Commenti al Paper di Bosh et Al su RAMIPRIL

Ricerca biomedica: definizione

Insieme di studi con finalità mediche tesi a stabilire una relazione tra una caratteristica o un intervento (trattamento) ed una malattia o una condizione predisponente ad una malattia.

La relazione alla quale si è interessati è quella di **causa-effetto**.

Si tratta di distinguere tra

SEGNALE

RUMORE DI FONDO

Caratteri distintivi di uno studio clinico o biomedico

- I ragionamenti, i metodi e le conclusioni sono basati sul confronto
- Le conclusioni sono estese dal particolare del campione al generale della popolazione (inferenza) sulla base di un modello statistico-probabilistico
- Tutto è pianificato in dettaglio ed in modo documentato prima dell'inizio dello studio
- Le conclusioni sono basate sul confronto tra gruppi "omogenei"

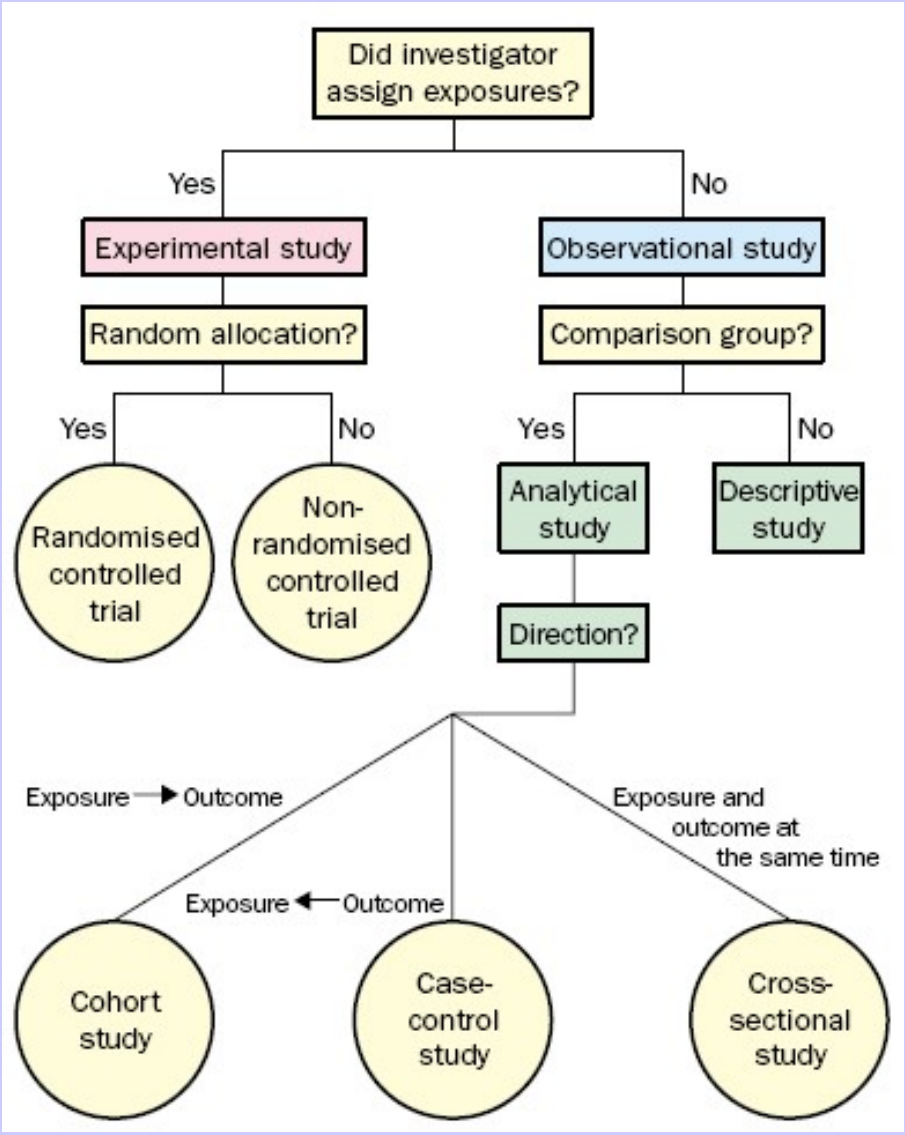
Una tassonomia degli studi nella ricerca clinica

- Clinical research has two large "kingdoms"

Experimental vs observational studies

D.A. Grimes, K.F. Schulz, An overview of clinical research: the lay of the land. Lancet 2002; 359: 57-61

Clinical research has two large "kingdoms"



Studi sperimentali o osservazionali

L'esposizione è assegnata dal ricercatore?

Sì → **Studio Sperimentale**

Implica la modifica (rispetto alla normale pratica clinica) del trattamento per studiarne l'effetto sull'esito. E' condotto in condizioni controllate. Può includere la randomizzazione.

