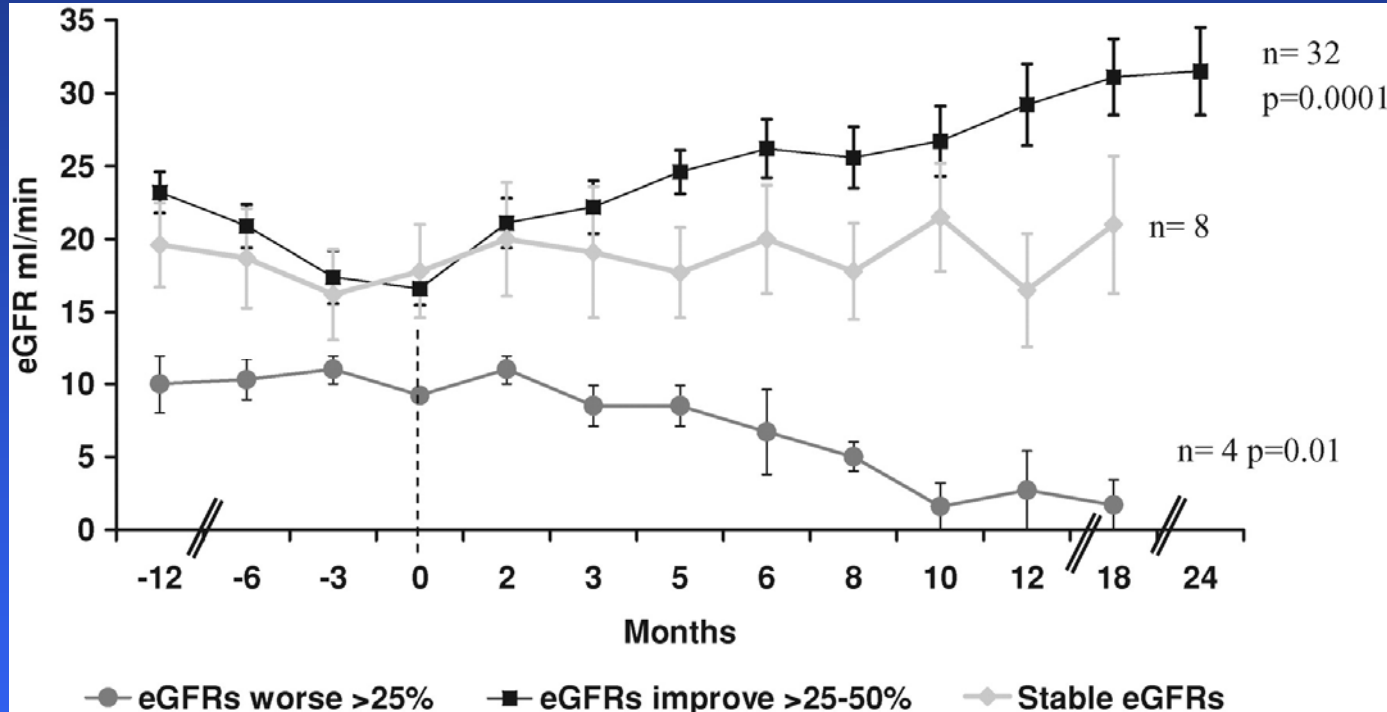
October 10-16, 2009



Research fraud is very common
So
Don't believe everything you read
Even
In the best of medical journals!



Changes in eGFR after stopping ACEi/ARB in patients with advanced CKD



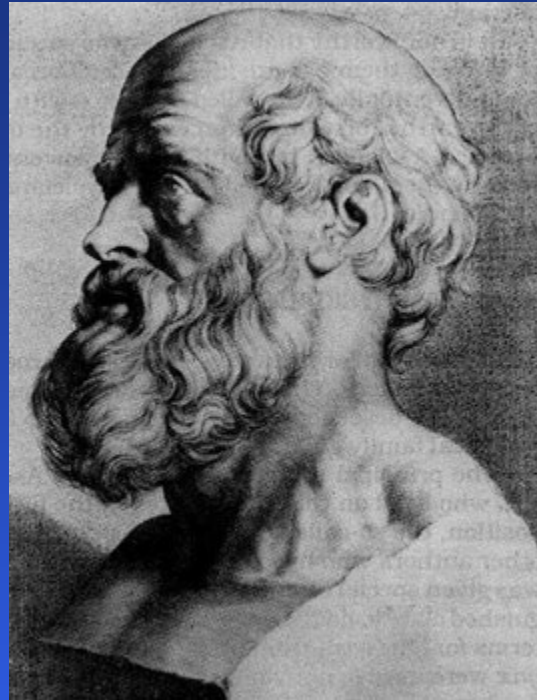
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“The **Conviction** with which many
Nephrologists hold an opinion
varies inversely with the
Evidence...”

Ed Lewis





“Primum Non Nocere...”