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European Statistical Meeting on Non-Inferiority

Non-inferiority trials are unethical

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Methodological requirements for clinical trials

Ask important questions…

…answer them reliably

The objective is the patient,

the goal is his benefit

Yusuf S, Collins R, Peto R.
Why do we need some large, simple randomized trials? Stat Med 1984; 3: 409-420

The European legislation does not require that authorisation decisions also take account of the

added therapeutic value

as supported by comparative clinical trials showing that the new medicinal product is more efficacious, or safer, than previously authorised products.

What kind of comparison?

- No comparison
- Superiority over placebo
- Non-inferiority with respect to active comparator

Placebo is sometimes not used when it should be

To test new drugs on patients resistant to already available medicines...

…would mean gaining approval for a restricted indication and, consequently, a limited market and profits.

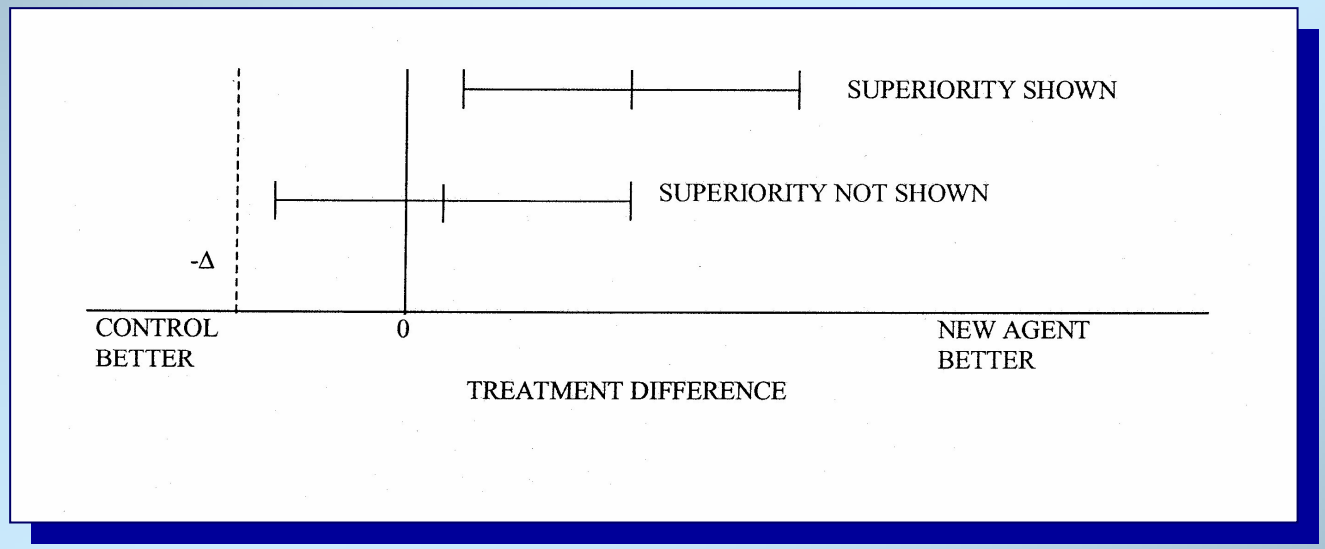
In these circumstances testing the non-inferiority of new drugs with respect to the available comparators give them no definite place in therapy but a sure place in the market.

Equivalence/non inferiority trials

from the search for better drugs

to the acceptance of drugs that are similar to, or not worse than, those already available