No → **Studio Osservazionale**

La decisione di prescrivere il farmaco al singolo paziente deve essere del tutto indipendente da quella di includere il paziente stesso nello studio (Prescrizione farmaco, procedure diagnostiche e valutative secondo normale pratica clinica) (**AIFA**)

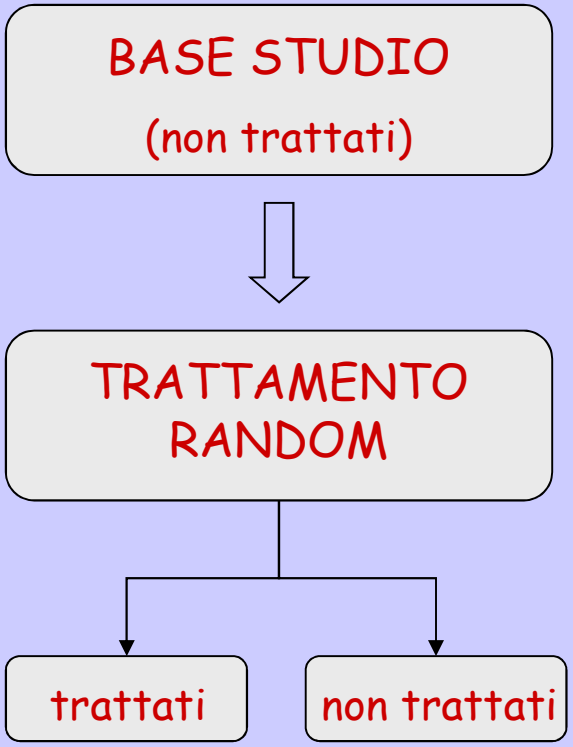
SE PARLIAMO DI FARMACI/TRATTAMENTI

Studi randomizzati

Tutti i pazienti hanno la stessa probabilità di ricevere uno dei trattamenti studiati.

I controlli sono per disegno concomitanti

Controlli randomizzati (RCT)



La randomizzazione

- Ripartisce casualmente fra i gruppi i fattori prognostici (noti e ignoti)
- Elimina gli errori sistematici nell'assegnazione dei trattamenti ai malati (consapevoli e inconsapevoli)
- E' il modo più eticamente accettabile di assegnare i malati ai trattamenti confrontati
- I risultati sono più credibili
- Garantisce la validità dei test statistici

Avoids selection bias and confounding

Reduces information bias

RANDOMIZZAZIONE:

Assegnazione "a caso" e non "a casaccio"!

Con metodi specifici

Nel titolo c'è spesso il tipo di studio……

Use of ramipril in preventing stroke: double blind randomised trial

Jackie Bosch, Salim Yusuf, Janice Pogue, Peter Sleight, Eva Lonn, Badrudin Rangoonwala, Richard Davies, Jan Ostergren, Jeff Probstfield on behalf of the HOPE Investigators

Abstract

Objective To determine the effect of the angiotensin converting enzyme inhibitor ramipril on the secondary prevention of stroke.

Design Randomised controlled trial with 2 x 2 factorial design.

Setting 267 hospitals in 19 countries.

Participants 9297 patients with vascular disease or diabetes plus an additional risk factor, followed for 4.5 years as part of the HOPE study.

Outcome measures Stroke (confirmed by computed tomography or magnetic resonance imaging when available), transient ischaemic attack, and cognitive function. Blood pressure was recorded at entry to the study, after 2 years, and at the end of the study.

Results Reduction in blood pressure was modest (3.8 mm Hg systolic and 2.8 mm Hg diastolic). The relative risk of any stroke was reduced by 32% (156 *v* 226) in the ramipril group compared with the placebo group, and the relative risk of fatal stroke was reduced by 61% (17 *v* 44). Benefits were consistent across baseline blood pressures, drugs used, and subgroups defined by the presence or absence of previous stroke, coronary artery disease, peripheral arterial disease, diabetes, or hypertension. Significantly fewer patients on ramipril had cognitive or functional impairment.

Conclusion Ramipril reduces the incidence of stroke in patients at high risk, despite a modest reduction in blood pressure.

The study had 90% power to detect a 13.5% reduction in relative risk for the primary outcome, with an annual event rate of 4% in 9000 patients studied for five years.
Assuming a stroke rate of 1.2% per year in the control group for five years, the study had 80%power to detect a 22% reduction in the relative risk of stroke (2-sided 0.05) with an intention to treat analysis.

Study organisation

The study was conducted in 267 hospital clinics in 19 countries. It was coordinated by the Canadian Cardio vascular Collaboration in Hamilton,

We estimated survival curves according to the KaplanMeier procedure and compared treatments by using the log rank test. Because of the factorial design, we stratified all analyses for the randomization to vitamin E or placebo. We conducted subgroup analyses by using tests for interactions in the Cox regression model. We used this model to estimate the reduction in relative risk and the 95% confidence intervals associated with ramipril treatment in unadjusted analyses and after controlling for changes in blood pressure.

