LA META-ANALISI CON LO STATA: L'ESEMPIO DEGLI STENTS MEDICATI NELLE PROCEDURE DI CARDIOLOGIA INTERVENTISTICA PERCUTANEA

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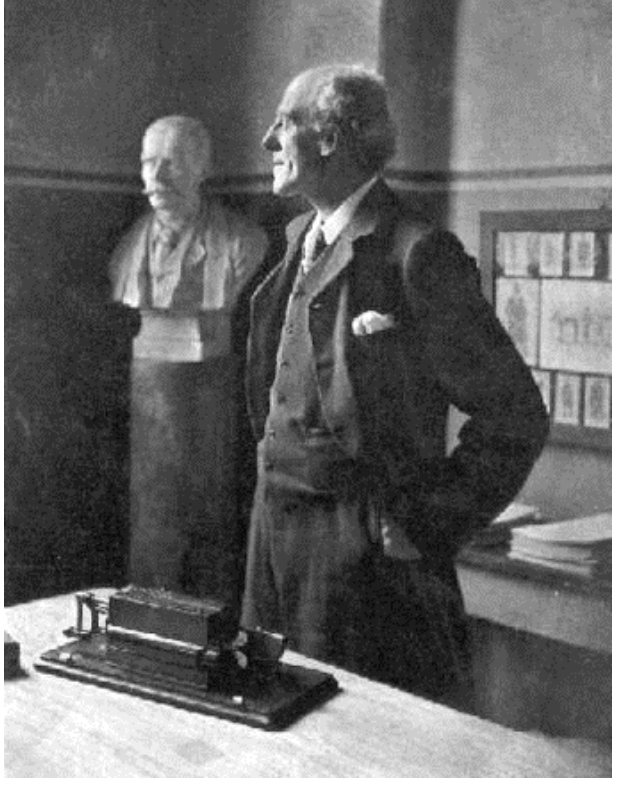

Karl Pearson, 1904

The British Medical Journal Nov. 5, 1904. pp. 1243-46.

REPORT ON CERTAIN ENTERIC FEVER INOCULATION STATISTICS.

PROVIDED BY LIEUTENANT-COLONEL R. J. S. SIMPSON, C.M.G., R.A.M.C.

BY KARL PEARSON, F.R.S.,
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THE statistics in question were of two classes: (A) Incidence (B) Mortality Statistics. Under each of these headings the data belonged to two groups: (i) Indian experience; (ii) South African War experience. These two experiences were of a somewhat different character. That for India covered apparently the European army, of whatever branch and wherever distributed; that for South Africa was given partly by locality, partly by column, and partly by special hospital. Thus the Indian and South African experiences seem hardly comparable. Many of the groups in the South African experience are far too small to allow of any definite opinion being formed at all, having regard to the size of the probable error involved. Accordingly, it was needful to group them into larger series. Even thus the material appears to be so heterogeneous, and the results so irregular, that it must be doubtful how much weight is to be attributed to the different results.

"Ciascun gruppo ... è di dimensioni troppo limitate per poter trarre conclusioni definitive..."

"... Si è reso necessario, pertanto, raggrupparli insieme"

L'analisi statistica dei dati di diversi studi individuali condotta con l'obiettivo di riassumerne i risultati

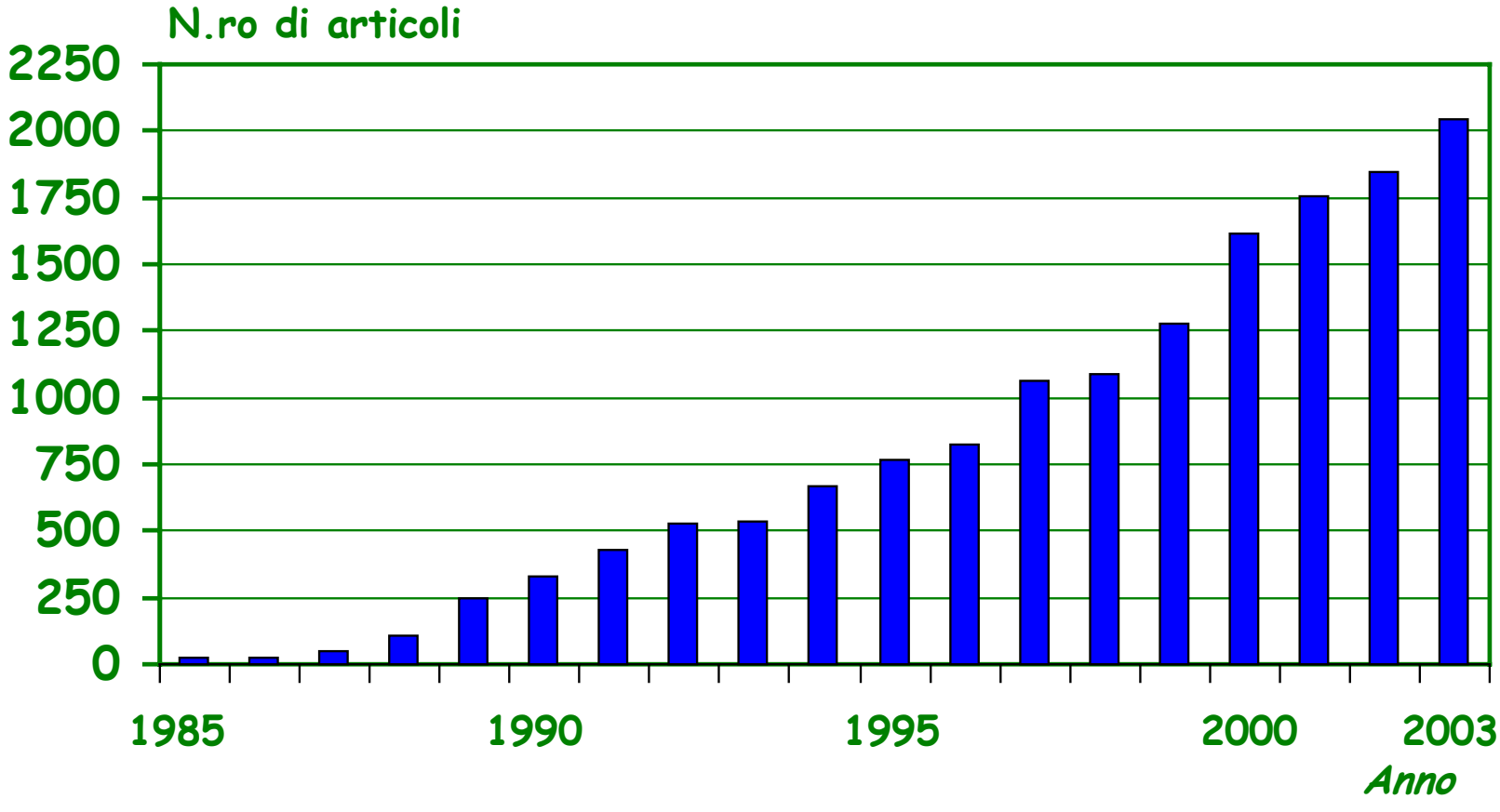
Analisi primaria
analisi originaria dei dati di uno studio