Superiority



Equivalence/non inferiority trials

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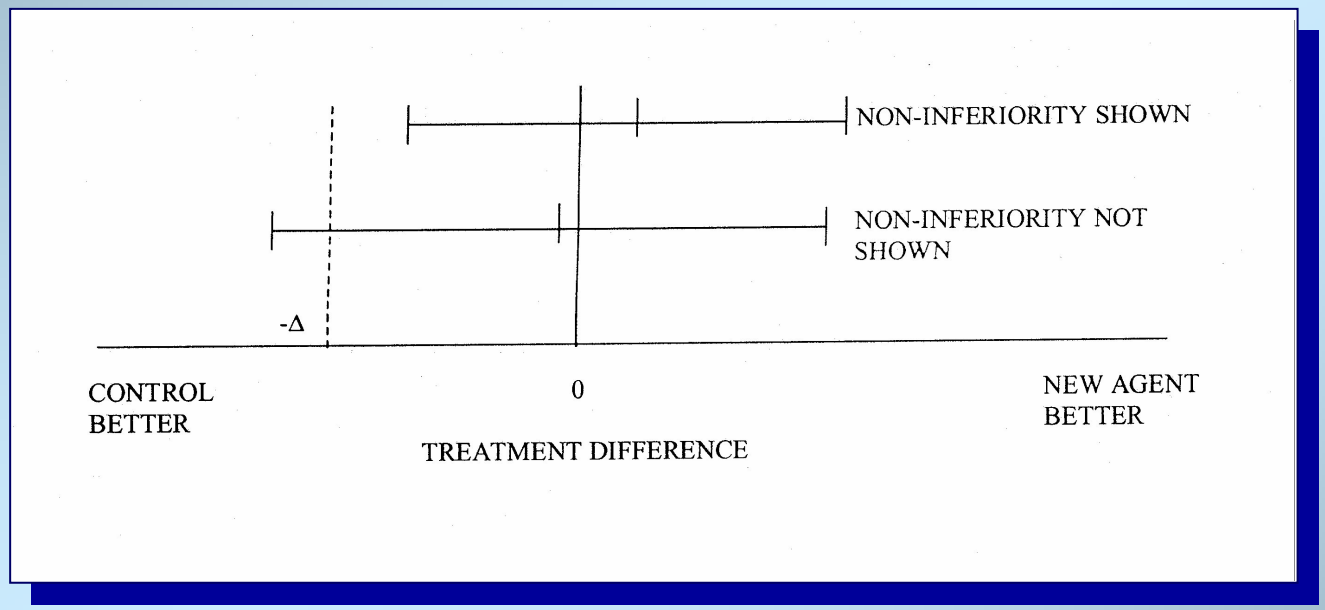
to the acceptance of drugs that are similar to, or not worse than, those already available

Non-inferiority



Equivalence/non inferiority trials

How to establish the limits (excess of outcome events) that define a drug as equivalent/not inferior?

Is a 10%, 5% or even 2% difference (possibly in mortality) acceptable as equivalent in the interest of patients?

The example of antidepressant drugs

Does placebo help establish equivalence in trials of new antidepressants?

Eur Psychiatry 2000 ; 15 : 268-73

C. Barbui[1], A. Violante[2], S. Garattini[1]

[1] Laboratory of Epidemiology and Social Psychiatry, WHO Collaborating Centre for Research and Training in Mental Health, Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy; [2] Unità Operativa di Farmacoepidemiologia Azienda USL Modena, Italy

Table I. Maximum difference between two antidepressant drugs accepted as equivalence of effect in published trials comparing SSRI, TCA and placebo

Reference [22–34]	*Antidepressant drug*	*Sample size*	δ	*Ref.*
Cassano et al., 1986	Fluvoxamine, imipramine, PLO	481	14 %	*22*
Cohn et al., 1985	Fluoxetine, imipramine, PLO	166	25 %	*23*
Dominguez et al., 1985	Fluvoxamine, imipramine, PLO	101	31 %	*24*
Doogan & Langdon, 1994	Sertraline, dothiepine, PLO	308	19 %	*25*
Dunbar et al., 1991	Paroxetine, imipramine, PLO	717	12 %	*26*
Feighner et al., 1989a	Fluvoxamine, imipramine, PLO	86	30 %	*27*
Feighner et al., 1989b	Fluoxetine, imipramine, PLO	145	25 %	*28*
Lapierre et al., 1987	Fluvoxamine, imipramine, PLO	63	39 %	*29*
Lydiard et al., 1989	Fluvoxamine, imipramine, PLO	54	43 %	*30*
March et al., 1990	Fluvoxamine, imipramine, PLO	54	43 %	*31*
Muijen et al, 1988	Fluoxetine, imipramine, PLO	81	34 %	*32*
Norton et al., 1984	Fluvoxamine, imipramine, PLO	91	33 %	*33*
Shrivastava et al., 1992	Paroxetine, imipramine, PLO	120	29 %	*34*

PLO = placebo.