The data and safety monitoring board monitored the study. Monitoring boundaries for the study were four standard deviations between the two groups in terms of benefit of ramipril in the first half of the study and three standard deviations in the second half. For harm, the boundaries were three standard deviations in the first half of the study and two standard deviations in the second half. Because of clear benefit, the study was terminated on 22 March 1999.

Use of ramipril in preventing stroke

From Bosch et al, BMJ 2002;324:

- **What is already known on this topic**

  Treatment with aspirin and lowering blood pressure reduce the incidence of stroke
- **What this study adds**

  Ramipril, an angiotensin converting enzyme inhibitor, reduces strokes in patients at high risk whose blood pressure is not elevated, despite a modest lowering of blood pressure

Use of ramipril in preventing stroke

Bosch et al, BMJ 2002;324

Outcome	Ramipril N=4645	Placebo N=4652	RR 95% CI	ARR
Total strokes	156 3.4%	226 4.9%	0.68 0.56-0.84	1.5%
• non fatal	139 3.0%	182 3.9%	0.76 0.61-0.94	0.9%
• fatal	17 0.4%	44 1.0%	0.39 0.22-0.67	0.6%

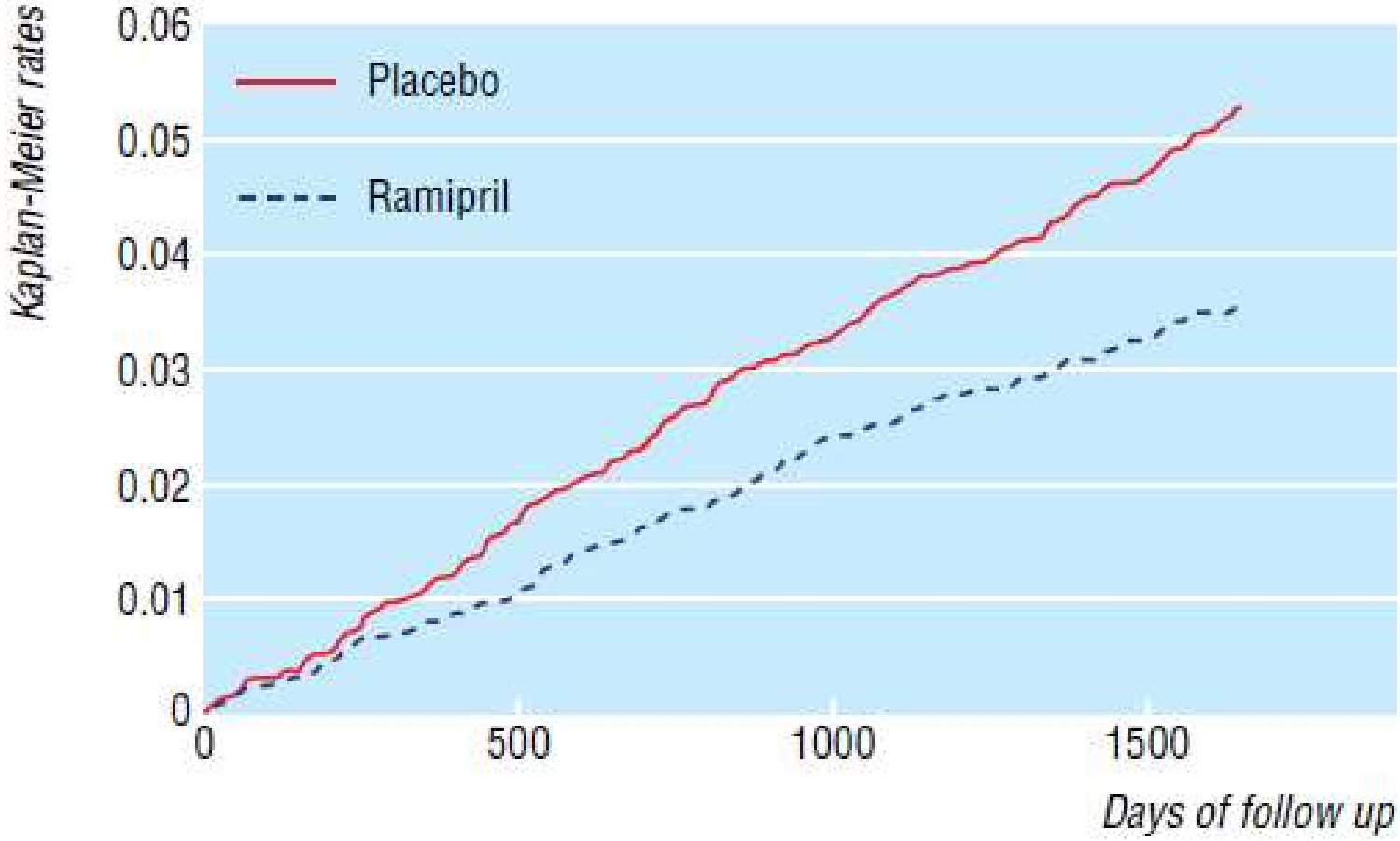


Fig 1 Kaplan-Meier estimates of the development of stroke by treatment group. The relative risk of developing stroke in the ramipril group compared with the placebo group was 0.68 (95% confidence interval 0.56 to 0.84; P=0.0002).