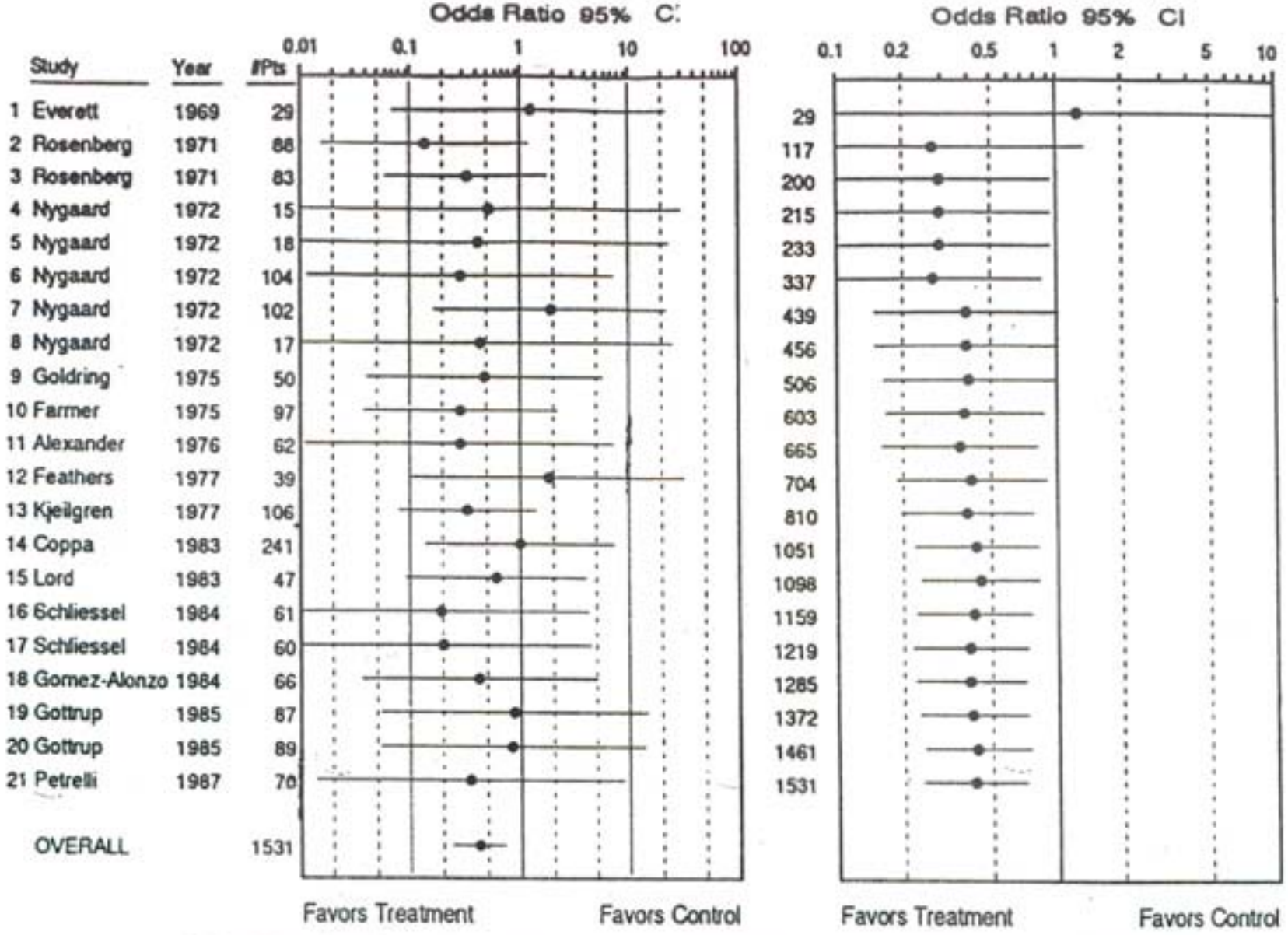
Analisi secondaria
rianalisi dei dati per testare una nuova ipotesi di ricerca

Meta-analisi
analisi finalizzata alla combinazione dei risultati di diversi studi

G. Glass, 1976

Risultati di una ricerca bibliografica effettuata con Medline utilizzando il termine "Meta-analysis" (text word medical subject heading, publication type), per anno.





Reduction of perioperative deaths by antibiotic prophylaxis for colorectal surgery. Studies were pooled by the Mantel–Haenszel method and cumulative meta-analysis is based on publication year.

produce a similar protective effect against reflex sympathetic dystrophy to that of regional sympathetic block immediately before general anaesthesia? Local anaesthetic nerve blocks are usually accompanied by some degree of sympathetic block, and would offer the bonus of postoperative pain relief, and so further reduce the risk of central-nervous-system sensitisation. The complications of local anaesthetic injections into peripheral nerves, especially when an indwelling catheter is used in a neurovascular sheath (eg, during a continuous axillary block), should not be overlooked; indeed, reflex sympathetic dystrophy can be the paradoxical result.

Conclusions

These suggestions for the relief and prevention of reflex sympathetic dystrophy are based on my hypothesis of failed opioid modulation and on the established general principle of avoiding sensitisation of the central nervous system. Although my experiences with treatment of patients with reflex sympathetic dystrophy and of other forms of sympathetically maintained pain tend to support the use of such preventive and therapeutic techniques, controlled studies will clearly be necessary to establish whether or not clinical outcome is significantly improved. Because of the rarity of dystrophic limb disorders, multicentre trials will probably be needed; prospective researchers will first have to address several difficult problems, not least of which will be to reach a satisfactory consensus as to what we really mean by reflex sympathetic dystrophy.