Equivalence/non inferiority trials

…require smaller sample sizes as they include in the "equivalence range" therapeutic differences that may well be clinically relevant …

looking for non-inferiority
looks like an excuse
for not seeking a difference

PRoFESS Study

N Engl J Med 2008; 359:1238-51c

Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke

PRoFESS Study

N Engl J Med 2008; 359:1238-51c

To ensure that the aspirin plus extended-release dipyridamole preserved at least half the effect of clopidogrel, the noninferiority margin was set at 1.075, an effect size equal to half the lower limit of the confidence interval (an increase of 7.5% in the hazard associated with aspirin plus extended-release dipyridamole)

PRoFESS Study

…in actual figures:

- **clopidogrel avoided about 30 (at least 10) strokes every 1,000 patients treated**

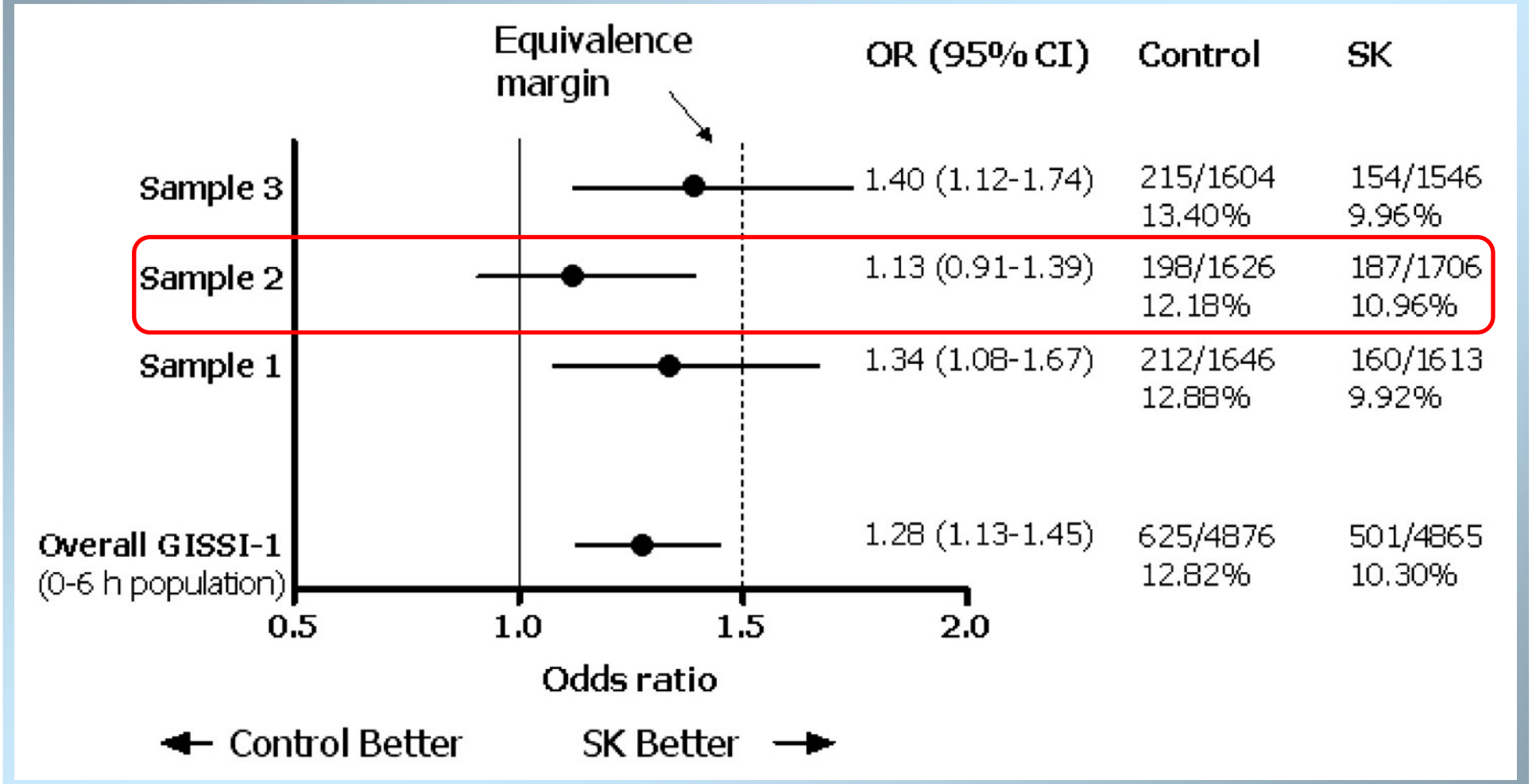
- **non-inferiority hypothesis: acceptable if ASA-ERDP preserved at least half the effect of clopidogrel**