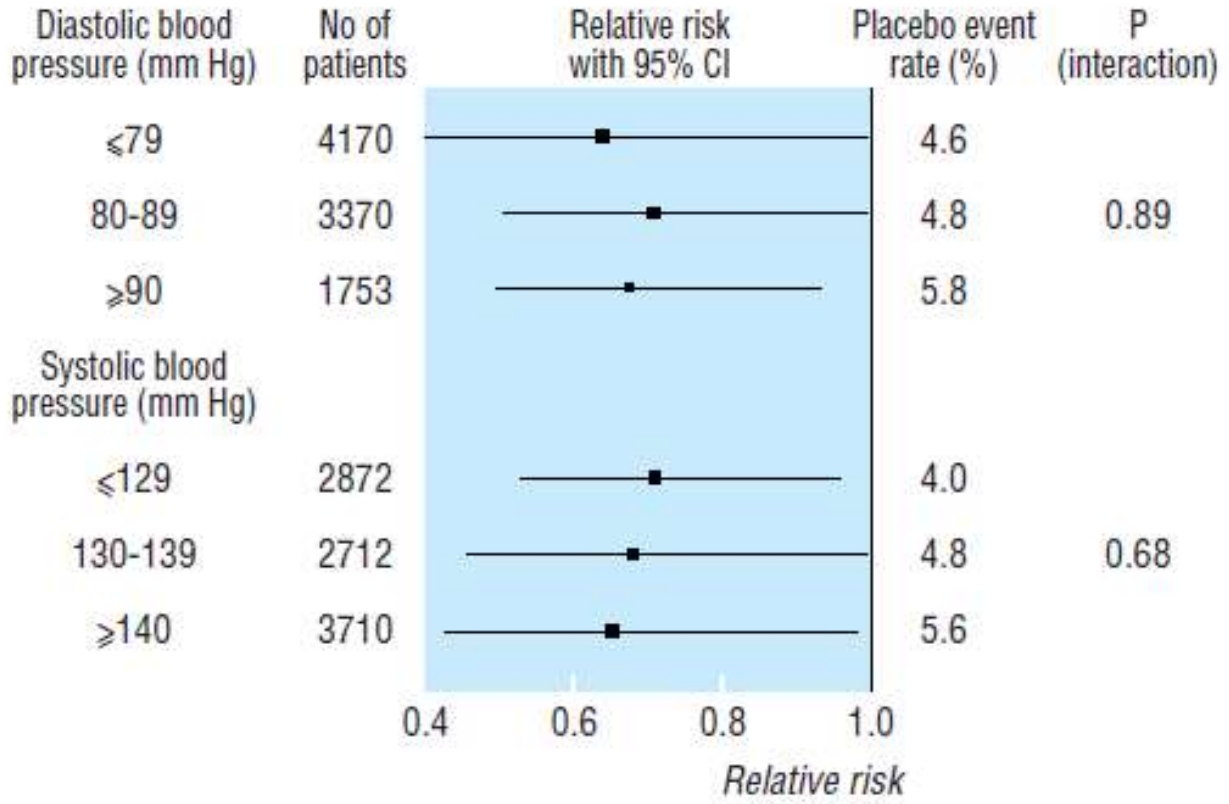


Fig 2 Impact of ramipril on stroke based on baseline blood pressure

Table 1 Impact of ramipril on stroke subdivided by non-fatal and fatal stroke, subtype of stroke, and presence or absence of functional impairment. Values are numbers (percentages) unless stated otherwise

Outcome	Ramipril (n=4645)	Placebo (n=4652)	Relative risk (95% CI)
Total strokes	156 (3.4)	226 (4.9)	0.68 (0.56 to 0.84)
Non-fatal:	139 (3.0)	182 (3.9)	0.76 (0.61 to 0.94)
No functional impairment	49 (1.1)	80 (1.7)	0.61 (0.43 to 0.87)
Some functional impairment*	85 (1.8)	108 (2.3)	0.78 (0.59 to 1.04)
Fatal	17 (0.4)	44 (1.0)	0.39 (0.22 to 0.67)
Subtype of stroke			
Ischaemic	101 (2.2)	157 (3.4)	0.64 (0.50 to 0.82)
Non-ischaemic†:	63 (1.4)	78 (1.7)	0.80 (0.57 to 1.12)
Haemorrhagic	12 (0.26)	16 (0.34)	0.74 (0.35 to 1.57)
Uncertain aetiology	52 (1.1)	65 (1.4)	0.79 (0.55 to 1.14)

*Any impairment from functional impairment that does not limit daily activities to assistance needed for all activities of daily living.
†Stroke of haemorrhagic or uncertain aetiology.