This hypothesis was presented to a symposium sponsored by the Somatosensory Committee of the International Union of Physiological Sciences, held at Guy's Hospital, London, in April, 1991.

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VIEWPOINT

Can meta-analyses be trusted?

SIMON G. THOMPSON STUART J. POCOCK

The enthusiasm for meta-analyses (or overviews) expressed by their proponents is not always shared by the broader medical community. To encourage constructive debate, we adopt a critical perspective on the conduct and interpretation of meta-analysis. We focus particularly on some of the statistical issues, especially heterogeneity between studies, and also on the extrapolation of meta-analysis findings to clinical practice. We conclude that meta-analysis is not an exact statistical science that provides definitive simple answers to complex clinical problems. It is more appropriately viewed as a valuable objective descriptive technique, which often furnishes clear qualitative conclusions about broad treatment policies, but whose quantitative results have to be interpreted cautiously.

Lancet 1991; **338**: 1127–30.

Introduction

A single clinical trial often fails to give clear-cut generalisable results, because of insufficient patient numbers and the particular way the study was done. Meta-analyses (or overviews) use formal statistical techniques to combine the results from similar trials not only to increase numbers but also to generalise conclusions to a more varied range of patients and treatment protocols. The greater objectivity of this approach is a clear advantage over the more subjective narrative review.[1] However, the conviction of some proponents of meta-analysis is often countered by scepticism from the broader medical profession. Two contrasting views are evident:[2] does meta-analysis provide "objective, quantitative methods for combining evidence from separate but similar studies" or merely "statistical tricks which make unjustified assumptions in producing oversimplified generalisations out of a complex of disparate studies"?

In exploring the reasons for such contrasting perceptions of meta-analysis, we will focus on the statistical issues, especially the problems of interpretation arising from clinical heterogeneity (ie, design differences) and statistical heterogeneity. Such a critical appraisal is essential in reaching a balanced view on how meta-analysis findings should be applied in clinical practice. Although we concentrate on clinical trials, similar (and often more serious) issues are relevant to meta-analysis of observational studies.

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POSSIAMO AVER FIDUCIA NELLA META-ANALISI?

RAZIONALE DELLA META-ANALISI SUGLI STENTS MEDICATI

- La "ristenosi" rappresenta il principale limite delle procedure interventistiche percutanee

- L'uso degli stents ha ridotto del 20-30% il rischio di "ristenosi" dopo angioplastica percutanea

- Esistono tuttavia evidenze sulla possibilità di ristenosi anche come risposta della parete vascolare alla presenza degli stents.

RAZIONALE DELLA META-ANALISI SUGLI STENTS MEDICATI

- La somministrazione locale di farmaci capaci di inibire la risposta vascolare si è rivelata molto promettente nella riduzione della "ristenosi" intra stent e quindi della necessità di ripetere le procedure di vascolarizzazione percutanea

STENT MEDICATI

SIROLIMUS

PACLITAXEL

RAZIONALE DELLA META-ANALISI SUGLI STENTS MEDICATI

- I trials finora realizzati hanno generato notevoli aspettative sull'efficacia degli stents medicati. Tuttavia:
  - spesso sono di piccole dimensioni
  - gli outcomes clinici sono solo secondari
  - i risultati sulla sicurezza non sono conclusivi a causa del numero limitato di effetti collaterali

OBIETTIVI DELLA META-ANALISI SUGLI STENTS MEDICATI

Valutare l'efficacia e la sicurezza degli stents medicati (sirolimus e paclitaxel) rispetto agli stents tradizionali (metallici) per il trattamento dei pazienti con malattia coronarica cronica

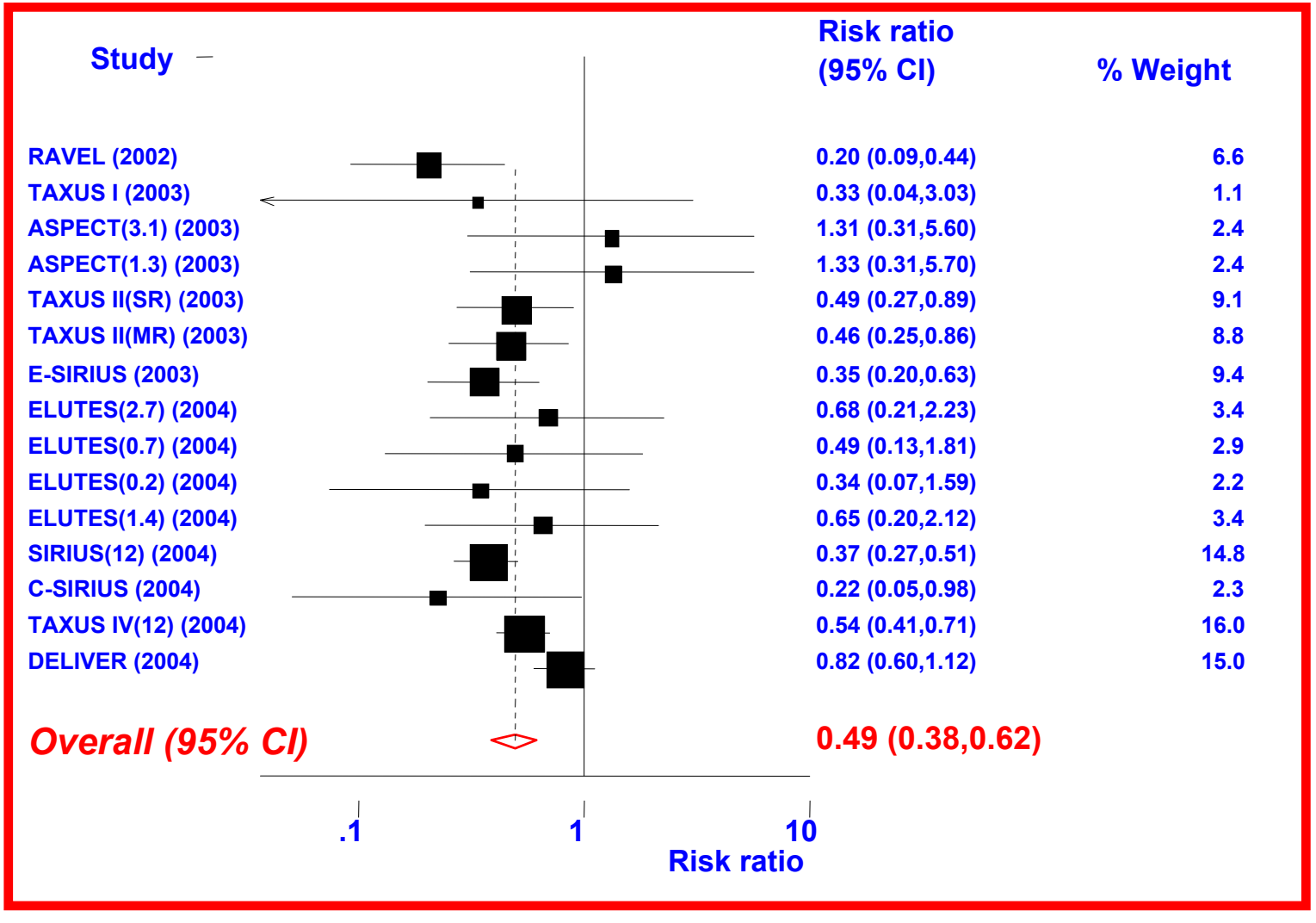
La meta-analisi sull'efficacia degli stents medicati nella riduzione dei Major Adverse Cardiac Events (MACEs) con lo STATA

```
metan mace1 diff1 mace0 diff0, rr random xlab(.1,1,10)
label(namevar=trialnam, yearvar=year)
```