- **this means at least five more strokes (actually 94-95 instead of the 88 reported with clopidogrel)**

- **i.e., 50 more strokes in the 10,000 patients randomized to ASA-ERDP**

the Compass hypothesis

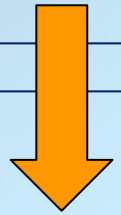
	Streptokinase (N. 1547)	Saruplase (N. 1542)	Saruplase Vs. streptokinase
Mortality	x %	+ 50%	=
Deaths/1000	70	105	



Bertele' V, Angelici L, Barlera S, Garattini S

Br J Clin Pharmacol 2008; 65 : 955-958

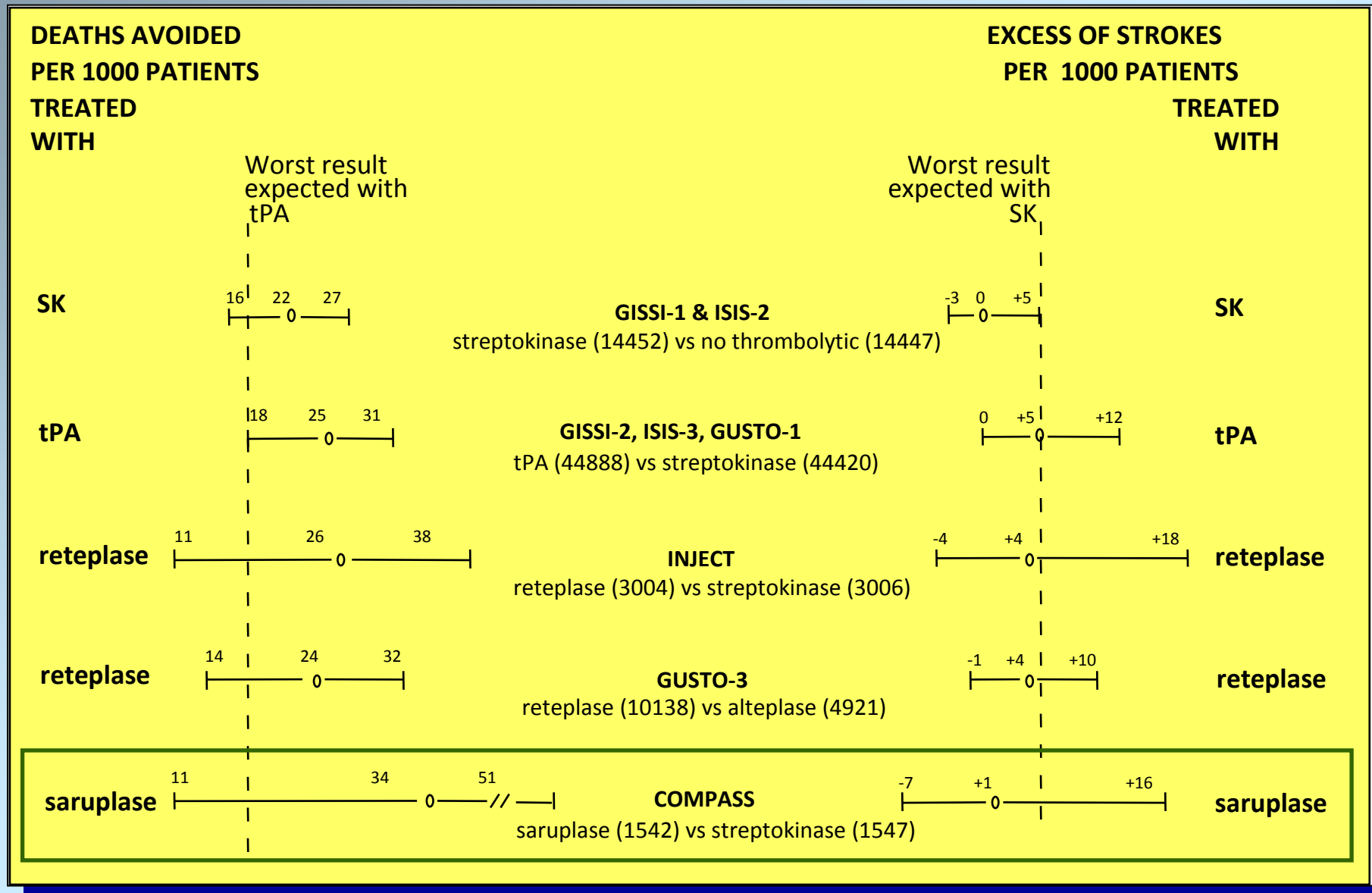
Non-inferiority trials



messages

- **misleading**
- inconclusive
- incoherent
- unethical

Inconclusive messages from equivalence trials in thrombolysis



Bertele' V, Torri V, Garattini S. *Heart 1999; 81: 675–76.*

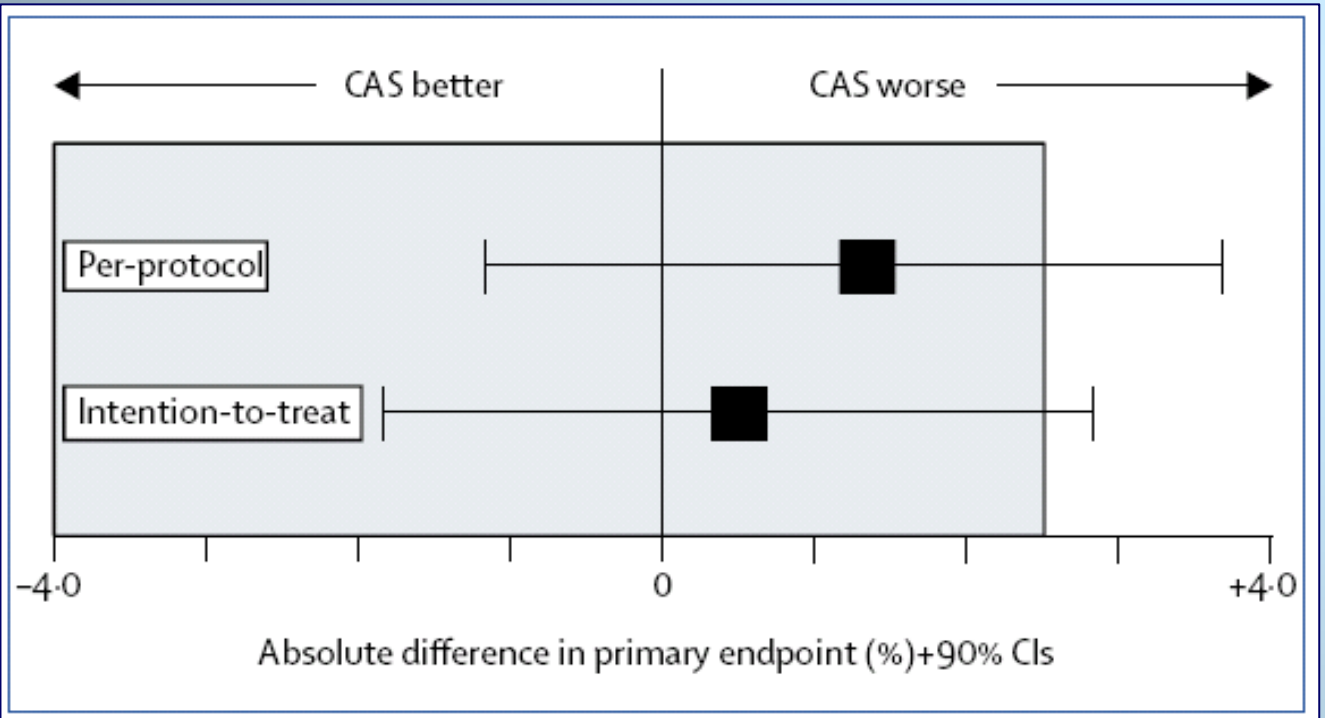


Figure: **Actual difference (90% CI) for primary endpoint in SPACE**
Primary endpoint was 30-day death or ipsilateral ischaemic stroke) between carotid endarterectomy and carotid angioplasty. Shaded box indicates upper limit for margin of non-inferiority in SPACE study (+2·5). Because upper CI is more than 2·5, study has failed to show non-inferiority for carotid angioplasty and stenting (CAS). However, because CIs cross zero, difference in primary outcome between carotid endarterectomy and carotid angioplasty and stenting was not statistically significant.

Naylor AR, Lancet 2006; 368:1215-6

PRoFESS Study

N Engl J Med 2008; 359:1238-51c

Results

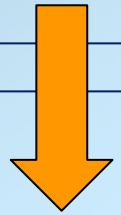
Outcome	Aspirin–ERDP (N=10,181)	Clopidogrel (N=10,151)	Hazard Ratio for Aspirin–ERDP (95% CI)
	number (percent)		
Primary outcome: recurrent stroke	916 (9.0)	898 (8.8)	1.01 (0.92–1.11)
Secondary outcome: composite of vascular events (stroke, MI, or death from vascular causes)	1333 (13.1)	1333 (13.1)	0.99 (0.92–1.07)

Conclusions

The trial did not meet the predefined criteria for noninferiority but showed similar rates of recurrent stroke with ASA–ERDP and with clopidogrel. There is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke.

Failure to prove non-inferiority of a treatment basically as effective as the standard control shows that non-inferiority trials may not even meet their obvious commercial aims.