Table 2 Details of cognitive and motor changes (24 hours after stroke) associated with stroke in patients with an event.* Values are numbers (percentages) unless stated otherwise

Outcome	Ramipril (n=4645)	Placebo (n=4652)	Relative risk (95% CI)
Change in cognition	28 (0.6)	47 (1.1)	0.59 (0.37 to 0.94)
Change in consciousness	19 (0.4)	28 (0.6)	0.67 (0.38 to 1.20)
Ocular or visual symptoms	30 (0.7)	33 (0.7)	0.90 (0.55 to 1.47)
Weakness in face or limb	92 (2.0)	127 (2.7)	0.72 (0.55 to 0.94)
Sensory symptoms	51 (1.1)	45 (1.0)	1.12 (0.75 to 1.67)
Dysarthria/dysphasia	49 (1.1)	71 (1.5)	0.68 (0.48 to 0.98)
Dysphagia	19 (0.4)	33 (0.7)	0.57 (0.32 to 1.0)

*Data were collected for all but 11 patients who had a stroke; five of the 11 died.

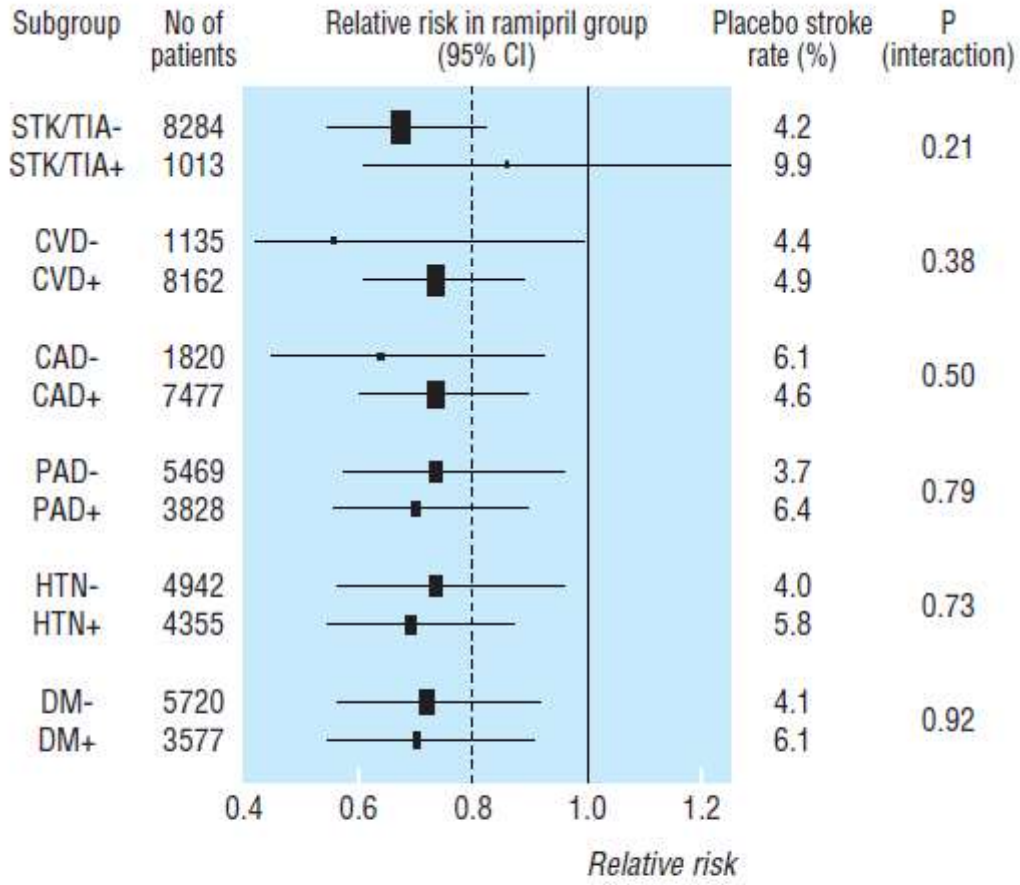


Fig 3 Impact of ramipril on stroke rates among subgroups of patients with different baseline conditions. ('–' indicates absence of condition; '+' indicates presence of condition; STK/TIA=stroke or transient ischaemic attack; CVD=cardiovascular disease; CAD=coronary artery disease; PAD=peripheral arterial disease; HTN=hypertension; DM=diabetes mellitus)