Study	RR	[95% Conf.	Interval]	% Weight
RAVEL (2002)	.202451	.093477	.438466	6.55754
TAXUS I (2003)	.333333	.036718	3.02604	1.12601
ASPECT(3.1) (200	1.31073	.306718	5.60132	2.42069
ASPECT(1.3) (200	1.33333	.312127	5.69569	2.42183
TAXUS II(SR) (20	.493986	.273859	.891049	9.12835
TAXUS II(MR) (20	.464286	.251869	.855847	8.76875
E-SIRIUS (2003)	.354	.199868	.626994	9.44329
ELUTES(2.7) (200	.684685	.210096	2.23133	3.44713
ELUTES(0.7) (200	.487179	.131198	1.80905	2.88868
ELUTES(0.2) (200	.342342	.073764	1.58884	2.19495
ELUTES(1.4) (200	.649573	.198873	2.12167	3.43626
SIRIUS(12) (2004	.370424	.267646	.51267	14.7526
C-SIRIUS (2004)	.222222	.050526	.977365	2.33838
TAXUS IV(12) (20	.538206	.410142	.706256	16.049
DELIVER (2004)	.818779	.598276	1.12055	15.0265
D+L pooled RR	.488385	.383834	.621415	

Heterogeneity chi-squared = 25.21 (d.f. = 14) p = 0.033
Estimate of between-study variance Tau-squared = 0.0749

Efficacia degli stents medicati nella riduzione dei Major Adverse Cardiac Events (MACEs)



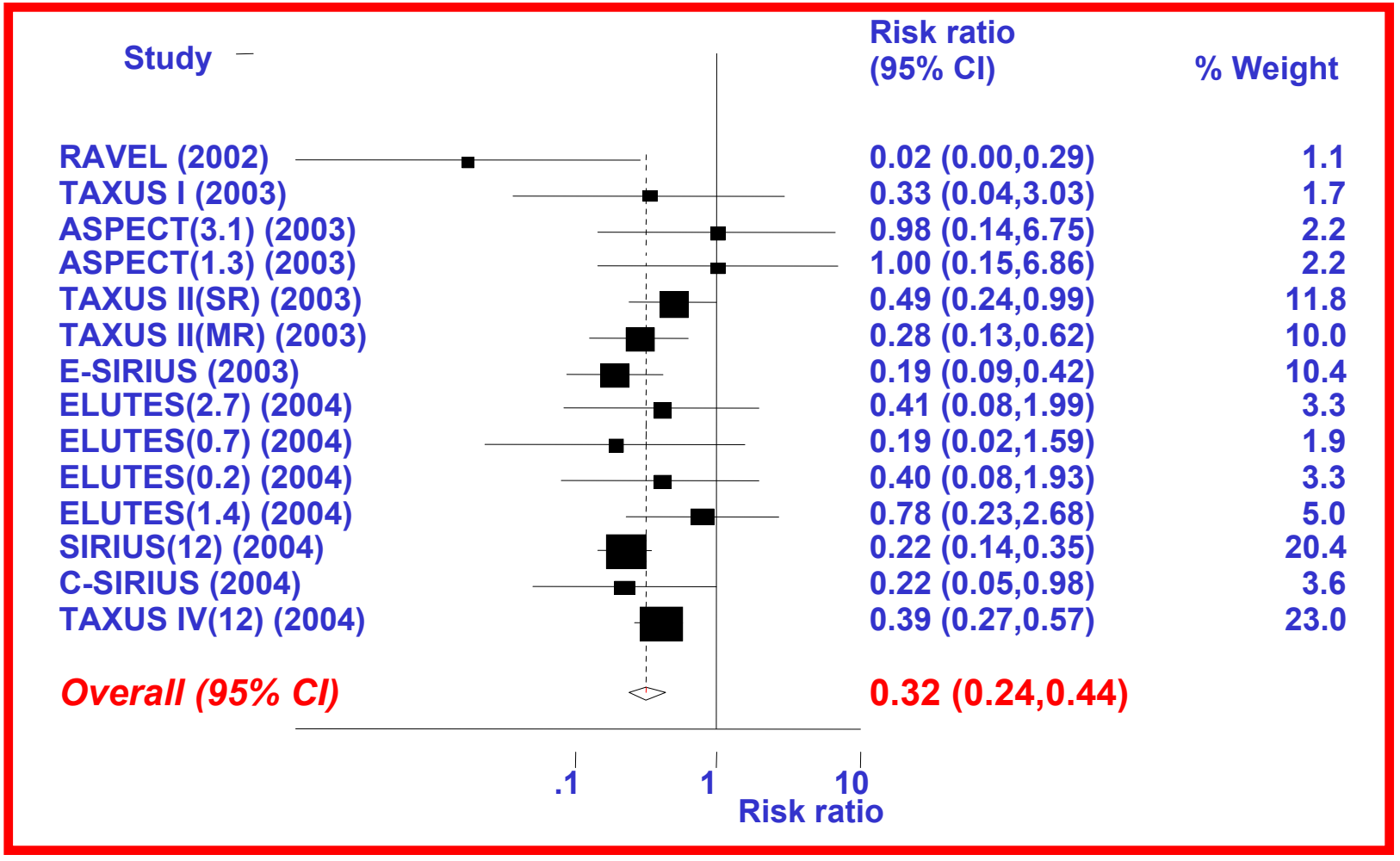
La meta-analisi sull'efficacia degli stents medicati nella riduzione della necessità di rivascolarizzazione percutanea con lo STATA

```
. metan revasc1 noreva1 revasc0 noreva0, rr random
xlab(.1,1,10) label(namevar=trialnam, yearvar=year)
```