Non-inferiority trials



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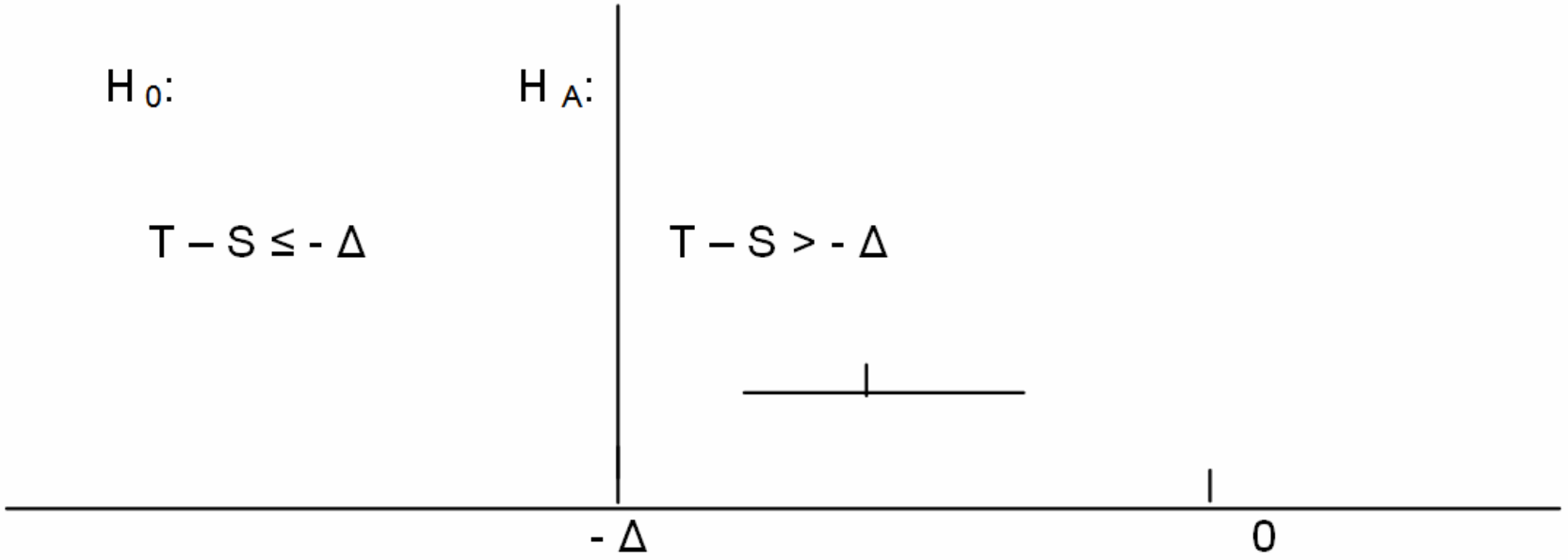