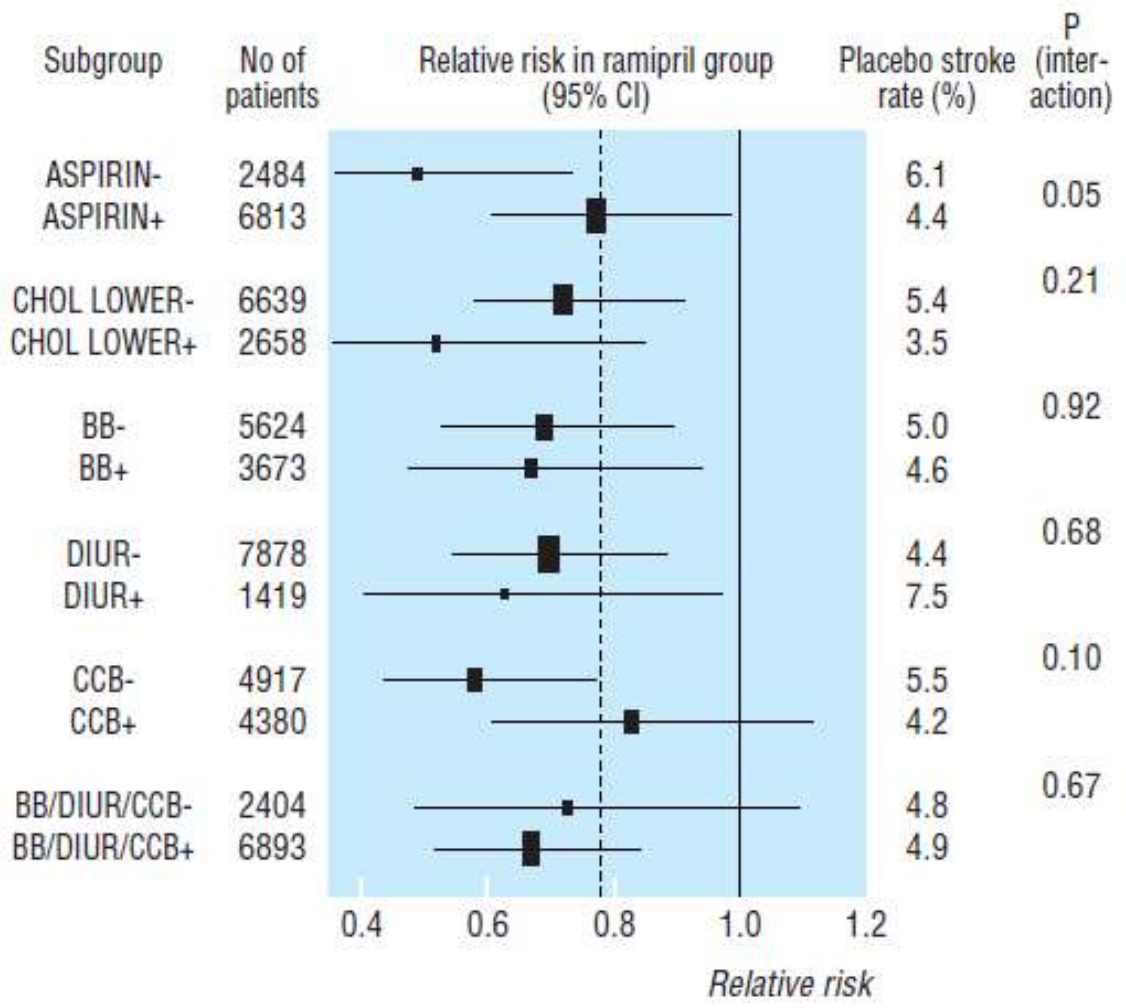


Fig 4 Impact of ramipril on stroke in subgroups of patients based on baseline drug use. *Interaction statistic derived from χ^2 test. ('–' indicates absence of condition; '+' indicates presence of condition; CHOL LOWER=cholesterol lowering agent; BB=β blocker; DIUR=diuretic; CCB=calcium channel blocker)

What is already known on this topic

Treatment with aspirin and lowering blood pressure reduce the incidence of stroke

What this study adds

Ramipril, an angiotensin converting enzyme inhibitor, reduces strokes in patients at high risk whose blood pressure is not elevated, despite only a modest lowering of blood pressure

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The benefits are observed even when patients receive aspirin and other blood pressure lowering treatments