Study	RR	[95% Conf.	Interval]	% Weight
RAVEL (2002)	.017881	.001103	.289796	1.10895
TAXUS I (2003)	.333333	.036718	3.02604	1.73669
ASPECT(3.1) (200	.983051	.143236	6.74683	2.24425
ASPECT(1.3) (200	1	.145748	6.86115	2.24489
TAXUS II(SR) (20	.487265	.238873	.993946	11.7932
TAXUS II(MR) (20	.28	.125515	.624627	9.99266
E-SIRIUS (2003)	.191351	.087686	.417574	10.4007
ELUTES(2.7) (200	.410811	.084947	1.98671	3.25269
ELUTES(0.7) (200	.194872	.023862	1.59142	1.90671
ELUTES(0.2) (200	.4	.082783	1.93276	3.25595
ELUTES(1.4) (200	.779487	.22635	2.68434	5.00438
SIRIUS(12) (2004	.224305	.144967	.347062	20.4078
C-SIRIUS (2004)	.222222	.050526	.977365	3.63984
TAXUS IV(12) (20	.393993	.270533	.573793	23.0113
D+L pooled RR	.324779	.241106	.437488	

```
Heterogeneity chi-squared =  16.96 (d.f. = 13) p = 0.201
Estimate of between-study variance Tau-squared =  0.0636
Test of RR=1 : z= 7.40 p = 0.000
```

Efficacia degli stents medicati nella riduzione della necessità di rivascolarizzazione percutanea



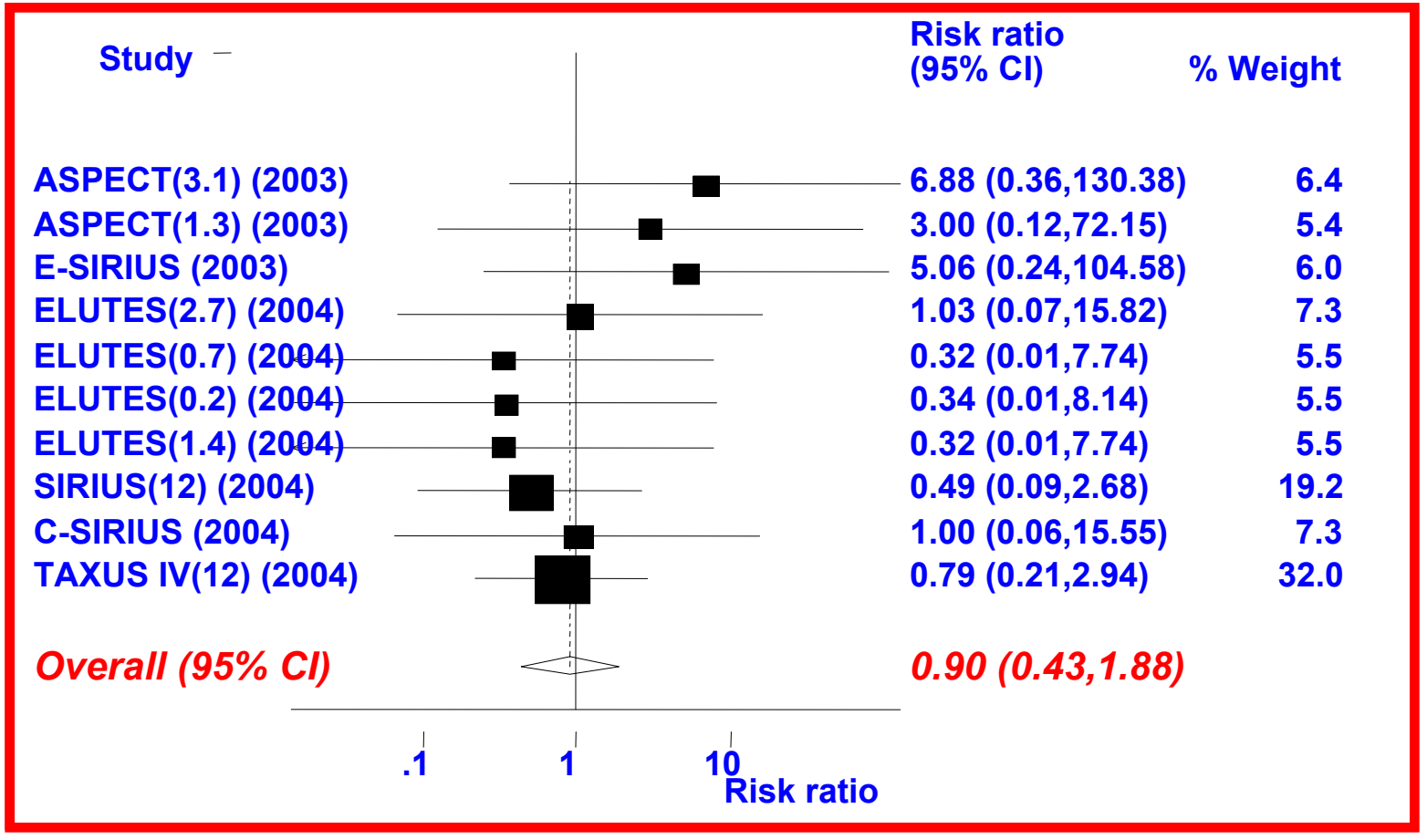
La meta-analisi sul rischio di trombosi con gli stents medicati con lo STATA

```
metan tromb1 notromb1 tromb0 notromb0, rr random xlab(.1,1,10)
label(namevar=trialnam, yearvar=year)
```