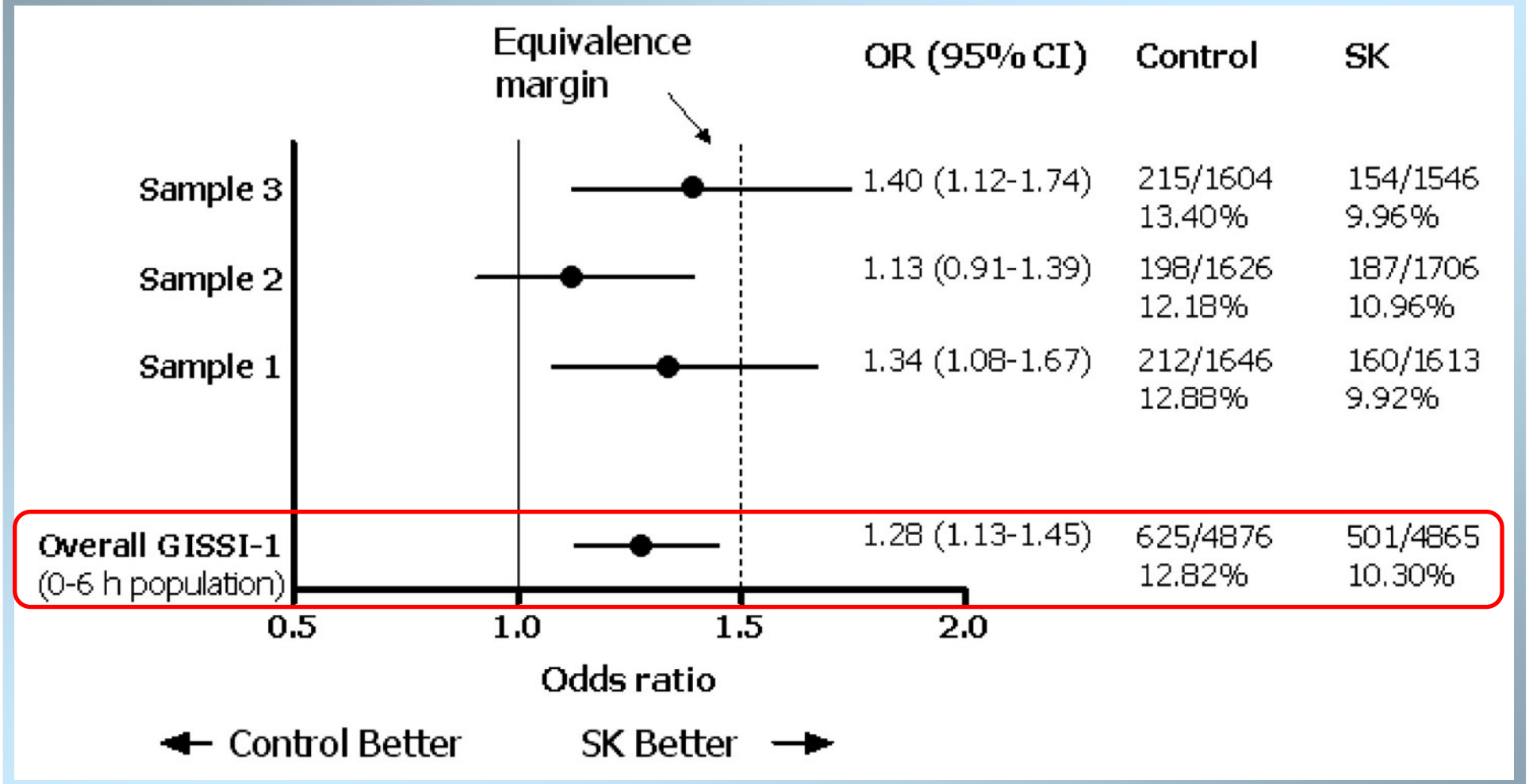
Equivalence/non inferiority trials only reflect economic considerations