Use of ramipril in preventing stroke Letters to the Editor

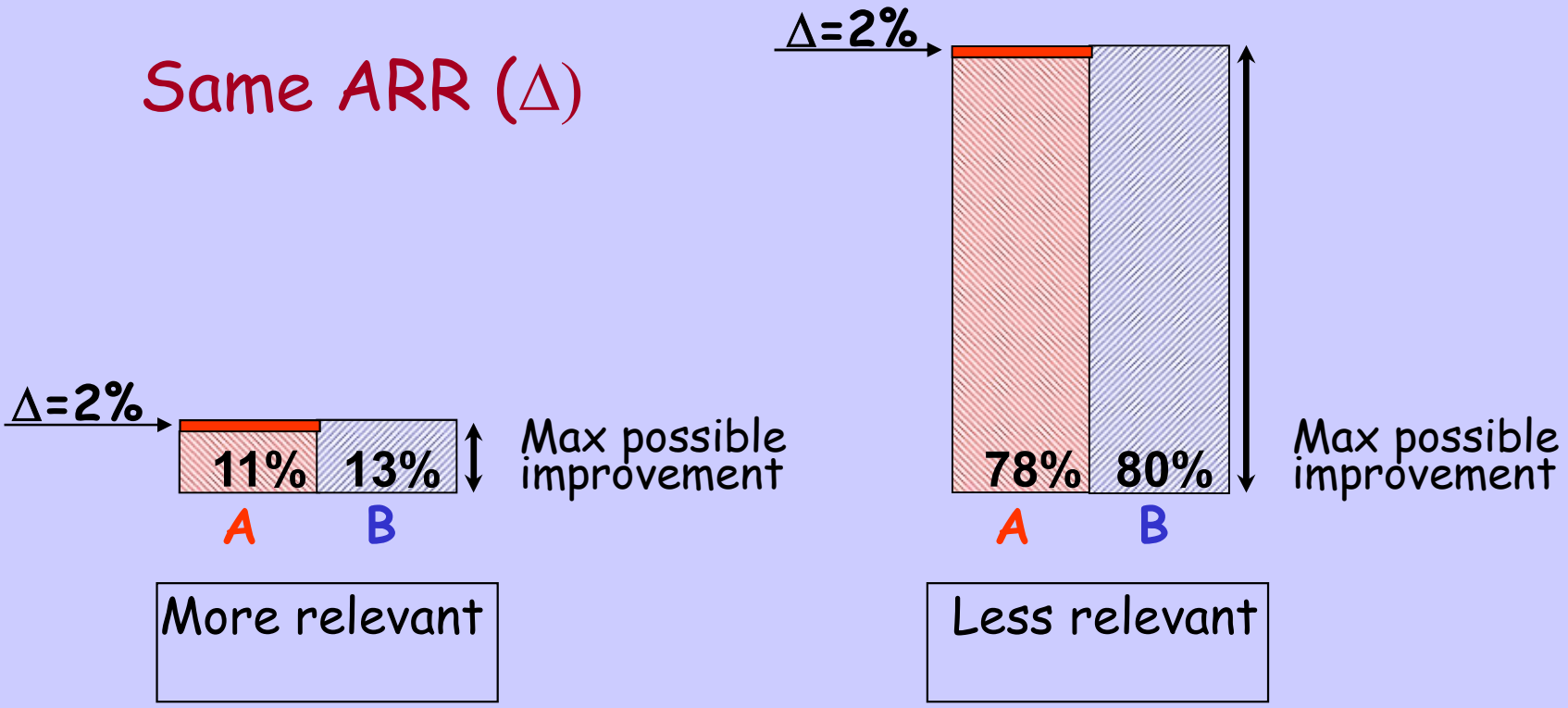
- "The trial presented the results in a way that exagerates the findings"
- "The absolute risk reduction, which is the clinically relevant outcome measure was 0.6 and 0.9 only"
- NNT=67 for 4.5 years of treatment is not convincing

Absolute or relative measure?