Study	RR	[95% Conf.	Interval]	% Weight
ASPECT(3.1) (200	6.88333	.363414	130.376	6.35116
ASPECT(1.3) (200	3	.124732	72.1547	5.43285
E-SIRIUS (2003)	5.05682	.244517	104.579	5.98796
ELUTES(2.7) (200	1.02703	.066675	15.8198	7.3477
ELUTES(0.7) (200	.325	.01365	7.73799	5.46763
ELUTES(0.2) (200	.342105	.01438	8.13876	5.47038
ELUTES(1.4) (200	.325	.01365	7.73799	5.46763
SIRIUS(12) (2004	.492495	.090594	2.67734	19.1679
C-SIRIUS (2004)	1	.064316	15.5483	7.29768
TAXUS IV(12) (20	.792488	.21379	2.93763	32.0091
D+L pooled RR	.895321	.426634	1.87889	

Heterogeneity chi-squared = 5.40 (d.f. = 9) p = 0.798
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.29 p = 0.770

Rischio di trombosi negli interventi con stent medicati rispetto agli stent tradizionali



LA VALUTAZIONE DELLA QUALITA' METODOLOGICA DEGLI STUDI

- Fase "obbligatoria" di una qualsiasi meta-analisi
- Esistono diversi approcci standardizzati per la valutazione quantitativa della qualità metodologica degli studi, nessuno dei quali "universalmente" accettato
- Diversi studi, soprattutto recenti, mostrano che gli studi di bassa qualità metodologica tendono a "sovrastimare" l'efficacia dell'intervento

IL PROBLEMA DELL'ETEROGENEITA' DEGLI STUDI INCLUSI NELLE META-ANALISI

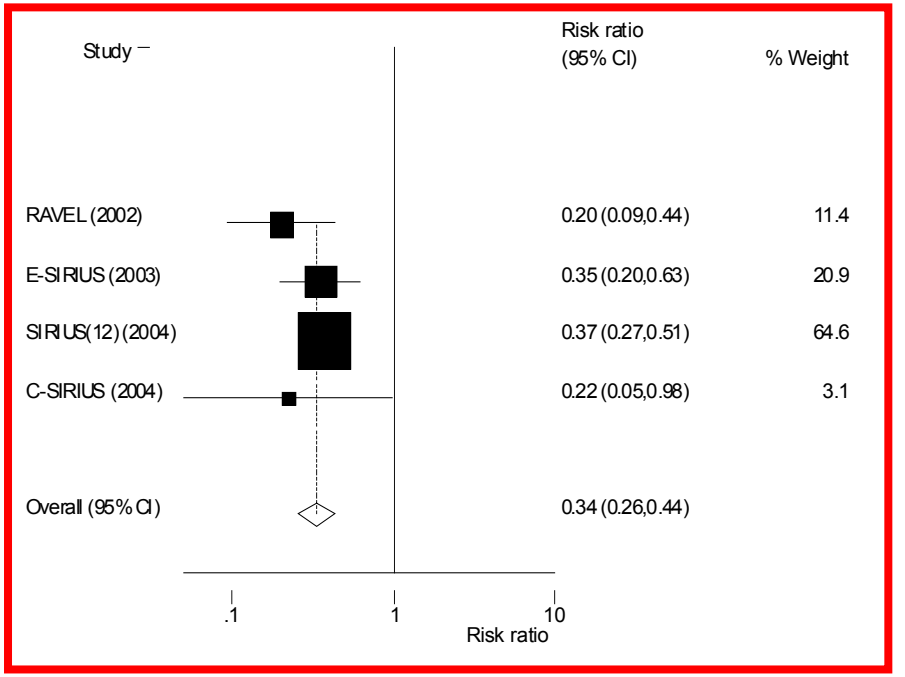
- Esistono diversi approcci statistici per valutare se esiste una eterogeneità statisticamente significativa tra i diversi studi individuali inclusi in una meta-analisi

- In caso di eterogeneità statisticamente significativa è ancora possibile combinare insieme i risultati dei diversi studi individuali, utilizzando metodiche che tengano in debito conto l'eterogeneità riscontata ("*random effect models*")

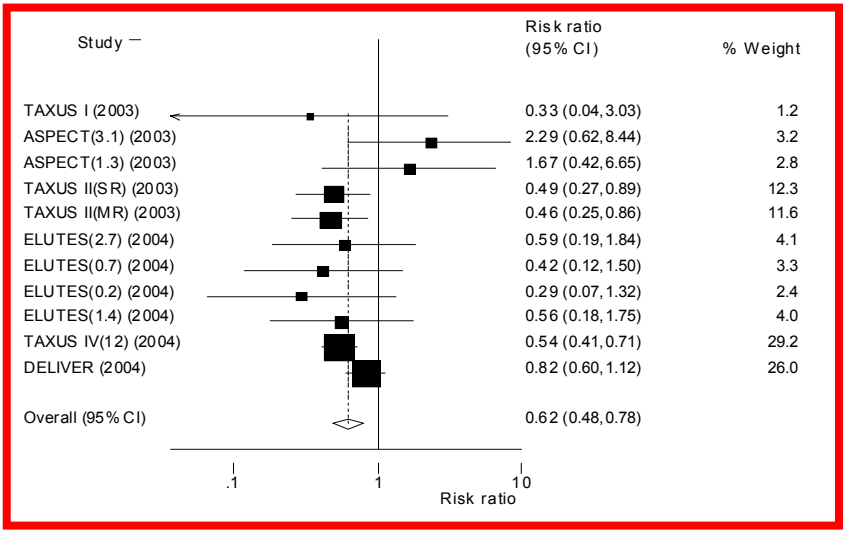
- In questi casi, tuttavia, la cosa più importante da fare è tentare di individuare le ragioni di tale eterogeneità, in quanto potenzialmente indicative di differenze di efficacia dell'intervento

Possibili fonti di eterogeneità tra i diversi trials sull'efficacia degli stents medicati rispetto agli stents tradizionali

SIROLIMUS



PACLITAXEL



Tipologia del farmaco (sirolimus o paclitaxel), percentuale diabetici, lunghezza della lesione, diametro della lesione, severità della stenosi, etc.