- easier to show equivalence than superiority
- easier to obtain marketing authorisation on the basis of equivalence than when superiority has not been achieved

Figure 1. 'Black' scenario of the non-inferiority trial. The new drug (T) tested against the standard (S). The point estimate for the new drug and confidence intervals (CI) are shown. The lower bound of CI is $> -\Delta$ (where Δ is accepted in advance, allowed difference from standard), the upper bound is < 0 (zero difference between tested and standard). H_0 an H_A denote null and alternative hypotheses, respectively.



Jacek Spławiński and Jerzy Kuźniar
Science and Engineering Ethics, 2004



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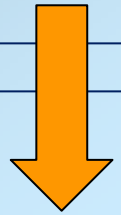

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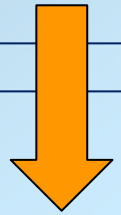
Superiority over placebo
and non-inferiority to active comparators

- may allow onto the market drugs that in fact are less active (or safe, tolerable, convenient, etc.) than those already available, usually with consolidated properties and lower costs

- do not meet patients' nor physicians' needs of defining the place in therapy and respective roles of new and available treatments

Non-inferiority trials



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Garattini S, Bertele' V.
How can research ethics committees protect patients better?
BMJ 2003; 326:1199-201

Draft informed consent

"Let us treat you with something that at best is the same as what you would have had before, but might also reduce - though this is unlikely - most of the advantages previously attained in your condition. It might even benefit you more than any current therapy but, should that actually happen, we shall not be able to prove it. Nor have we enough chance to let you know whether the new treatment may somehow bother or even harm you more than the standard one".

Equivalence/non-inferiority trials: when are they meaningful

?

Are there specific reasons for allowing a non-inferiority approach?

- There may be non-responders to current treatments and products with comparable activity may offer a useful alternative.

If the target is non-responders to current treatments, why not test their superiority over drugs with little effect in this subset of patients?

- Non-inferior drugs may be better tolerated or easier to use.

The advantage, if real, should translate into better compliance and in the end into a better rather than a "not worse" outcome.

- Non-inferior drugs may be available at a lower price.

Proving that a lower benefit in single patients is compensated by a greater advantage due to wider use in the overall population requires much larger studies than the usual non-inferiority trials.

- Superiority trials generally take much longer and require many more patients. Thus potentially advantageous drugs remain available only through clinical trials.

Non-inferiority trials do not necessarily require a smaller sample size: this is often the result of questionable methodological choices like setting a large inferiority margin or other tricks. In any case the later availability of proven effective drugs is preferable to the early availability of potentially advantageous drugs whose actual efficacy, however, will never be proved, since nobody will agree to be randomized any more to old drugs that non-inferiority tests considered no better than the new ones, and are less convenient or tolerable.

- Testing non-inferior efficacy for the sake of better safety.

This is reasonable if the outcome events measuring efficacy and safety have comparable clinical importance as, for instance, deaths and devastating haemorrhagic strokes after thrombolysis in AMI. In these circumstances, however, a superiority trial would compare the effectiveness of two treatments better in terms of survival without strokes by cumulatively measuring efficacy and safety events.

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…answer them reliably

The objective is the patient,

the goal is his benefit

Yusuf S, Collins R, Peto R.
Why do we need some large, simple randomized trials? Stat Med 1984; 3: 409-420

Non-inferiority trials

- should not be considered an option by the scientific community and

- should not be accepted as a basis for marketing authorisation by the regulatory authorities