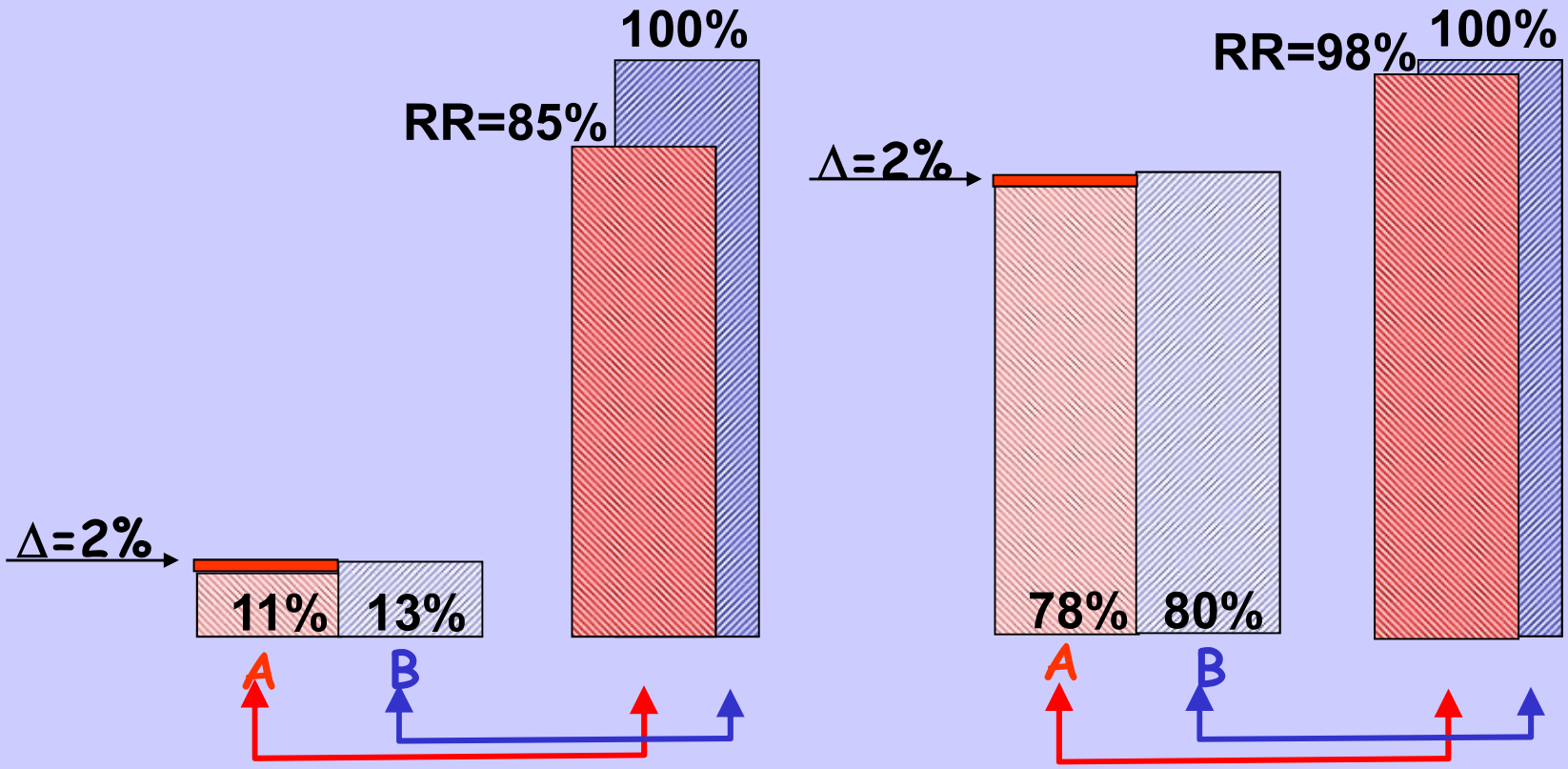
Absolute Measure: ARR

Absolute Risk Reduction Δ : expresses directly how many people will profit from an intervention and 1/ Δ is NNT. Relevance of Δ is related to baseline value (control)

Same ARR (Δ)



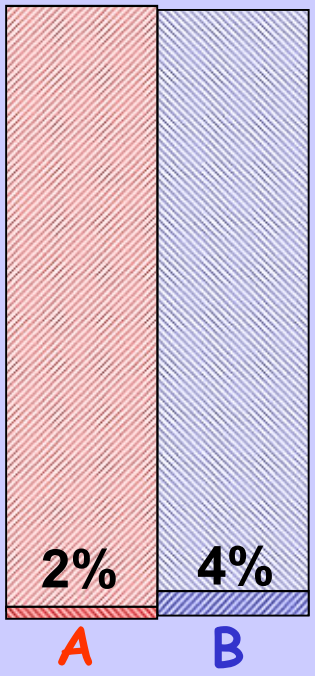
Relative measure: Relative Risk (RR)



RR (or OR) expresses more directly treatment effect as the focus is on the proportion of people who had events

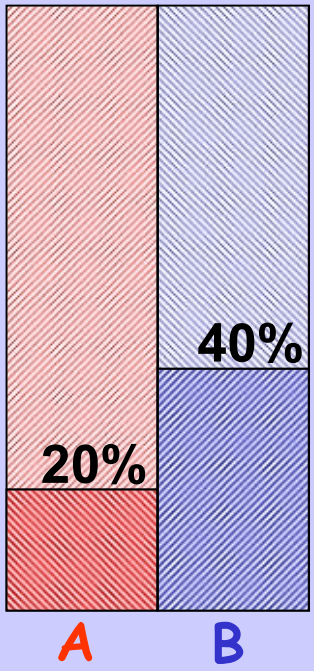
Relative measure

The same value of RR=0.5 for treatment A vs B (control), may correspond to completely different scenarios in terms of impact in clinical practice/public health



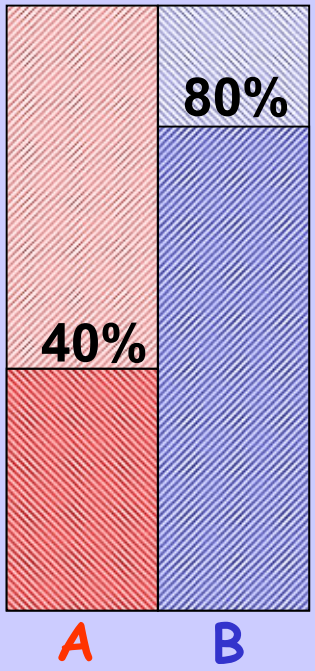
Scenario 1

NNT= 50



Scenario 2

NNT= 5



Scenario 3

NNT= 2.5

Use of ramipril in preventing stroke Letters to the Editor

- "trial participants labelled "high but had an absolute risk of stroke of only 4.9%"
- "No effect in group at higher risk (1013 who had experienced TIA – baseline risk 9.9%)"
- No effect on lowering blood pressure

But interaction "treatment*STK±TIA" is not significant!! (p=0.21)