Il comando "metareg" per la metaregression

```
. gen logrr=log((mace1/pop1)/(mace0/pop0))

. gen selogrr=sqrt((1/mace1)-(1/pop1)+(1/mace0)-(1/pop0))

meta logrr selogrr, eform

Meta-analysis (exponential form)

       |  Pooled      95% CI          Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-----------------------------------------------------
Fixed  |   0.511   0.442   0.591   -9.059    0.000      15
Random |   0.488   0.384   0.621   -5.845    0.000

Test for heterogeneity: Q= 25.093 on 14 degrees of freedom (p=
0.034)
Moment-based estimate of between studies variance =  0.074

.
```

Il comando "metareg" per la metaregression

```
metareg logrr tipo, wsse (selogrr)
```

```
Iteration 1: tau^2 = 0
Iteration 2: tau^2 = .01110636
Iteration 3: tau^2 = .00964967
Iteration 4: tau^2 = .00988852

Meta-analysis regression                        No of studies =    15
                                                tau^2 method      reml
                                              tau^2 estimate =   .0099

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        tipo |   .6172931   .1807378     3.42   0.001      .2630535    .9715327
       _cons |  -1.104275    .148931    -7.41   0.000     -1.396174   -.8123755
------------------------------------------------------------------------------
```

Il comando "metareg" per la metaregression

```
metareg logrr tipo diabete diametro lunghezza, wsse (selogrr)
Iteration 1: tau^2 = 0

Meta-analysis regression                          No of studies =    15
                                                  tau^2 method      reml
                                                  tau^2 estimate =     0

Successive values of tau^2 differ by less than 10^-4 :convergence achieved
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        tipo |   .5404233   .1999472     2.70   0.007       .148534    .9323126
     diabete |   .0319791    .016887     1.89   0.058    -.0011188     .065077
    diametro |   1.031267   .9173114     1.12   0.261    -.7666305    2.829164
   lunghezza |  -.0246144   .0611113    -0.40   0.687    -.1443903    .0951616
       _cons |  -4.343311   2.703949    -1.61   0.108    -9.642953    .9563315
------------------------------------------------------------------------------
```

Influenza di diverse variabili sulla efficacia degli stent medicati sulla riduzione dei MACEs

	REGRESSION COEFFICIENT	Z	p
Type of drug (sirolimus=0; paclitaxel=1)	+0.617	3.42	0.001
% Diabetics (continuous)	+0.009	0.39	0.7
Mean lesion length (continuous)	-0.059	-0.86	0.39
Mean vessel diameter (continuous)	+2.098	2.10	0.035
% C-lesions (continuous)	-0.018	-1.02	0.31

PUBLICATION BIAS
IL PROBLEMA DEI DATI E DEI LAVORI NEL CASSETTO

1. IN UNA META-ANALISI GLI STUDI SONO OSSERVAZIONI. SAREBBE DESIDERABILE AVERE UN CAMPIONE RANDOM O ADDIRITTURA LA POPOLAZIONE.

2. SUPPONIAMO CHE I RISULTATI SIGNIFICATIVI ABBIANO MAGGIORI POSSIBILITA' DI ESSERE PUBBLICATI. GLI STUDI CHE NON RIFIUTANO L'IPOTESI NULLA POSSONO ESSERE TENUTI NEL CASSETTO.

3. IN UNA RICERCA BIBLIOGRAFICA SE (2) E' VERA, IL CAMPIONE POTREBBE NON ESSERE RAPPRESENTATIVO.

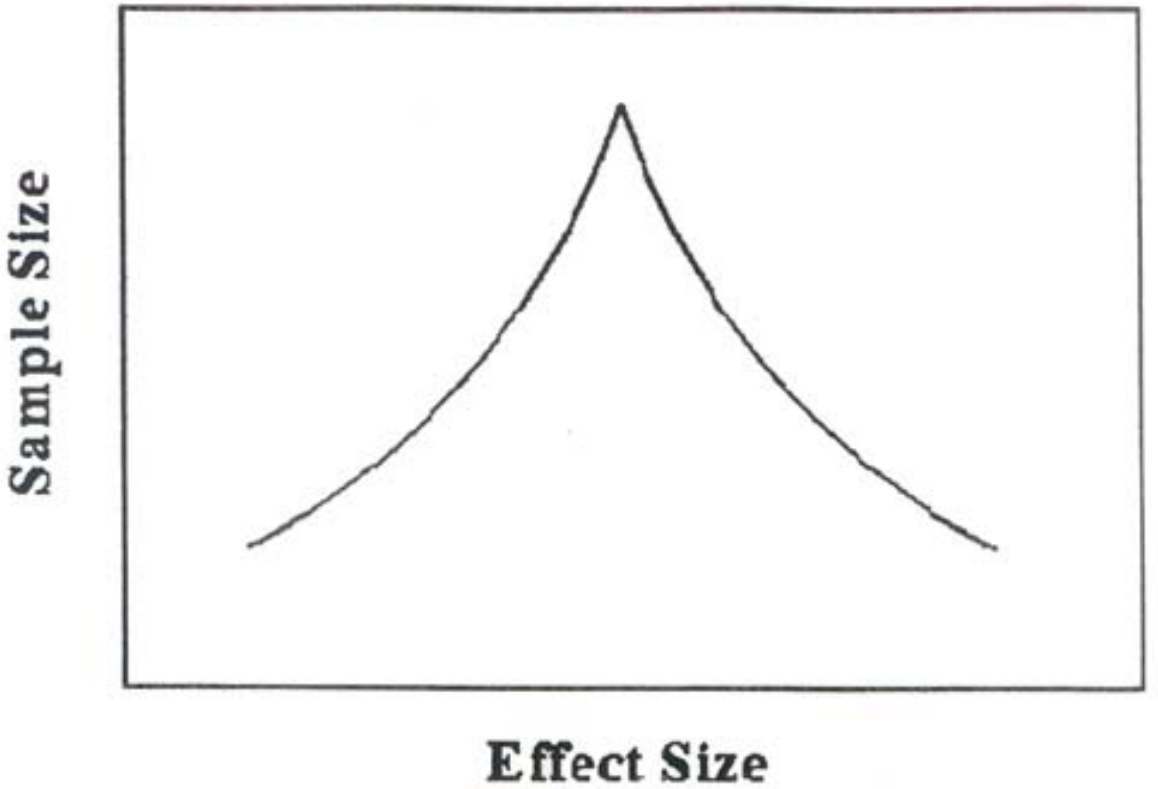
4. TUTTO CIO' POTREBBE PORTARE IN UNA META-ANALISI AD UNA SIGNIFICATIVITA' STATISTICA "SPURIA"

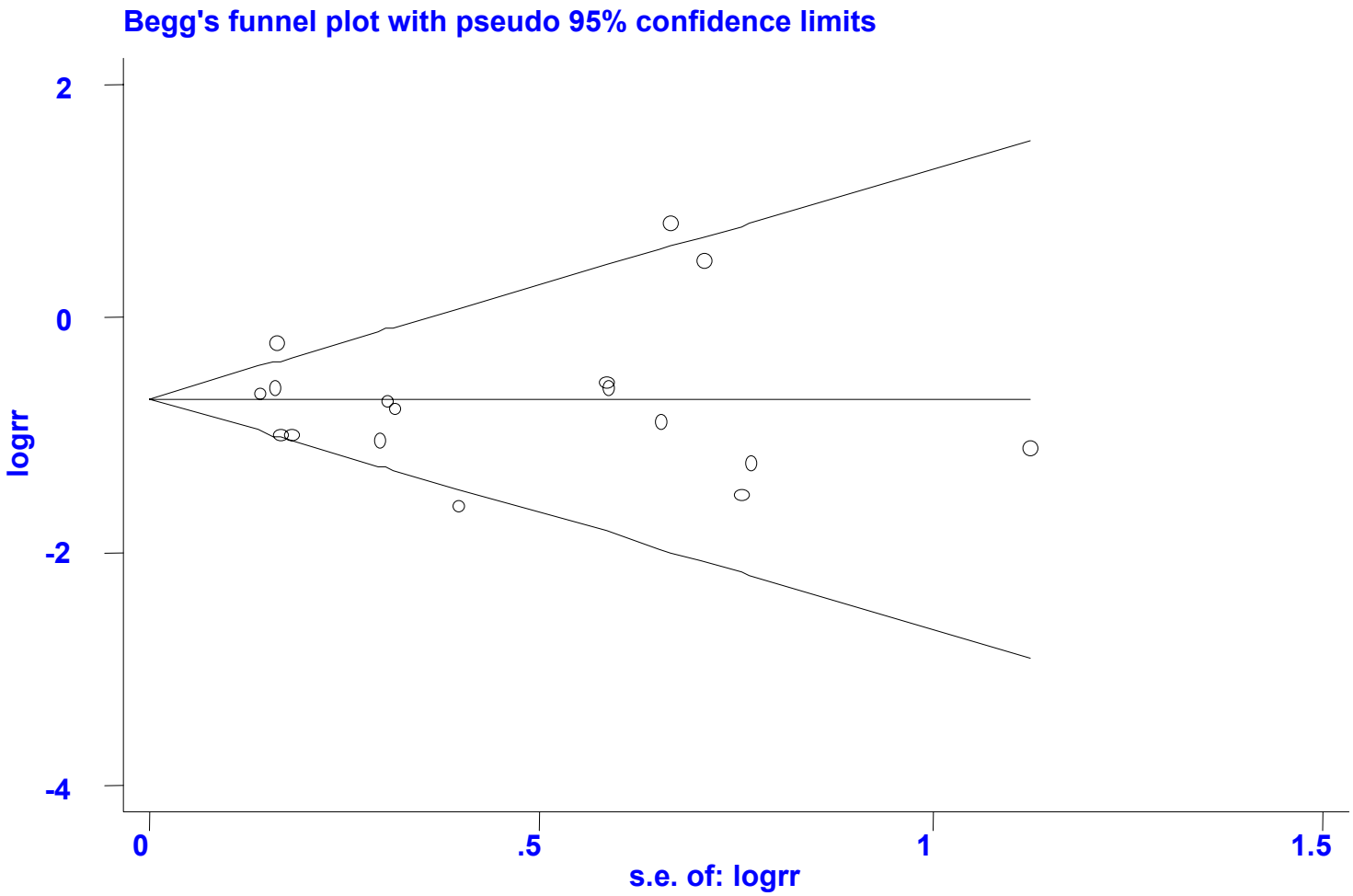
5. IN ALTRI TERMINI, SE (2) E (3) SONO VERE, LA META-ANALISI TENDEREBBE A SOVRASTIMARE L'EFFICACIA DELL'INTERVENTO. TUTTO CIO' E' DENOMINATO ***PUBLICATION BIAS***.

"MERE CONFIRMATION OF KNOWN FACTS WILL BE ACCEPTED ONLY IN EXCEPTIONAL CASES; THE SAME APPLIES TO REPORTS OF EXPERIMENTS AND OBSERVATIONS HAVING NO POSITIVE OUTCOME"

Manuscript guideline. Diabetologia, 1984, 25:4a

Idealized Shape of Funnel Plot in the Absence of Publication Bias





Funnel plot analysis dei trials sull'efficacia degli stent medicati nella riduzione dei MACEs

Il comando "metabias" per saggiare il publication bias -Test di Begg

```
. metabias logrr selogrr, graph(begg)

Note: default data input format (theta, se_theta) assumed.

Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =      -6
         Std. Dev. of Score =   24.28
          Number of Studies =      17
                          z  =   -0.25
                    Pr > |z| =   0.805
                          z  =    0.21 (continuity corrected)
                    Pr > |z| =   0.837 (continuity corrected)

Egger's test
------------------------------------------------------------------------------
     Std_Eff |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       slope |  -.6475008   .1705801    -3.80   0.002    -1.011084   -.2839179
        bias |  -.1894873   .6597061    -0.29   0.778    -1.595618    1.216643
------------------------------------------------------------------------------
```

CONCLUSIONI (I)

Gli stents medicati si sono rivelati significativamente più efficaci di quelli tradizionali nella riduzione della necessità di interventi di rivascolarizzazione percutanea e tali effetti non sembrano associati ad un aumento del rischio di trombosi

"Continue to randomize"

CONCLUSIONI (II)

- La meta-analisi svolge un ruolo fondamentale nel sintetizzare l'evidenza sull'efficacia degli interventi sanitari

- La meta-analisi ha svolto e svolge il compito fondamentale di evidenziare i limiti della letteratura scientifica, contribuendo in modo sostanziale al miglioramento della qualità metodologica della stessa ed alla genesi di quesiti di ricerca

CONCLUSIONI (III)

Lo STATA si è dimostrato uno strumento particolarmente utile e di facile utilizzazione per l'esecuzione di meta-analisi, in grado di supportare tutte le sue fasi dall'archiviazione dei dati estratti alla analisi ed interpretazione dei risultati